Abschlussbericht zum
DBU Projekt Nr. 27281-31

“Lösungsmittelfreie organische Synthesen in der Kugelmühle”

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Projektkennblatt
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Az	**27281-31**	Referat	**31**	Fördersumme	**124.500,00 €**

Antragstitel	**Lösungsmittelfreie organische Synthesen in der Kugelmühle**
Stichworte	Chemische Verfahrenstechnik, Umwelttechnologie, Prozessintensivierung

Laufzeit	Projektbeginn	Projektende	Projektphase(n)
2,5 Jahre	**01.07.2009**	**31.12.2011**	

Zwischenberichte

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Zielsetzung und Anlass des Vorhabens

Die Durchführung von chemischen Synthesen unter den Gesichtspunkten Nachhaltigkeit, Ressourcenschonung und Energieeinsparung ist eines der wichtigsten Betätigungsfelder der modernen organischen aber auch anorganischen Chemie. In diesem Zusammenhang ist die Durchführung von lösungsmittelfreien Reaktionen unter mechano-chemischen Bedingungen eine interessante Methode um Ressourcen einzusparen oder die Energieübertragung effizienter zu gestalten. Das Ziel dieses Projektes soll darin liegen, das allgemeine Verständnis von mechano-chemisch initiierten organisch-chemischen Reaktionen in Planetenkugelmühlen zu festigen und offenzulegen, welchen Einfluss verschiedene apparative Parameter einer ausgewählten Planetenkugelmühle auf organisch-chemische Reaktionen ausüben.

Darstellung der Arbeitsschritte und der angewandten Methoden

Anhand vorangegangener Arbeiten hat sich gezeigt, dass für eine erfolgreiche Reaktion unter mechanochemischen Bedingungen mindestens ein, besser alle Reaktionspartner fest sind. Da die Energieübertragung auf die Reaktanden (und damit die Initiierung der Reaktion) in diesen Fällen durch Schlag, Prall oder Reibung erfolgt, ist diese Übertragung im Falle von flüssigen Reaktionspartnern wenig effektiv. Des Weiteren haben jüngste Arbeiten gezeigt, dass neben chemischen Faktoren auch technische Parameter (z.B. Mahlmaterial, Mahldauer, Anzahl von Mahlkugeln, Umdrehungszahl) den Fortgang von mechanochemisch induzierten Reaktionen maßgeblich beeinflussen. Aus diesem Grund soll innerhalb dieses Vorhabens der Einfluss diverser technischer Parameter einer Planetenkugelmühle auf Beispielreaktionen zwischen festen Reaktionspartnern untersucht werden, mit dem Ziel diese Parameter hinsichtlich ihres Einflusses zu klassifizieren. Dazu sollen in einer ersten Phase geeignete Reaktionen ausgewählt werden unter der Maßgabe, dass sie ohne Lösungsmittel und in Kugelmühlen durchführbar sind. Im Anschluss daran ist geplant, am Beispiel einer Zweikomponentenreaktion und im Weiteren für eine Dreikomponentenreaktion den Einfluss unterschiedlicher apparativer Einflussfaktoren zu untersuchen. Daneben soll die Effizienz der Energieübertragung im Vergleich zu andern Methoden des nicht-klassischen Energieeintrages (Mikrowelle, Ultraschall) überprüft werden.

Ergebnisse und Diskussion

Innerhalb dieses Kooperationsprojektes wurde der Einsatz von Kugelmühlen als alternative Reaktoren für den Einsatz in der organischen Synthesechemie untersucht. Kugelmühlen im Allgemeinen und Planetenkugelmühlen im Speziellen sind Apparate aus der mechanischen Verfahrenstechnik und geeignet für die Zerkleinerung und Homogenisierung von Feststoffen. Dieser Effekt wird im vorliegenden Fall ausgenutzt, da in Folge der stattfindenden Mahlkörperbewegungen kinetische Energie in den Mahlraum eingetragen und diese durch Reibung in Wärme umgewandelt wird. Der daraus resultierende Temperaturanstieg konnte für die Initiierung verschiedenster chemischer Reaktionen genutzt werden. Die systeminhärente hohe Mischeffizienz sorgt für eine Aufhebung von Massentransportphänomenen, die ansonsten für Reaktionen zwischen Feststoffen typisch sind. Zusammengefasst hat sich gezeigt, dass die technologischen Vorraussetzungen von Kugelmühlen für eine Intensivierung chemischer Reaktionen im Labormaßstab hervorragend geeignet sind und dazu führen, dass diese Reaktionen in Bezug auf eine Energie- und Stoffbilanz im Vergleich mit herkömmlichen Synthesevarianten oder der Nutzung anderer alternativer Möglichkeiten des Energieeintrages wie Mikrowellen besser abschneiden. Dies konnt für unterschiedliche Reaktionen im Rahmen dieses Projektes demonstriert werden.

Obwohl der Einsatz flüssiger Reaktanden im Allgemeinen eine Limiteierung bezüglich des Einsatzes von Kugelmühlen darstellt, konnte durch geeignete Maßnahmen die Einsetzbarkeit entsprechender Ausgangsmaterialien an diversen Beispielen demonstriert werden. Auf diese Weise wurden unterschiedliche mechano-chemische Reaktionen im System Kugelmühle etabliert, darunter Vertreter aus dem Bereich der metallvermittelten Reaktionen, wie zum Beispiel die Sonogashira-Reaktion oder die Cycloaddition zwischen Aziden und Alkinen, aber auch Oxidationsreaktionen. Die Palette an Reaktionen konnte innerhalb des Projektes erheblich erweitert werden. Obwohl Reaktionen in Kugelmühlen ohne Lösungsmittel durchgeführt werden können, ist deren Einsatz für die Aufarbeitung bis auf wenige Ausnahmen notwendig. Allerdings kann die Anzahl und Menge der Lösungsmittel reduziert und damit zur Intensivierung der Prozesse beigetragen werden. Darüber hinaus wurde demonstriert, dass Reaktionen zwischen Feststoffen in Kugelmühlen vom Einsatz geringster Mengen an Lösungsmittel profitieren. Diese als *liquid-assisted grinding* bekannte Technologie führt zu einer verbesserten Diffusion durch Verlagerung der Reaktion in die den Feststoffen anhaftende Flüssigkeitsschicht.

Wie bei vielen chemische Prozesse, so existieren auch im Falle der Durchführung von Reaktionen in Kugelmühlen komplexe Zusammenhänge zwischen den einzelnen prozessrelevanten Parametern. Die Versuche haben für unterschiedliche Reaktionen gezeigt, dass eine Einteilung der Parameter in chemische, technologische, und Prozessparameter sinnvoll ist, wobei die zuletzt genannte Gruppe von Variablen (Reaktionszeit, Frequenz) den größten Einfluss zeigte. Bei der Wahl der technologischen Rahmenbedingungen (z.B. Art der Kugelmühle, Material für Mahlkörper und Mahlbecher) muss die chemische Resistenz gegenüber den eingesetzten Ausgangsmaterialien berücksichtigt werden. Im Vergleich zum Einsatz von Kugelmühlen für die Partikelzerkleinerung, müssen im Falle chemischer Reaktionen wesentlich mehr Parameter bei der Versuchsplanung berücksichtigt und optimiert werden.

Öffentlichkeitsarbeit und Präsentation

Ausgewählte Publikationen: Stolle et al., *Chem. Soc. Rev.* **2011**, *40*, 2317; Schmidt et al., *Chem.–Eur. J.* **2011**, *17*, 8129; Thorwirth et al., *Chem. Commun.* **2011**, *47*, 4370; Szuppa et al., *ChemSusChem* **2010**, *3*, 1181.

Ausgewählte Tagungsbesuche: 14th Annual Green Chemistry & Enginieering Conference (2010 Washington D.C.), 3rd International IUPAC Conference on Green Chemistry (2010 Ottawa), Umwelt 2010 – Von der Erkenntnis zur Entscheidung, (2010 Umweltbundesamt Dessau), The 2nd Symposium on Mechanochemistry and Solvent-free Synthesis (2011 Belfast), Woche der Umwelt 2012 (Schloss Bellevue, Berlin)

Fazit

Innerhalb des Projektes konnte gezeigt werden, dass organisch-chemische Reaktionen in Kugelmühlen erfolgreich durchführbar sind. Durch einen Verzicht von Lösemitteln während der Reaktionsstufe und der systembedingten Bereitstellung von Energie im Reaktor sowie der hohen Mischeffizienz werden Feststoffsynthesen ermöglicht. Darüber hinaus kann die Energie- und Stoffintensität solcher Prozesse signifikant verbessert werden. Hinsichtlich des Einsatzes der Technologie für maßstabsvergrößerte Synthesen unter kontinuierlichen Betriebsbedingungen sowie in Bezug auf eine umfassende ökologische und ökonomische Bewertung ergibt sich weiterer Forschungsbedarf.

Kurzzusammenfassung

Kugelmühlen sind verfahrenstechnische Apparate zur mechanischen Partikelzerkleinerung sowie zur Vereinzelung von Partikelagglomeraten. Durch Bewegungen von Mahlkörpern in einem Mahlraum wird durch Reibung und Schlagwirkung Energie auf das Mahlgut übertragen. Charakteristisch für diese Apparate sind deren inhärent hohe Mischeffizienz, die Bereitstellung von Energie direkt im Mahlraum sowie die durch mechanische Beanspruchung ständige Generierung von Oberflächen mit hohen Defektkonzentrationen. Diese Eigenschaften prädestinieren Kugelmühlen als Reaktoren für lösungsmittelfreie organische Reaktionen zwischen Feststoffen in entsprechenden Mahlbechern.

Mit diesem Projekt wurde demonstriert, dass Kugelmühlen eine interessante Prozessalternative für die Durchführung lösungsmittelfreier organischer Synthesen darstellen. Aus ökologischer und ökonomischer Sicht sowie unter den Aspekten der Arbeitssicherheit und Prozessstabilität ergeben sich bei Nutzung dieser Technologie interessante Möglichkeiten, klassische Syntheseprozesse auf verschiedenen Ebenen zu intensivieren. Dabei stellen der Verzicht von Lösungsmitteln während der Reaktion sowie eine Verkürzung von Reaktionszeiten die wesentlichen Aspekte dar, welche zu einer nachhaltigen Prozessintensivierung beitragen. Ein Verzicht von Lösemitteln verhindert entsprechende Emissionen mit Vorteilen für die Umwelt aber auch die Arbeitsplatzsicherheit. Eine Einsparung von Energie resultiert aus kürzeren Reaktionszeiten und der im Vergleich zu klassischen Methoden des Energieeintrages erhöhten Energieeffizienz von Kugelmühlen.

Wie viele Reaktoren und chemische Prozesse handelt es sich auch bei Kugelmühlen bzw. bei in diesen durchgeführten Reaktionen um Multiparametersysteme, wobei eine Klassifizierung in chemische, technologische und Prozessparameter eine Evaluierung dieser vereinfacht. Ausschlaggebend für den Erfolg einer Reaktion in Hinblick auf Ausbeute und Selektivität sind neben chemischen Faktoren die Wahl des Materials für Mahlbecher und Mahlkörper als technologische Variable sowie die regelbaren Prozessparameter Mahldauer und Frequenz. Letztere ist ein Maß für die eingetragenen Energie und bestimmt in signifikantem Maße die im Mahlraum herrschende Temperatur. Darüber hinaus konnte gezeigt werden, dass bei einer Maßstabsvergrößerung Faktoren wie die Art der eingesetzten Kugelmühle oder der Füllgrad der Mahlbecher an Bedeutung gewinnen. Untersuchungen zum elektrischen Wirkungsgrad verdeutlichen Unterschiede in den Antriebskonzepten verschiedener Kugelmühlen.

Vorwort

Für die Einordnung und Darstellung, der innerhalb des Projektes AZ 27281-31 erzielten und im folgenden Abschlussbericht skizzierten Ergebnisse, ist ein Vergleich mit Daten und Konzepten aus früheren oder anderen Projekten notwendig. Diese Arbeiten wurden nicht im Rahmen des oben genannten Projektes finanziert. Allerdings ist deren Erwähnung in diesem Zusammenhang notwendig, um die Bedeutung einzelner Aspekte hervorzuheben.

Entsprechende Arbeiten, die nicht kompletter Bestandteil dieses Projektes waren, sind im Abschnitt „Öffentlichkeitsarbeit“ mit dem Zusatz „anteilig“ versehen.

Inhaltsverzeichnis

Projektkennblatt 2

Kurzzusammenfassung 4

Vorwort 5

Inhaltsverzeichnis 6

Abkürzungsverzeichnis 7

1. Einführung 9

2. Chemische Parameter 12
    2.1 Screening von Reaktionsprotokollen 12
    2.2 Reaktionsnetzwerke 15
    2.3 Einsatz von Mahlhilfsmitteln 16

3. Apparative Einflussgrößen 20
    3.1 Typ der Kugelmühle 20
    3.2 Material der Mahlwerkzeuge 22
    3.3 Anzahl und Größe der Mahlkugeln 23
    3.4 Füllgrad der Mahlbecher 25

4. Prozessparameter 27
    4.1 Mahldauer 27
    4.2 Frequenz 27
    4.3 Energieeffizienz 28
    4.4 Vergleich mit anderen Methoden 30

5. Parameterevaluierung 34

6. Umweltrelevanz 36

7. Öffentlichkeitsarbeit 38

8. Zusammenfassung und Ausblick 40

9. Literaturverzeichnis 43

Anhang 46

Abkürzungsverzeichnis

ε	mittlere Porosität [-]	Gl. 8
η	Verhältnis Lösungsmittel/Feststoff [µl mg^{-1}]	Gl. 2
η_{el}	elektrischer Wirkungsgrad [-]	Gl. 11
$\nu_{Beanspruchung}$	Beanspruchungshäufigkeit [s^{-1}]	Gl. 7
ν	Frequenz [Hz ≙ s^{-1} ≙ 60 min^{-1}]	
ν/ν_{max}	dimensionslose Frequenz [-]	
ρ	Dichte [Si-Einheit = kg m^{-3}]	
ϕ	Füllgrad der Mahlbecher [-]	Gl. 8

d	Länge, Durchmesser, Abstand [SI-Einheit = m]	
E	Energie [kWh]	
$E_{Beanspruchung}$	mittlere Beanspruchungsenergie [J]	Gl. 6
E_{kin}	mittlere kinetische Energie [SI-Einheit = J]	Gl. 3
E_m	Energieintensität [kWh mol^{-1}]	
E_{netto}	in den Mahlraum übertragbare Energie [kWh]	Gl. 9
E_{netz}	gesamte eingesetzte elektrische Energie [kWh]	Gl. 9
E_{stress}	mittlere übertragene Beanspruchungsenergie [J]	Gl. 5
E_{SH}	Sheldon-Faktor [-]	Gl. 1
E_Y	Elastizitätsmodul [Pa]	Gl. 5
m	Masse [SI-Einheit = kg]	
n	Anzahl [-]	
n	Stoffmenge [SI-Einheit = mol]	
P_{blind}	gerätespezifische Blindleistung [Ws]	Gl. 9
T	Temperatur [℃, K]	
u	mittlere Geschwindigkeit [SI-Einheit = m s^{-1}]	Gl. 3
u_p	mittlere Bahngeschwindgkeit [m s^{-1}]	Gl. 4
V	Volumen [SI-Einheit = m^3]	
w	Massenbruch [-]	

AcO	Acetat
CuAAC	copper-catalyzed azide-alkyne-cycloaddition
DABCO	Diazabicyclo[2.2.2]octan
IUPAC	International Union of Pure and Applied Chemistry
LAG	liquid-assisted grinding (flüssigkeitsunterstütztes Mahlen)

MB [index]	Mahlbecher
MK [Index]	Mahlkugeln, Mahlkörper
MSZ	Magnesium-stabilisiertes Zirkonoxid
osz [Index]	Oszillation
PKM	Planetenkugelmühle
rot [Index]	Rotation
SKM	Schwingkugelmühle

1. Einführung

Innerhalb dieses von der DBU geförderten Kooperationsprojektes sollten die Einflussgrößen bei der Durchführung organisch-chemischer Synthesen in Kugelmühlen anhand ausgewählter Beispielreaktionen untersucht und validiert werden. Das Ziel des Projektes lag also darin, das allgemeine Verständnis von mechanochemisch initiierten Reaktionen in Planetenkugelmühlen zu festigen unter der Prämisse *apparative* (*technologische*) Einflüsse des Mahlvorganges und *prozessbezogene* Parameter (*Prozessparameter*) offenzulegen und nach ihrer Wichtigkeit zu ordnen. Unter *apparativen* Einflussgrößen werden all diejenigen Parameter zusammengefasst, die vor einer Reaktion festgelegt werden, wie zum Beispiel Material der Mahlbecher und Mahlkugeln oder die Anzahl und Größe der Mahlkugeln. Im Gegensatz dazu sind im Rahmen dieser Arbeit unter *prozessbezogenen* Parametern solche Variablen zu verstehen, die davon unabhängig geregelt werden können (Mahldauer t und Frequenz ν). Von diesen Größen unabhängig existiert noch eine Vielzahl weiterer Größen, welche den Ausgang einer chemischen Reaktion beeinflussen. Diese werden im Folgenden als „*chemische* Parameter“ zusammengefasst (z.B. Verhältnis von Reaktanden, Katalysatoren, Additive, Ansatzgröße). Die Abhängigkeit der Resultate von reaktiven Mahlprozessen von Prozessvariablen ist schematisch in *Abbildung 1* dargestellt.

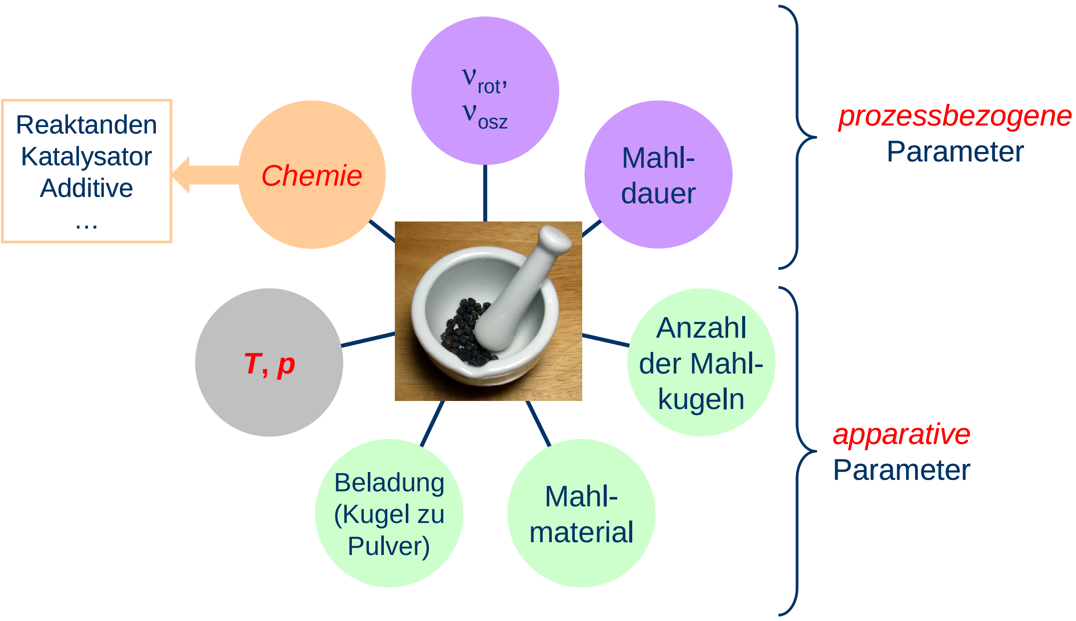

Abbildung 1. Klassifizierung der Einflussgrößen von chemischen Reaktionen welche in Kugelmühlen durchgeführt werden.

Aufgrund der zu erwartenden Komplexität der Zusammenhänge und im Sinne einer systematischen Herangehensweise an die zu beantwortenden Fragen wurde sich dafür entschieden, das Projekt nach dem Fließschema in *Abbildung 2* zu strukturieren und in verschiedene Projektphasen zu unterteilen. Die Zielsetzung der einzelnen Phasen wird im Folgenden skizziert.

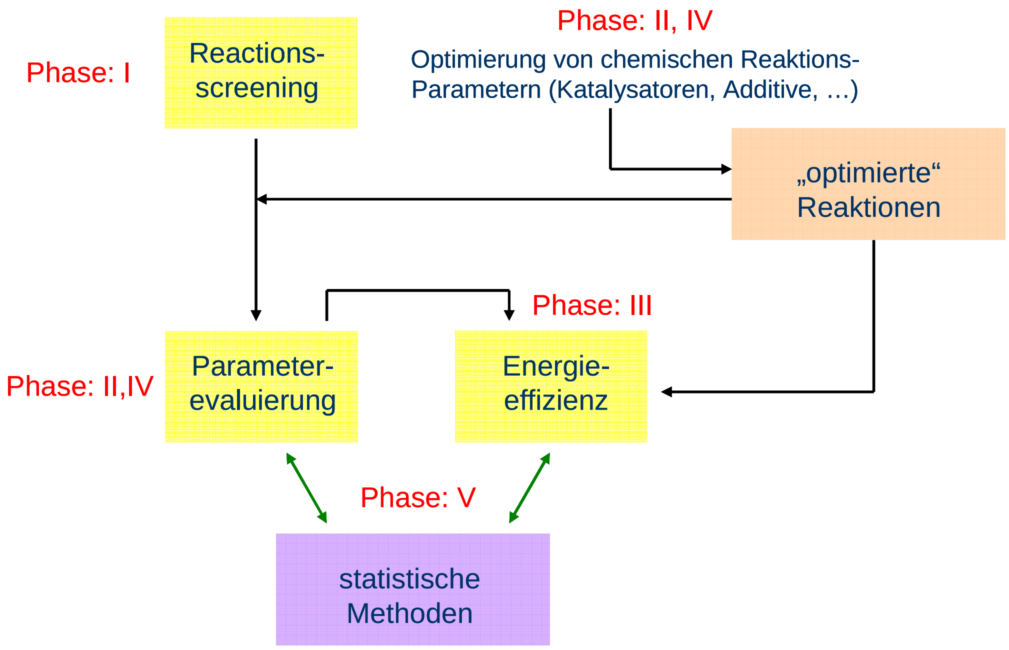

Abbildung 2. Schematische Darstellung der Projektstruktur.

Phase I: Um die erzielten Ergebnisse dahingehend zu homogenisieren, dass chemische Parameter bei der Validierung ausgeschlossen werden können, sollten im ersten Schritt des Projektes potentielle chemische Reaktionen auf ihre generelle Durchführbarkeit in Kugelmühlen getestet werden. Dabei sollten weder die Reaktionen an sich (z.B. Variation der Edukte oder Basen) noch apparative Parameter variiert oder optimiert werden. Der Auswahl der Reaktionen sollte dabei zugrunde liegen, dass diese durch die lösungsmittelfreie Durchführung[1] in der Kugelmühle im Vergleich zu klassischen Synthesevorschriften umweltverträglicher durchgeführt werden können (z.B. durch Verzicht von Lösungsmittel oder Additiven).

Phase II: Im Folgenden sollten an Beispielreaktionen mit zwei bei Raumtemperatur festen oder einem festen und einem flüssigen Reaktionspartner eine Variation der chemischen Parameter vorgenommen werden. Die Reaktion(en) sollte(n) dabei derart „optimiert" werden, dass bei der folgenden Variation von *apparativen* und *prozessbezogenen* Stellgrößen ein breiter Umsatz- bzw. Selektivitätsbereich abgedeckt werden kann. Innerhalb dieser Projektphase wurde angestrebt den Einfluss von Prozessgrößen wie zum Beispiel Rotationsfrequenz, Mahldauer oder Mahlmaterial tiefergehend zu untersuchen.

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[1] Im Englischen existiert darüber hinaus der Begriff „solvent-less reactions." Oft versteht man darunter lösungsmittelfreie Synthesen, bei denen auch zur Aufarbeitung kein Lösungsmittel verwendet werden muss. Allerdings ist diese Definition nicht allgemein anerkannt. Deshalb scheint es uns sinnvoll, nur die Begriffe „solvent-free" und „solid-state" zu verwenden.

Phase III: An einem ausgewählten Reaktionsbeispiel sollte die Energieeffizienz bezüglich der Bildung des entsprechenden Zielproduktes im Vergleich zu anderen Reaktionsapparaturen demonstriert werden. Zum einen wurden verschiedene Typen von Kugelmühlen untereinander verglichen und zum anderen die Leistungsfähigkeit dieser Methode in Relation zu Mikrowellen- oder Ultraschall-assistierten Reaktionsführungen untersucht.

Phase IV: Es sollte überprüft werden, inwieweit die Schlussfolgerungen, die aus den Experimenten laut Phase I gezogen wurden, auf komplexere Reaktionen übertragbar sind. Es wird angestrebt eine Dreikomponentenreaktion oder eine katalysierte Mehrkomponentenreaktion[2] unter den Gesichtspunkten der Parametervariation laut *Abbildung 1* durchzuführen und zu validieren.

Phase V: Die aus den unterschiedlichen Experimenten gewonnenen Erkenntnisse sollten mit Hilfe statistischer Methoden untereinander gewichtet werden. Damit wurde es ermöglicht, generelle Trends aufzuzeigen und damit die Vorhersagbarkeit von Ergebnissen zu stärken. Basierend auf diesen Resultaten ist geplant, allgemeine Regeln für das Arbeiten unter mechanochemischen Bedingungen zu formulieren, die dazu beitragen, derartige Reaktionen energieeffizient und damit nachhaltig durchzuführen.

Für die Erreichung der Projektziele war es somit notwendig, dass

a) Reaktionsprotokolle identifiziert und in Hinblick auf deren chemische Einflussgrößen teiloptimiert,
b) bei ausgewählten Reaktionen sowohl die apparativen als auch die Prozessparameter einer kritischen Bewertung unterzogen und
c) die Ergebnisse hinsichtlich ihres Einflussverhaltens bewertet werden.

Diese einzelnen Teilaspekte des Projektes werden im folgenden näher beleuchtet, wobei auf die Angabe von experimentellen Details verzichtet wird. Diesbezügliche Daten können den im Anhang befindlichen Originalpublikationen entnommen werden. Innerhalb des Berichtes werden demnach nicht Teilaspekte einzelner Reaktionen beleuchtet, sondern es soll durch einen übergeordneten Vergleich verdeutlicht werden, dass allgemeine Regeln und Zusammenhänge für organische Reaktionen in Kugelmühlen existieren.

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[2] Unter Drei- oder Mehrkomponentenreaktionen sind in diesem Zusammenhang die Anzahl, der an der Reaktion beteiligten Komponenten zu verstehen, egal ob es sich um Reaktanden, Katalysatoren oder Additive handelt.

2. Chemische Parameter (Phasen I, II, IV)

Anhand der nach Erscheinungsjahren gestaffelten Auflistung der Anzahl der Literaturzitate zum Thema „Organische Synthese in Kugelmühlen“ in *Abbildung 3* wird die Aktualität dieses Forschungsgebietes deutlich, da ein kontinuierlicher Anstieg in der Anzahl der Publikationen in den vergangenen Jahren zu verzeichnen ist.[1] Der Bereich der veröffentlichten Reaktionsprotokolle umfasst Beispiele, die ein weites Spektrum der organischen Synthesechemie abdecken. Angefangen von relativ simplen Oxidationen substituierter Aromaten bis hin zu komplexen Pd-katalysierten oder enantioselektiven Reaktionen wurde somit eine Vielzahl von Experimenten publiziert.

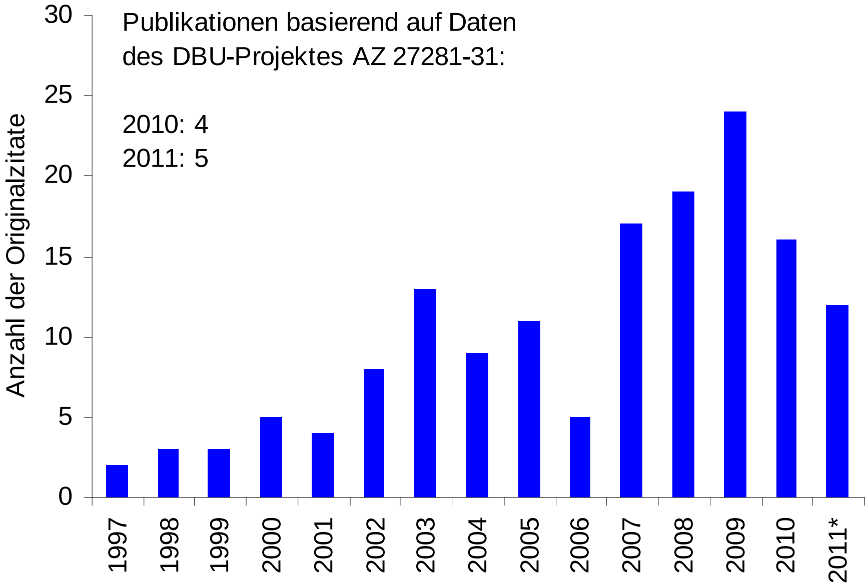


Abbildung 3. Anzahl von Originalzitaten zum Thema „Organische Synthese in Kugelmühlen“ geordnet nach dem Erscheinungsjahr (* Stand 12-2011).

2.1 Screening von Reaktionsprotokollen

Auf Basis dieser Resultate (Stand 07-2009) war es eines der Ziele des Projektes, das Spektrum an möglichen Reaktionen signifikant zu erweitern, um eine Basis für weitergehende Untersuchungen zu schaffen. Dabei war es nicht die zwingende Vorraussetzung, dass die avisierten Beispiele noch nicht publiziert wurden. Vielmehr stand im Focus der Betrachtungen die relativ einfache Durchführbarkeit bzw. Adaption der Reaktionen unter den Bedingungen einer solventfreien Synthese in Kugelmühlen. Es sollten vornehmlich solche Reaktionen zur Anwendung kommen, bei denen die Anzahl der an der Reaktion beteiligten Stoffe auf zwei bzw. drei begrenzt bleibt. Für weitergehende Untersuchungen (Phase IV) wurden allerdings auch schon in dieser frühen Phase katalytische Reaktionen auf ihre allgemeine Durchführbarkeit getestet. In *Tabelle 1* sind diejenigen Reaktionen zusammengefasst, welche im Rahmen dieser Untersuchungen erprobt wurden. All diese Reaktionen wurden unter solventfreien Reaktionsbedingungen in Kugelmühlen durchgeführt.

Tabelle 1. Übersicht der getesteten Reaktionen durchgeführt in der Kugelmühle.

Reaktion ^{1})	Anmerkung ^{2})	Referenz
Oxidation		
Aromatisierung (1/1/-)	DBU-Projekt AZ 27281-31	[2]
Oxidative C-C-Bindungsspaltung (1/1/-)	DBU-Projekt AZ 27281-31	[3]
Oxidative Homokopplung von Anilinen (1/1/-)	DBU-Projekt AZ 27281-31	[4]
Halogenierung von Aromaten (Cl, Br) (1/2/-)	DBU-Projekt AZ 27281-31 / DA	[5]
Metallkatalysierte Reaktionen		
Sonogashira-Reaktion (2/1/1)	DBU-Projekt AZ 27281-31	[6]
Glaser-Reaktion (1/1/1 bzw. 1/2/1)	DBU-Projekt AZ 27281-31	[7]
CuAAC (2/-/1 bzw. 2/1/1)	DBU-Projekt AZ 27281-31	[8]
C-N-Kopplung (2/1/1 bzw. 2/2/1)	proof-of-principle	
Veretherungen (1/-/2)	proof-of-principle	
Sonstige Reaktionen		
Hydroaminierungen (2/-/-)	DBU-Projekt AZ 27281-31	[9]
Diels-Alder-Reaktion (2/-/- bzw. 2/1/-)	proof-of-principle	
Iodierung von Anilinen (2/-/-)	proof-of-principle	
En-Reaktion (2/-/-)	proof-of-principle	

^{1}) Die Zahl in Klammern bezieht sich auf die an der Reaktion beteiligten Komponenten, wobei die erste Zahl die eigentlichen Reaktanden umfasst, die zweite Zahl mögliche Additive (z.B. Basen) und die dritte Zahl eingesetzte Katalysatoren.

^{2}) „Proof of principle" bedeutet, dass die jeweilige Reaktion in Einzelversuchen erfolgreich durchgeführt werden konnte. DA ≙ abgeschlossene Diplomarbeit.

Die innerhalb des Projektes untersuchten Reaktionen gliedern sich dabei in zwei wichtige Klassen: Oxidationsreaktionen und metallkatalysierte Reaktionen. Im Falle der Oxidationsreaktionen wurden im Rahmen dieses Projektes vier Reaktionen näher untersucht:

a) die Aromatisierung von γ-Terpinen zu *p*-Cymen,[2]
b) die oxidative Spaltung von β-Pinen zu Nopinon,[3]
c) die oxidative Homokopplung von Anilinen[4] und
d) die Chlorierung bzw. Bromierung von Aromaten mit NaX und $KHSO_5$.[5]

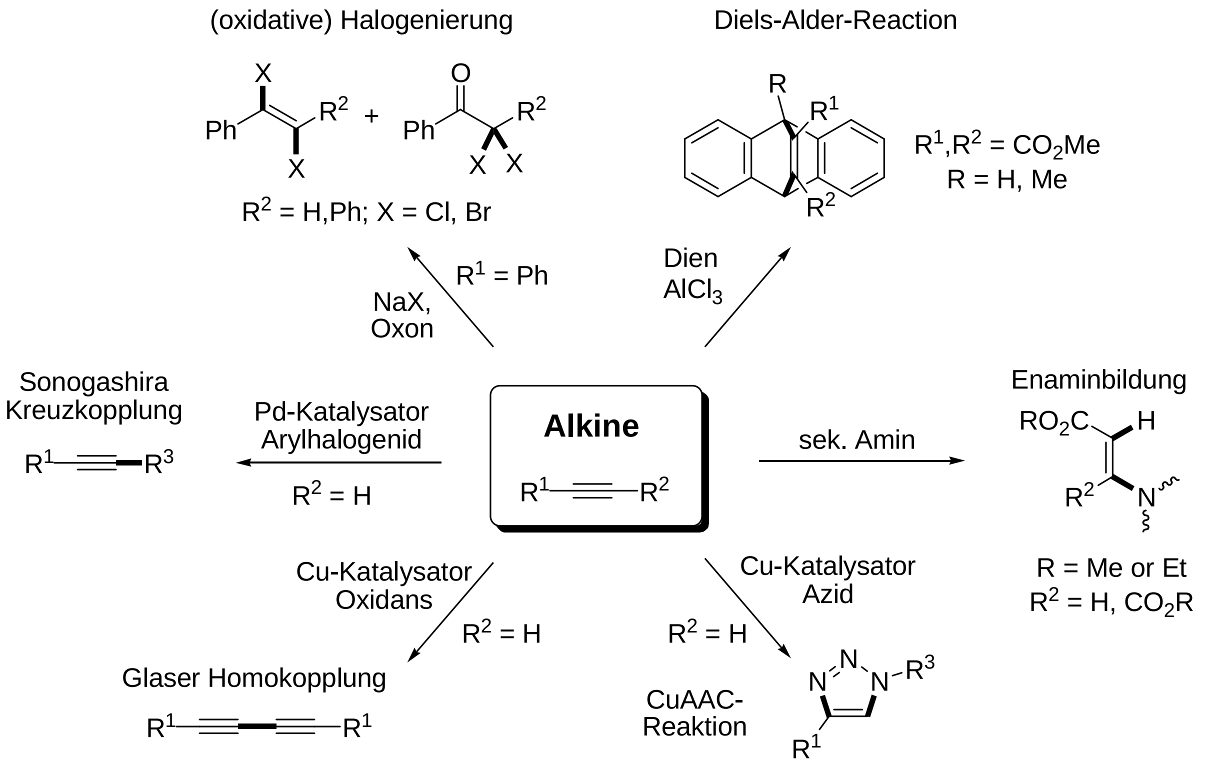
Während es sich bei der erstgenannten Reaktion um eine Modellreaktion handelt, mit deren Hilfe im Laufe der Untersuchungen wesentliche Zusammenhänge zwischen den einzelnen

Variablen geklärt werden konnten,[2] haben die anderen Varianten großes synthetisches Potential. Durch den Verzicht von Lösungsmitteln konnten Oxidationen mit anorganischen Oxidationsmitteln durchgeführt und auf den Einsatz von Lösungsmittelgemischen, Lösungsvermittlern oder von Phasentransferkatalysatoren verzichtet werden. Damit konnte die Stoffintensität der einzelnen Reaktionen signifikant verringert werden. Die Synthese von Nopinon aus β-Pinen mit $KMnO_4$ als Oxidationsmittel ist eine reale Alternative[3] zur klassischen Synthesevariante mittels Ozonolyse bei $T < -50\,°C$ und anschließender reduktiver Aufarbeitung.[10] Die Anzahl der Prozessschritte konnte verringert werden, ein Arbeiten bei tiefen Temperaturen ist nicht notwendig und es kann auf Ozon (gasförmig, explosiv) verzichtet werden. Bei der oxidativen Homokopplung von Anilinen konnte durch Wahl des Oxidationsmittels und des Malhilfsmittels die Selektivität für die Bildung der Azo- bzw Azoxyprodukte gesteuert werden.[4] Eine selektive Oxidation von *p*-Toluidin zu *p*-Nitrotoluen konnte ebenfalls demonstriert werden. Das heißt, man kann durch Einstellung unterschiedlicher Reaktionsbedingungen bei Reaktionen in Kugelmühlen die Selektivität von Reaktionen kontrollieren. Die Bereitstellung von halogenierten Aromaten ist ein wesentlicher Punkt für die Realisierung von Synthesesequenzen in Kugelmühlen, insbesondere dann wenn metallkatalysierte Kreuzkopplungsverfahren durchgeführt werden sollen. Eine Reihe von Aromaten konnten in der Kugelmühle in Anwesenheit von NaCl bzw. NaBr und $KHSO_5$ selektiv halogeniert werden.[5]

Die zweite große Gruppe von untersuchten Reaktionen umfasste die Klasse der metallkatalysierten Reaktionen mit dem Schwerpunkt auf Pd-[6, 11] und Cu-katalysierten Varianten.[7-8] Auf dem Gebiet der Pd-katalysierten Vertreter konnte das Feld der Kreuzkopplungsverfahren in Kugelmühlen um die Sonogashira-Reaktion[6, 12] erweitert werden. Neben Verfahren für die Suzuki-Miyaura-[11, 13] und die Mizoroki-Heck-Reaktion[14] wurde auch ein Protokoll für die Kopplung terminaler Alkine mit Halogenaromaten etabliert. Durch den Einsatz von $Pd(AcO)_2$ als Katalysator und Diazabicyclo[2.2.2]octan (DABCO) als Base[6] konnte auf den Einsatz komplexer Katalysatoren verzichtet und die Reaktionszeit signifikant von mehreren Stunden auf unter 20 min reduziert werden.[12] Ein Einsatz von Cu-Salzen als Cokatalysatoren war nicht notwendig. Substituiert man den Pd-Katalysator durch ein Cu-Salz wie CuI, war die Homokopplung terminaler Alkine (Glaser-Reaktion) möglich.[7] Diese Vorschrift stellte somit die erste rein Cu-katalysierte Reaktion in einer Kugelmühle dar. Mit dem Wechsel von Pd- auf Cu-Katalysatoren eröffnen sich neue Synthesemöglichkeiten und auch aus wirtschaftlichen Gründen ist das Arbeiten mit den billigeren Kupferverbindungen sinnvoll. Das Spektrum an Cu-katalysierten Reaktionen in Kugelmühlen wurde um Cycloadditionen von Alkinen mit Aziden (CuAAC) erweitert.[8] Diese Reaktion erfüllt alle Kriterien einer *Click-Reaktion* nach *Sharpless*[15] und ist somit von großem synthetischen Interesse. Das Verfahren der CuAAC konnte weiterhin erstmals für die Funktionalisierung von Polymeren und Polymerisationen in Kugelmühlen angewendet werden.[8] Eine Bereitstellung des Cu-Katalysators durch Mahlwerkzeuge aus Cu wurde ebenfalls demonstriert.

2.2 Reaktionsnetzwerke

Mit den untersuchten Reaktionen wurden Syntheseprotokolle entwickelt, die auf Basis diverser Synthesebausteine eine Vielzahl von chemischen Reaktionen ermöglichen. Dieser Zusammenhang sei in *Schema 1* für Reaktionen basierend auf Alkinen exemplarisch dargestellt.[16] Innerhalb dieses Projektes konnte gezeigt werden, dass sich einige Substanzklassen als Ausgangspunkt für chemische Synthesen in Kugelmühlen eignen (Alkine, Amine, Boronsäuren). Die jeweiligen Reaktionsnetzwerke weisen Verknüpfungspunkte untereinander auf, so dass sie als Basis für zukünftige Entwicklungen zu verstehen sind, bei denen nicht mehr die einzelne Reaktion an sich im Mittelpunkt steht, sondern sich produktorientiert komplette Synthesestrategien in Kugelmühlen entwickeln und durchführen lassen.



Schema 1. Alkine als zentrale Synthesebausteine bei Umsetzungen in Kugelmühlen.[16]

Neben den beschriebenen Substanzklassen wurde innerhalb des vorliegenden Projektes auch die Chemie von Monoterpenen bzw. -terpenoiden in Kugelmühlen untersucht.[2-3, 6, 8] So konnte gezeigt werden, dass sich entsprechende Vertreten mit dieser Technik chemisch modifizieren lassen, ohne dass die oft fragilen Strukturmotive verändert werden. Damit sollte es zukünftig möglich sein, durch das reaktive Vermahlen in Kugelmühlen Synthesebausteine für spezialchemische Anwendungen bereitzustellen, z.B. in der Lebensmitteltechnologie oder Pharmazie.

Erweitert man die Reaktionsnetzwerke um andere in der Literatur bereits beschriebene Reaktionen für die abgebildeten oder weitere Synthesebausteine, dann lässt sich festhalten, dass zum jetzigen Zeitpunkt eine Vielzahl von Reaktionen entwickelt wurden.[1c-e, 17] Teilweise unterscheiden sich diese Protokolle in Bezug auf deren Zeitaufwand, Materialintensität oder die Art der technischen und Prozessparameter erheblich, so dass eine umfassende Untersuchung einzelner Variablen notwendig ist. Diese Untersuchungen stehen im Mittelpunkt der folgenden Abschnitte.

2.3 Einsatz von Mahlhilfsmitteln

In den meisten Fällen der vorgestellten Reaktionsprotokolle war der Einsatz eines Füllmaterials für eine erfolgreiche Durchführung der Reaktion notwendig, wobei entweder das chemisch inerte SiO_2 (Quarzsand) oder chemisch aktiveres Al_2O_3 als Mahlhilfsmittel eingesetzt wurden. Zum Einen dienten diese Additive, die im übrigen nicht in die an der Reaktion beteiligten Komponenten mit einbezogen wurden (vergleiche *Tabelle 1*), als reine Mahlhilfsmittel, um die Ansatzgröße relativ gering zu halten, die Becher aber zu dem erforderlichen Füllgrad zu befüllen.

Die wesentliche Aufgabe des Mahlhilfsmittels ist allerdings das Ermöglichen des Einsatzes flüssiger Reaktanden bei chemischen Umsetzungen in Kugelmühlen. Mahlprozesse laufen in der Regel zwischen Feststoffen ab, wobei im Falle der Nasszerkleinerung die Feststoffe auch suspendiert in einem inerten Lösungsmittel vorliegen können.[18] Bei chemischen Umsetzungen wäre diese Technik zwar denkbar, allerdings stellt sich dann die berechtigte Frage, ob nicht eine Reaktion in klassischen Reaktionsgefäßen wirtschaftlicher wäre. Sollen flüssige Substrate bei entsprechenden Prozessen zum Einsatz kommen, müssen Strategien entwickelt werden, um dies zu ermöglichen, will man nicht auf den Einsatz entsprechender Stoffe verzichten, was eine signifikante Einschränkung bedeuten würde. Eine Möglichkeit stellt die chemische Derivatisierung und damit die Überführung in Feststoffe dar. Aus nachhaltigen Gesichtspunkten ist diese Variante allerdings nachteilig, da mindestens zwei zusätzliche Reaktionsschritte benötigt werden und damit der Gesamtaufwand steigt. Es sei denn, das Derivat kann direkt zum entsprechenden Produkt umgewandelt werden.[19] Eine weitere Möglichkeit um Flüssigkeiten für Reaktionen in Kugelmühlen zu konditionieren, ist die Vermahlung bei tiefen Temperaturen.[7, 20] Nachteilig sind allerdings die immensen Kosten, die bei der Temperierung anfallen, da oftmals Flüssigstickstoff als Kühlmedium zum Einsatz kommt. Kugelmühlen für den Einsatz im Syntheselabor mit anderen Kühlmedien sind zurzeit am Markt noch nicht verfügbar,[20b] befinden sich aber aktuell in der Entwicklung.[21]

Eine weiterer Nachteil des Arbeitens bei tiefen Temperaturen ist die Kinetik chemischer Reaktionen, da die Geschwindigkeitskonstante eine exponentielle Abhängigkeit von T aufweist. So konnte unter anderem beobachtet werden, dass chemische Reaktionen in Kugelmühlen zum Erliegen kommen, wenn die Mahlbecher auf $T < -70\,°C$ abgekühlt werden.[7, 20a]

Der Einsatz eines Mahlhilfsmittels kann den Einsatz von flüssigen Edukten ermöglichen, indem diese an der Oberfläche **sorbiert** werden. Allerdings das Arbeiten mit entsprechenden Substanzen nicht nur mit Vorteilen verknüpft, sondern bringt auch Nachteile mit sich, wie eine erhöhte Stoffintensität des Prozesses in Anlehnung an den *E-Faktor* nach *Sheldon* (*Gl. 1*).[22] Jeder der Synthese zugesetzte Stoff, der sich nicht im Produkt wiederfindet, muss nach der Synthese abgetrennt werden und wird demnach formal als Abfall angesehen. Der Einsatz von Mahlhilfsmitteln ist unter diesem Gesichtspunkt als wenig vorteilhaft zu bewerten.

$$E_{SH} = \frac{m_{Abfall}}{m_{\mathrm{Pr}odukt}} \quad (1).$$

Allerdings sind die Aufgaben des Mahlhilfsmittels (oder Mahlhilfe) weitaus vielfältiger, wie sich aus folgender Definition ableiten lässt:

> ***Mahlhilfsmittel** sind (anorganische) Verbindungen, welche die Prozessierung von organischen (soft matter) oder flüssigen Substanzen in Kugelmühlen oder vergleichbaren Apparaten unterstützen, indem sie die mechanischen und rheologischen Bedingungen beibehalten, die wichtig für den Energietransfer auf das Mahlgut sind.* (nach [16])

Eine wesentliche Aufgabe des Mahlhilfsmittels ist also die Unterstützung des Energietransfers bei Prozessen in Kugelmühlen insbesondere dann, wenn organische Substanzen zur Reaktion gebracht werden sollen. Diese besitzen grundsätzlich andere Materialparameter als anorganische Materialen. Insbesondere weisen sie einer geringere Materialdichte ρ und kleinere Elastizitätsmoduln E_Y auf.[16] Werden diese nicht in irgendeiner Form kompensiert, dann wird die Energiefreisetzung und -übertragung bei entsprechenden Prozessen gestört. Auf Basis von Untersuchungen zur Oxidation von β-Pinen zu Nopinon mit $KMnO_4$ als Oxidationsmittel wurde der Anteil des Mahlhilfsmittels im Vergleich zu den anderen Reaktanden variiert.[3] Der funktionale Zusammenhang zwischen der Ausbeute uns Selektivität des Reaktionsproduktes und den Massenbrüchen des Oxidationsmittels $w(KMnO_4)$ und der Mahlhilfsmittel w(Mahlhilfsmittel) ist in *Abbildung 4* dargestellt.[16] Mit einem Anstieg von $w(KMnO_4)$ ist eine Zunahme des Anteils flüssiger Reaktanden (β-Pinen, Nopinon) verbunden, da die Stoffmengenverhältnisse konstant gehalten wurden. Sinkt der

Anteil des Mahlhilfsmittels dann sinken auch Ausbeute und Selektivität (Der Zusammenhang zwischen relativer Ausbeute und den Variablen ist in [3] zu finden). Dies liegt unter anderem an den geänderten rheologischen und mechanischen Bedingungen im Mahlbecher, da sich die E_Y für $KMnO_4$ und die Mahlhilfsmittel signifikant unterscheiden und der Anteil an Flüssigkeit immer mehr zunimmt. Dadurch verändert sich die Haptik des Reaktionsgemisches von einem Pulver zu einer zähflüssigen Paste. Diese kann die Energie nicht mehr effektiv aufnehmen. Das heißt, für den stabilen Betrieb von Reaktionen mit flüssigen Substraten in einer Kugelmühle ist der Einsatz eines Mahlhilfsmittels hilfreich, wobei die optimale Zusammensetzung und die Art der Mahlhilfe von der jeweiligen Problemstellung abhängig ist.

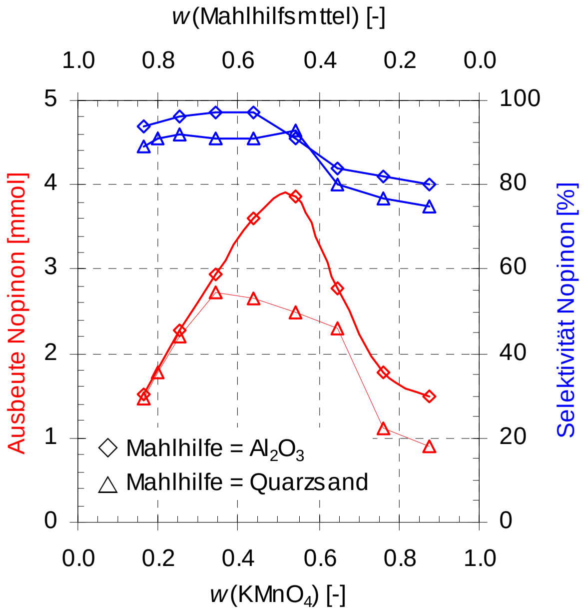


Abbildung 4. Auswirkung der Variation der Massenbrüche von $KMnO_4$ $w(KMnO_4)$ und des Mahlhilfsmittels w(Mahlhilfsmittel) auf Ausbeute und Selektivität an Nopinon bei der Oxidation von β-Pinen in einer Kugelmühle (nach [16]).

Neben der steuernden Funktion können Mahlhilfsmittel auch mit den Substanzen chemisch interagieren, d.h., zusätzlich zu einer rein sorptiven Aufgabe kann auch eine **chemische Aktivierung** von Substraten durch das Mahlhilfsmittel kommen. Durch die ständige Matrikelzerkleinerung infolge der Kugelstöße im Mahlraum werden Oberflächen mit einer hohen Defektkonzentration generiert, welche Zentren chemischer Reaktivität darstellen. So konnte exemplarisch gezeigt werden, dass bei der Synthese von Nopinon aus β-Pinen auch aus chemischen Gesichtspunkten ein Mahlhilfsmittel notwendig ist.[3] Säure- oder basenkatalysierte Reaktionen stellen eine weitere Klasse von Reaktionen dar, die von der Anwesenheit eines festen Mahlhilfsmittels profitieren, indem es die Funktion einer Lewis/Brønsted

Säure/Base übernimmt.[7, 11, 23] Das chemische Gleichgewicht von Kondensationsreaktionen kann durch Wasserentzug verschoben und somit die Ausbeute erhöht werden.

Mahlhilfsmittel können zum **Wärmemanagement** von Reaktionen in Kugelmühlen beitragen, indem sie die eingetragene Reibungswärme oder die freigesetzte Reaktionswärme verteilen. Die Materialien dienen somit als Wärmesenke und verhindern das Auftreten lokaler, makroskopischer Hot-Spots. Damit kann die Prozesssicherheit erhöht und eventuelle Nebenreaktionen unterdrückt werden. Insbesondere bei exothermen Reaktionen (Oxidationen)[2-4, 24] oder beim Arbeiten mit thermolabilen Substanzen (Alkine oder Azide)[7-8] hat sich der Einsatz von anorganischen Materialien bewährt. Damit kann auch die **Prozesssicherheit** entsprechender Verfahren erhöht werden.

Neben der erhöhten Materialintensität ist das **Aufarbeiten von Reaktionsmischungen** bei Anwesenheit eines Mahlhilfsmittels ein Problem, da für eine Stofftrennung meist Fest-Flüssig-Extraktionsverfahen zum Einsatz kommen. Es kommt also zum Einsatz von Lösungsmitteln. Dadurch, dass die Zielprodukte an der Oberfläche sorbiert vorliegen, kann die Menge an Lösungsmittel für die Aufarbeitung erheblich sein, was zu einer weiteren Steigerung der Materialintensität des Gesamtprozesses beitragen kann. Im Vergleich zu Syntheseverfahren in Lösungsmitteln ist dies nur auf den ersten Blick ein Nachteil, da auch hier oftmals eine extraktive Aufarbeitung (Flüssig-Flüssig-Extraktion) notwendig ist, um die Produkte zu isolieren.

3. Apparative Einflussgrößen (Phasen II, IV)

Wie eingangs erwähnt, versteht man unter apparativen Einflussgrößen (oder Technologische Parameter) solche Variablen, die sich während des Prozesses nicht beeinflussen lassen, d.h., die vor der Reaktion festgelegt werden und nicht zu den chemischen Parametern zählen. Wichtige apparative Stellgrößen bei der Durchführung von Syntheseaufgaben in Kugelmühlen sind die Art der Kugelmühle, das Material der Mahlwerkzeuge, die Anzahl n_{MK} und Größe der Mahlkugeln d_{MK} sowie der Füllgrad der Mahlbecher ϕ. Unter Mahlwerkzeugen versteht man in diesem Zusammenhang die Kombination aus Mahlbecher (Index MB) und Mahlkörpern (Index MK), d.h. den Apparateteilen die für die Zerkleinerung, Vermischung und den Energieeintrag verantwortlich sind. Als Mahlkörper werden für Syntheseaufgaben im Labor in der Regel Mahlkugeln eingesetzt.

3.1 Typ der Kugelmühle

Für Syntheseaufgaben im Labor – unabhängig ob auf dem Gebiet der Organischen oder Anorganischen Chemie – werden in der Regel zwei Typen von Kugelmühlen eingesetzt: Planetenkugelmühlen (PKM) und Schwingkugelmühlen (SKM; *Abbildung 5*). Beide Apparate unterscheiden sich wesentlich in den Antriebskonzepten und damit der Beanspruchungsenergieverteilung. Im Falle der PKM werden durch die gegenläufigen Rotationsbewegungen der Mahlbecher um die eigene Achse und um eine zentrale Drehachse den Mahlkugeln komplexe Bewegungsmuster aufgezwungen, die im Falle eines Kontaktes untereinander oder mit der Mahlraumwand zu einer Energiefreisetzung über Reibung und Stoß führen.[25]

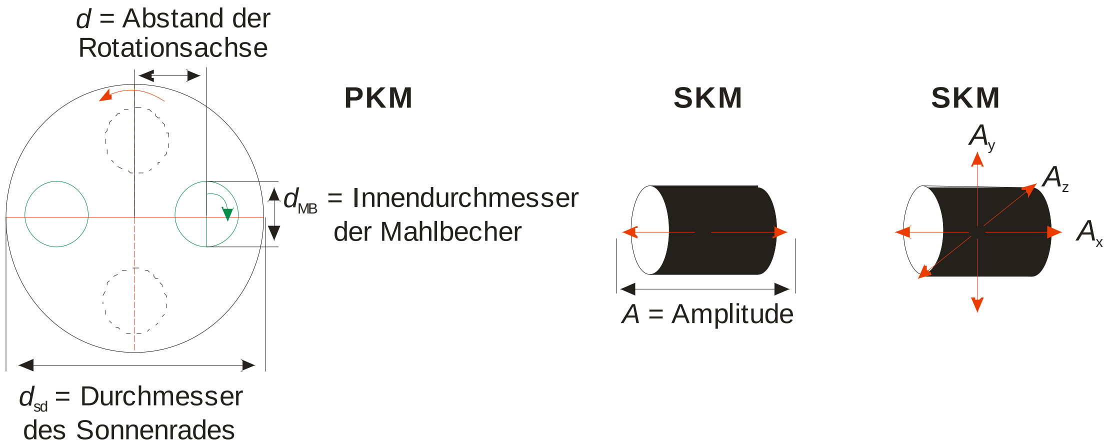


Abbildung 5. Prinzipskizze einer Planetenkugelmühle (PKM) und von Schwingkugelmühlen (SKM), wie sie für Synthesezwecke eingesetzt wurden.

