J|A|C|S COMMUNICATIONS

Published on Web 05/08/2007

Catalytic Enantioselective Petasis-Type Reaction of Quinolines Catalyzed by a Newly Designed Thiourea Catalyst

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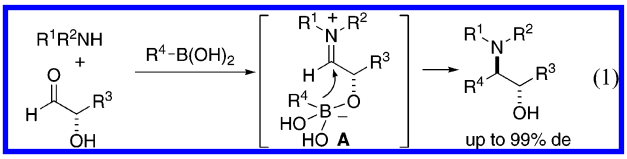
Nucleophilic addition to quinolines has been developed as a key step in the synthesis of tetrahydroquinolines, which are important synthetic intermediates and structural units of alkaloids and biologically active compounds.[1] However, less is known about asymmetric addition to quinolines because the resonance stability of heteroaromatic compounds might impede enantioselective transformation. The first enantioselective reaction of quinolines with TMSCN was achieved by Shibasaki's group, who relied on an unique Lewis acid−Lewis base catalyst.[2] Alexakis also investigated the addition of organolithium reagents to quinolines as well as isoquinolines.[3] As a related example, an organocatalyst has recently been reported to promote the enantioselective addition of silyl ketene acetal to isoquinoline by Jacobsen's group.[4] Despite such significant advances,[2−4] a high degree of stereocontrol has not been achieved and still remains a major challenge.



As a modern variation of the Mannich reaction using organoboronic acids, the Petasis reaction has recently been of great importance in synthetic chemistry.[5,6] However, the full potential of this reaction remains unrealized. Although studies on asymmetric induction have achieved some remarkable success by using chiral α-hydroxy aldehydes, amines, or boronates (eq 1), there have been no reports on catalytic asymmetric processes.[7] In this paper, we describe the first catalytic enantioselective variant of the Petasis transformation of quinolines. In our concept, the thiourea moiety could activate N-acylated quinolinium salts as a Brønsted acid (Figure 1).[8]

Recently, our laboratory introduced thiourea **1a** as a bifunctional organocatalyst, which accelerates the aza-Henry reaction and the Michael reaction of nitroolefins or α,β-unsaturated imides (Scheme 1).[9,10] However, the scope of suitable nucleophiles for catalyst **1a** was mainly limited to 1,3-dicarbonyl compounds. In the Petasis reaction, the formation of reactive "ate" complex **A** is assumed to play an important role in the reactivity and diastereoselectivity, although the intermediates are not well defined (eq 1).[5−7] On the basis of this mechanism, we have newly designed several catalysts **1b**−**i** that have a chelating functionality, which could activate the boronic acids and direct the stereochemical outcome, as shown for **B** in Figure 1.[11] We first reported the results of an experiment to probe the utility of new functionalized catalyst **1b** in the transformation of quinoline **2a** with vinylboronic acid **4A** into 1,2-adduct **5a**. All reactions were run in CH_2Cl_2 at −65 °C for 24 h.[12] Representative results are shown in Table 1. As an activating reagent, the addition of phenyl chloroformate (2 equiv) promoted the reaction at −65 °C (entries 1 and 2), while practically no reaction occurred in the absence of activating reagent, even after

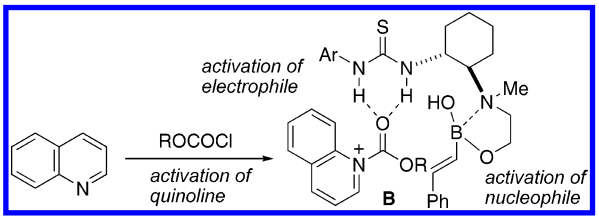


Figure 1. Concept of a newly designed thiourea catalyst.

