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Atroposelective organocatalytic synthesis of 1,2′-binaphthalene-3′-carbaldehydes under mechanochemical conditions

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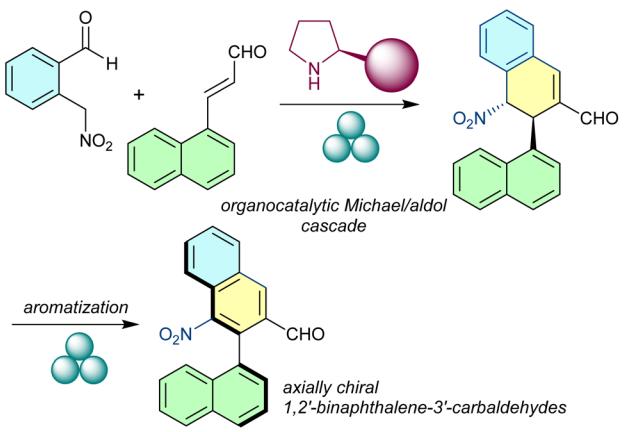
Ball-milling allowed the efficient realization of asymmetric organocatalytic Michael/aldol cascade, which affords 1′,2′-dihydro-1,2′-binaphthalene derivatives. These compounds were transformed into axially chiral 1,2′-binaphthalene-3′-carbaldehydes under mechanochemical conditions. Evaluation of milling parameters such as frequency or liquid-assisting agents led to optimum reaction conditions, which afforded products in high yields, and short times while preserving high enantiomeric purity.

Introduction

Organic compounds possessing stereogenic axes are beneficial as medicines, materials, chiral ligands, and catalysts in asymmetric catalysis. Axially chiral binaphthyl derivatives became highly successful as ligands and organocatalysts in asymmetric catalysis. Chiral diphosphanes such as BINAP ([1,1′-binaphthalene]-2,2′-diyl)bis(diphenylphosphane) or Segphos (2*H*,2′*H*-[4,4′-bi-1,3-benzodioxole]-5,5′-diyl)bis(diphenylphosphane) are considered privileged catalyst scaffolds. In asymmetric organocatalysis, BINOL-based ([1,1′-binaphthalene]-2,2′-diol) phosphoric acids,[1–4] disulfonimides,[5] or imidodiphosphorimidates proved highly versatile catalysts for a wide range of transformations.[6,7] Stereoselective syntheses of axially chiral compounds *via* either metal-catalyzed or organocatalytic methods has recently become a dynamic field of organic synthesis. Asymmetric organocatalysis proved highly instrumental in assembling axially chiral compounds *via* various activation modes.[8–13]

Influencing chemical processes by mechanical energy is becoming essential in materials, organic and inorganic synthesis, and other fields such as pharmaceutical chemistry.[14–20] Mechanochemistry facilitates the efficient synthesis of numerous organic and inorganic compounds, including medicines and pharmaceutically active substances or materials.[21–24] As was recently demonstrated, catalysis, including its various branches, such as metal-catalyzed reactions,[25,26] organocatalysis,[27,28] or even biocatalysis,[29] merges well with mechanochemistry. In the area of asymmetric organocatalysis, several significant advances have been made in the synthesis of centro-chiral compounds. Various activation modes were employed in mechanochemical transformations. Asymmetric aldol reactions,[30–36] Michael additions,[37–42] Mannich reactions,[43] ring-opening reactions,[44] alkylations,[45] α-functionalizations,[46] NHC-catalyzed acyl anion reactions,[47] Morita–Baylis–Hilman reactions,[48] and cycloadditions were demonstrated to benefit from mechanochemical conditions.[49,50] Axially chiral compounds were not yet synthesized *via* asymmetric organocatalysis under mechanochemical conditions. In this work, we decided to address this issue. Initially, we hypothesized that the somewhat forcing nature of mechanochemical activation of ball-milling processes might favor covalent organocatalytic processes. Covalent activation is more robust than non-covalent due to the formation of covalent bonds between reagents and catalysts. For this reason, we were inspired by the work of Jorgensen,[51] and Hayashi,[52–54] who described atroposelective organocatalytic cascades in solution, which employed pyrrolidine-based organocatalysts.

