Asymmetric Catalysis

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Direct Asymmetric Dearomatization of 2-Naphthols by Scandium-Catalyzed Electrophilic Amination**

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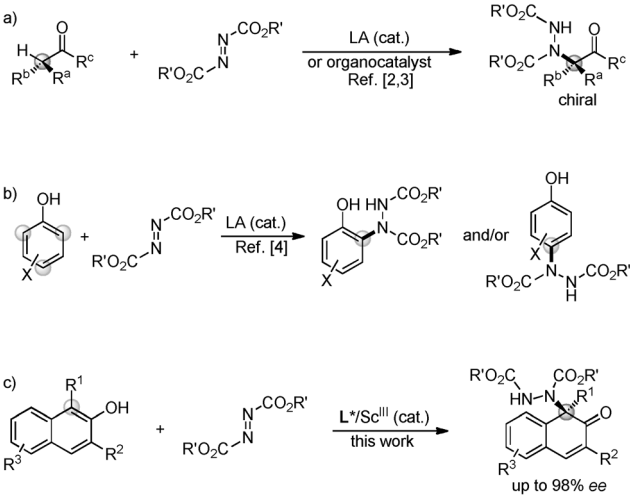
Abstract: *Catalytic asymmetric aminative dearomatization of 1-substituted 2-naphthols was successfully implemented with electrophilic azodicarboxylates under the catalysis of chiral Sc^{III}/pybox complexes. This intermolecular reaction represents a hitherto unknown enantioselective C–N bond-forming process through direct dearomatization of phenolic compounds to generate chiral nitrogen-containing quaternary carbon stereocenters.*

The direct asymmetric α-amination of carbonyl compounds constitutes one of the most straightforward and powerful approaches for constructing chiral α-amino carbonyl substructures,[1] which are highly valuable building blocks for a variety of biologically active compounds and therapeutics. Consequently, the development of reliable asymmetric variants in this area has been of very recent interest. To date, a great number of enantioselective amination reactions of versatile carbonyl compounds with electrophilic azodicarboxylates have been successfully realized by using chiral metal catalysts[2] or organocatalysts[3] (Scheme 1 a). Remarkably, this strategy has enabled the installation of nitrogen functionality adjacent to a carbonyl group in an enantioselective manner by the direct utilization of various unmodified carbonyl nucleophiles such as aldehydes,[3a,b] ketones,[3c] ketoesters,[2b,3e–f] cyanoacetates,[2d,3d] *N*-acyl oxazolidinones,[2a] alkoxycarbonyl amides,[2e] and oxindoles.[2f,g,3g–i] In spite of these impressive advances, further exploration of new types of nucleophiles to enrich the scope and utility of this category of synthetically important transformations is still challenging and in high demand.

In this context we will focus on applying the electrophilic amination protocol for prochiral 2-naphthols to prepare chiral molecular frameworks bearing nitrogen-substituted quaternary stereocenters. Notably, the known reactions between substituted phenols and azodicarboxylates lead to the *ortho*- and/or *para*-aminated phenol products (Scheme 1 b).[4,5] In contrast, the envisioned regiospecific amination process with 2-naphthols to access nitrogen-substituted cyclohexandienones remains a formidable pursuit, primarily because of the stringent difficulties associated with the requisite dearomatization of naphthyl rings. Dearomatization of arenes has been recognized as a useful tool to fabricate highly functionalized chiral alicyclic molecules from simple planar aromatic compounds, and great efforts have been devoted in this area.[6] However, progress of direct catalytic asymmetric dearomatization of phenols or naphthols has lagged dramatically. The limited number of successful achievements in this field include palladium- or iridium-catalyzed allylic alkylation,[7] palladium-catalyzed arylation,[8] iron-catalyzed nitroalkylation,[9] hypervalent-iodine-catalyzed spirolactonization,[10] and fluorination using a binol-derived phosphate catalyst,[11] thus relying on the construction of C–C, C–O, or C–F bonds. While dearomatizing aminations are known for indoles and pyrroles,[12] no example has been achieved for phenols or naphthols. Herein we present the first example of a catalytic asymmetric aminative dearomatization of 2-naphthols (Scheme 1 c). This intermolecular reaction between substituted 2-naphthols and azodicarboxylates is efficiently catalyzed by chiral $Sc(OTf)_3$/pybox complexes and renders the generation of nitrogen-containing quaternary stereocenters with excellent enantioselectivities.



