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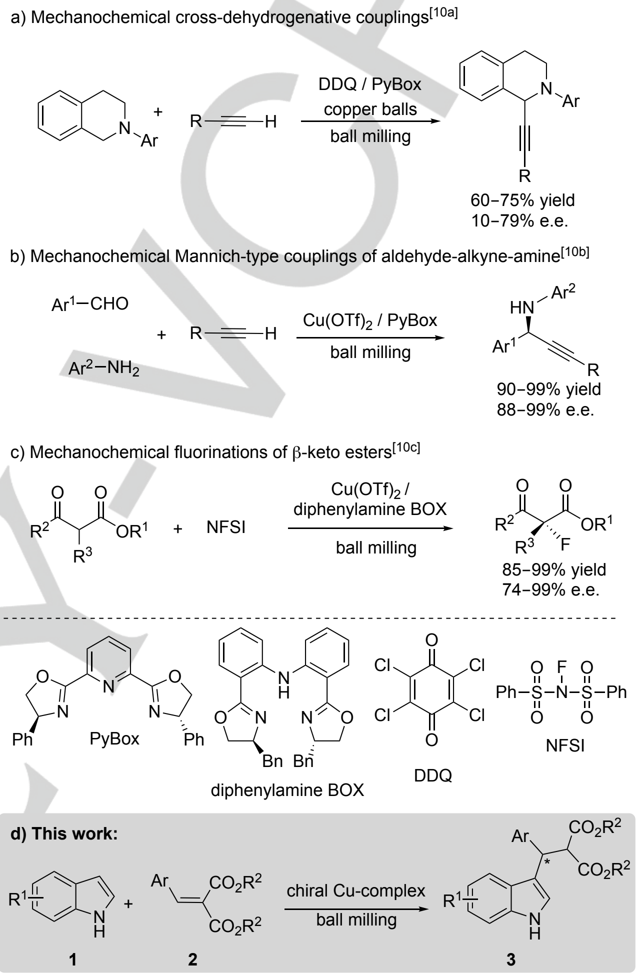
Mechanochemical copper-catalyzed asymmetric Michael-type Friedel-Crafts alkylations of indoles with arylidene malonates

Plamena Staleva, José G. Hernández, and Carsten Bolm*

Abstract: A mechanochemical version of the asymmetric Michael-type Friedel-Crafts alkylation of indoles with arylidene malonates was developed. The reaction proceeds under ambient atmosphere using a chiral copper bis(oxazoline) catalyst in a mixer mill. Under these reaction conditions nineteen 3-substituted indole derivatives were synthesized in good to excellent yields (up to 98%), and with good enantioselectivities (up to 91:9 e.r.) after short milling times.

Chiral indoles, in particular 3-substituted ones, represent valuable structural unit in organic chemistry due to their prevalence in bioactive natural products, pharmaceuticals, and synthetic chemicals.[1] Enantioenriched derivatives are often prepared by asymmetric Friedel-Crafts alkylation of indoles.[2] A typical example is the reaction of indole with arylidene malonates in the presence of chiral copper(II)-complexes.[3] Despite the effectiveness of these protocols in terms of yield and enantioselectivity, many of them still face drawbacks such as a strong dependence of the catalytic activity of the metal complex on the nature of the solvent. Additionally, in most cases, an inert atmosphere and prolonged cooling periods are required, thereby rendering cumbersome and lengthy synthetic procedures.

In recent years, the number of studies searching for novel concepts, new chemical reactivity, and more sustainable organic processes has steadily increased. In this context, mechanochemistry has proven to be a powerful alternative for the implementation of a wide range of chemical transformations, exhibiting benefits such as solvent-free conditions, higher reaction rates and the possibility to discover novel reaction pathways.[4,5] Specifically, in the field of metal catalysis a plethora of solvent-free reactions has been enabled using ball milling techniques.[6] Interestingly, metal complexes have shown remarkable stability under high mechanical stress,[7] a feature that allowed introducing metal-catalyzed mechanochemical C–H bond functionalization protocols.[8] Conversely, the mechanochemical formation of chiral metal complexes and their application in asymmetric reactions by mechanochemistry have remained underexplored. Presumably that is due to the generally very critical fine-tuning of all reaction conditions such as reaction media, concentration, inert atmosphere and, especially, temperature required for achieving high enantioselectivities.[9] As a result, to date, only a handful of examples of metal-catalyzed asymmetric transformations in ball mills have been reported (Scheme 1a–c).[10] Here, we extend this pallet and present Cu(I)-BOX-catalyzed asymmetric Michael-type Friedel-Crafts alkylations of indoles **1** with benzylidene malonates **2** under solventless conditions in a mixer mill (Scheme 1d).



