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Asymmetric Construction of Quaternary Stereocenters by Direct Organocatalytic Amination of α-Substituted α-Cyanoacetates and *β*-Dicarbonyl Compounds

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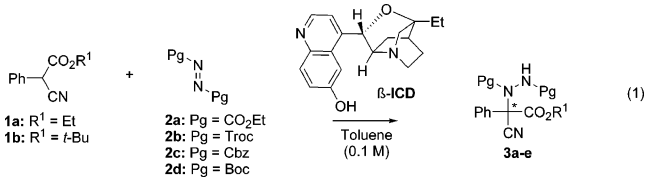
The development of catalytic asymmetric reactions with simple experimental procedures has been a rapidly growing area in synthetic organic chemistry over the past few years. In particular, the direct catalytic and enantioselective approach using unmodified reaction partners, avoiding the tedious preformation of, for example, highly reactive nucleophiles, has received much attention, and decisive progress has been obtained. The carbon−heteroatom bond formation is a fundamental process, and the construction of optically active nitrogen-containing compounds is an important task in chemistry due to their biological activity and pharmaceutical applications.[1] A simple and straightforward approach for the synthesis of optically active nitrogen-containing building blocks via *C*−*N* bond formation is the direct α-amination of unmodified aldehydes and ketones using chiral secondary amines as organocatalysts.[2] Direct α-amination of *β*-keto esters and pyruvic acid derivatives employing a bifunctional Lewis acid catalyst have also been reported.[3] In the latter case, the enantioselectivity is induced by interaction between the chiral Lewis acid catalyst, the enolized nucleophile, and the nitrogen electrophile.

Herein we report a general and highly enantioselective direct organocatalytic amination of α-substituted α-cyanoacetates and *β*-dicarbonyl compounds catalyzed by a chiral tertiary amine. First, we examined the feasibility of the reaction between ethyl α-phenyl α-cyanoacetate **1a** and diethyl azodicarboxylate **2a** using catalytic amounts of chiral bases of the cinchona alkaloid family[4] as a model reaction for further optimization (eq 1).



(1)

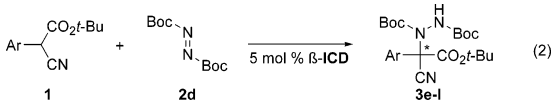
Despite the potential for further elaboration,[5] the use of α-cyanoacetates in asymmetric catalysis has been met with limited success.[6,7] Only in a recent study of Michael additions to α,*β*-unsaturated imides by Jacobsen et al. have enantioselectivities exceeding 90% ee been reported.[8] A thorough screening showed that all the alkaloids tested catalyzed a clean reaction affording the amination product **3a** in nearly quantitative yields, and we were pleased to find that the constrained quinidine-derived alkaloid *β*-isocupreidine[9] (*β*-ICD) was superior in terms of enantioselectivity. In the presence of 5 mol % *β*-ICD, the reaction reached full conversion within less than 30 s to give **3a** having a quaternary stereocenter[10] with 84% ee (Table 1, entry 1). Reactions were performed in toluene, as the use of more polar/coordinating solvents caused a significant drop in enantioselectivity. Varying the structure of the azodicarboxylates had a dramatic impact on both the rate and asymmetric induction (entries 1−4). When employing the synthetically attractive, but sterically encumbered, di-*tert*-butyl azodicarboxylate **2d**, the corresponding hydrazine adduct **3d** was isolated with a satisfying enantioselectivity of 94% ee (entry 4). With the aim of further optimization, the impact of ester substituent (R^1) was investigated, and a direct correlation between the size of R^1 and the rate and enantioselectivity was observed. The reaction of **1b** with **2d**, catalyzed by 5 mol % *β*-ICD, was complete within 4 h at −78 °C, and **3e** was isolated with an excellent optical purity of >98% ee (entry 5). It should be noted that the reactions of α-cyanoacetates are notoriously difficult to render asymmetric.[11] The reaction is easily monitored by disappearance of the yellow color of the azodicarboxylate **2**, and pure product can be obtained using stoichiometric amounts of **1** and **2** upon filtration through a plug of silica gel. At more practical temperatures satisfactory levels of optical purities were also obtained (entries 6,7). An often recognized practical limitation, using organocatalysis as a synthetic tool on large-scale synthesis, is the required amount of catalyst relative to substrate (typically 5−10 mol %). However, the present catalytic system tolerates catalyst loading down to 0.5 mol % without compromising either the yield or the enantioselectivity (entry 9).