Im Gegensatz zu PKM werden die Mahlbecher bei SKM nicht in Rotation, sondern in Oszillation um einen Ruhepunkt versetzt. Man unterscheidet dabei SKM, bei denen diese Schwingung nur in einer Raumrichtung stattfindet (in der Regel horizontal; engl. mixer ball mills) oder in alle drei Raumrichtungen (engl. vibration ball mill; *Abbildung 5*). Die Beanspruchungsarten sind dabei identisch zur PKM, allerdings mit einer veränderten Beanspruchungsenergieverteilung. Bei beiden Kugelmühlen treten neben den wirkenden Kräften, die sich aus den axialen und tangentialen Geschwindigkeitsvektoren der Kugeln ableiten, zusätzlich Zentrifugalkräfte in nicht unerheblichem Maße auf. Diese sorgen dafür, dass ständig Energie in das System eingetragen wird, so dass in der Regel ein adiabatisches Reaktionssystem vorliegt. Das heißt, es wird mehr Energie freigesetzt als für die eigentliche Reaktion als Aktivierungsenergie notwendig ist.

Die Kugelmühlen unterscheiden sich lediglich in ihren Betriebsparametern, was durch einen Vergleich der Ausbeute einer Suzuki-Miyaura-Reaktion bei unterschiedlichen Frequenzen in einer PKM und SKM gezeigt werden konnte.[11b] Es ist zu erkennen, dass mit beiden Apparaten Ausbeuten > 95% erzielt werden können, sich die Frequenzen ν, ab denen sich dieser Wert einstellt, aber unterscheiden. Innerhalb dieses Projektes aber auch durch andere Autoren konnte gezeigt werden, dass viele Reaktionen in beiden Mühlentypen durchführbar sind.[4, 7, 11b, 26] Die Wahl der Mühle richtet sich eher nach den vorherrschenden Gegebenheiten und sollte keinen Einfluss auf die Reaktion haben.

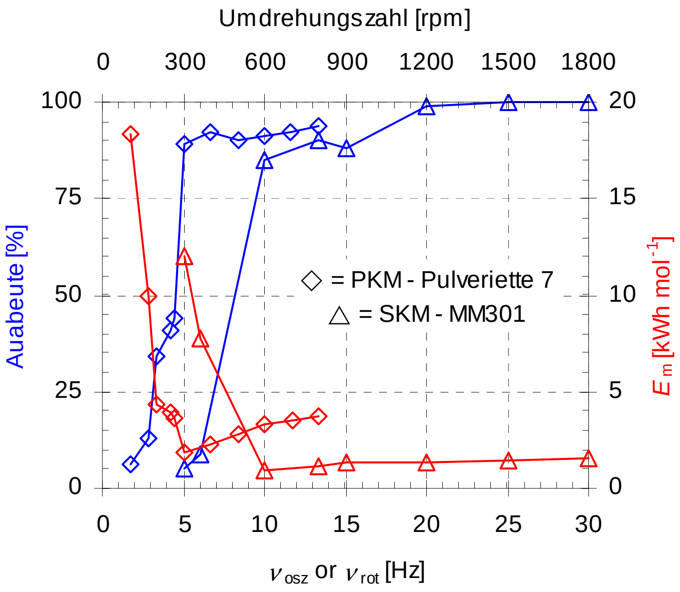


Abbildung 6. Vergleich zweier Kugelmühlen in Hinblick auf Ausbeute und Energieintensität E_m in Abhängigkeit der Arbeitsfrequenz ν für eine Suzuki-Miyaura-Reaktion (nach [11b]).

Ein weiterer Unterschied betrifft die apparativen Voraussetzungen für ein Scale-Up von Reaktionen in den jeweiligen Kugelmühlen. Kommen SKM zum Einsatz, dann ist das Volumen der Mahlbecher V_{MB} in der Regel auf 80 ml begrenzt, wohingegen im Falle von PKM Mahlbecher mit einem Volumen von bis zu 500 ml eingesetzt werden können. Weiterhin besitzen viele PKM die Option, bis zu vier Mahlbecher parallel auf dem Sonnenrad zu installieren, während bei SKM nur zwei Mahlbecherhalterungen installiert sind. Vergleicht man auf Basis dieser Daten beide Systeme, dann stellt man fest, dass man volumenbezogen in einer PKM 12.5-mal mehr Volumen durchsetzen kann als in einer SKM.

3.2 Material der Mahlwerkzeuge

Die kinetische Energie E_{kin} eines bewegten Körpers ist definiert als das Produkt aus Masse m und dem Quadrat der Geschwindigkeitsvektoren u für die jeweilige (Vorzugs)Bewegungsrichtung:[1e]

$$E_{kin} = 0.5 \cdot m \cdot u^2 \quad (2).$$

Diese Gleichung kann auch auf schwingende oder rotierende Systeme übertragen werden, wobei es dann sinnvoll ist die Masse durch das Trägheitsmoment I und die Geschwindigkeit durch die Kreisfrequenz ω, die Frequenz ν oder die Bahngeschwindigkeit u_{p} zu ersetzen. Letztere steht in direkter Relation zu ν und kann über den Abstand zum Rotations- oder Schwingungszentrum r berechnet werden:

$$u_p = \pi \cdot r \cdot \nu \quad (3).$$

Für Mahlprozesse in Rührwerkskugelmühlen konnte gezeigt werden, dass *Gl. 2* und *3* miteinander kombiniert ein Maß für die mittlere Beanspruchungsenergie eines Teilchens E_{stress} zwischen zwei Mahlkugeln oder zwischen einer Mahlkugel und der Mahlraumwand darstellt:[27]

$$E_{stress} = d_{MK}^3 \cdot u_p^2 \cdot \rho_{MK} \cdot \left(1 + \frac{E_{Y,feed}}{E_{Y,MK}}\right)^{-1} \quad (4).$$

Ein Korrekturfaktor, welcher die Elastizitätsmoduln des Mahlgutes $E_{\mathrm{Y,feed}}$ und der Mahlkugeln $E_{\mathrm{Y,MK}}$ berücksichtigt, führt zu einer besseren Modellierung der Energieverteilung, da hiermit auch elastische Stöße zwischen den einzelnen Partikeln oder Kugeln mit einbezogen werden.[27b, 28] *Gl. 4* verdeutlicht den Einfluss der Materialdichte der Mahlkugeln ρ_{MK}, steht diese doch in direkter Proportionalität zur übertragbaren Energie. Da diese wiederum ein Maß für die Temperatur und damit für die Reaktionsgeschwindigkeit ist, kann ein direkter Zusammenhang zwischen Ausbeute und ρ erwartet werden. In der Tat konnte für die Sonogashira-Reaktion[6] und die oxidative Homokopplung von Anilinen[4] ein entsprechender Zusammenhang offengelegt werden. Ein Wechsel von Achat (ρ = 2,65 g cm^{-3}) zu ZrO_2 (ρ = 5.7 g cm^{-3}) führte zu einem Anstieg der Ausbeuten. Auch wenn diese Aussage generell richtig ist und die physikalischen Zusammenhänge bestätigt, konnte bereits in anderen Untersuchungen für die Suzuki-Miyaura-Reaktion[11c] sowie innerhalb dieses Projektes für die Synthese von Nopinon aus β-Pinen[3] ein anderer Zusammenhang beobachtet werden. Die

Ausbeuten waren unabhängig von der Dichte des Mahlmaterials ($2.65 \leq \rho \leq 7.9$; Achat, ZrO_2, gehärteter Stahl) auf einem hohen Niveau (> 90%). Offensichtlich existieren auch Reaktionsbeispiele bei denen die mittlere kinetische Energie unerheblich ist und andere Prozesse im Vordergrund stehen.

Neben energetischen Gesichtspunkten sollten bei der Wahl des Mahlmaterials aber auch Material- und chemische Eigenschaften berücksichtigt werden.[1e] So sind zum Beispiel poröse Materialien wie Achat oder Stahl für katalytische Reaktionen aufgrund von eventuellen Memoryeffekten ungeeignet. Die Reinigung der Mahlwerkzeuge ist beim Einsatz von Stahl begrenzt auf solche Medien, die das Material nicht angreifen (keine starken Mineralsäuren), wohingegen keramische (ZrO_2) und oxidische Materialen (Achat, Sinterkorund) relativ robust sind. Auch wenn der Preis für keramische Mahlwerkzeuge hoch ist, für Anwendungen in der Synthesechemie scheinen diese am besten geeignet zu sein, da sie neben der hohen chemischen Beständigkeit und der geringen Porosität auch ein gutes Abriebverhalten aufweisen.[4]

3.3 Anzahl und Größe der Mahlkugeln

In *Gl. 2* und *4* wird angedeutet, dass sowohl die Masse als auch der Durchmesser der Mahlkugeln eine entscheidende Rolle bei der Energiefreisetzung und -übertragung spielen. Es ist davon auszugehen, dass nicht nur die Materialdichte ρ sondern auch die die Anzahl n_{MK} und die Größe (d.h. der Durchmesser) der Mahlkugeln d_{MK} einen signifikanten Einfluss beim reaktiven Mahlen besitzen. Da n_{MK} in direkter Proportionalität zur Masse der bewegten Körper und damit zu E_{kin} steht, wurde dieser Sachverhalt für verschiedene Reaktionen in einer Planetenkugelmühle untersucht. *Abbildung 7* stellt den Zusammenhang zwischen n_{MK} und der jeweils erzielten Ausbeute dar. Bei den Versuchen wurde der Durchmesser der Mahlkugeln nicht variiert ($d_{MK} = 15$ mm) und $n_{MK,max} = 7$ entspricht den Hinweisen des Herstellers für den Einsatz dieses Mahlkugeln in Mahlbechern mit $V_{MB} = 45$ ml. Es ist deutlich zu erkennen, dass unabhängig vom Reaktionstyp und eventueller Variation des Mahlhilfsmittels ein linearer Zusammenhang zwischen Ausbeute und n_{MK} besteht. Im Falle des Einsatzes von saurem α-Al_2O_3 als Mahlhilfsmittel bei Oxidation 1 (γ-Terpinen zur *p*-Cymen)[2] und Oxidation 2 (β-Pinen zu Nopinon)[3] wird bei $n_{MK} \geq 4$ ein Plateau erreicht und keine weitere Zunahme der Ausbeute verzeichnet. Der Grund für dieses Verhalten liegt in der hohen Reaktivität dieser Reaktionssysteme, die dazu führt, dass ein hoher Umsatz schon bei vergleichsweise geringen Beanspruchungsenergien auftritt. Im Falle der oxidativen Homokopplung von *p*-Toluidin mit $KMnO_4$[4] sowie bei Einsatz von Quarzsand als Mahlhilfsmittel für die Oxidationsreaktionen[2-3] ist die Linearität über den gesamten Bereich nachweisbar.

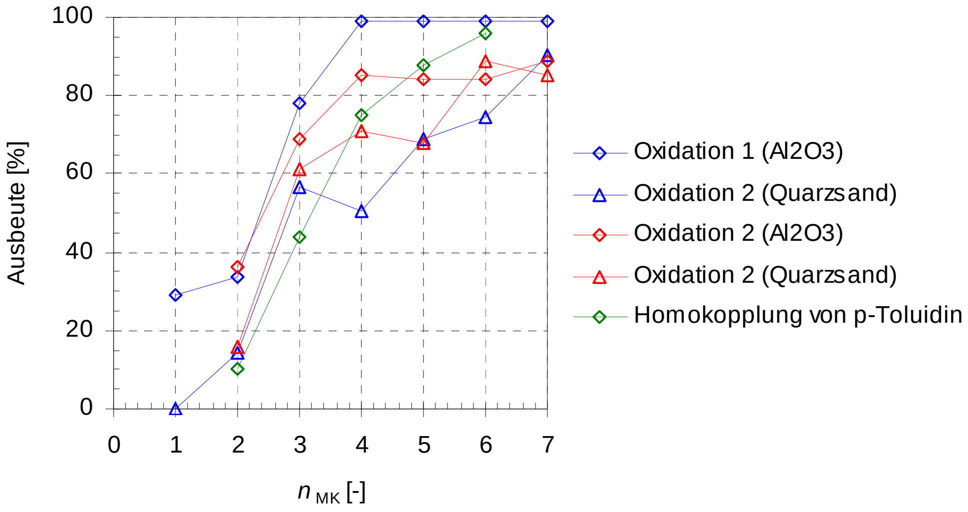


Abbildung 7. Zusammenhang zwischen der Ausbeute und der Anzahl der Mahlkugeln n_{MK} für verschiedene Reaktionen in Kugelmühlen (weitere Erläuterungen siehe Text; nach [16]).

In direktem Zusammenhang mit n_{MK} steht der Durchmesser der einzelnen Mahlkugel d_{MK}, da dieser über das Kugelvolumen und ρ_{MK} in Proportionalität zur Masse der bewegten Körper und damit zu E_{kin} steht (*Gl. 2* und *4*). Wird zum Beispiel d_{MK} reduziert und n_{MK} konstant gehalten (d.h. Σm_{MK} ist nicht konstant), dann folgt daraus eine Abnahme der Ausbeute.[11c] Die auf das Mahlgut übertragbare Energie E_{stress} bei Mahlprozessen ist proportional zur Beanspruchungsenergie einer einzelnen Kollision $E_{Beanspruchung}$ und der Häufigkeit der Beanspruchungen $\nu_{Beanspruchung}$ (≙ Kollisionswahrscheinlichkeit):[29]

$$E_{stress} \propto E_{Beanspruchung} \cdot \nu_{Beanspruchung} \qquad (5).$$

Die Beanspruchungsenergie wiederum proportional zur Masse der Mahlkugeln, also zu deren Dichte und Volumen und daraus folgend zu n_{MK}. Bei der Auswahl von n_{MK} sollte weiterhin berücksichtigt werden, dass $\nu_{Beanspruchung}$ proportional zur Anzahl der Kugeln ist:

$$\nu_{Beanspruchung} \propto \frac{\text{Anzahl der Beanspruchungen}}{\Delta t} \qquad (6).$$

Das heißt, auch dieser Parameter steigt mit zunehmenden n_{MK}. Wird der Durchmesser der Mahlkugeln variiert, dann wird bei geringen d_{MK} die übertragenen Energie eines einzelnen Kollisionsereignis $E_{Beanspruchung}$ geringer, allerdings nimmt die Anzahl der Kollisionen zu, sofern die Gesamtmasse der Mahlkörper konstant gehalten wird, also wenn gilt Σm_{MK} = konstant. Diese Tatsache lässt sich experimentell bestätigen und ist in *Tabelle 2* für die Dehydrierung von γ-Terpinen zu *p*-Cymen verdeutlicht.[3] Unter den gewählten Bedingungen sind die Auswirkungen durch den Wechsel zu kleineren Mahlkugeln auf die Ausbeute $Y_{p\text{-Cymen}}$ unerheblich, und zwar unabhängig vom eingesetzten Mahlhilfsmittel. Dieses beeinflusst lediglich das Niveau der gemessenen Ausbeuten (siehe *Abbildung 7*). Die erhöhte Kollisionshäufigkeit wird durch die geringere pro Ereignis übertragenen Energie kompensiert (*Gl. 5*).

Tabelle 2. Variation des Mahlkugeldurchmessers d_{MK} and der Anzahl der Mahlkugeln n_{MK} bei der Oxidation von γ-Terpinen mit $KMnO_4$ in einer Planetenkugelmühle.[3] 1)

d_{MK} [mm]	n_{MK} [-]	$\Sigma m_{\mathbf{MK}}$ [g]	$A_{\mathrm{s,MK}}$ [cm^2]	$Y_{p\text{-Cymen}}$ [%] 2)	$Y_{p\text{-Cymen}}$ [%] 3)
5	120	45.8	34.3	99	72
10	15	45.4	47.1	99	79
15	5	46.3	93.4	99	75

1) Reaktionsbedingungen: 2 mmol *p*-Cymen, 6 mmol $KMnO_4$, 0.1 g H_2O, 3.8 g Mahlhilfsmittel; Mahlbecher (MSZ, 45 ml), Mahlkugeln (MSZ); PKM, t = 5 min, ν_{rot} = 13.3 Hz.

2) Mahlhilfsmittel = saures α-Al_2O_3.

3) Mahlhilfsmittel = Quarzsand.

Das Ergebnis ist insofern erstaunlich, als dass bei Zerkleinerungsprozessen beobachtet wurde, dass kleinere Mahlkugeln bessere Ergebnisse hinsichtlich der erreichbaren Partikelgröße liefern.[18a, 18b, 30] Für chemische Umwandlungen scheint dies nicht zu gelten, da hier die Partikelgröße nicht das ausschließliche Kriterium chemischer Aktivität darstellt. Darüber hinaus ist die Unabhängigkeit der Ausbeute von der aktiven Oberfläche, wie in *Tabelle 2* gezeigt,[3] ein Indiz dafür, dass die untersuchte Reaktion thermisch angeregt ist und keine rein mechanochemische Anregung vorliegt, wie sie von der IUPAC für mechanochemische Reaktionen (engl. Mechano-chemical reaction) definiert ist.[31]

3.4 Füllgrad der Mahlbecher

Neben den Parametern, welche die Art und Größe der Mahlkugeln beschrieben, ist der Füllgrad der Mahlbecher ein entscheidender Faktor für den sicheren und reproduzierbaren Betrieb von Kugelmühlen. Dabei ist der Füllgrad ϕ wie folgt definiert:

$$\phi = \frac{V_{\mathrm{MK}} + V_{\mathrm{Reaktanden}}}{V_{\mathrm{MB}}} \cong \frac{\frac{\pi}{6}\cdot n_{MK}\cdot d_{MK}^{3} + \sum_{i} \frac{m_{\mathrm{Reaktant},i}}{\rho_{\mathrm{Reaktant},i}}\cdot\left(1-\varepsilon_{\mathrm{Reaktant},i}\right)^{-1}}{V_{\mathrm{MB}}} \quad (7).$$

Mit Hilfe von Basisdaten der Mahlkugeln (n_{MK}, d_{MK}), des Mahlbechers (V_{MB}) und Stoffparametern des Mahlgutes (Porosität ε, ρ, m) lässt sich der Gesamtfüllgrad des Mahlbechers abschätzen. Die Porositäten der an der Reaktion beteiligten Feststoffe wurden nach DIN ISO 697 (EN ISO 60) bestimmt. *Abbildung 8* zeigt den Zusammenhang zwischen der Stoffmenge an β-Pinen und der Ausbeute an Nopinon für die trockenen Oxidation mit $KMnO_4$ in zwei unterschiedlichen PKM. Im Falle der Kugelmühle *P7 classic line* wurde die Reaktion in 45 ml Mahlbechern (2 mmol β-Pinen) und im Falle der PKM *P5 classic line* in Mahlbechern desselben Materials (MSZ) mit einem Volumen von 250 ml durchgeführt (20-50 mmol β-Pinen). Berechnet man ϕ für beide Systeme, dann ist zu erkennen, dass in der kleineren Mühle trotz des niedrigen Füllgrades akzeptable Ausbeuten erzielt wurden, während in der größeren diese durch Anpassung von ϕ sogar noch steigerungsfähig waren bzw. sich auf einem ähnlichen Niveau bewegen.

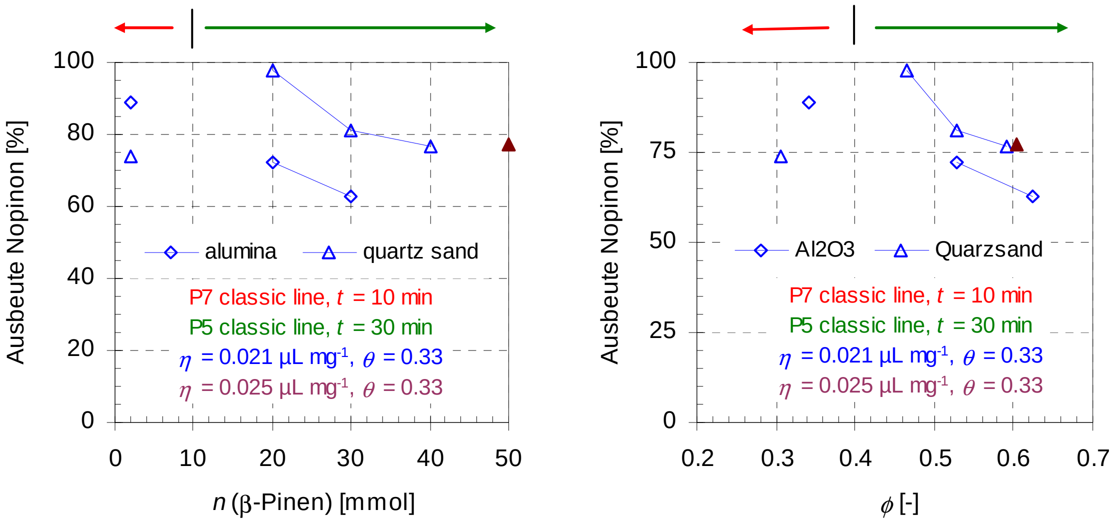


Abbildung 8. Zusammenhang zwischen der Ausbeute an Nopinon und der Stoffmenge an β-Pinen (links) sowie dem Füllgrad der Mahlbecher ϕ (nach *Gl. 7*; rechts) für die Oxidation mit $KMnO_4$ in zwei Planetenkugelmühlen unterschiedlicher Größe (nach [16]).

Festzuhalten bleibt, dass auch der Füllgrad den Ausgang einer chemischen Reaktion maßgeblich mitbestimmt. Bei der Wahl der Mahlbecher sollte berücksichtigt werden, dass ein zu niedriger Füllgrad und ein zu geringes Mahlgut-zu-Kugel Verhältnis zu einem relativ großen Materialverschleiß der Mahlkugeln führt, da bei entsprechenden Stößen ein direkter Kontakt zwischen den Mahlkugeln nicht mehr ausgeschlossen werden kann. Ein zu hoher Füllgrad wiederum behindert die Bewegungen der Mahlkugeln und damit die Energiefreisetzung und -weiterleitung.

4. Prozessparameter (Phasen II, IV)

Wie eingangs erläutert, versteht man im vorliegenden Zusammenhang unter Prozessparametern solche Variablen, die während des Prozesses eingestellt bzw. gesteuert werden können. Beim Einsatz klassischer Reaktoren und Systemen zum Energieeintrag sind dies in der Regel Druck p, Temperatur T und die Reaktions- bzw. Prozesszeit t. Kugelmühlen, wie sie bisher für Syntheseaufgaben im Labor zum Einsatz kommen, sind dadurch gekennzeichnet, dass nur eine der „klassischen“ Prozessvariablen direkt steuer- und regelbar ist: die Reaktionszeit oder auch Mahldauer t. Als weitere direkt einstellbare Regelgröße kommt der jeweiligen Rotations- ν_{rot} (bei PKM) oder Oszillationsfrequenz ν_{osz} (bei SKM) eine besondere Bedeutung zu. Beide Größen wurden in statistischen Bewertungen von Versuchen als wesentliche Einflussparameter identifiziert.[1e, 11c]

4.1 Mahldauer

Beim Einfluss der Mahldauer auf chemische Reaktionen verhält es sich ähnlich wie mit Reaktionen in klassischen Reaktionssystemen in Lösungsmitteln. Über die Geschwindigkeitskonstante, welche für jede Reaktion spezifisch ist, und deren Temperaturabhängigkeit definiert sich die Reaktionsgeschwindigkeit. Übertragen auf das System Kugelmühle wurde festgestellt, dass hier kein allgemeiner Zusammenhang abgeleitet werden kann, sondern reaktionsspezifisch die optimale Mahldauer zu bestimmen ist.[1e, 2-3, 11b, 11c] Allgemein lässt sich sagen, dass eine Erhöhung von t mit einer Umsatz- und damit in der Regel auch Ausbeutesteigerung verbunden ist. Dieser Fakt wurde für unterschiedliche Reaktionen innerhalb dieser Arbeit bestätigt[2-3, 5-6] wurde aber auch schon durch andere Autoren demonstriert.[11c, 19a, 26b, 32] In einigen Fällen konnte beobachtet werden, dass bei längeren Reaktionszeiten in Kugelmühlen kein Reaktionsfortschritt mehr zu verzeichnen ist, obwohl noch kein Vollumsatz erreicht wurde.[11c, 32d] Dies lässt sich aber vielmehr mit reaktionsspezifischen Phänomenen erklären (z.B. Gleichgewichtslimitierung oder Katalysatordesaktivierung) und ist kein allgemeines Merkmal von Reaktionen in Kugelmühlen.

4.2 Frequenz

Der Energieeintrag bei Kugelmühlen wird über die Bewegungsenergie der Mahlkugeln geregelt, welche entweder durch Rotation (PKM) oder Oszillation (SKM) in Bewegung versetzt werden. Der funktionale Zusammenhang zwischen der kinetischen Energie des Systems bzw. der auf das Mahlgut übertragenen Energie wird durch *Gl. 3-5* zum Ausdruck gebracht. Das heißt, die Frequenz ν, mit welcher die entsprechende Kugelmühle betrieben wird, ist neben der Materialdichte ρ der wesentliche Parameter zur Regelung der Energiedichte, wobei letzterer während des Prozesses nicht mehr variiert werden kann. Durch den

Zusammenhang zwischen E_{kin} und der Inneren Energie eines Systems kann die im Mittel herrschende Temperatur T im Mahlbecher geregelt werden. Dichte Materialien und hohe Frequenzen führen in der Regel zu hohen Oberflächentemperaturen von > 100 °C (Mahlwerkzeuge aus Stahl).[11b] Mit keramischen oder oxidischen Materialien erreicht man bei identischer Frequenz deutlich geringere Oberflächentemperaturen von $60 \leq T \leq 80$ °C.[7, 11b] Die beobachteten T sind an der Oberfläche der Mahlbecher bzw. des Mahlgutes nach erfolgter Reaktion gemessen und entsprechen nicht den real in den Kollisionszonen auftretenden Temperaturen. Hier werden deutlich höhere T und Drücke postuliert, allerdings nur für sehr kurze Zeiträume ($< 10^{-9}$ s).[33]

Der Zusammenhang zwischen ν und der Ausbeute einer chemischen Reaktion ist vergleichbar zum Einfluss von t mit dem wesentlichen Unterschied, dass ein quadratische Zusammenhang besteht, wie ihn *Gl. 4* für die Korrelation zwischen v_p und E_{stress} andeutet.[27] Die Bahngeschwindigkeit u_p ist dabei direkt proportional zur Frequenz ν (*Gl. 3*). Dies bedeutet, dass die beobachtete Ausbeute ein Maximum durchläuft,[11b] wobei der Abfall nach Passieren des Maximums zu hohen Frequenzen weniger stark ins Gewicht fällt und auch als Plateau interpretiert werden kann. Entsprechende Beobachtungen wurden für viele der hier beschriebenen Reaktionen gemacht[2-3, 5, 7] und auch von anderen Autoren bestätigt.[11b, 11c, 26b, 32, 34] Der Abfall bei zu hohen ν kann damit erklärt werden, dass durch die hohen Energiedichten Nebenreaktionen promoviert sowie Abbaureaktionen initiiert werden und somit zu einer Verringerung des Umsatzes führen.

4.3 Energieeffizienz

Für die Beurteilung neuer Verfahren oder von Verfahrensalternativen spielt die Bewertung aus energetischer Sicht eine entscheidende Rolle, da sich darauf basierend das ökonomische Potential ableiten lässt. Für die Bewertung im vorliegenden Fall muss berücksichtigt werden, dass bei mechanochemischen Verfahren nicht die gesamte eingetragene elektrische Leistung E_{netz} (≙ Bruttoenergie) an das Mahlgut übertragen wird E_{netto}:

$$E_{netto} = E_{netz} - P_{blind} \cdot t \quad (8),$$

sondern in Abhängigkeit von Prozess- und apparativen Parametern ein Wirkungsgrad verschieden von eins besteht. Durch Reibungsprozesse in der Antriebseinheit sowie für den Betrieb gerätespezifischer Steuer- und Regeltechnik geht ein gewisser Prozentsatz der eingetragenen Energie als Blindleistung P_{blind} verloren. Diese Leistung kann durch Messungen des Energie- oder Leistungsbedarfs der jeweiligen Mühle beim Betrieb ohne Mahlkugeln und Mahlgut frequenzabhängig bestimmt werden. Die durch Subtraktion von E_{netz} erhaltene Nettoenergie steht in direkter Proportionalität zum auf das Mahlgut übertragbaren Energieanteil:[16, 35]

$$E_{netto} \propto E_{stress} \quad (9).$$

In erster Näherung stellt sie also ein gutes Maß für die Energie dar, welche für alle im Mahlraum ablaufenden Prozesse (Zerkleinerung, Aktivierungsenergie, Temperaturerhöhung) zur Verfügung steht. Der daraus abgeleitete elektrische Wirkungsgrad η_{el} wurde für die Bewertung und den Vergleich von Kugelmühlen eingeführt:

$$\eta_{el} = \frac{\text{Nettoenergie}}{\text{Bruttoenergie}} = \frac{E_{netto}}{E_{brutto}} = 1 - \frac{P_{blind} \cdot t}{E_{netz}} \quad (10).$$

Ein Vergleich der in den Mahlraum übertragenen Netto- E_{netto} mit der gesamten benötigten elektrischen Energie E_{brutto} sowie von η_{el} für verschiedene Kugelmühlen ist in *Abbildung 9* dargestellt. Drei verschiedenen Kugelmühlen wurden in die Betrachtungen einbezogen: zwei PKM (*P7cl* und *P5*) sowie eine SKM (*MM301*). Die Betrachtungen leiten sich aus Daten für die Suzuki-Miyaura-Reaktion von *p*-Bromacetophenon mit Phenylboronsäure ab, die im Rahmen früherer Untersuchungen am ITUC erhoben wurden.[11b] Die Ansatzgrößen unterscheiden sich bei den jeweiligen Versuchen und betragen für die PKM *P7cl* und die SKM *MM301* jeweils 5 mmol pro Mahlbecher, während Reaktionen in der PKM *P5* im 10-fachen Maßstab (50 mmol) durchgeführt wurden.[16] Die Werte in Klammern nach der Gerätebezeichnung beziehen sich auf die dimensionslose Frequenz ν/ν_{max}, bei welcher die Versuche durchgeführt wurden. Für die eingesetzten Mühlen beträgt ν_{max} 13,3 (*P7cl*), 6 (*P5*) sowie 30 Hz (*MM301*). Auf Auswirkungen der Betriebsbedingungen in Abhängigkeit vom Mühlentyp wurde schon im Kapitel zu den apparativen Parametern eingegangen. Die Daten zeigen den Unterschied zwischen beiden Mühlentypen. Während für PKM deutlich höhere E_{brutto} notwendig sind, ist dieser Betrag im Falle von SKM aufgrund der niedrigeren bewegten Masse geringer. Hier machen sich die unterschiedlichen Antriebskonzepte bemerkbar. Der elektrische Wirkungsgrad η_{el} nach *Gl. 10* für Reaktionen in kleinen Labormühlen (*P7cl*, *MM301*) ist mit 20-30% deutlich geringer als im Falle der maßstabsvergrößerten Reaktion in der PKM *P5* (η_{el} = 91%). Daraus resultiert, dass für diese Mühle relativ wenig Energie für die installierte MSR-Technik aufgewendet werden muss bzw. bei der Umwandlung von elektrischer in kinetischer Energie verlorengeht. Somit steht mehr Energie für Prozesse, welche im Mahlraum ablaufen sollen, zur Verfügung.

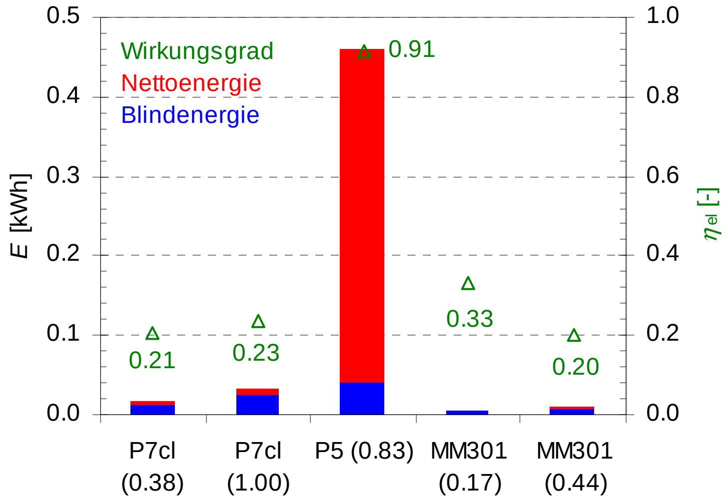


Abbildung 9. Energiebedarf und elektrischer Wirkungsgrad η_{el} (*Gl. 10*) für verschiedene Kugelmühlen (weitere Informationen im Text; nach [16]).

Bezieht man die so gewonnenen Energien auf die produzierte Menge an Produkt gelangt man zur stoffmengenbezogenen Energieintensität E_{m}:[11b]

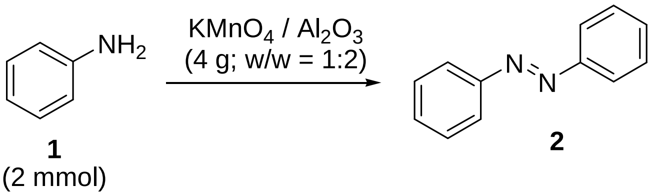
$$E_m = \frac{E_{netz}}{\sum_i n_{\mathrm{Produkt},i}} \qquad (11).$$

Der Index *i* in *Gl. 11* bezieht sich auf die Anzahl, der im jeweiligen Verfahren/der jeweiligen Mühle eingesetzten Reaktoren (in der Regel zwei), wobei sich die gebildeten Mengen an Produkt aus verschiedenen Gründen in den einzelnen Mahlbechern unterscheiden können. Vergleicht man die zum Einsatz gekommenen unterschiedlichen Mühlentypen auf Basis von E_{m}, dann treten die apparativen Unterschiede ebenfalls zu Tage (*Abbildung 6*), da sich entsprechende lokale Energieoptima in Bezug auf ν unterscheiden.[11b] Generell weisen SKM geringere Energieintensitäten als PKM auf, was durch verschiedene Modelluntersuchungen bestätigt werden konnte.[4, 7, 11b, 26b] Das bessere Abschneiden des einen Mühlentyps gegenüber dem anderen hat konstruktionsbedingte Gründe und kann somit keine Rechtfertigung darstellen, aus energetischen Gründen den einen Mühlentyp zu bevorzugen. Vielmehr sind bei der Auswahl auch andere Kriterien, wie Ansatzgröße oder verfügbare Materialien für Mahlwerkzeuge zu berücksichtigen.

4.4 Vergleich mit anderen Methoden (Phase III)

Neben der Energieeffizienz und -intensität einzelner Kugelmühlen sollte innerhalb dieser Projektphase auch ein Vergleich mit anderen Möglichkeiten des Energieeintrages durchgeführt werden.[17b] Um eine diesbezügliche Betrachtung vornehmen zu können, muss gelten, dass „up-“ und „down-stream“-Prozesse für die zu bewertende Reaktion identisch sind, so dass die entsprechenden Prozessketten nicht in die Berechnung mit einfließen.[11b] Die in *Gl. 11* wiedergegebene mathematische Beziehung erfüllt dieses Kriterium in erster Näherung und kann somit für einen energetischen Vergleich herangezogen werden. Dieses Verfahren soll nunmehr auch innerhalb dieses Projektes zur energetischen Bewertung eingesetzt werden. Eine im Gegensatz dazu viel komplexere, gleichwohl aussagekräftigere Lebenswegbilanzierung in Form einer Ökobilanz sollte im Mittelpunkt zukünftiger Untersuchungen auf diesem Gebiet stehen.

Im Folgenden sollen die Ergebnisse für Energieeffizienzbetrachtungen der oxidativen Kopplung von Anilin (**1**) zu Azobenzen (**2**) mit $KMnO_4$ als Oxidationsmittel präsentiert werden (*Schema 2*).[4] Als Standardreaktion wurde die Reaktion im 2 mmol-Maßstab durchgeführt und es wurden für die Oxidation 4 g $KMnO_4$-γ-Al_2O_3 (*w*/*w* = 1:2) verwendet. Verschiedene Möglichkeiten des Energieeintrages wurden miteinander verglichen, wobei sich die Ansätze und Reaktionszeiten geringfügig voneinander unterschieden. Auf dieser Stufe der Untersuchungen wurde die solventfreie Umsetzung in der Kugelmühle mit der Umsetzung im Lösungsmittel (30 ml Acetonitril) verglichen. Im letzten Fall wurden die Reaktion mittels klassischer Wasserbadheizung bzw. mikrowellen- und ultraschall-assistiert durchgeführt. Experimente zur lösungsmittelfreien Umsetzung unter Mikrowellenassistenz führten zu nicht reproduzierbaren Ergebnissen. Die unterschiedlichen Ansätze und Bezeichnungen sind in *Tabelle 3* zusammengefasst.



Schema 2. Oxidative Kopplung von Anilin (**1**) zu Azobenzen (**2**).

Tabelle 3. Apparate und Ansätze1) für die Durchführung der Energieeffizienzuntersuchungen mit der in *Schema 2* wiedergegebenen Modellsynthese.

Bezeichnung	Gerät / Ansatz / Reaktionsbedingungen
Planetenkugelmühle (PKM)	*Fritsch Pulverisette 7 classic* line Standardansatz pro Mahlbecher, lösungsmittelfrei Mahlbecher: 45 ml, Achat, Mahlkugeln: 7×15 mm Achat; Bedingungen: ν_{rot} = 13.3 Hz, *t* = 20 min
Schwingkugelmühle (SKM)	*Retsch MM301* Standardansatz pro Mahlbecher, lösungsmittelfrei Mahlbecher: 50 ml, Achat, Mahlkugeln: 7×15 mm Achat; Bedingungen: ν_{osz} = 13.3 Hz, *t* = 20 min
Mikrowelle, multimode (muMW)	*MLS Praktika* Standardansatz 100-ml Zweihalskolben, Faseroptiksensor; Bedingungen: *t* = 30 min, P_{max} = 300 W, *T* = 80 ℃
Mikrowelle, monomode (moMW)	*CEM Dicover* Standardansatz

	100-ml Zweihalskolben, Faseroptiksensor; Bedingungen: $t = 30$ min, $P_{\max} = 130$ W, $T = 80$ °C
Klassisches Heizen (KH1 / KH6)	*Redleys Discovery* (6-fach Reaktor) Standardansatz pro Reaktionskolben 100-ml Einhalskolben, elektronische T-Regelung; Bedingungen: $t = 60$ oder 360 min, $T = 80$ °C
Ultraschall (US20 / US100)	*Hielscher UP200ns* 1/3 Standardansatz 25-ml Dreihals-Ultraschallreaktor, elektronische T-Regelung; Bedingungen: $t = 20$ min, $P = 20$ oder 100% $P_{\max}$, $T = 80$ °C

[1]) Die Bezeichnung Standardansatz bezieht sich auf folgende Ansatzgröße: 2 mmol Anilin (**1**), 4 g $KMnO_4$-γ-Al_2O_3 (*w*/*w* = 1:2), 30 ml Acetonitril.

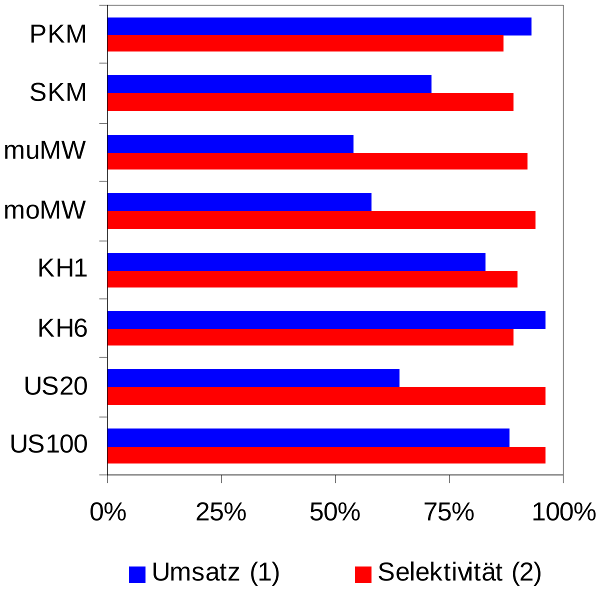


Abbildung 10. Umsatz an Anilin und Selektivität für Azobenzen für die Umsetzungen nach *Tabelle 3*.

Die Durchführung der Experimente anhand von *Tabelle 3* führte zu der interessanten Erkenntnis, dass sich die Apparate nicht nur in ihrer Energieintensität E_m (*Gl. 11*) unterscheiden, sondern auch in den dazugehörigen Umsatz- und Selektivitätsdaten, die in *Abbildung 10* zusammengefasst sind.[4] Es ist deutlich zu erkennen, dass die Selektivität für die Bildung von **2** aus **1** unabhängig von der zum Einsatz gekommenen Verfahrensweise stets größer 95% ist. Die Unterschiede in den Ausbeuten sind allerdings signifikant. Es zeigt sich, dass beim Einsatz einer PKM unter lösungsmittelfreien Bedingungen ein ähnliches Umsatzniveau erreicht werden kann, wie es nach 6 h klassischem Heizen (KH6) im Wasserbad oder einer Ultraschallbehandlung bei voller Ultraschallleistung nach 20 min (US100) zu erreichen ist. Der Einsatz von Mikrowellen hat eine Umsetzung von **1** zu 55% zur Folge, ähnlich wie die Ultraschallbehandlung mit 20% Ultraschallleistung (US20). Kommt eine SKM zum Einsatz, liegt der Umsatzgrad 20% unter dem für den Einsatz einer PKM. Dies hängt mit den unterschiedlichen Antriebsbewegungen der Mahlkugeln zusammen (vgl. Abschnitt apparative Parameter). Im Falle der PKM rotieren die Kugeln, was einer höhere

Energiedichte auch schon bei niedrigen ν_{rot} zur Folge hat, während bei der SKM die Kugeln durch eine horizontale Oszillation in Bewegung gehalten werden. Insbesondere bei niedrigen ν_{osz} wird die Kugelbewegung maßgeblich durch die wirkende Schwerkraft mit beeinflusst, was die Kugelbewegung einschränkt und damit zu relativ niedrigen Energiedichten führt. Ähnliche Schlussfolgerungen konnten auch für andere Reaktionen (zum Beispiel *Abbildung 6*) getätigt werden.[7, 11b, 26b, 36]

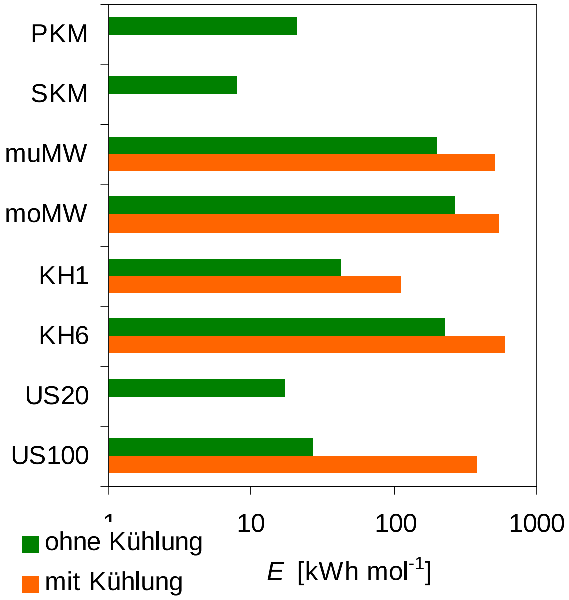


Abbildung 11. Energieeffizienz für die Umsetzungen nach *Abbildung 10* und nach *Tabelle 3*.

Berechnet man die Energieintensität der Prozesse nach *Gl. 11*, so zeichnet sich ein anderes Bild ab (*Abbildung 11*).[4] Trotz der im Vergleich zur PKM niedrigeren chemischen Ausbeuten zeichnet sich die SKM durch die höchste Energieeffizienz aus, was wiederum mit den unterschiedlichen Antriebskonzepten beider Mühlen zu begründen ist und bereits in Zusammenhang mit *Abbildung 9* hinreichend diskutiert wurde.[16] Vergleicht man die Resultate der lösungsmittelfreien Umsetzungen in den Kugelmühlen mit denen anderer Reaktionsführungen so wird schnell die Energieeffizienz dieser Methode deutlich.[4, 7, 11b, 26b] Einzig die Durchführung im Ultraschallbad zeigt annähernd die Effizienz der vorgenannten Methoden.[4] Das Heizen mit Mikrowellen und Reaktionen im Mehrfachreaktor zeigt mit Abstand die niedrigste Energieeffizienz. Einschränkend muss zu den Ergebnissen in *Abbildung 10* und *11* konstatiert werden, dass in diesem Falle lösungsmittelfreie Reaktionen mit der Reaktionsführung im Lösungsmittel verglichen wurden. Das hat zur Folge, dass vor- und nachgeschaltete Prozessschritte nur eingeschränkt miteinander zu vergleichen sind.

5. Parameterevaluierung (Phase V)

In den vorangehenden Kapiteln wurde gezeigt, dass verschiedene Parameter, gruppiert in chemische, technologische und Prozessparameter, chemische Reaktionen in Kugelmühlen auf unterschiedlichen Ebenen beeinflussen. Eine Validierung der Einflussfaktoren ist deshalb wünschenswert, um für zukünftige Arbeiten zeigen zu können, inwieweit einzelne Variablen für eine Optimierung von Bedeutung sind. Aufgrund der Tatsache, dass reaktionsspezifische Erfordernisse durch die Gruppe der chemischen Parameter abgedeckt werden, soll auf diese innerhalb der folgenden Betrachtungen nicht weiter eingegangen werden. Vielmehr ist diese Parameterklasse von wesentlicher Bedeutung für die Auswahl von Reaktionen und bestimmt im Allgemeinen, ob eine Reaktion in Kugelmühlen durchführbar ist. Einzelaspekte (z.B. Eignung von festen bzw. flüssigen Reaktanden, Art von eingesetzten Basen, usw.) können zwar für bestimmte Reaktionsklassen verallgemeinert werden, allerdings folgen daraus keine übergeordneten Regeln, Reaktionen in Kugelmühlen betreffend.

Ein wesentliches Kriterium für die erfolgreiche Durchführung chemischer Reaktionen in den untersuchten Mühlentypen ist das Vorhandensein mindestens eines Feststoffes mit einem hinreichend hohen Schmelzpunkt. Der Zusatz bzw. Einsatz flüssiger oder niedrigschmelzender Reaktanden muss derart erfolgen, dass die rheologischen und mechanischen Eigenschaften des Mahlguten eine Energieübertragung erlauben. Im Optimalfall sollten rieselfähige Pulver vorliegen, wobei flüssige Substanzen an festen sorbiert werden können. Die Ausbildung hochviskoser bzw. pastöser Zustände während des Mahlvorganges ist insbesondere mit Hinblick auf eine Maßstabsvergrößerung oder für eine kontinuierliche Prozessführung zu vermeiden. Das Auftreten derartiger Materialkonsistenzen erfordert den Einsatz anderer verfahrenstechnischer Apparate zum Eintrag mechanischer Energie (z.B. Extruder). Kugelmühlen sind für derartige Prozesse nicht geeignet.

Die wesentlichen technologischen Parameter, welche die Reaktion beeinflussen sind, mit absteigender Reihenfolge ihres Einflusses auf Variablen wie Umsatz oder Ausbeute: die Materialdichte ρ, die Anzahl n_{MK} und Größe der Mahlkörper d_{MK} ($\Sigma m_{\mathrm{MK}} \neq$ konstant), der Füllgrad der Mahlbecher ϕ und die Art der Kugelmühle.[1e, 2-3, 11c] Der Füllgrad der Mahlbecher ϕ sowie die Art der eingesetzten Kugelmühle haben keinen Einfluss auf die Reaktion, können aber insbesondere bei einer Maßstabsvergrößerung an Bedeutung zunehmen und zu den bestimmenden Parametern werden. In Einklang mit *Gl. 4* und *5* sind n_{MK} und d_{MK} nur dann von Bedeutung, wenn gilt $\Sigma m_{\mathrm{MK}} \neq$ konstant. Anderenfalls, d.h., wenn die Gesamtmasse der bewegten Teile konstant ist und somit $\Sigma m_{\mathrm{MK}} =$ konstant gilt, wurde nachgewiesen, dass diese Parameter für den Ausgang chemischer Reaktionen nicht ausschlaggebend sind.[2, 7]

Die Prozessparameter Frequenz ν und Mahldauer t haben den größten Einfluss auf Umsatz bzw. Ausbeute, wie in *Abbildung 12* für die gemeinsame Evaluierung beider Parameter demonstriert. Allgemein lässt sich ableiten, dass Umsatz bzw. Ausbeute proportional zu ν^2 und t sind. Die erste Abhängigkeit lässt sich mit *Gl. 4* belegen,[1e, 11b, 16] während die Proportionalität zur Mahldauer t über die jeweilige Reaktionskinetik erklärbar ist.[1e]

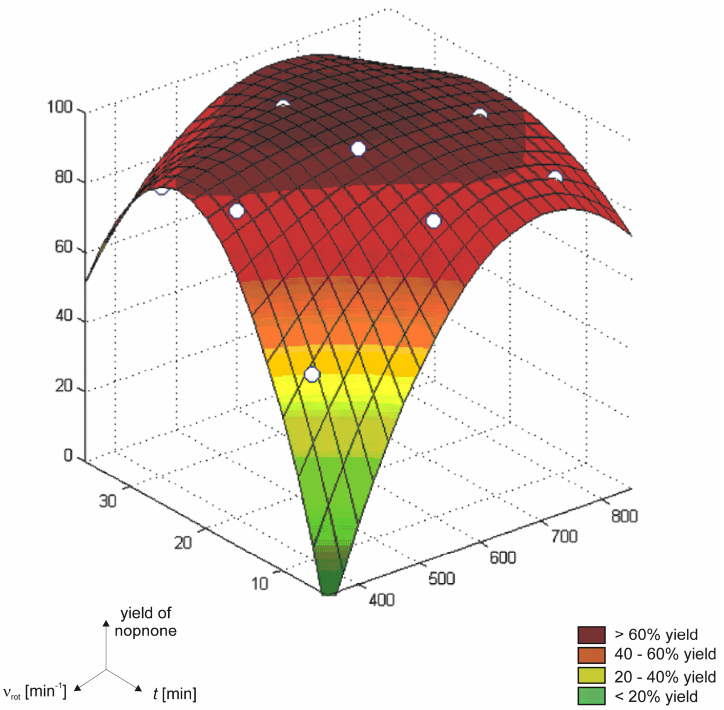


Abbildung 12. Zusammenhang zwischen Rotationsfrequenz ν_{rot}, Mahldauer t und der Ausbeute an Nopinon für die Oxidation von β-Pinen mit $KMnO_4$ in einer Planetenkugelmühle.[1e]

Die oben geschilderten Zusammenhänge konnten mit Hilfe statistischer Auswerteverfahren entsprechender Versuchsreihen für verschiedene Reaktionen bestätigt werden.[3, 11c] Eine Evaluierung führte zu dem Schluss, dass die Prozessparameter sowie das Material der Mahlmaterialien wesentlich Reaktionen in Kugelmühlen unter der Vorraussetzung beeinflussen, dass chemische Parameter in entsprechenden Optimierungsstudien unverändert bleiben. Im Falle einer Maßstabsvergrößerung kommen der Füllgrad der Mahlbecher sowie die Art der Kugelmühle als wichtige Steuergrößen hinzu.

6. Umweltrelevanz

Kugelmühlen stellen eine interessante Prozessalternative für die Durchführung chemischer Reaktionen im Labormaßstab dar. Dabei kommen mehrere Vorteile zur Geltung, welche die Umweltrelevanz der untersuchten Reaktionsführung beeinflussen.

Aus Sicht der Prozessintensivierung bzw. der Steigerung der Nachhaltigkeit chemischer Prozesse oder Reaktionen im Labormaßstab konnte gezeigt werden, dass sich eine Vielzahl von Reaktionen in der Kugelmühle durchführen lassen. Derartige Reaktionen sind dadurch gekennzeichnet, dass sie in der Festphase ablaufen. Auf ein vermittelndes Lösungsmittel kann also während der Reaktion verzichtet werden, d.h. die Reaktionen sind unter lösungsmittelfreien Bedingungen durchführbar. Gleichwohl, wird für eine Isolierung der Produkte weiterhin Lösungsmittel benötigt,[17a, 37] was zur Folge hat, dass der Prozess als solcher nicht als lösungsmittelfrei angesehen werden sollte.[3] Durch den Verzicht von Lösungsmitteln während der Reaktion kann sowohl die Anzahl als auch die Menge dieser im Gesamtprozess (Edukte → Rektion → Isolierung → Produkte) verringert werden, was eine Reduktion der Stoffintensität und damit auch des *E-Faktors* E_{SH} (*Gl. 1*) zur Folge hat. Darüber hinaus lassen sich Lösungsmittel, wenn sie nur bei der Isolierung eingesetzt werden, leichter rezyklisieren, da sie einer geringeren thermischen Belastung ausgesetzt sind, als wenn sie während der Reaktion in intensiven Kontakt mit den Reaktanden stehen.

Durch die den Kugelmühlen systeminhärente ständige, intensive Vermischung des Mahlgutes kann eine effektive Verteilung der Reaktionskomponenten im Mahlraum erfolgen. Damit können Massentransportlimitierungen (geringe Diffusionskoeffizienten), wie sie oftmals bei Reaktionen zwischen Festkörpern auftreten, effizient umgangen werden. Insbesondere im Vergleich zu anderen Möglichkeiten für die Durchführung von Feststoffreaktionen ist dies ein wesentlicher Vorteil mit der Folge, dass Reaktionszeiten signifikant reduziert werden können. Damit wird die Energiemenge reduziert und somit zu einer Verbesserung der Nachhaltigkeit beigetragen. Die Erzeugung der Energie im Reaktionsraum macht Wärmeübergangs bzw. Wärmeleitungsprozesse, wie sie bei strahlungsbasierten Heizmethoden auftreten (klassisches Heizen, Heizen mit Mikrowellen), überflüssig. Dies trägt weiterhin zu einer Verringerung des Energiebedarfs und zu einer Reduzierung der Energieintensität entsprechender Reaktion bei.

Der Verzicht von Lösungsmitteln während der Reaktionsstufe kann auch aus anderen Gesichtspunkten zu einer Steigerung der Nachhaltigkeit beitragen. Die untersuchten Reakti-

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[3] Eine Realisierung von lösungsmittelfreien Prozessen (bei Reaktionen zwischen Feststoffen) scheint aus Sicht der Autoren dieses Berichtes nicht möglich, auch wenn dies an der ein oder anderen Stelle propagiert wird.[17a,37] Aus Gründen der Gleichgewichtsthermodynamik aber auch aufgrund der begrenzten Reinheit von Edukten ist eine ideale chemische Reaktion mit „100% Ausbeute“ thermodynamisch nicht möglich. Damit muss zwangsläufig bei der Isolierung eine Abtrennung unerwünschter Nebenprodukte oder nicht umgesetzter Reaktanden vom Reaktionsgemisch erfolgen. Im Falle von Reaktionen zwischen Feststoffen müssen dann zwangsläufig Lösungsmittel zum Einsatz kommen.

onen benötigen, wenn sie klassisch in Lösung durchgeführt werden, oft wasserfreie Lösungsmittel, welche in der Regel aufwendig getrocknet werden müssen. Werden diese nur für die Isolierung eingesetzt, sind die Reinheitsanforderungen weniger hoch. Somit kann auf den Prozess der Lösungsmitteltrocknung verzichtet werden, was sich in einem reduzierten Zeit-, Stoff- und Energiebedarf des Syntheseprozesses äußert.

