ORGANIC LETTERS

2011
Vol. 13, No. 10
2638–2641

Primary Amine/CSA Ion Pair: A Powerful Catalytic System for the Asymmetric Enamine Catalysis

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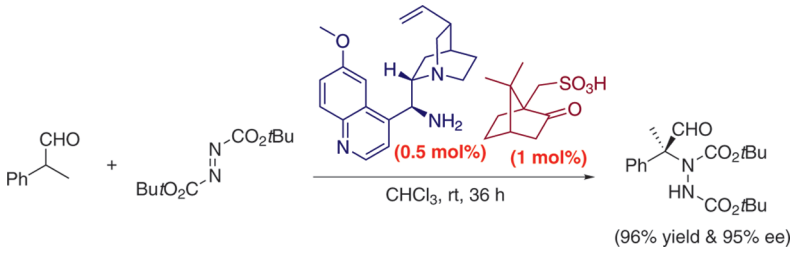
Received March 21, 2011

ABSTRACT



A novel ion pair catalyst containing a chiral counteranion can be readily derived by simply mixing cinchona alkaloid-derived diamine with chiral camphorsulfonic acid (CSA). A mixture of 9-amino(9-deoxy)*epi*-quinine 8 and (−)-CSA was found to be the best catalyst with matching chirality, enabling the direct amination of α-branched aldehydes to proceed in quantitative yields and with nearly perfect enantioselectivities. A 0.5 mol % catalyst loading was sufficient to catalyze the reaction, and a gram scale enantioselective synthesis of biologically important α-methyl phenylglycine has been successfully demonstrated.

Aminocatalysis via the enamine mechanism has been well-established in the field of asymmetric synthesis and catalysis.[1] Ever since the seminal discovery by List, Barbas, and Lerner on the proline-catalyzed intermolecular aldol reaction in 2000,[2] proline and its structural analogues have been utilized extensively in a wide range of asymmetric organic reactions. Pyrrolidine-based secondary amine catalysts were found to be extremely powerful in activating carbonyl substrates, aldehydes in particular, via the enamine intermediates. In the past few years, primary amines have received much attention in the aminocatalysis.[3] Notably, ketones have been shown to be suitable substrates for the primary amine-based enamine activation, which complements well with secondary amine-derived catalysts in this important mode of activation. Our group has been investigating primary amine-mediated enamine processes in the past few years.[4] While we have achieved a certain degree of success in a number of asymmetric reactions, we indeed felt the intrinsic limitation of chiral structural scaffolds in stereocontrol posed restriction to the effectiveness of our catalytic

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10.1021/ol200747x
Published on Web 04/21/2011

reactions. Thus, we set out to develop more powerful primary amine-based catalytic systems for the enamine activations.

Asymmetric counteranion-directed catalysis (ACDC) was recently introduced by List and co-workers as a powerful strategy in asymmetric catalysis.[5] The introduction of a chiral counteranion to the catalytic system enables the reactions proceeding through cationic intermediates to be conducted in a highly enantioselective manner; stereochemical control could be effectively induced by the chiral couteranion. To the best of our knowledge, efficient catalytic systems engaging chiral counteranions for the enamine catalysis are yet to be developed. We recently showed that the combination of 9-amino-9-deoxy-*epi*-cinchonine and (+)-camphorsulfonic acid (CSA) yielded a new primary amine-based organocatalyst useful for iminium activation of α,β-unsaturated ketones.[6] We reasoned that the introduction of a chiral counteranion to the existing catalyst may result in a more efficient catalytic system for the enamine activation. Thus, a chiral diamine[7] and a chiral acid were selected for the creation of a new ion pair catalyst (Figure 1).[8] Such catalytic systems can be easily derived via modular assembly of the amino and acid components. The resulting ammonium moiety in the ion pair catalyst serves as a Brønsted acid to interact with the substrate. Moreover, the presence of a chiral counteranion may further enhance the chiral communications between the chiral diamine and the substrates. Compared to the currently existing chiral primary amine catalysts, which rely on the structural scaffolds of chiral amines for the asymmetric induction, the proposed ion pair catalyst engages an extra chiral counteranion for stereocontrol. We hypothesize that judicious selection of the two chiral components may create a powerful chiral diamine−acid catalyst for an effective enamine catalysis. In this communication, we document that the combination of a cinchona alkaloid-derived primary amine and chiral CSA results in a powerful ion pair catalyst for the enamine activation.