Scheme 1. Previous work and our work on the direct electrophilic amination reaction. a) Existing direct catalytic asymmetric amination of carbonyl compounds. b) Existing direct amination of phenols. c) New direct catalytic asymmetric aminative dearomatization of 2-naphthols. LA = Lewis acid.

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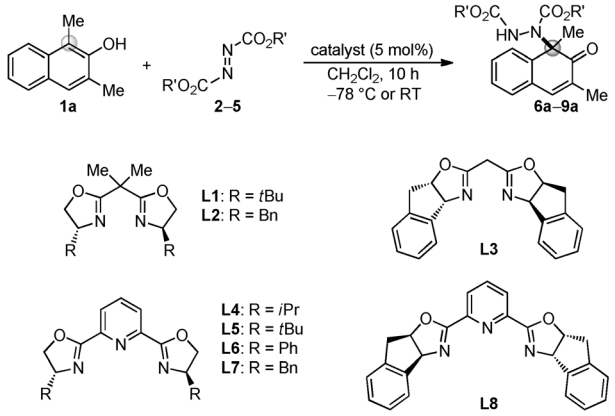
Inspired by the successful examples of catalytic dearomatization of substituted 2-naphthols reported by others[7c,9,13] and us,[14] we began the amination studies by choosing 1,3-dimethylnaphthalen-2-ol (**1a**) as the model nucleophile. Importantly, this 1,3-disubstitution pattern on the naphthol ring of **1a** is expected to prevent the unwanted formation of aminated naphthol products. At the outset, $Cu(OTf)_2$ and the box ligands **L1–L3** were employed to generate complexes $[(box)Cu(OTf)_2]$, which have proven to be excellent chiral promoters for several asymmetric amination processes in the literature,[2b–c] to catalyze the anticipated aminative dearomatization of **1a** with **2** (DEAD) in CH_2Cl_2 at −78 °C (Table 1, entries 1–3). The results indicated that the envisioned reaction proceeded smoothly to afford the desired dearomatized product **6a** in high yields (73–78 %), albeit with no stereocontrol. When copper salt was switched with $Sc(OTf)_3$, similar results were obtained (entries 4–6). Accordingly, cinchona alkaloids often serve as effective catalysts for the enantioselective α-amination of carbonyl compounds.[3d,g–i] Thereby, four commonly utilized organocatalysts were tested and the reactions were promoted efficiently, but no appreciable enantioselectivity was observed (entries 7–10). Subsequently, we sought to screen a number of other catalysts, and the combination of $Sc(OTf)_3$ with commercially available pybox ligands was finally found to provide very promising results (entries 11–15).[15] Notably, $Sc(OTf)_3$/**L7** enabled the preparation of **6a** in 85 % yield with 87 % *ee* (entry 14). To further improve the enantioselectivity for this valuable transformation, a variety of solvents (DCE, 1,4-dioxane, THF, toluene, CH_3CN, and Et_2O) were screened, but no beneficial result was obtained in comparison to the utilization of CH_2Cl_2. To overcome the background reaction (entry 16), a slow addition technique was introduced, and **6a** was obtained in 92 % yield with 94 % *ee* (entry 17). Encouraged by this exciting enantioselectivity, different electrophiles (**3–5**) were evaluated by using the same technique (entries 18–20). Much to our delight, the compound **9a** was prepared in 98 % yield with 98 % *ee* by using the dibenzyl azodicarboxylate **5** (entry 20).

