Solid-Phase Synthesis

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An Inexpensive and Recyclable Silver-Foil Catalyst for the Cyclopropanation of Alkenes with Diazoacetates under Mechanochemical Conditions

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Abstract: *The diastereoselective cyclopropanation of various alkenes with diazoacetate derivatives can be achieved under mechanochemical conditions using metallic silver foil and a stainless-steel vial and ball system. This solvent-free method displays analogous reactivity and selectivity to solution-phase reactions without the need for slow diazoacetate addition or an inert atmosphere. The heterogeneous silver-foil catalyst system is easily recyclable without any appreciable loss of activity or selectivity being observed. The cyclopropanation products were obtained with excellent diastereoselectivities (up to 98:2 d.r.) and in high yields (up to 96 %).*

The transition-metal-catalyzed decomposition of diazoacetates has been used in various synthetic strategies to afford natural products and other biologically active compounds, many requiring high enantioselectivity.[1] The catalytic intermolecular [2+1] cyclopropanation of alkenes in the presence of diazoacetates is a well-studied transformation that is often used as a baseline reaction for testing the activity and selectivity of newly developed catalysts.[2] Whereas several transition-metal salts have been shown to be catalytically active for the cyclopropanation of alkenes in the presence of carbene precursors, dirhodium(II) salts are widely recognized as the benchmark catalysts for these transformations as they enable the cyclopropanation of a wide range of substrates with high chemo-, regio-, and stereoselectivity.[3] At the same time, a significant financial cost is incurred by these precious-metal catalysts. To alleviate some of the economic concerns associated with homogeneous catalysts, several reports have sought to immobilize them on a solid support to render the catalysts recoverable and recyclable for future use.[4] Still, multistep ligand syntheses and the cost of the solid support place an additional burden on yielding a higher catalytic activity (e.g., improved turnover numbers and frequencies) to recover the initial cost of investment. Furthermore, over the catalyst lifetime, rhodium metal is leached from the solid support into the product mixture, and the support must be continually charged with additional catalyst, which constitutes an additional expense to the operation costs.[5] Alternatively, replacing precious-metal catalysts with more earth-abundant materials would have many wide-ranging benefits for developing sustainable processes. Towards this goal, Pericàs and co-workers have developed a polystyrene-supported tris(triazolyl) methyl copper(I) complex for carbene transfer reactions of ethyl diazoacetate to a wide range of organic compounds both in batch and in continuous-flow setups.[6] More recently, Jones, Davies, and co-workers also developed a flow reactor system for highly enantioselective C−H insertion reactions with immobilized chiral dirhodium salts.[7]

Transition-metal-catalyzed reactions under mechanochemical conditions have been shown to have many advantages over traditional solution-based methods.[8] Furthermore, many research groups have successfully carried out mechanochemical reactions on the multikilogram scale.[9] It has been shown that the milling reaction vessel can exert a heterogeneous catalytic influence on the mechanochemical reaction.[10] For the past few years, our research group has been able to conduct copper-catalyzed reactions simply by using a copper reaction vessel as the heterogeneous surface for the catalytically active species.[11] These mechanochemical reactions are conducted under aerobic reaction conditions and in the absence of ligands or solvent. Furthermore, as the source of the catalytic material is the reaction vial, which is recoverable and reusable, the whole synthetic process is environmentally benign, safe, convenient to set-up, inexpensive, and recyclable. We envisioned that these reaction conditions would be extremely versatile and suitable for the cyclopropanation of alkenes with diazoacetates.

For our initial experiment, we milled methyl phenyldiazoacetate (**1**) and styrene as a neat reaction mixture in a copper vial with a copper ball bearing, which afford the corresponding cyclopropane product **2** in 70 % yield and a low diastereomeric ratio (65:35) favoring the *E* isomer (Table 1, entry 1). For comparison, when a nickel vial and ball system was used, **2** was formed in a lower yield and with comparably low diastereoselectivity (< 31 % yield, 60:40 d.r.; entry 2). Two catalytically inactive metals/materials were also tested and yielded no product or dimer side products, which suggests that the cyclopropanation reaction is not a purely mechanical phenomenon (entries 3 and 4). Encouraged by the activity and selectivity achieved in the homogenous $AgSbF_6$ catalyzed cyclopropanation of sterically demanding alkenes in dichloro-

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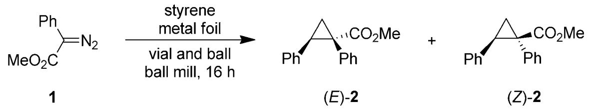
Table 1: Mechanochemical cyclopropanation of styrene with methyl phenyldiazoacetate.