In this context, we investigated the mechanochemical enantioselective synthesis of axially chiral biaryls using chiral organocatalysts (Scheme 1). Herein, we describe atroposelective organocatalytic synthesis of 1,2′-binaphthalene-3′-carbaldehydes using ball milling.



Scheme 1 Concept of this work.

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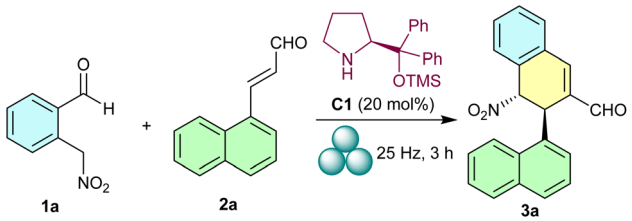


Scheme 2 Organocatalytic Michael/aldol cascade.

Table 1 Screening of LAG additives in the Michael/aldol reaction of **1a** with **2a**[a]

Entry	LAG	Yield of **3a** (%)	ee of **3a** [b] (%)
1	—	80	82
2	Hexane	68	88
3	PhMe	72	90
4	H_2O	78	82
5	MeCN	81	84
6	DCM	82	94
7	$CHCl_3$	68	92
8	EtOH	82	90
9	Et_2O	84	94
10	^{t}BuOMe	84	94
11	CpOMe	82	94
12	THF	90	88
13	MeTHF	81	92
14	1,4-Dioxane	83	94
15	EtOAc	80	92

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.15 mmol), **C1** (0.024 mmol, 20 mol%), LAG amount (22 μL, $\eta = 0.4$), 25 Hz, 3 h. [b] Enantiomeric purity was determined by HPLC on CHIRALPAK IC (hexane : *i*PrOH = 9 : 1). DCM = dichloromethane, CpOMe = cyclopentyl methyl ether; MeTHF = 2-methyltetrahydrofurane.

Results and discussion

We have started our investigation with the reaction of an aromatic aldehyde **1a** possessing a nitromethyl substituent in the ortho position and a naphthalene-derived unsaturated aldehyde. These compounds, under the catalysis of Hayashi–Jorgensen catalyst **C1**,[29,30] undergo enantioselective Michael/aldol cascade, furnishing a 1′,2′-dihydro-1,2′-binaphthalene derivative **3a** (Scheme 2).

Initially, catalyst loading of 20 mol% was used, and the reaction mixture was milled at 25 Hz for 3 h. This procedure afforded derivative **3a** in 80% yield and enantiomeric purity of 82% ee. All ball-milling experiments were realized in a shaker mill, in which milling jars perform radial oscillations with frequencies from 3 to 30 Hz. The experiments were performed in stainless steel milling jars with an internal volume of 1.5 mL using one stainless steel ball with a diameter of 6 mm.

We continued with the study of reaction parameters. Firstly, we evaluated the effect of liquid-assisting grinding additives (LAG) on the reaction. We have tested a range of organic solvents in the Michael/aldol cascade reaction of **1a** with **2a** (Table 1). As can be seen from Table 1, the influence of these solvent additives either on yield or enantioselectivity was not significant. The best LAG additives were etheric solvents of medium polarity Et_2O and ^{t}BuOMe, which afforded product **3a** with the highest yield and enantiomeric purity (Table 1, entries 9 and 10). Also, CpOMe and 1,4-dioxane are highly promising in this respect. With THF, the yield of **3a** was even higher, but the enantioselectivity was somewhat lower (Table 1, entry 12). However, the use of etheric solvents carries some risks for large scale operations due to their low flash point. Due to these concerns, we have tested also ethyl acetate. EtOAc afforded a balanced results as the Michael/aldol product **3a** was obtained in 80% yield and with 92% ee.

