

Enantioselective Organocatalytic Allylic Amination

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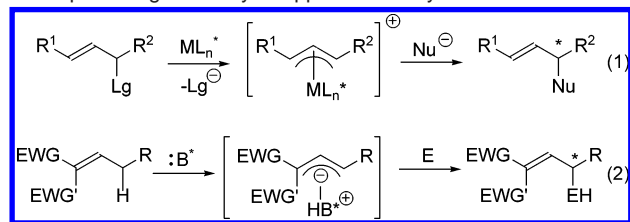
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The enantioselective functionalization of allylic positions is a major goal in organic chemistry due to the broad synthetic potential of the enantioenriched alkenes obtained for the preparation of complex molecules.¹ The most widely used and developed approach to this challenge has been the transition metal-catalyzed allylic substitution,^{2,3} which can now be considered one of the most firmly established methodologies in asymmetric catalysis and has therefore been frequently utilized in total synthesis.¹ This strategy relies on the oxidative addition of the metal to a substrate having a leaving group (Lg) on the allylic position, enabling it to undergo a nucleophilic addition reaction (Scheme 1, eq 1).

We envisioned the possibility of developing a new concept in catalytic asymmetric allylation chemistry by performing enantioselective *electrophilic* additions to allylic C–H bonds activated by a chiral base (Scheme 1, eq 2). Recently, we have documented the catalytic generation of chiral nucleophiles using cinchona alkaloid derivatives as the catalysts.⁴ In this communication we introduce this novel strategy by reporting the first enantioselective metal-free allylic amination.⁵

Scheme 1. Equation 1 Shows the Nucleophilic Allylic Substitution Catalyzed by Metal Complexes, while Equation 2 Presents the Electrophilic Organocatalytic Approach to Allylic Substitution



In relation to the organocatalytic reaction shown in eq 2, several obstacles need to be overcome: the regioselectivity issue (α - vs γ -amination) and two possible drawbacks arising from the presence of another acidic proton in the γ -aminated compound: (i) the formation of double amination products and (ii) the racemization of the tertiary stereocenter created under the basic reaction conditions. Hence, the right combination of substrate pK_a and catalyst activity that addresses these difficulties must be found.

We have studied the reaction of alkylidene cyanoacetates (**1**) with dialkyl azodicarboxylates catalyzed by cinchona alkaloids and derivatives (eq 3). When a monomeric catalyst (e.g., quinine) was employed at ambient temperature, mixtures of α -, γ -, and double amination products were formed. Gratifyingly, the use of dimeric catalysts at lower temperatures (-24°C) gave rise to the γ -amination product only, along with traces of the byproducts.

A survey of some reaction parameters was then performed, and some representative results are presented in Table 1. First, commercially available cinchona alkaloid derivative (DHQD)₂PYR was identified as the optimal catalyst affording **2a** with 94% ee (entry 3). Surprisingly, the solvent polarity does not affect the enantioselectivity

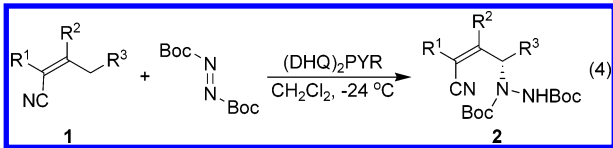
Table 1. Screening Results for the Enantioselective Organocatalytic Allylic Amination Reaction^a

entry	R	catalyst	solvent	yield (%) ^b	ee (%) ^c
1	Bn (1a)	(DHQD) ₂ PHAL ^d	CH ₂ Cl ₂	2a – nd	75
2	Bn (1a)	(DHQD) ₂ AQN ^d	CH ₂ Cl ₂	2a – nd	75
3	Bn (1a)	(DHQD) ₂ PYR	CH ₂ Cl ₂	2a – 83	94
4	allyl (1b)	(DHQ) ₂ PYR	CH ₂ Cl ₂	2b – 90	97
5	allyl (1b)	(DHQ) ₂ PYR	toluene	2b – 20	95
6	allyl (1b)	(DHQ) ₂ PYR	Et ₂ O	2b – 19	94
7	allyl (1b)	(DHQ) ₂ PYR	EtOAc	2b – 61	96
8	Me (1c)	(DHQD) ₂ PYR	CH ₂ Cl ₂	2c – 90	90
9	Et (1d)	(DHQD) ₂ PYR	CH ₂ Cl ₂	2d – 71	90
10	allyl (1b)	(DHQD) ₂ PYR	CH ₂ Cl ₂	2b – 90	93
11	<i>i</i> -Pr (1e)	(DHQD) ₂ PYR	CH ₂ Cl ₂	2e – 62	93
12	<i>t</i> -Bu (1f)	(DHQD) ₂ PYR	CH ₂ Cl ₂	2f – 21	91