Modified peptides are used extensively in medicinal chemistry and biological sciences;[9] thus, asymmetric synthesis of optically enriched unnatural amino acids has

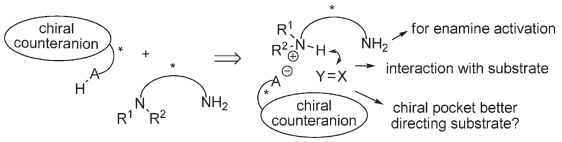

Figure 1. Primary amine−chiral acid catalytic system for the enamine catalysis.

been an actively pursued research area in the past few decades.[10] In this context, α,α-disubstituted α-amino acids are of extreme importance; the presence of a quaternary carbon center renders these unnatural amino acids with increased proteolytic stability, and they have been employed as inhibitors to probe enzymatic mechanisms. Moreover, their incorporation into peptides provides conformational restrictions to the resulting peptides.[11] In particular, the derivatives of α-alkylated phenylglycine have been shown to be selective group I/group II metabotropic glutamate receptor antagonists,[12] in addition to their potential applications as enzyme inhibitors. Given their biological significance, an efficient and practical synthesis of this type of unnatural amino acids is highly desirable.

To demonstrate the power of diamine−chiral acid ion pair catalysts in the enamine catalysis, and to develop an efficient synthesis of α-alkylated phenylglycine derivatives, we turned our attention to the direct amination of branched aldehydes. In 2002, List and Jørgensen disclosed their pioneering studies on the proline-catalyzed asymmetric α-amination of aldehydes.[13] Shortly after, Bräse showed that proline could catalyze amination of α,α-disubstituted aldehydes with moderate enantioselectivity.[14] Recently, the same group reported an improved protocol employing microwave irradiation.[15] Proline-derived thiourea was also utilized by Wang et al. for the same reaction.[16] Very recently, Maruoka disclosed an organocatalytic conjugate addition of heterosubstituted aldehydes to vinyl sulfones for

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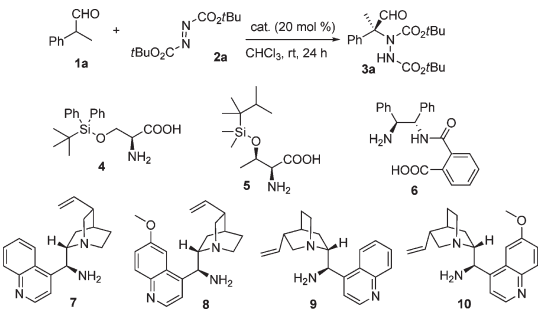
the construction of α,α-dialkylamino aldehydes.[17] Our group recently reported a primary amine-mediated conjugate addition of branched aldehydes to vinyl sulfone for the asymmetric creation of quaternary carbon centers.[4f,18] Given the steric hindrance of α-branched aldehydes, we reasoned primary amines may serve as suitable catalysts for the activation of such challenging substrates in the enamine catalysis, and herein we demonstrate that our novel ion pair catalyst with a chiral counteranion could promote the aminations of α-branched aldehydes in a highly enantioselective manner.

We began our investigation by choosing the amination reaction of 2-phenylpropanal **1** with di-*tert*-butyl azodicarboxylate **2** (DBAD) as a model reaction, and the catalytic effects of various primary amine catalysts were studied (Table 1). Different amino acids, L-serine-derived **4**, L-threonine-derived **5**, and diamine-based **6**, were found to be effective, affording the desired products in moderate yields and enantioselectivities (entries 1−3). 9-Amino(9-deoxy)*epi*-cinchonidine **7**, in combination with different acids, could promote the amination, and good chemical yield and enantioselectivity were achieved when TFA was employed (entry 6). However, the inclusion of methanesulfonic acid (MsOH), *p*-toluenesulfonic acid (TsOH), or trifluoromethanesulfonic acid (TfOH) in the catalytic system resulted in being ineffective (entries 7−10).[19] To our delight, the introduction of a chiral CSA resulted in highly efficient catalytic systems (entries 11−12). The (+)-CSA/**7** ion pair induced better enantioselectivity than the (−)-CSA/**7** ion pair; this prompted us to consider the matching chirality between the diamine and CSA may play an important role in the stereocontrol. The use of 9-amino(9-deoxy)*epi*-quinine **8** with CSA led to further improvement, and the (−)-CSA/**8** ion pair afforded the desired amination product in quantitative yield and with 97% ee (entry 14). The molar equivalence of CSA to diamine **8** can be varied, but more than 2 equiv of CSA were found to be detrimental (entries 15−18). Mixing 9-amino(9-deoxy)*epi*-cinchonine **9** or 9-amino(9-deoxy)*epi*-qunidine **10** with chiral CSA resulted in mismatched chiral pairs, and the products were formed in low ee, and with opposite configurations, suggesting the stereochemical outcome of the reaction was mainly controlled by the chiral scaffolds of the cinchona alkaloid (entries 19−22).