Entry	Catalyst	Vial and ball	Yield[a] [%]	E/Z[b]
1	–	copper	70	65:35
2	–	nickel	31	60:40
3	–	stainless steel	NR	–
4	–	Teflon	NR	–
5	Ag shot	stainless steel	92	97:3
6	Ag shot	copper	90	90:10
7	Ag shot	nickel	92	95:5
8	Ag shot	Teflon	65	97:3
9	Ag foil	copper	75	95:5
10[c]	Ag foil	stainless steel	88	98:2
11	Ag foil	stainless steel	96	98:2
12	Ag foil	Teflon	40	97:3
13	Ag foil	nickel	72	97:3
14[d]	CuI	stainless steel	62	55:45
15[d]	CuI	copper	75	55:45
16[d]	CuI	nickel	52	55:45
17[d]	$Pd(OAc)_2$	stainless steel	45	90:10
18[d]	$Pd(OAc)_2$	copper	38	90:10
19[d]	$Pd(OAc)_2$	nickel	35	90:10

All reactions were conducted with a 1:5 ratio of the diazoacetate and the olefin at 17.4 Hz. [a] Yield of isolated product (< 5 % of the diazoacetate dimer was observed). [b] Determined by ^{1}H NMR spectroscopy. [c] 20.3 Hz. [d] Catalyst loading: 2.5 mol%.

methane, we set out to test the efficacy of a heterogeneous silver metal catalyst.[12] Gratifyingly, milling **1** and styrene in a stainless-steel vial charged with a silver shot generated the cyclopropanation product in nearly quantitative yield (92 % yield) and high diastereomeric ratio (97:3) when the reaction mixture was mechanically mixed with a stainless-steel ball bearing (entry 5). This is in good agreement with the yield and stereoselectivity achieved in the homogenous silver(I)-catalyzed counterpart.[12] Interestingly, bimetallic heterogeneous mixtures yielded inferior results irrespective of the source of the silver catalyst that was added to the metallic reactor and ball system (entries 6, 7, 9, and 13). Moreover, Teflon vials and balls also resulted in inferior yields but maintained the high diastereoselectivity (97:3) in the presence of silver, suggesting that the decreased ball mass likely resulted in a significantly lower mechanical force that occurred during the molecular collision events (entries 8 and 12). The addition of a catalytic amount of copper(I) iodide to the metal vial and ball system was found to be detrimental to both the yield and the diastereoselectivity (entries 14–16). On the other hand, the addition of palladium(II) acetate, a metal that is rarely used for cyclopropanation reactions with diazoacetates, resulted in good diastereoselectivity (90:10), but only modest yields of the cyclopropanation product (entries 17–19).[13]

Having identified optimized conditions for the heterogeneous silver(0)-catalyzed cyclopropanation reaction, we set out to test the recyclability of this mechanochemical process. We conducted the cyclopropanation reaction five consecutive times, with an ethyl acetate solvent wash between consecutive runs to remove the crude reaction mixtures, and observed highly reproducible yields and no appreciable decrease in the diastereoselectivity (97:3 d.r.; Figure 1).

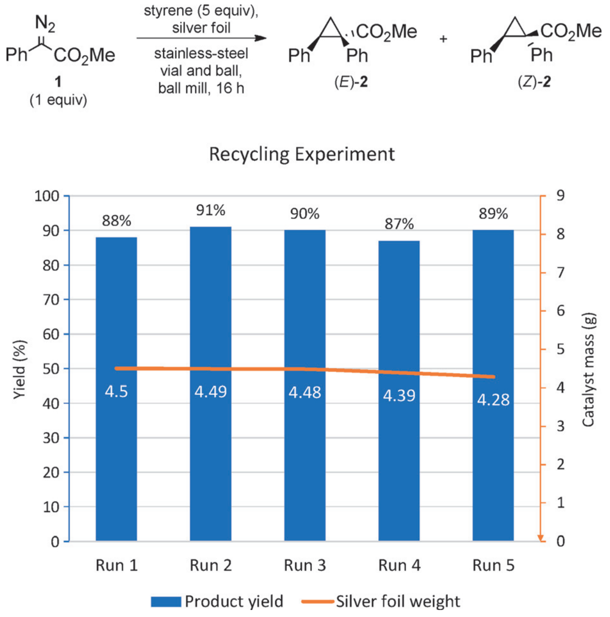
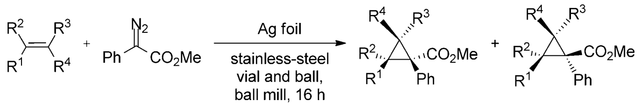


Figure 1. Recyclability of the silver foil as a cyclopropanation catalyst.

Using the same silver-metal foil, we extended the scope of the cyclopropanation by exploring the electronic and steric effects of substituted styrene derivatives and various other olefins in the presence of diazoacetate **1** (Table 2). Both

Table 2: Effect of the alkene structure on the reactivity.