Die Reaktionsführung in der Kugelmühle hat im Vergleich zum Vermahlen in Mörser und Pistill neben einer höheren Reproduzierbarkeit und Robustheit auch eine wesentliche Steigerung der Arbeitssicherheit zur Folge. Weiterhin erlaubt die technische Regelung des Energieeintrages über die Frequenz einen wesentlichen Vorteil in Hinblick auf die Prozessstabilität.

Im Rahmen der vorliegenden Arbeit konnte demonstriert werden, dass Reaktionen in Kugelmühlen in mehreren Punkten dem Leitbild einer „Grünen Chemie“ nahe kommen, wie es durch die Formulierung entsprechender Leitsätze von verschiedenen Autoren geprägt wurde.[38]

7. Öffentlichkeitsarbeit

Veröffentliche Manuskripte (in umgekehrter chronologischer Reihenfolge)

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Qualifikationsarbeiten

T. Szuppa, Dissertation: Reaktionstechnische Studien an Terpenkohlenwasserstoffen, FSU Jena, **2010** (anteilig).

R. Schmidt, Diplomarbeit: Synthese von O-, N- und X (Cl, Br)-funktionalisierten Aromaten in einer Schwingkugelmühle, FSU Jena, **2011**.

R. Thorwirth: Dissertation: Ball mill chemistry with alkynes and amines, FSU Jena, **2011**.

A. Stolle: Habilitation: Assessment of ball mills as reactors for organic synthesis from technological and chemical viewpoint, FSU Jena, **2012** (anteilig).

Posterbeiträge

European Conference on Solid State Chemistry (ECSSC XII), 20.-23.9.2009 Münster (D) – F. Schneider, A. Stolle, B. Ondruschka: “Organic Solid State Chemistry – *Quo Vadis*?”

43. Jahrestreffen Deutscher Katalytiker, 10.-12.3.2010 Weimar (D) – R. Thorwirth, A. Stolle, B. Ondruschka: “Fast ligand-, copper- and solvent-free Sonogashira coupling in a ball mill”.

44. Jahrestreffen Deutscher Katalytiker, 16.-18.3.2011 Weimar (D) – A. Stolle, B. Ondruschka: “Solvent free, mechano-chemical metal catalysis – a new option for catalysis in chemical synthesis?”

44. Jahrestreffen Deutscher Katalytiker, 16.-18.03.2011 Weimar (D) – R. Thorwirth, A. Stolle, B. Ondruschka, A.Wild, U.S. Schubert: “Fast, ligand- and solvent-free Click reaction in a ball mill”.

Vorträge

14th Annual Green Chemistry & Enginieering Conference, 21.-23.06.2010 Washington D.C. (USA) – T. Szuppa, A. Stolle, B. Ondruschka, Präsentation: “Solvent-free Oxidation of Monoterpenes under Ball Milling Conditions”.

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3rd International IUPAC Conference on Green Chemistry, 15.-18.8.2010 Ottawa (Kanada) – R. Schmidt, R. Thorwirth, A. Stolle, B. Ondruschka: “Solvent-free reactions of alkynes in ball mills – It’s definitely more than mixing”.

Umwelt 2010 – Von der Erkenntnis zur Entscheidung, 6.-9.9.2010 Dessau – A. Stolle, R. Thorwirth, T. Szuppa, B. Ondruschka, W. Hopfe, W. Simon: “Organische Synthesechemie in Kugelmühlen: Ein Konzept für die grüne Synthesechemie?”.

DBU-Fachgespräch: Lösemittelfreie chemische Synthese, 3.3.2011 Osnabrück – A. Stolle: “Lösungsmittelfreie organische Synthesen in der Kugelmühle”.

Italia-German Meeting: Green and Sustainable Approach to Process Intensification, 2.-3.6.2011 Turin (Italy) – A. Stolle: “Ball milling: An old technique reinvented for application on organic synthesis”.

The 2nd Symposium on Mechanochemistry and Solvent-free Synthesis, 18.-19.8.2011 Belfast (Northern Ireland) – A. Stolle: “Alkynes as building blocks for synthesis in ball mill”.

Wissenschaftsforum Chemie 2011, 4.-7.09.2011 Bremen (D) – R. Thorwirth, A. Stolle, B. Ondruschka, poster presentation: “Solvent-free alkyne and amine chemistry in a ball mill”.

Sonstige

Das Projekt wurde im Rahmen der von der DBU und des Bundespräsidialamtes organisierten „Woche der Umwelt 2012“ vom 5.-6.6.2012 in Berlin (D) durch die projektbeteiligten Organisationen vertreten.

8. Zusammenfassung und Ausblick

Im Rahmen des DBU Projektes 27281-31 „Lösungsmittelfreie organische Synthese in der Kugelmühle“ wurde die Durchführung chemischer Reaktionen in Kugelmühlen untersucht. Es konnte demonstriert werden, dass Kugelmühlen neben ihrem Einsatz als verfahrenstechnische Apparate zur Partikelzerkleinerung oder -vereinzelung auch für Synthesezwecke im organischen Syntheselabor erfolgreich eingesetzt werden können. Um dies zeigen zu können, wurden unterschiedliche Reaktionen auf ihre Durchführbarkeit in Kugelmühlen untersucht und für ausgewählte Reaktionsbeispiele eine detailliertere Untersuchung des Einflusses von Reaktionsvariablen vorgenommen.

Die Entwicklung von Reaktionsprotokollen für Kugelmühlen konzentrierte sich auf zwei wichtige Klassen von Reaktionen: Redoxreaktionen und metallkatalysierte Reaktionen. Darüber hinaus stand die Chemie verschiedener Synthesebausteine wie Alkine, Amine oder Boronsäuren im Mittelpunkt der Untersuchungen. Auf dem Gebiet der Redoxreaktionen konnte gezeigt werden, dass sich Oxidationsreaktionen in der Kugelmühle hinsichtlich der zu erwartenden Selektivität beeinflussen lassen und Nebenreaktionen, wie sie zum Beispiel bei der Durchführung in Lösung auftreten, unterdrückt werden können. Mit der Festphasensynthese von Nopinon aus β-Pinen wurde eine Synthesevariante entwickelt, die im Vergleich zur klassischen Synthese eine höhere Prozesssicherheit aufweist, verbunden mit höheren Ausbeuten und Selektivitäten. Untersuchungen zu metallkatalysierten Reaktionen führten zu der Entwicklung verschiedener Reaktionsprotokolle für die Kreuz- oder Homokopplung unterschiedlicher Substrate mit Pd-Katalysatoren. Des weiteren konnte erstmalig gezeigt werden, dass sich auch Kupfersalze als Katalysatoren für entsprechende Reaktionen in der Kugelmühle eignen. Mit dem Wechsel von teuren Pd- hin zu billigeren Cu-Verbindungen war eine Intensivierung der Reaktionen aus ökonomischer Sicht möglich.

Innerhalb der vorliegenden Arbeit wurde gezeigt, dass es sich bei Reaktionen in Kugelmühlen um Prozesse handelt, die von vielen Parametern abhängig sind. Eine Einteilung der Parameter in chemische, technologische und Prozessparameter hat sich für die Evaluierung und Validierung als sinnvoll erwiesen.

Chemische Parameter fassen all solche Einflussgrößen zusammen, die direkt mit der Reaktion zusammenhängen, wie zum Beispiel Reaktionstyp, Art der Reaktanden oder dem Einsatz von Katalysatoren. Des weiteren konnte in diesem Zusammenhang gezeigt werden, dass Mahlhilfsmittel für den Einsatz flüssiger Edukte in Kugelmühlen von Bedeutung sind. Durch Sorption an einem Feststoff werden Bedingungen geschaffen, welche vorteilhaft für die Energieübertragung und -freisetzung sind, und somit zur Prozesssicherheit aber auch -stabilität beitragen.

Die Gruppe der technologischen Parameter fasst solche Variablen zusammen, die während einer Reaktion in einer Kugelmühle invariant sind und nicht zu den chemischen Parametern zählen. In diesem Zusammenhang konnte gezeigt werden, dass die Wahl des Materials der Mahlwerkzeuge von entscheidender Bedeutung für die Energiefreisetzung ist. Aber auch aus chemischen Gesichtspunkten ist die Auswahl wichtig, da chemische Interaktionen mit den Reaktanden zu vermeiden sind. Für organisch chemische Synthesen haben sich Mahlwerkzeuge aus Zirkonoxid bewährt. Andere Parameter wie die Art der eingesetzten Kugelmühle oder der Füllgrad der Mahlbecher beeinflussen die Reaktion hinsichtlich Ausbeute und Selektivität unwesentlich, sind aber bei Maßstabsvergrößerungen von entscheidender Bedeutung.

Als wesentliche Einflussgrößen von Reaktionen in Kugelmühlen mit direktem Einfluss auf Umsatz, Selektivität und Ausbeute haben sich die Prozessparameter erwiesen. Die Frequenz als Maß für die eingetragenen Energie korreliert dabei mit der im System erzeugten Energie, kann also als Äquivalent zur Temperatur angesehen werden. Die Mahldauer wiederum steht in direktem Zusammenhang zur Reaktionsgeschwindigkeit und damit zur Reaktionskinetik.

Für verschiedene Reaktionen wurde weiterhin der Wirkungsgrad von Kugelmühlen unterschiedlicher Bauart und -größe untersucht. Es konnte gezeigt werden, dass Schwingkugelmühlen gegenüber Planetenkugelmühlen einen geringeren Energiebedarf aufweisen, was mit unterschiedlichen Antriebskonzepten erklärt werden kann. Der elektrische Wirkungsgrad ist bei beiden Apparaten bei Mahlraumvolumina bis zu 50 ml und Ansatzgrößen bis zu 10 mmol vergleichbar (20-30%). Eine Maßstabsvergrößerung hat eine signifikante Steigerung des elektrischen Wirkungsgrades auf 90% zur Folge. Für derartige Untersuchungen sind nur Planetenkugelmühlen geeignet (im Rahmen der in diesem Projekt verwendeten Mühlentypen), da sie es erlauben entsprechend große Reaktoren in Bewegung zu versetzen, was mit dem Konzept der Schwingkugelmühle nicht möglich ist. Ein Vergleich der Energieintensität von Reaktionen in Kugelmühlen mit anderen Formen des Energieeintrages macht die Überlegenheit dieser Technik deutlich. Insbesondere im Vergleich zu strahlungsbasierten Methoden (klassisches Heizen. Mikrowellen) zeichnen sich Kugelmühlen durch einen wesentlich geringeren Energiebedarf aus.

Im Rahmen dieses Projektes konnte gezeigt werden, dass Kugelmühlen aufgrund der hohen Mischeffizienz, der Möglichkeit zur Erzeugung von Energie im Reaktionsraum, der Verkürzung von Reaktionszeiten bei Festphasenreaktionen sowie ihrer hohen Robustheit und

Reproduzierbarkeit Vorteile für den Einsatz im organischen Syntheselabor aus ökologischen, ökonomischen und aus dem Blickwinkel der Prozess- und Arbeitssicherheit aufweisen. Gleichwohl haben die Untersuchungen gezeigt, dass auf diesem Feld noch dringenden Forschungsbedarf hinsichtlich einzelner Aspekte der Prozessführung und der verfahrenstechnischen Auslegung besteht. Generell ist es aus Sicht der Autoren notwendig die Möglichkeiten von Reaktionen in Kugelmühlen weiter zu untersuchen mit dem Schwerpunkt auf Multikomponentenreaktionen, Dominoreaktionen oder Fe-katalysierten Reaktionen. Aus Sicht der Prozesskontrolle wäre eine direkte Regelung der Temperatur bei Kugelmühlen für den Laboreinsatz sinnvoll, um die freigesetzte Reibungswärme kontinuierlich abführen zu können. Eine Maßstabsvergrößerung unter Ausnutzung anderer Arten von Kugelmühlen in Kombination mit einer kontinuierlichen Prozessführen scheint ein weiteres wichtiges Forschungsgebiet, dem bisher wenig Beachtung geschenkt wurde.

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Anhang

Als Anhang werden die im Rahmen des Projektes veröffentlichte Manuskripte zur Verfügung gestellt in der Reihenfolge, wie sie im Bericht erwähnt werden. Diese entspricht nicht der chronologischen Reihenfolge der Veröffentlichung.

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Ball milling in organic synthesis: Solutions and challenges

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During the last decade numerous protocols have been published using the method of ball milling for synthesis all over the field of organic chemistry. However, compared to other methods leaving their marks on the road to sustainable synthesis (e.g. microwave, ultrasound, ionic liquids) chemistry in ball mills is rather underrepresented in the knowledge of organic chemists. Especially, in the last three years the interest in this technique raised continuously, culminating in several high-quality synthetic procedures covering the whole range of organic synthesis. Thus, the present tutorial review will be focused on the highlights using this method of energy transfer and energy dissipation. The central aim is to motivate researchers to take notice of ball mills as chemical reactors, implementing this technique in everyday laboratory use and thus, pave the ground for future activities in this interdisciplinary field of research.

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TUTORIAL REVIEW

Ball milling in organic synthesis: solutions and challenges†

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During the last decade numerous protocols have been published using the method of ball milling for synthesis all over the field of organic chemistry. However, compared to other methods leaving their marks on the road to sustainable synthesis (*e.g.* microwave, ultrasound, ionic liquids) chemistry in ball mills is rather underrepresented in the knowledge of organic chemists. Especially, in the last three years the interest in this technique raised continuously, culminating in several high-quality synthetic procedures covering the whole range of organic synthesis. Thus, the present *tutorial review* will be focused on the highlights using this method of energy transfer and energy dissipation. The central aim is to motivate researchers to take notice of ball mills as chemical reactors, implementing this technique in everyday laboratory use and thus, pave the ground for future activities in this interdisciplinary field of research.

1. Introduction and scope

What methods are applicable to distribute energy for chemical processes as efficient as possible? This is one of the central questions of chemical research in past, present and future. With regard to the electromagnetic spectrum the answer seems simple: Almost all kinds of energy can be applied for the initiation of chemical reactions or for heating of reaction mixtures. The most effective way is for sure the direct activation of covalent bonds by light. However, thermal heating and inverse heating with microwaves are the most common techniques for the controllable accomplishment of chemical reactions. Apart from radiation-based mechanisms other methods of energy entry are applicable: electricity (electrochemistry), cavitation processes (acoustic, hydrodynamic) and mechanical energy (friction, impact, collision).

Regarding the last mentioned method of energy entry for chemical transformations the term *mechanochemistry* has to be mentioned. According to *IUPAC* a *mechano-chemical reaction* is defined as "a chemical reaction that is induced by the direct absorption of mechanical energy".[1] However, mechanochemistry is more than the reactive treatment of substances. The area is furthermore divided into (i) mechanical activation of solids, (ii) mechanical alloying and (iii) the reactive milling of solids.[2–5] Particle refinement due to comminution leads to an increase of surface area, surface energy and number of defects. The increased surface energy can result in a *mechano-chemical activation* if alterations in structure, chemical composition or chemical reactivity occurred throughout milling.[5]

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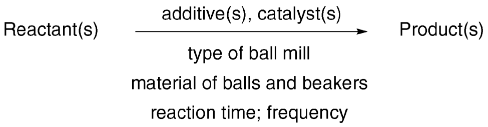
† Electronic supplementary information (ESI) available: Getting started with ball milling: a tutorial. See DOI: 10.1039/c0cs00195c



Scheme 1 Generic reaction scheme for syntheses in ball mills discussed in this tutorial review.

In the simplest case mechanical energy can be generated and transferred to the reactants by working with mortar and pestle. This technique will furthermore be defined as *grinding*. In contrast, the term *milling*‡ will describe processes carried out in ball mills. Due to technical regulation of process parameters like time and energy entry, the results are expected to be more reproducible. The main fields of application for ball mills in industry are for sure, particle refinement processes, disagglomeration and the cracking of bacteria. The largest examples can be found in ore treatment plants as down-stream processes before the separation of gangue and metal ore by froth flotation. For bench-scale applications ball mills§ are the reactors of choice used for the synthesis of various organic chemicals by mechanical activation of solid or solidified reactants (Scheme 1). The generic reaction scheme reflected the major influences which have to be considered when working with ball mills. Besides the type of ball mill, the material of milling ball(s) and beaker(s) influences the chemical reaction just like reaction time and milling frequency [Hz] ($1\ \mathrm{Hz} = 1\ \mathrm{s}^{-1} = 60\ \mathrm{min}^{-1}$; *cf.* Section 7).

In conventional chemical synthesis the energy dispersion and the transport of chemicals are assured by the action of solvents. If chemical reactions between solids are not performed in solution the mass and energy transport is hampered. The efficient mixing process in ball mills is one of the solutions for this problem, enabling *solvent-free reactions* in ball mills between solids or solidified reagents.[3–11]

The employment of ball mills for organic synthesis is a strong emerging field of research. With respect to the wide range of applications in organic chemistry the highlights will be presented in this tutorial review only, covering the past five years. For studies published earlier the reader is referred to respective reviews.[3–7] Beside classical organic synthesis the method of ball milling is applied also in borderline research areas between inorganic and organic chemistry like the synthesis of metal complexes,[12] the formation of metal–organic frameworks[13] and the synthesis of catalysts.[14] From the pharmaceutical point of view the assembly of co-crystals between pharmacologically-active compounds initiated by grinding or milling is an actual field of research.[15,16] Contrarily to the above-mentioned examples[3–7,12–15] and the reactions discussed herewith, the formation of co-crystals depends rather upon coordinative interactions between molecular dipoles than on the formation of covalent bonds.

The present paper is divided into different sections highlighting different aspects of organic synthesis in ball mills: (i) C–C bond formation reactions, (ii) synthesis of heterocycles, (iii) chemistry of protection groups, (iv) redox processes and (v) chemistry of fullerenes. The last two sections discuss the parameters of ball mills and the comparison to other methods of energy entry. In addition, a *tutorial* for those who wanted to explore their organic chemistry with ball mills is provided with the ESI.†

2. C–C bond forming reactions

Among the fields of synthetic organic chemistry the formation of carbon–carbon bonds for the construction of large molecules from smaller building blocks is an important reaction. Almost all the reaction procedures discussed herein are originally developed for solution-based synthesis. However, in the last few decades these transformations have been transferred to solvent-free reaction conditions.[6,7,9–11] Not only

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‡ Other terms describing the same or related techniques: grindstone chemistry, high-energy ball milling, high-speed ball milling (HSBM), ion- and liquid-assisted grinding (ILAG), liquid assisted grinding (LAG).

§ Possible suppliers of laboratory ball mills: Fritsch GmbH, Hosokawa Alpine, Netzsch-Group, Retsch GmbH, SPEX CertiPrep, UnionProcess, Zoz Group.

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demonstrating the general possibility to carry out several reactions without solvents, but also finding new or advanced selectivities and reactivities compared to those described in solution. In this regard, carbon–carbon bond formations have also been picked as a central theme in the regard of this review.[8,10,17]

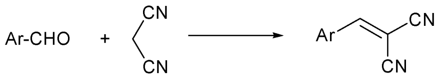
As a classical solvent intensive example, the Wittig reaction has been attempted to be carried out in a ball mill.[18] In the presence of K_2CO_3 as base for deprotonation, ball milling of phosphoranes allowed to discriminate between stabilized and non-stabilized ylides. Whereas the former furnished phosphorous ylides in almost quantitative yields, the more reactive species were trapped in the presence of carbonyl compounds affording the alkenes *via* the Wittig reaction in 85–93% yield. *In situ* formation of ylides and subsequent reaction with carbonyls has been demonstrated by comminution of PPh_3, β-naphthylbromomethane, *p*-bromobenzaldehyde and K_2CO_3 forming the alkene after 8 h in the ball mill in 93% yield. Another difference to Wittig chemistry in solution is the preference for *E*-alkene formation in the solid state.

The Horner–Wadsworth–Emmons (HWE) variant of the Wittig reaction is focused on the use of stabilized phosphonate ylides. Comminution of solid amino-phosphoryl acetate with solid aldehydes gave access to various unsaturated amino esters with a high *Z*-to-*E*-ratio after 7 h ball milling.[19] Reactions are mediated by K_2CO_3, whereas Cs_2CO_3 worked also, but from a sustainable point of view the former is preferred. Furthermore, high conversion and yield minimized the use of solvent during work-up and product isolation.

Zhang *et al.* broached the issue of the chemistry between (aza)chalcones and 1,3-dicarbonyl compounds (Michael addition; Scheme 2).[20,21] In the presence of 10 mol% K_2CO_3 the addition of ethyl acetoacetate or diethyl malonate furnished the products in 86–99% and 76–99% yield, respectively. Authors reported that other bases lead to unselective addition (KF–Al_2O_3) or to inferior yields (NaOH, Na_2CO_3). Both types of Michael addition run faster and with higher selectivity in the ball mill than in solution. For the 1,2-addition of ethyl acetoacetate the reaction showed a clear preference for the formation of the *anti*-products.[21]

Another important reaction of carbonyls for the formation of carbon–carbon bonds is the Knoevenagel reaction. The earliest attempts to perform this condensation reaction in ball mills have been undertaken by Kaupp *et al.*[22] as well as by Wada and Suzuki.[23] Whereas the former protocol involves comminution of the aromatic aldehyde with CH-acidic 1,3-dicarbonyl compounds without the addition of any other reagents, the later exemplified that this reaction is efficiently catalyzed by solid calcite or fluorite. Reassessment of the reactions allowed for the conclusion that the two-component condensation runs through an eutectic melt as intermediate before product crystallization.[24] Probably the thermal input by the milling process facilitates the melt and subsequent crystallization of the condensate. Working without inorganic additives enabled the direct crystallization of the products, if driving the reaction to complete conversion and removing the water *in vacuo*.[22,24] The yield could be controlled by choosing the ideal energy input controllable by the rotation or oscillation frequency in the case of a planetary or a mixer ball mill as reactor, respectively.[24] Results in terms of isolated yields are comparable with microwave-assisted synthesis, exemplifying the potential of the method of ball milling (Table 1).

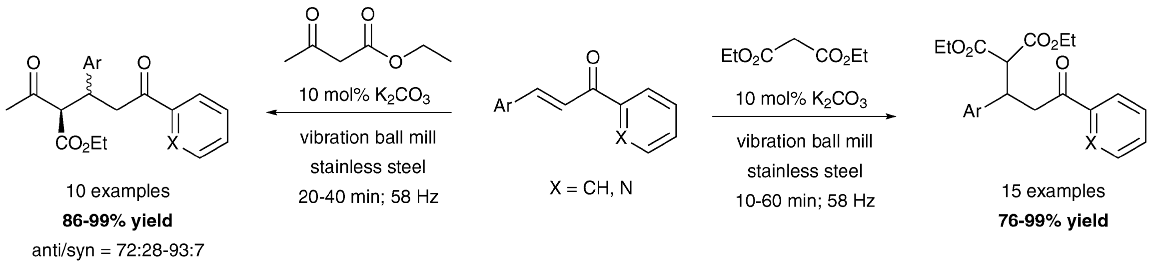
Table 1 Knoevenagel condensation between aromatic aldehydes and malonodinitrile[a] in a planetary ball mill (PBM) and in a microwave (µw)[24]



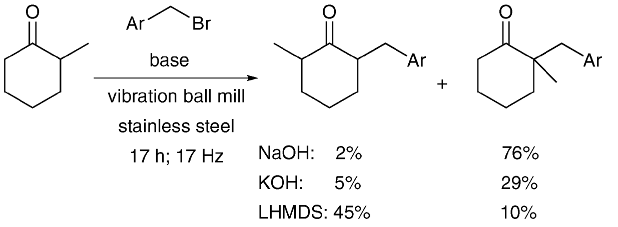
	Yield addition product (%)		
Aromatic aldehyde	PBM[b]	PBM[c]	µw[d]
Benzaldehyde	31	97	83
p-Nitrobenzaldehyde	99		95
p-(*N*,*N*-dimethyl)aminobenzaldehyde	2	68	40
Vanillin	2	5	91
2,3-Dimethoxybenzaldehyde	6	94	92
p-Chlorobenzaldehyde	10	99	96
o-Chlorobenzaldehyde	30	99	95

[a] Reaction time = 60 min. [b] Rotation frequency = 6.7 Hz. [c] Rotation frequency = 13.3 Hz. [d] Circular monomode; 100 W, 150 °C.

Discrimination between kinetic and thermodynamic enolate addition has been demonstrated most recently under the conditions of high energy ball milling.[25] The substitution of 2-methylcyclohexane by *p*-bromobenzylbromide in the presence of different bases is described in Scheme 3. Using alkali metal hydroxides (NaOH, KOH), the preferable formation of the thermodynamic enolate intermediate is indicated by the higher yields for the 2,2-substituted product, whereas NaOH is significantly more reactive and selective. Instead the bulky, nucleophilic base lithium-bis(trimethylsilyl)amide (LHMDS) allowed access to the kinetically controlled reaction pathway forming the 2,6-substituted cyclohexanone, preferably.



Scheme 2 K_2CO_3-mediated reactions of (aza)chalcones and with 1,3-dicarbonyl compounds carried out in a vibration ball mill.



Scheme 3 Differentiation of kinetic- and thermodynamic-driven enolate formation in a ball mill by different bases (Ar = *p*-bromophenyl).¶

2.1 Metal-catalyzed C–C bond formation

The metal-catalyzed formation of carbon–carbon bonds using ball mills as reactors is up to now limited to Pd-catalyzed cross-coupling reactions (Table 2).[8] Protocols for variants of the Suzuki–Miyaura,[26–30] the Mizoroki–Heck[31–33] and the Sonogashira reaction[25,34] have been developed throughout the last decade. All of them have in common that they are carried out under aerobic conditions. In the most cases the reaction times are significantly shorter compared to reactions carried out in solution.

The historic evolution of Pd-catalyzed Suzuki–Miyaura reaction in ball mills is a very nice example, displaying the advancements of different research groups in this field. Starting with a complex $Pd(PPh_3)_4$-catalyst, which was able to couple aryl bromides with phenylboronic acid in the presence of K_2CO_3 as base,[27] further development leads to more advanced procedures. The next step was taken by Klingensmith and Leadbeater who described the application of plain $Pd(OAc)_2$ in the NEt_3-mediated cross-coupling of phenylboronic acid with aryl halides (X = Br, I).[28] These two protocols operate in the presence of NaCl as milling auxiliary using steel as milling media. Based on these studies a protocol using $Pd(OAc)_2$ and KF-Al_2O_3 as catalyst and base, respectively, was published whereas the last unifies the function of the base and milling auxiliary.[29,30] This variant has shown to work with other boronic acids then phenylboronic acid also.[29] Furthermore, the Pd-loading could be reduced from 5 mol%[27] to 0.8 mol% without a negative effect on yield or selectivity and it was demonstrated that pure alumina is able to mimic the base.[30] A nice but interesting distinction to solution-based Suzuki–Miyaura reactions is a different order of reactivity concerning the aryl halides. In agreement, aryl chlorides are less reactive than comparable bromides and iodides. However, aryl bromides are significantly more reactive than the iodo derivatives in the case of ball milling reactions.[28,29]

Comminution of *N*-Boc-protected aminoacrylate benzyl or methyl esters with (hetero)aryl halides in a planetary ball mill (Scheme 4) applying 5 mol% of $Pd(OAc)_2$ as catalyst afforded exclusively the *Z*-Mizoroki–Heck cross-coupled products in medium to high yields.[32,33] Apart from aryl chlorides, *p*-iodonitrobenzene and 2-bromo-6-methylpyridine, the reaction tolerates various functional groups on the aryl halide. The presence of sodium formiate is essential, since it *in situ* reduces the pre-catalyst ($Pd(OAc)_2$) and tetra-*n*-butylammonium chloride probably mimics the function of a ligand. In accordance with respective Suzuki–Miyaura protocols,[27,28] NaCl is applied as a milling auxiliary.[32,33] Compared to the HWE-route[19] leading to similar products, the cross-coupling[32,33] is more time efficient, but the yields and regioselectivities are lower.

Cross-coupling of terminal alkynes with *p*-substituted aryl halides (X = Br, I) has first been described by Fulmer *et al.* using $Pd(PPh_3)_4$ and K_2CO_3 as catalyst and base, respectively.[34] Reactions were carried out with phenyl- and TMS–acetylene as the alkyne component under aerobic conditions without occurrence of side reactions. Originally, the authors reported a procedure requiring CuI as a co-catalyst, demonstrating that without Cu the cross-coupling furnished inferior yields only (Table 3). Replacing the tungsten carbide milling ball by one made from Cu and carrying out the reaction in a copper vial afforded yields comparable to the CuI-mediated synthesis. Thus, abrasion of Cu-metal from the milling ball and reactor surface provides enough material to co-catalyze the cross-coupling.

Further developments lead to a reaction protocol working completely in the absence of copper, using $Pd(OAc)_2$ as standard catalyst and 1,4-diazabicyclo[2.2.2]-octane (DABCO) as base for the deprotonation of the terminal alkyne.[35] Furthermore, the reaction time is reduced from 17 h[34] to 20 min under standard reaction conditions.[35] Authors have demonstrated that a broad variety of (hetero)aryl halides (X = Br, I) can be cross-coupled with various terminal alkynes (aromatic, aliphatic, propargylic alcohols). In addition, the conversion of bis-ethynyl compounds is exemplified selectively affording the bis-coupled reaction products. Contrarily to Fulmer *et al.*,[34] the application of a copper co-catalyst is rather counterproductive than yield- or selectivity-enhancing.[35]

2.2 Organocatalyzed C–C bond formation

Besides Aldol-type and metal-catalyzed protocols for the formation of C–C bonds, reactions using organocatalysts have also been implemented in ball mills. Following this path of modified Aldol reaction allows the formation of enantiomeric or diastereomeric pure products from readily available building blocks.[17,36–38] The asymmetric synthesis of β-hydroxy carbonyl compounds (Aldol reaction) in the ball mill takes advantage of the catalytic action of (*S*)-proline.[17,36] Different ketones (mainly cyclohexanone and -pentanone) were milled together with mono-substituted benzaldehydes (nitro-, chloro, methoxy) in the presence of (*S*)-proline to give the corresponding β-hydroxy carbonyl compound in high yield and enantioselectivity (variant **A** in Scheme 5). Using 10 mol% of (*S*)-proline, after milling times between 5 and 35 h at low rotation frequency the *anti*-product was formed in high enantiomeric excess (ee). The authors worked under such mild conditions to avoid a heating up of the reaction vessel in fact of abrasion of the milling balls inside. Due to the fact that after a short milling time the process was stopped to guarantee a cooling down of the reaction mixture inside the vessels, long reaction times were unavoidable.

Interestingly, yield and ee of the corresponding aldol product were at the low level of 53% and 45%, respectively, if non-substituted benzaldehyde was used as a coupling agent in the presence of cyclohexanone. The product yields

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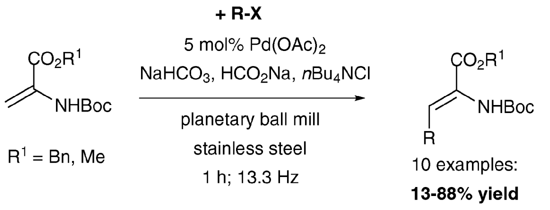
¶ The oscillation frequency is not provided. Due to power drain of the applied ball mill, a frequency of 17 Hz is assumed: D. Maurice and T. H. Courtney, *Metall. Mat. Trans. A*, 1996, **27A**, 1973–1979.

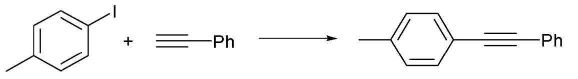
Table 2 Pd-catalyzed cross-coupling reactions in ball mills

Reaction type	Catalyst	Standard base	Substrates	*t*	Ref.
Suzuki–Miyaura	5 mol% $Pd(PPh_3)_4$	K_2CO_3	Aryl bromides with phenylboronic acid	30–60 min	27
	4.5 mol% $Pd(OAc)_2$	NEt_3	Aryl bromides/iodides with phenylboronic acid	10 min	28
	3.6 mol% $Pd(OAc)_2$	KF–Al_2O_3	Aryl bromides/iodides with arylboronic acid	10 min	29
Mizoroki–Heck	5 mol% $Pd(OAc)_2$, nBu_4NCl, HCO_2Na as reducing agent	$NaHCO_3$	(Hetero)aryl bromides/iodides with aminoacrylates	60 min	32
Sonogashira	2.5 mol% $Pd(PPh_3)_4$, 1 mol% CuI as co-catalyst	K_2CO_3	Aryl bromides/iodides with phenylacetylene/TMS–acetylene	17 h	34
	5 mol% $Pd(OAc)_2$	DABCO	(Hetero)aryl bromides/iodides with terminal alkynes (aromatic, aliphatic, propargylic alcohols, *bis*-alkynes)	20 min	35



Scheme 4 Reaction protocol for Mizoroki–Heck reaction of aminoacrylates with aryl halides in a ball mill (X = Br, I; R = (hetero)aryl).

Table 3 Influence of copper source in the Sonogashira coupling of *p*-iodotoluene and phenylacetylene[a] in a mixer ball mill[34]



Copper source	Reactor material[b]	Yield (%)
None	6.4 mm WC-ball in stainless steel vial	17
1 mol% CuI	6.4 mm WC-ball in stainless steel vial	84
Cu-ball	2.4 mm Cu-ball in stainless steel vial	46
Cu-ball + Cu-vial	2.4 mm Cu-ball in copper vial	83

[a] 0.98 mmol *p*-iodotoluene, 1.05 mmol phenylacetylene, 2.5 mol% $Pd(PPh_3)_4$, 0.99 mmol K_2CO_3; oscillation frequency = 17 Hz,‖ reaction time = 17 h. [b] WC = tungsten carbide.

decreased in the row cyclohexanone, cyclopentanone and acetone, if *p*-nitrobenzaldehyde was used as electrophile.

Similar results were observed, if (*S*)-proline was substituted by the binaphthyldiamine of (*S*)-proline and benzoic acid as co-catalyst (variant **B** in Scheme 5). Within shorter reaction times, the *anti*-product of the Aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde was formed in 88% ee at complete conversion.[37]

Another surprising fact is the difference in the correlation between enantiomeric purity of the organocatalyst and the

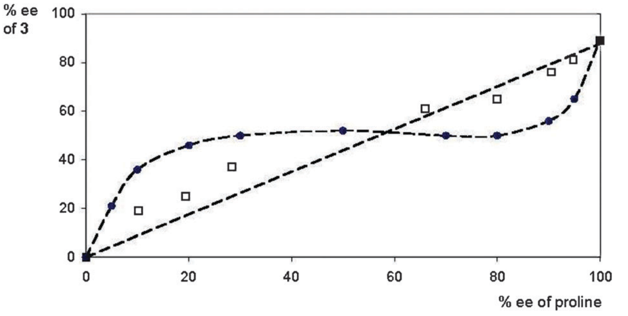
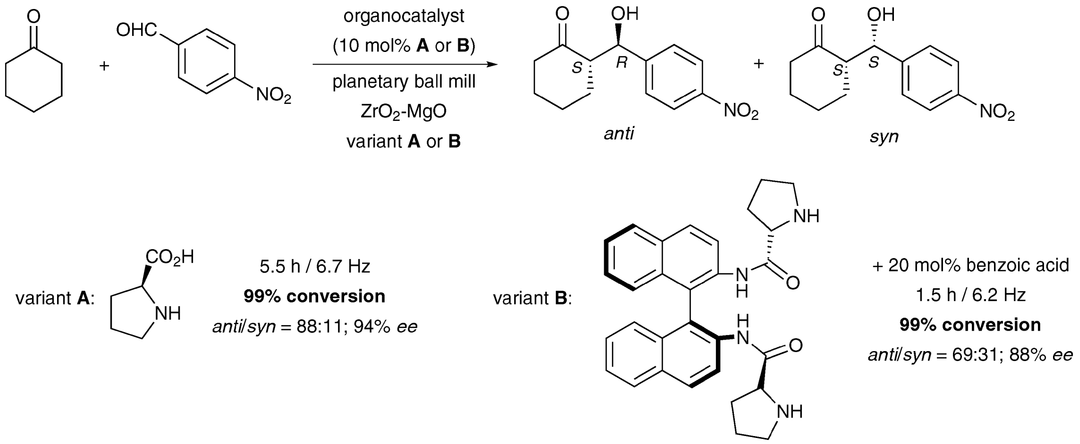
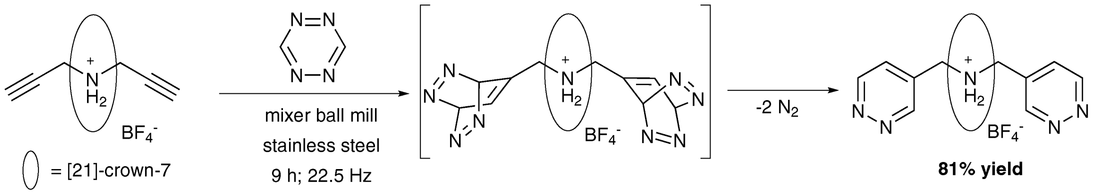


Fig. 1 (a) Circles, ee of product **3** *versus* ee of proline for the Aldol reaction between 4-*tert*-butylcyclohexanone and *p*-nitrobenzaldehyde (according to Scheme 5) performed in the ball mill; (b) squares, same as (a) but under conventional stirring at 42 °C.[38] (Reproduced by permission of The Royal Society of Chemistry).



Scheme 5 Enantioselective Aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde in a planetary ball mill organocatalyzed by (*S*)-proline (variant **A**)[36] and by the binaphthyldiamide of (*S*)-proline (variant **B**).[37]



Scheme 6 Diels–Alder and retro Diels–Alder reaction for the transformation of a [2]pseudorotaxane into an end-capped [2]rotaxane.

resulting product, when performing the reaction in a ball mill or under conventional stirring (Fig. 1).[38] Under conventional conditions and as expected, a linear relation between the ee of proline and the product was found. Contrarily, when 4-*tert*-butylcyclohexanone was comminuted with *p*-nitrobenzaldehyde the ee of the product remained constant at 50%, whereby the ee of (*S*)-proline was successively increased to 80%. With higher ee of proline up to 100% the ee of the product increased to 80%. This phenomenon is a great example for the "black box"-character of ball milling chemistry. Therefore, it is very important not only to do synthesis in ball mills, but also to monitor and investigate such effects occurring during a milling process.

2.3 Cycloaddition reaction

Cycloadditions or related electrocyclic reactions are underrepresented within the list of reactions that have already been performed in ball mills. However, the elegance of these synthetic sequences with high atom efficiency has been applied in fullerene chemistry (*cf.* Section 6),[7,39] in thymol-catalyzed Diels–Alder reaction between dimethylanthracene and benzoquinone[40] and for the synthesis of small rotaxanes.[41,42] *Via* coordination of [21]-crown-7 and dipropargylammonium tetrafluoroborate, the templated synthesis of a [2]pseudorotaxane was realized. Reaction of this precoordinated template with 1,2,4,5-tetrazine in a ball mill furnished the end-group functionalized target molecule after 9 h reaction time. During ball milling the macrocycle undergoes alkyne-hetero Diels–Alder reaction with the alkyne functions of the central ammonium salt axis. Retro Diels–Alder reaction under release of two moles of nitrogen afforded the rotaxane with pyridazin-4-yl end groups in 81% yield (Scheme 6).[41] Heating a pre-ground (1 h) mixture of [2]pseudorotaxane and tetrazine at 80 °C for 12 h afforded the addition product in 30% yield, only. The attempts to extend the procedure to other pseudorotaxanes with different ammonium ions and macrocycles using diphenyl-1,2,4,5-tetrazine as the dienophile were not successful up to date. The reaction mixtures required heating for prolonged time (3 d) at 100 °C to drive to completion.[42] Obviously the bulkier dienophile is not as reactive as the unsubstituted tetrazine. The isolation of the intermediate containing the bicyclic end-groups has not been reported in either case.

3. Synthesis of heterocycles

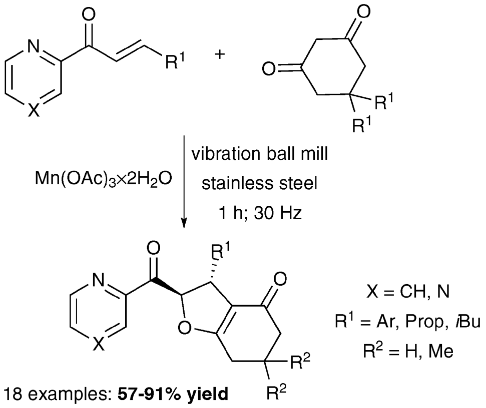
The synthesis of heterocycles in ball mills is a problematic reaction since most of the formations include a condensation step and set free water, which cannot be removed from the closed vessel system. However, there are many examples of such syntheses taking advantage of the thermodynamic stability of the formed products.[10,11]

The functionalization of diamines, anthranilic acid and of polyols with phenylboronic acid has been carried out forming N–B–N, N–B–O and O–B–O (boronic acid ester) heterocycles, respectively.[43] Beyond the polyols, the reactions with catechol, pinacol, mannitol and *myo*-inositol were investigated. The hexoses smoothly reacted with three equivalents of phenylboronic acid forming the protected sugar alcohols. Since the synthesis of boronic acid esters is a valuable method for the formation of organoboron reagents for Suzuki–Miyaura reaction, this chemistry has been extended to the cyclization of other boronic acids and diols under ball milling conditions.[44]

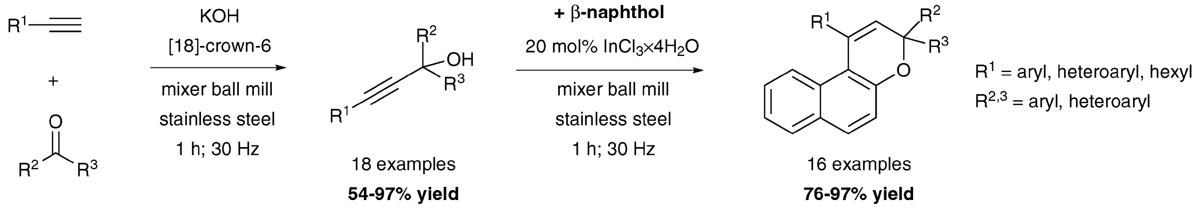
A multi-component condensation between pentaerythrol, *p*-formylphenylboronic acid and 1,3,5-trisaminomethyl-2,4,6-triethylbenzene was applied for the synthesis of a molecular nanostructured heterocycle with dimensions of 1.7 × 2.3 nm.[45] Compared to inferior yields from solution-based synthesis, the formation of 18 covalent bonds between 11 building blocks forming the rugby-shaped macrocycle in a ball mill is superior. Using 4-(4-formylphenyl)phenylboronic acid instead leads to an even larger cage with a size of 1.9 × 3.1 nm.

A straightforward synthesis of 2,3,6,7-tetrahydro-4(5*H*)-benzofuranone derivatives initiated by $Mn(OAc)_3 \times 2H_2O$ was communicated by Wang *et al.* (Scheme 7).[46] Ball milling of 1,3-dicarbonyl compounds (dimedone, cyclohexan-1,3-dione) with (aza)chalcones afforded the products in moderate to high yields after 1 h reaction time. The method has shown to be applicable for a wide range of chalcone-type materials, which themselves are accessible through solvent-free synthesis also. The radical reaction in Scheme 7 is initiated by hydrogen abstraction of the centered carbon atom in the dicarbonyl and did not need any additional base for completion.

The incorporation of terminal alkynes as building blocks for a two-step synthesis of 3*H*-benzo[*f*]furanes has been assessed



Scheme 7 Synthesis of 2,3,6,7-tetrahydro-4(5*H*)-benzofuranone derivatives using ball milling conditions.



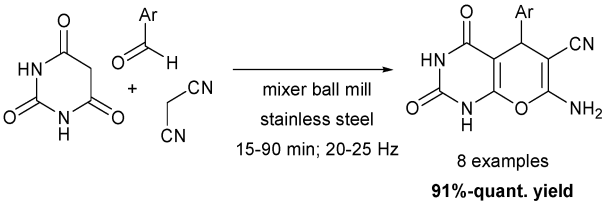
Scheme 8 Two-step synthesis of 3*H*-benzo[*f*]furanes from terminal alkynes, ketones and β-naphthol in a ball mill.

by Dong *et al.* recently.[47] The first step of the sequence afforded propargylic alcohols *via* insertion of ketones into the terminal C–H bond of the alkynes in the presence of KOH and stoichiometric amounts of [18]-crown-6 (Scheme 8). The application of other inorganic and organic bases as well as the use of catalytic amounts of the crown ether afforded inferior yields. The subsequent coupling of the isolated propargylic alcohols with β-naphthol has been catalyzed by $InCl_3 \cdot 4H_2O$, whereas other Lewis-acid catalysts ($ZnCl_2$, $SnCl_4$) showed activity also. Interestingly, the formation of the final 3*H*-benzo[*f*]furane was successful for *S*-heterocyclic substituents, whereas the presence of 2-pyridyl or pyrazin-2-yl at R^1 and R^2, respectively, leads to unreacted mixtures (*cf.* Scheme 8).

Pyrano[2,3-*d*]pyrimidine-6-carbonitriles are accessible through comminution of benzaldehydes, malonodinitrile and barbituric acid in a mixer ball mill for 15–90 min (Scheme 9).[48] Since the reaction afforded no other reagents and the educts have been weighted in equimolar amounts, the formation of the heterocycles is possible without formation of additional waste, if complete conversion is assumed and abrasive effects of the milling material are neglected. The removal of water, which is released by the condensation process, has been realized by heating the reacted mixtures to 80 °C *in vacuo* allowing the products to crystallize.

Gérad *et al.* have published an interesting method for the ball milling synthesis of (2,3,4,4a)-tetrahydroxanthenones from salicylaldehyde and cyclohexanone using DABCO as base.[49] Natural products like *secalonic acid*, *diversonol* and *blennolide C* contain the synthesised xanthenones as leading structural motive. The envisioned domino-oxa-Michael–Aldol reaction was investigated thoroughly on the basis of technical parameters (time, rotation frequency, number of milling balls) as also demonstrated for Suzuki–Miyaura[50,51] and oxidation reactions (see also Section 7).[52,53]

The two-component synthesis of 1,3,5-triaryl-2-pyrazolines has been performed in a planetary centrifugal mill *via* $NaHSO_4 \cdot 2H_2O$ mediated comminution of various arylhydrazines and chalcones.[54] Reactions furnished the heterocycles in 82–93% yield after 5–15 min of ball milling. It has been shown that the product formation is favoured if the condensation is carried out in the presence of silica as water-capturing material.



Scheme 9 Three-component condensation in a ball mill forming substituted pyrano[2,3-*d*]pyrimidine-6-carbonitriles.

4. Protecting group chemistry‖

The synthesis of natural oligo- and polymers with respect to carbohydrates, peptides and nucleosides afforded an intensive use of protecting groups accompanied with a vast amount of solvent(s) especially in the case of solid-phase synthesis (*e.g.* 2000–5000 kg solvent for a large peptide). Omission of solvent(s) in general would strongly decrease the Sheldon-factor and the solvent intensity of such syntheses.[9] With this regard, a number of protection strategies for nucleosides,[55,56] glycosides[56–58] and hexoses (*cf.* Section 3)[43] have been developed based on comminution in ball mills. The persilylation of ribonucleosides with cytosine, guanine, hypoxanthine, uracil and adenine as nucleobases was successfully carried out in a mixer ball mill, affording the TBDMS-protected building blocks after 45–180 min in 87–99% isolated yield.[55] Furthermore, the *in situ* persilylation with TBDMSCl and benzoylation of the amino group in the cytidine ribonucleoside has been demonstrated.

The protection of glycosides has been carefully studied by Patil and Kartha.[56–58] In the presence of DABCO as base the regioselective tritylation of methyl α-D-glucopyranoside in a planetary ball mill has been demonstrated affording the product in 80% yield after 15 h (Scheme 10).[56] Probably, the reaction passes through a melt transition state and is strongly influenced by the rotation frequency. Up-scaling of the reaction to a multigram scale (77 mmol, 15 g) has been reported with a positive effect on the yield. Although the base has been changed from DABCO to Na_2CO_3, which showed in the respective 1 mmol experiments inferior yields. Furthermore, the method is useful to regioselectively protect glycosides, hexoses and partially protected (acetone diacetal) furanoid and pyranoid sugars. Protection with O-DMTCl, TBDPSCl and TBDMSCl has been carried out successfully also.

Applying similar reaction conditions but working in the presence of K_2CO_3 allowed the formation of thioglycosides from readily available bromo and chloro glycosides and thiophenols.[58] Intermediate formation of the isothiourea derivative and subsequent transformation in the presence of iodoethane or 1-chloro-2,4-dinitrobenzene furnished the thiolated products without the application of aryl sulfides. Furthermore, thiodisaccharides were accessible following this route. The similar oxy-functionalization with various phenols

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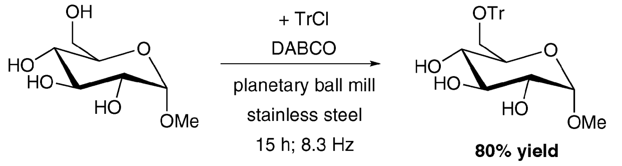
‖ O-DMTCl = 3,3′-oxybis(dimethoxytrityl chloride), TBDMSCl = *tert*-butyldimethylsilyl chloride, TBDPSCl = *tert*-butyldiphenylsilyl chloride, TrCl = trityl chloride.



Scheme 10 Regioselective tritylation of methyl α-D-glucopyranoside in a planetary ball mill.

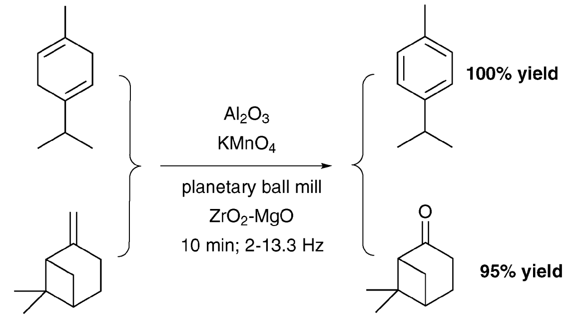
has also been reported.[57] Both types of modification followed a classical S_N2-mechanism affording the anomeric carbohydrate derivative.[57,58]

Declerck *et al.* reported the first solvent-free formation of a peptide bond using urethane-protected α-amino acid *N*-carboxyanhydride derivatives and α-amino acid esters as the coupling partners as well as $NaHCO_3$ as base (Scheme 11).[59] Syntheses of 16 different dipeptides and of one tripeptide have been reported using valine, phenylalanine, leucine, alanine and glycine as amino acid building blocks. Except for reactions with Fmoc-protected urethane derivatives the isolated yields are in between 55–100% after 1 h ball milling at 30 Hz. Systematic studies revealed that only the combination of the three reactants lead to a reaction proved by solid-state FTIR and cross polarization/magic-angle spinning ^{13}C NMR. Authors claimed that the reaction follows a zero-order kinetics, independently from the preset oscillation frequency of the ball mill. Furthermore, it has been shown that this method is suitable for the synthesis of various α,β- and β,β-depeptides from α- as well as β-amino acid precursors.[60]

The method of Declerck *et al.* has been applied for the first solvent-free synthesis of the artificial sweetener aspartame hydrochloride.[59] In a two-step process the yield was 97%, whereby the yield-determining step is the dipeptide formation (Scheme 11). Subsequent and quantitative deprotection with HCl gas in the absence of solvent furnished the hydrochloride after 3 h. Dissolution in water and neutralization to the isoelectric point with aqueous Na_2CO_3 afforded aspartame in 84% overall yield.[59]

5. Redox processes in ball mills

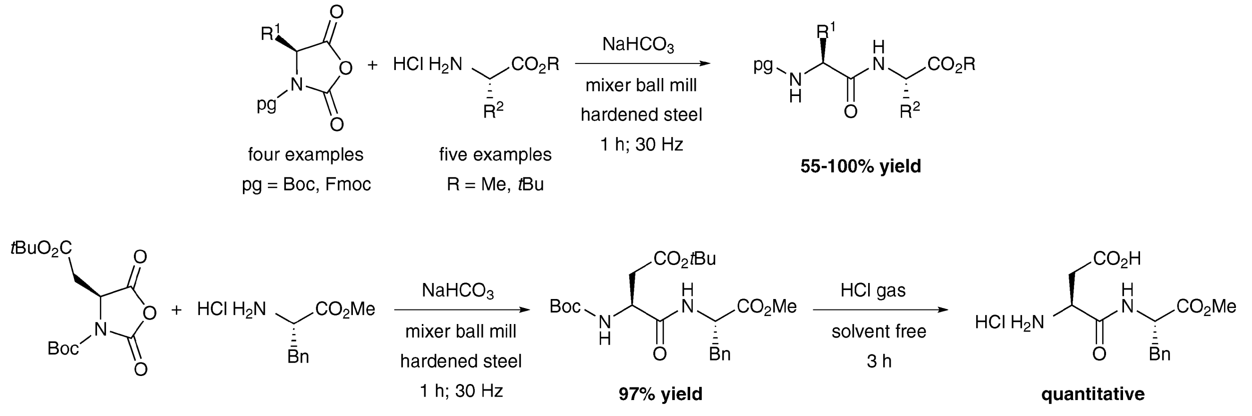
Both oxidation and reduction reactions are important transformations in synthetic organic chemistry. Nevertheless, both types are poorly investigated in the field of ball milling chemistry. Especially the great availability of solid oxidation and reduction agents makes these reaction types interesting for the use in ball mills. In the field of oxidation Szuppa *et al.* demonstrated that terpenes could be oxidized by different solid oxidants under ball milling conditions (Scheme 12).[52,53] Besides $KMnO_4$, other oxidants like $NaIO_4$, $KHSO_5$ or *p*-benzoquinone have shown to be suitable for these reactions. Besides chemical parameters, technical influences on the reaction have been investigated for both model systems: (i) the dehydrogenation of γ-terpinene to *p*-cymene[52] and (ii) the oxidation of β-pinene to nopinone.[53] Experiments allowed for the conclusion that rotation frequency and reaction time are the variables showing the highest influence on product yield. Interestingly, when changing the number of milling balls the optimum quantity (4 × ZrO_2 with d = 15 mm) was equal for both reactions.



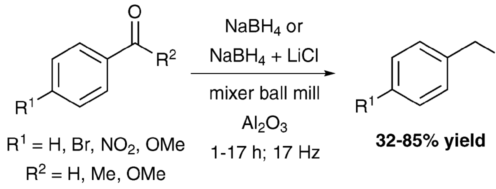
Scheme 12 Selective oxidation of monoterpenes in the solid state using a planetary ball mill.

A similar approach to the oxidative C–C bond cleavage in β-pinene forming nopinone[53] was claimed for the oxidation of benzylic CH_2-groups to the respective carbonyls for aromatics like 9*H*-fluorene, 9,10-dihydroanthracene, acetophenone and 4-benzyl pyridine.[61] Investigation of the reaction parameters identified $KMnO_4$ in combination with alumina as the most potent oxidant system affording high yields and selectivities for the desired products.[52,53,61] Furthermore, it has been proven that the addition of small amounts of water enhanced the reactions described.[52,53,61] Apparently, water is necessary to hydrate the alumina surface enabling the formation of an alumina–$KMnO_4$–complex as the terminal oxidant species.[53]

The suitability of the solid oxidants applied for the reactions presented in Scheme 12 has also been proven in the



Scheme 11 Synthesis of dipeptides and a two-step solvent-free route to aspartame hydrochloride.