The influence of different ester moieties in the azodicarboxylates on the reactions was next investigated (Scheme 1). Di-isopropyl azodicarboxylate offered a slightly decreased enantioselectivity, and the employment of dibenzyl azodicarboxylate led to a substantial decrease in enantioselectivity. Thus, DBAD was used as the aminating reagent for our following studies.

Having identified the best catalytic system, we next proceeded to examine the generality of the reaction

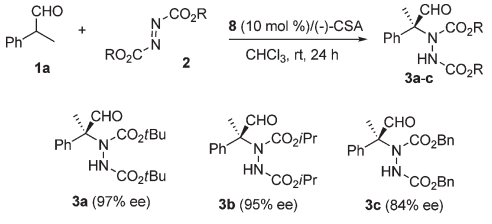
Table 1. Screening of Chiral Primary Amines/Acids for the Amination of 2-Phenylpropanal **1a** with Di-*tert*-butyl Azodicarboxylate **2a**[a]



entry	cat.	additive	yield (%)[b]	ee (%)[c]
1	**4**	none	74	−77
2	**5**	none	57	−60
3	**6**	none	73	76
4	**7**	benzoic acid	50	49
5	**7**	4-NO_2-PhCOOH	47	75
6	**7**	TFA	89	81
7	**7**	MsOH	30	88
8	**7**	TsOH·H_2O	<10	–
9	**7**	TsOH	<10	–
10	**7**	TfOH	<10	–
11	**7**	(+)-CSA	90	93
12	**7**	(−)-CSA	99	87
13	**8**	(+)-CSA	98	91
14	**8**	**(−)-CSA**	**99**	**97**
15	**8**	(−)-CSA[d]	97	97
16	**8**	(−)-CSA[e]	97	97
17	**8**	(−)-CSA[f]	70	93
18	**8**	(−)-CSA[g]	<10	–
19	**9**	(+)-CSA	96	−14
20	**9**	(−)-CSA	99	−13
21	**10**	(+)-CSA	83	−26
22	**10**	(−)-CSA	97	−42

[a] Reaction conditions: di-*tert*-butyl azodicarboxylate **2a** (0.1 mmol), 2-phenylpropanal **1a** (0.15 mmol), the catalyst (0.02 mmol), the acid (0.04 mmol), $CHCl_3$ (0.2 mL), room temperature. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] With 0.02 mmol of acid. [e] With 0.03 mmol of acid. [f] With 0.045 mmol of acid. [g] With 0.05 mmol of acid.

Scheme 1. Effects of Different Azodicarboxylates



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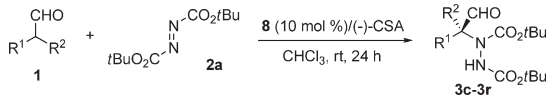
(19) Extensive decompositions were observed; we suspect the aldehyde substrate may decompose under the reaction conditions.

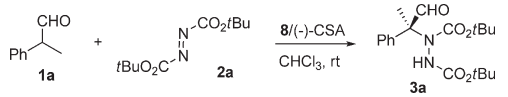
Table 2. Direct Aminations of Various Branched Aldehydes[a]



entry[a]	R^1/R^2	**3**	yield (%)[b]	ee (%)[c]
1	Ph/Me	**3a**	99	97
2	Ph/Et	**3d**	91	99
3	Ph/*i*Pr	**3e**	95	96
4	1-naphthyl/Me	**3f**	97	98
5	2-naphthyl/Me	**3g**	97	97
6	2-BrC_6H_4/Me	**3h**	92	99
7	2-$NO_2C_6H_4$/Me	**3i**	80	96
8	2-$OMeC_6H_4$/Me	**3j**	99	99
9	3-BrC_6H_4/Me	**3k**	83	97
10	3- $NO_2C_6H_4$/Me	**3l**	99	95
11	3,5-$OMeC_6H_3$/Me	**3m**	99	99
12	4-BrC_6H_4/Me	**3n**	99	96
13	4-$NO_2C_6H_4$/Me	**3o**	82	96
14	4-MeC_6H_4/Me	**3p**	85	99
15	4-$OMeC_6H_4$/Me	**3q**	99	97
16	Pr/Me	**3r**	99	68