With the optimized reaction conditions in hand, the substrate scope was first examined by varying the substituents on both the 1- and 3-positions of 2-naphthols (Table 2). The results indicated that various substituents were tolerated, and the reactions between **1a–l** and **5** proceeded smoothly to afford the corresponding dearomatized products in good yields (80–98 % yield) with excellent enantioselectivities (90–98 % *ee*). Gratifyingly, the 3-position of 2-naphthols could be substituted with alkyl groups such as methyl (**9a,i**), ethyl (**9b**), benzyl (**9c,j**) and 2-methylallyl (**9d**), aromatic groups featuring differential electronic properties (**9e–g**), and heterocycles (**9h**). Moreover, aliphatic substituents such as ethyl (**9i**) and allyl (**9j**) groups were compatible at the 1-position of the naphthyl ring without compromising the enantioselectivity.

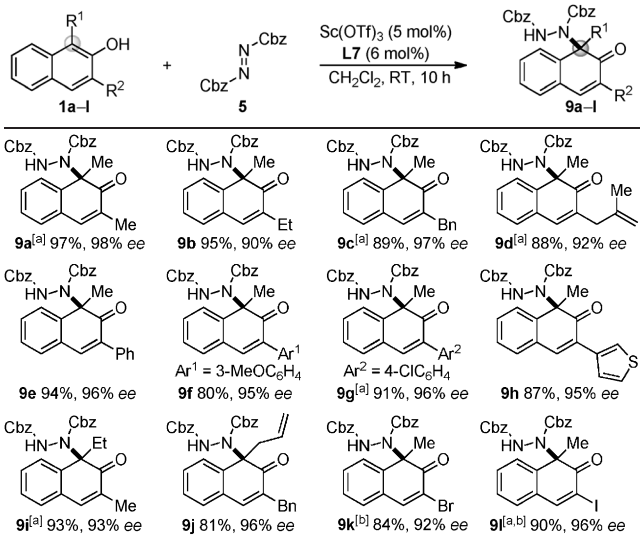
Table 1: Optimization of the reaction conditions.



Entry	Catalyst	R′	*T* [°C]	Yield [%][a]	*ee* [%][b]
1	$Cu(OTf)_2$/**L1**	Et	−78	73	3
2	$Cu(OTf)_2$/**L2**	Et	−78	78	0
3	$Cu(OTf)_2$/**L3**	Et	−78	78	0
4	$Sc(OTf)_3$/**L1**	Et	−78	71	0
5	$Sc(OTf)_3$/**L2**	Et	−78	75	0
6	$Sc(OTf)_3$/**L3**	Et	−78	64	0
7	quinine	Et	−78	96	4
8	quinidine	Et	−78	97	−11
9	cinchonine	Et	−78	97	2
10	$(DHQ)_2PHAL$	Et	−78	47	7
11	$Sc(OTf)_3$/**L4**	Et	−78	75	2
12	$Sc(OTf)_3$/**L5**	Et	−78	92	0
13	$Sc(OTf)_3$/**L6**	Et	−78	87	37
14	$Sc(OTf)_3$/**L7**	Et	−78	85	87
15	$Sc(OTf)_3$/**L8**	Et	−78	69	−33
16	–	Et	−78	61	0
17[c]	$Sc(OTf)_3$/**L7**	Et	RT	92	94
18[c]	$Sc(OTf)_3$/**L7**	*i*Pr	RT	83	62
19[c]	$Sc(OTf)_3$/**L7**	*t*Bu	RT	86	75
20[c]	$Sc(OTf)_3$/**L7**	Bn	RT	98	98

[a] Yield of isolated product. [b] Determined by HPLC analysis using a chiral stationary phase. [c] Substrate **1a** was added slowly over 1 h. Tf = trifluoromethanesulfonyl.

Table 2: The reaction substrate scope of 1,3-disubstituted 2-naphthols.