Scheme 1

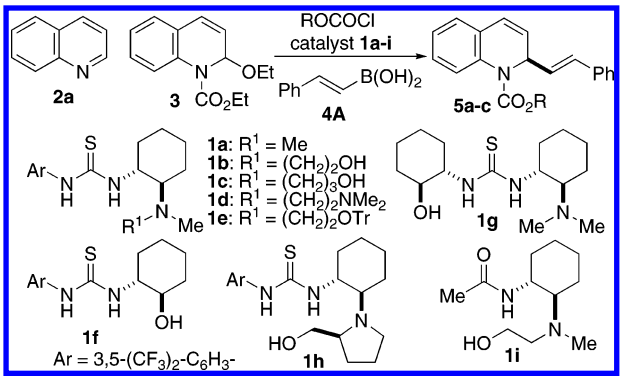


Table 1. Reaction of **2a** with **4A** in the Presence of Catalysts **1a**−**i**[a]

entry	catalyst	ROCOCl	additive	yield (%)	ee (%)
1	**1a**	PhOCOCl	none	34	−9
2	**1b**	PhOCOCl	none	70	90
3	**1b**	EtOCOCl	none	33	42
4	**1b**	BnOCOCl	none	44	67
5	**1c**	PhOCOCl	none	47	27
6	**1h**	PhOCOCl	none	60	68
7	**1i**	PhOCOCl	none	70	50
8	**1b**	PhOCOCl	H_2O[b]	27	93
9	**1b**	PhOCOCl	H_2O and $NaHCO_3$[b]	65	94

[a] Reaction was carried out with catalysts **1a**−**i** (10 mol %) in CH_2Cl_2 at −65 °C. [b] $NaHCO_3$ (2 equiv) and H_2O (56 equiv, CH_2Cl_2/H_2O = 10:1).

the reaction mixture was stirred at room temperature for 24 h. As expected, the use of new thiourea **1b** with a 1,2-amino alcohol functionality (10 mol %) increased the chemical efficiency to give the 1,2-adduct **5a** in 70% yield with 90% ee without formation of a 1,4-adduct (entry 2), while the reaction with the original catalyst **1a** gave the nearly racemic product adduct **5a** in 34% yield (entry 1). The activating reagent affected the enantioselectivity. Among several reagents tested,[13] phenyl chloroformate gave the best results (entries 2−4). Yoon and co-workers recently reported that dihydroquinoline **3** coupled with electron-sufficient boronic acids.[14] Although the dihydroquinoline **3** showed excellent reactivity toward **4A**, stereocontrol was not achieved and the racemic product **5b** was obtained in 68% yield. Several catalysts **1c**−**h** were also tested to determine the role of the amino alcohol moiety (entries 5−7). When the reaction was performed in the presence of catalyst **1c**

10.1021/ja071470x CCC: $37.00

Scheme 2

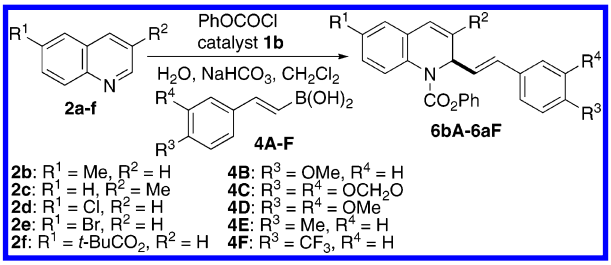
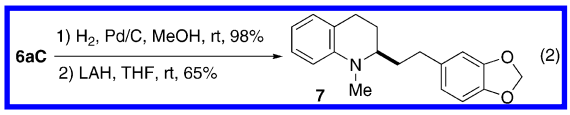


Table 2. Reaction of **2a**−**f** with **4A**−**F** in the Presence of Catalyst **1b**[a]

entry	substrate	boronic acid	*T* (°C)	product (yield)	ee (%)
1	**2b**	**4A**	−65	**6bA** (75%)	95
2	**2c**	**4A**	−78	**6cA** (70%)	96
3	**2d**	**4A**	−65	**6dA** (63%)	94
4	**2e**	**4A**	−65	**6eA** (78%)	95
5	**2f**	**4A**	−65	**6fA** (61%)	96
6	**2a**	**4B**	−78	**6aB** (70%)	97
7	**2a**	**4C**	−78	**6aC** (59%)	82
8	**2a**	**4D**	−78	**6aD** (60%)	89
9	**2a**	**4E**	−65	**6aE** (60%)	91
10	**2a**	**4F**	−40	**6aF** (28%)	95