Scheme 1. Mechanochemical metal-catalyzed asymmetric reactions.

Initially, a non-asymmetric version of Friedel-Crafts alkylations under mechanochemical conditions was examined. Thus, a mixture of indole (**1a**) and benzylidene malonate (**2a**) were ground in the presence of $Cu(OTf)_2$ (10 mol%) at 25 Hz in a mixer mill. Pleasingly, after a milling time of only 60 min the desired product **3a** was formed in 94% yield (Table 1, entry 1). This result evidenced the feasibility of the reaction to be realized in the ball mill, but at the same time it also highlighted the high reactivity of the copper salt to facilitate the formation of *rac*-**3a**, a potential challenge to develop an asymmetric version of the Friedel-Crafts alkylation by ball milling. To overcome this challenge, $Cu(OTf)_2$ and the chiral ligands (**L1**–**L4**) were first milled for 10 min to favor the formation of the chiral copper complexes. Then, **1a** and **2b** were added into the jar, and the milling was continued for another 60 min of milling at 25 Hz.[11] In general, the presence of the C_2-symmetric bis(oxazoline) ligands **L1**-**L4** did not significantly affect the reaction rate of the Friedel-Crafts alkylation, and product **3a** was obtained in excellent yield

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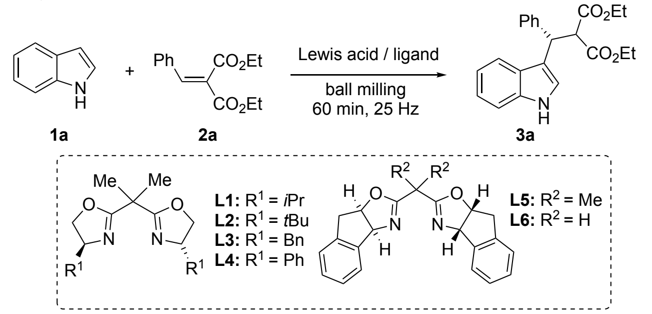
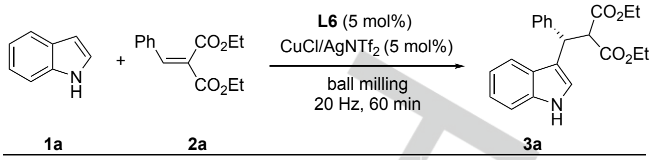
Table 1. Screening of the catalytic system for the alkylation of indole (**1a**) with benzylidene malonate (**2a**).[a]



Entry	Lewis acid	Ligand	Yield [%][b]	e.r.[c]
1	$Cu(OTf)_2$	–	94	–
2	$Cu(OTf)_2$	**L1**	98	50:50
3	$Cu(OTf)_2$	**L2**	95	65:35
4	$Cu(OTf)_2$	**L3**	90	52:48
5	$Cu(OTf)_2$	**L4**	96	50:50
6	$Cu(OTf)_2$	**L5**	97	62:38
7	$Cu(OTf)_2$	**L6**	97	78:22
8	$CuCl_2/AgNTf_2$	**L6**	97	81:19
9	$CuCl/AgNTf_2$	**L6**	97	85:15
10[d]	$CuCl/AgNTf_2$	**L6**	97	85:15
11[e]	**$CuCl/AgNTf_2$**	**L6**	**97**	**85:15**

[a] Reaction conditions: **1a** (0.30 mmol), **2b** (0.30 mmol), Lewis acid / ligand (10 mol%), silica gel [as milling auxiliary (60 mg per 0.30 mmol of **1a**)], for entries 8–11: use of $AgNTf_2$ (10 mol%). [b] Yield after purification by column chromatography; for entries 8–11: determined by ^{1}H NMR spectroscopy with dimethylsulfone as an internal standard. [c] Determined by CSP-HPLC analysis. [d] The chiral copper complex was prepared in solution. [e] Use of 5 mol% of Lewis acid / ligand.