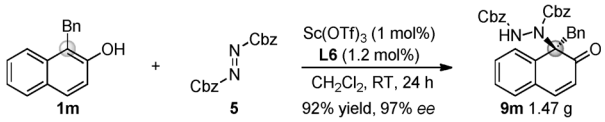
Yields are those of the isolated product and the *ee* values were determined by HPLC analysis using a chiral stationary phase. [a] Substrate **1** was added slowly over 1 h. [b] **L6** was used in place of **L7**. Cbz = carbobenzyloxy.

More importantly, substrates bearing halogen functionalities could also undergo the desired dearomatizing transformation with very impressive performance by using the ligand **L6** (**9k,l**), thus offering excellent handles for further synthetic manipulations. Additionally, it should be noted that the NMR spectra of the products **9** are rather complex and difficult to interpret, and is very common for the aminated compounds using azodicarboxylates.[2c–e,g,3] Therefore, the single-crystal X-ray diffraction studies for compounds (±)-**9a**, (±)-**9c**, and (±)-**9i** were performed to further confirm the structural assignments.[16]

In the course of studying the reaction scope, we noticed one literature precedent which demonstrated that a variety of phenols could be aminated directly with DEAD to generate new phenolic derivatives using a catalytic amount of $Sc(OTf)_3$ in CH_2Cl_2 at room temperature.[4a] Therefore, we were compelled to examine the reaction performance of 2-naphthols which were substituted at the 1-position by employing this freshly established protocol. The substrate **1m** was initially synthesized and subjected to the reaction conditions. Satisfactorily, the compound **9m** was successfully obtained as the single product in 98% yield with 98% *ee* under the catalysis of complex $Sc(OTf)_3$/**L6** (Table 3). Next, a variety of monosubstituted 2-naphthols were then systematically investigated under the same reaction conditions. Overall, a series of aminative dearomatization products were successfully prepared in 85–98% yield with 90–98% *ee*. As shown in Table 3, the benzylic ring in **1m** could be substituted with various functional groups featuring diverse electronic and steric properties, and their corresponding products **9m–s** were consistently formed with excellent enantioselectivities (94–98%). Next, several 1-alkyl-2-naphthols were found to tolerate the diisopropyl azodicarboxylate **3** as the electrophile, and the enantioselectivities of the products **9t** and **9u** were slightly dependent on the length of the alkyl chain. With the 1-allyl-2-naphthols, the anticipated reactions proceeded smoothly to deliver the compounds **9v–x** in 94–98% yield with 92–98% *ee*. Notably, allyl groups are rather valuable handles for additional synthetic manipulations. Moreover, this method was also found to be compatible with different substituents (Me, Br, and MeO) on the naphthyl ring thus generating the products **9p**, **9q**, and **9w** in excellent enantioselectivities.

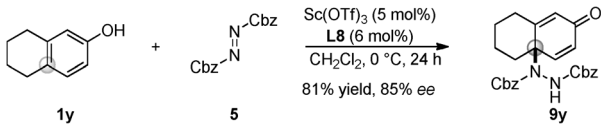
From the viewpoint of synthetic application, the catalytic reactions using a lower catalyst loading are obviously more valuable. To date, most of the successful examples of asymmetric α-amination of carbonyl compounds with azodicarboxylates require a 5 mol% or higher catalyst loading.[2–5] Therefore, we evaluated the reactions with substrates **1m–x** using 1 mol% catalyst. Much to our delight, the results indicated that the desired products **9m–x** (**9u** as the only exception) could be prepared without notable loss of reactivity (81–95% yield) and enantioselectivity (89–98% *ee*; Table 3).

To further highlight the efficiency and practicality of this catalytic methodology, a scaled-up experiment using **1m** with a 1 mol% catalyst loading was carried out (Scheme 2). As a result, gram-scale preparation of **9m** (1.47 g) was successfully achieved in 92% yield with 97% *ee*.



Scheme 2. Gram-scale preparation of **9m**.