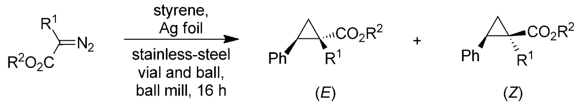
Entry	R^1	R^2	R^3	R^4	Product	Yield[a] [%]	E/Z[b]
1	$4\text{-}MeOC_6H_4$	H	H	H	**3**	90	92:8
2	$4\text{-}MeC_6H_4$	H	H	H	**4**	92	96:4
3	$4\text{-}BrC_6H_4$	H	H	H	**5**	89	98:2
4	$4\text{-}ClC_6H_4$	H	H	H	**6**	90	95:5
5	$4\text{-}FC_6H_4$	H	H	H	**7**	85	98:2
6	$4\text{-}t\text{Bu}C_6H_4$	H	H	H	**8**	96	98:2
7	C_6H_5	CH_3	H	H	**9**	88	85:15
8	C_6H_5	H	CH_3	H	**10**	86	92:8
9	C_4H_9	H	H	H	**11**	82	85:15
10	C_6H_5	H	C_6H_5	H	**12**	35	NA
11	C_6H_5	H	H	C_6H_5	**13**	58	NA
12	C_6H_5	C_6H_5	H	H	**14**	89	NA
13	1-naphthyl	H	H	H	**15**	85	95:5
14	2-naphthyl	H	H	H	**16**	89	98:2
15	C_6H_5	C_6H_5	C_6H_5	C_6H_5		NR	–
16	C_6H_5	C_6H_5	C_6H_5	H		NR	–

All reactions were conducted with a 1:5 ratio of the diazoacetate and the olefin. [a] Yield of isolated product (< 5 % of the diazoacetate dimer was observed). [b] Determined by ^{1}H NMR spectroscopy.

electron-rich and electron-poor styrene derivatives afforded the corresponding cyclopropane products **3**–**8** in high yields and diastereoselectivities (entries 1–6). A modest diastereomeric ratio (85:15) was observed for α-methylstyrene (entry 7), whereas β-methylstyrene afforded the corresponding cyclopropane **10** in both good yield and diastereoselectivity (entry 8). Under our optimized ball-milling conditions, 1-hexene was converted into cyclopropane **11** with a slightly lower diastereomeric ratio (85:15) than in previous reports (entry 9).[14] Both *trans*- and *cis*-stilbene smoothly underwent the mechanochemical reaction to give the corresponding products **12** and **13** in high diastereomeric ratios, but low yields (entries 10 and 11). 1,1-Diphenylethylene and vinylnaphthalene compounds are also highly effective substrates for the diastereoselective cyclopropanation reaction under ball milling (entries 12–14). Finally, 1,1,2,2-tetraphenylethylene and 1,1,2-triphenylethylene were found to be unreactive under these mechanochemical reaction conditions, likely because of steric hindrance (entries 15 and 16).

The electronic character of substituted diazoacetate compounds can be generally categorized by their resultant characteristic reactivities. As such, three distinctly different classes, namely acceptor-only, acceptor–acceptor, and donor–acceptor diazoacetate families, were tested for the silver(0)-catalyzed cyclopropanation of styrene under mechanochemical milling conditions (Table 3). Both electron-rich and electron-poor donor–acceptor diazoacetates were efficiently decomposed in the presence of silver foil in a stainless-steel vial and ball reactor to afford the corresponding cyclopropane derivatives **17**–**20** in high yields and good diastereomeric ratios (entries 1–4). Ethyl diazoacetate, a commercially available acceptor-only diazo compound, gave the desired product in good yield and with poor diastereoselectivity (60:40; entry 5). Likewise, dimethyl 2-diazomalonate, an acceptor–acceptor diazoacetate, was completely unreactive under the mechanochemical conditions (entry 6), which is in agreement with the previously reported findings for the solution-phase homogeneous silver(I)-catalyzed reaction.[15]

Table 3: Effect of the diazoacetate structure on the reactivity.



Entry	R^1	R^2	Product	Yield[a] [%]	*E*/*Z*[b]
1	4-MeOC_6H_4	Me	**17**	95	98:2
2	4-$CF_3C_6H_4$	Me	**18**	85	88:12
3	4-BrC_6H_4	Me	**19**	90	90:10
4	4-*t*BuC_6H_4	Me	**20**	95	98:2
5	H	Et	**21**	88	60:40
6	CO_2Me	Me	**22**	NR	–

All reactions were conducted with a 1:5 ratio of the diazoacetate and the styrene. [a] Yield of isolated product (< 5% of the diazoacetate dimer was observed). [b] Determined by ^{1}H NMR spectroscopy.

In conclusion, we have developed a simple, inexpensive, environmentally benign, and recyclable heterogeneous silver-foil catalyst for the efficient and diastereoselective cyclopropanation of alkenes with diazoacetates under solvent-free mechanochemical reaction conditions. The chemically inert stainless-steel vial and ball reactor transfers sufficient kinetic energy and mixes the reaction mixture to enable product formation without producing any detectable amounts of the cyclopropane ring-opening side products. Future work will apply these mechanochemical reaction conditions to other metal-catalyzed reactions for the development of catalytically active and selective heterogeneous catalysts for carbene transfer reactions.

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