Organocatalysis

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Chirally Aminated 2-Naphthols—Organocatalytic Synthesis of Non-Biaryl Atropisomers by Asymmetric Friedel–Crafts Amination**

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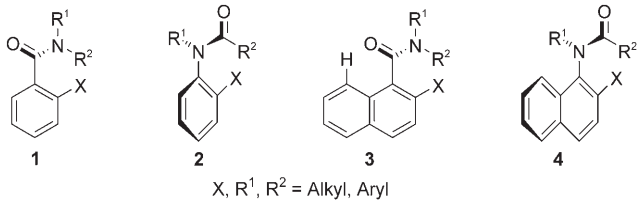
Atropisomers, compounds in which the chirality originates from restricted rotation along a chiral axis rather than a stereogenic center, have received much attention, since they are among the most useful ligands in asymmetric catalysis.[1] In most of the known structures, the chiral axis is between two aromatic moieties, but there are examples of non-biaryl atropisomers.

Several reports followed the pioneering work by Curran et al. disclosed in 1994 on atropisomeric anilides.[2] Two classes of compounds emerged afterwards, namely atropisomeric amides **1** and anilides **2** (Scheme 1), and both have been



Scheme 1. Non-biaryl atropisomers.

employed in asymmetric catalysis.[3] The rotation along the chiral axis in structures of type **1** and **2** is hindered by a substituent in the aromatic *ortho* position of the aryl group. Compounds of class **3** with *peri* substitution have also been investigated. The hydrogen atom in the 8-position of the naphthyl moiety causes a rotational barrier of sufficient magnitude to generate optical antipodes, although these compounds readily racemize ($t_{1/2}{}^{25}{}_{rac}$ less than 1 s).[4] There is no reported data on the chiral properties of the corresponding compounds of class **4**, in which the nitrogen atom is directly attached to the aromatic ring, such as *N*,*N*-disubstituted 1-naphthamides or carbamates.

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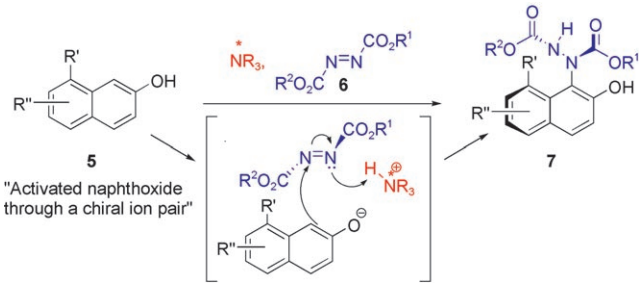
The preparation of compounds **1**–**3** is usually a tedious multistep sequence, and in most cases a resolution of the racemate is required to obtain enantiopure material.[5] Only recently Taguchi and co-workers reported a highly enantioselective catalytic synthesis of atropisomeric anilides **2**.[6] It is of no doubt that efficient and enantioselective methods to access these compounds can trigger the discovery of new applications. Herein, we report the properties and the easy asymmetric organocatalytic synthesis of atropisomers of class **4**. The strategy of the formation of this new class of atropisomer is based on the organocatalytic asymmetric amination of 2-naphthols (Scheme 2).

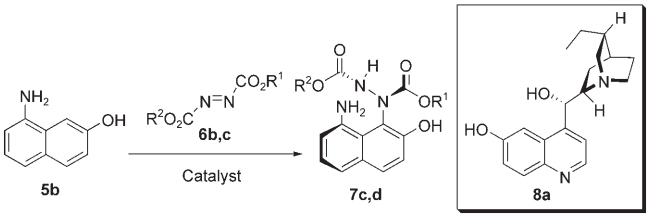


Scheme 2. Organocatalytic asymmetric amination of 2-naphthols.

The reaction of activated naphthalenes and azodicarboxylates was described by Diels and Back in 1921,[7] and it was later shown that it can be catalyzed by metals.[8] Although aminated naphthalenes have been known for nearly a century, they have not been recognized as chiral compounds. By employing tertiary amines as catalysts, 2-naphthol **5a** (R′, R″ = H) is activated through deprotonation of the hydroxy group, and the addition of diethyl azodicarboxylate (**6a**) ($R^1 = R^2 = Et$) is completed within minutes at room temperature or overnight at −20 °C. The aminated naphthol **7a** ($R^1 = R^2 = Et$, R′, R″ = H) is indeed a chiral compound, since the two enantiomers can be readily separated by chiral HPLC and one of the two CH_2 groups of the carbamate moiety turned out to be diastereotopic.[9] We then employed a chiral amine to access these compounds by an asymmetric catalyzed reaction (Scheme 2). In the first screening of the reaction of **5a** with di-*tert*-butyl azodicarboxylate (**6b**) ($R^1 = R^2 = t$Bu), we succeeded in achieving a modest level of enantiomeric excess (15 % *ee*) by using cinchonine as the chiral catalyst. Unfortunately, products **7a**,**b** are not configurationally stable at room temperature. We measured the half life ($t_{1/2}{}^{29}{}_{rac}$ = 26 min) for **7b** ($R^1 = R^2 = t$Bu, R′, R″ = H) and determined the energy barrier for the rotation along the C(aryl)–N axis to be $\Delta G_{rac} = 84\ kJ\,mol^{-1}$ (see the Supporting Information). We then employed 8-amino-2-naphthol (**5b**), as the substrate and were able to generate more stable atropisomers.[10]