Scheme 13 Solid-state reduction of arylic carbonyl compounds to the corresponding benzylic alcohols.¶

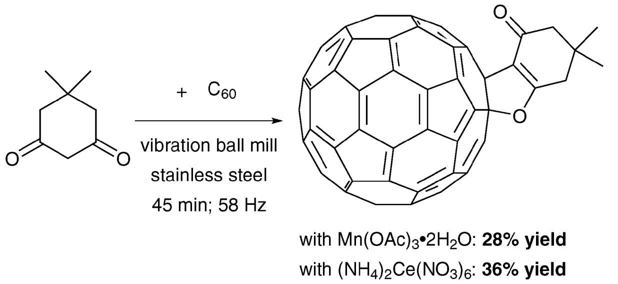
chemoselective oxidative coupling of anilines.[62] In addition, conscious selection of the oxidant allowed either the selective formation of the azo (oxidant = $KMnO_4$) or azoxy compounds (oxidant = Oxone®) from the aniline. Nitro aromatics were accessible also with Oxone® by changing the milling auxiliary from alumina to quartz sand.

On the side of reduction reactions boranes like $NaBH_4$ or $LiBH_4$ have been shown to be suitable for solvent-free reduction in ball mills. For example the reduction of *p*-substituted aryl aldehydes and ketones as well as methyl benzoates has been demonstrated by Mack *et al.* (Scheme 13).[63] In the case of the methyl benzoates, $LiBH_4$ was generated *in situ* by grinding $NaBH_4$ in the presence of LiCl.

The great variety of $NaBH_4$ as a reducing agent in ball milling chemistry has been recognized by Naimi-Jamal *et al.* who converted different alkenyl and aryl aldehydes as well as ketones to the corresponding alcohols. They were able to isolate sodium tetraalkoxyborates.[64] Compared to reaction in solution, those are able to be isolated, enabling a smooth and clean reaction to the alcohols. In contrast to other reactions discussed herein (*mechano-chemical activation*), the reaction of paraformaldehyde with $NaBH_4$ to the tetramethoxyborate is a real *mechano-chemical reaction*, since the polymer is split into HCHO-monomers due to mechanical agitation before addition to the borane.

6. Chemistry of fullerenes

Chemical reactions with fullerenes, especially with polar or ionic reagents, are difficult to perform in solution, since those carbon allotropes are highly hydrophobic molecules. Thus, only lipophilic solvents are applicable affording the employment of phase transfer reagents, detergents or biphasic solvent systems, if one of the reagents is hydrophilic. A nice alternative which overcomes these problems are solid state reactions carried out in ball mills. Various types of reaction protocols have been published up to date and were reviewed by Komatsu[7] and Wang.[39] Transformations include di- and trimerization of C_{60} fullerene, [4 + 2]- and 1,3-dipolar cycloadditions, reactions with nucleophiles as well as complexation of C_{60} with γ-cyclodextrine. In most cases comminution of the reactants was performed in high-speed vibration mills leading to improved yields compared to the solution-based protocols. Sometimes reactions furnished unexpected products that are not described if the same reactions were performed in solution. Thus, under ball milling conditions the reaction of C_{60} fullerene with KCN afforded the C_{120} [2 + 2]-adduct with high selectivity, whereas in the liquid phase the 1,2-addition of KCN was observed in 29% yield, only.[7] Recently, the oxidative addition of 1,3-dicarbonyls to C_{60} was described by Cheng *et al.* furnishing dihydrofurane-fused derivatives (Scheme 14).[65] Assessment of $Mn(OAc)_3$ and ceric ammonium nitrate as oxidants revealed that the latter is more prone to selective formation of the heterocycle.



Scheme 14 Formation of dihydrofurane-fused C_{60} fullerene-derivatives by high-speed vibration milling.

The formation of C_{60} fullerene-oxides with different oxygen contents was successfully carried out by comminuting of the carbon allotrope in an oxygen atmosphere.[66] The oxygen content *n* in the reaction products $C_{60}O_n$ differs from 1.4–12.4, depending on milling time and milling material.

7. Parameter assessment

Chemical reactions in ball mills are challenging, since different variables influence the success of the individual reaction. Besides chemical parameters like type of catalyst, additive or substrate the investigation of technical and process parameters is a severe challenge. However, this field requires special attention, since apart from chemistry these indicators significantly determine the possibility of up-scaling and energy efficiency. Thorough studies identified several important process and technical variables:[49–53,67]

- Type of ball mill (*cf.* Section 8),
- Rotation/oscillation frequency ($\nu_{\text{rot}}/\nu_{\text{osc}}$),
- Reaction time = milling time (t),
- Type of milling material (density, ρ_{MB}),
- Size of milling balls (d_{MB}),
- Number of milling balls (n_{MB}) and
- Mode of operation (continuous, cycled).

7.1 Frequency: ν

The basic physical equation for the rotation and oscillation energy indicates a strong correlation to the frequency ν a ball mill is operated with:[51]

$$E_{\text{kin}}(\text{rot or osc}) = 0.5I\omega^2 = 2\pi^2 I\nu^2 \qquad (1)$$

In line with this basic kinematic equation, the rotation ν_{rot} or oscillation frequency ν_{osc} is one of the most important parameter to consider. Thus, it influences yield, selectivity or similar properties during ball milling.[20,24,36,49–53,56,66,68] Depending on the type of the reaction it might appear that ν has no influence at all or that increase of ν over a specific number has no further effect.[51,59] However, these observations are strongly related to the type of reaction, the reactivity of the reactants and the kinetics of the reactions. For instance, if side or consecutive reactions occur the higher energy entry induced by an increased frequency might promote those pathways and negatively influence the yield.

7.2 Reaction time: *t*

As a chemical reaction progresses with reaction time *t*, the yield normally increases unless side and consecutive reactions do not lead to a conversion of the product(s). Besides ν, the consideration of *t* is as almost important. In the most cases of organic synthesis in ball mills an increase of *t* leads to higher yields.[24,36,49,50,52,53,56,59,66,68] As eqn (1) indicates, both *t* and ν_{rot} contribute to the energy entry. Thus, combined effects of both variables are of special interest. Evaluation of the process parameters in the case of β-pinene oxidation (Scheme 12, bottom)[53] allowed for a statistical assessment based on a factorial plan (Fig. 2). Based on this hyperplane, it is possible to optimize reaction conditions in the most fashioned way.

Similar to the considerations in the case of ν, correlations might indicate a static relation of product yield to *t*, when reaching a defined reaction time (Section 7.1).[36,49] Furthermore, it has been described that sometimes a product specification (yield, enantiomeric ratio) decreases upon prolonged reaction time.[36,50] In this case, the operation of the ball mill in a cyclized mode is an often applied alternative. Due to pauses between milling cycles, the reaction mixture is cooled down and the thermal stress can be reduced.[36,68]

7.3 Milling material: ρ_{MB}

The applied milling material (milling balls as well as beakers) determines the moment of inertia *I* by its material density ρ_{MB} (eqn (1)). Thus, the choice of the grinding material is crucial for the reaction. However, it is not valid to state in general that the higher the material density, the higher the transferred energy and thus the product yield. It is rather connected to the type of reaction. As for some types no effect is measurable[50,53] some reactions showed increasing yields when changing from a light-weight to a more heavier milling material.[34,35,62,64] This conflicting effect is determined by the activation energy of the reaction and the reaction mechanism. Whereas in the former case, either the activation energy is low or the reactions are driven by the formation of thermodynamically stable products, the last needs more energy to reach similar levels of product yield. Especially, for catalytic reactions in ball mills the promoting effect of particle refinement processes leads to active surfaces which are able to increase the overall reactivity of reactants and catalysts. For those examples, the application of milling materials with a higher density may be helpful.[35,62]

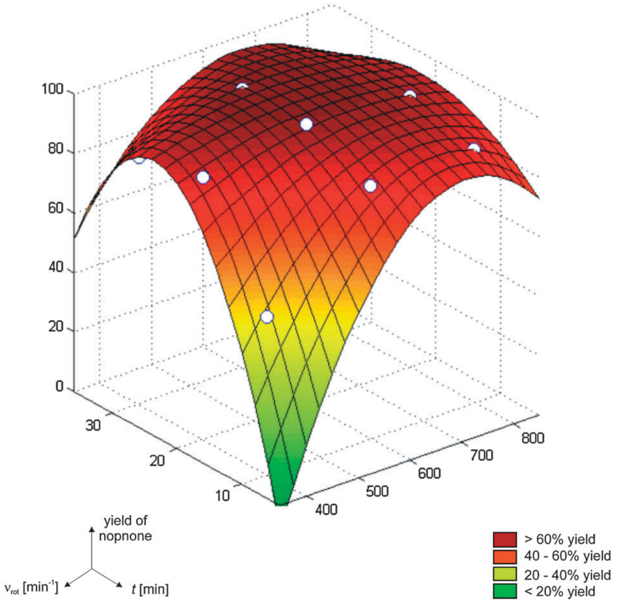


Fig. 2 Correlation between rotation frequency ν_{rot}, milling time *t* and yield of nopinone *via* dry oxidation of β-pinene (Scheme 12, bottom) with $KMnO_4$ in a planetary ball mill (adopted from ref. 53).

Besides energy intensity, abrasion or memory effects of the materials are also important to be considered. The most abundant used milling materials are (arranged by decreasing material density): tungsten carbide, steel, zirconia, corundum and agate. Some of these materials are natural occurring minerals which have a high porosity. Memory effects might occur if reactions (*e.g.* metal catalysis) are carried out with beakers and balls made from corundum or agate. Furthermore, the choice of material is determined by the ongoing chemistry itself. It is well understandable that for instance oxidation reactions with inorganic oxidants also affect the material of beakers and balls (*e.g.* steel). Unless, they are not inert towards the reactants. Besides chemical instability, material abrasion can be crucial from economic and synthetic point of view, since the attrited particles often remain in the product and complex separation strategies have to be applied. However, in some cases, abrasion is used to deliver material (*e.g.* catalyst) essential for a reaction (Table 3).[34]

7.4 Size and number of milling balls: d_{MB}, n_{MB}

The diameter of the milling balls d_{MB} applied for a chemical synthesis in a ball mill is crucial, if the overall mass is not constant.[50,69] Adjustment of a constant mass of milling balls m_{MB} by changing d_{MB} *and* the number of milling balls n_{MB} leads to a different impression. In this case no effect on the product yield is observable (Table 4).[52]

If the material density ρ_{MB} and the diameter of the milling balls d_{MB} are kept constant, the number of milling balls n_{MB} significantly influences the reaction.[49,51–53,62] The correlation between yield and n_{MB} is almost linear due to the linear correlation between mass *m*, moment of inertia *I* and kinetic energy of the system E_{kin} (eqn (1)).

Table 4 Effect of varied diameter (d_{MB}) and number of milling balls (n_{MB}) on the yield of *p*-cymene (Scheme 12, top)[a] by dehydrogenation of γ-terpinene in a planetary ball mill[52]

d_{MB}/mm	n_{MB}	m_{balls}/g	Yield (%)
2	120	45.8	72
10	15	45.4	79
15	5	46.3	75

[a] 3.8 g Quartz sand, 2 mmol *p*-cymene, 6 mmol $KMnO_4$, 0.1 g H_2O; milling material: ZrO_2–MgO, 45 ml beaker; rotation frequency = 13.3 Hz, reaction time = 5 min.

8. Comparison to other methods

Comparison of the aforementioned experimental protocols for ball milling with other methods for energy entry is important since it provides a more detailed understanding of the processes taking place.[5,17] Furthermore, an energetic assessment would give information on the *greenness* of the methods.

The most obvious thing to do is to compare the method of *ball milling* with *stirring* of the reactants in a flask[24,32,36,41] or with the idea of *grindstone chemistry* (grinding, mortar with pestle).[51] Regarding the last mentioned technique, accomplishment of any reaction in a ball mill is more advantageous with respect to reproducibility and safer handling of reagents. Grinding is often used to demonstrate the advantage of ball milling. Indeed, ball milling is much faster and thus more economic. However, grinding experiments force the insight into the mechanisms of activation. Reactions between solid organic reactants induced by grinding or milling based on different activation mechanisms. Due to the refinement of the particles, surface and gas diffusion as well as the formation of amorphous phases can contribute to the product formation.[5,10,16,70] Such mechanisms are not restricted to reactions without additives only, but also provide an explanation for catalytic procedures in ball mills or for processes that need an additional reagent to proceed. Furthermore, the occurrence of eutectic melts is observed as intermediate states.[16,56,70] From those melts the products are able to crystallize in very pure form.[24,36,56]

Tullberg *et al.* investigated the Mizoroki–Heck reaction between iodobenzene and the methyl ester of *N*-Boc-protected aminoacylate under different conditions of energy entry (Scheme 4 and Table 5).[32] Experiments revealed that each thermal, pressure or refinement processes alone do not account for the yield found in the ball milling experiment. Rather a cooperative effect of these and further strains are responsible for the observed results[32] which have been confirmed by similar experiments regarding the HWE reaction[19] and the formation of a rotaxane.[41]

Besides comparison to grinding method, the evaluation of different types of ball mills is interesting.[24,51,62,67] However, the published results are hardly comparable since the operating mechanisms of a mortar grinder is not comparable to a mixer ball mill, which itself is different to a planetary ball mill. The basic principle for all types of ball mills is the generation of impact, collision, friction and shear strains to the loaded materials originating from collisions between milling balls or between milling balls and the containment surface. The general difference between planetary and vibration ball mills (as the most common ones for laboratory applications) is the driving force for motion of the milling beakers. In the first case it is tracked back to rotations in the horizontal plane, whereas in the case of vibration mills the beakers are accelerated by back-and-forth oscillations in the horizontal or vertical plane.[71] Due to the different physical background, a comparison between those types of ball mills is challenging. Indication of the operation frequency for different ball mills cannot ignore the fact that the same number does not represent a similar energy entry, which is furthermore related to the torque of the propulsion unit.[72] Thus, the harmonization using the frequency is only the first step to a model taking into account modes of operation and dimension of the apparatus.

Table 5 Effect of mode of activation on the Mizoroki–Heck reaction[a] between iodobenzene and the methyl ester of *N*-Boc-protected aminoacrylate (Scheme 4) in a planetary ball mill[32]

Technique	Yield (%)
Planetary ball mill (stainless steel, 13.3 Hz)	77
Heating in a test tube (80 °C)	18
Heating and stirring in a test tube (80 °C)	33
Hydraulic press with preheated anvil (80 °C, 19.6 MPa)	13

[a] 5 mol% $Pd(OAc)_2$, 2.5 equivalents $NaHCO_3$, 0.2 equivalents HCO_2Na, 1.2 equivalents $n\mathrm{Bu}_4NCl$, NaCl; reaction time = 60 min.

Another option to assess different methodologies is the calculation of molar energies available through the batch sizes and the line power consumption.[51] Using those data from different ball mills and from microwave and ultrasound reactors gave access to the following order of energy efficiency: mixer ball mill $\geq$ planetary ball mill $>$ ultrasound $\gg$ microwave (see also Table 1).[24,51,62,73] Thus, the method of ball milling is not only a tool to omit solvents in chemical synthesis, but also a tool to make a process more energy efficient.

Conclusion and outlook

The broad field of ball milling procedures discussed in the sections above prove the fact that this field of research is a general method applicable to various synthesis examples in organic chemistry. Besides stoichiometric reactions for the formation of carbon–carbon bonds or heterocycles from small building blocks, some key publications paved the way for the implementation of catalytic methodologies for a carbon–carbon linkage. Often the described reactions take advantage of the fact that different and often increased selectivities and reactivities have been found when working in a ball mill. In some cases even unique selectivities have been demonstrated, which are not contrivable in solution. Thus, the route is opened for the synthesis of new products with advanced properties.† Also the handling of sensitive (*e.g.* terminal alkynes) and highly functionalized materials (*e.g.* peptides, carbohydrates) is possible in a ball mill seeking for further applications in organic synthesis and materials science.

Despite the advantages of ball milling in organic synthesis some problems exist, which should be overcome in the future. Two of the most important parameters in synthetic chemistry—temperature and pressure—are difficult to control and regulate inherently if operating a ball mill in the lab scale. According to large-scale industrial ball mills, tools have to be developed for lab-scale apparatus, which will allow controllable heat dissipation and removal during the process. Another challenge to solve is the harmonization of reaction variables. Comparison of processes on the basis of frequency lacks of fundamental basis. Thus, methods have to be provided to calculate radial velocities in different types of ball mills. This would result in a simplified up-scaling from bench to production scale.

However, in comparison to solution-based processes, the methods of ball milling offer several advantages making them an interesting tool for organic synthesis.

(i) A decrease of solvent intensity for the production of chemicals will lower risk potential by reducing the amount of volatile compounds.

(ii) The intensive mixing efficiency overcomes mass transport limitations in the solid state and thus reduces reaction times significantly. Additionally, the mixing problems if working with hydrophilic (inorganic) and lipophilic (organic) compounds are minimized. Application of biphasic solvent systems, phase-switching reagents or phase transfer catalysts is not necessary.

(iii) Due to efficient energy transfer to the reaction mixture, reactions in ball mills are characterized by a low energy intensity.

(iv) An up-scaling of the reactions accompanied by a switch to continuous processing is possible.[74] The principle *economy-of-scale* seems also be valid.

To conclude, the described examples conspicuously refute *Aristotles* famous citation *No coopora nisi fluida* (no reaction occurs in the absence of solvent). Or to speak with *T. Welton*: *All solutions have a solvent*,[75] unless they are carried out in ball mills. Comparably to microwaves, ultrasound or ionic liquids, ball mills will find their representation in the toolbox of organic chemists.

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Referenz [2]

Solvent-free dehydrogenation of γ-terpinene in a ball mill: Investigation of reaction parameters

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The present article reports on the solvent-free dehydrogenation of γ-terpinene (**1**) in a planetary ball mill affording *p*-cymene (**2**) as the predominant reaction product. The influence of various reaction parameters and technical variables on the transformation of **1** has been assessed. Thus, it is shown that KMnO4 can be substituted by other, less-toxic and environmentally-benign oxidation agents (Oxone®, $NaIO_4$, I_2). In most cases the reaction yielded **2** with high selectivities, whereby conversion can be fine-tuned by variation of the oxidant-to-substrate ratio, the rotation frequency ν_{rot}, the number of milling balls n_{ball} or the type of grinding auxiliary employed. Contrary to particle refinement processes, the size of the milling balls d (constant mass) has no influence on the conversion and chemical yield.

Solvent-free dehydrogenation of γ-terpinene in a ball mill: investigation of reaction parameters†

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The present article reports on the solvent-free dehydrogenation of γ-terpinene (**1**) in a planetary ball mill affording *p*-cymene (**2**) as the predominant reaction product. The influence of various reaction parameters and technical variables on the transformation of **1** has been assessed. Thus, it is shown that $KMnO_4$ can be substituted by other, less-toxic and environmentally-benign oxidation agents (Oxone®, $NaIO_4$, I_2). In most cases the reaction yielded **2** with high selectivities, whereby conversion can be fine-tuned by variation of the oxidant-to-substrate ratio, the rotation frequency ν_{rot}, the number of milling balls n_{ball} or the type of grinding auxiliary employed. Contrary to particle refinement processes, the size of the milling balls *d* (constant mass) has no influence on the conversion and chemical yield.

Introduction

In organic chemistry oxidation is an important method for the synthesis of basic compounds in complex synthetic sequences. The growing interest in the implementation of sustainable chemistry in scientific work has led to the development of a myriad of new methods to perform chemical reactions. In this regard, the replacement of organic solvents is an important issue culminating in the accomplishment of solvent-free syntheses, whereby solvent is omitted during chemical synthesis. Solid inorganic oxidants are widely-used in organic transformations at the lab-scale,[1–5] but catalytic procedures employing oxygen or hydrogen peroxide as oxidizing agent are preferred in large scale synthesis.[6,7] Transformation of catalytic heterogeneous oxidation into solvent-free reaction procedures is difficult, whereas in the case of stoichiometric oxidants such experimental procedures are well-known.[1–7] Solvent-free oxidation reactions can be arranged by simple grind-stone chemistry using mortar and pestle,[1,2] by stirring either heated conductively[3,6] or by microwave irradiation,[4,5] and by the employment of specialized laboratory ball mills.[4a] Within this work we take a closer look at the solvent-free oxidation of γ-terpinene (**1**) to *p*-cymene (**2**; Scheme 1) enhanced by grinding in a planetary ball mill.

The selective synthesis of **2** is a poorly investigated area of chemical research. Predominantly, **2** plays a major role as a by-product during the isomerization of terpenes like α- and β-pinene, or of *p*-menthadienes like limonene or α-phellandrene.[8] Predominantly, **2** is used as a solvent or as a ligand in ruthenium(II) complexes: $[(\eta^6\text{-cymene})RuCl_2]_2$, which are often applied in selective hydrogenation or catalytic transfer hydrogenation reactions.[9] In solution it has been shown that **2** can be generated by dehydrogenation of **1** or α-terpinene, whereby inorganics (permanganates, manganates, chromates)[10] or oxygen[11] are the most common oxidants. The insolubility of inorganic oxidants in most organic solvents requires the application of biphasic reaction mixtures or the employment of phase transfer catalysts or similar auxiliaries (*e.g.* [18]crown-6). Accordingly, the employment of oxygen necessitates the presence of a catalyst to induce electron transfer. The oxidative dehydrogenation of **1** in acetone at 0 °C with $KMnO_4$ was investigated by Singaram and co-workers.[12] Nüchter *et al.* performed the oxidation of aromatic compounds with $KMnO_4$, but without any solvents in a ball mill.[4a] In the present work this procedure was applied to perform the oxidative dehydrogenation of **1**.

Scheme 1 Oxidative dehydrogenation of γ-terpinene (**1**).

Therefore, a solvent-free method for the oxidative dehydrogenation of **1** to **2** in a ball mill was established. The use of solvents was unnecessary during the reaction process. After completion, an easy extraction procedure followed. The product **2** could be formed in quantitative yields after a reaction time of 5 min. In addition, the investigation of reaction parameters (oxidant, reaction time), the influence of variables like number of milling balls (n_{ball}) or rotation frequency (ν_{rot}) was assessed.

Results and discussion

The oxidative dehydrogenation of **1** (Scheme 1) was performed under solvent-free conditions, applying a planetary ball mill

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† Electronic supplementary information (ESI) available: Experimental results for different aluminas and silicas as grinding auxiliaries and the influence of doped solvents are reported. DOI: 10.1039/c002819c

Table 1 Time-dependency of the solvent-free oxidative dehydrogenation of γ-terpinene (**1**) in the presence of alumina or quartz sand as milling auxiliaries[a]

	alumina		quartz sand	
t/min	X_1 [%]	Y_2 [%]	X_1 [%]	Y_2 [%]
5	96	95	74	73
10	97	96	85	84
20	99	99	93	92
30	99	99	96	94

[a] Batch (per beaker): 3.8 g auxiliary, 2 mmol **1**, 6 mmol $KMnO_4$, 0.1 g H_2O; Ball milling: 2 milling beakers (ZrO_2, $V = 45$ ml), 6 milling balls (ZrO_2, $d = 15$ mm) per beaker; $v_{rot} = 800$ rpm (13.3 Hz).

(*Pulverisette 7*, Fritsch GmbH, Idar-Oberstein Germany) for efficient mixing of the reactants and for the application of energy. Before the investigation of various variables and their influence on the reaction course, the dependency of conversion X_1 and yield Y_2 from reaction time t of **1** and **2** was studied. The reaction time was concluded as the limiting factor for transformations in a ball mill within previous studies.[13] Within these experiments we studied the difference between alumina‡ and quartz sand§, which have been applied as common grinding auxiliaries. As shown in Table 1, reactions in the presence of alumina afforded nearly quantitative conversion, accompanied by high selectivity S after 5 min. In contrast to experiments in solution, side-chain oxidation products (*e.g.* toluene, benzoic acids) were not identified during the reaction in a planetary ball mill under solvent-free conditions. In the case of quartz sand a conversion of 81% was reached within a similar time range. An extension of t to 30 min resulted in complete conversion of **1** in the presence of quartz sand. Neither in the case of experiments with alumina or quartz sand was a decrease in S observed, when increasing t. Therefore, it was decided to perform all following reactions at $t = 5$ min to guarantee a fast procedure.

It was shown recently, that addition of water or the presence of physiosorbed water on the grinding auxiliary surface is beneficial for solvent-free transformation in ball mills.[4a] However, reactions in the presence of different amounts of water (0–0.1 g) resulted in indifferent yields and selectivities (*cf.* Electronic Supporting Information; ESI†). Nonetheless, doping the reaction mixture with water, non-agglomerated free-flowing powders after treatment in the ball mill were obtained. Thus, it was easy to remove the reaction mixture from the beaker prior to following work-up by extraction.

Grinding auxiliaries

As mentioned in the section above the grinding auxiliary influences X_1 and therein Y_2. However, the product selectivity remains unaffected (Table 1). Generally the applied auxiliaries are also used as solid supports for the preparation of catalysts or as catalysts themselves.[14] Different surface properties often influence reactions. In this work the materials should mimic the function of a classical solvent. Thus, they are responsible for diluting the reactants, and therewith realizing a homogeneous reaction mixture. Furthermore, the support is responsible for heat transport through the whole beaker. Therewith, overheating and side-reactions can be minimized or completely avoided.

The reactions were performed as described above, once with $KMnO_4$ as oxidant and once without any oxidant to determine the oxidation potential of the pure auxiliary. As shown in Fig. 1, all filling materials render yields between 70 and 99% in the presence of $KMnO_4$. The aluminium oxides are all suitable to give yields between 90 and 99%. Five different aluminas were employed, which mainly differ in their surface characteristics, modification and particle size distribution (*cf.* ESI†). Due to insignificant differences in Y_1 and S_2, the mean value is provided within Fig. 1. Similar to aluminas, four different silicas have been employed as auxiliaries. Concerning X_1, Y_2, and S_F^2 they resemble each other. Thus, Fig. 1 reports the mean value (*cf.* ESI†). Contrary to silicas, quartz sand induces only moderate yields about 70%. This effect can be attributed to differences in particle sizes between silicas and quartz sand. The former (as well as alumina) offers a narrow particle size distribution (0.063–0.5 mm), which guarantees a good dispersion of the reaction mixture and therefore an efficient mass- and heat-transfer. In the case of quartz sand, the particle size is unknown but it is recognizable that it consists of small pebbles. Normally the energy generated by the movement of the milling balls is devolved to the reaction mixture and initiates the reaction. In the case of larger particle sizes, parts of the kinetic energy are consumed for particle refinement. Hence, quartz sand

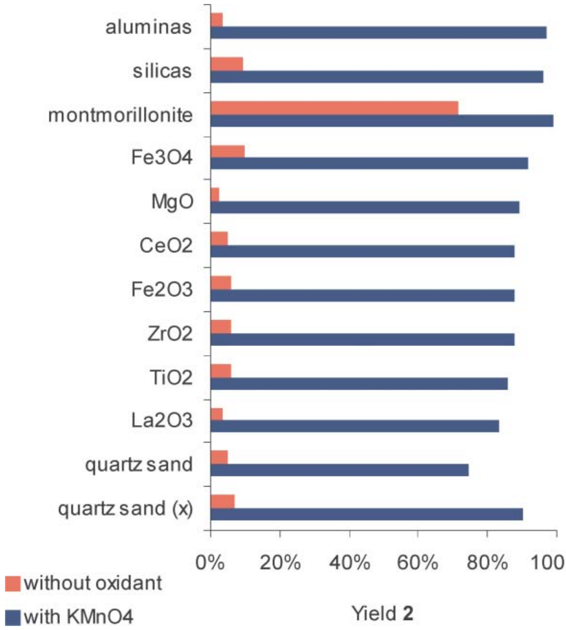

Fig. 1 Solvent-free oxidative dehydrogenation of γ-terpinene (**1**, 2 mmol) to *p*-cymene (**2**) in the presence of different milling auxiliaries (3.8 g) and in the presence or absence of $KMnO_4$ (6 mmol; 0.1 g H_2O; Ball milling: 2 milling beakers (ZrO_2, $V = 45$ ml), 6 milling balls (ZrO_2, $d = 15$ mm) per beaker; $v_{rot} = 800$ rpm (13.3 Hz), $t = 5$ min; x: pre-grinded quartz sand – *cf.* text).

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‡ If not otherwise indicated "alumina" refers to acidic α-Al_2O_3 for chromatography purchased from Fluka® with a particle size between 0.063–0.2 mm (purity >95%).

§ If not otherwise stated "quartz sand" refers to crude, calcinated SiO_2 (purity >95%) for cleaning of platinum crucibles purchased from Sigma-Aldrich®.

afforded moderate yields, because a part of the overall kinetic energy is used to refine the quartz grains. This statement can be supported by an experiment where quartz sand was grinded before its use. Hence, 3.8 g quartz sand were ground without the reactants. After $t = 10$ min the reactants were added and the mixture was treated for another 5 min. As shown in Fig. 1 the yield of **1** rises up to 90% in the presence of $KMnO_4$, and therewith to a level comparable with alumina or silica. Beside aluminas and silicas, basic and amphoteric metal oxides as well as montmorillonite (phyllosilicate) have been employed as grinding auxiliaries. Except for the latter, the conversions in the presence of the oxidant are between 85 (La_2O_3) and 90% (Fe_3O_4).

All grinding auxiliaries revealed negligible reactivity in the dehydrogenation of **1** without potassium permanganate, except montmorillonite. Pure montmorillonite is known to act as a catalytically active material, because of its acidity. Therefore it is used for ring-opening and isomerization reactions.[15] Beside its inherent acidic properties, this phyllosilicate also offers a natural oxidation potential (bleaching soil).[16] Assessment of the natural oxidation potential of montmorillonite in the dehydrogenation of **1** to **2** (Scheme 1) is pictured in Fig. 2. With increasing amounts of montmorillonite both Y_2 and S_2 reach up to 70%. Lower amounts of montmorillonite support isomerization affording various *p*-menthadiene-isomers ($C_{10}H_{16}$; *e.g.* terpinolene, α-terpinene). In the case of pure montmorillonite ($w_{\text{montmorillonite}} = 1$) the conversion of **1** is quantitative whereby the formation of **2** predominates ($S = 72\%$). Nevertheless, 28% of **1** undergoes a rearrangement reaction (*p*-menthadiene-isomers) instead of dehydrogenation to **2**.

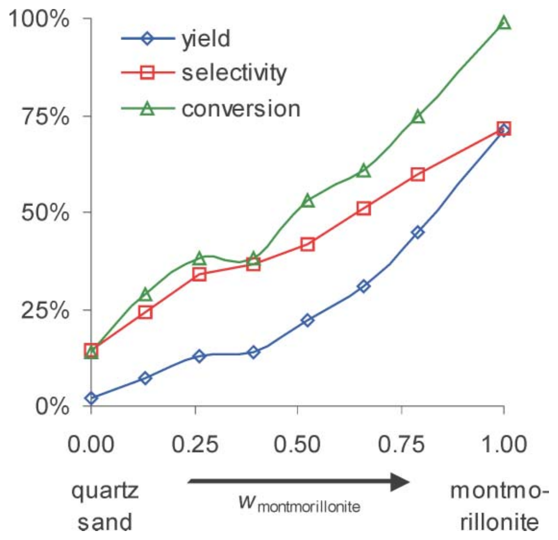


Fig. 2 Solvent-free oxidative dehydrogenation of γ-terpinene (**1**, 2 mmol) to *p*-cymene (**2**) with montmorillonite as oxidation agent in different mass fractions with quartz sand ($\Sigma = 3.8$ g; 0.1 g H_2O; Ball milling: 2 milling beakers (ZrO_2, $V = 45$ ml), 6 milling balls (ZrO_2, $d = 15$ mm) per beaker; $v_{\text{rot}} = 800$ rpm (13.3 Hz), $t = 5$ min).

Oxidation agents

Potassium permanganate is a commonly-used and well-established solid oxidant in organic synthesis.[17] It was proved to be a suitable oxidizing agent for the oxidative dehydrogenation of **1** in the presence of aluminium oxide (Table 1, Fig. 1). In comparison to quartz sand, an increased yield of **2** was observed. However, $KMnO_4$ has a high toxicity and a complete removal of manganese residues is required for the application of reaction products in further synthesis. Due to this fact, a variety of other inorganic as well as organic oxidants were employed in the model reaction (Table 2). For application as the oxidant in the reaction according to Scheme 1, the reagents have to be unable to oxidize the substrate by oxygen transfer. Rather, they must have the ability to abstract the hydrogen atoms.

Table 2 Solvent-free oxidative dehydrogenation of γ-terpinene (**1**) to *p*-cymene (**2**) in the presence of alumina or quartz sand as milling auxiliaries and different oxidation agents[a]

	Y_2 [%][a]	
Oxidation agent	alumina	quartz sand
$KMnO_4$	99	53
p-Benzoquinone	95	37
I_2	93	52
Oxone®[b]	84	8
$NaMnO_4$	82	73
$(NH_4)_4Ce(SO_4)_4 \cdot 2H_2O$	71	11
$NaIO_4$	67	41
K_2MnO_4	54	18
$BaMnO_4$	47	24
KIO_4	47	40
V_2O_5	39	19
DDQ[c]	29	29
KIO_3	22	8
PCC[d]	16	13
$NaBrO_3$	13	36
$K_2Cr_2O_7$	12	7
2,6-Dimethoxy-*p*-benzoquinone	11	5
$Na_2S_2O_8$	11	10
$Mn(AcO)_3 \cdot 2H_2O$	10	4
$(NH4)_2S_2O_8$	7	7
Anthraquinone	5	4
urea-H_2O_2-adduct (28%)	5	6
MnO_2	4	2
$NaBO_3 \cdot 4H_2O$	2	4
9-Fluorenone	0	7

[a] Batch (per beaker): 3.8 g auxiliary, 2 mmol **1**, 6 mmol oxidant, 0.1 g H_2O; Ball milling: 2 milling beakers (ZrO_2, $V = 45$ ml), 6 milling balls (ZrO_2, $d = 15$ mm) per beaker; $v_{\text{rot}} = 800$ rpm (13.3 Hz), t = 5 min. [b] Triple salt: 2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. [c] 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone. [d] Pyridiniumchlorochromate: $[PyH][CrO_3Cl]$.

In the majority of all experiments, the dehydrogenation is more effective with alumina as the grinding auxiliary than with quartz sand. However, the results underline the good performance of $KMnO_4$ in combination with alumina as the grinding auxiliary. As shown in Fig. 3 a great excess of $KMnO_4$ is necessary to guarantee quantitative yields. Ball milling in the presence of alumina afforded a molar ratio of 3 : 1 for quantitative conversion after 5 min. A maximum yield of >95% at an oxidant-to-substrate ratio of 4 : 1 was assigned for reactions with quartz sand as a milling auxiliary. A further increase of the oxidant afforded a decrease in selectivity due to formation of *p*-cymenene (**3**; 1-methyl-4-(prop-1-en-2-yl)benzene; $S = 4\%$) as major side product (Scheme 2). The envisioned ideal molar ratio of $KMnO_4$ to **1** of 2 : 3, as indicated by the redox-equation (eqn (1)) is far away from reality. However, elongation of t might enhance the exploitation of the oxidant; thus, lower molar ratios can be chosen.

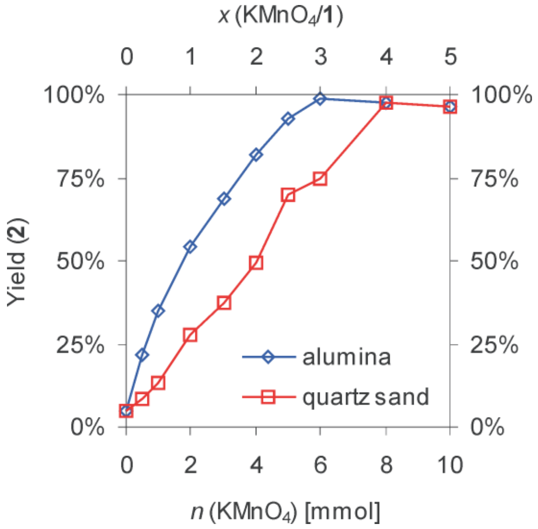
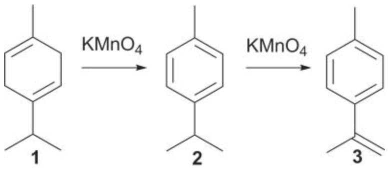


Fig. 3 Solvent-free oxidative dehydrogenation of γ-terpinene (**1**, 2 mmol) to *p*-cymene (**2**) with $KMnO_4$ as oxidant (3.8 g auxiliary, 0.1 g H_2O; Ball milling: 2 milling beakers (ZrO_2, V = 45 ml), 6 milling balls (ZrO_2, d = 15 mm) per beaker; ν_{rot} = 800 rpm (13.3 Hz), t = 5 min).



Scheme 2 Dehydrogenation of γ-terpinene (**1**) with excess of $KMnO_4$.

$$3C_{10}H_{16}\ (\mathbf{1}) + 2KMnO_4 \rightarrow 3C_{10}H_{14}\ (\mathbf{2}) + 2MnO_2 + 2KOH + 2H_2O \qquad (1)$$

Beside $KMnO_4$, further potent oxidizing agents have been identified (Table 2). *p*-Benzoquinone (BQ) is also known as an effective dehydrogenation agent in organic synthesis.[18] Nearly quantitative yields of **2** are formed by way of transfer hydrogenation affording *p*-hydroquinone as a side product. Further oxidation by-products were not observed. Compared to $KMnO_4$, the remaining BQ and the formed *p*-hydroquinone have to be removed from the extraction mixture during purification. Thus BQ is disadvantageous due to complex work-up. DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone), 2,6-dimethoxy-*p*-benzoquinone, and anthraquinone have a similar structure to BQ. Thus, their oxidation potential should be in the same range. Table 2 reports yields of 29, 11, and 5%, respectively. Apparently, steric repulsion of the crowded benzoquinones prevent a higher reactivity under solvent-free reaction conditions.

Interestingly, elemental iodine is suitable for the dehydrogenation of **1** also.[19] High yields combined with high selectivity (94%) were received. Neither, the formation of addition products to the double bond (iodination, hydroiodination) nor core-substitution products of **2** (from electrophilic substitution) were identified. However, the employment of iodine has a big disadvantage: excess oxidant has to be removed by washing with an aqueous solution of $Na_2S_2O_8$, prior to extraction to prevent solution of iodine in the organic eluent. A rather simple solution for overcoming the problem is the application of $NaIO_4$ as the oxidizing agent, which revealed a similar performance as shown for $KMnO_4$ (Table 2). Due to its ionic nature, it is insoluble in organic solvents and therefore no further purification step was necessary. Similar to the employment of $KMnO_4$ (Fig. 3), the molar ratio of $NaIO_4$-to-**1** has been assessed (Fig. 4). An increased ratio of $NaIO_4$ to **1** only resulted in linear increase of Y_2 with alumina as the grinding auxiliary. In contrast, the reaction in the presence of quartz sand afforded a maximum Y of 50% at the ratio of 2 : 1. The product selectivity (>99%) is independent from both the amount of $NaIO_4$ and the grinding auxiliary. Thus, the reported yields in Fig. 4 represent the overall conversion of **1**.

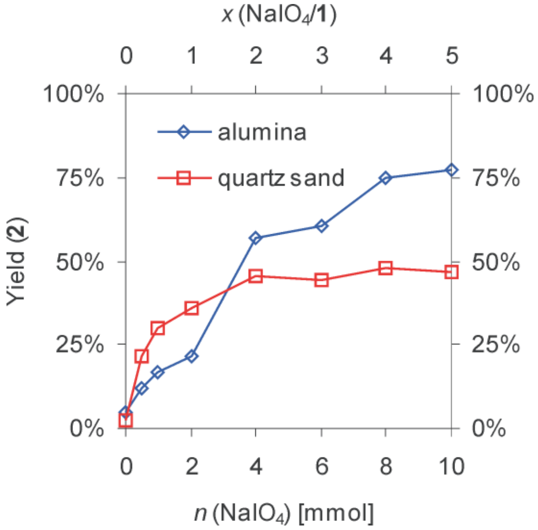


Fig. 4 Solvent-free oxidative dehydrogenation of γ-terpinene (**1**, 2 mmol) to *p*-cymene (**2**) with $NaIO_4$ as oxidant (3.8 g auxiliary, 0.1 g H_2O; Ball milling: 2 milling beakers (ZrO_2, V = 45 ml), 6 milling balls (ZrO_2, d = 15 mm) per beaker; ν_{rot} = 800 rpm (13.3 Hz), t = 5 min).

Oxone® (triple salt $2KHSO_5\cdot KHSO_4\cdot K_2SO_4$) is well known as a good oxidation agent;[20] it is also suitable for this reaction type (Scheme 1), but only in combination with aluminium oxide (Y_2 = 85%; Table 2). With quartz sand as the auxiliary, a lower conversion of **1** was observed (Y_2 = 8%). In comparison to $KMnO_4$ and $NaIO_4$, Oxone® is non-toxic and also insoluble in organic solvents. However, due to its high molecular weight and combined with the high price it is an expensive oxidation agent.

Contrary to Oxone®, the oxidation potential of $NaMnO_4$ is independent from the milling auxiliary since yields of 80% were reached (Table 2). Instead of $KMnO_4$, the yields in the presence of quartz sand are 20% higher (Y_2 = 80%). Other Mn-containing compounds (K_2MnO_4, $BaMnO_4$, MnO_2, $Mn(AcO)_3$) afforded moderate yields only, which is assumed to be due to their lower oxidation potential. Additionally, Mn(IV) and Mn(V) species are the reaction products when $KMnO_4$ is employed as the oxidant (eqn 1). Despite their acceptable oxidation potential, the high molar weight of Na_2MnO_4 and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ is the reason for the lower overall efficiency (economic and ecologic) of these oxidants. Other tested oxidation agents provided **2** in yields below 50% (*e.g.* PCC = [PyH][CrO_3Cl], $K_2Cr_2O_7$, $Na_2S_2O_8$, urea-H_2O_2-adduct). It has to be stated, that further improvement of reaction parameters (t, ν_{rot}) might enhance the reaction.

Rotation frequency ν_{rot}

Besides chemical variables, technical parameters like rotation frequency or the density of the milling material also significantly influence the outcome of reactions performed in ball mills. These effects are well understood in the case of particle refinement and inorganic processing.[21] Recent publications indicate that for organic synthesis consideration of these parameters is also important.[13] Therefore, the influence of the rotation frequency ν_{rot} on the yield of the solvent-free dehydrogenation of **1** is assessed. Reactions at different frequencies from 100 to 800 rpm (1.7–13.3 Hz) were performed for two milling auxiliaries (Fig. 5). From 500 to 800 rpm (8.3–13.3 Hz) a relatively constant level for Y_2 occurs in the presence of Al_2O_3. With regards to energy costs, this seems to be an interesting fact: lower ν_{rot} means less energy consumption and therewith lower costs, thus improvement of the energy efficiency of the process.[22] Within the decrease of ν_{rot} below 500 rpm (8.3 Hz), significantly lower product yields were found (75%). In the case of quartz sand, the increase is more distinctive, since below 500 rpm Y_2 just reaches values about 50%.

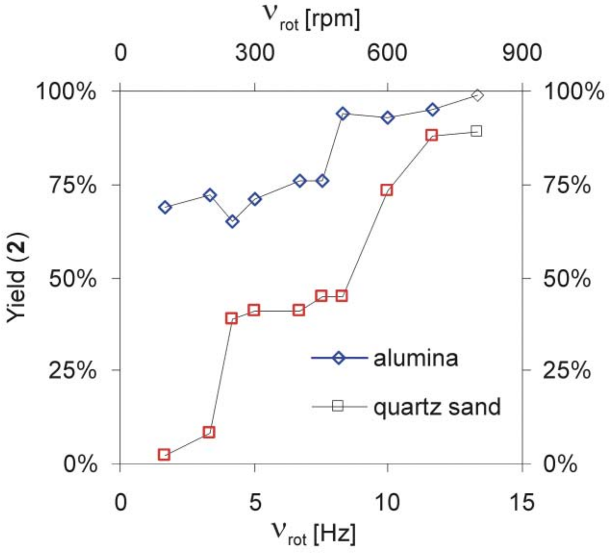


Fig. 5 Influence of rotation frequency ν_{rot} on the solvent-free oxidative dehydrogenation of γ-terpinene (**1**, 2 mmol) to *p*-cymene (**2**) with $KMnO_4$ as oxidant (6 mmol; 3.8 g auxiliary, 0.1 g H_2O; Ball milling: 2 milling beakers (ZrO_2, $V = 45$ ml), 6 milling balls (ZrO_2, $d = 15$ mm) per beaker; $t = 5$ min).

Number of milling balls n_{ball}

Another critical parameter in ball-milling experiments is the number of milling balls, n_{ball}. So far, the experiments were performed with 6 milling balls made of ZrO_2 with a diameter d of 15 mm. Fig. 6 summarizes the results from experiments with n_{ball} varying from 1–7. It has to be stated expressly that the performance of experiments with one milling ball is not in line with the manufacturer's advice, due to strong abrasion.[23] In the presence of alumina as the milling auxiliary, a minimum of 4 milling balls are necessary to guarantee a quantitative yield of **2**. In the case of quartz sand, an increasing amount of milling balls lead to a rise of Y_2 up to 90% when applying 7 milling balls. Loading of the milling beakers with $n_{ball} > 7$ ($d = 15$ mm) is not possible, since the required space prevents homogeneous mixing and therefore enhances abrasion of the milling balls. According to the manufacturer, a volume-ratio of substance to milling balls to free space of 1 : 1 : 1 is ideal.[22]

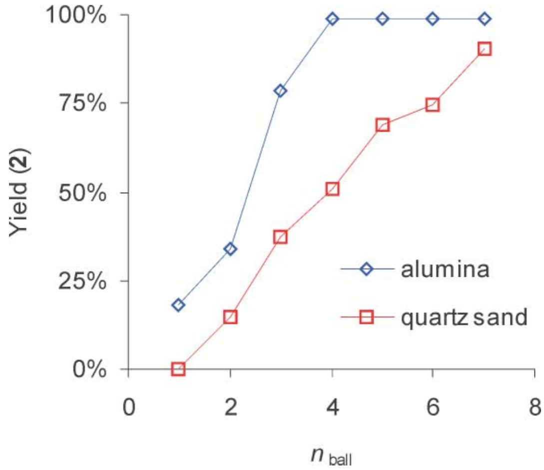


Fig. 6 Influence of number of milling balls n_{ball} on the solvent-free oxidative dehydrogenation of γ-terpinene (**1**, 2 mmol) to *p*-cymene (**2**) with $KMnO_4$ as oxidant (6 mmol; 3.8 g auxiliary, 0.1 g H_2O; Ball milling: 2 milling beakers (ZrO_2, $V = 45$ ml), milling balls (ZrO_2, $d = 15$ mm) per beaker; $\nu_{rot} = 800$ rpm (13.3 Hz), $t = 5$ min).[23]

Diameter of milling balls d

The following experiment should demonstrate the coherence between energy and mass. From physical mechanics it is known that kinetic energy is a function of mass and velocity. For our conception this means, independently Y_2 must be the same when using milling balls with different d but with the same total mass (Σm_{ball}). Our results verify this theory. As shown in Table 3 ball milling experiments with 120 milling balls with a diameter of 2 mm have nearly the same mass as 15 and 5 milling balls of 10 and 15 mm, respectively. Therefore, the same application of energy at the same rotation speed should be assured. With both, alumina and quartz sand, variation of d but constant Σm_{ball} leads to similar yields of **2**. This is due to the theory mentioned above. The energy, which depends on mass and velocity, is similar in all three cases. The surface area of the different milling ball diameters does not seem to have any effect on the yield, which

Table 3 Variation of the diameter of milling balls d in the solvent-free oxidative dehydrogenation of γ-terpinene (**1**) in the presence of alumina or quartz sand as milling auxiliaries[a]

			Y_2 [%]	
d/mm[b]	n_{ball}	Σm_{balls}/g[c]	alumina	quartz sand
15	5	46.33	99	75
10	15	45.37	99	79
2	120	45.84	99	72

[a] Batch (per beaker): 3.8 g auxiliary, 2 mmol **1**, 6 mmol $KMnO_4$, 0.1 g H_2O; Ball milling: 2 milling beakers (ZrO_2, $V = 45$ ml), ZrO_2 milling balls; $\nu_{rot} = 800$ rpm (13.3 Hz), t = 5 min. [b] Average milling ball diameter. [c] Overall mass of milling balls = $1/6\pi \cdot \rho_{ZrO2} \cdot n_{ball} \cdot (d)^3$.

is in clear contrast to the application of ball mills in particle refinement processes.[21]

Conclusion

As shown, the solvent-free oxidative dehydrogenation of γ-terpinene (**1**) to *p*-cymene (**2**) initiated by grinding in a planetary ball mill is a very time-efficient method. After 5 min and in the presence of alumina as a grinding auxiliary, with $KMnO_4$ as the oxidant quantitative yields were obtained. Other auxiliary materials like silica or other metal oxides can also be applied. The employment of montmorillonite causes moderate yields without the addition of any further oxidizing agent. The assessment of other oxidants like *p*-benzoquinone, $NaIO_4$ or Oxone® revealed high conversions, accompanied by excellent selectivities. Widely-used oxidation agents like $K_2Cr_2O_7$ or H_2O_2 (as urea-H_2O_2-adduct) are less effective. Finally, $KMnO_4$ and $NaIO_4$ are the best oxidants regarding cost, toxicity, and work-up of the reaction mixture. Nevertheless, an excess of these oxidants has to be applied to receive quantitative yields. The assessment of variables like rotation frequency or number of milling balls, revealed a significant influence on the outcome of the reaction. Thus, variation of these parameters and of the reaction time allows fine-tuning of the reaction conditions, achieving high yields and excellent selectivities. As optimum milling parameters $t = 5$ min at $v_{rot} = 800$ rpm (13.3 Hz) with 6 milling balls were identified.

Experimental

General

All chemicals were purchased from commercial suppliers and used without further purification. Montmorillonite K-10 was purchased from Sigma-Aldrich. The parameters of employed aluminas and silicas are provided within the ESI.†

Analyses were carried out with a 6890 Series GC-MSD and a 7890 Series II GC-FID from Agilent Technologies. Products were identified by comparison with either retention times and/or mass spectra of pure reference compounds. GC-FID: HP 5, 30 m × 0.32 mm × 0.25 μm, 5 psi H_2; program: 35 °C (hold 1 min), 4 K min^{-1} up to 80 °C, 4.5 K min^{-1} up to 90 °C, 35 K min^{-1} up to 280 °C (hold 3 min); injector temperature: 250 °C; detector temperature: 280 °C. GC-MS: HP 5, 30 m × 0.32 mm × 0.25 μm, 7 psi He; program: 55 °C (hold 1 min), 5 K min^{-1} up to 150 °C, 20 K min^{-1} up to 280 °C (hold 5 min); injector temperature: 280 °C, EI (70 eV).

All product yields reported herein are GC-determined yields and are comparable with the isolated ones. Nevertheless, the reported yields were corrected by means of different FID-sensitivity for substrate and product. The reported yields are mean values from at least two independent experimental runs.

The grinding beakers and the milling balls were purified with 10 wt% hydrochloric acid in ethanol for complete removal of residual Mn-species.

Reaction procedure

A milling beaker was equipped with 6 milling balls (ZrO_2, *d*: 15 mm). Afterwards, the grinding auxiliary (3.8 g), γ-terpinene (**1**; 2 mmol, 272 mg), the oxidant (6 mmol), and H_2O (0.1 g) were placed into the milling beaker (ZrO_2, $V = 45$ ml). Finally, the beaker was sealed with a PTFE-gasket and the ZrO_2-lid. Two similar loaded beakers are mounted into the planetary ball mill (*Pulverisette 7 classic line*, Fritsch GmbH, Idar-Oberstein, Germany). The parameters, rotations per minute and milling time, were set-up and the milling process was started. After the milling process, the beakers were opened and the milling balls were removed. The reaction mixture was transferred into a glass tube and subsequently demineralized water (3 ml) as well as ethyl acetate (5 ml) were added. The organic layer was separated and the composition was analyzed by GC-FID respective GC-MSD.

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23 Reproduction of experiments with one milling ball is critical, due to extreme abrasion. Manufacturers of planetary ball mills advise to employ at least 2 milling balls.

Referenz [3]

An alternative solvent-free synthesis of nopinone under ball-milling conditions: Investigation of reaction parameters

T. Szuppa, A. Stolle, B. Ondruschka, W. Hopfe

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A new method for the oxidative cleavage of β-pinene (**1**) yielding nopinone (**2**) with potassium permanganate as oxidant under solvent-free conditions was established. The reaction was performed in a conventional ball mill with use of a grinding auxiliary. The auxiliary has the ability to sorb liquid reactants such as **1** on its surface to make liquid(s) accessible for mechanical impact. Different reaction parameters and technical variables were assessed concerning their influence on yield and selectivity of **2**. Different chemical parameters such as oxidants, grinding auxiliaries, and quantities were investigated. Also tuning parameters including milling time, rotation frequency, and number of milling balls were explored.

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An Alternative Solvent-Free Synthesis of Nopinone under Ball-Milling Conditions: Investigation of Reaction Parameters

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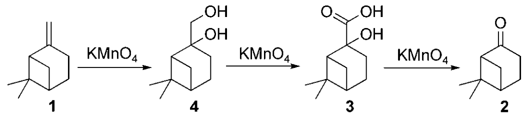
A new method for the oxidative cleavage of β-pinene (**1**) yielding nopinone (**2**) with potassium permanganate as oxidant under solvent-free conditions was established. The reaction was performed in a conventional ball mill with use of a grinding auxiliary. The auxiliary has the ability to sorb liquid reactants such as **1** on its surface to make liquid(s) accessible for mechanical impact. Different reaction parameters and technical variables were assessed concerning their influence on yield and selectivity of **2**. Different chemical parameters such as oxidants, grinding auxiliaries, and quantities were investigated. Also tuning parameters including milling time, rotation frequency, and number of milling balls were explored.

Introduction

The synthesis of nopinone (**2**) through the oxidation of β-pinene (**1**) with potassium permanganate in aqueous media is well-known, reported for the first time by Wallach in 1900.[1] However, the main product is the sodium salt of nopinic acid (**3**); the reaction yields only 2% of **2** as side product (Scheme 1). Consistent with the ability of $KMnO_4$ to form vicinal diols from alkenes, it is speculated that the reaction runs through pinene-2,10-diol (**4**) as intermediate, which is then oxidized to form **3**. Finally, this carboxylic acid undergoes decarboxylation, and dehydration of the remaining geminal diol affords **2** in the presence of $KMnO_4$.[2] It is known today that the selectivity for **2** is increased in the presence of different solid supports, such as aluminum oxide or cation exchange resins, resulting in yields of up to 95%.[3]



Scheme 1. Oxidation of β-pinene (**1**) with $KMnO_4$ to nopinone (**2**) according to Wallach.[2]

Another established method for the synthesis of **2** is the ozonolysis of **1**. In 1909 Harris et al. treated turpentine with ozone and noticed small amounts of **2**, besides **3**.[4] The work of Criegee et al. established ozonolysis as a common procedure in organic chemistry for the synthesis of carbonyls from alkenes.[5] Based on his work, the formation of **2** with retention of optical activity and in moderate yields (ca. 70%) was reported.[6] Starting from **1**, this procedure was further advanced leading to a selective synthetic procedure for **2** accompanied by high yields.[7] Nevertheless, expensive equipment and extreme reaction conditions (low temperatures and long reaction times, while there is an explosion hazard) are necessary to guarantee the success of the reaction.

Therefore, since the beginning of the 1990s another procedure has been gaining interest among synthetic chemists. In the presence of transition-metal compounds such as ruthenium(III) chloride and osmium(VIII) oxide, it is possible to use sodium periodate as oxidant to convert **1** into **2** with yields up to 70% and excellent selectivities.[8] Nowadays, oxidation agents such as H_2O_2 or O_2 are also suitable for this reaction, in connection with $RuCl_3$ or OsO_4.[9] Furthermore, highly functionalized iron, vanadium, and manganese complexes offer the possibility to use H_2O_2 and O_2 as oxidants.[10] With regard to the reaction conditions, long reaction times (up to 20 h), harmful solvents (CH_2Cl_2, CCl_4), and toxic metal compounds (OsO_4) are still necessary to obtain good yields.

