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Silicon-Based Lewis Acid Assisted Cinchona Alkaloid Catalysis: Highly Enantioselective Aza-Michael Reaction under Solvent-Free Conditions

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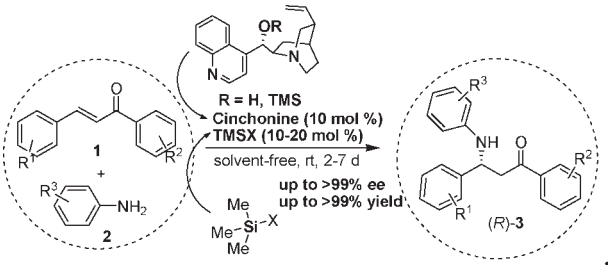
ABSTRACT



The study showed that a combination of an achiral silicon-based Lewis acid and chiral Lewis base, such as iodotrimethylsilane (TMSI) and cinchonine, generated a highly enantioselective catalyst system under solvent-free conditions which gave aromatic β-amino ketones with up to >99% *ee*. Mechanistic studies demonstrate the enhanced asymmetric induction may be due to the combined and competitive activation of a carbonyl moiety of chalcone with cinchonine and the silicon-based Lewis acid in the aza-Michael reaction.

An aza-Michael reaction of a nitrogen-centered source is a convenient and important way to prepare pharmacologically and synthetically useful β-amino carbonyl compounds, including β-amino acids, and β-lactams.[1] Over the past decade tremendous progress has been achieved by employing different nitrogen nucleophiles and new acceptors as well as more efficient catalyst systems for this important organic transformation.[2] Especially in the past several years, the development of novel and efficient synthetic methods leading to chiral β-amino ketones, β-amino acids, and their derivatives has attracted much attention in organic synthesis; however, most of asymmetric aza-Michael reactions with high asymmetric induction or excellent enantioselectivities rely on the use of chiral auxiliaries, chiral starting materials, or stoichiometric amounts of chiral ligands.[1−3] Since the first example was reported by the Jørgensen group in 1996,[4] much effort has been expended on seeking both chiral transition-metal-based catalysts[5] and organocatalysts[6] for asymmetric aza-Michael reaction. However, the catalytic, highly enantioselective aza-Michael reaction is still one of the major challenges in

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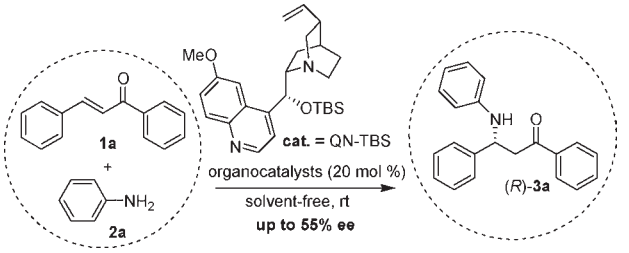
synthetic organic chemistry and asymmetric catalysis. Therefore, the development of new chiral catalyst systems for aza-Michael reaction is highly desired. Combining chiral catalysts having different or similar properties is currently an important and promising strategy for developing highly efficient catalytic transformations.[7]

Cooperative combined catalyst systems inspired from metalloenzymes with multiple cooperative noncovalent interactions is currently a popular and important research topic in asymmetric catalysis.[7e] Various bifunctional metal and organocatalysts including the strategy of combined catalyst systems, such as Lewis acid/Brønsted acid or base,[8] Lewis acid/Lewis acid or base,[9] Lewis base/Brønsted acid or base,[10] and combined transition metal/organocatalysis,[11,12] have been developed to provide unique catalytic activities during the past decade. Herein, we describe a different and idiographic class of combination catalysts for aza-Michael reaction, in which chiral Lewis base catalysis was assisted by an achiral silicon-based Lewis acid catalyst.

Scheme 1



On the basis of previous results (Scheme 1)[13] and studies on silicon-based Lewis acids[14] and a pioneering report by Scettri and Acocella et al.[15] for the aza-Michael reaction of aromatic amines to chalcones, we hypothesized that the silicon-based bulky group acts not only as a simple moiety to provide a steric bias in the transition state (Thorpe–Ingold effect)[16] but also as a Lewis acid to electronically modify the properties of the Lewis basic cinchona alkaloid. To test this hypothesis involving silicon-based Lewis acid (SLA) assisted Lewis base catalysis, we decided to search for a new catalyst system.

Among the Lewis acids screened in combination with cinchonine for the aza-Michael reaction aniline to chalcone, a catalytic amount of iodotrimethylsilane (TMSI) and trimethylsilyl acetate (TMSOAc) were promising. The optimization studies were summarized in Table S1 (see Supporting Infromation, SI). Initial investigations using different silicon-based Lewis acids (SLAs) revealed that, while most of bulky silicon Lewis acids provided poor enantioselectivities, the combinational use of cinchonine and TMSI or TMSOAc was uniquely efficient in affording completed conversion with good enantioselectivity (80% *ee*) of the aza-Michael adduct **3a** at room temperature. When the SLA used is trimethylsilyl trifluoromethanesulfonate (TMSOTf) the decrease in the asymmetric induction (28% *ee*) may be due to the unfavorable functionality of the stronger Lewis acidity. Efforts to optimize this result led to the following observations. (1) Enantioselectivities and conversions were independent of the silicon-based Lewis acid catalyst loading (from 10 to 20 mol % of TMSI). (2) Best results were obtained under solvent-free conditions. Similar enantioselectivities were obtained in hexamethyldisiloxane (79% *ee*) but at the expense of yields for the same time. Other solvents, such as diethyl ether, resulted in poorer enantioselectivity and conversion (62% *ee*, 91% yield). (3) Interestingly, an increase or decrease in the reaction temperature was detrimental or unprofitable to enantioselectivities.