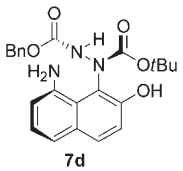
A screening of azodicarboxylates **6b**,**c** and different solvents, concentrations, and catalysts[11] (see Table 1) showed that the symmetric azodicarboxylate **6b** in combination with catalyst **8a** (dihydrocupreidine)[12] gave **7c** in high yield with up to 88 % *ee* (entry 8). The enantiomeric excess of **7c** does not appreciably change when kept at −20 °C, and we measured a decrease of only 3 % *ee* after 10 days at room temperature. In the reaction with the nonsymmetric azodicarboxylate **6c**, only a single regioisomer was isolated (up to 87 % *ee*; entry 9); the other regioisomer yielded a cyclized compound (see the Supporting Information). The HPLC traces of the racemate and the optically active compound **7d** are shown in Figure 1.

Table 1: Screening of catalysts and conditions for the organocatalyzed (20 mol %) asymmetric Friedel–Crafts reaction of **5b** with azodicarboxylates **6b**,**c**.[a]



Entry	Catalyst	(*T* [°C])	Solvent	R^1, R^2	Yield [%][b]	*ee* [%][c]
1	quinine	(RT)	toluene	*t*Bu, *t*Bu (**6b**)	85, **7c**	16
2	**8a**	(RT)	toluene	*t*Bu, *t*Bu (**6b**)	91, **7c**	58
3	**8a**	(−20)	toluene	*t*Bu, *t*Bu (**6b**)	95, **7c**	71
4	**8a**	(RT)	DCE	*t*Bu, *t*Bu (**6b**)	95, **7c**	82
5	**8a**	(−20)	DCE	*t*Bu, *t*Bu (**6b**)	92, **7c**	84
6	**8b**[d]	(RT)	DCE	*t*Bu, *t*Bu (**6b**)	85, **7c**	−61[e]
7	**8b**[d]	(−20)	DCE	*t*Bu, *t*Bu (**6b**)	85, **7c**	−22[e]
8[f]	**8a**	(−20)	DCE	*t*Bu, *t*Bu (**6b**)	90, **7c**	88
9	**8a**	(−20)	DCE	*t*Bu, Bn (**6c**)	62, **7d**	87

[a] Reaction performed with 0.20 mmol of **5b** and 0.20 mmol of **6b**,**c** in 0.4 mL of solvent [0.5 M]; 99 % conversion in all reactions. [b] Yield of isolated product after flash chromatography. [c] *ee* determined by HPLC. [d] Catalyst: dihydrocupreine, a pseudoenantiomer of **8a**. [e] The atropisomer with the opposite sign of optical rotation is formed. [f] The concentration of **5b** was [0.05 M], instead of [0.5 M]. DCE = dichloroethane.



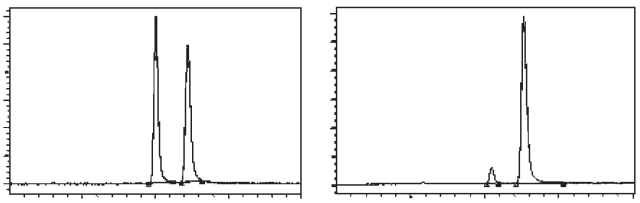
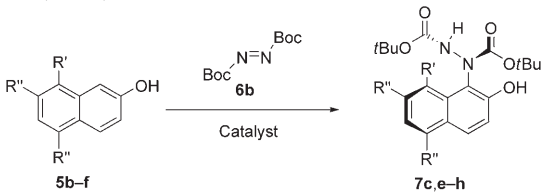


Figure 1. HPLC traces (Chiralpak AD, hexane/*i*PrOH 80:20) of **7d** as a racemate (left) and with 87 % *ee* (right).