Table 1. Optimization of the Reaction between α-Phenyl-α-cyanoacetates **1** and Azodicarboxylates **2** Catalyzed by *β*-**ICD**

entry	substrate	Pg	cat. load (mol %)	temp (°C)	time	product	conv (%)	ee[b] (%)
1	**1a**	CO_2Et	5	−78	≤30 s	**3a**	>95	84
2	**1a**	Troc	5	−78	≤30 s	**3b**	>95	7
3	**1a**	Cbz	5	−78	≤30 s	**3c**	>95	64
4	**1a**	Boc	5	−78	1 min	**3d**	>95	94
5	**1b**	Boc	5	−78	4 h	**3e**	>95	>98
6	**1b**	Boc	5	rt	45 min	**3e**	>95	90
7	**1b**	Boc	5	−20	90 min	**3e**	>95	94
8	**1b**	Boc	1	−78	23 h	**3e**	>95	>98
9	**1b**	Boc	0.5	−78	96 h	**3e**	>95	>98

[a] Reactions performed with 1.2 equiv of α-cyanoacetate relative to the azodicarboxylate. [b] ee determined by CSP-HPLC analysis.

With the optimized reaction conditions in hand, the scope of the enantioselective *β*-ICD-catalyzed amination was investigated. A series of α-aryl-α-cyanoacetates **1b**−**i** were reacted with azodicarboxylate **2d** catalyzed by 5 mol % *β*-ICD (eq 2, Table 2).



(2)

Substrates bearing ortho, meta, and para substituents underwent clean reactions affording the corresponding products **3f**−**h** in quantitative yields and with excellent enantioselectivities of >97% ee (entries 2−4). Interestingly, introduction of Lewis basic substituents (electron-donating/withdrawing) in the para position resulted in slightly lower enantioselectivities (entries 5,6). Polyaro-

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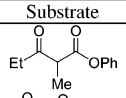
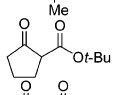
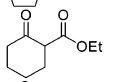
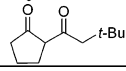
Table 2. Organocatalytic Asymmetric Reactions of *tert*-Butyl α-Aryl-α-cyanoacetates **1** and Di-*tert*-butyl Azodicarboxylate **2d**[a]

entry	substrate	Ar	product	temp (°C)	yield[b] (%)	ee[c] (%)
1	**1b**	Ph	**3e**	−78	99	>98
2	**1c**	*o*-F-C_6H_4	**3f**	−50	99	98
3	**1d**	*m*-Me-C_6H_4	**3g**	−78	99	97
4	**1e**	*p*-Cl-C_6H_4	**3h**	−78	99	98
5	**1f**	*p*-NO_2-C_6H_4	**3i**	−50	99	91
6	**1g**	*p*-MeO-C_6H_4	**3j**	−78	95	89
7	**1h**	2-naphthyl	**3k**	−78	99	98
8	**1i**	2-thienyl	**3l**	−78	99	97
9[d]	**1i**	2-thienyl	**3l**	−50	84[e]	93

[a] Reactions were carried out in toluene (0.1 M) with 1.1 equiv of *tert*-butyl α-aryl-α-cyanoacetate relative to the azodicarboxylate in the presence of 5 mol % β-ICD (16−20 h). [b] Yield of isolated product. [c] ee determined by CSP-HPLC analysis. [d] Reaction performed in the presence of 0.1 mol % catalyst. [e] Formation of ∼10% FC product detected by ^{1}H NMR.