^a Reactions performed with **1** (0.2 mmol), (NBoc)₂ (0.24 mmol), and catalyst (0.02 mmol) in 1 mL of solvent for 41–47 h. ^b Isolated yield. ^c Ee determined by HPLC. ^d 20 mol % of the catalyst was used. nd: not determined. For catalyst structures, see Supporting Information.

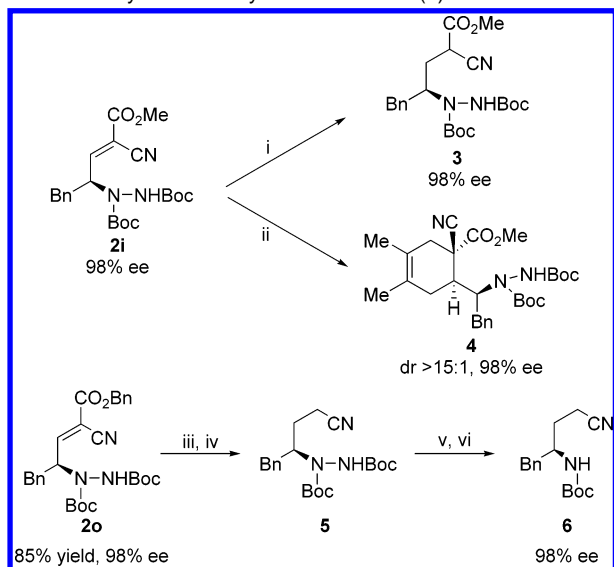
lectivity (entries 4–7), and excellent enantiomeric excesses are obtained, even in highly polar media, such as EtOAc (entry 7), a very unusual solvent for chiral ion-pair-based reactions. Low solubility of the reactants accounts for the diminished reaction rate observed in solvents other than CH₂Cl₂. The nature of the ester group (R) also has a scarce influence on the stereochemical outcome (entries 3, 4, 8–12) of the process but a significant impact on the yield of the reaction (entry 8 vs 12).⁶ Thus, benzyl (**1a**), allyl (**1b**), methyl (**1c**), ethyl (**1d**), and isopropyl (**1e**) are tolerated as ester substituents giving both high yields and enantioselectivities.⁷ Finally, both pseudoenantiomers of the catalyst gave consistent results (compare entries 4 and 10).

The tolerance of this organocatalytic enantioselective allylic amination reaction to the presence of different substituents in α , β , and γ positions was then evaluated (eq 4, Table 2). Long chain (**1g**, entry 2), branched (**1h**, entry 3), functionalized (**1i,j**, entries 4, 5), and heteroatom-containing (**1k**, entry 6) substituents in the allylic position (R³) consistently gave good yields and very high enantioselectivities. The alkoxycarbonyl group is not essential for a successful reaction, and satisfactory results were also achieved with dicyano compounds (**1l–n**, entries 7–9). Furthermore, tetra-substituted alkenes (**1m,n**, entries 8, 9) can smoothly be converted to the desired γ -amination products under the same reaction conditions with similar efficiency and enantioselectivities up to 88% ee. The reaction is amenable to scale-up; thus, 5 mmol of the cyano ester **1i** was transformed to the corresponding amination product **2i**, without any decrease in the yield (89%) or the enantioselectivity (98% ee).