At this stage, we realized and observed that the catalyst can also act as a substrate for the Friedel–Crafts reaction. However, it is obvious that the quinoline-6-ol system is deactivated towards electrophilic aromatic substitution relative to the 2-naphthol system. As expected, catalysts **8a**,**b** do not appreciably react under the asymmetric catalytic exper-

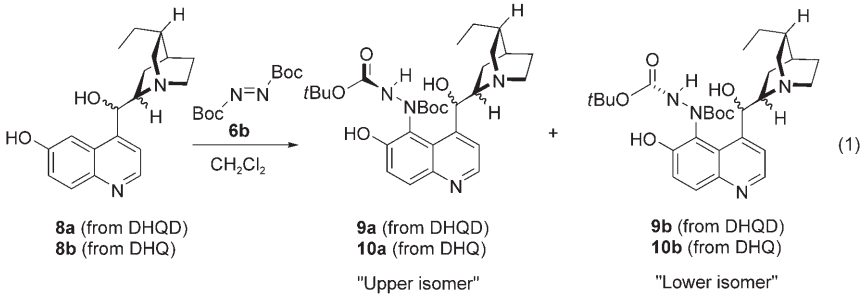
imental conditions (see the Supporting Information). On the other hand, the phenol group of **8a**,**b** is more acidic with respect to a simple 2-naphthol unit, and these catalysts can be seen as a zwitterionic species. Therefore a considerable portion of the molecules might be in an activated form. By forcing the reaction conditions, we could isolate two diastereoisomers (herein named "upper" and "lower" according to their respective TLC R_f values) in good yield from the treatment of **8a**,**b** with **6b** [Eq. (1); DHQD = dihydroquinidine, DHQ = dihydroquinine]. The **9a**/**9b** and **10a**/**10b** ratios were 3.5:1 and 1:2.3, respectively. This notable example of quinoline-core functionalization gives access to a new class of cinchona-alkaloid catalyst. These compounds are stable toward racemization when stored as solids at room temperature.

Table 2: Asymmetric Friedel–Crafts reaction of different 2-hydroxy-8-amino naphthols **5b–f** with azodicarboxylate **6b** catalyzed by **8a**, **9b**, and **10b**.[a]



Entry	Substrate R′, R″	Product	Catalyst **8a** *ee* [%]	Catalyst **8a** (yield [%])[b,c]	Catalyst **9b** *ee* [%]	Catalyst **9b** (yield [%])[b,c]	Catalyst **10b** *ee* [%]	Catalyst **10b** (yield [%])[b,c]
1	NH_2, H (**5b**)	**7c**	88	(90)	87	(87)	−96	(91)[d]
2	NHMe, H (**5c**)	**7e**	33	(95)	93	(91)	−96	(94)[d]
3	NHBn, H (**5d**)	**7f**	48	(98)	98	(92)	−98	(80)[d]
4	NHC_5H_{11}, H (**5e**)	**7g**	78	(98)	94	(95)	−94	(98)[d]
5	NH_2, Br (**5f**)	**7h**	80	(96)	98	(85)	−96	(95)[d]

[a] Reaction performed with 0.20 mmol of **5b–f**, 0.20 mmol of **6b**, and 0.04 mmol of catalyst in 4 mL of DCE [0.05 M]; 99% conversion in all reactions. [b] *ee* determined by HPLC. [c] Yield of isolated product after flash chromatography. [d] The atropisomer with the opposite sign of optical rotation is formed.



(1)

After screening a large number of different cinchona-alkaloid derivatives as catalysts for the asymmetric Friedel–Crafts amination, we decided to test these four new compounds also in the hope of finally increasing the enantioselectivity. To our delight, catalyst **10b** increased the enantiomeric excess of **7c** from 22% *ee* (see Table 1, entry 7) to 96% *ee*. This very promising result prompted us to investigate the generality of the asymmetric Friedel–Crafts amination.

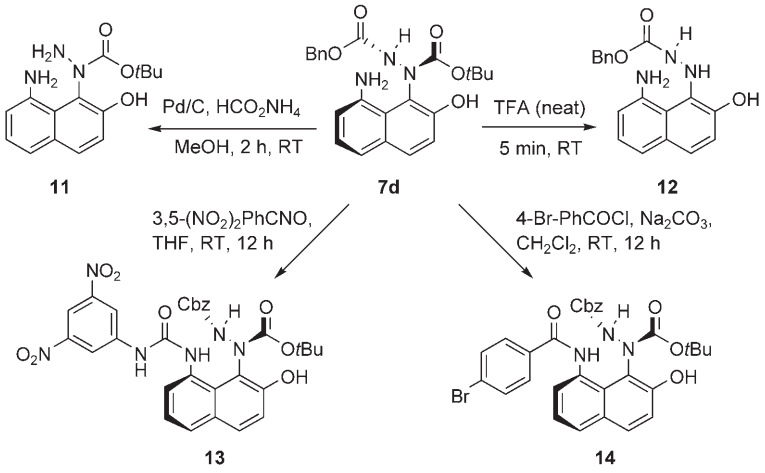
A significant improvement in enantioselectivity takes place when using the new cinchona-alkaloid catalysts **9b** and **10b** compared with **8a**. The results obtained for a variety of different substrates with these catalysts are shown and compared in Table 2.[13]