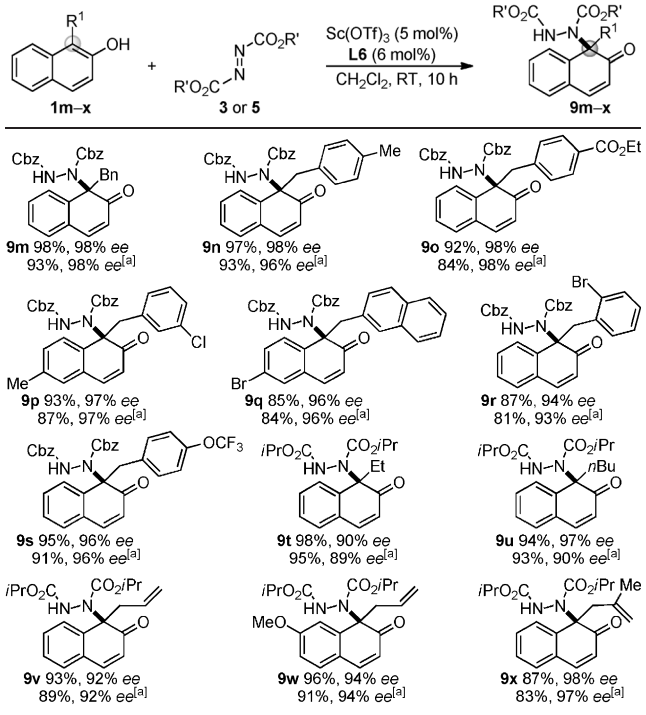
Furthermore, several substituted phenols and 1-naphthols were also attempted, and the phenol **1y** was found to be suitable for this transformation under slightly modified reaction conditions (Scheme 3). Gratifyingly, an intriguing bicyclic molecule, **9y**, the basic ring system of which appears in a number of biological active natural products,[17] was obtained in 81% yield with 85% *ee*. In addition, the structure of (±)-**9y** was confirmed by X-ray analysis.[16]



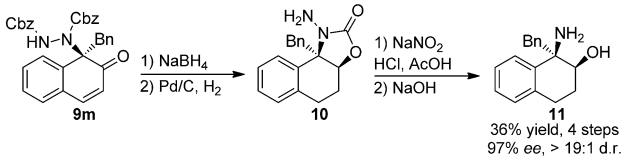
Scheme 3. Reaction behavior of the phenol substrate **1y**.

To demonstrate the synthetic utility of this enantioselective amination method, further transformations of the dear-

Table 3: The reaction substrate scope of 1-substituted 2-naphthols.



Yields are those of the isolated product and the *ee* values were determined by HPLC analysis using a chiral stationary phase. [a] Reactions were conducted with 1 mol% $Sc(OTf)_3$ and 1.2 mol% **L6** for 10 h.



Scheme 4. Synthetic transformation of **9m**.

omatized compound **9m** were conducted (Scheme 4). Reduction of the enone functionality in **9m** proceeded in a highly diastereoselective manner (>19:1 d.r.) using excess $NaBH_4$, and after removal of the Cbz group gave **10**. Further N–N bond cleavage and oxazolidinone hydrolysis afforded an uncommon 1,2-amino alcohol **11**[18] in 36% overall yield while maintaining the enantiomeric excess of **9m**. The relative stereochemistry of (±)-**10** and the absolute stereochemistry of **11** were determined by X-ray analysis.[16]

In conclusion, we have developed an unprecedented scandium-catalyzed asymmetric aminative dearomatization reaction of substituted 2-naphthols, thus leading to the formation of a nitrogen-containing quaternary carbon stereocenter with excellent enantioselectivities (90–98% *ee*). To the best of our knowledge, this method represents the first example of a catalytic, enantioselective carbon–nitrogen bond-forming reaction through direct dearomatization of phenol derivatives.

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[18] Chiral 1,2-amino alcohols often serve as the essential building blocks for the preparation of chiral oxazoline ligands, and the unique 1,2-amino alcohol **11** might be useful in this area.