We followed our investigation by evaluating catalyst loading and reaction time (Table 2). We varied the catalyst loading from 5 to 25 mol%. The data in Table 2 show that catalyst loading higher than 10 mol% is adequate for this transformation to achieve high yield and enantioselectivity. Only at 5 mol% of **C1**, the yield of **3a** decreased. The optimum reaction time seems to be 3 h from the perspective of the highest yield and enantiomeric purity of product **3a**.

Table 2 Evaluation of catalyst loading and reaction time[a]

Entry	Catalyst loading (mol%)	Time (h)	Frequency (Hz)	LAG	Yield (%)	ee[b] (%)
Catalyst loading						
1	5	3	25	Et_2O	63	94
2	10	3	25	Et_2O	83	94
3	15	3	25	Et_2O	84	92
4	20	3	25	Et_2O	84	94
5	25	3	25	Et_2O	85	90
Reaction time						
6	20	1	25	Et_2O	68	92
7	20	2	25	Et_2O	73	90
8	20	3	25	Et_2O	84	94
9	20	4	25	Et_2O	90	90

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.15 mmol), **C1** (5–25 mol%), LAG amount (22 μL, $\eta = 0.4$), 25 Hz, 1–4 h. [b] Enantiomeric purity was determined by HPLC on CHIRALPAK IC (hexane : *i*PrOH = 9 : 1).

Table 3 Influence of milling frequency on the yield and enantioselectivity[a]

Entry	Frequency (Hz)	Catalyst (mol%)	Time (h)	LAG	Yield (%)	ee[b] (%)
1	15	20	3	Et_2O	70	92
2	20	20	3	Et_2O	88	90
3	25	20	3	Et_2O	84	94
4	30	20	3	Et_2O	87	86

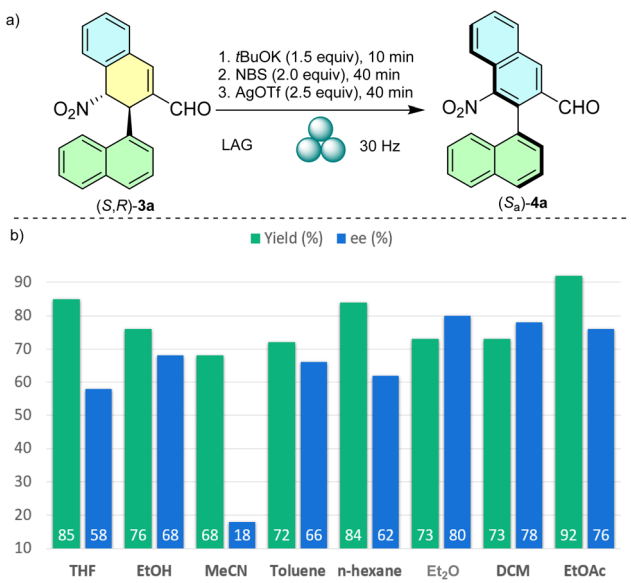
[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.15 mmol), **C1** (0.024 mmol, 20 mol%), LAG amount (22 μL, $\eta = 0.4$), 15–30 Hz, 3 h. [b] Enantiomeric purity was determined by HPLC on CHIRALPAK IC (hexane : *i*PrOH = 9 : 1).

Frequency is an essential reaction parameter for ball milling. It has an expected influence related to the amount of mechanical energy transferred to the reaction system, which typically impacts the yield of the process. For asymmetric transformations, there is another crucial consideration connected with temperature and, consequently, the enantioselectivity of the reaction. Due to the typically low energy difference between diastereomeric arrangements between the chiral catalyst and reagents, which lead to enantiomers of products, the temperature often needs to be as low as possible. Therefore, we investigated the influence of the milling frequency on chemical yield and, crucially, on the enantiomeric purity of **3a**. We evaluated milling frequencies from 15 to 30 Hz. We conclude that the best compromise regarding yield and enantioselectivity is 25 Hz (Table 3, entry 3). A relatively small variation in enantioselectivity with changing milling frequency and, thus, energy input to the system also agrees with Emmerling's finding. They showed that internal temperature does not increase dramatically during mechanochemical processes.[55]