These facts prompted us to investigate $KMnO_4$ as oxidant for the synthesis of **2**. Reactions with $KMnO_4$ as oxidant are normally performed in aqueous conditions. However, earlier work by our group on the oxidative cleavage of **1** has shown that it is possible to work under solvent-free conditions.[11] The reaction was performed with $KMnO_4$ under solvent-free conditions in a planetary ball mill. After a milling time of only 20 min, 56% of **2** (25 mmol!) was isolated in enantiomerically pure form (by column chromatography). Under solvent-free conditions, the C–C double bond in **1** is cleaved by treatment

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with $KMnO_4$ in a planetary ball mill and in the presence of a grinding auxiliary. The auxiliary is necessary for milling processes that employ liquid substrates. It acts as a "solid solvent," whereby the liquid flows into the space of the grinding auxiliary particles.

However, the described procedure was not optimized and the yield of **2** was rather low. Furthermore, a two-component reaction is an ideal model for the evaluation of reaction parameters in solvent-free oxidation reactions. Based on these considerations, the present work is aimed at an improved understanding of this new sustainable synthetic route affording **2**.

The use of mechanical energy as input to perform chemical reactions is becoming more and more common in chemical research.[12] Recently, scientists have been confronted with the necessity of a step-by-step analysis of different parameters to obtain reproducible results.[12b,c,h,j,m,n] Variables such as the rotation frequency (ν_{rot}), milling time (t), and variations in the milling beaker and ball size or material can be summarized as mechanical parameters. Chemical parameters are the type of oxidant, as well as the molar or weight ratios of **1** (n_1), $KMnO_4$ (n_{ox}), and of the grinding auxiliary (m_{aux}) to each other. In this work the oxidative cleavage of **1** to **2** with $KMnO_4$ was adopted as model reaction to show the influence of the different parameters mentioned above to the conversion of **1** (X_1) and yield and selectivity of **2** (Y_2 and S_2, respectively).

Results and Discussion

Compared to literature results on the solvent-free synthesis of nopinone (**2**) from β-pinene (**1**) on a scale of 44 mmol,[11] a downscaling to 2 mmol is appropriate for the assessment of chemical and mechanical reaction parameters. This, at first sight, contradictory approach for parameter evaluation was chosen to enable the variation of many more parameters than would be possible in large-scale experiments. It is also more appropriate, from an ecological and economic perspective, to optimize a reaction on a smaller scale and make use of the conclusions of such experiments to up-scale a reaction. The literature procedure for solvent-free nopinone synthesis is not optimized and strictly oriented on product purity, and not on yield, selectivity, or energy efficiency.[11] The reactions were performed in a planetary micro mill, in milling beakers ($V = 45$ mL) made from zirconium oxide ($\rho = 6.5\ g\,cm^{-3}$) that were, if not mentioned otherwise in the text, equipped with six milling balls ($d = 15$ mm) of the same material. The ball mill was limited to a maximum rotation frequency ($\nu_{rot,max}$) of 800 min^{-1} ($\equiv 13.3$ Hz).

The grinding of liquids can be performed by prefreezing the reaction mixture below the eutectic melting point (liquid N_2). From an economical point of view this method is rather disadvantageous and the high mechanical stress during the milling process results in a fast heat-up of the mixture. Thus, auxiliary grinding is advantageous over prefreezing. Two different grinding auxiliaries were compared: aluminum oxide and quartz sand (SiO_2). If not otherwise indicated "alumina (Al_2O_3)" refers to acidic α-Al_2O_3 for chromatography, purchased from Fluka with a particle size between 0.063–0.2 mm (purity $>95\%$). If not otherwise stated "quartz sand (SiO_2)" refers to crude, calcinated SiO_2 (purity $>95\%$) for cleaning of platinum crucibles, purchased from Sigma–Aldrich. Both materials differed in their particle sizes, bulk densities, and surface characteristics.

These parameters are important for the grinding process and will allow fine-tuning of the reaction parameters X_1, Y_2, and S_2.[13] At the beginning a screening with different amounts of $KMnO_4$ was performed with different rotation frequencies. Due to $\nu_{rot,max} = 800\ min^{-1}$, the parameter screening started at $\nu_{rot} = 400\ min^{-1}$ to allow an up- or down-scaling of this variable. The absolute amount of $KMnO_4$ (n_{ox}) was varied from 0–6 mmol, whereby the masses of **1** ($n_1 = 2$ mmol) and of the grinding auxiliary ($m_{aux} = 3.8$ g) were kept constant. As shown in Table 1, a large excess of $KMnO_4$ and high ν_{rot} were necessary to achieve high yields of nopinone (Y_2).

Table 1. Screening of $KMnO_4$ concentration (n_{ox}) at different rotation frequencies (ν_{rot}) in the presence of alumina and quartz sand as grinding auxiliaries for the solvent-free synthesis of nopinone (**2**) from β-pinene (**1**).[a]

		Grinding auxiliary[b]			
		Al_2O_3		SiO_2	
n_{ox} [mmol][c]	ν_{rot} [min^{-1}]	Y_2	S_2	Y_2	S_2
0	400	0%	–	0%	–
0.5	400	8%	67%	2%	50%
1	400	14%	61%	6%	46%
2	400	25%	67%	8%	53%
4	400	49%	69%	36%	68%
6	400	44%	73%	15%	65%
6	600	72%	90%	60%	73%
6	**800**	**79%**	**95%**	**89%**	**91%**
6[d]	–	27%	73%	5%	33%

[a] Batch per beaker: 3.8 g grinding auxiliary, 2 mmol **1**, 0.1 g water; Ball milling: 2 milling beakers (ZrO_2, $V = 45$ mL), 6 milling balls (ZrO_2, $d = 15$ mm) per beaker, $t = 10$ min. [c] Oxidant: $KMnO_4$. [b] Yield (Y_2) and selectivity of nopinone (S_2). [d] Experiment performed with mortar and pestle.

With both raising n_{ox} and increasing ν_{rot}, the selectivity of nopinone (S_2) reached maximum values of 95 and 91% for Al_2O_3 and SiO_2 as grinding auxiliaries, respectively. Accordingly, also Y_2 can be maximized to 79 and 89%. When performing the reaction as simple grindstone chemistry, using mortar and pestle, the default batch furnished 27% of **2** ($S_2 = 73\%$) in the presence of Al_2O_3 after a grinding period of 10 min. With SiO_2 as auxiliary only 5% of **2** ($S_2 = 33\%$) was obtained under equivalent conditions.

Interaction of milling time and rotation frequency

The screening experiment has shown the correlation between rotation frequency (ν_{rot}) and the yield of nopinone (Y_2). Accordingly, with a constant batch the following results were obtained by variation of both ν_{rot} and the milling time (t).

As shown in Figure 1 and as expected, Y_2 rises along the x-axis (ν_{rot}) from the left to the right and along the z-axis (t) from the front to the back, independent of the grinding auxiliary. In

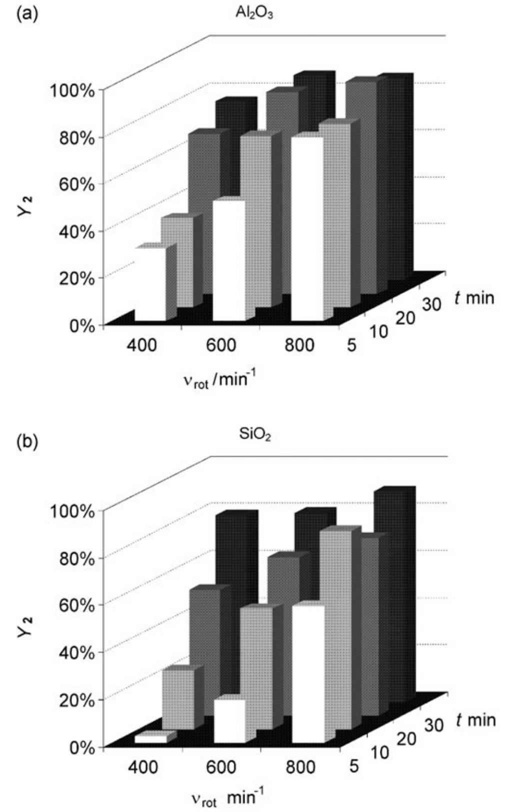


Figure 1. Influence of rotation frequency (ν_{rot}) and milling time (t) on the yield of nopinone (Y_2) from the oxidation of β-pinene (**1**) with a) alumina and b) quartz sand as grinding auxiliaries.

case of SiO_2 the influence of ν_{rot} is higher than observed for experiments with Al_2O_3. The increase of Y_2 along the x-axis seems to proceed linearly for silica and exponentially for alumina. Generally, the decline increases while either increasing ν_{rot} or t. In the case of Al_2O_3 this means that when leaving ν_{rot} constant at 800 min^{-1}, the yield increases less by a prolonged milling time than observed at a lower ν_{rot} of 400 min^{-1}. When keeping t constant, the conclusions for variation of ν_{rot} are vice versa. Considering finally the diagonal increase, a stronger variation of Y_2 is observed for SiO_2 than for comparable experiments with Al_2O_3 as grinding auxiliary. Y_2 increases from 30% ($\nu_{rot}=$ 400 min^{-1}, $t=5$ min) to 90% ($\nu_{rot}=800$ min^{-1}, $t=30$ min) and from 10 to 80% in case of Al_2O_3 and SiO_2 as the auxiliary, respectively. Similar correlations between milling time and/or frequency (rotation, oscillation, vibration) have been described recently for the Suzuki–Miyaura reaction,[12b,c] domino oxa-Michael aldol reaction,[12j] reactions of 1,3-dicarbonyls with chalcones,[12m] organocatalysis,[14] dehydrogenation,[15] and Knoevenagel condensations.[16] This effect is also known from other processes performed in ball mills (e.g., alloying, polymer grafting).[17]

Number of milling balls

The manufacturer of the ball mill advised to use a minimum of 2 milling balls for grinding. Using 1 milling ball only would cause extreme material abrasion and will result in destruction of the milling ball and the milling beaker. Furthermore, the manufacturer suggests a volume ratio of balls, grinding material, and free space of 1:1:1. The free space is important for the trajectories of the milling balls and for the energy transfer. To assess the influence of the milling balls, their number (n_{balls}) was varied between 2 and 7. Both, the conversion of **1** (X_1) and the selectivity of **2** (S_2), were affected by n_{balls} and the ratio of volume balls to volume beaker [V_{balls}/V_{beaker}; Equation (1)], as shown in Figure 2.

$$\frac{V_{balls}}{V_{beaker}} = n_{balls} \times \frac{m_{ball}}{V_{beaker} \times \rho_{ZrO_2}} \tag{1}$$

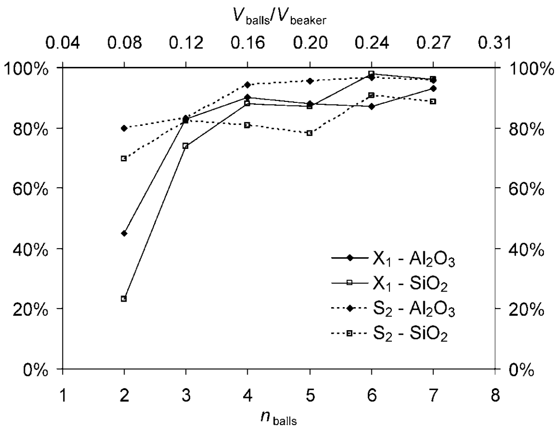


Figure 2. Effect of the number of milling balls (n_{balls}) on the conversion of β-pinene (X_1) and the selectivity of nopinone (S_2) in the solvent-free oxidation of β-pinene (**1**).

Regarding the X_1, the greatest difference can be found between 2 and 3 milling balls, independent of the grinding auxiliary (Figure 2). In the case of Al_2O_3, X_1 rises from 40 to 80% when increasing the number of milling balls from 2 to 3. Further addition of milling balls leads to smaller changes in X_1. With 7 milling balls, a maximum conversion of 90% was achieved. Starting with 3 milling balls, S_2 rises from 80 to 90% during the addition of milling balls up to 7. For SiO_2 the effect of more milling balls on X_1 is a little more pronounced. Starting with 2 milling balls, an increase of 20 to 70% was observed, when n_{balls} is increased to 3. Within further addition of milling balls to a number of 7, X_1 reaches up to 90%. The changes in selectivities are less pronounced, varying between 70 and 80%. The increase of X_1 was as expected, considering the relationship between mass and energy. While the amount of the reaction mixture was kept constant, the total mass of the balls rises continuously. Hence, more energy is transferred by impact and friction of the balls on the ground material.[12c,15] Interestingly, higher conversions are accompanied by a rise of nopinone selectivity (S_2). The formation of byproducts is obviously favored by lower n_{balls} going along with a lower level of kinetic energy. Thus, the activation energy for side-product formation is lower than for the complete oxidative cleavage of the C=C double bond in **1**. For optimal conditions a number of milling balls (n_{balls}) between 4 and 7 ($d=15$ mm) for a beaker volume of 45 mL is necessary (Figure 2).

Influence of the milling material

For grinding experiments, different materials for the milling beakers and milling balls can be employed. Usually ZrO_2 is used as milling material due to its chemical stability towards oxidants such as $KMnO_4$ and its mechanical properties (e.g., abrasion). Compared to the density of other materials such as agate (SiO_2; $\rho=2.65\ g\,cm^{-3}$) or sintered corundum (Al_2O_3; $\rho=3.8\ g\,cm^{-1}$), the density of zirconium oxide ($\rho=5.9\ g\,cm^{-3}$) is high.[18] Thus, the energy input into the mill material is high, which should in consequence lead to higher conversion.[12a,17] Contrarily to stainless or hardened steel, these three materials are chemically inert to $KMnO_4$. Accordingly, they were assessed for their usability for the oxidative cleavage of **1**. Even when taking into account that hardened steel is not inert against oxidizing agents, it is interesting because of its high density ($\rho=7.9\ g\,cm^{-1}$).[18] Therefore, the reaction was also carried out with milling beakers made from hardened steel. The results are summarized in Figure 3.

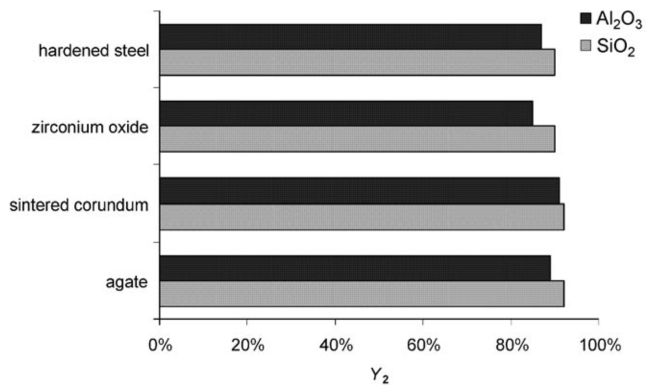


Figure 3. Different milling materials (beaker and balls) and their effect on the yield of nopinone (Y_2) by solvent-free oxidation of β-pinene (**1**).

Surprisingly, no significant differences were observed when applying different grinding materials. This results are in accordance with similar experiments concerning Suzuki–Miyaura reactions at $\nu_{rot}\geq 400$ rpm.[12c] The material with the highest density, hardened steel, furnishes the same yield of nopinone (Y_2) as agate with the lowest density. The difference between the grinding auxiliaries Al_2O_3 and SiO_2 is a mere 5%. Nopinone selectivities (S_2) of 95 and 93% are achieved with Al_2O_3 and SiO_2 as grinding auxiliaries, respectively. Overall, the previous experiments have shown that Y_2 can increase up to a maximum of 90%. Longer milling times (t), higher rotation frequencies (ν_{rot}) or heavier materials revealed no significant improvements in Y_2, comparing the results with the standard approach listed in Table 1. Notwithstanding that quantitative conversion is possible, the occurrence of byproducts limits the product selectivity to a maximum of 95%. This deficiency could be further remedied by variation of chemical parameters such as grinding auxiliary, oxidation agent, and ratio of the different reaction compounds.

Variation of the grinding auxiliary

As mentioned above, when grinding a liquid substance it is necessary to sorb it with a suitable grinding auxiliary. Without such auxiliaries, the energy transfer from the milling balls to the grinding material is hampered. Instead of a solid mixture, a mud-like mixture would be formed with different texture and mechanical properties, which does not allow inelastic interaction between balls and substances. Thus, the efficiency of the energy transfer is strongly reduced, due to lower power of resistance of the fluid-like dispersions. Without a grinding auxiliary, no conversion of **1** was observed when the standard approach was ground for 10 min at $\nu_{rot}=800\ min^{-1}$. Finally, it can be stated that the grinding aid assumes the functions of a "solid solvent." On the one hand, it provides good milling conditions, on the other hand, it ensures that heat is transferred to, and removed from, the reaction mixture.

The grinding auxiliaries that were used in this work are well-known as solid supports in heterogeneous catalysis.[19] For more information about the properties of the aluminas and silicas the reader is referred to Table S1 (Supporting Information). We investigated three different kinds of Al_2O_3, differing in their surface-pH value (basic, γ-Al_2O_3; neutral, γ-Al_2O_3; and acidic, α-Al_2O_3; Figure 4). The acidic Al_2O_3 was used beside quartz sand (SiO_2) as standard grinding auxiliary. Grinding experiments with the aluminas showed similar conversions up to 90% in accordance to previous studies.[13] Even the differences in the yields are insignificantly low. Even so, with the acidic Al_2O_3, the highest yield ($Y_2=87\%$) was achieved. The other two differ by just 3% of this value.

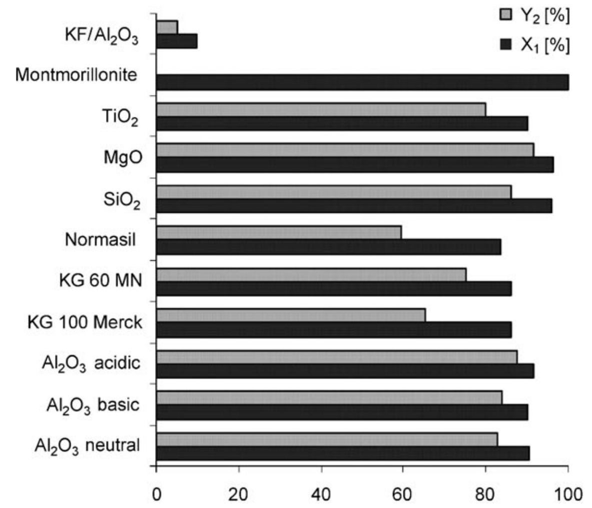
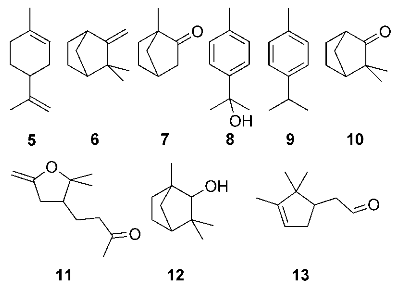


Figure 4. Effect of different grinding auxiliaries on the conversion of β-pinene (X_1) and the selectivity of nopinone (S_2) in the solvent-free oxidation of β-pinene (**1**)

Secondly, the influence of different varieties of silica (KG 100 Merck, KG 60 MN, and Normasil; see Table S1) was tested. As a special modification of silicon oxide, quartz sand (indicated as SiO_2 in the text) was compared to silica. As shown in Figure 4, SiO_2 is the best-suited grinding auxiliary compared to other varieties of silica ($Y_2 = 90\%$). The individual silicas provided yields between 60 and 70 %. Compared to the aluminas, the conversion of β-pinene (X_1) is even higher in case of quartz sand (SiO_2). Despite the higher conversion, the product yield is on the same level for SiO_2 ($Y_2 = 90\%$) as for the aluminas. Consequently, the selectivity of **2** (S_2) is lower for SiO_2, than for Al_2O_3. The other varieties of silicas provide Y_2 of approximately 85 %.

Finally, magnesium oxide (MgO), titanium oxide (TiO_2), Montmorillonite, and a mixture of potassium fluoride on alumina (KF/Al_2O_3; $w_{KF} = 40$ wt %) were employed as grinding auxiliaries.[14,19] In terms of results, MgO ($X_1 = 95\%$, $Y_2 = 90\%$) is comparable to SiO_2, pointing out the similar surface characteristics of those oxides. In case of TiO_2, the resulted X_1 and S_2 of 90 and 85 %, respectively, are similar to the results achieved with Al_2O_3. However, with respect to economic issues the application of Al_2O_3 is advantageous over the employment of MgO or TiO_2.

It is well known that Montmorillonite is able to isomerize or dimerize terpenes such as α- or β-pinene (**1**), which is due to its acidic character.[20] As can been seen in Figure 4, X_1 is nearly quantitative when using $KMnO_4$ on montmorillonite as oxidant and grinding auxiliary. In contrast, no **2** was found during the whole milling process. From GC-MS analysis it can be stated that primarily compounds arise that indicate an acid-catalyzed rearrangement of **2**, followed by an oxidation of these rearranged compounds. The major isomerization products of **1** in the presence of montmorillonite are limonene (**5**) and camphene (**6**) (Scheme 2).[21] In the presence of $KMnO_4$, we were not able to find **5** or **6**. As main product camphor (**7**) was obtained in 38 % yield. Furthermore, *p*-cymene-α-ol (**8**; $Y = 18\%$), camphenilone (**10**; $Y = 13\%$), *p*-cymene (**9**; $Y = 5\%$), and cyclic ether (**11**; $Y = 15\%$) have been identified. These are interesting results which should be aim of another work, but finally Montmorillonite is not suitable for the oxidative cleavage of **1** leading to **2**.



Scheme 2. Isomerization and oxidation products of β-pinene (**1**) in the presence of montmorillonite with $KMnO_4$ as oxidant (**5**–**11**) and in the presence of Al_2O_3 with Oxone as oxidant (**12**–**13**).

In the last years KF/Al_2O_3 has become a famous base for a great diversity of chemical reactions, mainly under solvent-free conditions.[22] It is known that in basic environment the permanganate ion (MnO_4^-) reacts to the green manganate ion (MnO_4^{2-}) in the presence of reducing agents.[23] This is consistent with the observation that the reaction mixture turns green after grinding **1** with $KMnO_4$ in the presence of KF/Al_2O_3 (cf. Figure S1 in the Supplementary Information).

The standard reduction potentials (E_0) of MnO_4^- at pH 0 and 14 (Table 2) can explain the behavior of KF/Al_2O_3. Because of the high oxidation potential ($E_0 = +2.09$ V) of Equation (3) at pH 0, the stability of the green MnO_4^{2-} is low in an acidic environment. Therefore, the MnO_4^- reacts directly to brown MnO_2. In a basic environment, all reaction steps of the MnO_4^- ion [Equations (2–4)] have nearly the same E_0. In this case the reaction rate from MnO_4^{2-} to MnO_2 is slow enough that the green MnO_4^{2-} can be found.

Table 2. Standard reduction potentials for various oxidation states of the permanganate ion.[24]

Reaction		E_0 [V], pH 0	E_0 [V], pH 14
$MnO_4^- + e^- \rightarrow MnO_4^{2-}$	(2)	+0.90	+0.564
$MnO_4^{2-} + 2e^- + 4H^+ \rightarrow MnO_2 + 2H_2O$	(3)	+2.09	+0.60
$MnO_4^- + 3e^- + 4H^+ \rightarrow MnO_2 + 2H_2O$	(4)	+1.695	+0.588

The formation of MnO_4^{2-} from MnO_4^- expends only one electron. Therefore, we suspect that one electron per MnO_4^-, together with the low oxidation potential, inhibits the oxidative cleavage of **1**. In fact only low conversions and yields ($X_1 = 10\%$, $Y_2 = 5\%$; Figure 4) can be achieved. With these experiments we have shown that the low-cost grinding auxiliaries Al_2O_3 and SiO_2 are most suitable for the oxidative cleavage of **1**. Subsequently, the influence of various oxidants to conversion and yield of the oxidative cleavage of **1** has been investigated.

Effect of oxidants

A selection of oxidants, mainly inorganic ones, was examined for their applicability for the oxidative cleavage of β-pinene (**1**) affording nopinone (**2**). The influence of the oxidant on the conversion of **1** (X_1) and the yield of **2** (Y_2) is summarized in Figure 5. The results are sorted by Y_2 from up (low yields), to down (high yields). In this case $KMnO_4$ seems to be the most suitable oxidant for the reaction (Scheme 1). With both grinding auxiliaries (Al_2O_3 and SiO_2), high conversions ($X_1 \approx 95\%$) together with high yields ($Y_2 \approx 90\%$) were obtained. When comparing $KMnO_4$ to the homologue alkali compound sodium permanganate monohydrate ($NaMnO_4 \cdot H_2O$), considerably better yields were obtained with the former. The latter provided Y_2 of 65 % independent of the grinding auxiliary. In case of SiO_2, Y_2 is 10 % higher than with Al_2O_3 ($Y_2 = 70\%$), which indicates a lower S_2.

The results with potassium manganate (K_2MnO_4) support the statements regarding the application of KF/Al_2O_3 as grinding auxiliary in the last section (Figure 4, Figure S1). In the case of the acidic alumina (Al_2O_3), the yields are still higher than with SiO_2, where almost no X_1 was observed. However, in the overall

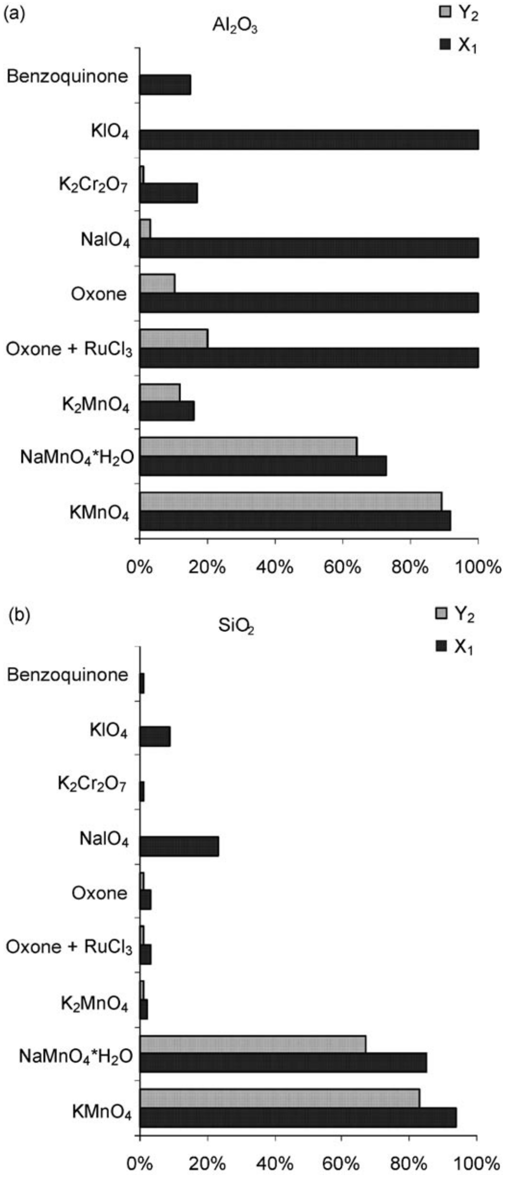


Figure 5. Influence of oxidants on the solvent-free conversion of β-pinene (X_1) and the yield of nopinone (Y_2) employing a) alumina and b) quartz sand as grinding auxiliary.

comparison both deliver poor results. This point out the strong pH-dependency of the oxidation potential of manganate species (Table 2): Even the higher surface acidity of the applied alumina is sufficient to induce a significant higher reactivity than for the neutral silica.

Another well-known and established mild oxidant in organic chemistry is Oxone,[12i,25] which is also known as triple-salt. It is composed of 2 $KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, and able to react with alkenes in the presence of $RuCl_3$ under oxidative cleavage of the C=C double-bond.[26] We tried to work both with and without $RuCl_3$ as catalyst. As shown in Figure 5, without $RuCl_3$ the results between Al_2O_3 and SiO_2 are completely different. With Al_2O_3, a nearly quantitative conversion of **1** appears, but only 10% of desired **2** can be found. The remaining 90% of the products consisted of a mixture of fenchol (**12**; $Y = 7\%$), campholenal (**13**; $Y = 5\%$), and of 50 more unidentified substances (Scheme 2). By contrast, with SiO_2 as grinding auxiliary neither conversion of **1** nor yield of **2** was observed. The experiment was repeated with $RuCl_3$ as catalyst. In the presence of 3.5 mol% $RuCl_3$, the yield of **2** increased to 20%, which is unsatisfactory.

Employing sodium and potassium periodate ($NaIO_4$ and KIO_4) as oxidants results in similar conclusions. With Al_2O_3 as auxiliary X_1 is nearly quantitative, while only small amounts of **2** were identified. The product mixture mainly consists of different oxidized ring-opening products of **1**. In case of SiO_2 as grinding auxiliary, only small conversions of **1** and no **2** can be found. With Al_2O_3 as grinding auxiliary and potassium dichromate ($K_2Cr_2O_7$) or benzoquinone as the oxidizing agents, X_1 is 20%, while no **2** was found. In case of SiO_2 absolutely no conversion occurred, and thus no products could be identified.

By comparing the results of different auxiliaries it is obvious that Al_2O_3 is more reactive than SiO_2. It has long been known that the support material has an effect to the selectivity and the reactivity of the oxidant.[27] Lee et al. attributed this difference on the one hand to the ability of a carrier to absorb water, and on the other hand to its Lewis acidity.[28] In the following section, this is examined in more detail by adding different amounts of water to the grinding auxiliary.

Influence of water

Nüchter et al. reported that small amounts of water have a positive effect on different oxidation reaction with $KMnO_4$ under solvent free conditions.[29] This statement is supported by the works of Lee et al. who compared the reactivity of permanganate in the presence of moist Al_2O_3 and bentonite (aluminum phyllosilicate). With bentonite no reaction was observed, whereby with Al_2O_3 oxidative cleavage appeared.[27] Therefore, we have examined the influence of different amounts of water on the yield and selectivity of nopinone (Y_2 and S_2; Figure 6) below.

Without additional water, high S_2 (ca. 90%) but low Y_2 (Al_2O_3: 65%; SiO_2: 55%) were observed. Independent of the grinding auxiliary, the addition of water leads to an increase of X_1 up to a quantitative level. By contrast, S_2 decreases rapidly,

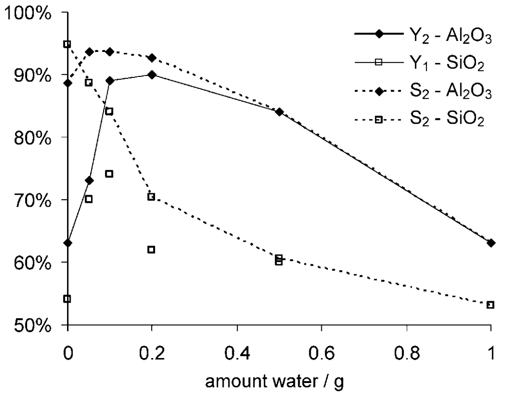
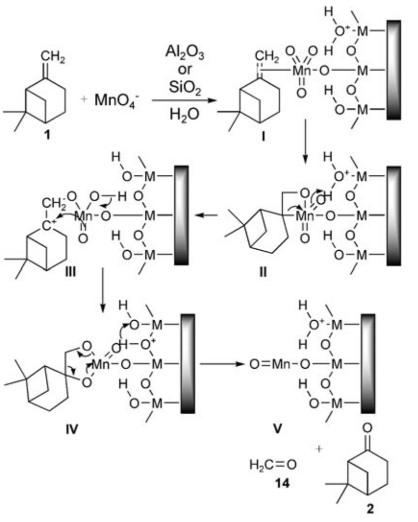


Figure 6. Influence of water on yield and selectivity of nopinone (Y_2 and S_2).

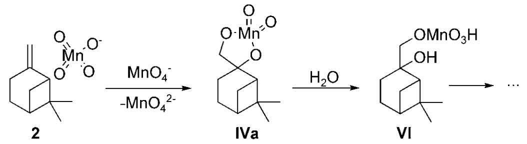
which has a negative effect on Y_2. With 0.1 g water an optimum of Y_2 can be found at 75% with SiO_2. Using Al_2O_3, the optimum is at 0.2 g water and $Y_2 = 90\%$. If too much water is added to the reaction mixture, Y_2 and S_2 decrease. The reason can be found in the principle of *hard* and *soft* acids and bases.[30] The polar strength of the grinding auxiliary is rather weak, like that of water. Permanganate is classified based on the free ion charge as hard. Therefore, preferably water is deposited on grinding auxiliary. If the amount of water is too large, no permanganate is able to deposit on the auxiliary. Finally, the oxidant is not activated for the oxidative cleavage.

Nevertheless, small amounts of water are necessary. It is assumed that water and the MnO_4^- ion are added to the surface of the grinding auxiliary.[28,31] The MnO_4^--ion is now activated and therefore able to coordinate the C–C double bond of **1**, forming a π-complex (**I**, Scheme 3). Subsequently, **I** shifts via the metallaoxetane (**II**) to the cyclic manganate(V) ester (**IV**). The formation of **IV** requires cleavage of the C–Mn bond followed by generation of a C–O bond via transition state **III**. Probably, Al_2O_3 is able to support this reaction step because of its Lewis-acidity.[27] Nevertheless, SiO_2 seems likely to support the formation of **III** and **IV**. Finally, the cyclic ester **IV** rearranges to **2**, formaldehyde (**14**), and the manganate(IV) intermediate **V**, which on hydrolysis afforded MnO_2. As shown in Scheme 3 the presence of water is necessary to generate **III**. Nevertheless, also without water small amounts of **2** can be formed (Figure 6). The reason is that the used substances and auxiliaries for the reaction were not dry. Therefore, a basic amount of water in the reaction mixture is always present, which can be related to the observed yields of 60%.



Scheme 3. Oxidative cleavage of β-pinene (**1**) with $KMnO_4$ and a grinding auxiliary (M = Al, Si) under ball-milling conditions with reference to Lee et al.[28]

As already mentioned above, the formation of **2** by ball milling of **1** with $KMnO_4$ in the presence of a grinding auxiliary is completely different to permanganate oxidation in aqueous solutions. The early works of Wallach indicated the formation of nopinic acid (**3**) as main product in solution.[2] This can be explained by the works of Dash et al.[23] Hereby, intermediate **IVa** (Scheme 4, comparable to intermediate **IV** in Scheme 3) seems to be unstable in aqueous solution. Rather than a rearrangement of the cyclic manganate(V) ester, a ring opening by the addition of water is supposed. The generated transition state (**VI**) is starting point for the formation of compounds represented in Scheme 1.



Scheme 4. Oxidative cleavage of β-pinene (**1**) with $KMnO_4$ in aqueous solution with reference to Dash et al.[23]

Although Scheme 3 seems to be very conclusive, we were not able to detect **14** with GC-FID or GC-MSD. The total oxidation of **14** affording CO_2 and water is as possible as the formation of formic acid (HCOOH). However, the authors believe that consecutive oxidation products of **14** are rather the potassium salts (K_2CO_3, $KHCO_3$, HCOOK; or aluminate species) than the free acids. Under these conditions, completely different hypothetic reaction equations seem plausible (Table 3), which require different ratios of oxidant to **1** (n_{ox}/n_{1},).

Table 3. Possible reaction equations of the oxidative cleavage of β-pinene, regarding to the oxidation products

Reaction		n_{ox}/n_1
$8\,KMnO_4 + 3\,C_{10}H_{16} \rightarrow$ $8\,MnO_2 + 3\,C_9H_{14}O + 3\,K_2CO_3 + 2\,KOH + 2\,H_2O$	(5)	$8:3 \approx 2.67$
$2\,KMnO_4 + C_{10}H_{16} \rightarrow 2\,MnO_2 + C_9H_{14}O + HCO_2K + H_2O$	(6)	$6:3 = 2.00$
$4\,KMnO_4 + 3\,C_{10}H_{16} \rightarrow 4\,MnO_2 + 3\,C_9H_{14}O + 3\,HCHO + 2\,K_2O$	(7)	$4:3 \approx 1.33$
As found ideal:		$6:2 = 3.00$

Comparing the ratios of Equations (5–7) with the experimentally approved ratio n_{ox}/n_1 of 3 (Table 1) we expected that Equation (5) fits best. This is also consistent to the fact that neither formic acid (HCOOH) nor formaldehyde (**14**) could not been found. Another supporting fact is the absence of $KMnO_4$ after ball milling. By quenching the reaction mixture with water after ball milling, no violet coloration of the aqueous solution, due to excess $KMnO_4$, was observed. This observation may attribute to a self-decomposition of $KMnO_4$ to manganese oxide (MnO_2) and oxygen [O_2; Equation (8)].[22]

$$4\,KMnO_4 + 2\,H_2O \rightarrow 4\,MnO_2 + 4\,KOH + 3\,O_2 \tag{8}$$

In this case, the generation of gas during ball milling should have occurred, which was not the case. Nevertheless, the great amounts of $KMnO_4$ are unavoidable for proper results. And yet, no further regeneration of the reaction mixture by reducing excess $KMnO_4$ is necessary.[31] Compared to other works, it is known that solvent-free oxidations with $KMnO_4$ in ball mills require high excess of $KMnO_4$.[11,29] As said above and, if not otherwise mentioned in the text, a ratio of $KMnO_4$ to **1** of $n_{ox}/n_1 = 3:1$ ($n_{ox} = 6$ mmol; $n_1 = 2$ mmol) was adopted as standard batch.

There is another positive influence from the addition of water. Without water the reaction mixture became hard and acted as sintered. Only with a hammer it was possible to obtain the mixture from the milling beaker. With 0.1 g of water the reaction mixture can easily be poured out of the milling beakers. For this reason and because water is necessary for good results, 0.1 g water was always added to the reaction mixture before treatment in the ball mill.

Variation of the oxidant-to-substrate ratio

Different quantities of $KMnO_4$ (n_{ox}) were investigated at different rotation frequencies (ν_{rot}), whereby the amount of β-pinene (n_1) remained constant at 2 mmol. For further experiments n_{ox} remained constant at 6 mmol and n_1 was varied between 1 and 10 mmol. This is equivalent to a ratio of **1** to $KMnO_4$ (n_1/n_{ox}) of 1/6 to 10/6, respectively. The mass of the grinding auxiliary (m_{aux}) was kept constant for these experiments. The results are shown in Figure 7.

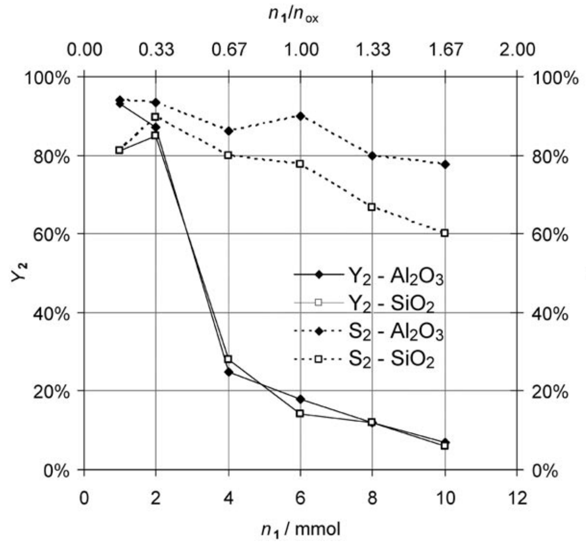


Figure 7. Influence of the ratio β-pinene (**1**) to $KMnO_4$ (n_1/n_{ox}) on the yield and selectivity of nopinone (Y_2 and S_2) within the solvent-free oxidation of β-pinene (**1**) employing Al_2O_3 or SiO_2 as grinding auxiliary.

Both grinding auxiliaries showed approximately the same behavior. Yields between 90 (Al_2O_3) and 80% (SiO_2) are observed when 1 mmol of **1** is grinded in the presence of 6 mmol $KMnO_4$. With increasing amounts of **1**, Y_2 first decreases sharply (until $n_1 = 4$ mmol) to 25%. At higher n_1 the decline is not as distinct as for $n_1 \leq 3$ mmol. Loss of conversion goes hand in hand with lower selectivities, S_2 decreasing from 90 (1 mmol) to 70% (10 mmol). The large loss of yield is due the fact that nonpolar **1** cannot be absorbed by the auxiliary grinding. As a result, with rising amounts of **1** the reaction mixture changes its texture to a mud-like consistency, rather than a free flowing powder at $n_1 \leq 3$ mmol. Finally, the energy input is not as high as a muddy reaction mixture can avoid the impact of the milling balls better. Less impact means less conversion and thus low yield. The optimum of the reaction was observed, when 2 mmol of **1** were grounded with 6 mmol $KMnO_4$, which is equivalent to molecular ratio of 1/3. The reaction time was about 10 min. Because of the unsatisfying results reported in Figure 7, the experiments were expended studying the influence of the milling time (t) on Y_2 (Figure 8) and S_2 (Figure 9).[12c,j,14,16,17] Thus, different amounts of β-pinene ($n_1 = 1$–8 mmol) were ground together with 6 mmol $KMnO_4$ for 5, 10, 20, and 30 min.

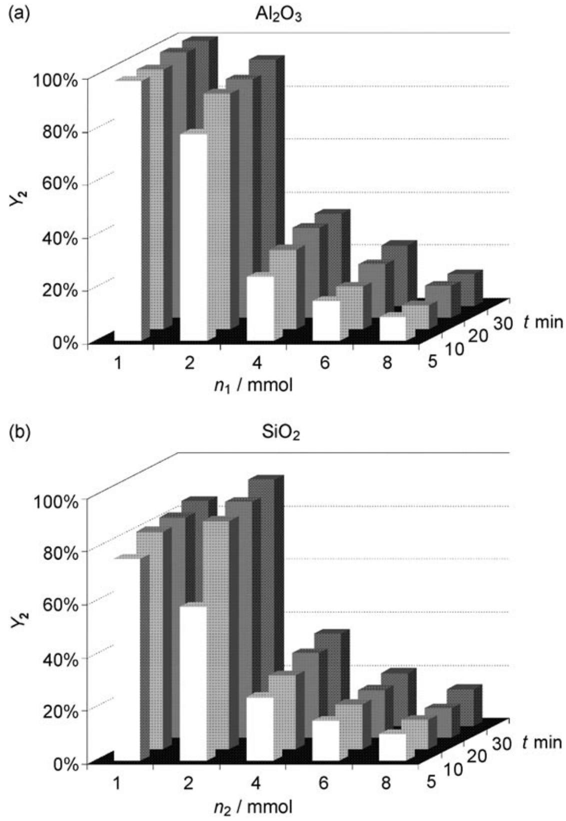


Figure 8. Correlation of nopinone yield (Y_2) with the milling time (t) and the amount of β-pinene (n_1) within the solvent-free oxidation of **1** employing a) Al_2O_3 or b) SiO_2 as grinding auxiliary.

As can be seen, Y_2 decreases in the case of Al_2O_3 along the x-axis (n_1) from a quantitative value to nearly 10%. As already suggested (Figure 7), the decrease in Y_2 is very strong between $n_1 = 2$–4 mmol. This observation can also be made with quartz sand (SiO_2). Along the x-axis, Y_2 decreases rapidly between n_1 of 2 mmol and 4 mmol. Contrarily to Al_2O_3, with SiO_2 the optimum of Y_2 along the x-axis can be found at $n_1 = 2$ mmol. Independent of the employed grinding auxiliary, along the z-axis an increase of the relative yields of **2** is observed when elongating t. Comparing the declines with each other, the decrease along the x-axis seems to be exponential, whereas the increase

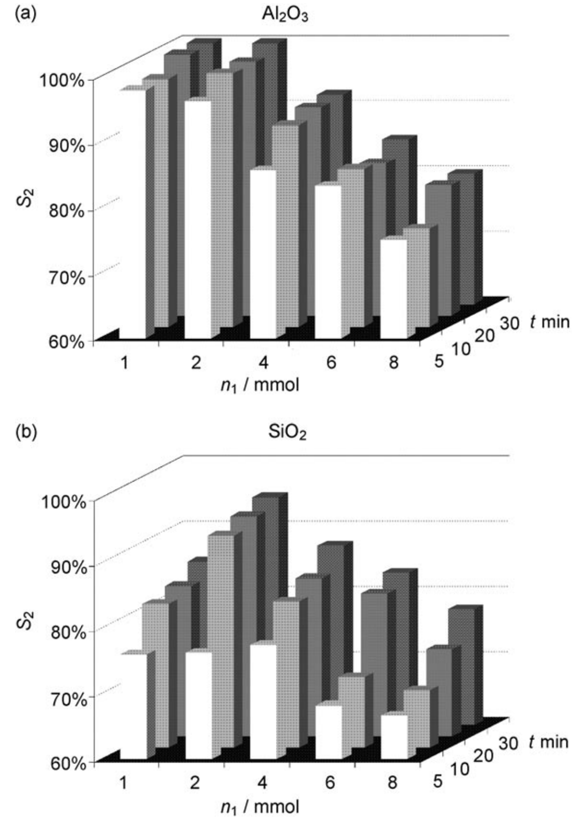


Figure 9. Correlation of nopinone selectivity (S_2) with the milling time (t) and the amount of β-pinene (n_1) within the solvent-free oxidation of **1** employing a) Al_2O_3 or b) SiO_2 as grinding auxiliary.

along the z-axis is linear. Finally, for SiO_2 the optimum of the reaction is at $n_1 = 2$ mmol and $t = 30$ min based on Y_2. In case of Al_2O_3 best results are obtained at $n_1 = 1$ mmol and $t = 30$ min. These results, regarding on Y_2, are comparable to selectivity of nopinone (S_2, Figure 9).

More interesting than the relative yield of nopinone (Y_2) is the absolute yield ($Y_{2,abs}$, Figure S2; cf. Supporting Information). The highest amount of **2** was obtained when using 2 mmol **1** with 6 mmol $KMnO_4$ at $t = 30$ min. With rising amounts of **2** and with a constant mass of grinding auxiliary $Y_{2,abs}$ decreases nearly linear below 1.0 mmol. This observation is due to the mudlike consistency mentioned above. Nonpolar **1** is not able to sorb on the surface of polar Al_2O_3 or SiO_2.

In case of Al_2O_3 as grinding auxiliary, at low quantities of **1** (≤ 2 mmol) S_2 reaches quantitative values (Figure 9). Starting at $n_1 = 4$ mmol, Y_2 decreases along the x-axis (n_1) from 95 to 75% ($t = 5$ min). Along the z-axis (t) Y_2 increases slightly. Regarding to S_2, best results were obtained at $n_1 = 1$ mmol and $t = 30$ min (close to 100% selectivity). Contrarily to Al_2O_3, with SiO_2 as grinding auxiliary the maximum of S_2 was obtained at $n_1 = 2$ mmol ($t = 30$ min). Starting with $n_1 = 1$ mmol, along the x-axis (n_1), S_2 increases and after reaching a maximum at $n_1 = 2$ mmol a significant decline is observed. Similar to the results shown in Figure 9, for Y_2 the selectivity also increases when elongating t, independent from the grinding auxiliary applied.

At the beginning of this article, the influence of amount of $KMnO_4$ (n_{ox}) and of rotation frequency (ν_{rot}) on both, yield and selectivity of nopinone (Y_2 and S_2) were investigated (Table 1). These basic experiments are now repeated under slightly changed experimental conditions. Instead of 400 min^{-1}, $\nu_{rot} = 800\ min^{-1}$ is used as default setting, since Figure 1 and Table 1 indicated this value as the most suitable. The experiments have been performed with constant amounts of β-pinene ($n_1 = 2$ mmol) and grinding auxiliary ($m_{aux} = 3.8$ g). The amount of $KMnO_4$ (n_{ox}) was varied from 0 to 10 mmol. This is similar to a variation in the ratio of n_{ox}/n_1 from 0.5 to 5 (Figure 10).

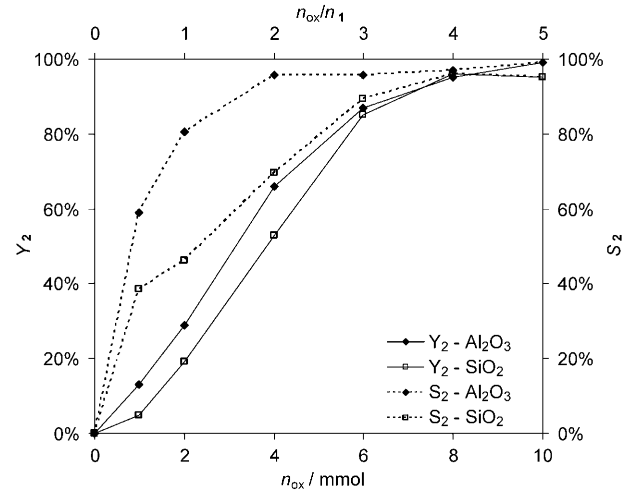


Figure 10. Influence of the amount of $KMnO_4$ (n_{ox}) on yield and selectivity of nopinone (Y_2 and S_2) during the solvent-free oxidation of β-pinene (**1**) with Al_2O_3 and SiO_2 grinding auxiliary.

Compared to the results presented in Table 1 ($\nu_{rot} = 400\ min^{-1}$), at higher rotation frequency of $\nu_{rot} = 800\ min^{-1}$, an increase of Y_2 and S_2 were observed. This is due to the fact of the enlarged energy input at higher ν_{rot}. With regarding to Figure 10, with Al_2O_3 as grinding auxiliary better results were obtained, compared to SiO_2. However, the differences are not as significant as reported for some parameter variation before (e.g., Figures 8 and 9). At $n_{ox} = 8$ mmol there was no further improvement in Y_2 when more oxidant was added. With both grinding auxiliaries, Y_2 up to 98% can be achieved, which are almost quantitative yields. As shown above [Equation (1)], the theoretical molar ratio of $KMnO_4$ to **1** is 4:3. With the experiment it is shown that a ratio of 8:2 is ideal for $t = 10$ min. This means, a high excess of $KMnO_4$ is necessary for quantitative yields. We have been working basically with $n_{ox} = 6$ mmol, because of the relatively small improvement of Y_2 between 6 and 8 mmol. However, it has been exemplified in Figure 8 and 9 that an increase of t is always accompanied with an increase of Y_2.[12c,j,14–17] Thus, high conversions are also possible with ratios of $KMnO_4$ to **1** below 3.

Amount of grinding auxiliary

As already noted, the grinding auxiliary is necessary to perform solvent-free reaction under ball milling condition with the presence of liquid reactants. Depending to the auxiliary, it is important to know, which ratio of n_{ox} and n_1 is necessary to obtain good results. Therefore, for the next experiment the ratio of $KMnO_4$ to **1** (n_{ox}/n_1) was kept constant at 6:2. Furthermore, the total mass of fractions m_1, m_{ox}, m_{water}, and m_{aux} were constant [5.1 g; Equation (9)].

$$m_1 + m_{ox} + m_{water} + m_{aux} = 5.1\ \mathrm{g} \tag{9}$$

As already mentioned, the grinding auxiliary can act as "solid solvent." It provides sufficient mass transfer in the reaction mixture and prevents the formation of by-products by heat transfer. This fact can be derived from Table 4. With an increasing proportion of auxiliary, Y_2 and S_2 are also increasing. With nearly no auxiliary, only small amounts of **2** can be found. For the grinding auxiliary Al_2O_3 the best results were obtained when using 3.5 g. SiO_2 has shown the same reactivity. This agrees well with our approach, in which we used 3.8 g of the respective grinding auxiliary.

Table 4. Influence of the amount grinding auxiliary (m_{aux}) on the solvent-free oxidation of β-pinene (**1**) affording nopinone (**2**).[a]

			Grinding auxiliary[b]			
			Al_2O_3		SiO_2	
m_{aux} [g]	m_1 [g]	m_{ox} [g]	Y_2	S_2	Y_2	S_2
0.5	1.0081	3.5144	20%	80%	12%	75%
1.0	0.8966	3.1259	27%	82%	17%	77%
1.5	0.7852	2.7373	48%	84%	40%	80%
2.0	0.6737	2.3488	78%	91%	50%	83%
2.5	0.5622	1.9602	87%	97%	64%	91%
3.0	0.4508	1.5717	89%	97%	82%	91%
3.5	0.3394	1.1831	91%	96%	88%	92%
4.0	0.2279	0.7946	90%	94%	88%	89%

[a] Batch per beaker: oxidant: $KMnO_4$, **1**, 0.1 g water; Ball milling: 2 milling beakers (V=45 mL), 6 milling balls (d=15 mm), ν_{rot}=800 min^{-1}, t=10 min).
[b] Yield (Y_2) and selectivity of nopinone (S_2).

Conclusions

We have shown a possibility to cleave β-pinene (**1**) oxidatively into nopinone (**2**) with $KMnO_4$ as oxidant under solvent-free ball milling conditions. High yields (95%) were obtained within short reaction times (10 min). Compared with classical ozonolysis, under solvent-free conditions we are able to avoid long reaction times (hours compared to several minutes), the use of solvents, and the generation before reaction and work-up of O_3 and ozonides after the reaction. High yields together with high selectivity guarantee an easy work-up (quenching and extraction) of the reaction mixture. An excess of potassium permanganate is necessary. However, due to the self-decomposition of $KMnO_4$ during the process of milling, only MnO_2 and the grinding auxiliary have to be removed by a simple filtration. By co-grinding of 2 mmol **1** with 6 mmol $KMnO_4$ and 3,8 g of Al_2O_3, the best results were received within only 10 min. Other oxidants have shown worse reactivity and less or no selectivity with regard to the selective oxidative cleavage of **1** furnishing **2**. As grinding auxiliary different aluminas, silicas or metal oxides are suitable. Due to costs and considerations about the yield and selectivity, the use of alumina is definitely preferable. With regard to the standard batch, the material of milling beakers, respectively milling balls, have no influence on the reactivity. From an economic point of view, ball milling tools made of agate are preferable. However, agate is a naturally occurring porous material with low material stability. Thus, its lifetime under laboratory conditions is rather short and due to its porosity, agate is hardly to clean (memory effects). Best suitable for the oxidative cleavage with $KMnO_4$ is zirconium oxide (ZrO_2), respectively corundum. Based on these results an up-scaling and (re)assessment of the reaction on larger scale is possible. Thus a time- and cost-efficient route from **1** to **2** with readily available reagents is presented.

Experimental Section

General

All chemicals were purchased from commercial suppliers and used without further purification. Montmorillonite K-10 was purchased from Sigma–Aldrich. Analyses were carried out with a 6890 Series GC-MSD and a 7890 Series II GC-FID from Agilent Technologies. Products were identified by comparison with either retention times and/or mass spectra of pure reference compounds. GC-FID: HP-5, 30 m×0.32 mm×0.25 μm, 5 psi H_2; program: 35 °C (hold 1 min), 4 Kmin^{-1} up to 80 °C, 4.5 Kmin^{-1} up to 90 °C, 35 Kmin^{-1} up to 280 °C (hold 3 min); injector temperature: 250 °C; detector temperature: 280 °C. GC-MS: HP-5, 30 m×0.32 mm×0.25 μm, 7 psi He; program: 55 °C (hold 1 min), 5 Kmin^{-1} up to 150 °C, 20 Kmin^{-1} up to 280 °C (hold 5 min); injector temperature: 280 °C, EI (70 eV). NMR spectra were recorded with a Bruker Avance 200 MHz system (measurement frequency was 200 MHz for ^1H NMR and 50 MHz for ^{13}C NMR) in a 5 mm tube at room temperature. Measurements were carried out using trichloromethane-D ($CDCl_3$) as solvent. IR spectra were measured with a Perkin–Elmer FT-IR spectrum 100 series device equipped with a universal ATR sampling accessory. All product yields reported herein are GC-determined yields and are comparable with the isolated ones. Nevertheless, the reported yields were corrected by means of different FID sensitivity for substrate and product. The reported yields are mean values from at least two independent experimental runs. The grinding beakers and the milling balls were purified with hydrochloric acid (10 wt%) in ethanol for complete removal of residual Mn-species.