Table 2. Screening of the ball milling conditions and additives in the alkylation of indole (**1**) with benzylidene malonate (**2a**) using indane-BOX **L6** as ligand.[a]



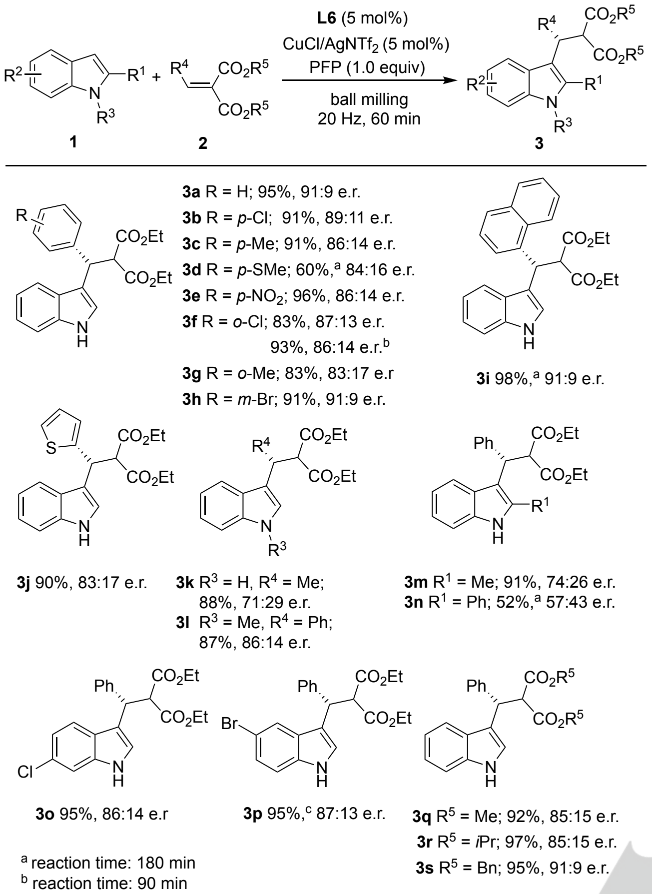
Entry	Freq. [Hz]	Additive	Yield [%][b]	e.r.[c]
1	25	–	97	85:15
2	20	–	92	87:13
3	15	–	41	87:13
4	20	*i*PrOH	99	85:15
5	20	TFE	99	87:13
6	20	HFIP	99	88:12
7	**20**	**PFP**	**95**	**91:9**
8[d]	20	PFP	95	90:10
9[e]	20	PFP	37	85:15

[a] Reaction conditions: **1a** (0.30 mmol), **2b** (0.30 mmol), $CuCl/AgNTf_2$/**L6** (5 mol%), silica gel [as milling auxiliary (60 mg per 0.30 mmol of **1a**)], for entries 4–9: additive (0.30 mmol). [b] Determined by ^{1}H NMR spectroscopy with dimethylsulfone as an internal standard. [d] Use of 2.5 mol% of $CuCl/AgNTf_2$/**L6**. [e] Use of 1 mol% of $CuCl/AgNTf_2$/**L6**.