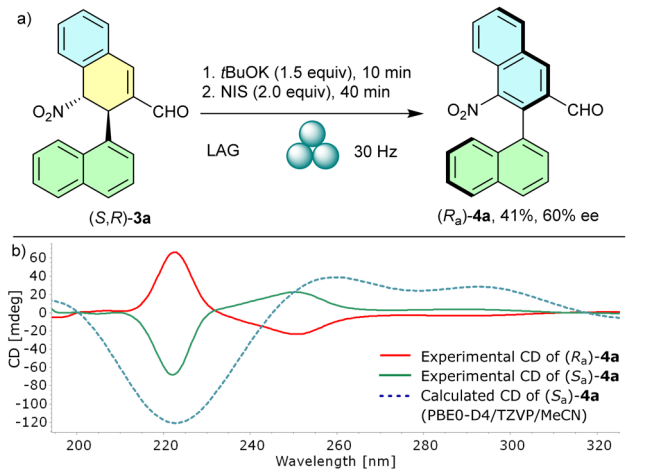
Next, we investigated the oxidative aromatization of derivative **3a**. As a starting point, we employed conditions from solution synthesis suggested by Hayashi.[54] The application of ^{t}BuOK on nitroaldehyde **3a**, followed by NBS and AgOTf, produces 1,2′-binaphthalene derivative **4a**. Evaluation of the LAG effect on this reaction under ball-milling conditions showed that apolar solvents such as hexane or THF provide higher yields of product **4a** (Scheme 3). The use of EtOAc afforded the reaction product in high yield (92%) and good enantioselectivity of 76% ee. Regarding enantioselectivity, diethyl ether, and dichloromethane provided derivative **4a** with the highest enantiomeric purities. We concluded that Et_2O is the most suitable LAG solvent, providing the highest enantioselectivity while keeping the chemical yield high.

We have performed oxidative aromatization of (*S*,*R*)-**3a** also using *N*-iodosuccinimide (NIS) that was described in solution as providing the opposite enantiomer of (R_a)-**4a** (Scheme 4a). Mechanochemical realization of this synthesis yielded the (R_a)-**4a** in slightly lower yield (41%) and somewhat compromised enantiomeric purity (60% ee). The absolute configuration of 1,2′-binaphthalene derivative **4a** was determined by comparison of experimental electronic CD with DFT-calculated CD spectra (Scheme 4b). Experimental CD spectra (red and green lines) confirm the enantiomeric relationship of (R_a) and (S_a)-**4a**, which were obtained by the two aromatization methods. For (S_a)-**4a**, the CD spectrum was calculated at PBE0-D4/TZVP/MeCN level (blue dashed line). The character of the calculated CD matches the experimental CD for (S_a)-**4a**. For calculated CD spectra by several different methods, see ESI.

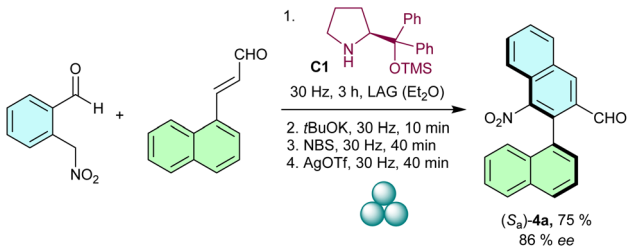
We have also tested the one-pot realization of Michael/aldol organocatalytic sequence followed by oxidative aromatization without isolating intermediate compounds **3**. In this reaction, after nitroaldehyde **1a** reacted with unsaturated aldehyde **2a**,



Scheme 3 Mechanochemical oxidative aromatization of **3a** to 1,2′-binaphthalene derivative **4a**.