Table 2. Organocatalytic Enantioselective Allylic Amination of Compounds **1c–n** with Di-*tert*-butyl Azodicarboxylate^a


entry	substrate	R ¹	R ²	R ³	yield (%) ^b	ee (%) ^c
1	1c	CO ₂ Me	H	Et	2c – 84	98
2	1g	CO ₂ Me	H	<i>n</i> -hexyl	2g – 90	99
3 ^d	1h	CO ₂ Me	H	<i>i</i> -Pr	2h – 87	90 ^g
4 ^e	1i	CO ₂ Me	H	Bn	2i – 89	98
5	1j	CO ₂ Me	H	allyl	2j – 85	96
6	1k	CO ₂ Me	H	(CH ₂) ₃ OTBS	2k – 80	97
7 ^f	1l	CN	H	Et	2l – 65	91
8	1m	CN	Ph	Me	2m – 85	86
9	1n	CN	Ph	Bn	2n – 84	88

^a Reactions performed with **1** (0.2 mmol), (NBoc)₂ (0.24 mmol), and **2d** (0.02 mmol) in 1 mL of CH₂Cl₂ for 41–47 h. ^b Isolated yield. ^c Ee determined by HPLC. ^d Reaction performed at 4 °C. ^e 96% ee and 53% yield are obtained when the reaction is performed at –24 °C. ^f Reaction performed on a 5 mmol scale. ^g Reaction time was 15 h.

Scheme 2. Synthetic Utility of the Products (**2**)^a

^a Conditions: (i) H₂, Pd/C, EtOH, 0 °C, 45 min, 90% (dr 1.5:1). (ii) 2,3-Dimethyl-1,3-butadiene, toluene, 80 °C, 23 h, 86%. (iii) H₂, Pd/C, EtOH, rt, 2 h. (iv) DMF, 150 °C, 2 h, 76% (over two steps). (v) Ac₂O, pyridine, DMAP, 50 °C, 48 h, 73% (+20% recovered **5**). (vi) SmI₂, HMPA, THF, rt, 30 min, 93%.

The absolute configuration of the products was established to be (*S*) by chemical correlation with α-hydrazino aldehydes obtained by proline-catalyzed α-amination (see Supporting Information).

Several synthetic manipulations of the aminated products can be envisioned (Scheme 2).

The double bond in the allylic aminated product can be reduced in high yield to afford **3** without compromising the enantiomeric excess. An important feature of the organocatalytic allylic amination is the presence of a highly electron-deficient double bond in **2**, thus enabling these to react as electrophiles. Additionally, the relative asymmetric induction from additions to the double bond might possibly be influenced by the chiral center already present in **2**. As an example, we employed **2i** as a dienophile in the Diels–

Alder reaction with 2,3-dimethyl-1,3-butadiene. Pleasingly, the cycloadduct **4** was obtained in good yield (86%) and with high diastereoselectivity (>15:1). The structure of **4** was confirmed by X-ray analysis (see Supporting Information). Finally, we devised an effective protocol for obtaining chiral γ-amino nitriles—a class of chiral building blocks which could be further elaborated to give the 1,4-diamino motif found in various important bioactive compounds such as quinacrine, chloroquine, and analogues thereof.⁸ Under the standard catalytic conditions, compound **2o** carrying a Bn-ester was prepared with 98% ee. Treatment with H₂ and Pd/C effectively both reduces the double bond and cleaves the Bn ester. Simply heating the compound in DMF after filtration of the Pd catalyst brings about decarboxylation to give **5** (76% yield over two steps). To cleave the N–N bond, the reductive power of SmI₂ was relied upon.⁹ Some experimentation revealed that just an acetylation was sufficient to activate the bond toward reduction, and under optimized conditions Boc-protected γ-amino nitrile **6** could be obtained in 93% yield.

In conclusion, we have presented the first example of a highly enantioselective direct allylic electrophilic functionalization by addition of dialkyl azodicarboxylates to alkylidene cyanoacetates and malononitriles using commercially available organocatalysts. It is our belief, that the concept introduced herein can be applied to other electrophilic addition reactions, and studies toward this aim are already well underway in our laboratories.

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Supporting Information Available: Experimental procedures, structure of the catalysts, characterization data for all new compounds and stereochemical proof. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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