In this reaction, significant variations in the stereoselectivity (0–77% *ee*) were observed depending on the nature of Lewis acids. Among the metallic Lewis acids screened,

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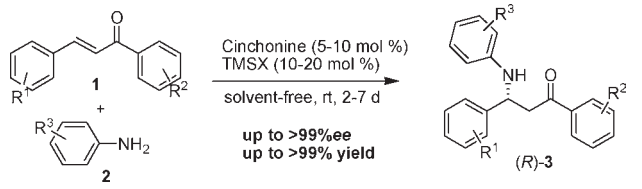
Table 1. Catalytic Aza-Michael Reaction with Various Aromatic Amines to Chalcones Using Silicon-Based Lewis Acid (SLA) as Cocatalysts[a]



entry	R^1	R^2	R^3	X	*t*/d	yield (%)[b]	*ee* (%)[c]
1	H	H	H	I	2	>99	80
2	2-OMe	H	H	I	7	>99	>99
3	2-OMe	H	H	Cl	7	>99	>99
4	4-Me	H	H	I	2	>99	>99
5	4-Me	H	H	Cl	2	>99	>99
6	H	4-Cl	H	I	3	>99	57
7	H	H	4-Me	I	3	>99	>99
8	4-Me	4-OMe	H	I	3	54 (50)	96
9	4-Me	H	3-Me	I	3	>99	60
10	4-Br	4-OMe	H	I	3	>99	97
11	4-Me	H	3-Me	I	2	>99	82[d]
12	H	H	3-Me	I	2	>99	71[d]

[a] Aza-Michael additions were performed under solvent-free conditions similarly to that of Table 1. [b] NMR yield with isolated yield in parentheses. These reactions occurred completely, and yields of isolated products were >90%. [c] Enantioselectivity of aza-Michael adduct was determined by HPLC with chiral column. [d] 5 mol % of catalyst systems were used.

$Ti(O\textit{i}\text{-}Pr)_4$, $NbCl_5$, CuCl, and CuI gave an aza-Michael adduct in >70% *ee*. It is noteworthy that lower enantioselectivities were observed for strong Lewis acidic $Bi(OTf)_3 \cdot 4H_2O$, $YbCl_3 \cdot 7H_2O$, and Cu(II) salts. Therefore, the TMSI was found to be the best Lewis acid in the cinchonine-based cooperative catalyst system.

Having successfully discovered complementary catalyst systems for the highly efficient asymmetric aza-Michael reaction of aniline to chalcone under solvent-free conditions, the scope and generality of the aza-Michael reaction of aromatic amines and chalcones was explored (Table 1). The combined cinchonine/TMSI catalytic reaction conditions proved general for a range of aromatic amines to chalcones with better enantioselectivities in comparison to previous reports. The aza-Michael reaction of aniline with some chalcones, such as the substrates of entries 2−5, exhibited excellent enantioselectivities (>99% *ee*) in completed conversions (>99%) in the presence of TMSI or TMSCl. It should be noted that the crude mixture was directly purified by column chromatography (silica gel, petroleum ethyl acetate mixtures) to obtain the aza-Michael adducts without crystallization. Undoubtedly, the combined use of a silicon-based Lewis acid and cinchonine in this aza-Michael reaction had a very positive effect on the enhancement of asymmetric induction in comparison to that of only catalyst **4** under solvent-free conditions.

Introduction of a methyl group to the *para*-position of aniline also led to similarly and highly stereoselective aza-Michael addition (entry 7). Interestingly, when the substitutents on either the anilines or chalcones were replaced with other groups, the *ee* outcome was decreased dramatically (entries 6 and 9). Although the enantioselectivities obtained in some cases were moderate to good (57−82% *ee*), the aza-Michael reaction is an interesting reaction as it is sensitive to an aromatic or alkyl structure for enones.

We have tried different receptors such as α,β-unsaturated ester or amide and different nitrogen sources, such as $BzNH_2$, $TsNH_2$, and $BnONH_2$, for various aza-Michael reactions. Unfortunately, it was found that trace or no aza-Michael adducts were obtained under the reported conditions. Although not perfect in broad substrate scopes in the presence of this catalyst system, to the best of our knowledge, it is the first example that the enantioselectivities of aza-Michael reaction of aromatic amines to chalcones could reach up to 99% *ee* easily, which provided a new direct method for the preparation of aromatic β-amino ketones.