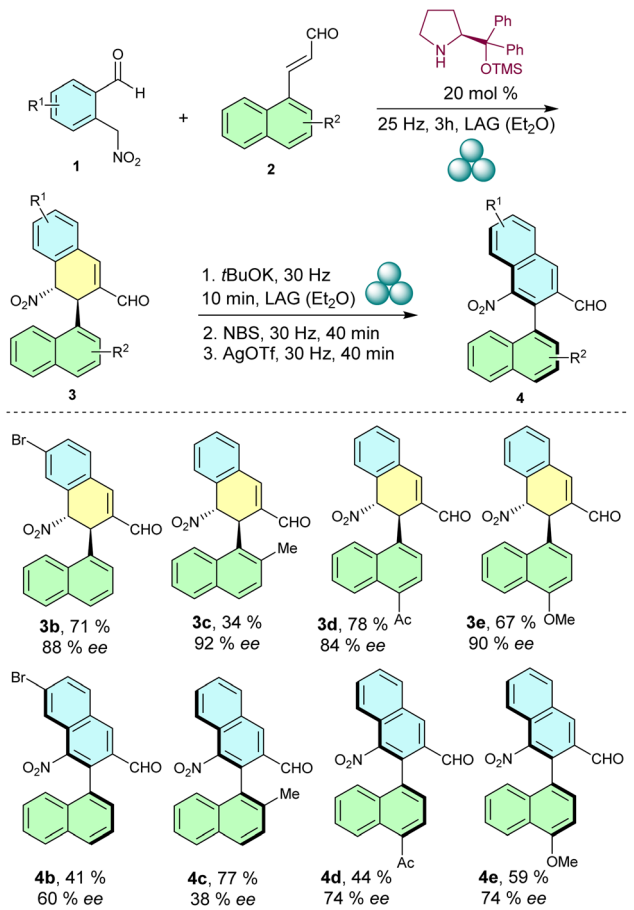
Scheme 4 (a) Oxidative aromatization towards (R_a)-**4a**; (b) experimental and DFT-calculated CD spectra for (R_a) and (S_a)-**4a**.



Scheme 5 One-pot synthesis of (S_a)-**4a**.

the corresponding derivative **3a** was not isolated, and ^{t}BuOK, NBS, and AgOTf were sequentially added to the milling jar. Interestingly, this procedure was also quite efficient and provided the 1,2′-binaphthalene derivative (S_a)-**4a** in 75% yield and enantiomeric purity of 86% ee (Scheme 5).

We have probed several other starting materials to explore the generality of the mechanochemical sequence. With the organocatalyst **C1** under standard reaction conditions, we synthesized derivatives **3b–3e** in good yield and enantiomeric purities (Scheme 6). The only exception was the derivative **3c**, which was obtained with a lower yield of 34%. Lower reactivity of the corresponding starting material **2c** was probably caused by increased steric hindrance resulting from additional substituent in position-2 at the naphthalene ring. Furthermore,



Scheme 6 Related 1,2′-binaphthalene derivatives.

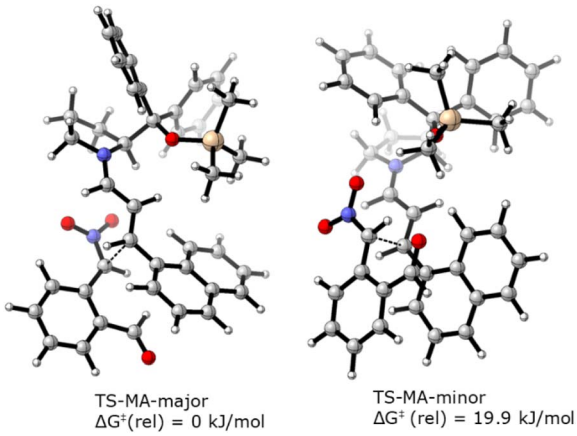


Fig. 1 DFT calculated transition states for Michael addition (PBEh-3c/def2-mSVP//PW6B95-D4/def2-TZVP).

atroposelective aromatization of this compound was also problematic, leading to 1,2′-binaphthalene derivative **4c** with compromised enantiomeric purity of 38% ee.