[a] Reaction was carried out with **1b** (10 mol %) in CH_2Cl_2 by using PhOCOCl (2 equiv), $NaHCO_3$ (2 equiv), and H_2O (56 equiv) for 24 h.

with a 1,3-amino alcohol functionality, only moderate selectivity was achieved (entry 5). The use of catalysts **1d**−**g** led to lower ee.[15] A 1,2-amino alcohol functionality on the catalyst was necessary for valuable stereocontrol, as shown in the reaction with catalyst **1h** as well as **1b** (entry 6). The effect of a thiourea moiety in catalysts was confirmed by using the simple 1,2-amino alcohol catalyst **1i** (entry 7). As expected, catalyst **1i** also showed excellent catalytic activity in this process, although the enantioselectivity was decreased. These observations indicate that a 1,2-amino alcohol functionality on catalysts activates boronic acid and the thiourea moiety controls the distribution of s-*trans*/s-*cis* isomers of the amide bond in *N*-phenoxycarbonyl quinolinium salt.[2a] To improve the enantioselectivity of **5a**, various reaction conditions were examined.[16] The addition of H_2O as a proton source increased the enantioselectivity with a decrease in the yield (entry 8), and the combination of H_2O and $NaHCO_3$ improved the chemical yield (entry 9). A remarkable effect of H_2O and $NaHCO_3$ is assumed to be the in situ regeneration of catalyst **1b** promoted by a proton source and removal of the resulting boronic acid by base.[17]An outstanding level of enantioselectivity was also achieved in the reaction of other quinolines **2b**−**f** (Table 2, entries 1−5). The reaction of quinoline **2c** proceeded smoothly despite the presence of a methyl group at the 3-position (entry 2). Under analogous conditions, various boronic compounds **4B**−**E** gave good results (entries 6−9). As a general trend, electron-rich boronic acids are more reactive in the Petasis reaction.[5−7] Indeed, the reaction with **4B**−**D**, which have an electron-donating substituent, took place even at −78 °C. Although the formation of **6aF**, which has an electron-withdrawing substituent, was remarkably diminished, a high degree of stereocontrol was achieved (entry 10).[18]



The absolute configuration was determined by converting the adduct **6aC** into (+)-galipinine **7** (eq 2).[1] The reaction of quinolines is frequently plagued by the generation of regioisomeric 1,2- and 1,4-adducts;[3] thus, it is also specifically noteworthy that this reaction provides a powerful method for the enantio- and regioselective synthesis of the 1,2-adduct.

In conclusion, an organocatalyst provides sufficient activation of organoboronic acids to facilitate stereocontrol in the Petasis transformation of quinolines as a result of the catalytic generation of a chiral complex as well as the dual activation of an electrophile and nucleophile.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research (B) (Y.T.) and Scientific Research on Priority Areas: Advanced Molecular Transformations of Carbon Resources (Y.T. and H.M.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, 21st Century COE Program "Knowledge Information Infrastructure for Genome Science".

Supporting Information Available: Experimental procedures and characterization data of all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Urea catalyst with a sulfinamide moiety was recently reported to promote allylation of acylhydrazones using an indium reagent. See: Tan, K. L.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315.

(12) The solvent influenced the reactivity and enantioselectivity. A protic solvent such as EtOH increased the addition rate, although no enantioselectivity was observed. Good stereocontrol was achieved with the use of aprotic and nonpolar solvents such as CH_2Cl_2 and toluene.

(13) The addition of AcCl, BzCl, Tf_2O, Ac_2O, or Boc_2O instead of chloroformate led to lower ee.

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(15) The results of reactions using catalysts **1d**−**g** are given in the Supporting Information.

(16) For example, the addition of Et_3N or Na_2CO_3 as a base gave product **5a** in 32 or 91% ee, respectively. The addition of EtOH or CF_3CH_2OH as a proton source was less effective and led to a lower ee.

(17) A similar trend was observed in the reaction of another quinoline **2b**. Thus, the use of H_2O and $NaHCO_3$ was found to be optimal for not only enantioselectivity but also chemical efficiency.

(18) The reaction with arylboronic acids bearing phenyl and *p*-methoxyphenyl groups gave no desired products owing to their low reactivities.

JA071470X