To explain the combined effect of a silicon-based Lewis acid and cinchonine in this aza-Michael reaction, the mechanism of TMSI/cinchonine-catalyzed aza-Michael reaction was proposed in Scheme 2 on the basis of experimental results and ^{29}Si NMR analysis (see SI), in which the Lewis acid assisted Lewis base (LLB)[17] catalysis is exhibited possibly in the catalytic aza-Michael reaction of aniline with chalcone (Route I in Scheme 2). The assisted functionality of a silicon-based Lewis acid could also be confirmed because we have observed that other Lewis acids such as Cu- or Ti-based Lewis acids also resulted in promising enantioselectivities (Table S1 of SI, entries 12−24), and significant variations in the stereoselectivity (0−77% *ee*) were observed for these Lewis acids. The origin of higher stereoselectivity with an (*R*)-adduct relative to an (*S*)-adduct in the presence of a silicon-based Lewis acid can be explained as follows: (1) the SLA could strongly activates the carbonyl substrates via a carbonyl silylation reaction[18] (**I-2**), and the more active silicon-based Lewis acid/Lewis base catalyst system is *in situ* generated from or interacted with cinchonine and a trimethylsilane halide (for example, TMSCl). (2) It would be a considerable factor for the higher stereoselectivity that the steric bulkiness of counterion $[CN/TMS]^+X^-$ (**I-1**) brings about effective shielding of the activated olefin functionality with the well-known Thorpe−Ingold effect[16] to enhance the chirality transfer from cinchonine. (3) It is speculated that the key points include that the role of the silicon element in this catalyst system is not only as a bulky group to strengthen the steric repulsion but also as a promoter/activator[19] to accelerate the initial step of the reaction between cinchonine and the substrate (chalcone). It is interesting that the

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extremities (57% *ee* vs >99% *ee*) with only relatively minor modifications in the substrates were observed, in accordance with an earlier report on the cinchonine-catalyzed aza-Michael reaction (11−58% *ee*).[15] We suggested that the effect of the substituent of the aromatic rings on stereoselectivity is derived from a change in the $\pi-\pi$ stacking interaction between the aromatic rings of aniline and chalcones. Although several trials including kinetic experiments to establish the true mechanism were unsuccessful, on this basis, the fine-tuning of the reaction conditions and selectivity−reactivity balance for the aza-Michael reaction should be beneficial to the enantioselectivity enhancement.

In summary, an effective protocol for the enantioselective aza-Michael addition of aromatic amines to chalcones is disclosed. The study showed that a combination of an achiral silicon-based Lewis acid and a chiral Lewis base, such as TMSI and cinchonine, generated a highly enantioselective catalyst system under solvent-free conditions which gave aromatic β-amino ketones with up to >99% *ee*. The aza-Michael reaction was optimized for a range of aromatic primary amines possessing both electron-deficient and -rich substitution patterns. Mechanistic studies demonstrate the enhanced asymmetric induction may be due to the combined and competitive activation of the carbonyl moiety of chalcone with hydrogen bonding and the achiral silicon-based Lewis acid assisted chiral Lewis basic cinchonine in the aza-Michael reaction. We believe these results encourage further research efforts to develop novel Lewis acid assisted chiral Lewis base catalyst systems in the presence of organosilicon compounds with bulky groups for asymmetric transformation through combined and competitive activation. Although the present combined catalyst system has some limitations in terms of catalytic efficiency and enantioselectivities, this aza-Michael reaction constitutes a direct catalytic asymmetric route to chiral β-amino ketones and supports that modifying the existing and classic chiral catalysts with the introduction of silicon-based Lewis acid to a combined catalyst system would facilitate the enhancement of stereoselectivity in certain asymmetric transformations and sets the basis for further development.

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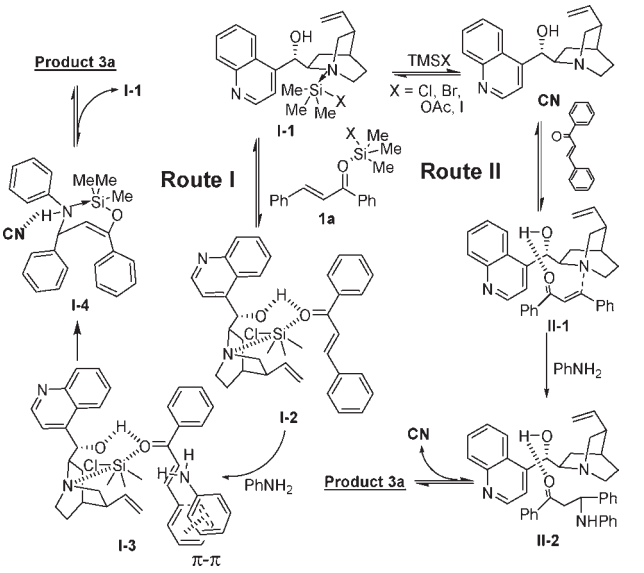
Scheme 2. Plausible Reaction Mechanism of Aza-Michael Reaction



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Supporting Information Available. Experimental procedures, characterization of the products, and other detailed results and discussions. This material is available free of charge via Internet at http://pubs.acs.org.