To gain insight into a stereoinduction of this process, we carried out a DFT investigation of the organocatalytic Michael addition. In this step, two new stereogenic centers are generated, eventually transforming into axial chirality during oxidative aromatization. The stereoselectivity of the Michael addition is governed by iminium salt formation between organocatalyst **C1** and unsaturated aldehyde **2**. The corresponding iminium salt then reacts with nitronate anion generated from aldehyde **1a**. Fig. 1 shows DFT calculated transition states for asymmetric Michael addition between anion of aldehyde **1a** and iminium salts generated from enal **2a** and catalyst **C1**. In the preferred transition state TS-MA-major, the aldehyde anion **1a** attacks catalyst bound iminium from re phase opposite to the C(Ph)$_2$-OTMS group of the catalyst.

Experimental

All milling experiments were conducted in a Retsch Mixer Mill MM400, using stainless-steel milling jars with internal volume of 1.5 mL, and stainless-steel balls, ø 6 mm.

General experimental procedures Michael–aldol reaction

Benzaldehyde **1** (0.12 mmol, 1.0 equiv.), naphthyl alkenyl aldehyde **2** (0.15 mmol, 1.2 equiv.), pyrrolidine organocatalyst **C1** (7.9 mg, 0.024 mmol, 20 mol%), Et$_2$O (22 μL, $\eta = 0.4$) and stainless-steel ball (ø 6 mm) milled in stainless steel reactor (1.5 mL) for 3 h at 25 Hz. The contents of the reactor were transferred with DCM (5 mL) and concentrated under reduced pressure. Column chromatography (hexane : EtOAc = 4 : 1) provided product **3**.

General procedure for oxidative cyclization with NBS

(*S*,*R*)-Dihydronaphthalene **3** (0.10 mmol, 1.0 equiv.), potassium *tert*-butoxide (0.15 mmol, 1.5 equiv.), Et$_2$O (59 μL; $\eta = 0.4$) and stainless-steel ball (ø 6 mm) milled in a stainless steel reactor (1.5 mL) for 10 min at 30 Hz. NBS (0.20 mmol, 2.0 equiv.) was

added, and milling continued for another 40 min at 30 Hz. After the addition of AgOTf (0.25 mmol, 2.5 equiv.), reagents were milled for the final 40 min at 30 Hz. Contents of the reactor were transferred with EtOAc (5 mL) and aqueous NH_4Cl (5 mL) into a separatory funnel and extracted with EtOAc (2 × 3 mL). Combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and filtered and concentrated under reduced pressure. Column chromatography (hexane : EtOAc = 9 : 1) provided the final product **4**.

Conclusions

We have developed mechanochemical atroposelective synthesis of axially chiral 1,2′-binaphthalene-3′-carbaldehydes. This transformation comprises two steps, which can be efficiently realized under ball-milling conditions. The initial step, the covalently catalyzed Michael/aldol sequence, is followed by an oxidative aromatization. Optimization of milling frequency and LAG additives allowed for achieving high enantioselectivities whilst retaining high yields. The aromatization step proved somewhat more sensitive to mechanochemical activation as slight decrease in enantiomeric purities of final 1,2′-binaphthalene products were observed. Further explorations of atroposelective organocatalytic transformations under mechanochemical conditions are underway in our laboratory.

Author contributions

H. S conducted the experiments, gathered and analyzed data, and prepared SI. R. S formulated research goals, coordinated research activities and wrote the initial manuscript draft. Both authors participated in the preparation of the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The datasets supporting this article have been included as part of the SI: additional experiments, experimental procedures, characterization data, pictures of NMR spectra, and HPLC chromatograms. See DOI: **https://doi.org/10.1039/d5mr00058k**.

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