after only 60 min of milling (Table 1, entries 2-5). More importantly, the use of *t*Bu-BOX ligand **L2** provided the desired product **3a** with an enantiomeric ratio of 65:35 in favor of the (*S*)-**3a** enantiomer (Table 1, entry 3).[3d] Encouraged by this result, the screening was extended by applying additional ligands, e. g. **L5** and **L6** (for a full ligand list, see the Supporting Information). Also indane-BOX **L5** gave an active catalyst under the milling conditions, and the results were similar to the ones obtained with BOX-ligand **L2** (Table 1, entries 3 and 6). On the other hand, the presence of unsubstituted indane-BOX **L6** had a positive effect on the enantioinduction of the reaction, and product **3a** was obtained with an e.r. of 78:22 (Table 1, entry 7). A further fine tuning of the reaction conditions revealed that the cationic complex generated in situ from $AgNTf_2$ and $CuCl_2$ gave **3a** in 97% yield and 81:19 e.r (Table 1, entry 8). An additional improvement in the enantioselectivity of the reaction was achieved when CuCl was used instead of $CuCl_2$ (Table 1, entry 9). A control experiment in the ball mill using the chiral Cu-complex prepared in solution resulted in product **3a** being formed in identical yield and with the same enantioselectivity (Table 1, entries 9 and 10), indicating that both the anion exchange and the complex formation were completed under ball milling conditions. Moreover, reducing the catalyst loading from 10 mol% to 5 mol% proved possible while the yield and the enantioselectivity of the mechanochemical reaction were maintained (Table 1, entry 11).[12]

Having identified the $CuCl/AgNTf_2$/**L6** combination (5 mol%) as the best catalytic system for the asymmetric alkylation reaction, the influence of some milling parameters and additives on the outcome of the reaction was investigated. Reducing the milling frequency from 25 Hz to 20 Hz led to the formation of product **3a** in slightly lower yield, but pleasingly, an improvement in the stereoselectivity of the reaction was noticed. Probably, that was a result of an overall lowering of the temperature of the reaction mixture due to the reduced energy input, resulting in better enantioselectivity (Table 2, entry 2). However, performing the reaction at 15 Hz led to a dramatic drop in the yield without further improvement of the enantioselectivity (Table 2, entry 3). Next, the effect of additives on the reaction was studied (Table 2, entries 4–7). The addition of *i*PrOH and trifluoroethanol (TFE) accelerated the formation of **3a**, but did not improve the enantioselectivity (Table 2, entries 4 and 5). Using the more acidic hexafluoroisopropanol (HFIP) led to full conversion of the starting materials, and product **3a** was isolated with an enantiomeric ratio of 88:12 (Table 2, entry 6). The enantioselectivity of the reaction was further improved by using pentafluorophenol (PFP) as an additive. After this modification, **3a** was obtained in 95% yield with an e.r. of 91:9 (Table 2, entry 7). Decreasing the catalyst loading to 2.5 mol% was possible without significantly affecting the yield and enantioselectivity (Table 2, entries 8). Applying only 1 mol% of the catalyst led to a drastic erosion in the yield of **3a** (Table 2, entry 9).

With the optimized conditions established (Table 2, entry 7), the substrate scope of the reaction was investigated. Various structurally diverse indoles **1** and arylidene malonates **2** were applied (Scheme 2). A number of substituents on the aryl ring of the arylidene malonates **2a**–**h** were tolerated, regardless of the steric hindrance and electronic properties, affording products



3a R = H; 95%, 91:9 e.r.
3b R = *p*-Cl; 91%, 89:11 e.r.
3c R = *p*-Me; 91%, 86:14 e.r.
3d R = *p*-SMe; 60%,[a] 84:16 e.r.
3e R = *p*-NO$_2$; 96%, 86:14 e.r.
3f R = *o*-Cl; 83%, 87:13 e.r.
93%, 86:14 e.r.[b]
3g R = *o*-Me; 83%, 83:17 e.r
3h R = *m*-Br; 91%, 91:9 e.r.

3i 98%,[a] 91:9 e.r.

3j 90%, 83:17 e.r.

3k R^3 = H, R^4 = Me; 88%, 71:29 e.r.
3l R^3 = Me, R^4 = Ph; 87%, 86:14 e.r.

3m R^1 = Me; 91%, 74:26 e.r.
3n R^1 = Ph; 52%,[a] 57:43 e.r.

3o 95%, 86:14 e.r

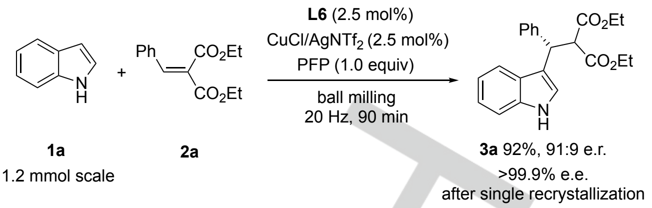
3p 95%,[c] 87:13 e.r.