For 8-amino-2-naphthol (**5b**), the enantiomeric excess of **7c** was improved (up to 96% *ee*; Table 2, entry 1). An even larger improvement was observed for the *N*-substituted naphthols **5c–e**; from these substrates, the optically active aminated naphthols **7e–g** are obtained in high yields and with excellent enantioselectivities (93–98% *ee*; Table 2, entries 2–4). The introduction of further substituents in the naphthol ring (**5f**) gave also excellent results, as **7h** was obtained with 98% *ee* (Table 2, entry 5).

This organocatalytic asymmetric Friedel–Crafts amination reaction represents easy access to a novel class of chiral compounds which can undergo various transformations. The carbamate protective groups of **7d** can be orthogonally deprotected to afford **11** or **12** (see Scheme 3); however, the products were found to be non-chiral.

The presence of both a hydroxy and an amino group in the product offers several possibilities for further elaborations. As an example, **7d** was converted in good yields and without racemization into both chiral ureas and anilides, such as **13** or **14**, respectively.

The latter compound was recrystallized to be enantiopure, and a crystal suitable for X-ray diffraction analysis was obtained.[14] The absolute configuration and regiochemistry of **14** were thereby determined. The crystal belongs to the chiral space group $P2_12_12_1$. The crystal structure shows intramolecular hydrogen bonding between the amide NH moiety and the



Scheme 3. Chemical transformation of **7d**. TFA = trifluoroacetic acid, Cbz = carbonylbenzyloxy.

carbonyl oxygen atom of the carbonylbenzyloxy (Cbz) group (Figure 2). The value of the torsion angle between the two carbamate carbonyl functions bound to the hydrazine is 92°.

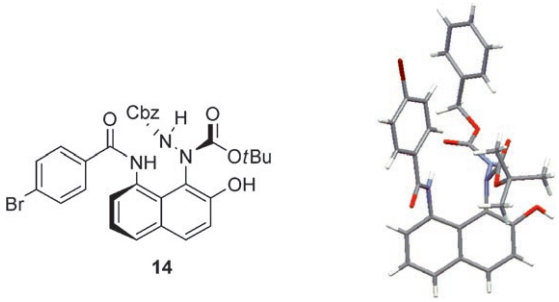
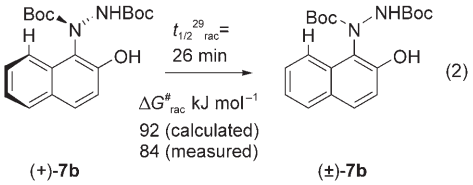


Figure 2. X-ray structure of **14**.

Based on the measured $t_{1/2}{}^{29}{}_{rac} = 26$ min for **7b** and the experimentally calculated energy barrier for rotation along the C–N axis ($\Delta G_{rac} = 84\ kJ\,mol^{-1}$), we performed a series of quantum-chemical calculations. The rotation along the C–N axis for **7b** has been estimated (see the Supporting Information) at the HF/6-31G level of theory[15] to be $\Delta G_{rac} = 92\ kJ\,mol^{-1}$ in the gas phase [Eq. (2)], which is in good



agreement with the experimental value. Furthermore, the experimental and computational values also fit with, for example, the barriers of rotation of compounds related to class **3**.[4a]

In conclusion, we have reported an unprecedented example of a cinchona-alkaloid organocatalyzed Friedel–Crafts amination of 2-naphthols.[16] The reaction represents easy access to a novel class of non-biaryl atropisomers, which can be further elaborated to several new chiral molecules. The use of new aminated cinchona alkaloids for the Friedel–Crafts amination reaction leads to a general reaction that proceeds for a series of different 2-naphthol derivatives with excellent enantioselectivities. Further work is in progress to clearly define the scope of this reaction, as well as employing these optically active aminated 2-naphthol derivatives and aminated cinchona alkaloids as, for example, chiral catalysts.

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[11] Besides the catalysts mentioned in Table 1, a variety of other catalysts were tested (**6b**, toluene, −20 °C, [0.5 M]); among these were (*ee* (%) given in parentheses, +/− refers to the opposite stereochemistry): quinidine (0), cinchonine (0), cinchonidine (8), dihydroquinine (18), $[DHQ]_2PYR$ (−70), $[DHQD]_2PYR$ (28), $[DHQ]_2PHAL$ (−12), $[DHQD]_2PHAL$ (10); PYR = 2,5-diphenyl-4,6-pyrimidinediyl diether, PHAL = 1,4-phthalazinediyl diether.

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