Table 3. β-ICD-Catalyzed Reactions of β-Keto Esters and a β-Diketone with Di-*tert*-butyl Azodicarboxylate **2d**[a]

Entry		Substrate	Temp/°C	Time/h	Prod	Yield[b]/%	Ee[c]/%
1[d]	**4a**		rt	16	**5a**	99	90 (*R*)
2	**4b**		-52	66	**5b**	99	89
3[e]	**4c**		rt	143	**5c**	86	83
4	**4d**		-50	91	**5d**	90	83

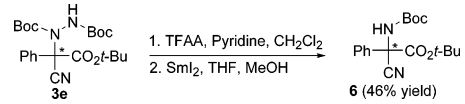
[a] The reactions were carried out in toluene (0.1 M) with 1.1 equiv of substrate relative to the azodicarboxylate in the presence of 5 mol % β-ICD. [b] Yield of isolated product. [c] ee determined by CSP-HPLC analysis. [d] Absolute configuration of **5a** was determined by correlation of the specific optical rotation with literature data.[3b] [e] The reaction was carried out with 1.1 equiv of azodicarboxylate relative to the substrate.

matic compounds may also be employed as substrates, as **3k** was isolated in quantitative yield with 98% ee (entry 7). It is commonly recognized that heteroaromatic compounds are prone to undergo Friedel−Crafts (FC) substitutions in the presence of highly reactive electrophiles and that reactivity is dramatically enhanced with increasing anionic character.[12] While the reaction of heteroaromatic substrate **1i** with **2d** catalyzed by Et_3N mainly resulted in FC substitution in the 5-position of the thiophene moiety, the same reaction catalyzed by 5 mol % β-ICD selectively gave the desired amination product **3l** and only a trace amount of FC product (selectivity: >99:1, 99% yield, 97% ee) (entry 8).[13] Most notably, the reaction can be performed in the presence of as little as 0.1 mol % catalyst, which is among the highest organocatytic activities reported to date affording products with more than 90% ee. It should be noted that α-alkyl-α-cyanoacetates also reacts with **2d** catalyzed by β-ICD, giving the corresponding aminated products in excellent yields; however, lower enantioselectivities were obtained compared to those from the α-aryl-α-cyanoacetates (see Supporting Information). The absolute configuration of **3h** was assigned as (*S*) based on X-ray analysis (see Supporting Information).

The substrate generality of the present organocatalytic system was further demonstrated by the reaction of various β-keto esters **4a**−**c** and a β-diketone **4d** with azodicarboxylate **2d** (Table 3). Both open-chain and cyclic structures were successfully employed, and the desired amination products were obtained in high to quantitative yields with good enantioselectivities ranging from 83 to 90% ee.

Cleavage of the hydrazine *N*−*N* bond was of the utmost interest to gain access to optically active quaternary α-amino acid derivatives. Owing to recent studies[14] on reductive TFA-promoted hydrazine cleavage, product **3e** was converted into **6** by a two-step

Scheme 1. Nitrogen−Nitrogen Bond Cleavage Using SmI_2



procedure under mild reaction conditions (Scheme 1). The chemical transformations were performed without loss of optical purity.

In summary, the first organocatalytic highly enantioselective amination of substituted α-cyanoacetates and β-dicarbonyl compounds is reported with a remarkable catalyst turnover number reaching 1000. Studies, aimed at mechanistic elucidation and generality of the concept, are currently in progress and will be reported in due course.

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Supporting Information Available: Complete experimental procedures and characterization of products (PDF). This material is free of charge via the Internet at http://pubs.acs.org.

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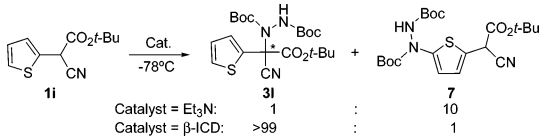

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