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Dual-Activation Asymmetric Strecker Reaction of Aldimines and Ketimines Catalyzed by a Tethered Bis(8-quinolinolato) Aluminum Complex

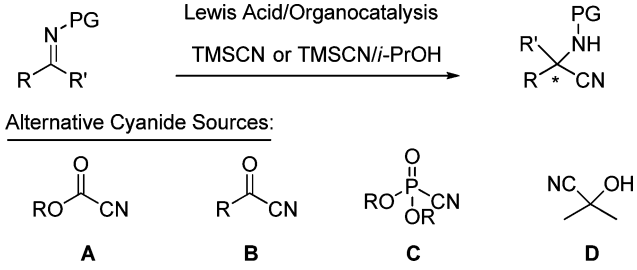
Joshua P. Abell and Hisashi Yamamoto*

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637

Received August 27, 2009; E-mail: yamamoto@uchicago.edu

The asymmetric catalytic synthesis of α-amino acids via hydrocyanation of imines, the Strecker reaction,[1] has seen a large number of reports since the first one slightly more than a decade ago.[2] After this initial report, several organocatalytic and metal-catalyzed asymmetric Strecker syntheses have been reported that have focused on the use of TMSCN or in situ generation of HCN (via TMSCN and a protic additive) as the cyanide source, limiting their use in organic syntheses (Scheme 1).[3,4] Meanwhile, significant progress has been made toward using alternative cyanide sources for carbonyl compounds in asymmetric cyanohydrin synthesis,[5] but the extension to their imine counterparts remains limited.[6,7] Because of their high toxicity, volatility, expense, and difficulty to handle, alternatives to these cyanide sources are required.

Scheme 1. Cyanide Sources

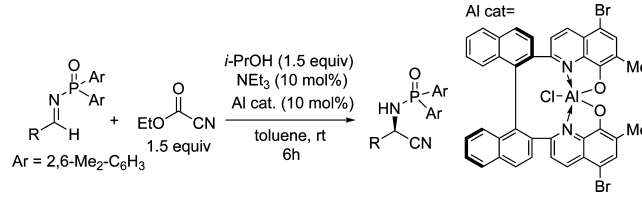


The recent success of our aluminum catalyst has shown wide applicability in various asymmetric reactions.[8] Herein, we report dual chiral Lewis acid/achiral Lewis base activation in the asymmetric Strecker reaction of aldimines and ketimines with broad substrate applicability using ethyl cyanoformate as the cyanide source.

A variety of tethered bis(8-quinolinolato) aluminum complexes were synthesized[10] and screened with alternative cyanide sources.[11] Gratifyingly, ethyl cyanoformate and ethyl cyanophosphorylate provided the product in almost quantitative yield and excellent enantioselectivity.[12] In contrast, cyanide sources of type **B** or **D** provided no α-amino-protected hydronitrile product. Since ethyl cyanoformate provided the product in nearly quantitative yield and high enantioselectivity, the use of this readily available cyanide source was selected for further investigation.

The reaction with alternative sources of cyanide, such as those of type **A** or **C**, did not proceed without a catalytic amount of amine base. Additionally, the reaction did not proceed without the aluminum catalyst, realizing the dual activation nature of the electrophile and nucleophile.[5,13] A survey of common nucleophilic amine bases revealed DMAP and NEt_3 to be the best in terms of yield and enantioselectivity.[11] Moreover, the inclusion of an equimolar amount of *i*-PrOH was effective in the cleavage of the aluminum−amide bond due to product inhibition in the rate-determining step of the reaction, as well as a slight rate enhancement of the reaction.[4k,9]

Table 1. Aldimine Scope[c]



entry	R	yield (%) [a]	*ee* (%) [b]
1	Ph	96	97
2	4-Br-C_6H_4	92	94
3[d]	4-Cl-C_6H_4	88	93
4[d]	4-F-C_6H_4	85	94
5	2-furyl	99	96
6	2-thienyl	93	96
7	3-MeO-C_6H_4	99	98
8	2-Me-C_6H_4	99	98
9	4-MeO-C_6H_4	88	95
10	4-MeC_6H_4	93	97
11[d]	1-Naphthyl	82	95
12[d]	2-Naphthyl	80	94
13[e]		85	90
14[e]	t-Bu	94	90

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis. [c] Absolute stereochemistry confirmed by X-ray analysis of entry 2. [d] Reaction was allowed to run for 14 h. [e] DMAP was used as a nucleophilic catalyst (10 mol %).