3q R^5 = Me; 92%, 85:15 e.r.
3r R^5 = *i*Pr; 97%, 85:15 e.r.
3s R^5 = Bn; 95%, 91:9 e.r.

[a] reaction time: 180 min
[b] reaction time: 90 min
[c] with 1.5 equiv of indole

Scheme 2. Mechanochemical Cu-catalyzed asymmetric Friedel−Crafts alkylations of indoles **1** with various arylidene malonates **2**.

3a–**h** in excellent yields and good enantioselectivities (Scheme 2). 1-Naphthyl and 2-thiophenyl substituted arylidene malonates also reacted well under the standard reaction conditions giving the corresponding products **3j** and **3i** in yield of 98% and 90% having 91:9 and 83:17 e.r., respectively. The reaction with ethylidene malonate (**2k**) provided product **3k** in high yield, but the enantioselectivity (71:29 e.r.) was significantly lower than the ones with aryl-containing substrates. Meanwhile, the effect of the substituents on the indole reaction partner was investigated. *N*-Methyl indole and **2a** reacted in the ball mill to give product **3l** in good yield and enantioselectivity. Introducing a substituent on the 2-position of the indole negatively affected the yield and the enantioselectivity of the alkylation reaction. Although 2-methyl indole gave the corresponding product **3m** in excellent yield, the e.r. of **3m** was only 74:26. Even more pronounced was this effect for 2-phenyl indole product **3n**, which was formed in only 52% yield after 180 min of milling with an enantiomeric ratio of 57:43. Pleasingly, 5- or 6-halogen substituted indoles reacted well affording the respective products **3o** and **3p** in high yields and good asymmetric induction (Scheme 2). The use of substituted indoles bearing electron donating groups such as 4- and 5-methyl indole derivatives proved more challenging, and only 5-methyl indole provided the alkylated product, albeit in low yield (22% yield after 60 min of milling). Next, the nature of the ester group in the benzylidene malonates **2** was varied. Thus, methyl, isopropyl and benzyl esters were tested giving the corresponding products **3q**–**s** in excellent yields and with enantioselectivities close to the values obtained using the model substrate benzylidene malonate (**2a**).



1a
1.2 mmol scale

2a

3a 92%, 91:9 e.r.
>99.9% e.e.
after single recrystallization

Scheme 3. Up-scaled mechanochemical Cu-catalyzed asymmetric Friedel−Crafts alkylation of indole (**1**) with benzylidene malonate (**2a**).

While the results depicted in Scheme 2 were obtained with a catalyst loading of 5 mol%, a reduction to 2.5 mol% was possible in many cases without significantly affecting the reaction outcome (for details, see the Supporting Information).

Finally, to further demonstrate the synthetic potential of the mechanochemical approach, a four-fold scale up experiment was conducted. After 90 min of milling at 20 Hz, the reaction provided product **3a** with an e.r. of 91:9 in 90% yield (Scheme 3). Notably, recrystallization of **3a** from a mixture of heptane/chloroform afforded a solid sample of **3a** with >99.9% e.e.

In summary, we developed a mechanochemical copper-catalyzed asymmetric alkylation of indoles in a mixer mill. The transformation features short reaction times, solvent-free conditions, ambient atmosphere and low catalyst loading. The products are formed in high to excellent yields and good enantioselectivities. The reaction times are shorter compared to those required for analogous couplings in solution. Additionally, an up-scaling of the mechanochemical catalysis proved successful providing the enantioenriched product in excellent yield, without any loss of enantioselectivity.

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Keywords: asymmetric alkylation • ball milling • indole • Friedel-Crafts • mechanochemistry

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[11] A full list of reaction conditions and ligands tested can be found in the Supporting Information.

[12] Replacing the copper salts by other metal salts led to the formation of *rac*-**3a**. For details see the Supporting Information.

COMMUNICATION

In mixer mills, Cu(I)-BOX complexes catalyze asymmetric Michael-type Friedel-Crafts alkylations of indoles with benzylidene malonates under solvent-free conditions. With low catalyst loadings, the transformations proceed under ambient atmosphere and lead to products with good enantioselectivities in high to excellent yields after short reaction times.

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