Reaction procedure

The beaker was equipped with 6 milling balls (ZrO_2, d=15 mm). The grinding auxiliary (3.8 g), β-pinene (**1**; 2 mmol, 272 mg), oxidant (6 mmol), and H_2O (0.1 g) were placed into the milling beaker (ZrO_2, V=45 mL), which was then sealed with a PTFE gasket and a ZrO_2-lid. Two similar-loaded beakers were mounted into the planetary ball mill (PULVERISETTE 7 classic line, Fritsch GmbH, Idar-Oberstein, Germany). The parameters rotations per minute and milling time were set-up and the milling process was started. After the milling process the beakers were opened and the milling balls were removed. The reaction mixture was transferred into a glass tube and subsequently demineralized water (2 mL), as well as ethyl acetate (EtOAc, 3 mL), was added. The organic layer was separated and the composition was analyzed by GC-FID or GC-MSD. Compounds **5--13** were determined by GC-MSD and/or by comparing with retention time of GC-standards.

For one standard example with SiO_2 as grinding auxiliary, the reaction mixture was extracted after grinding using EtOAc as eluent. After removal of the solvent in vacuo, the crude product was purified by column chromatography (silica gel 40, 0.063–0.2 mm, Merck) using a mixture of EtOAc/*n*-hexane (1:3) as solvent. Yield: 0.25 g per beaker (91 % based on β-pinene after purification). Nopinone (**2**): $n_D^{20} = 1.480$ [reference (1*R*)-(+)-nopinone: 1.479]. ^1H NMR ($CDCl_3$): $\delta = 0.85$ (s, 3 H), 1.33 (s, 3 H), 1.59 (d, 1 H), 1.96–2.06 (m, 2 H), 2.24–2.25 (m, 1 H), 2.35–2.38 (dd, 1 H), 2.51–2.58 (m 3 H) ppm. ^{13}C NMR (CDCl3): $\delta = 21.3$, 21.9, 25.3, 25.7, 32.7, 40.2, 41.0, 57.7, 214.8 ppm. IR (ATR): $\tilde{\nu} = 2949$, 2928, 2837 ($\nu_{\text{aliph.C-H}}$), 1706 ($\nu_{C=O}$), 1459 (δ_{C-H}) cm^{-1}. MS (EI 70 eV, $C_9H_{14}O$): *m/z* (%) = 139 (0.9) [$M^+ + 1$], 138 (8.6) [M^+], 123 (16.5), 109 (26.3), 95 (40.8), 83 (100), 81 (37.3), 67 (23.1), 55 (41.4).

Acknowledgements

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Keywords: ball milling · cleavage reactions · green chemistry · oxidation · renewable resources

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Switchable selectivity during oxidation of anilines in a ball mill

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A solvent-free method for the direct oxidation of anilines to the corresponding azo and azoxy homo-coupling products by using a planetary ball mill was developed. Various oxidants and grinding auxiliaries were tested and a variety of substituted anilines were investigated. It was possible to form chemoselectively either azo, azoxy, or the nitro compounds from reaction of aromatic anilines. The selectivity of the solvent-free reaction is switchable by applying a combination of oxidant and grinding auxiliary. Furthermore, a comparison with other methods of energy input (microwave, classical heating, and ultrasound) highlighted the advantages of the ball mill approach and its high energy efficiency.

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Switchable Selectivity during Oxidation of Anilines in a Ball Mill

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Abstract: A solvent-free method for the direct oxidation of anilines to the corresponding azo and azoxy homocoupling products by using a planetary ball mill was developed. Various oxidants and grinding auxiliaries were tested and a variety of substituted anilines were investigated. It was possible to form chemoselectively either azo, azoxy, or the nitro compounds from reaction of aromatic anilines. The selectivity of the solvent-free reaction is switchable by applying a combination of oxidant and grinding auxiliary. Furthermore, a comparison with other methods of energy input (microwave, classical heating, and ultrasound) highlighted the advantages of the ball mill approach and its high energy efficiency.

Keywords: azo compounds • mechanical properties • oxidation • peroxides • solid-state reactions • synthetic methods

Introduction

The importance of green chemistry and sustainability are becoming more important for routine organic synthesis.[1] In this regard, the omission of solvents is advantageous due to the fact that supply, purification, and disposal of potentially environmentally problematic chemicals can be omitted. The reduction of solvent waste is one of the major motivations for the development of a broad variety of solvent-free synthetic reaction protocols.[2] Furthermore, the problem of insolubility of inorganic reagents (oxidants etc.) in organic solvents can be bypassed under solvent-free conditions. Although reactions can be carried out in a solvent-free manner using classical laboratory equipment or by using microwave heating, the application of ball milling conditions is a small, but emerging field of research. Ball milling was found to be an excellent method for some organic reactions, for example, aldol-type reactions, oxidations or reductions.[2e,g,3]

Herein we describe a solvent-free method for the chemoselective oxidation of anilines to the corresponding azo or azoxy homocoupling products using a planetary ball mill. Aromatic azo compounds are usually synthesized by coupling diazo compounds with amines or phenols,[4] coupling of primary arylamines with nitroso compounds (Mills reaction),[5] oxidation of hydrazo compounds,[6] or the reduction of nitro compounds.[7] In addition to the above-mentioned routes to azo compounds, the direct oxidation of anilines to symmetric azo compounds is also feasible.[8] Aromatic azo and azoxy compounds are important dyes and are widely used in biological and chemical analysis as chromophores. Furthermore, they are applied in chemical synthesis as reducing agents, stabilizers, and polymerization inhibitors.

An accepted mechanism for the direct oxidation describes a partial oxidation of anilines, furnishing either hydroxyl amines or nitroso compounds. Consecutive condensation of the nitroso-derivative either with remaining aniline or with hydroxyl amines afforded the azo or azoxy compounds, respectively (Scheme 1).[9] Overoxidation of the nitroso group gives rise to nitro compounds. There are many protocols for this type of reaction available in the literature whereby oxidation can be accomplished both by chemical oxidants and by electrochemical reaction. However, although there are many examples in the literature dealing with solution protocols, there is only one example for a solvent-free approach to amine oxidation.[10] In contrast, the oxidation of other compounds (aromatics, alcohols) using potassium permanga-

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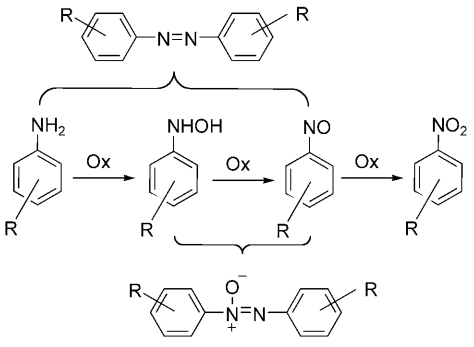


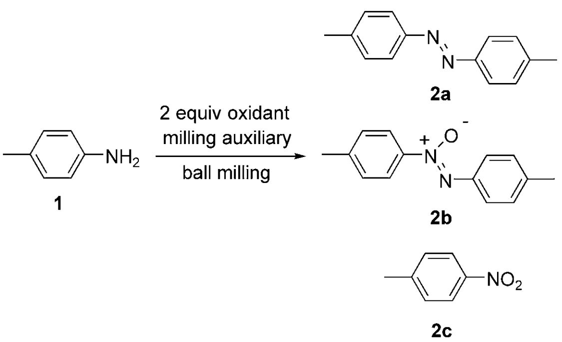
Scheme 1. Mechanism for the oxidation of primary aromatic amines.[9]

nate or other oxidants has successfully been established under solvent-free conditions.[2a,b,11] The reactions are usually initiated by classical heating or by microwave heating, whereas oxidations conducted in ball mills are rarely discussed.[31,12]

Results and Discussion

Within this work, a solvent-free method for the selective oxidation of primary aromatic amines using a planetary ball mill was developed. Beside the oxidants, several filling materials (milling auxiliaries) were used in the milling beakers to enable work with small batch sizes. For the first experiments, milling beakers and balls made from agate (a naturally-occurring variety of quartz) were employed.

Effects of oxidation agents and milling auxiliaries: Various oxidants were tested to investigate their influence on the selectivity of product formation in the oxidation of *p*-toluidine (**1**; Scheme 2). Two milling auxiliaries were applied in the syntheses: fused quartz sand (denoted as SiO_2) and γ-aluminium oxide (activity 90, neutral; denoted as Al_2O_3; Table 1). Surprisingly, not only were differences between the oxidants observed (e.g., $KMnO_4$ and H_2O_2/urea), but also significant differences were observed for the same oxidant in combination with different grinding auxiliaries (e.g., Oxone = $2KHSO_5/KHSO_4/K_2SO_4$, and H_2O_2/urea). This was very interesting because it allowed the reaction to be directed towards all three major oxidation products (azo, azoxy, nitro) by choosing the right combination of oxidant and grinding auxiliary. For example, to generate the azo product, $KMnO_4$ plus Al_2O_3 seemed to be the best choice, whereas the application of Oxone, H_2O_2/urea or sodium percarbonate with Al_2O_3 led to high selectivity for the azoxy product. In contrast, with Oxone and SiO_2 as the oxidant and grinding auxiliary, respectively, it was even possible to drive the reaction to the nitro product. Other common oxidants, such as $K_2Cr_2O_7$ or $NaBO_3$ showed only very low activity. Although many more oxidants are described in literature that would be suitable for the direct oxidation of anilines,[13] the potential application of the ball mill approach to oxidation was initially assessed here with the given selection.



Scheme 2. Oxidation of *p*-toluidine (**1**) with different oxidants and milling auxiliaries.

Table 1. Oxidation[a] of *p*-toluidine (**1**) with various oxidants in combination with the milling auxiliaries Al_2O_3 and SiO_2.

Oxidant	X(**1**) [%][b]		S(**2a**) [%][b]		S(**2b**) [%][b]		S(**2c**) [%][b]	
	Al_2O_3	SiO_2	Al_2O_3	SiO_2	Al_2O_3	SiO_2	Al_2O_3	SiO_2
$KMnO_4$	96	95	95	88	2	3	2	–
K_2MnO_4	71	49	98	94	–	3	–	–
$NaIO_4$	48	97	74	91	2	–	–	–
Oxone[c]	94	99	3	2	88	10	6	85
H_2O_2/urea	96	7	1	20	92	45	4	–
$Na_2S_2O_8$	29	88	83	97	6	–	1	–
sodium percarbonate[d]	84	2	4	99	84	–	11	–
K_2CrO_7	5	3	67	50	–	–	–	–
KIO_3	3	2	50	–	–	–	–	–
$KMnO_2$	3	3	50	50	–	–	–	–
$NaBO_3$	6	3	50	50	–	–	–	–

[a] Reaction conditions: *p*-toluidine (2 mmol), oxidant (4 mmol), grinding auxiliary (4 g); 800 rpm, 10 min, agate beaker (45 mL), six agate milling balls (15 mm). [b] Conversion (X) and selectivity (S) were determined by GC–FID measurements of extracted products in relation to *p*-toluidine (**1**; Scheme 2). [c] Triple salt: $2KHSO_5/KHSO_4/K_2SO_4$. [d] $2Na_2CO_3{\cdot}3H_2O_2$.

To verify the structure of the oxidation products, ^{1}H NMR spectroscopic analysis was considered suitable (Figure 1). Only one stereoisomer each was formed for the azo and azoxy products, presumably the more stable Z isomer, be-

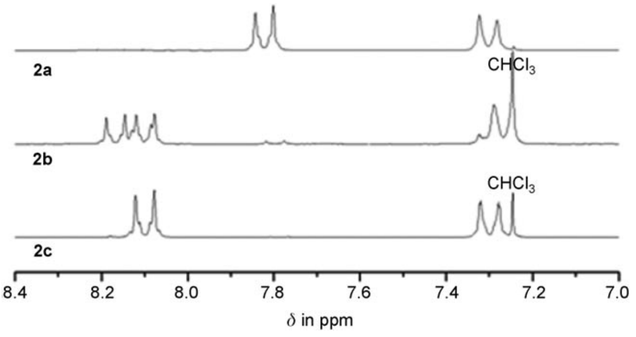
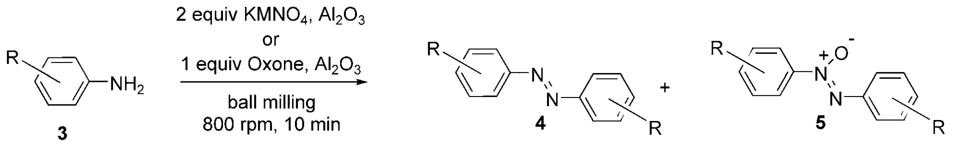


Figure 1. ^{1}H NMR spectra of the aromatic region of the oxidation products of *p*-toluidine (**1**; Scheme 2) in $CDCl_3$ at 200 MHz.

cause otherwise the presence of further signals arising from the aromatic protons would be expected.



Scheme 3. Solvent-free chemoselective oxidation of anilines **3** either with KMnO$_4$ to the corresponding azobenzenes **4** or with Oxone to the respective azoxy compounds **5**.

Table 2. Oxidation[a] of *p*-toluidine (**1**) with KMnO$_4$ varying the milling auxiliary.

Milling auxiliary	X(**1**) [%][b]	S(**2a**) [%][b]	S(**2b**) [%][b]	S(**2c**) [%][b]
quartz sand (SiO$_2$)	96	88	3	–
silica gel 60	98	91	1	1
γ-alumina (Al$_2$O$_3$)[c]	96	95	2	2
α-alumina[d]	83	89	3	1
γ-alumina[e]	94	94	2	1
CeO$_2$	96	87	4	–
montmorillonite K-10	99	95	–	1
KF/Al$_2$O$_3$[f]	96	94	2	1

[a] Reaction conditions: *p*-toluidine (2 mmol), KMnO$_4$ (4 mmol), milling auxiliary (4 g); 800 rpm, 10 min, agate beaker (45 mL), six agate milling balls (15 mm). [b] Conversion (X) and selectivity (S) were determined by GC–FID measurements of extracted products in relation to *p*-toluidine (**1**; Scheme 2). [c] Activity 150, basic. [d] Activity 90, acidic. [e] Activity 90, neutral. [f] Commercially available form, 40 wt % KF.

Table 3. Oxidation of anilines **3** with KMnO$_4$ to the corresponding azobenzenes **4**,[a] by using agate or ZrO$_2$ as material for milling beakers and balls.

R (**3**; Scheme 3)	X(**3**) [%][b]		S(**4**) [%][b]		S(**5**) [%][b]	
	Agate	ZrO$_2$	Agate	ZrO$_2$	Agate	ZrO$_2$
H (**3a**)	89	97	95	95	2	3
m-MeO (**3b**)	66	80	94	91	4	3
o-Me (**3c**)	81	92	84	80	2	3
m-Me (**3d**)	80	93	91	89	3	3
p-Me (**3e**)	96	98	95	95	2	2
p-Ac (**3f**)	29	32	67	75	17	15
o-Cl (**3g**)	61	79	82	85	7	5
m-Cl (**3h**)	79	92	92	86	6	7
p-Cl (**3i**)	97	99	93	92	4	5
o-Br (**3j**)	61	76	82	78	9	10
m-Br (**3k**)	78	89	86	84	6	6
p-Br (**3l**)	92	98	91	88	6	6
o-I (**3m**)	48	70	84	80	9	7
p-I (**3n**)	77	88	92	78	3	1

[a] Reaction conditions: amine (2 mmol), KMnO$_4$ (4 mmol), γ-Al$_2$O$_3$ (4 g; activity 90, neutral); 800 rpm, 10 min, beaker (45 mL), six milling balls (15 mm). [b] Conversion (X) and selectivity (S) were determined by GC–FID measurements of extracted products in relation to amine (**3**; Scheme 3). For isolated yields of **4a–n**, see the Supporting Information.

To further examine the influence of the milling auxiliary, experiments were conducted with KMnO$_4$ as the oxidant (Table 2). With Al$_2$O$_3$ (γ-modification, activity 90, neutral) and montmorillonite K-10, the azo product was generated with the highest conversion and selectivity. Despite the excellent results obtained with montmorillonite K-10, its handling was very problematic due to its low material density. With regard to conversion, further experiments revealed that other materials were also applicable as grinding auxiliaries (e.g., CeO$_2$, KF/Al$_2$O$_3$). However, taking into account the selectivity towards the azo compound, CeO$_2$, acidic α-alumina, or quartz sand could be disregarded. Comparing the influence of various oxidants on the selectivity revealed only small effects (Table 1). With regard to economic and ecological issues, Al$_2$O$_3$ (activity 90, neutral) was thus chosen as the milling auxiliary of choice for further experiments.

Formation of azo compounds from anilines: A screening of some primary aromatic amines was performed to assess the generality of the approach. As exemplified in Table 1 for the oxidation of **1** (Scheme 2), the reaction conditions could be adjusted to form either azo, azoxy, or nitro compounds. Due to the fact that the oxidation of anilines to the aromatic nitro compounds is relatively straightforward, only the formation of azo and azoxy compounds were investigated further.

First, the oxidation was performed with KMnO$_4$ and Al$_2$O$_3$ as oxidant and grinding auxiliary, respectively, to chemoselectively transform anilines into the corresponding symmetric azo product (Scheme 3). As can be seen in Table 3, aniline and *p*-substituted amines (except *p*-amino acetophenone) showed the highest conversions and selectivities, presumably due to the relatively low steric influence of the substituent. In contrast, *o*-substituted anilines afforded lower conversion and produced larger amounts of side products (nitro, and side-chain oxidation products). As shown in Table 3 (and also the other tables), the sum of product selectivities did not equal 100 % in every case. In some cases, low amounts of side chain oxidation products (aldehydes and acids) or dehalogenated products were identified. However, the concentrations of these side products were rather low compared to those obtained when the oxidation was conducted in solution. Furthermore, the reaction conditions, especially the reaction time, were significantly more efficient than alternative procedures reported in the literature.[10,14]

A range of grinding materials for beakers and balls (tungsten carbide, agate, stainless steel, ZrO$_2$, corundum) can be employed in experiments with ball mills. These differ in their material properties (hardness, abrasion) and bulk density. Generally, the use of a more heavy-weight milling material, such as tungsten carbide, results in a significantly higher kinetic energy than the use of a low-density material, such as agate. Higher kinetic energy, in turn, delivers more energy to the reaction mixture through friction and impact. This energy transfer is strongly correlated to chemical conversion.[3l,15] As shown for the reaction of anilines to generate azo (Table 3) and azoxy compounds (Table 4), the conversions could be increased by changing the milling material from agate (SiO_2; $\rho = 2.65\,g\,cm^{-3}$) to ZrO_2 ($\rho = 6.5\,g\,cm^{-3}$), while keeping the other reaction conditions constant.

Table 4. Oxidation of anilines **3** with Oxone to the corresponding azoxybenzenes **5**,[a] by using agate or ZrO_2 as material for milling beakers and balls.

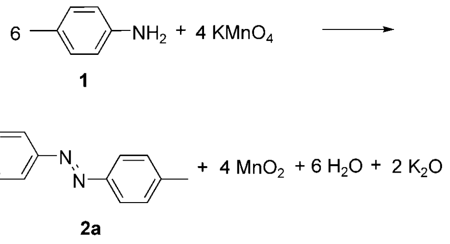
R (**3**; Scheme 3)	X(**3**) [%][b]		S(**4**) [%][b]		S(**5**) [%][b]	
	Agate	ZrO_2	Agate	ZrO_2	Agate	ZrO_2
H (**3a**)	83	98	3	4	92	89
m-MeO (**3b**)	81	96	3	5	93	87
o-Me (**3c**)	79	97	3	3	89	88
m-Me (**3d**)	81	97	3	4	93	88
p-Me (**3e**)	94	99	3	4	88	87
p-Ac (**3f**)	52	82	14	17	81	70
o-Cl (**3g**)	70	94	4	3	84	89
m-Cl (**3h**)	69	92	6	8	89	87
p-Cl (**3i**)	76	96	5	8	86	83
o-Br (**3j**)	79	95	3	4	87	87
m-Br (**3k**)	67	92	3	6	86	81
p-Br (**3l**)	73	95	7	8	85	76
o-I (**3m**)	60	82	13	17	73	58
p-I (**3n**)	61	88	16	23	69	41

[a] Oxone = triple salt: $2KHSO_5{*}KHSO_4{*}K_2SO_4$; reaction conditions: amine (2 mmol), Oxone (4 mmol), γ-Al_2O_3 (4 g; activity 90, neutral); 800 rpm, 10 min, beaker (45 mL), six milling balls (15 mm). [b] Conversion (X) and selectivity (S) were determined by GC–FID measurements of extracted products in relation to amine (**3**; Scheme 3). For isolated yields of **5a–n**, see the Supporting Information.

Formation of azoxy compounds from anilines: When Oxone was used as oxidant instead of $KMnO_4$ but still with γ-Al_2O_3 (activity 90, neutral), the main product of aniline oxidation was the azoxy products, as already exemplified for *p*-toluidine (Table 1). In contrast to the reactions of anilines with $KMnO_4$ (Table 3), no clear substituent effect could be recognized for the oxidation with Oxone (Scheme 3, Table 4).[9] The results varied more randomly and the selectivity for the target product (69–93 % azoxy) was also not as high as those obtained under the previous conditions (84–95 % azo). Especially for *p*-amino acetophenone (**3f**) and iodinated anilines (**3m** and **3n**), significant amounts of the azo products were identified. Lower selectivities for oxidation reactions of halogenated anilines in the presence of Oxone are known from other examples also.[9b] However, the occurrence of side reactions did not account for the observations (Table 4). Rather it seems that the oxidation potential is the limiting factor. According to the mechanism depicted in Scheme 1, the employed triple salt is clearly not able to form the hydroxyl amine for theses substrates, which is a prerequisite for the subsequent condensation with the nitroso intermediate to form the azoxy product.

As mentioned above for the specific formation of azobenzenes (**4**; Table 3), the overall conversion can be increased by changing the milling material from agate to the more dense ZrO_2 without a reduction in selectivity. Similar results were found for the formation of **5** from **3** (Table 4). For the formation of both **4** and **5** in the presence of ZrO_2, the yield of the isolated product was enhanced (for isolated yields, see the Supporting Information). However, the difference between GC-based yield and isolated yield was approximately 10 % in favor of the former, mainly due to the work-up procedure, which was not optimized.

Effect of the amount of $KMnO_4$ and the number of milling balls: The model reaction depicted in Scheme 2 was chosen to investigate the effect of $KMnO_4$ concentration and the number of milling balls on the course of reaction. Theoretically, a ratio of $KMnO_4$ to *p*-toluidine (**1**) of 2:3 is sufficient for complete oxidation to the azo product, as shown in the overall redox equation for the oxidation of **1** (Scheme 4). Comparison with literature procedures describing the oxidation in solution and in the solid state revealed that those protocols require more than stoichiometric amounts of $KMnO_4$.[10,12f,14]



Scheme 4. General redox equation for the oxidation of *p*-toluidine (**1**) with $KMnO_4$.

As expected, the rate of conversion of **1** in the reaction with $KMnO_4$ and Al_2O_3 as the oxidant and the grinding auxiliary, respectively, depended on the amount of $KMnO_4$ used (Figure 2). Interestingly, the selectivity for the main azo product remained almost unchanged; down to one equivalent of $KMnO_4$, a nearly linear dependence was found, whereas with less than one equivalent, the rate of conversion decreased significantly, presumably because of con-

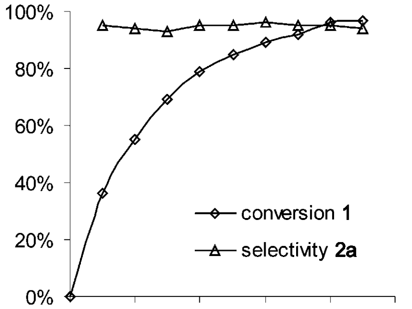


Figure 2. Influence of $KMnO_4$ concentration on the solvent-free conversion of *p*-toluidine (**1**; 2 mmol) into the corresponding azo-compound with γ-Al_2O_3 (activity 90, neutral; 4 g) as grinding auxiliary in a ball mill (agate beaker (45 mL), six agate milling balls (15 mm); 800 rpm; 10 min).

sumption of $KMnO_4$ through side-reactions and self-reduction. With amounts lower than 0.66 equivalents of $KMnO_4$, complete oxidation of **1** is not possible, as shown in Scheme 4.

An interesting phenomenon occurred when the number of milling balls was reduced (Figure 3). The rate of conversion decreased in a linear fashion when five or four balls instead of six balls were used. Employing three and two balls led to a more distinct decrease in conversion. This is an indication that the conversion is only affected by temperature, whereby the energy is dispersed into the system by the input of kinetic energy of the milling balls (four or more milling balls).[31] With three or less milling balls, insufficient mixing of the reactants also influences the course of reaction. This could be a general effect that is important for the application of reactions in a planetary ball mill. In conclusion, at least four milling balls are required to ensure thorough mixing.

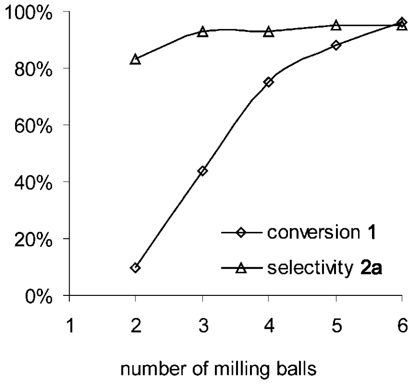


Figure 3. Effect of the number of milling balls for the solvent-free conversion of *p*-toluidine (**1**; 2 mmol) into the corresponding azo-compound with $KMnO_4$ (4 mmol) as the oxidant and γ-Al_2O_3 (activity 90, neutral; 4 g) as the grinding auxiliary in a ball mill (agate beaker (45 mL), agate milling balls (15 mm); 800 rpm; 10 min).

Measurement of the milling ball mass after each run revealed the influence of the grinding auxiliary on the deterioration of the milling balls caused by friction and impact processes. Milling with the auxiliary SiO_2 led to more than threefold mass loss compared to the use of Al_2O_3 as auxiliary (Table 5), in which the mass lost did not affect the reproducibility of the results. In fact, the variation in terms of conversion when using completely new milling balls compared with those obtained with older balls that had been applied more than 100 times, was less than 2%.

Table 5. Deterioration of milling balls.

Milling material	Average weight loss of milling balls per trial [wt%][a] SiO_2	γ-Alumina (Al_2O_3)[b]
Agate	0.22	0.06
ZrO2	0.27	0.07

[a] Milling conditions for one trial: batch-sizes according to Figure 2; agate beaker (45 mL), six agate milling balls (15 mm), 800 rpm, 10 min. [b] Activity 150, basic.

Comparison to methods in solution: Finally, a comparison between solvent-free ball milling procedures (planetary and vibration ball mill) and four methods in solution (microwave heating, conventional heating, ultrasound) for five anilines was performed (Scheme 3; Table 6).[2f] It is clear that the solvent-free methods are competitive and even more effective than the oxidation performed in a microwave, in a round-bottom flask, or in an ultrasound reactor. Reactions in solution were performed at 80 °C and, in the case of sonication, the mixture was cooled down to 20 °C. Compared to surface temperatures measured after the reaction in the ball mills (40 °C), those temperatures are higher. In combination with the fact that the reaction time was longer, higher conversions would have been expected for the reactions conducted in solution. Clearly the heterogeneous solid-state reaction procedure was superior to classical methods. In particular, for the sterically hindered *o*-toluidine (**3c**) and the deactivated *m*-anisidine (**3b**) substrates, the yields using the solid-state approach were significant higher. One literature example that dealt with the oxidation of amines with $KMnO_4$ using microwave and ultrasonic irradiation showed that solvent effects may also cause side reactions at higher temperatures.[16] It is remarkable that reactions conducted in an ultrasound reactor gave similar conversion and selectivity with all five amines to reactions performed with ball mills. However, it has to be considered that only one third of the standard reaction mixture (0.7 mmol instead of 2 mmol amine) was employed.

Table 6. Influence of energy input on the oxidation of anilines with $KMnO_4$ and Al_2O_3.[a]

Amine	Conversion of amine [%]/selectivity for the azo product [%][b] solvent-free planetary ball mill[c]	vibration ball mill[d]	in solution (30 mL; H_2O/acetonitrile, 1:1 v/v) conventional heating[e]	multimode microwave[f]	monomode microwave[g]	ultrasound[h]
aniline (**3a**)	93/95	71/89	83/88	90/91	58/91	88/94
m-anisidine (**3b**)	70/90	40/91	53/89	22/91	27/90	73/96
o-toluidine (**3c**)	94/89	81/97	89/88	39/87	63/88	82/87
m-toluidine (**3d**)	95/91	87/92	84/72	54/81	84/72	67/87
p-toluidine (**3e**)	>99/96	>99/95	96/90	91/93	96/90	97/97

[a] Standard batch size: amine (2 mmol), $KMnO_4$ (4 mmol), γ-Al_2O_3 (4 g; activity 90, neutral). [b] Determined by GC–FID measurements of extracted products in relation to amine. [c] Fritsch Pulverisette 7 classic line: two agate beaker (45 mL), six agate milling balls per beaker (15 mm), 800 rpm, 20 min. [d] Retsch MM301: two agate beaker (50 mL), six agate milling balls per beaker (15 mm), 13.3 Hz, 20 min. [e] Round-bottom flask (100 mL); 80 °C, 60 min. [f] MLS ETHOS Plus: 80 °C (P_{max} = 300 W), 30 min. [g] CEM Discover: 80 °C (P_{max} = 130 W), 30 min. [h] Hielscher UP200 s: 33% of standard batch size; 100% P_{max}, 20 °C, 20 min.

Another major advantage of the ball mill procedure is the easy workup. In the case of reactions in solution, the manganese dioxide resulting from the reduction of $KMnO_4$ tends to form a muddy mass that can be rather difficult to work up. In contrast, the ball milling procedure results in a powder that is easily extractable with an organic solvent prior to analysis or isolation. The solvent-free, conventionally heated or microwave-assisted performance of the reaction was also assessed. However, the corresponding yields were not reliable with regard to statistical spread of the results. Clearly, improper mixing of the solid reactants was responsible for this artifact. Another advantage of the use of ball mills is the intense mixing, which enables the apparatus to be used for both reaction and mixing in one device.

In addition to the comparison of chemical performance, the reaction of *p*-toluidine in different reaction environments was assessed with respect to energy conversion. Energy consumption of 0.035, 0.02, 0.38, 0.20, 0.29, and 0.015 kWh were measured for the reaction conditions listed in Table 6, respectively. Considering that both of the ball mills were operated with two equally filled milling beakers and that, in the case of sonication, a reduced batch size was used, the molar energy conversion could be calculated (Figure 4).[17] The data indicate that the solvent-free procedure is superior to solvent-based methods. Only the reaction performed in an ultrasound reactor had comparable energy efficiency, and only if the energy for cooling was neglected. Generally, the reactions in solution needed 0.01 kWh min^{-1} to operate the cryostat (the same cryostat was used for all processes; cryostat temperature = 10 °C). Including this fact, the efficiency of the ball milling procedure is highlighted even more. The lower energy efficiency of the planetary ball mill compared to the vibration ball mill was due to technical differences.[18] Because the moving masses are significantly higher for the former, a higher moment of inertia has to be overcome to provide proper movement of the milling balls. However, reaction scale-up is only possible with the planetary ball mill.

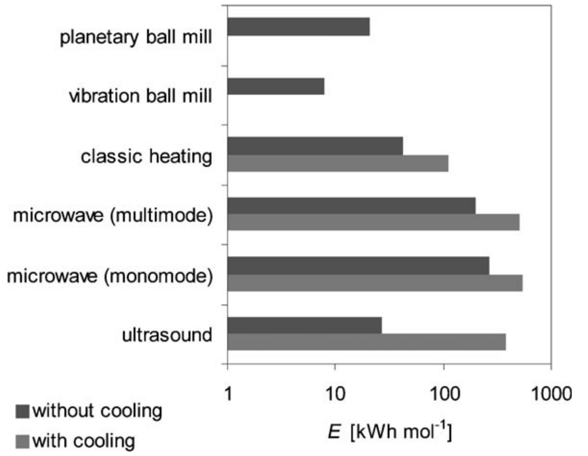


Figure 4. Energy consumption for the oxidation of *p*-toluidine (2 mmol) with $KMnO_4$ using the reaction conditions listed in Table 6 (calculated according to Schneider et al.[17]).

Conclusion

A fast and solvent-free method for the oxidation of primary aromatic amines to azo and azoxy compounds in a planetary ball mill is described. It was shown that conversion and selectivities can be controlled by the choice of oxidant and grinding auxiliary. Furthermore, the experiments showed good reproducibility. Reaction screening of various anilines showed substituent effects for the oxidation with $KMnO_4$ furnishing the azo compounds with high selectivities. Employing Oxone instead of $KMnO_4$ afforded the corresponding azoxy compounds with similar selectivities. Again, conversion is related to the substitution of the starting materials. Compared to methods in solution (microwave, conventional heating, ultrasound), the solvent-free procedure in the ball mill is more efficient in terms of both chemical yield and energy consumption. The avoidance of organic solvents and the easy, fast, and energy-saving aspects of the reaction make this ball-milling method a real alternative to conventional reaction protocols.

Experimental Section

General: Chemicals are commercially available from Sigma–Aldrich or Alfa Aesar and were used as received. Reactions were performed in a Fritsch "Pulverisette 7 classic line" planetary ball mill using 45 mL grinding beakers (agate or ZrO_2) and milling balls (6×15 mm; agate or ZrO_2). All reaction vessels were cleaned with ethanolic HCl (1 M) prior to use to avoid any contamination or memory effects.

GC–FID and GC–MSD measurements were performed with a 6890-GC or a 6890N-GC-MS instrument, respectively, both from Agilent Technologies. Conditions for GC–FID: HP 5, 30 m×0.32 mm×0.25 μm, H_2-10 psi, program: 70 °C (hold for 3 min), 15 K min^{-1} up to 280 °C (hold for 10 min), injector temperature: 280 °C, detector temperature: 300 °C. Conditions for GC–MSD: HP 5, 30 m×0.32 mm×0.25 μm, He-10 psi, program: 70 °C (hold for 3 min), 15 K min^{-1} up to 280 °C (hold for 7 min), injector temperature: 280 °C, detector: EI (70 eV). NMR spectra were recorded with a Bruker Avance 200 MHz system at RT in $CDCl_3$ as solvent using tetramethylsilane as internal standard.

Data reported herein (conversion, selectivity) were calculated from the GC data and are comparable with those for the isolated products. The reported yields were adjusted by correcting for the different FID sensitivity for substrate and product. Isolated yields for the target products in Tables 3 and 4 are provided within the Supporting Information and are given in relation to the employed amine. Isolation was performed for those reactions in Tables 3 and 4 that were performed with ZrO_2 as the grinding material.

General reaction procedure for the oxidation of anilines: Grinding beakers (45 mL; agate or ZrO_2) were equipped with six milling balls of the same material (d = 15 mm), and the milling auxiliary (4 g), the amine (2 mmol), and the oxidant (4 mmol) were added in the given order. Milling was performed at 800 rpm for 10 min. After cooling of the grinding beakers to RT, the crude products were washed through a thin silica layer using methyl *tert*-butyl ether (MTBE; 3×10 mL). The solvent was evaporated in vacuum and the crude products were dried, redissolved in MTBE (1.5 mL) and analyzed by GC–FID and GC–MS. Analytical samples for NMR spectroscopic investigations were isolated by column chromatography using a *n*-hexane/toluene mixture as eluent. Products were identified by comparison with literature data. For analytical details of the isolated products, see the Supporting Information.

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[18] Although the reactions in the planetary and vibration ball mill were performed at the same frequency (800 rpm = 13.3 Hz), the energy inputs are not equivalent to each other. Whereas, for the former, the maximum has been adjusted, the maximal vibration frequency for the second mill is 30 Hz.

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Referenz [6]

Fast copper-, ligand- and solvent-free Sonogashira coupling in a ball mill

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A solvent-free method for the Sonogashira coupling reaction was established under ball milling conditions without the use of copper or additional ligands. $Pd(OAc)_2$ or $Pd(PPh_3)_4$ in combination with 1,4-diazabicyclo[2.2.2]octane (DABCO) were chosen as catalysts and base, respectively. The reaction was investigated using a variety of aryl halides and acetylenes and with different amounts of the Pd-catalyst and DABCO. Results indicated that the employment of $Pd(OAc)_2$ in combination with SiO_2 as a grinding auxiliary preferentially induces the transformation of aryl iodides to the corresponding Sonogashira coupling products. In contrast, both the substitution of SiO_2 by Al_2O_3 or replacement of $Pd(OAc)_2$ with $Pd(PPh_3)_4$ enable the reaction of aryl bromides with phenylacetylenes. The selective reaction of bis-ethynyl compounds to double-coupled products and the influence of further common bases on the reaction was also scrutinized, confirming the high reactivity of DABCO as a base for solvent-free transformations.

Fast copper-, ligand- and solvent-free Sonogashira coupling in a ball mill†

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A solvent-free method for the Sonogashira coupling reaction was established under ball milling conditions without the use of copper or additional ligands. $Pd(OAc)_2$ or $Pd(PPh_3)_4$ in combination with 1,4-diazabicyclo[2.2.2]octane (DABCO) were chosen as catalysts and base, respectively. The reaction was investigated using a variety of aryl halides and acetylenes and with different amounts of the Pd-catalyst and DABCO. Results indicated that the employment of $Pd(OAc)_2$ in combination with SiO_2 as a grinding auxiliary preferentially induces the transformation of aryl iodides to the corresponding Sonogashira coupling products. In contrast, both the substitution of SiO_2 by Al_2O_3 or replacement of $Pd(OAc)_2$ with $Pd(PPh_3)_4$ enable the reaction of aryl bromides with phenylacetylenes. The selective reaction of bis-ethynyl compounds to double-coupled products and the influence of further common bases on the reaction was also scrutinized, confirming the high reactivity of DABCO as a base for solvent-free transformations.

Introduction

Green chemistry and sustainability are becoming more and more important in everyday organic synthesis.[1] Within this subject, the elimination of solvents is advantageous, since supply, purification, and disposal of these can be omitted. The accompanying reduction of solvent waste is the major motivation for the development of a broad variety of solvent-free synthetic reaction protocols.[2] While reactions are often carried out in a solvent-free manner using classical laboratory equipment or microwave heating, the application of ball milling is a rather small, but strongly emerging field of research. Ball milling was found to be an excellent method for some organic reactions: *e.g.* aldol-type reactions, oxidation or reduction.[2e,g,3] Besides these stoichiometric reactions, metal-catalyzed and organocatalytic protocols have also been proven to work.

Within these investigations, a fast, copper-, ligand-, and solvent-free protocol for the Sonogashira coupling of aryl halides with aryl- and alkylacetylenes using a commercial planetary ball mill is described. The Sonogashira reaction is an important C–C cross-coupling reaction between sp- (aryl-, alkenyl- and alkylacetylenes) and sp^2-hybridized carbon atoms (aryl halides or triflates) catalyzed by transition metals (Pd, Au, Cu, Ni).[4] The coupling products are widely used as starting materials for the synthesis of molecular organic systems (*e.g.* electro-optical switches, conducting polymers), pharmaceuticals or natural products.[4c–g] Additionally, this synthetic transformation is the tool of choice for the construction of carbon-rich materials (*e.g.* radialenes, graphenes) from simple building blocks.[5]

The reaction is normally carried out in organic solvents under inert conditions.[4a,b] Besides the countless numbers of publications dealing with the development of new catalytic systems, a few more recent articles report experimental protocols under solvent-free conditions.[6] Compared to other Pd-catalyzed cross-coupling reactions, like the Suzuki–Miyaura or Mizoroki–Heck reactions,[7,8] only one very recent implementation in a ball mill has been published to date for the Sonogashira reaction.[9] In that work, $Pd(PPh_3)_4$ + CuI was used as the catalytic system and the reactions were accomplished with distinctly longer reaction times than described in the current work, as will be reported below.

Results and discussion

Reactions were performed under aerobic conditions using air-stable Pd(II) acetate ($Pd(OAc)_2$) and 1,4-diazabicyclo[2.2.2]-octane (DABCO) as the catalyst and basic component responsible for the deprotonation of alkynes, respectively. DABCO has been found to be an excellent base for the Sonogashira reaction,[10] and it is a solid, which is a major advantage for an implementation of the reaction in a ball mill (compared to other commonly used amine bases like triethylamine or diisopropylamine). In addition, fused quartz sand (SiO_2) was used as an inert filling material for the milling beakers to enable work with small batch sizes. In contrast to the work of Mack and coworkers,[9] no copper co-catalyst has been employed and the reaction time was restricted to 20 min of ball milling.

Sonogashira reaction between aryl iodides and phenylacetylenes

Reaction screening of different aryl iodides (**1a–f**) and conjugated acetylene derivatives (**2a–d**; Table 1) was carried out using constant reaction parameters to investigate the influence of substituents on the acetylene derivatives and aryl halides on the course of reaction.

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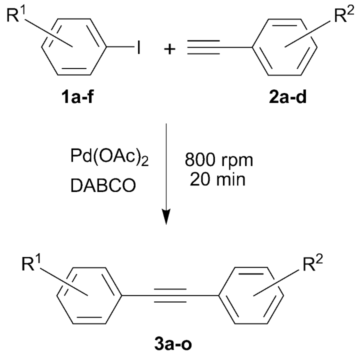
† Electronic supplementary information (ESI) available: Experimental details and characterization data for the coupling products. DOI: 10.1039/c000674b

Table 1 Sonogashira reactions[a] of aryl iodides (**1**) with substituted phenylacetylenes (**2**)

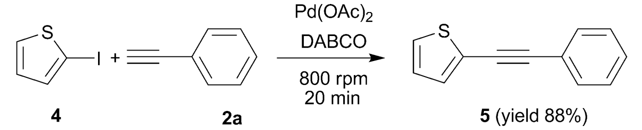


Product	Aryl iodide (R^1)	Acetylene (R^2)	X(**1**) [%][b]	S(**3**) [%][b]
3a	**1a** (H)	**2a** (H)	68	99
3a (ZrO_2)[c]	**1a** (H)	**2a**	80	99
3b	**1b** (*o*-Me)	**2a**	54	98
3c	**1c** (*p*-Me)	**2a**	47[d]	>99
3c (ZrO_2)[c]	**1c** (*p*-Me)	**2a**	74[c]	>99
3d	**1d** (*o*-MeO)	**2a**	51	98
3e	**1e** (*p*-MeO)	**2a**	58[d]	98
3f	**1f** (*p*-Ac)	**2a**	98	99
3g	**1a** (H)	**2b** (*p*-Me)	67	97
3g (ZrO_2)[c]	**1a** (H)	**2b**	83[c]	98
3h	**1c** (*p*-Me)	**2b**	55	98
3h (ZrO_2)[c]	**1c** (*p*-Me)	**2b**	77[c]	97
3j	**1e** (*p*-MeO)	**2b**	53	98
3k	**1f** (*p*-Ac)	**2b**	95	92
3l	**1e** (*p*-MeO)	**2c** (*p*-MeO)	61	>99
3m	**1f** (*p*-Ac)	**2c**	99	>99
3n	**1e** (*p*-MeO)	**2d** (*p*-F)	53	96
3o	**1f** (*p*-Ac)	**2d**	93	99

[a] Reaction conditions: 2 mmol aryl iodide (**1a–f**), 2.5 mmol acetylene compound (**2a–d**), 2.5 mmol DABCO, 5 mol% $Pd(OAc)_2$, 5 g SiO_2, 800 rpm, 20 min, agate beaker (45 ml), 6 × agate milling balls (15 mm). [b] Determined with GC-FID measurements of extracted products in relation to **1**. [c] ZrO_2 milling beakers and balls were used instead of agate ones. [d] No change in conversion was observed when $PdCl_2$ was used instead of $Pd(OAc)_2$ in the same molar amount.

It was found that only aryl iodides **1a–f** showed noticeable conversions, whereas in the case of aryl bromides, none or only traces of the Sonogashira coupling product were found under the reaction conditions employed ($Pd(OAc)_2$ + DABCO). Similar behaviour was reported for a solvent-free microwave-assisted attempt using KF–alumina and Pd–CuI–PPh_3 as the base and catalyst system, respectively.[6a] No coupling product was found if either $Pd(OAc)_2$ or DABCO were absent, or if $Pd(OAc)_2$ was substituted by palladium powder. This suggests that either Pd(II) is the active species in the catalytic cycle, or that *in situ* reduction of Pd(II) to Pd(0) furnishes more active Pd species. The latter way may be supported by the fact that small amounts of 1,4-diarylbuta-1,3-diyne (homocoupling product of **2**) have been identified in the reaction mixture, whose concentration was independent of conversion. For some examples the application of $PdCl_2$, instead of the acetate, yielded products with similar yields and identical selectivities (**3c**,**e**; Table 1). Employment of $Pd(PPh_3)_4$ as a catalyst was investigated, enabling the transformation of aryl bromides (**1g–l**; see Tables 6 and 7 and the following text) as indicated recently by Mack and coworkers.[9]

Certain combinations of aryl halides and acetylenes tested (**1a–f** with **2a–d**) showed high selectivities for the Sonogashira coupling product related to the employed aryl halide (Table 1). Also the reproducibility was quite good; the deviation of the values of conversion and selectivity did not exceed 1–2%. Using agate, which is a relatively light-weight material, as the material for milling beakers and balls led to medium and high conversions of the aryl iodides. A more heavy-weight milling material, such as ZrO_2, resulted in significantly higher conversions for the same reaction conditions, caused by the higher energy input of the milling balls (**3a**,**c**,**g**,**h**; Table 1).[7d,11] Conversions were significantly higher for aryl iodides with electron-withdrawing substituents (*p*-iodoacetophenone, **1f**) and neutral substituents (iodobenzene **1a**) than for those with electron-donating substituents (*p*-iodotoluene and *p*-iodoanisole, **1c** and **1e**). The electron-poor 2-iodothiophene (**4**) showed high conversion and selectivity (98%) in the reaction with phenylacetylene (**2a**; Scheme 1) under the reaction conditions reported for examples listed in Table 1.



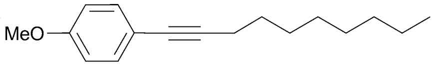
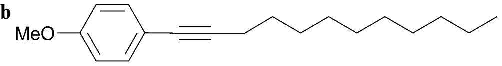
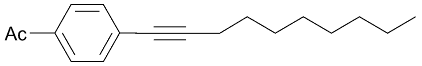
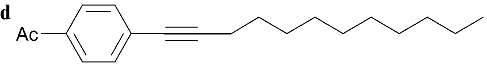
Scheme 1 Coupling reaction of 2-iodothiphene (**4**) and phenylacetylene (**2a**; for conditions see Table 1).

Sonogashira reaction between aryl iodides and alkynes

The variation of the acetylene seems to have little influence on the conversion of the aryl iodides. This suggests that the oxidative addition of the aryl iodide to the Pd-catalyst, which is faster for electron-poor aryl iodides with a weaker carbon–halogen bond than for electron-rich aryl iodides, could be the rate-determining step within the catalytic cycle of this solvent-free method. This dependency could be confirmed by employing decyne (**6a**) and dodecyne (**6b**) as the coupling component (Table 2). Sonogashira coupling of **6** with *p*-iodoanisole (**1e**) and **1f** furnished coupling products **7a–d** (Table 2) in similar yields as demonstrated in the corresponding reactions with phenylacetylenes **2a–d** (see Table 1). The treatment of alkynes **6** under the described experimental conditions did not afford any destructive bond breakage in the alkyl chain, which is due to the employment of mild reaction conditions. The application of milling materials with a higher density (steel, copper, tungsten carbide) resulted in destructive shortening of the alkyl substituents by the occurrence of stronger frictional forces and higher reaction temperatures.

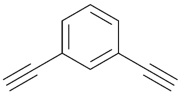
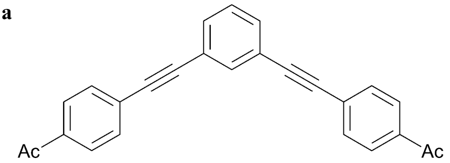
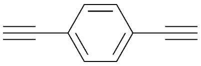
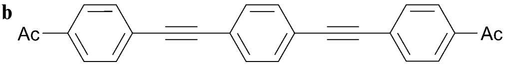
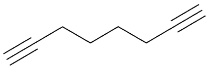
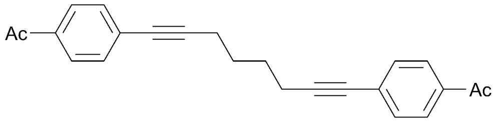
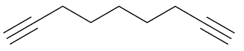
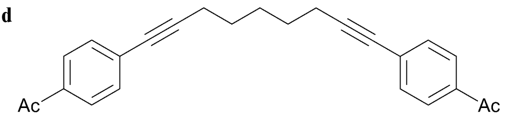
In addition to alkynes **6** bearing an alkyl chain as a substituent only, three acetylenes containing an OH-group at carbon atom 3 (**8a–c**; Scheme 2) were employed in the Sonogashira coupling with **1f**. After ball milling (agate) in the presence of 5 mol% $Pd(OAc)_2$ and 2.5 mmol of DABCO, the products (**9a–c**) were isolated in acceptable yields. The selectivities for the Sonogashira coupling products were as high as reported for the previous examples (> 98%; Tables 1 and 2). The successful coupling of **8a** is remarkable, since the 2-hydroxyprop-2-yl group is an excellent protecting group. In contrast to TMS or TIPS this end group is tolerable to fluoride ions and can easily be removed in the

Table 2 Sonogashira reactions[a] of aryl iodides (**1**) with alkynes (**6**)

Product		Aryl iodide	Acetylene	*X*(**1**) [%][b]	*S*(**7**) [%][b]
7a		*p*-Iodoanisole (**1e**)	Decyne (**6a**)	48	93
7b		*p*-Iodoacetophenone (**1f**)	Decyne (**6a**)	92	93
7c		*p*-Iodoanisole (**1e**)	Dodecyne (**6b**)	50	>99
7d		*p*-Iodoacetophenone (**1f**)	Dodecyne (**6b**)	92	>99

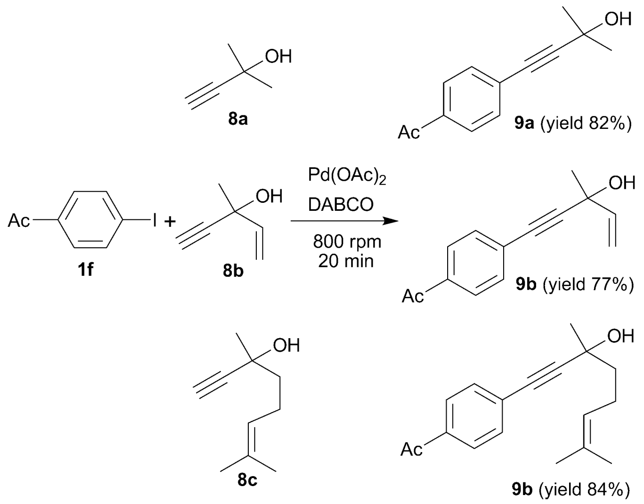
[a] Reaction conditions: 2 mmol aryl iodide (**1e**,**f**), 2.5 mmol alkyne (**6**), 2.5 mmol DABCO, 5 mol% Pd(OAc)$_2$, 5 g SiO$_2$, 800 rpm, 20 min, agate beaker (45 ml), 6 × agate milling balls (15 mm). [b] Determined with GC-FID measurements of extracted products in relation to **1**.

Table 3 Double Sonogashira reactions[a] of *p*-iodoacetophenone (**1f**) with bis-ethynyl compounds (**10**)

Bis-ethynyl compound		Sonogashira coupling product		Yield [%][b]
10a		**11a**		63
10b		**11b**		69
10c		**11c**		75
10d		**11d**		74

[a] Reaction conditions: 2 mmol *p*-iodoacetophenone (**1f**), 1 mmol bis-ethynyl compound (**10a–d**), 2.5 mmol DABCO, 5 mol% Pd(OAc)$_2$, 5 g SiO$_2$, 800 rpm, 20 min, ZrO$_2$ beaker (45 ml), 6 × ZrO$_2$ milling balls (15 mm). [b] Determined with ^{1}H-NMR measurements of extracted products in relation to **1f**.

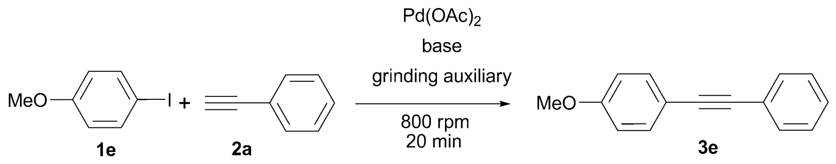
presence of alkali hydroxides (retro-Favorski elimination). In the case of **8b**, the possible competing Mizoroki–Heck coupling reaction on the terminal double bond did not occur.



Scheme 2 Reaction of *p*-iodoacetophenone (**1f**) and 3-hydroxy-acetylenes (**8**; for conditions see Table 1).

Sonogashira reaction with bis-ethynyl compounds

Surprisingly, only di-coupled products could be isolated when **1f** was applied in the Sonogashira reaction with bis-ethynyl compounds (**10**; Table 3). ZrO$_2$ beakers and milling balls were used, instead of agate ones, to achieve satisfactory results. Furthermore, the conversions of *p*-iodoacetophenone **1f** were limited by side reactions of the bis-ethynyl compounds, assumed to be oligomerization reactions. The products were not suitable for GC-FID analysis so ^{1}H-NMR analysis of the crude reaction mixture was used to determine the conversion and selectivity. Since ^{1}H-NMR spectra revealed a highly symmetrical peak distribution and there were no signals for acetylenic protons, it was clear that mono-coupled products were absent. The ^{1}H-NMR spectra of the crude and isolated products revealed no differences, apart from the absence of signals for non-converted **1f**.



Scheme 3 Sonogashira model reaction of *p*-iodoanisole (**1e**) with phenylacetylene (**2a**).

Influence of catalyst, base and grinding auxiliary

The reaction between *p*-iodoanisole (**1e**) and phenylacetylene (**2a**; Scheme 3) was taken as a model reaction for investigation of the influence of the amounts of catalyst $Pd(OAc)_2$ and DABCO on the conversion of **1e**. This reaction shows medium conversion under screening reaction conditions (Table 1), assuming that influences of the above-mentioned variations should be easily recognizable by changes in conversion.

The amount of $Pd(OAc)_2$ was varied in the range of 1–5 mol% related to *p*-iodoanisole (**1e**), whilst keeping other reaction parameters constant (Fig. 1). A nearly linear dependence of the conversion and the amount of $Pd(OAc)_2$ can be observed, while the selectivity is unaffected. The turnover-frequencies (TOF) for the coupling reactions of aryl iodides **1a–f** with phenylacetylene listed in Table 1 range from 28 to 59 h^{-1}. Compared to previous studies of solvent-free Sonogashira reactions in ball mills (TOF: ~2 h^{-1})[9] the herein-reported reaction conditions are advantageous due to short reaction times. Decreasing the Pd-concentration to 1 mol% (Fig. 1) resulted in an increase of TOF to 110 h^{-1}, which is remarkable considering the fact that the reaction has a strongly heterogeneous nature.

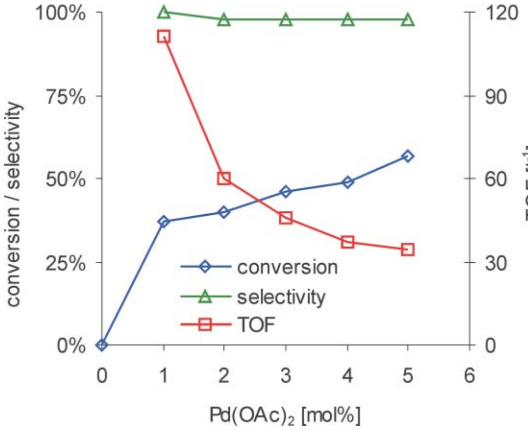


Fig. 1 Conversion of *p*-iodoanisole (**1e**; 2 mmol) in the coupling reaction with phenylacetylene (**2a**; 2.5 mmol) for different amounts of $Pd(OAc)_2$ (reaction conditions: 2.5 mmol DABCO, 5 g SiO_2; ball milling: agate beaker (45 ml), 6 × agate balls (15 mm) per beaker, 800 rpm, 20 min).