[a] Reaction conditions: di-*tert*-butyl azodicarboxylate **2a** (0.1 mmol), aldehyde **1** (0.15 mmol), the catalyst (0.01 mmol), (−)-CSA (0.02 mmol), $CHCl_3$ (0.2 mL), room temperature, 24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

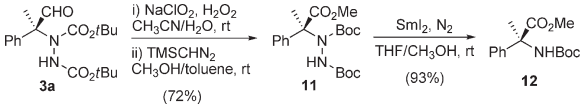
Table 3. Lowing the Catalyst Loading of the Reaction[a]



entry[a]	mol % **8**	*t* (h)	yield (%)[b]	ee (%)[c]
1	20	24	99	97
2	10	24	99	97
3	1	24	99	96
4	0.5	36	96	95
5	0.1	72	47	3

[a] Reaction conditions: di-*tert*-butyl azodicarboxylate **2a** (0.1 mmol), aldehyde **1** (0.15 mmol), the molar ratio of **8** to CSA is 1 to 2, $CHCl_3$ (0.2 mL), room temperature. [b] Isolated yield [c] The ee value was determined by HPLC analysis on a chiral stationary phase.

Scheme 2. A Gram-Scale Synthesis of α-Methyl Phenylglycine



(Table 2). In addition to methyl-substituted phenylglycine, other alkyl-substituted phenylglycines could be prepared in excellent yields and with nearly perfect enantioselectivities (entries 1−3). The reaction proved to be versatile for the synthesis of various α-aryl-substituted phenylglycine analogues; a wide range of 2-arylpropanals could be employed, and very high chemical yields and excellent enatioselectivities were attainable (entries 4−15). Notably, this reaction could even offer a certain degree of stereochemical differentiation between the two alkyl groups; α-methylpentanal could be aminated with 68% ee (entry 16).

The turnover numbers of organocatalytic reactions are in general lower than those of transition-metal-mediated processes, and high catalyst turnovers are certainly ideal for industrial applications. The feasibility of reducing our catalyst loading to a more practical level was examined (Table 3). The loading of diamine **8** could be reduced to 1 mol % with little effects on the chemical yield and enantioselectivity (entry 3). When the catalyst loading was further decreased to 0.5 mol %, the yield and stereoselectivity of the reaction were virtually maintained, although a longer reaction time was required (entry 4).

To demonstrate the value of our catalytic asymmetric synthetic method in the scaleable synthesis of unnatural α,α-disubstituted amino acids, a gram-scale synthesis of α-methyl phenylglycine was performed (Scheme 2). Aldehyde **3a**, prepared via our amination protocol with only a 0.5 mol % catalyst loading, was readily converted into methyl ester **11**. The N−N bond was cleaved by treatment with SmI_2, and the *N*-Boc α-methyl phenylglycine **12** was obtained in good yield at a gram scale.

In conclusion, we designed novel ion pair catalysts containing a chiral counteranion for the enamine catalysis for the first time, and such catalysts can be easily derived by simply mixing a cinchona alkaloid-derived diamine with chiral CSA. Our ion-pair catalysts were found to be very effective in promoting the direct amination reactions of α-branched aldehydes. A mixture of 9-amino(9-deoxy)*epi*-quinine **8** and (−)-CSA was shown to be the best catalyst with matching chirality, affording the desired amination product in quantitative yield and nearly perfect enantioselectivity. Remarkably, a catalyst loading of as little as 0.5 mol % was sufficient for maintaining an excellent chemical yield and stereoselectivity. A gram-scale asymmetric synthesis of biologically important α-methyl phenylglycine was realized, suggesting the great potential of the chiral ion-pair catalyst for industrial applications. We believe the novel ion-pair catalysts described in this report will find wide applications in the enamine catalysis, and we are currently extending their applications to other important organic transformations.

Acknowledgment. We are grateful for the generous financial support from the National University of Singapore and the Ministry of Education (MOE) of Singapore (R-143-000-362-112).

Supporting Information Available. Representative experimental procedures, determination of the absolute configurations of the products, HPLC chromatogram, and NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.