Under the optimized conditions, a variety of aldimines were subjected to this protocol (Table 1). Functional groups around the aromatic ring were well-tolerated, providing high enantiomeric excess in all cases. Electron-deficient and larger aromatic aldimines showed reduced reactivities and yields, requiring slightly prolonged reaction times (entries 3, 4, 11, and 12). Typically problematic substrates, such as heteroaromatic imines, also provide α-amino-protected hydronitrile products without deleterious effects on the enantioselectivity (entries 5 and 6). Furthermore, unsaturated and aliphatic aldimines also demonstrated high enantiomeric excess under the optimized conditions, although a more nucleophilic base, 4-dimethylaminopyridine (DMAP), was required (entries 13 and 14).[14]

We further extended this optimized methodology to ketimines, which provide access to enantiomerically enriched quaternary stereocenters.[15] Ketimines are inherently less reactive and more challenging substrates than their aldimine counterparts because of the steric demands during formation of the carbon−carbon bond and discrimination of the prochiral faces. Although several notable and highly selective metal-catalyzed and organocatalyzed variants of this reaction have been accomplished using TMSCN as the cyanide source, applications with alternative sources have

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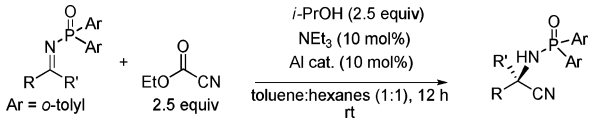
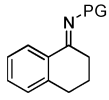
yet to be investigated.[3,4,16] Typical complications arise when changing substrates, such as the need to retune or reoptimize the reaction conditions, but we found that the same catalyst that was found to be optimal for aldimines was equally effective for ketimines (Table 2).

Table 2. Ketimine Scope[d]



entry	R	R'	yield (%) [a]	*ee* (%) [b]
1	Ph	Me	82	96
2	4-Br-C_6H_4	Me	91(80)[c]	94(99)[c]
3	Ph	Et	75	94
4	Ph	*n*-Pr	71	96
5[e]			72	95
6	2-furyl	Me	83	92
7	*t*-Bu	Me	95	82

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis. [c] Values in parentheses are for recrystallized crystals. [d] Absolute stereochemistry confirmed by X-ray analysis of entry 2. [e] PG = di-(*o*-tolyl)phosphinoyl

Various α-amino-protected hydronitriles bearing enantiomerically enriched quaternary stereocenters were produced in good to high yields and good to excellent enantioselectivities. Particularly noteworthy is the enantioselective addition of cyanide to substrates other than acetophenone-derived ones. In this regard, propiophenone-, butyrophenone-, tetralone-, and furyl-derived *N*-diarylphosphinoyl ketimines provided the desired products in synthetically useful yields and excellent ee's (entries 3−6). Moreover, aliphatic substrates such as that derived from pinacolone proved to be suitable for our catalyst system (entry 7). X-ray analysis of the product revealed that the same facial selection was observed for both aldimines and ketimines. This observed facial selectivity is the same as in our hydrophosphonylation of imines[8b] and agrees with the proposed model for stereocontrol already reported with this catalyst.[8a]

In summary, we have developed an efficient protocol for dual Lewis acid/Lewis base activation in a highly enantioselective Strecker synthesis utilizing ethyl cyanoformate as a cyanide source for both aldimines and ketimines at room temperature. This system provides an environmentally benign protocol for the asymmetric Strecker reaction that does not require the use of toxic stoichiometric or superstoichiometric amounts of TMSCN or HCN. Investigations into other complexes that display the cis-β configuration are currently underway.

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Supporting Information Available: Complete experimental procedures, full spectral data for all new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) North and Moberg independently reported a mechanistically related reaction with aldehydes for asymmetric cyanohydrin synthesis using a titanium SALEN dimer catalyst with alternative cyanide sources (see ref 5f, g).
(13) NMR analysis of the reaction mixture (Table 1, entry 8) revealed the appearance of new ethoxy peaks [(q, 3.91) and (t, 0.97)] immediately after the addition of the catalyst to the mixture without *i*-PrOH. This should indicate the presence of the expected carbamate, given its mechanistic relation to ref 5f, g. Also, GC−MS analysis of the reaction mixture indicated the presence of a product with a mass corresponding to carbamate (474.8) that, after aqueous workup and column purification, was hydrolyzed to the secondary amine product in Table 1. See the Supporting Information for NMR and GC−MS charts.
(14) Triethylamine provided the products in entries 13 and 14 in 56 and 68% yield, respectively.
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