Next, the amount of DABCO was varied between 0.5–3 molar equivalents (1.25–7.5 mmol) relative to phenylacetylene (**2a**; Fig. 2). The relationship to **2a** was chosen as the determinant parameter, because the base is responsible for abstraction of the propargylic hydrogen from **2**, **6**, **8** or **10** (Schemes 1–3, Tables 1–3). Similar to the effect described in Fig. 1, a nearly linear dependence of conversion and amount of DABCO is apparent, though the selectivities remain high. A 1.5-fold molar excess (3.75 mmol) of DABCO seems to be an upper limit for this reaction, since no further increase of conversion for higher amounts of DABCO were noticed.

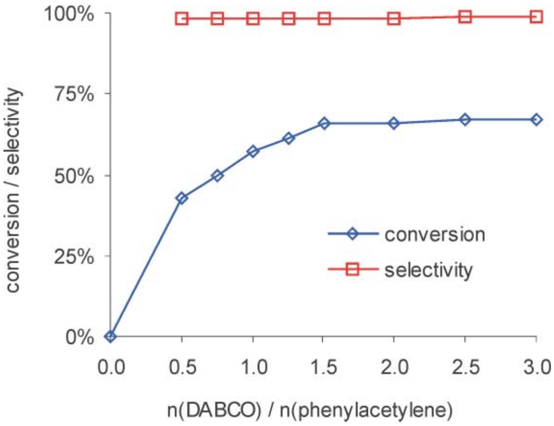


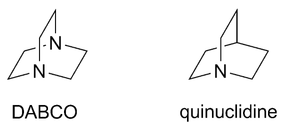
Fig. 2 Conversion of *p*-iodoanisole (**1e**; 2 mmol) in the coupling reaction with phenylacetylene (**2a**; 2.5 mmol) for different amounts of DABCO (reaction conditions: 5 mol% $Pd(OAc)_2$, 5 g SiO_2; ball milling: agate beaker (45 ml), 6 × agate balls (15 mm) per beaker, 800 rpm, 20 min).

Compared to other common amine bases like triethylamine or diisopropylamine and inorganic bases, DABCO afforded the highest conversions for the model reaction of **1e** with **2a** (Table 4), which is in fact proof that DABCO is the best choice for the Sonogashira coupling reaction under solvent-free conditions.[10] Only quinuclidine (1-azabicyclo[2.2.2]octane) showed slightly higher conversion, which is a stronger base than DABCO (pK_a 11.0 compared to 8.8 and 3.0 for DABCO) and has a similar chemical structure (Scheme 4). But compared to DABCO, quinuclidine is much more expensive and toxic, therefore DABCO is more applicable, particularly with regard

Table 4 Sonogashira reaction[a] in the presence of different bases for the reaction of *p*-iodoanisole (**1e**) and phenylacetylene (**2a**)

Base	*X*(**1e**) [%][b]	*S*(**3e**) [%][b]
DABCO	66	98
Triethylamine	27	99
Diisopropylamine	12	99
Quinuclidine	73	97
K_2CO_3	13	99
KOH	28	99
TBAB	—	—
Triphenylamine	—	—
Tribenzylamine	—	—
4-Phenylmorpholine	—	—

[a] Reaction conditions: 2 mmol *p*-iodoanisole (**1e**), 2.5 mmol phenylacetylene (**2a**), 3.75 mmol base, 5 mol% $Pd(OAc)_2$, 5 g SiO_2, 800 rpm, 20 min, agate beaker (45 ml), 6 × agate milling balls (15 mm). [b] Determined with GC-FID measurements of extracted products in relation to **1e**.



Scheme 4 Structures of 1,4-diazabicyclo[2.2.2]octane (DABCO) and of 1-azabicyclo[2.2.2]octane (quinuclidine).

to the principles of green chemistry (avoiding toxicity)[1a,b,d,11] and green engineering (avoiding high costs).[1c,11]

Furthermore, sterically hindered bases like triphenylamine or tribenzylamine did not initiate any reaction. The inactivity of these bases may be an indication that the base is intermittently coordinated to the catalyst. Considering the fact that *o*- and *p*-iodotoluene (**1b**,**c**) resulted in similar product yields upon coupling with **2a** (Table 1), the independence of the experimental outcomes on the variation of substituents at **2a** supports the fact that the oxidative addition of the aryl iodide is the rate-determining step. This step is obviously independent from the nature of the base, allowing the conclusion that the latter is responsible for the activation of the acetylene coupling partner. However, an acetylene–DABCO adduct could not be identified in the reaction mixture, but it could be concluded that DABCO forms an addition product (probably DABCO·HI) at the end of the reaction. The low conversions resulting from the employment of bases other than DABCO (Table 4) emphasizes its special role in Sonogashira reactions. In the case of other Pd-mediated cross-coupling reactions, the main function of the base is the interception of the HI molecules. In contrast, in the case of the Sonogashira coupling a Lewis or Brønsted basicity is essential for the abstraction of the acidic proton in **2a**.

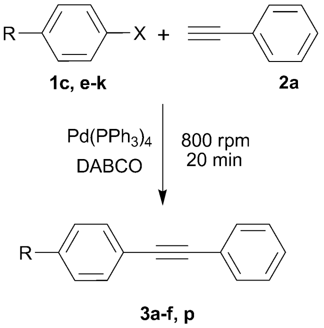
Different grinding auxiliaries were tested for their influence on the reaction of *p*-iodoanisole (**1e**) and phenylacetylene (**2a**; Table 5). The use of CeO_2 and TiO_2 led to the same conversions as for SiO_2, whereas both neutral (γ-modification) and basic alumina (α-Al_2O_3) significantly increased the conversion. The application of silica gel and KF–Al_2O_3 (32 wt% KF) revealed an opposite trend concerning the transformation to product **3e**. This negative effect is in contrast to the results reported for the solvent-free Suzuki–Miyaura reaction performed using KF–alumina as a base and under ball milling conditions.[7c–e]

Table 5 Sonogashira reaction[a] between *p*-iodoanisole (**1e**) and phenylacetylene (**2a**) in the presence of different grinding auxiliaries

Base	X(**1e**) [%][b]	S(**3e**) [%][b]
SiO_2 (fused quartz sand)	58	99
SiO_2 (silica gel)	25	99
CeO_2	58	98
TiO_2	59	99
γ-Al_2O_3 (neutral)	83	99
α-Al_2O_3 (basic)	85	99
KF–Al_2O_3 (32 wt% KF)	45	99

[a] Reaction conditions: 2 mmol *p*-iodoanisole (**1e**), 2.5 mmol phenylacetylene (**2a**), 2.5 mmol DABCO, 5 mol% $Pd(OAc)_2$, 5 g grinding auxiliary, 800 rpm, 20 min, agate beaker (45 ml), 6 × agate milling balls (15 mm). [b] Determined with GC-FID measurements of extracted products in relation to **1e**.

Table 6 Screening reactions[a] of aryl halides (**1**) and phenylacetylene (**2a**) using $Pd(PPh_3)_4$ as catalyst



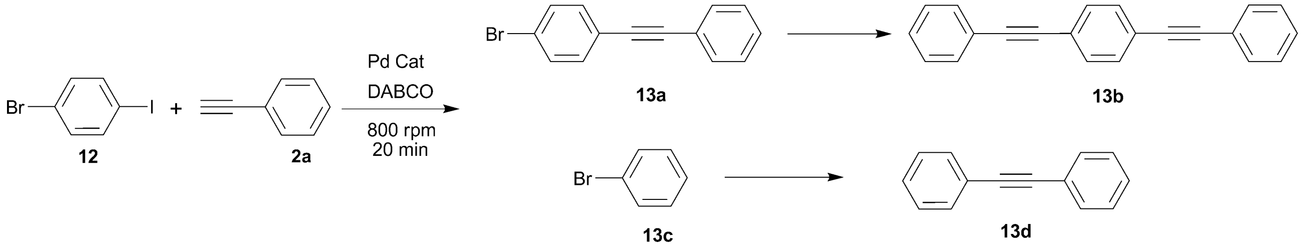
			Agate:		ZrO_2:	
Product	Aryl halide (R)	Y	X(**1**) [b][%]	S(**3**) [b]	X(**1**) [b][%]	S(**3**) [b]
3c	**1c** (Me)	I	24	99	99	98
3e	**1e** (MeO)	I	26	98	99	98
3f	**1f** (Ac)	I	35	99	99	99
3a	**1g** (H)	Br	4	98	71	98
3c[c]	**1h** (Me)	Br	1	98	61	99
3e	**1i** (MeO)	Br	3	99	52	98
3f	**1j** (Ac)	Br	34	99	97	98
3p	**1k** (CF_3)	Br	26	98	99	97
3q	**1l** (NO_2)	Br	94 (32)[c]	99	99	98

[a] Reaction conditions: 2 mmol aryl halide (**1c**,**e–l**), 2.5 mmol phenylacetylene (**2a**), 2.5 mmol DABCO, 5 mol% $Pd(PPh_3)_4$, 5 g α-Al_2O_3 (basic), 800 rpm, 20 min, beaker (45 ml), 6 × milling balls (15 mm). [b] Determined with GC-FID measurements of extracted products in relation to **1**. [c] $Pd(OAc)_2$ was used instead of $Pd(PPh_3)_4$.

Influence of copper, Pd(0) and grinding auxiliary

A very interesting result was obtained when the Sonogashira reaction between **1e** and **2a** was performed in the presence of 5 mol% CuI in addition to the $Pd(OAc)_2$. The conversion of **1e** decreased by 10%, caused by the increasing conversion of **2a** to the homo-coupling product 1,4-diphenylbuta-1,3-diyne (Glaser reaction). Obviously, CuI has no positive influence on the Sonogashira coupling mechanism itself under solvent-free reaction conditions. It is also worth mentioning that only traces of the coupling product **3e** were achieved if 20 mol% of PPh_3 was added to the reaction mixture (5 mol% $Pd(OAc)_2$, 2.5 mmol DABCO). However, only the respective phosphine oxide could be detected after ball milling. Apparently, *in situ* formation of $Pd(PPh_3)_4$ had not occurred. In contrast, the application of 5 mol% $Pd(PPh_3)_4$ (also containing 20 mol% of PPh_3) instead of $Pd(OAc)_2$ resulted in the formation of the Sonogashira coupling products, as indicated in Table 6. Bromides (**1g–l**) were also suitable for coupling reactions when using this Pd-complex in combination with basic α-Al_2O_3 as a grinding auxiliary, as demonstrated by Mack and co-workers, before performing the reaction in a 8000M SpexCertiprep (vibration ball mill).[9] The herein-presented reaction is also advantageous with respect to the fact that no additional copper was required, and milling balls or containers made of copper were not needed. Remarkably *p*-nitro-bromobenzene (**1l**) showed the highest conversion under the given conditions and was also suitable for coupling with $Pd(OAc)_2$, but with lower conversion than for $Pd(PPh_3)_4$.

Table 7 Reaction[a] of *p*-iodobromobenzene (**12**) and phenylacetylene (**2a**)



Pd-source	Milling material	*X*(**12**) [%][b]	*S*(**13a**) [%][b]	*S*(**13b**) [%][b]	*S*(**13c**) [%][b]	*S*(**13d**) [%][b]
Pd(OAc)$_2$	Agate	87	81	19	0	0
Pd(PPh$_3$)$_4$	Agate	39	100	0	0	0
Pd(OAc)$_2$	ZrO$_2$	91	78	20	1	1
Pd(PPh$_3$)$_4$	ZrO$_2$	99	94	2	1	3

[a] Reaction conditions: 2 mmol *p*-iodobrombenzene (**12**), 2.5 mmol phenylacetylene (**2a**), 2.5 mmol DABCO, 5 mol% Pd, 5 g Al$_2$O$_3$ (basic), 800 rpm, 20 min, beaker (45 ml), 6 × milling balls (15 mm). [b] Determined by GC-FID measurements of extracted products in relation to **12**.

The application of milling tools made of copper or tungsten carbide for Sonogashira reactions, as used in the literature, would certainly enhance the energy required, due to the higher kinetic energy of the milling balls. Indeed, the presence of ZrO$_2$ or agate is preferable, due to lower thermal stress which could cause side reactions especially at longer reaction times, *e.g.* dehalogenation of aryl halides. The data shown in Table 6 reveals the dependence of conversion on the density (weight) of the milling material. ZrO$_2$ milling balls again afforded higher conversions, whereas the selectivity remained unchanged compared to the employment of agate.

If the results for the aryl iodides with agate milling material are compared with those of the screening reactions (Table 1), it can be seen that Pd(OAc)$_2$ is more effective for the coupling of iodo-aromatics *via* ball milling than Pd(PPh$_3$)$_4$; not only with respect to the reaction itself but also regarding economic (price) and environmental issues (no bulky ligands).[1a–d,11]

Using this approach to perform an asymmetric coupling of *p*-iodobromobenzene (**12**) with phenylacetylene (**2a**; Table 7), the selectivity for the product **13a** was significantly higher for Pd(PPh$_3$)$_4$, but the conversion of **12** was distinctly lower than with the application of Pd(OAc)$_2$ as catalyst with agate milling equipment. Surprisingly, the double-coupled product 1,4-bis(phenylethynyl)benzene (**13b**) is only formed with the use of Pd(OAc)$_2$ although Pd(PPh$_3$)$_4$ should be more reactive for the conversions of aryl bromides, as shown for the conversion of *p*-nitro-bromobenzene (**3q**, Table 6). As indicated in Tables 1 and 6, switching to higher-weight milling equipment (ZrO$_2$) afforded higher conversions of **12**,[7d,12] accompanied by a decreased selectivity for **13a**. Instead, noticeable amounts of de-iodinated starting material (**13c**) and the corresponding Sonogashira coupling product of **13c** (**13d**) were found.

Conclusions

An improved copper-, ligand-, and solvent-free experimental protocol for the Sonogashira coupling of aryl halides with aryl- and alkyl-substituted acetylenes in a planetary ball mill was developed. The employment of air-stable Pd(OAc)$_2$in combination with 1,4-diazabicyclo[2.2.2]octane as a catalyst and base, respectively, allowed for the chemoselective trasformation of aryl iodides. All coupling reactions showed high selectivities according to the desired Sonogashira products. Conversions of aryl iodides were controllable *via* variation of either the amount of Pd(II)-acetate or DABCO and showed good reproducibility. Furthermore, DABCO showed higher efficiency than other commonly used bases. Modification of the standard reaction procedure by three different methodologies also allowed the transformation of aryl bromides: i) substitution of Pd(OAc)$_2$ by Pd(PPh$_3$)$_4$, ii) replacement of agate milling beakers and balls by higher-weight equipment made of ZrO$_2$ or/and iii) employment of alumina as filling material instead of fused quartz sand.

The avoidance of organic solvents and the easy, fast and energy-saving accomplishment of the reaction makes this method a real alternative to conventional reaction protocols, especially in regard to the concept of green chemistry. This was proven by the employment of unusual, but synthetically important, substrates like 3-hydroxyalkynes or bis-ethynyl compounds. The presence of terminal carbon–carbon triple and double bonds in one molecule chemoselectively afforded the Sonogashira coupling product, instead of the Mizoroki–Heck coupling product.

Experimental

General

All chemicals were purchased from Sigma Aldrich or Alfa Aesar and were used as received. Reactions were accomplished in a Fritsch "Pulverisette 7 classic line" (Fritsch GmbH, Idar-Oberstein, Germany) planetary ball mill using 45 ml grinding beakers (agate, ZrO$_2$) and milling balls (6 × 15 mm; agate or ZrO$_2$). All reaction vessels were cleaned with *aqua regia* prior to use to avoid any contamination or memory effects.

GC-FID measurements were performed on a 6890-GC and GC-MSD measurements were accomplished with a 6890N-GC-MS, both from Agilent Technologies. Measurement conditions GC-FID: HP 5, 30 m × 0.32 mm × 0.25 µm, H$_2$ 10 psi, program: 70 °C (hold for 3 min), 15 K min^{-1} up to 280 °C (hold for

10 min), injector temperature: 280 °C, detector temperature: 300 °C. Measurement conditions GC-MSD: HP 5, 30 m × 0.32 mm × 0.25 μm, He 10 psi, program: 70 °C (hold for 3 min), 15 K min^{-1} up to 280 °C (hold for 7 min), injector temperature: 280 °C, detector: EI (70 eV). NMR spectra were recorded with a Bruker Avance 200 MHz system at room temperature in deuterochloroform ($CDCl_3$) as a solvent, using tetramethylsilane as internal standard.

All product yields reported herein are calculated from GC-data and are comparable with the isolated ones. Nevertheless, the reported yields were corrected by means of different FID-sensitivity for substrate and product. The reported yields are mean values from at least two independent experimental runs.

Typical reaction procedure for the Sonogashira coupling

The grinding beakers (45 ml; agate or ZrO_2) were equipped with 6 milling balls of the same material (d = 15 mm). Afterwards SiO_2 (= fused quartz sand; 5 g), the acetylene compound (2.5 mmol), 1,4-diazabicyclo[2.2.2]octane (= DABCO; 2.5 mmol, 280 mg), the aryl halide (2 mmol) and $Pd(OAc)_2$ (5 mol%, 25 mg) were added in the given order. Milling was carried out at 800 rpm for 20 min. After cooling of the grinding beakers to room temperature (10 min), the crude products were extracted on a frit with a thin silica layer using chloroform (3 × 10 ml). The solvent was evaporated in vacuum, the crude products were dried, re-dissolved in 1.5 ml of chloroform and analyzed by GC-FID and GC-MS.

Analytical samples for NMR investigations were isolated by column chromatography using a n-hexane–toluene mixture (1 : 1) as the eluent. Products were identified according to the literature data. For the analytical details of the isolated products, see the ESI.†

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Referenz [7]

Fast, ligand-. and solvent-free synthesis of 1,4-substituted buta-1,3-diynes by Cu-catalyzed homocoupling of terminal alkynes in a ball mill

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Chem.-Eur. J. **2011**, *17*, 8129-8138

A method for the Glaser coupling reaction of alkynes by using a vibration ball mill has been developed. The procedure avoids the use of ligands and solvents during the reaction. Aryl- and alkyl-substituted terminal alkynes undergo homo-coupling if co-ground with KF-Al_2O_3 and CuI as a milling auxiliary and catalyst. Furthermore, an alternative protocol has been developed incorporating 1,4-diazabicyclo-[2.2.2]octane (DABCO) as an additional base allowing the use of KF–Al2O3 with a lower KF loading. Besides Cu salts, the homo-coupling of phenylacetylene is also catalyzed by Ni- or Co-salts, as well as by $PdCl_2$. TMS-protected phenylacetylene could be directly converted into the homo-coupling product after in situ deprotection of the alkyne by fluoride-initiated removal of the trimethylsilyl group.

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Fast, Ligand- and Solvent-Free Synthesis of 1,4-Substituted Buta-1,3-diynes by Cu-Catalyzed Homocoupling of Terminal Alkynes in a Ball Mill

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Abstract: A method for the Glaser coupling reaction of alkynes by using a vibration ball mill has been developed. The procedure avoids the use of ligands and solvents during the reaction. Aryl- and alkyl-substituted terminal alkynes undergo homocoupling if co-ground with KF–Al_2O_3 and CuI as a milling auxiliary and catalyst. Furthermore, an alternative protocol has been developed incorporating 1,4-diazabicyclo[2.2.2]octane (DABCO) as an additional base allowing the use of KF–Al_2O_3 with a lower KF loading. Besides Cu salts, the homocoupling of phenylacetylene is also catalyzed by Ni or Co salts, as well as by $PdCl_2$. TMS-protected phenylacetylene could be directly converted into the homocoupling product after in situ deprotection of the alkyne by fluoride-initiated removal of the trimethylsilyl group.

Keywords: alkynes · ball milling · copper · cross-coupling · homocoupling · materials science

Introduction

The first homocoupling of terminal alkynes was reported by Glaser in 1869.[1] He discovered that the dimerization of phenylacetylene to form 1,4-diphenylbuta-1,3-diyne proceeds with high selectivity in the presence of copper salts and air as the oxidant. Similar products with a buta-1,3-diyne moiety are now widely applied within materials science and molecular electronics, for the synthesis of polymers, supramolecular materials, and drugs.[2,3]

In general, this reaction requires an organic solvent, for example, methanol or pyridine, to take place in noticeable quantities. Focused research to improve the classical procedure has led to interesting variations of the original method. Thus, the quantity of volatile or hazardous organic solvents can be reduced by the employment of supercritical CO_2,[4] ionic liquids,[5] (near-critical) water,[6] or polyethylene glycol (PEG) as the solvent.[7] However, protocols are also known that totally omit the solvent.[8–12] The first solvent-free procedure for an alkyne homocoupling involved a $CuCl_2$–pyridine complex as the catalyst.[8] Kabalka et al. took advantage of dielectric heating in a microwave oven to perform the Glaser reaction in the absence of a solvent.[9] The best results occurred in the presence of KF–Al_2O_3 (40 w% KF) and $CuCl_2$. Within very short reaction times they achieved a 75% yield for the model reaction with phenylacetylene, but an excess of the copper salt (3.7 equiv) was necessary. Sharifi et al. optimized this reaction by reducing the requirement for the copper salt to 5 mol% and replacing the fluoride loaded alumina with neutral Al_2O_3.[10a] However, morpholine was then required for this procedure. They also reported a coupling reaction with good yield by stirring the alkyne with morpholine, KF–Al_2O_3, and $Cu(OAc)_2$ at room temperature for 3 h.[10a] In comparison with the microwave enhanced route, the yield of 96% is an improvement, but the reaction time (3 h) is greatly increased.

The step from a solvent-free synthesis in a microwave oven to comminution in ball mills is often a small one. Ball mills have a range of applications in materials science, in which they are used to grind and homogenize, for example, minerals, or in the manufacturing of catalysts and nanoparticles.[13] However, ball mills have recently become interesting tools for organic synthesis because of the relatively mild reaction conditions they allow.[14] Examples of the use of ball mills are found for carbonyl reactions,[15] in fullerene chemistry,[16] and in Suzuki–Miyaura,[17] Mizoroki–Heck,[18] and Sonogashira cross-coupling reactions.[19] Additionally, the synthesis of peptide building blocks and heterocycles by this type of procedure has been reported.[20] Regarding metal catalysis, Pd is generally applied as the catalytically active component.[17–19] Only in a few cases are other metals employed; examples of these are 1) $InCl_3$ for naphthopyrane synthesis,[21] 2) Al flakes for intermolecular Aldol reactions of valeraldehyde,[22] 3) copper or CuI as a cocatalyst in Sonogashira cross-coupling reactions that use K_2CO_3 as the base,[19a] and 4) copper salts as catalysts in Huisgen 1,3-dipolar cycloaddition reactions between alkynes and azides.[23]

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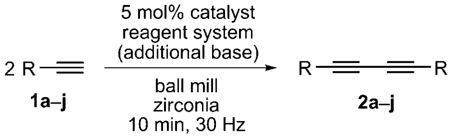
Interestingly, the last two, which involve Cu-(co)catalyzed reactions, lack the occurrence of homocoupling products, despite of the fact that Cu is present and may provoke this reaction pathway.

Results and Discussion

Recently, a procedure for the Sonogashira cross-coupling reaction in a ball mill was reported by using a Pd catalyst and 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base for deprotonation of the terminal alkyne.[19b] Solution-based procedures for this reaction often employ Cu^I as the cocatalyst, yielding Cu–acetylides as the reaction intermediates. In contrast, the ball mill variation runs in the absence of copper. Furthermore, the presence of Cu^I salts yielded product mixtures showing a decreased selectivity for the cross-coupled product. Instead, an increase in the amount of alkyne homocoupling product (the Glaser reaction) was reported for the reaction in ball mills in the presence of strong bases like DABCO.[19b] In the absence of strong bases no effect on the selectivity for the products due to homocoupling was reported.[19a,23]

These results motivated us to develop a reaction protocol for the Glaser reaction in a ball mill. Thus, the challenge was to find catalysts that allowed the transformation of terminal alkynes (**1**) into the corresponding 1,4-substituted buta-1,3-diynes (**2**, Scheme 1) in a time- and energy-efficient manner. The reactions were carried out in a ball mill by using zirconia (ZrO_2) as the material for the milling beakers and balls. The reactions were carried out by using the maximum oscillation frequency ($\nu_{osc}=30$ Hz) of the ball mill used in the experiments.



Scheme 1. Generic reaction scheme for the Glaser coupling reaction of terminal alkynes (**1**) to form 1,4-substituted buta-1,3-diynes (**2**) initiated by ball milling (model reaction: **1a** to **2a**, R = Ph).

Table 1. The correlation between the milling auxiliary and the yield of 1,4-diphenylbuta-1,3-diyne (**2a**; Scheme 1).[a]

Entry	Type of solid reagent system[b]	Yield of **2a** [%][c]
1	commercial KF–Al$_2$O$_3$[d]	42
2	commercial KF–Al$_2$O$_3$[d,e]	96
3	commercial KF–Al$_2$O$_3$	89
4	commercial KF–Al$_2$O$_3$[e]	99
5	α-Al$_2$O$_3$ (acidic)	0
6	γ-Al$_2$O$_3$ (neutral)	0
7	γ-Al$_2$O$_3$ (basic)	0
8	quartz sand	0
9	silica gel 60	0
10	KF–Al$_2$O$_3$ (α; acidic)	31
11	KF–Al$_2$O$_3$ (γ; neutral)	76
12	KF–Al$_2$O$_3$ (γ; basic)	53
13	KF–quartz sand	0
14	KF–silica gel 60	0
15	KF–Al$_2$O$_3$ (γ; neutral), impregnation method[f]	91
16	KF–Al$_2$O$_3$ (γ; neutral), calcined[f]	46

[a] Reaction conditions: **1a** (2 mmol), CuI (5 mol %), 4 g reagent system, ZrO_2 beaker (35 mL), 12 × ZrO_2 milling balls (10 mm), $\nu_{osc}=30$ Hz, $t=$ 10 min. [b] Unless otherwise stated the KF content was 40 w %. [c] Found by GC-FID analysis after intermediate workup. Product selectivity >99 %. [d] KF content = 32 w %. [e] Reaction was carried out in the presence of DABCO (2.5 mmol). [f] Impregnation and calcination performed by following to reference [24c].

Influence of the base and milling auxiliary: The first challenge was to identify the best base for the homocoupling reaction. In the presence of CuI as the catalyst,[10a] the reaction of phenylacetylene (**1a**) to form 1,4-diphenylbuta-1,3-diyne (**2a**) was used as the model system to find bases suitable for the reaction (Table 1). Oxides like silica and alumina, which showed high activity in the Sonogashira reaction in presence of DABCO,[19b] failed in the model reaction both in the presence and absence of DABCO (entries 5–9, Table 1). The use of commercially available KF–Al$_2$O$_3$ with 32 or 40 w % KF furnished **2a** in 42 and 89 % yield, respectively (entries 1 and 3, Table 1). Quantitative yields were achieved with these reagents if the reactions were carried out in the presence of DABCO (2.5 mmol) as an additional organic base (entries 2 and 4, Table 1). The application of KF–Al$_2$O$_3$ in solvent-free reactions appears prominently for many types of transformation.[17d–e,24] The present results confirm the general ability of KF–Al$_2$O$_3$ reagent systems to perform this type of reaction. In comparison to the homocoupling reaction procedure involving grinding the reactants by using a stirring bar,[10b] morpholine has been replaced by the less toxic base DABCO or the reaction occurs without additional base. Microwave-assisted reaction protocols for the Glaser reaction that run with KF–Al$_2$O$_3$ in the absence of an organic base suffer from the fact that the catalyst ($CuCl_2$) has to be applied in greater than stoichiometric quantities.[9]

The general applicability of KF–Al$_2$O$_3$ for the synthesis of **2a** has thus been demonstrated. However, the commercial reagents are based on different alumina modifications. Thus, physical mixtures of acidic α-, neutral γ-, and basic γ-Al$_2$O$_3$ with a KF content of 40 w % and similar particle size distributions have been applied in the same reaction. Neutral γ-Al$_2$O$_3$ furnished the highest yields under the experimental conditions (entries 10–12, Table 1). Rather than simply mixing KF and Al$_2$O$_3$ with **1a** and the catalyst (CuI), KF–Al$_2$O$_3$ can also be prepared by an impregnation method. This material was prepared by suspending neutral γ-Al$_2$O$_3$ in an aqueous KF solution with subsequent removal of the solvent in vacuo.[9,10b,17c–e,24c,25] Simple physical mixing of the reactants afforded lower yields for both concentrations of KF than commercial KF–Al$_2$O$_3$, but the reaction with KF–Al$_2$O$_3$ prepared by the impregnation method yielded 91 % **2a** after 10 min of ball milling, which is in the same range as with the respective commercial reagent (89 %).[26] Calcination of the synthesized KF–Al_2O_3 for 2 h at 300 °C prior to application in the homocoupling of **1a** to form **2a** (Scheme 1) resulted in moderate yields (46 %). This result is in accordance with the deactivation reported for $Pd(OAc)_2$-catalyzed Suzuki–Miyaura cross-coupling reactions in a planetary ball mill.[24c]

Considering the mass content of 40 w% KF in the KF–Al_2O_3 reagent and the applied amount in the reaction (4 g), 27.5 mmol of fluoride is available to deprotonate the terminal alkyne and initiate the reaction. Replacing the alkali cation and keeping the fluoride-content constant by using CsF as the fluoride source gave a 32 % yield of **2a**, whereas the application of NaF and MgF_2 failed to facilitate the reaction.[27] The employment of more complex fluoride anions, such as $NH_4[BF_4]$ and $Na_3[AlF_6]$ (kryolithe), was also unsuccessful. Thus, the combination of KF and neutral γ-Al_2O_3 seems to be required for the Glaser reaction in a ball mill, since the reagent combination KF–SiO_2 (entries 13 and 14, Table 1) also failed. As indicated previously, the alumina modification[24c] is as important to the reaction as the KF content if working with KF–Al_2O_3 reagents.[17c,24c,28] The correlation between the yield of homocoupling product **2a** (Y_{2a}) and the mass fraction of KF (w_{KF}) in the solid reagent system is illustrated in Figure 1. A clear linear relationship between Y_{2a} and w_{KF} is shown over a data range that almost reaches quantitative yield with a KF loading of 60 w%. This behavior is also in line with the application of the commercial reagent systems listed in Table 1, entries 1 and 3.

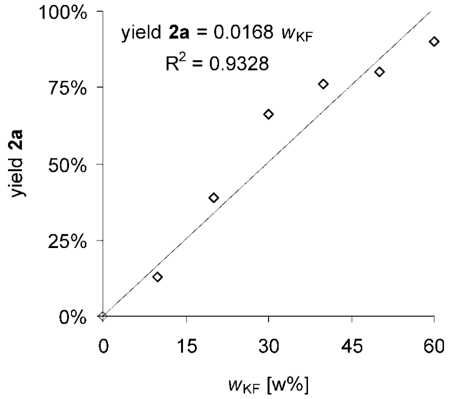


Figure 1. The correlation between KF content and yield of **2a** (see Scheme 1) resulting from homocoupling of **1a** (for reaction conditions, see Table 1; reagent system: KF–Al_2O_3 (γ; neutral), intermediate workup).

However, the application of low loadings of KF–Al_2O_3 required the presence of an additional organic base to drive the reaction to completion in a reasonable time. Table 2 displays the influence of bases on the reaction of **1a** to form **2a** with commercial KF–Al_2O_3 (32 w%). Alternative organic (NEt_3) and inorganic (KOH, K_2CO_3) bases to DABCO showed only minor effects on product yield compared to the reaction with only KF–Al_2O_3. However, the selectivity for **2a** was almost completely independent of the base applied.

Table 2. Screening of bases for the Glaser reaction of phenylacetylene (**1a**; Scheme 1).[a]

Base	Yield of **2a** [%][b]
without additional base	42
1,4-diazabicyclo[2.2.2]octane	96
triethylamine	51
tetrabutylammonium bromide	0
KOH	54
K_2CO_3	43

[a] Reaction conditions: **1a** (2 mmol), base (2.5 mmol), CuI (5 mol %), KF–Al_2O_3 (4 g, 32 w%, commercial), ZrO_2 beaker (35 mL), 12 × ZrO_2 milling balls (10 mm), $\nu_{osc} = 30$ Hz, $t = 10$ min. [b] Found by GC-FID analysis after intermediate workup. Product selectivity > 99 %.

The positive effect of *N*-coordinating bases on this reaction is also stressed by mechanistic DFT calculations at the B3LYP/LACVP level of theory.[29] These calculations indicated that no solvent molecules are involved in the Cu-catalyzed homocoupling of alkynes. The total inactivity of tetrabutylammonium bromide (TBAB) and the unobserved additional effect of triethylamine (NEt_3) can be traced back to different origins. Since NEt_3 is a liquid,[11] its incorporation in the reaction is less successful than that of the solid base DABCO. In contrast to DABCO and Et_3N, TBAB has no free coordination site on the nitrogen atom, making it a less active base and hindering its interaction with both copper and the alkyne in the transition state.

The influence of oxygen and catalyst: The generally accepted reaction mechanism for the catalytic cycle of the Glaser reaction involves oxidative regeneration of the Cu catalyst after reductive elimination of the 1,3-diyne product.[3a,29,30] Generally, the reactions are carried out in air either under active mass transport of the oxidant into the solution (solvent saturation) or by passive exposure to air. The latter technique is favored in solvent-free methods.[8–12] One limitation of ball milling technology is the restricted volume of the reactor. Assuming material densities for KF (60 w%), γ-Al_2O_3, and zirconia (milling balls) of 2.5, 4.0, and 6 $g\,cm^{-3}$, respectively, a free reaction volume in the milling beaker of 28 mL can be calculated, excluding the amount of catalyst and substrate. Due to preparation of the reaction mixtures in an air atmosphere, approximately 0.25 mmol of oxygen (as O_2) are present for reoxidation of the catalyst. Thus, an oxidant deficiency is normally present that will prevent the reaction from proceeding to completion under standard conditions. Opening of the reactor after milling exposes the reaction mixture to air and incorporates oxygen into the reaction mixture.[31] This fast post-milling process probably accounts for the high yields discussed in Tables 1 and 2, as well as in Figure 1. To guarantee reproducibility, the reaction of **1a** to form **2a** (Scheme 1) was performed with different metal(II) chlorides (M = Cu, Ni, Co, Pd), as well as with CuI. Samples of the reaction mixture were withdrawn from the milling beakers immediately after opening and after various air-exposure times (Figure 2). Apart from $PdCl_2$, the metal salts revealed similar behavior. The samples taken im-

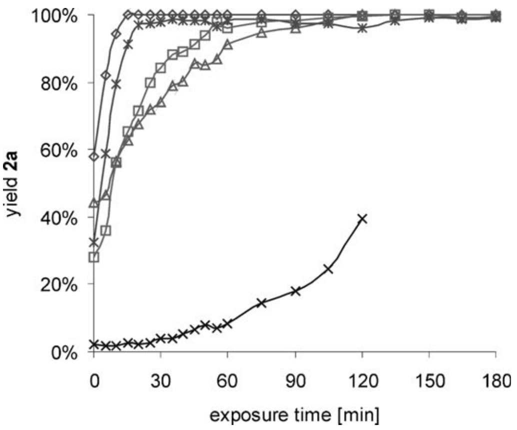


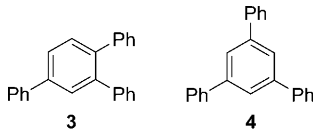
Figure 2. Dependence of the yield of **2a** (see Scheme 1) on the time the reaction mixture is exposed to air for different metal salts as the catalyst (phenylacetylene (2 mmol), catalyst (5 mol%; ◇ = $CuCl_2$, □ = $NiCl_2$, △ = $CoCl_2$, × = $PdCl_2$, ∗ = CuI), $KF–Al_2O_3$ (4 g, γ-Al_2O_3, neutral, 60 w% KF), ZrO_2 beaker (35 mL), 12 × ZrO_2 milling balls (10 mm); $\nu_{osc} = 30$ Hz, $t = 10$ min).

mediately after opening the reaction vessel indicate that Y_{2a} ranges from 28 ($NiCl_2$) to 58% ($CuCl_2$). After exposure to air for 30 min, $CuCl_2$ and CuI provided quantitative yields, whereas reactions with $NiCl_2$ and $CoCl_2$ needed three times as long to reach a similar level of conversion.

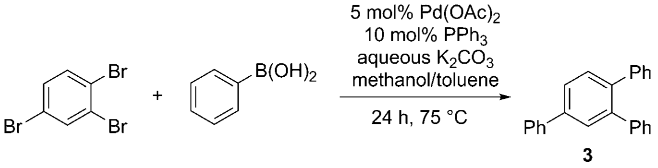
In contrast to 1,3-dipolar cycloaddition between alkynes and azides,[23] the oxidation state of the Cu catalyst seems to be essential for the homocoupling in a ball mill. Comparing the initial values for $CuCl_2$ (58%) and CuI (32%) proves the influence of the oxidation state of the copper salt. Cupric chloride converts twice the amount of reactant before it is reduced to Cu and requires reoxidation for further reaction cycles (see also Table 3 shown later). Similar experiments with ferric and ferrous chloride led to no conversion at all over the time range.[32] For the Cu-, Ni-, and Co-catalyzed reactions a pseudo-zero-order reaction rate was determined concerning the formation of **2a**. This is typical for reactions suffering from mass-transport limitations, such as diffusion of the oxidant towards the catalyst.

Experiments with CuI in the presence of different inorganic oxidants afforded significantly higher yields than under only the enclosed air. The addition of Oxone (0.5 mmol), $(NH_4)_2S_2O_8$ (1 mmol), or aqueous H_2O_2 (100 μL, 60 w%) to the reaction mixture before ball milling furnished **2a** in 64, 72, and 98% yield, respectively. These results are in clear contrast to the inactivity of CuI in combination with "Na_2BO_4" as the oxidant in the microwave-assisted homocoupling of **1a**,[9] in which the application of the reagents in both 3.7:1 and 7.4:1 ratios compared to **1a** provided only 9% **2a** compared to 17% in the absence of the oxidant.[9]

As already demonstrated in similar Sonogashira reactions, $PdCl_2$ is inactive in the transformation of terminal alkynes in a ball mill if the reaction mixture is subsequently worked up after the reaction (Figure 2).[19b] Thus, only small amounts of **2a** are formed, along with the formation of Pd^0, which is inactive in the homocoupling process. Further exposure to air leads to an exponential increase in the yield of **2a**. Compared to other Pd-catalyzed homocoupling reactions, the reaction proceeded in the absence of a cocatalyst[33] and did not need the addition of *p*-iodophenol.[11] After 120 min of exposure to air no starting material was detected and **2a** was formed in only 40% yield. Instead, oligomerization of **1a** was detected. Two trimers of **1a** have been identified from the reaction mixture: 1,2,4-triphenyl- (**3**) and 1,3,5-triphenylbenzene (**4**; Scheme 2). Identification of **3** and **4** was difficult, since their concentration in the reaction mixture was relatively low and isolation was therefore not possible. However, comparison of mass spectra (see the Supporting Information) and retention times in GC-MS, as well as GC-FID, analyses with those from reference compounds was successful. Reference compound **3** was synthesized from 1,2,4-tribromobenzene and phenylboronic acid by Suzuki–Miyaura cross-coupling (Scheme 3).[34] The gas chromatogram of the crude reaction mixture from the $PdCl_2$-catalyzed reaction after 120 min of exposure to air is pictured in Figure 3. The results indicate that **3** and **4** are the only cyclic trimers formed.



Scheme 2. The cyclotrimerization products of phenylacetylene (**1a**) identified in the product mixture of the reaction carried out in the presence of $PdCl_2$ (for the reaction conditions, see Figure 2).



Scheme 3. Reference synthesis for the identification of compound **3** in the Pd-catalyzed reaction of **1a** (see Figure 2).

The ratio of **3** to **4** is 5:4 (Figure 3) showing that formation of the symmetrical structural isomer is disfavored. The formation of cyclotrimerization products from terminal alkynes catalyzed by Pd^0 and Pd^{II} is well studied.[35] Besides trimerization, oligo- and polymerization have been reported with $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) and in the absence of phosphine ligands.[35a] In the present case, a thermal [2+2+2] cycloaddition can be ruled out since reaction in the absence of the catalyst did not show any conversion of **1a**. Other metal salts tested for the reaction (see Table 3) did not yield side-products **3** and **4**. In contrast to the reactions with the Cu, Ni or Co salts (Figure 2), the reaction in the presence of $PdCl_2$ is of pseudo-first order with regard to formation of **2a**.

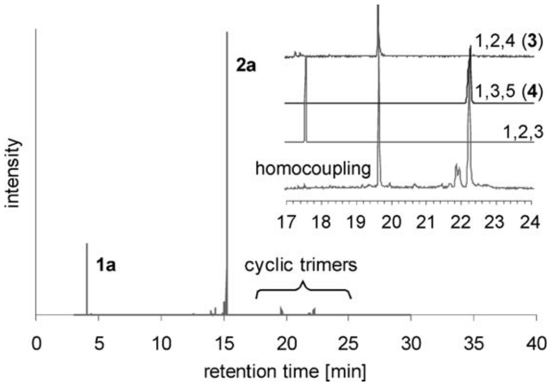


Figure 3. Gas chromatogram of the crude reaction mixture resulting from the $PdCl_2$-catalyzed Glaser reaction of **1a** (exposure time = 120 min; for conditions see Figure 2) and the identification of cyclic trimers **3** and **4** (Scheme 2).

Screening of catalysts: Based on the aforementioned evaluation of the reagent system (KF content, fluoride source, Al_2O_3 modification), the presence of an additional base and the air-exposure time after ball milling, three different reaction procedures have been used for screening different metal catalysts (Table 3). Procedures **A** and **B** were carried out with KF–Al_2O_3 (γ, neutral, 4 g, 60 w%); in the former the product mixture is immediately worked up, whereas in the latter the mixture is exposed to air for a further 30 min. Procedure **C** involves the employment of KF–Al_2O_3 (commercial, 4 g, 32 w%) and DABCO (2.5 mmol). Following procedure **A** the mixture is extracted immediately after opening the milling beaker. Common metal salts were tested for their applicability as a catalyst in the homocoupling of phenylacetylene (**1a**) to form 1,4-diphenylbuta-1,3-diyne (**2a**; Scheme 1) in a mixer ball mill. Results for this variation are summarized in Table 3. The general trend, already discussed above in connection with Figure 2, was also observed in the case of metal salts with other anions, provided that the reaction worked at all. Thus, procedure **B** lead to higher yields than **A**. Compared to the reaction in the presence of the diamine DABCO (**C**), method **B** lead to superior results in most cases.

Table 3 demonstrates that the formation of **2a** by homocoupling of **1a** (Scheme 1) can be catalyzed by various Cu, Ni, and Co salts, whereas no reaction occurred in the presence of ferrous and ferric salts or $RuCl_3$. $PdCl_2$ afforded only low yields. The reactivity of the different metals decreases in the order: Cu > Ni ≥ Co ≫ Pd. Generally, the selectivity for the Glaser coupling product (**2a**) was nearly 100%, with no side-products being found regardless of the type of catalyst. Thus, the obvious differences in yields are traced back to different degrees of conversion. The application of CuO or copper metal (powder) afforded very low conversion. In situ comproportionation of CuO and Cu in equal amounts, furnishing Cu_2O, yielded minor amounts of **2a**. Despite the fact that CuI and $Cu(NO_3)_2$ are the most suitable catalysts, it is astonishing that the reaction proceeds at all with Ni and Co salts. Thus, the first solvent-free procedures for the homocoupling of **1a** in the presence of these catalysts have been found. Additionally, the reaction did not require Cu salts as cocatalysts, nor the presence of ligands, and the catalyst concentrations are relatively low, compared to literature procedures working with Ni,[36] Co,[37] and Pd catalysts.[11,33b,c]

Table 3. The influence of different metal salts employed as catalysts on the yield of 1,4-diphenylbuta-1,3-diyne (**2a**; Scheme 1).[a]

Catalyst	Yield of **2a** [%] for workup procedure:[b] **A**[c]	**B**[d]	**C**[e]
Cu	0	0	0
CuCl	40	90	62
CuBr	39	69	64
CuI	32	>99	96
CuOAc	50	97	66
$CuCl_2$	59	>99	73
$Cu(OAc)_2$	58	92	72
$Cu(acac)_2$	45	69	74
$Cu(NO_3)_2{\cdot}3H_2O$	84	>99	89
CuO	4	14	4
$NiCl_2$	28	87	37
$NiBr_2$	14	67	32
$Ni(OAc)_2{\cdot}4H_2O$	27	72	40
$Ni(acac)_2$	23	56	40
$Ni(NO_3)_2{\cdot}6H_2O$	11	44	45
$CoCl_2$	50	70	57
$Co(acac)_3$	29	49	37
$FeCl_2$	0	0	–
$FeSO_4$	0	0	–
ferrocene	0	0	–
$FeCl_3$	0	0	–
$K_3[Fe(CN)_6]$	0	0	–
$PdCl_2$	2	4	–
$RuCl_3{\cdot}H_2O$	0	0	0

[a] Reaction conditions: **1a** (2 mmol), catalyst (5 mol%), KF–Al_2O_3 (4 g, γ-Al_2O_3, neutral, 60 w% KF), ZrO_2 beaker (35 mL), 12 × ZrO_2 milling balls (10 mm), ν_{osc} = 30 Hz, t = 10 min; acac = acetylacetone. [b] Found by GC-FID analysis. Product selectivity >99%. [c] **A**: immediate work up after the reaction. [d] **B**: after milling the mixture was exposed to air for 30 min without further mixing. [e] **C**: the reaction was carried out with KF–Al_2O_3 (32 w%, commercial) and DABCO (2.5 mmol) and subsequently worked up.

Substrate screening: Based on the screening reactions (Scheme 1; variation of milling auxiliary, catalyst, and base), the scope of the reaction was then extended to the coupling of different alkynes. Thus the influence of substituents on the course of the reaction has been studied (Table 4) by using procedures **B** and **C**. Although other aryl- and alkyl-substituted terminal alkynes (**1a**–**i**) were suitable for Glaser coupling following both procedures, 3-ethynylpyridine (**1j**) showed no conversion if the reaction was carried out in the presence of DABCO (procedure **C**). However, the effects of electron-donating substituents like methyl or methoxy groups on conversion were recognizable. With these substrates, lower yields of buta-1,3-diynes were observed. By doubling the amount of CuI (10 mol%) and the reaction time (20 min), the less reactive alkynes (**1b**, **c**, **e**, **h**, and **i**) could also be converted quantitatively. However, all of the alkynes preserve excellent selectivity (>96%) for the homo-

Table 4. Screening of different terminal alkynes (**1**) in the homocoupling furnishing buta-1,3-diynes (**2**; Scheme 1).[a]

R group	2	Workup procedure **B**[b] Yield [%]	Selectivity [%]	Workup procedure **C**[c] Yield [%]	Selectivity [%]
C_6H_5	**2a**	>99	>99	96	>99
C_6H_5[d]	**2a**	3	98	13	99
C_6H_5[e]	**2a**	–	–	1	99
o-Me-C_6H_4	**2b**	88	97	99	>99[f]
p-Me-C_6H_4	**2c**	88	95	77	>99
o-MeO-C_6H_4	**2d**	72	89	92	>99[f]
m-MeO-C_6H_4	**2e**	80	91	98	>99[f]
p-MeO-C_6H_4	**2f**	68	90	70	>99
p-F-C_6H_4	**2g**	90	98	93	>99
C_8H_{17}	**2h**	92	93	96	>99[f]
$C_{10}H_{21}$	**2i**	89	91	89	>99[f]
3-pyridyl	**2j**	88	92	0	–

[a] Reaction conditions: **1** (2 mmol), catalyst (5 mol %), KF–Al_2O_3 (4 g, γ-Al_2O_3, neutral, 60 w% KF), ZrO_2 beaker (35 mL), 12 × ZrO_2 milling balls (10 mm), ν_{osc} = 30 Hz, t = 10 min. [b] **B**: after milling the mixture was exposed to air for 30 min without further mixing. [c] **C**: reaction was carried out with KF–Al_2O_3 (32 w%, commercial) and DABCO (2.5 mmol) and subsequently worked up. [d] Cryogenic milling: milling beakers were cooled with liquid nitrogen prior to ball milling. [e] Cryogenic milling under constant cooling with liquid nitrogen. [f] Catalyst (10 mol %); t = 20 min.

coupling product. Considering the fact that only 5 mol % of copper was used, the solvent-free conversion in the ball mill is much more efficient than its solvent-free counterpart in a microwave envisioned by Kabalka et al., for which 3.7 equivalents of copper salt were required to achieve similar yields.[9]

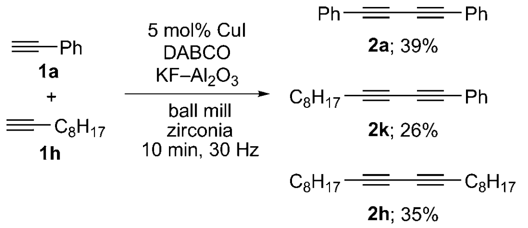
The alkynes summarized in Table 4 are liquids at room temperature (**1a**–**e**, **h**, and **i**) or possess a melting point below 50 °C (**1f** = 28–29, **g** = 26–27, and **j** = 39-40 °C).[35] Due to the fact that high-energy collisions of milling balls result in heating of the reaction mixture up to 50–60 °C[17e] these reagents remain liquid or are adsorbed onto the solid milling auxiliary. Another option to solidify liquid reagents is cryogenic milling, that is, the comminution of reactants cooled down to the temperature of liquid nitrogen[15e,39] or the performance of reactions in temperature-controlled reaction vessels.[40] The first method was applied to the synthesis of **2a** from **1a**, yielding the product in 3 and 13 % yields, working with 60 w% KF–Al_2O_3 or with the commercial 32 %-loaded reagent with DABCO (2.5 mmol), respectively (Table 4). The lowered yield is in agreement with cryogenic milling experiments using the Knoevenagel condensation[15e] and Tishchenko reaction[39] procedures in a mixer and vibration ball mill, respectively. If the reaction is carried out under constant cooling of the milling beakers with liquid nitrogen the reaction is totally suppressed and only 1 % of **2a** was identified after ball milling. Prolonged standing at room temperature resulted in unfreezing of the reactants. Thus, reversible freezing of molecular motion does not inhibit the particle refinement and the formation of new, active surfaces at which the reaction takes place. The recovered molecular flexibility allowed the reaction to proceed (Table 5) and the presence of DABCO increased the reactivity of the mixture, as already shown in Table 1.

Table 5. Cryogenic milling of phenylacetylene (**1a**) to yield 1,4-diphenylbuta-1,3-diynes (**2a**; Scheme 1).[a]

Exposure time [min]	KF–Al_2O_3 (60 w%) Yield [%]	Selectivity [%]	KF–Al_2O_3 (32 w%), DABCO (2.5 mmol)[b] Yield [%]	Selectivity [%]
0	3	>99	13	>99
10	12	>99	38	98
30	55	98	88	90

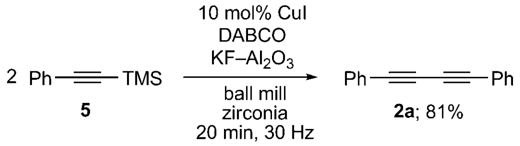
[a] Reaction conditions: **1a** (2 mmol), CuI (5 mol %), KF–Al_2O_3 (4 g, γ-Al_2O_3, neutral), ZrO_2 beaker (35 mL), 12 × ZrO_2 milling balls (10 mm), closed milling beakers were cooled to the temperature of liquid nitrogen prior to milling, ν_{osc} = 30 Hz, t = 10 min. [b] Reaction was carried out with KF–Al_2O_3 (32 w%, commercial).

An attempt to cross-couple two different alkynes (**1a** and **h**; Scheme 4) resulted in a mixture of all three possible products in comparable yields, although the homocoupled products **2a** and **h** were slightly preferred. Similar reactions in a microwave preferentially gave rise to the cross-coupling product **2k**.[9,32,37c] In comparison with the Co-catalyzed procedure ($CoBr_2$, Zn, nitrobenzene, P(O*i*Pr)$_3$),[37c] the absence of a defined coordination sphere allows the formation of the statistical mixture of products only. These results indicate that either greater than stoichiometric amounts of copper initiate the cross-coupling or both modes of activation pass through different activation pathways. In the presence of high concentrations of Cu the possibility for the formation of Cu–alkyne species is much higher. These species can undergo oxidative coupling to the mixed product more easily. In the present case it seems more plausible that both reaction partners are coordinated to the same Cu center during the course of the reaction. Extrusion of the metal in the final step then provides the buta-1,3-diyne.[3a,29,30]



Scheme 4. The coupling reaction of phenylacetylene (**1a**) and decyne (**1h**; reaction procedure **C**, see Table 4; full conversion).

In addition, it was found that the nature of the alkyne and the scope of the reaction can be further extended. It is, for example, possible to use trimethylsilyl (TMS)-protected phenylacetylene (**5**) directly in the coupling reaction (Scheme 5).[9] It is known that the TMS group can be cleaved by KF deprotection procedures in solution.[41] Milling of **5** in the presence of KF–Al_2O_3 furnished the free alkyne in situ and the Cu catalyst converted it to the homo-



Scheme 5. In situ deprotection and Glaser coupling of TMS–acetylene (**3**; reaction procedure **C**, see Table 4; 100 % selectivity).

coupling product. Analysis indicates that no free phenylacetylene is present in the reaction mixture. However, conversion of **5** was lower than that of free phenylacetylene (**1a**), although the selectivity for the coupling product was still high (95 %). Thus, it can be concluded that the removal of *p*-TMS is the rate-determining step. As well as deprotection of **5**, this reaction variant was possible with *p*-(TMS-ethynyl)toluene and 4-(TMS-ethynyl)trifluoromethylbenzene, but resulted in considerably lower yields of the homocoupling products. The importance of the fluoride ion in this reaction is underlined when comparing the results with those reported recently by Mack and co-workers.[19a] TMS-acetylene was applied as a substrate for Sonogashira reactions in a ball mill by using K_2CO_3 as the base instead a fluoride reagent. Thus, no deprotection was reported after ball milling for 17 h.

Comparison of methods and energy entry: Comparison of different reaction conditions that have been published for a solvent-free Glaser reaction revealed the pre-eminence of reactions carried out in microwave ovens[9,10a] or ball mills with respect to reaction time (Table 6).[8–12] Apart from the solvent-free syntheses of **2a** presented herein (Table 6), two protocols exist wherein the formation of **2a** is reported as a side-reaction in Cu-catalyzed[42] or DABCO-mediated metal-free[43] Sonogashira cross-coupling reactions. Maximum yields of 56 and 16 % are achieved, respectively. Calculation of the turn-over frequencies (TOF) for the different protocols in Table 6 indicate that ball milling is as powerful as microwave irradiation,[10a] giving TOFs of 115 and 98 h^{-1}, respectively. However, it must be noted that in the microwave reaction protocol with a TOF of 98 h^{-1} the reactants were mixed in a mortar and pestle prior to the reaction.[10a] This step is not considered in the calculation of the catalyst activity. Ball mills inherently have a very high mixing efficiency. Thus, diffusion and mass transport problems are avoided due to the fast movement of the milling balls during the process.[13c,d,44]

Besides the practical advantages associated with the application of ball mills to solvent-free organic syntheses, the energy efficiency of such processes is also higher than for comparable reactions carried out in microwaves or under the influence of ultrasound.[15e,17e,45] Performing the model reaction with 2 mmol of **1a** (Scheme 1) in a mixer ball mill following protocol **C** furnished **2a** in 96 and 13 % yield for normal and cryogenic milling, respectively (Table 6). Calculation of the energy intensity[17e] resulted in values of 8.9 and 63.2 kWh mol^{-1}. Scaling up of the reaction in a ball mill required a change of apparatus and thus a change in the type of motion from oscillation (mixer ball mill) to rotation (planetary ball mill).[46] However, results indicated that scaling up the reaction to 3 and 4.5 mmol has little effect on the yield and TOF (Table 6). Keeping the reaction time the same gave 78 and 80 % yield of **2a**. The energy intensity increased slightly to 17.6 and 22.5 kWh mol^{-1} for reactions on a 3 and 4.5 mmol scale, respectively. Similar results have also been found for the scaling up of Suzuki–Miyaura cross-coupling reactions in ball mills.[17e] Compared to the application of ball mills in particle refinement processes,[13c,d] the size of the milling balls did not affect the experimental results. Performing the reaction with 10 × 10 or 6 × 12 mm milling balls resulted in similar yields since the masses of the milling balls are equal, which has also been proven for Suzuki–Miyaura[17d] and oxidation reactions[47] carried out in ball mills.

Conclusion

A new ligand- and solvent-free method for the Glaser coupling reaction in a vibration ball mill has been developed. Assessment of different metal salts identified Cu, Ni, and

Table 6. A comparison of different reaction conditions for solvent-free protocols for the Glaser reaction of phenylacetylene (**1a**) to form 1,4-diphenylbuta-1,3-diyne (**2a**; Scheme 1).[a]

Reference	Reaction conditions	Catalyst	Base	Additive	$n_{\mathbf{1a}}$ [mmol]	$n_{\mathbf{1a}}/n_{\text{catalyst}}$	t [min]	Yield of **2a** [%]	TON	TOF [h^{-1}]
[9]	microwave irradiation	$CuCl_2$	–	KF–Al_2O_3	1	0.27[b]	8	75	<1	1.5
[10a]	microwave irradiation[a]	CuI	morpholine	Al_2O_3	1	20	10	82	16	98
[10b]	stirring[a]	$Cu(OAc)_2$	morpholine	KF–Al_2O_3	1	5	180	96	5	1.6
[11]	stirring	[Pd][c]	Et_3N	*p*-iodophenol	1	100	720	84	84	7.0
[12]	stirring	$CuCl_2$	Et_3N	–	1	33	360	96	32	5.3
this work	mixer ball mill[d]	CuI	DABCO	KF–Al_2O_3	2	20	10	96	19	115
this work	mixer ball mill[d,e]	CuI	DABCO	KF–Al_2O_3	2	20	10	13	3	16
this work	planetary ball mill[f]	CuI	DABCO	KF–Al_2O_3	3	20	10	78	16	94
this work	planetary ball mill[g]	CuI	DABCO	KF–Al_2O_3	4.5	20	10	80	16	96

[a] Reactants were preground with a mortar and pestle prior to reaction; $n_{\mathbf{1a}}$ = amount of **1a**, n_{catalyst} = amount of catalyst. [b] Due to greater than stoichiometric employment of $CuCl_2$ the metal salt is not a catalyst in this case. [c] Immobilized Pd complex. [d] Reaction variant **C** (see Table 4). [e] Cryogenic milling: milling beakers were cooled with liquid nitrogen prior to ball milling. [f] Batch size: 1.5 × variant **C** in Table 4, ZrO_2 beaker (45 mL), 18 × ZrO_2 milling balls (10 mm), $\nu_{\text{rot}} = 13.3$ Hz, $t = 10$ min. [g] Batch size: 2.25 × variant **C** in Table 4, ZrO_2 beaker (80 mL), 30 × ZrO_2 milling balls (10 mm), $\nu_{\text{rot}} = 13.3$ Hz, $t = 10$ min.

Co compounds as potential catalysts for application in the homocoupling of phenylacetylene, although CuI was identified as the most effective catalyst. In combination with KF–Al_2O_3 as the base, high selectivity and conversion have been achieved in the reactions of various terminal alkynes with (hetero)aromatic, as well as aliphatic, substituents. Variation of the KF content in the KF–Al_2O_3 reagent and alteration of the alumina modification revealed a major influence of both variables on the product yield, although the selectivity remained unaffected. The use of 60 w% KF and neutral γ-alumina allowed the reaction to be performed in the absence of additional base, whereas lower loadings of these reagents required the presence of DABCO as an additional base. The complications connected with the lack of oxidant present in the closed reaction vessels were vanquished by allowing post-reaction exposure to air. Additionally, the application of peroxides as oxidants led to similar results. Besides the homocoupling of terminal alkynes, the method is also suitable for the in situ deprotection of TMS-protected alkynes.

Compared with other solvent-free reaction protocols for alkyne homocoupling, the reaction conditions are mild with respect to the reaction time and temperature. Thus, the method is competitive with microwave-assisted protocols with the advantage that the reactions can be accomplished without the need for mixing the reagents prior to the reaction.

Experimental Section

General information: All chemicals were purchased from Sigma–Aldrich or Alfa Aesar and were used as received. Reactions were accomplished in a Retsch MM 301 vibration ball mill by using milling beakers (35 mL) made from yttrium-stabilized zirconia (Y–ZrO_2). Either 10×10 or 6×12 mm milling balls were applied that consisted of yttrium- and magnesia-stabilized zirconia, respectively. GC-FID measurements were performed on an HP-6890 GC machine and GC-MS measurements were recorded on an Agilent Technologies GC 6890N machine with MS detector 5973. Conditions for GC-FID: HP 5, 30 m×0.32 mm×0.25 μm; H_2: 10 psi; temperature program: 70 °C (hold for 3 min), 15 $K\,min^{-1}$ up to 280 °C (hold for 10 min); injector temperature: 280 °C; detector temperature: 300 °C. Conditions for GC-MS: HP 5, 30 m×0.32 mm×0.25 μm; He: 10 psi; temperature program: 70 °C (hold for 3 min), 15 $K\,min^{-1}$ up to 280 °C (hold for 7 min); injector temperature: 280 °C; detector: electron impact (70 eV). NMR spectra were recorded with a Bruker Avance 200 MHz system at room temperature in chloroform-$[^2H]_3$ ($CDCl_3$).

General reaction procedure A: The milling beakers were filled with milling balls and then KF–Al_2O_3 (60 w% KF, 4 g), phenylacetylene (**1a**; 2 mmol, 204 mg), and CuI (5 mol%, 18 mg) were added sequentially. Milling was performed at 30 Hz for 10 min. After cooling to room temperature, the crude products were extracted on a frit with a thin silica layer by using chloroform (3×10 mL). The solvent was evaporated in vacuo; the crude products were dried and analyzed by GC-FID and GC-MS.

General reaction procedure B: The milling beakers were filled with milling balls and then KF–Al_2O_3 (60 w% KF, 4 g), the alkyne (2 mmol), and CuI (5 mol%, 18 mg) were added sequentially. Milling was performed at 30 Hz for 10 min. After cooling to room temperature, the milling beaker was opened and allowed to stand in an air atmosphere for 30 min. Following this post-reaction oxidation, the crude products were extracted on a frit with a thin silica layer by using chloroform (3×10 mL). The solvent was evaporated in vacuo, the crude products were dried and analyzed by GC-FID and GC-MS. Analytical samples for NMR investigation were isolated by column chromatography using *n*-hexane/toluene mixtures. Products were identified according to literature data. Both ^1H and ^{13}C NMR spectra are provided in the Supporting Information.

General reaction procedure C: The milling beakers were filled with the milling balls and then KF–Al_2O_3 (32 w% KF, 4 g), the alkyne (2 mmol), DABCO (2.5 mmol, 280 mg), and CuI (5 mol%, 18 mg) were added sequentially. Milling was performed at 30 Hz for 10 min. After cooling to room temperature, the crude products were extracted on a frit with a thin silica layer by using chloroform (3×10 mL). The solvent was evaporated in vacuo, the crude products were dried and analyzed by GC-FID and GC-MS. Analytical samples for NMR investigation were isolated by column chromatography using *n*-hexane/toluene mixtures. Products were identified as described above.

1,4-Diphenylbuta-1,3-diyne (2a):[48] ^1H NMR (200 MHz, $CDCl_3$): δ=7.55–7.47 (4H, m), 7.37–7.27 ppm (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=132.50, 129.20, 128.44, 121.83, 81.53, 73.90 ppm; GC-MS: *m*/*z* (%): 202 (100).

1,4-Bis(*o*-tolyl)buta-1,3-diyne (2b):[49] ^1H NMR (200 MHz, $CDCl_3$): δ=7.47 (2H, d, *J*=7.5 Hz), 7.29–7.07 ppm (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=141.61, 132.90, 129.55, 129.08, 125.64, 121.70, 81.11, 77.22, 20.70 ppm; GC-MS: *m*/*z* (%): 230 (100).

1,4-Bis(*p*-tolyl)buta-1,3-diyne (2c):[48] ^1H NMR (200 MHz, $CDCl_3$): δ=7.39 (4H, d, *J*=8.2 Hz), 7.09 (4H, d, *J*=7.9 Hz), 2.34 ppm (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ=139.47, 132.38, 129.20, 118.80, 81.53, 73.45, 21.58 ppm; GC-MS: *m*/*z* (%): 230 (100).

1,4-Bis(*o*-methoxyphenyl)buta-1,3-diyne (2d):[49] ^1H NMR (200 MHz, $CDCl_3$): δ=7.44 (2H, d, *J*=7.5 Hz), 7.28 (2H, t, *J*=8.0 Hz), 6.92–6.81 (4H, m), 3.86 ppm (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ=161.33, 134.39, 130.52, 120.46, 111.32, 110.74, 78.63, 77.99, 55.78 ppm; GC-MS: *m*/*z* (%): 262 (100).

1,4-Bis(*m*-methoxyphenyl)buta-1,3-diyne (2e):[49] ^1H NMR (200 MHz, $CDCl_3$): δ=7.18 (2H, t, *J*=8.0 Hz), 7.08 (2H, d, *J*=7.6 Hz), 7.00 (2H, s), 6.88–6.81 (2H, d, *J*=8.1 Hz), 3.76 ppm (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ=159.31, 129.48, 125.06, 122.66, 117.08, 115.99, 81.45, 73.62, 55.28 ppm; GC-MS: *m*/*z* (%): 262 (100).

1,4-Bis(*p*-methoxyphenyl)buta-1,3-diyne (2f):[48] ^1H NMR (200 MHz, $CDCl_3$): δ=7.43 (4H, d, *J*=8.7 Hz), 6.82 (4H, d, *J*=8.7 Hz), 3.79 ppm (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ=160.26, 134.00, 114.09, 113.92, 81.19, 72.92, 55.28 ppm; GC-MS: *m*/*z* (%): 262 (100).

1,4-Bis(*p*-fluorophenyl)buta-1,3-diyne (2g):[49] ^1H NMR (200 MHz, $CDCl_3$): δ=7.53–7.42 (4H, m), 7.00 ppm (4H, t, *J*=8.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ=165.56, 160.55, 134.58, 134.42, 117.83, 117.76, 116.11, 115.66, 80.40, 73.51 ppm; GC-MS: *m*/*z* (%): 238 (100).

Icosa-9,11-diyne (2h):[49] ^1H NMR (200 MHz, $CDCl_3$): δ=2.19 (4H, t, *J*=6.9 Hz), 1.58–1.18 (12H, m), 0.83 ppm (6H, t, *J*=6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ=77.48, 65.21, 31.76, 29.06, 28.99, 28.78, 28.29, 22.57, 19.15, 14.01 ppm; GC-MS: *m*/*z* (%): 274 (100).

Tetracosa-11,13-diyne (2i):[49] ^1H NMR (200 MHz, $CDCl_3$): δ=2.19 (4H, t, *J*=7.0 Hz), 1.56–1.15 (16H, m), 0.83 ppm (6H, t, *J*=6.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ=77.47, 65.20, 31.83, 29.49, 29.41, 29.23, 29.03, 28.79, 28.30, 22.61, 19.15, 14.04 ppm; GC-MS: *m*/*z* (%): 330 (100).

Synthesis of 1,2,4-triphenylbenzene (3):[50] A mixture of 1,2,4-tribromobenzene (1.89 g, 6 mmol), $Pd(OAc)_2$ (67.5 mg, 0.3 mmol), triphenylphosphine (157.5 mg, 0.6 mmol), phenylboronic acid (3.30 g, 27 mmol), toluene (90 mL), methanol (30 mL), and aqueous K_2CO_3 (24 mL, 2 $mol\,L^{-1}$) was heated at 75 °C for 24 h while maintaining intensive stirring. After the reaction mixture was cooled to room temperature, it was quenched with water (30 mL) and extracted with dichloromethane (3×50 mL). The unified organic phase was dried with anhydrous Na_2SO_4 and the solvent was removed in vacuo.

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Fast, ligand- and solvent-free copper-catalyzed click reactions in a ball mill

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A new, ligand- and solvent-free method for the Huisgen 1,3-dipolar cycloaddition (click reaction) was developed using a planetary ball mill. Besides various alkynes and azides, a propargyl functionalized polymer was converted by mill clicking. Moreover, it was possible to carry out a click polymerization in a ball mill.

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Fast, ligand- and solvent-free copper-catalyzed *click* reactions in a ball mill†

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A new, ligand- and solvent-free method for the Huisgen 1,3-dipolar cycloaddition (*click* reaction) was developed using a planetary ball mill. Besides various alkynes and azides, a propargyl functionalized polymer was converted by mill clicking. Moreover, it was possible to carry out a *click* polymerization in a ball mill.

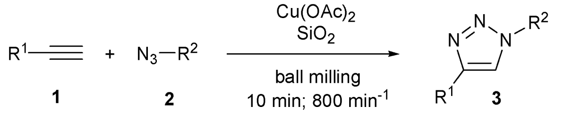
Metal-catalyzed bond forming reactions represent the state-of-the-art synthetic tool in organic chemistry. An important class of copper-catalyzed reactions are the Huisgen 1,3-dipolar cycloadditions.[1] This reaction between alkynes and azides as dipolarophiles and 1,3-dipoles, respectively, fulfils the criteria for a *click* reaction (high chemical yield, simple reaction conditions, stereospecificity)[2] and is a highly important method for the straightforward synthesis of pharmaceuticals, polymers and for the derivatization of biomolecules.[3] However, only a few very recent articles discuss solvent-free procedures for this type of chemistry.[4] In this contribution, a solvent-free implementation of the Huisgen 1,3-dipolar cycloaddition between alkynes and azides in a planetary ball mill is reported.

Synthetic chemistry carried out in ball mills has attracted increasing attention within the last years, as indicated by the rising number of publications in this area of research.[5,6] Throughout evolution of this field of chemistry, in the last decade catalyzed bond-forming reactions became the most prominent examples.[6a,c,7–10] Ball mill protocols are often as capable as their solvent-based counterparts in solution. Categorization of catalysis in ball mills leads to two major groups: organocatalysis[6b,7] and Pd-mediated cross-coupling reactions.[6c,8–10] Amongst the last group of reactions such prominent examples have shown to work: Mizoroki–Heck,[8] Suzuki–Miyaura[6c,9] and Sonogashira reactions.[10]

Due to the fact that azides with small number of carbons are sensitive to shock, decyl azide (**2a**) was used for a model reaction with phenylacetylene (**1a**) forming 1-decyl-4-phenyl-1*H*-1,2,3-triazole (**3a**; Scheme 1). First, the influence of different copper salts and sodium ascorbate on the conversion of **2a** and the selectivity to **3a** was investigated (Table S1, ESI†). Additionally, fused quartz sand (SiO_2) was used as inert milling auxiliary to enable small batch sizes. Remarkably, the use of copper acetate ($Cu(OAc)_2$) and sodium ascorbate quantitatively yielded the product within 5 min reaction time only. Without sodium ascorbate the reaction is completed in 10 min. Thus, sodium ascorbate as an additive is useful for the reaction of less active substrates. Other copper salts like cuprous iodide and cupric sulfate showed similar results. In the absence of copper salts, no reaction occurred during the tested reaction times. Competing homo-coupling reaction of **1** (Glaser reaction) has not been observed.

With $Cu(OAc_2)$ showing the best results, a screening of different alkynes (**1**) and azides (**2**) was performed (Table 1). Almost all tested combinations revealed high conversions and selectivities. Furthermore, the triazole products were pure according to ^1H NMR spectroscopy after extraction of the reaction mixtures. Even ethynylpyridines **1g** and **1h** yielded the corresponding triazoles (**3g,h**) while they were not reactive in Sonogashira reactions operated under similar conditions in a planetary ball mill.[10b]

Besides (hetero)aryl alkynes (**1a–h**), decyne (**1i**) and propargyl alcohols (**1j,k**), also 4-ethynyl[2.2]*para*-cyclophane (**1m**) was successfully reacted with **2a**, but with lower conversion as the other alkynes. It was also possible to prove that other azides can be employed in the reaction with **1a**. 1-Mesityl- (**3n**), 1-benzyl- (**3o**) and 1-adamantyl-4-phenyl-1*H*-1,2,3-triazole (**3p**) were obtained almost quantitatively from the reaction with the respective azides. Functionalization of 1-ethoxy-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**2d**) with **1a** was successful, demonstrating the capability of this method to handle also complex molecules. In addition, the electron poor dimethylacetylenedicarboxylate (**1n**) was



Scheme 1 Cu-catalyzed 1,3-dipolar cycloaddition of alkynes (**1**) with azides (**2**) forming 1,4-substituted-1*H*-1,2,3-triazoles (**3**).

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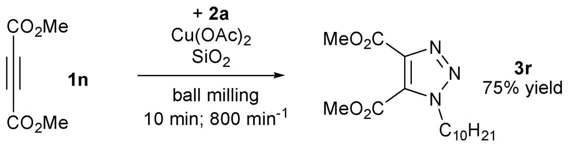
† Electronic supplementary information (ESI) available: Complete experimental procedure, analytical characterization of the products, catalyst screening as well as analytical data of polymers **12a** and **12b**. See DOI: 10.1039/c0cc05657j

Table 1 Selected results of screening 1,3-dipolar cycloadditions between alkynes (**1**) and azides (**2**; Scheme 1)[a]

3	R^1	Azide[b]	$X(\mathbf{2})$[c] (%)	$S(\mathbf{3})$[c] (%)
3a	C_6H_5 (**1a**)	**2a**	>99	95
3b	*p*-Me-C_6H_4 (**1b**)	**2a**	94	93
3c	*o*-Me-C_6H_4 (**1c**)	**2a**	91	93
3d	*p*-OMe-C_6H_4 (**1d**)	**2a**	96	94
3e	*o*-OMe-C_6H_4 (**1e**)	**2a**	95	95
3f	*p*-F-C_6H_4 (**1f**)	**2a**	>99	98
3g	2-C_5H_4N (**1g**)	**2a**	>99	93
3h	3-C_5H_4N (**1h**)	**2a**	99	94
3i	*n*-C_8H_{17} (**1i**)	**2a**	98	93
3j	Propan-2-ol-1-yl (**1j**)	**2a**	>99	87
3k	But-3-en-2-ol-1-yl (**1k**)	**2a**	98	90
3l	6-Methylhept-5-en-2-ol-1-yl (**1l**)	**2a**	98	89
3m	[2.2]*Para*-cyclophane-1-yl (**1m**)	**2a**	84	89
3n	C_6H_5 (**1a**)	**2b**	98	92
3o	C_6H_5 (**1a**)	**2c**	>99	94
3p	C_6H_5 (**1a**)	**2d**	98	97
3q[d]	C_6H_5 (**1a**)	**2e**	98	96

[a] Reaction conditions: 1.1 mmol **1**, 1 mmol **2**, 5 mol% $Cu(OAc)_2$, 5 g SiO_2; ZrO_2 beaker (45 mL), 6 × ZrO_2 milling balls (15 mm), 800 min^{-1}, 10 min. [b] **2a** = decyl azide, **2b** = mesityl azide, **2c** = benzyl azide, **2d** = adamantyl azide, **2e** = 1-ethoxy-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide. [c] Conversion (*X*) and selectivity (*S*) based on GC-FID analysis. Yields were determined by ^1H NMR analysis of the extracted crude product. [d] 5 mol% Na-ascorbate are added.

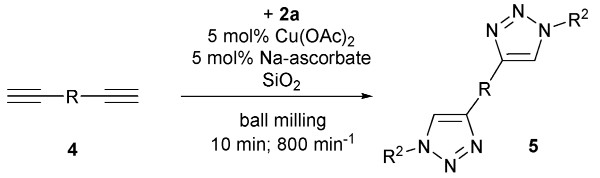


Scheme 2 Synthesis of dimethylester **3r** from dimethylacetylendicarboxylate (**1n**) and decyl azide (**2a**; conditions *cf.* Table 1).

suitable for cycloaddition reaction, but with slightly lower conversion (**3r**, Scheme 2) than other examples (Table 1).

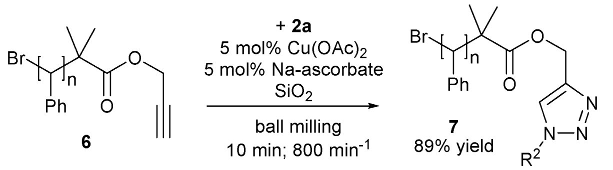
Subsequently, bis-ethynyl compounds were employed in the reaction with **2a** (Table 2). To force the reaction to the double *clicked* product, sodium ascorbate and a 2.2-fold excess of **2a** were used. This approach worked well for 1,3-bis-ethynylbenzene (**4a**) and 1,4-bis-ethynyl-2,5-bis-octyloxybenzene (**4c**), but in the case of the symmetrically 1,4-bis-ethynylbenzene (**4b**), only the single coupled product 1-decyl-4-(*p*-ethynylphenyl)-1*H*-1,2,3-triazole (**5d**) was isolated with high selectivity. The bis-ethynyl educts (**4**) were converted quantitatively in every case. The products could not be investigated by GC-FID analysis; as alternative ^1H NMR spectroscopy of the extracted crude products was used to calculate the yields. Using similar reaction conditions, 1,3,5-tris-ethynylbenzene was tested in the *click* reaction with **2a**. As a result the threefold *clicked* triazole (*cf.* ESI†) was obtained as the only product with 97% yield; neither single nor twofold *clicked* products could be obtained.

Table 2 *Click* reaction of bis-ethynyl benzenes (**4**) and decyl azide (**2a**)[a]



Entry	R	Yield (**5**)[b] (%)
5a	1,3-C_6H_4 (**4a**)	96
5b	1,4-C_6H_4 (**4b**)	97[c]
5c	1,4-C_6H_2-2,5-OC_8H_{17} (**4c**)	95

[a] Reaction conditions: 0.5 mmol **4**, 1.1 mmol **2a** (R^2 = *n*-decyl), 5 g SiO_2; ZrO_2 beaker (45 mL), 6 × ZrO_2 milling balls (15 mm). [b] Calculated by ^1H NMR analysis of the extracted crude products. [c] One ethynyl function was converted only: 1-decyl-4-(*p*-ethynylphenyl)-1*H*-1,2,3-triazole (**5d**).



Scheme 3 Schematic representation of the *click* reaction of a propargyl-functionalized polystyrene (**6**, 0.05 mmol) and decyl azide (**2a**, R^2 = *n*-decyl, 0.15 mmol; conditions *cf.* Table 1).

Furthermore, a terminal propargyl-functionalized polystyrene (PS_{2500}, **6**) was tested in a cycloaddition with **2a** (Scheme 3),[11] the extracted product (**7**) was analyzed with matrix assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF-MS; Fig. 1) and size exclusion chromatography (SEC; Fig. 2). The SEC analysis (PS standard) revealed an increase of the average molar mass of **9** (2720 g mol^{-1}) compared to **6** (2470 g mol^{-1}) while the PDI value (1.08)

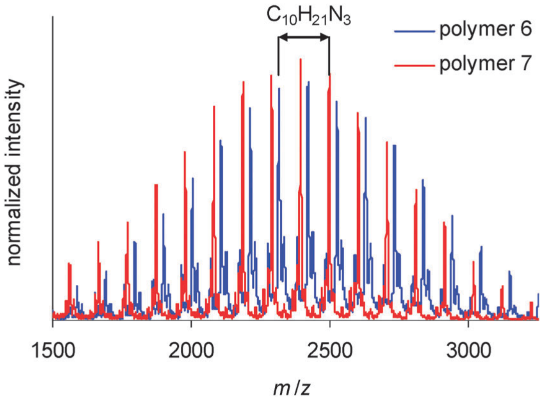


Fig. 1 MALDI-TOF-MS of polymers **6** and **7** (Scheme 3).

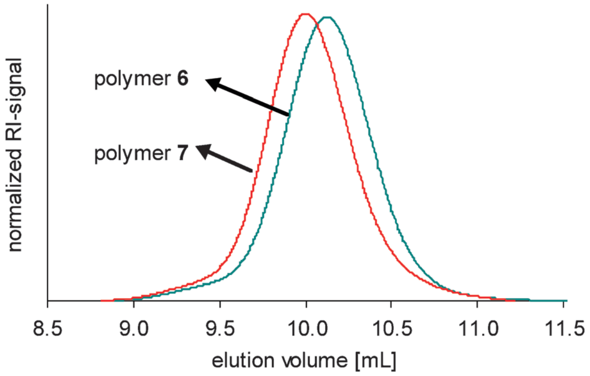
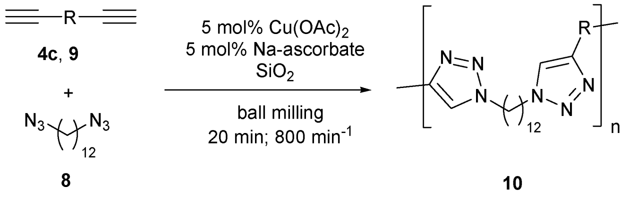


Fig. 2 SEC of polymers **6** and **7** (Scheme 3).

Table 3 Polymerization of 1,12-diazidododecane (**8**) and bis-ethynyl compounds (**4c** and **9**)[a]



Entry	R	$M_n{}^b$/g mol^{-1}	PDI^b
10a	n-C_4H_8 (**9**)	2200	2.43
10b	1,4-C_6H_2-2,5-OC_8H_{17} (**4c**)	7500	2.44

[a] Reaction conditions: 1 mmol **8**, 1 mmol **4c** or **9**, 5 g SiO_2; ZrO_2 beaker (45 mL), 6 × ZrO_2 milling balls (15 mm). [b] Calculated by SEC analysis (PS standard) of the extracted crude.

remained unaffected. MALDI-TOF-MS indicated a shift between the main mass distribution signals of **6** and **7** which is fitting to the mass of **2a**. The solvent-free *click* reaction is obviously also possible for polymer modification reactions without any notable influence of the high-energy ball milling process on the integrity of the polymer chain as proven by SEC.

Based on the results (polymer functionalization and reactions with bis-functional molecules **4**) we also investigated a polymerization in the ball mill. For this purpose, 1,12-diazidododecane (**8**) was reacted with bis-ethynyl compounds **4c** and **9** and the extracted crude products were analyzed with SEC (Table 3, PS standard). The reaction with the rigid 1,4-bis-ethynyl-2,5-bis-octyloxybenzene (**4c**) led to a significantly higher average molar mass than the reaction with the flexible octa-1,7-diyne (**9**). PDI values are in the expected range for a step-growth polymerization. Assumedly, the higher amount of oligomers in **10a** (Fig. S1, ESI†) can be explained by possible formation of cyclic systems due to the flexible alkyl spacers preventing further chain growth. With the rigid phenyl spacer in **10b**, formation of cyclic systems should be more unlikely.

In conclusion, a fast, ligand- and solvent-free method for the Huisgen 1,3-dipolar cycloaddition using a planetary ball mill was developed. Almost no side products were formed due to the gentle reaction conditions and the short reaction times (10 min). The isolated crude products were pure according to ^{1}H NMR spectroscopy and MALDI-TOF mass spectrometry. The broad variety of suitable substrates enables a wide range of potential applications of this protocol for complex substrates and reactions. For instance, a terminal ethynyl functionalized polystyrene could be modified in the ball mill without destroying the polymer backbone. Moreover, polymerizations could be performed in the future.

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Solvent-free synthesis of enamines from alkyl esters of propiolic or but-2-ynedicarboxylic acid in a ball mill

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Synlett **2011**, 2200-2202

A solvent-free method for the addition of amines to dialkylacetylendicarboxylates or alkylpropiolates using a planetary ball mill was developed. Conversion of educts was quantitative within 5 min without use of any catalyst or base. Beside the *E*- / *Z*-isomers, no side products were formed.

Solvent-Free Synthesis of Enamines from Alkyl Esters of Propiolic or But-2-yne Dicarboxylic Acid in a Ball Mill

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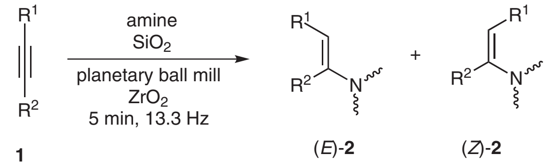
Abstract: A solvent-free method for the addition of amines to dialkylacetylendicarboxylates or alkylpropiolates using a planetary ball mill was developed. Conversion of educts was quantitative within five minutes without use of any catalyst or base. Beside the *E*-/*Z*-isomers, no side products were formed.

Key words: addition, amines, alkynes, enamines, green chemistry

Enamines based on dialkylacetylendicarboxylates or alkylpropiolates are important intermediates in the synthesis of heterocycles and multicomponent reactions,[1] also with potential medicinal application.[2] The synthesis and stereochemistry of enamines is well investigated.[3] A common method for their synthesis is the reaction between dialkylacetylendicarboxylates and alkylpropiolates with amines in MeOH.[1a] Recently Zhu et al. discovered that the solvent has a strong influence on the *E*/*Z* ratio of the product.[4] Also, kinetic studies for those amine–alkyne additions revealed that reactions follow a first-order kinetics, whereby the initial addition of the reactants is the rate-determining step.[5] However, noncatalyzed procedures in the absence of solvents have not been reported so far.

In this work a solvent-free reaction protocol for the addition of amines to dialkyl acetylenedicarboxylates or alkylpropiolates using a planetary ball mill is presented (Scheme 1). Synthetic chemistry carried out in ball mills is an emerging field of research, as indicated by the rising number of publications. It was found that ball milling is an excellent method for some organic reactions,[6,7] e.g. aldol-type reactions, oxidations, reductions, and metal-catalyzed bond-forming reactions. Ball mill protocols are often as capable as their solvent-based counterparts in solution or outperform the reactions regarding time and yield.



1a: $R^1 = R^2 = CO_2Me$
1b: $R^1 = R^2 = CO_2Et$
1c: $R^1 = CO_2Me$, $R^2 = H$
1d: $R^1 = CO_2Et$, $R^2 = H$

Scheme 1 Reaction of dialkyl acetylenedicarboxylates or alkylpropiolates with amines

Reactions were carried out in a planetary ball mill. Additionally, fused quartz sand (SiO_2) was used as inert grinding auxiliary to enable work with small batch sizes and facilitate the energy entry in the presence of liquid substrates by adsorbing them on the surface.[7m,n] No further additives or catalysts were needed for the azide–alkyne reaction of dimethyl (**1a**) or diethylacetylendicarboxylate (**1b**) as well as for amine addition to propargylic acid methyl (**1c**) or ethyl ester (**1d**). Reactions with several anilines and secondary alkyl amines were completed within five minutes reaction time only (Scheme 1 and Table 1). Structural analyses of the product mixtures indicate in the case of primary anilines the formation of the *E*- and *Z*-enamine exclusively (see Supporting Information and Figure 1). Neither the imine has been detected, nor an isomerization of the stereoisomers in solution during analysis took place.

For all examples, the conversion of the educts was quantitative and, aside from the stereoisomeric enamines, no side products were found in NMR and GC–MS analysis of the crude and isolated products. Isolated yields were about 90%; losses are a result of the workup procedure for removal of the milling auxiliary. In the case of dialkyl acetylenedicarboxylates, mainly the *E*-isomers have been identified as the major products by comparison of the chemical shift of the vinylic proton in ^1H NMR data with the literature data.[3b,c] In contrast, reactions with propiolates and anilines yielded favorably the *Z*-isomer (Table 1). Secondary alkyl amines furnished the *E*-isomer preferably, proven by comparing the coupling constants of the vinylic protons in ^1H NMR data which are approximately 8 Hz and 13 Hz for *Z*- and *E*-isomer, respectively (see Supporting Information). This is shown for enamine **2j** obtained from the reaction of methyl propargylate (**1c**) and aniline (Figure 1).[3a,b]

Comparative experiments with **1a** and aniline using a normal flask were done under solvent-free conditions by simple stirring of the reactants (Scheme 2). A mixture was obtained with only 80% conversion and a *E*/*Z* ratio of 87:13. Furthermore, side products were formed limiting the overall selectivity of the enamine isomers to 83%. Us-

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Table 1 Reaction of Dialkylacetylendicarboxylates or (**1a**,**b**) Alkylpropiolates (**1c**,**d**) with Amines[a]

Entry	Alkyne	Amine	Yield (%)[b]	Ratio E/Z[c]
2a	**1a**	aniline	91	97:3
2b		*p*-toluidine	87	98:2
2c		*o*-toluidine	88	96:4
2d		*m*-anisidine	89	97:3
2e		piperidine	82	>99:<1
2f		morpholine	84	>99:<1
2g		diisopropylamine	94	>99:<1
2h	**1b**	aniline	92	97:3
2i		*p*-toluidine	93	97:3
2j	**1c**	aniline	89	7:93
2k		*p*-toluidine	85	8:92
2l		piperidine	81	>99:<1
2m		morpholine	83	>99:<1
2n		diisopropylamine	96	>99:<1
2o	**1d**	aniline	92	7:93
2p		*p*-toluidine	87	7:93

[a] Reactions conditions: alkyne (1 mmol), amine (1 mmol), SiO_2 (5 g), 13.3 Hz, 5 min, 45-mL ZrO_2 milling beaker, 6 × 15 mm ZrO_2 milling balls.

[b] Isolated yields.

[c] ^1H NMR spectroscopy.

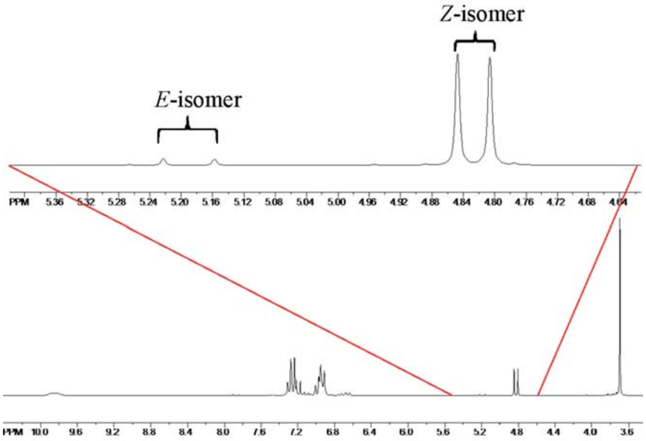
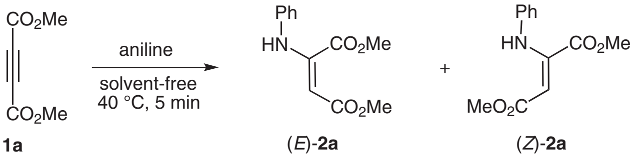


Figure 1 ^1H NMR spectrum of extracted crude product of **2j** (bottom); zoom-in of vinylic proton region (top)

ing a ball mill the reaction was chemoselective and resulted in a E/Z ratio of 97:3 (Table 1).

In conclusion, a new solvent-free protocol for the addition of amines to dialkylacetylendicarboxylates or alkylpropiolates using a planetary ball mill has been developed. Yields were nearly quantitative within five minutes reaction time without noticeable formation of side products, and in case of secondary alkyl amines the resulting enamines were stereoisomerically pure as well.



Scheme 2 Reaction of **1a** (5 mmol) and aniline (5 mmol) in a flask under solvent-free conditions (40 °C, 5 min)

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental details and NMR characterization data.

Acknowledgment

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Referenz [36]

Solvent-free reactions of alkynes in ball mills: It is definitely more than mixing

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This contribution presents two solvent-free reactions of terminal alkynes in ball mills: Pd-catalyzed Sonogashira cross-coupling and Cu-catalyzed homo-coupling (Glaser reaction). The results are compared to other solvent-free reaction protocols, which have been published up to date for those types of reactions. Reactions are assessed on the basis of reaction variables like type of catalyst and base or reaction time. Furthermore, performance-based parameters (yield, selectivity, turnover number, TON, and turnover frequency, TOF) are considered and evaluated. Findings from ball-milling experiments indicate that those processes are comparable to the energy entry by microwave irradiation with respect to reaction time and TOF.

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Solvent-free reactions of alkynes in ball mills: It is definitely more than mixing*

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Abstract: This contribution presents two solvent-free reactions of terminal alkynes in ball mills: Pd-catalyzed Sonogashira cross-coupling and Cu-catalyzed homo-coupling (Glaser reaction). The results are compared to other solvent-free reaction protocols, which have been published up to date for those types of reactions. Reactions are assessed on the basis of reaction variables like type of catalyst and base or reaction time. Furthermore, performance-based parameters (yield, selectivity, turnover number, TON, and turnover frequency, TOF) are considered and evaluated. Findings from ball-milling experiments indicate that those processes are comparable to the energy entry by microwave irradiation with respect to reaction time and TOF.

Keywords: alternative energy entry; copper; Glaser reaction; metal catalysis; palladium; Sonogashira reaction.

INTRODUCTION

The omission of solvents or the reduction of solvent intensity in chemical reactions is one of myriad possibilities to decrease the *E*- or *Sheldon*-factor for chemical syntheses and thus improve the "greenness" of a chemical process [1]. It is generally understood that reactions performed in the absence of a classical, volatile, or hazardous organic solvent(s) are classified as *solvent-free* or *-less* reactions. This categorization seems to be arbitrary, because it often includes reactions conducted either in neoteric solvents or in the reactant(s) itself [2–5]. Following the definition of Tanaka and Toda [4], solvent-free reactions are solely those transformations carried out between solid reactants and thus are also called *solid-state* chemical transformations [4,6–8]. From the general viewpoint of organic synthesis, solvent-free reactions indicate those reaction protocols which are carried out in the absence of solvents, either in neat or in the solid state [8].

Despite this classification, solvent-free reactions can be initiated by different methods of energy entry. Starting with classical heating devices in combination with mechanical mixing to the application of microwave apparatus or the employment of cavitation phenomena (acoustic or hydrodynamic), the range of possibilities for the case of liquid-phase reactions is very wide. Using reacting reagents in the (quasi) solid state, another method has become popular within the last decade: comminuting in laboratory ball mills [7,9]. This technique is practically the advancement of grindstone chemistry, allowing for reproducible reaction conditions and for the definite control of reaction variables (energy entry, degree of mixing, reaction time).

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The present investigation describes the performance of metal-catalyzed reactions of alkynes in ball mills. Using the Sonogashira cross-coupling [10] and the homo-coupling of terminal alkynes (Glaser reaction) as the reaction models, the performance of ball-milling technique is compared with other methods of energy entry. The prerequisite for the reactions selected is their solvent-free accomplishment, without the limitations that through work-up solvents are required for isolation and analysis. Besides yield and selectivity, performance-based parameters are considered assessing the different solvent-free reaction protocols.

EXPERIMENTAL

Sonogashira reaction

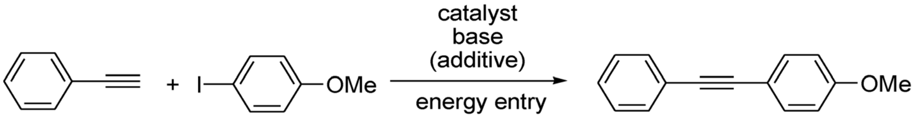
The grinding beakers (45 ml; agate or ZrO_2) were equipped with 6 milling balls of the same material (d = 15 mm). Afterwards, fused quartz sand (5 g), phenylacetylene (**1**; 2.5 mmol, 255 mg), 1,4-diazabicyclo[2.2.2]octane (= DABCO; 2.5 mmol, 280 mg), *p*-iodoanisole (**2**; 2 mmol, 468 mg), and $Pd(OAc)_2$ (5 mol %, 25 mg) were added in the given order. Milling was carried out at a rotation frequency ν_{rot} of 13.3 Hz for 20 min using the planetary ball mill Fritsch Pulverisette 7 classic line. After cooling of the grinding beakers to room temperature, the crude products were extracted on a frit with a thin silica layer using chloroform (3 × 10 ml). The solvent was evaporated in vacuo, the crude product was dried, re-dissolved in 1.5 ml of chloroform, and analyzed by gas chromatography-flame ionization detection (GC-FID) and GC-MS. Analytical samples for NMR investigations were isolated by column chromatography using *n*-hexane/toluene mixtures. The reaction afforded the product in 65 and 57 % GC and isolated yield, respectively. Spectroscopic analyses (^1H, ^{13}C) are in agreement with those reported in literature.

Glaser reaction

The grinding beakers (35 ml; ZrO_2) were equipped with 12 milling balls of the same material (d = 10 mm). KF-Al_2O_3 (32 wt % KF; 4 g), phenylacetylene (**1**; 2 mmol, 204 mg), DABCO (2.5 mmol, 280 mg), and CuI (5 mol %, 18 mg) were added in the given order. Milling was accomplished with an oscillation frequency ν_{osc} of 30 Hz for 10 min using the mixer mill *Retsch MM301*. After cooling to room temperature, the crude product was extracted on a frit with a thin silica layer using chloroform (3 × 10 ml). The solvent was evaporated in vacuo, the crude product was dried and analyzed by GC-FID and GC-MS. Analytical samples for NMR investigations were isolated by column chromatography using *n*-hexane/toluene mixtures. Reaction afforded the product in 96 % GC and 93 % isolated yield. Spectroscopic analyses (^1H, ^{13}C) are in agreement with those reported in the literature.

RESULTS AND DISCUSSION

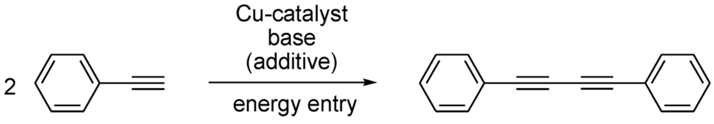
Two types of metal-catalyzed reactions of alkynes have been chosen to assess different reaction protocols omitting the solvent during the reaction step. In all cases, solvent is applied for isolation and analysis of the reaction products. However, these amounts will not be considered in the present assessment, but they should be considered if the reactions are scaled up or evaluated in a kind of life-cycle assessment. On the one side, a C(sp)-C(aryl) cross-coupling (Sonogashira reaction) between phenylacetylene (**1**) and *p*-iodoanisole (**2**) affording *p*-(phenylethynyl)anisole (**3**; Scheme 1) was investigated. Solvent-free protocols incorporating either Pd [10–14], Cu [15,16,] or Ni catalysts [17] have been reported, whereby the Pd-mediated reactions employ in some cases Cu compounds as co-catalyst [13,17].



1 **2** **3**

Scheme 1 Sonogashira reaction of phenylacetylene (**1**) and *p*-iodoanisole (**3**).

On the other side, the Cu-catalyzed homo-coupling of **1** affording 1,4-diphenylbuta-1,3-diyne (**4**; Glaser reaction) has been chosen as a model reaction to assess the different methods of energy entry (Scheme 2). Solvent-free reaction protocols published so far for this type of reaction are catalyzed by both Cu(I) and Cu(II) compounds [18–21]. Furthermore, Bandini et al. proposed a solvent-free Glaser-type reaction catalyzed by an immobilized Pd complex in the presence of *p*-iodophenol for re-oxidation of the Pd in the reaction cycle [14].



1 **4**

Scheme 2 Glaser reaction of phenylacetylene (**1**) to 1,4-diphenylbuta-1,3-diyne (**4**).

Reactions in ball mills

Metal-catalyzed reactions in ball mills are so far restricted to Suzuki–Miyaura and Mizoroki–Heck cross-coupling reactions [9,22–24]. Recently, Fulmer et al. and Thorwirth et al. reported the successful performance of the air-sensitive Sonogashira reaction in a vibration ball mill and a planetary ball mill, respectively [10,13]. The difference between these two proposals are the reaction conditions applied. In the former case, $Pd(PPh_3)_4$, Cu(I), and potassium carbonate have been used as catalyst, co-catalyst, and base, respectively. Ball milling of the reactants for 17 h afforded **3** in 86 % isolated yield. Authors have demonstrated by employing phenylacetylene as the alkyne that the co-catalyst may be replaced by milling balls and beakers custom-made from Cu [13]. As described in the experimental section and in [10] the application of a planetary ball mill significantly reduces the reaction time to 20 min, affording **3** in 57 % isolated yield. The reaction was performed in the presence of DABCO, $Pd(OAc)_2$, and quartz sand as base, catalyst, and milling auxiliary*, respectively. The addition of Cu leads to a significantly reduced product selectivity compared to 98 % for the Cu-free procedure. Furthermore, the authors have demonstrated that the Pd-salt can be exchanged by $PdCl_2$ or $Pd(PPh_3)_4$ without a negative effect on yield or selectivity [10]. Both procedures proved their versatility in terms of alkyne and aryl halide.

Extended analysis of the side products in the case of the Sonogashira reaction (Scheme 1) in the presence of Cu and Pd [10] led to the identification of noticeable amounts of homo-coupling product **4**. Modification of the reaction conditions and total replacement of $Pd(OAc)_2$ by Cu(I) allowed for the synthesis of **4** from **1** in 93 % isolated yield (Scheme 2). The proposed experimental protocol is the first reaction protocol for a Cu-catalyzed reaction in a ball mill**. This solvent-free Glaser reaction furnishes **4** with >99 % selectivity. Although the type of planetary ball mill has been exchanged, the reac-

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*The milling auxiliary helps solidify liquid reactants by surface absorption, making them accessible to energy transfer by the milling process.

Meanwhile, Cu-catalyzed azide-alkyne cycloaddition in a ball mill has been published: R. Thorwirth, A. Stolle, B. Ondruschka, A. Wild, U. S. Schubert. *Chem. Commun.* **47, 4370 (2011).

tion time is still 10 min only. Cu(I), DABCO, and KF-Al_2O_3 with a KF-content of w = 32 wt % have been applied as catalyst, base, and milling auxiliary. Both the cross- and homo-coupling reactions are performed under aerobic conditions without the need for additional ligands or solvents during the reaction.

Reaction parameters

Tables 1 and 2 summarize the reaction conditions and reaction parameters for solvent-free Sonogashira cross- and Glaser homo-coupling reactions, respectively. The data reveal that for the cross-coupling reaction $PdCl_2(PPh_3)_2$ and high-performance Pd EnCat^{TM} 40 outperform the other catalysts with respect to turnover frequency (TOF; Table 1). The latter especially needs low catalyst loading and furnishes the product in 90 % yield within reasonable time [12]. Apart from the TOF, all reactions afford the cross-coupling product in 58 to 92 % yield, independently from the metal and the method for energy entry. Comparison of the application of different metals as catalyst reveals a clear decrease in reactivity: Pd >> Cu > Ni. For the less active metals, the addition of *N*-mono- (**5**) or bi-dentate ligands (**6**; Scheme 3) [15,16] or PPh_3 [17] is necessary to yield reasonable amounts of the product.

Table 1 Comparison of reaction conditions for solvent-free Sonogashira reaction between phenylacetylene (**1**) and *p*-iodoanisole (**2**; Scheme 1).[a]

Reference	Condition	Catalyst	Base	Additive	Time (h)	Yield **3** (%)	TON	TOF (h^{-1})
[10] – this work	Ball milling	$Pd(OAc)_2$	DABCO	Quartz sand[b]	0.33	58	12	35
[11]	Stirring (N_2)	$PdCl_2(PPh_3)_2$	TBAF	–	0.50	92	30	61
[12]	Stirring	Pd EnCat^{TM} 40	Pyrrolidone	–	3	90	900	300
[13]	Ball milling	$Pd(PPh_3)_4$	K_2CO_3	Cu(I)	17	86	34	2.0
[15]	Stirring	$Cu(OAc)_2$	TBAF	**5**	20	83	8	0.42
[16]	Stirring	$Cu(OAc)_2$	TBAF	**6**	14	86	9	0.61
[17]	Microwave	Ni-powder	KF-Al_2O_3	Cu(I) + PPh_3	0.15	73	3	19

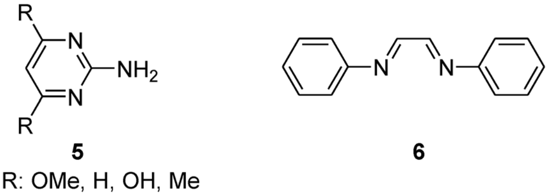
[a] DABCO = 1,4-diazabicyclo[2.2.2]octane, TBAF = tetrabutylammonium fluoride, **5** = 4,6-dimethoxypyrimidin-2-amine, **6** = 1,4-diphenyl-1,4-diazabuta-1,3-diene.

[b] Quartz sand was employed as milling auxiliary and is not incorporated in the reaction.

Table 2 Comparison of reaction conditions for solvent free homo-coupling reactions of phenylacetylene (**1**; Scheme 2).

Reference	Condition	Catalyst	Base	Additive	Time (h)	Yield **4** (%)	TON	TOF (h^{-1})
[14]	Stirring	[Pd][a]	Et_3N	[a]	12	84	84	7.0
[18]	Microwave	$CuCl_2$	KF-Al_2O_3	–	0.13	75	0.20	1.6
[19]	Microwave	CuI	Morpholine	Al_2O_3	0.17	82	16	96
[20]	Stirring	$Cu(OAc)_2$	Morpholine	KF-Al_2O_3	3	96	5	1.6
[21]	Stirring	$CuCl_2$	Et_3N	–	6	96	32	5.3
This work	Ball milling	CuI	DABCO	KF-Al_2O_3	0.17	96	19	113

[a] An immobilized Pd complex was used as catalyst. Reaction was only successful in presence of 2 equiv *p*-iodophenol.



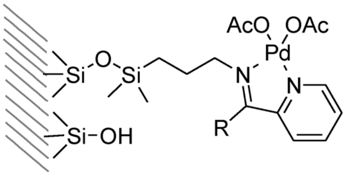
Scheme 3 Ligands applied in Cu-catalyzed Sonogashira reactions [15,16].

The procedures for the solvent-free Sonogashira reaction can be operated in most cases without a co-catalyst [10–12,15,16]. Only in case of the Ni-catalyzed reaction [17] and for the ball-milling procedure employing an inorganic base [13] the addition of CuI is necessary, whereas in the last case co-catalyst (CuI) could be substituted by milling balls and beakers made from Cu. Due to high energy impact during grinding, Cu is released from the surfaces and is made available for reaction. The ball-milling procedures are especially interesting to compare: on the one side, the active Pd-0 catalyst $Pd(PPh_3)_4$ is combined with a less active base (potassium carbonate) [13] and on the other side the reactivity is exchanged by applying plain $Pd(OAc)_2$ in combination with an amine-base (DABCO) [10]. The capability of this bicyclic diamine is demonstrated also by a metal-free reaction procedure employing DABCO as base [25]. Interestingly, the optimal ratios between base and substrate are similar to those reported for the ball-milling procedure [10,25]. Consideration of the reaction time and thus the TOF for the model reaction favors the later ball-milling arrangement. The method of energy entry (stirring, microwave, ball milling) shows no significant effect on the TOF. However, the reaction time can be reduced significantly by applying microwave irradiation or ball milling in a planetary ball mill. With respect to this, another important fact has to be considered: the state of aggregation of the reaction mixtures. For both types of ball mills, a strongly heterogeneous mixture is present [10,13], whereas in the case of liquid-base pyrrolidone a solution probably exists [12]. This could also account for the high TOF due to low catalyst loading. At least in this case the definition of solvent-free reaction conditions is questionable [2,8,26], since the reactants are homogeneously dispersed in the solvent pyrrolidone.

Beside those solvent-free Sonogashira cross-couplings of aryl halides with terminal alkynes discussed above (Scheme 1), the Pd-catalyzed solvent-free reaction of acyl chlorides with terminal alkynes has been described in the literature also [27,28]. Equimolar amount of NEt_3 and 0.2 mol % $Pd(OAc)_2$ are employed as base and catalyst, respectively, and the reaction yielded ynones in 40–98 % yield within 10 min. In the presence of secondary amines a sequential Michael addition furnished β-enaminones in reasonable yields. Reactions are carried out in neat substances by stirring the reactants at room temperature.

Hitherto existing solvent-free reaction procedures for Glaser homo-coupling of **1** furnishing **4** (Scheme 2) are summarized in Table 2. Furthermore, solid-state homo-coupling of propargylic alcohols in the presence of a $CuCl_2 \times$ pyridine complex has been described gaining access to several symmetrical hexa-2,4-diyn-1,6-diols [29]. Except for [14], all reactions employ Cu as catalysts either in its cupric or cuprous compounds [18–21], whereas the last ones are distinctly more reactive manifested in the lower catalyst loading and the higher TOF of 96 and 113 h^{-1}. The bases applied for the deprotonation of **1** are another difference. Cyclic amines like morpholine and DABCO are distinctly more prone to abstract the hydrogen than NEt_3 or $KF-Al_2O_3$ [10,25]. In the case of the ball-milling procedure presented, KF-loaded Al_2O_3 was employed as milling auxiliary. Blind tests without the amine base following the above-mentioned protocol yielded **4** in 42 % isolated yield, approving the activity proposed by Kabalka et al. [18]. Thus, a cooperative effect of DABCO and $KF-Al_2O_3$ account for the high TOF in the heterogeneous ball-milling reaction. Interestingly, comminuting the reactants and heating of the reactants in the microwave field for an adequate period of time result in a similar yield and TOF [19]. This is also demonstrated for solvent-free cross-coupling procedures summarized in Table 1. At least for these reaction types and for Suzuki–Miyaura cross-coupling [30], grinding processes seem to be an interesting tool as powerful as the irradiation of reaction mixtures with microwaves. Furthermore, from the viewpoint of energy efficiency ball milling seems to be superior compared to dielectric heating, proved for Suzuki–Miyaura reaction [30], Knoevenagel condensation [31], and the oxidative homo-coupling of anilines to azo dyes [32].

Two of the six procedures summarized in Table 2 employ the liquid-base NEt_3 for deprotonation and trapping of the proton [14,21]. In the case of the Pd-catalyzed reaction [14], it has to be mentioned that a supported Pd complex is employed as the catalyst (Scheme 4). The Glaser-type homo-coupling of **1** could only be realized in the presence of electron-rich aryl halides such as *p*-iodophenol. In their absence, no reaction occurred at all or the selectivities between cross- and homo-coupling product were equal. A twofold excess of *p*-iodophenol furnishes 1,4-diphenylbuta-1,3-diyne in 84 % yield and the product selectivity was 50:1 disfavoring the Sonogashira reaction. Authors propose that the iodophenol reoxidizes the Pd to the reactive Pd(II) complex during the reaction. However, reduction products of the haloarenes have not been identified [14]. In contrast, the Cu-catalyzed reactions are performed under aerobic conditions [18–21]. Thus, air oxygen is responsible for reoxidation of the catalyst in the reaction cycle [33].



Scheme 4 Pd catalyst for solvent-free Glaser reaction (R = H, Me) [14].

CONCLUSION

Two solvent-free reactions of alkynes in ball mills are presented. Results are compared with other methods of energy entry, which have been published until today for solvent-free accomplishment of the respective reactions. Whereas in the case of Sonogashira cross-coupling reaction, comminuting in a planetary ball mill results in medium yield after 20 min, phenylacetylene is almost completely converted to the homo-coupling product (Glaser reaction) within 10 min. Both reactions made use of DABCO as base and are catalyzed by plain $Pd(OAc)_2$ or Cu(I), respectively. For both model reactions the product selectivity was very high. Comparison to other methods of energy entry revealed that ball milling is as powerful as irradiation by microwave if the reaction conditions (catalyst, base) are comparable. Reactions carried out in ball mills are characterized by a high mixing efficiency. Thus, the dispersion of the reactants of the heterogeneous starting mixture is high and the possibility for reactive contacts is significantly increased compared to mechanical mixing by a stirring bar.

However, assessment of the different solvent-free reaction protocols is difficult, since in some cases most of the reactants are liquid. Those reaction protocols are rather more comparable to solvent-based experiments than to heterogeneous reactions in the solid state. From this point of view, a harmonized definition of solvent-free or -less processes is needed for an assessment and categorization of reactions performed in the absence of solvents.

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