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Amine-Salt-Controlled, Catalytic Asymmetric Conjugate Addition of Various Amines and Asymmetric Protonation

Yoshitaka Hamashima, Hidenori Somei, Yuta Shimura, Toshihiro Tamura, and Mikiko Sodeoka*

Institute of Multidisciplinary Research for Advanced Materials (IMRAM), Tohoku University, Katahira, Sendai, Miyagi 980-8577, Japan, and PRESTO, Japan Science and Technology Agency (JST)

sodeoka@tagen.tohoku.ac.jp

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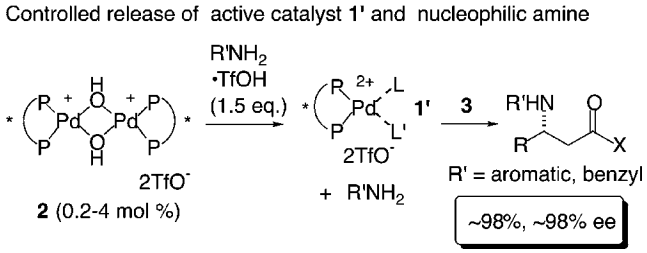
ABSTRACT



The combined use of chiral Pd complex 2 and amine salt enabled completely regulated release of free nucleophilic amine. Under these conditions, an efficient catalytic asymmetric conjugate addition of various amines was achieved to afford *β*-amino acid derivatives in high chemical yields with up to 98% ee. Furthermore, a highly enantioselective protonation in 1,4-addition of amine was also developed.

The catalytic asymmetric conjugate addition of nitrogen nucleophiles is a useful reaction in synthetic organic chemistry because the products are generally recognized as key compounds for the synthesis of not only chiral natural and unnatural *β*-amino acids but also clinically important *β*-lactams.[1] Therefore, considerable efforts to develop efficient methods for this transformation have been made, and excellent enantioselectivity was achieved in several examples using hydroxylamine or azide as a nitrogen source.[2] In contrast, the reaction with simple amines is still difficult. Although the products are extremely useful for the synthesis of chiral dihydroquinoline derivatives via the intramolecular Friedel−Crafts-type acylation,[3] the usage of aromatic amines has not been thoroughly investigated.[4] Furthermore, only a little work has been done on the use of alkylamines.[4b,5] To address this issue, we began to examine the catalytic asymmetric conjugate addition of amines using the chiral Pd−aqua complex **1**, which was developed by us and performed as an excellent catalyst in various reactions.[6] However, the

(1) (a) Juaristi, E., Ed. *Enantioselective Synthesis of β-Amino Acids*; Wiley-VHC: New York, 1997. (b) Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4377−4379. (c) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035. (d) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290−4299. (e) Sewald, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5794−5795.

(2) (a) Falborg, L.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2823−2826. (b) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616. (c) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959−8960. (d) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635−3638. (e) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134−2136. (f) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796−11797. For a recent example in the case of enones: (g) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178−16179 and references therein.

(3) Paradisi, M. P.; Romeo, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 596−600.

(4) (a) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240−1241. (b) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30−31. (c) Li, K.; Hii, K. K. *Chem. Commun.* **2003**, 1132−1133.

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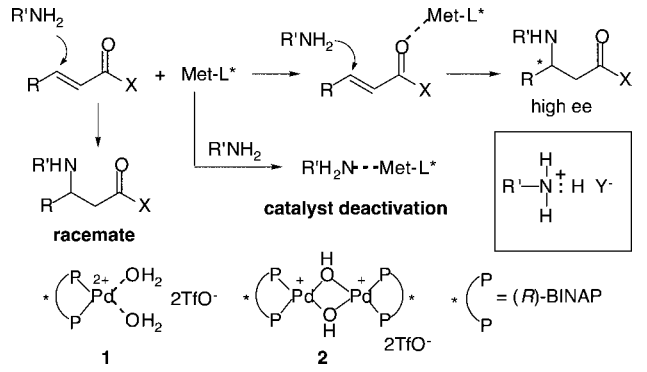
results were found to depend strongly on the nature of the amine used.[7] For example, while aromatic amine bearing an electron-deficient group on the aromatic ring (*p*-CF_3−$C_6H_4NH_2$) afforded high enantioselectivity (83% ee), negligible asymmetric induction (∼2% ee) was observed in the case of amines of higher nucleophilicity such as anisidine and benzylamine (2.5 mol % **1** in toluene).[7] Independently, Hii et al. reported a similar reaction last year,[4c] and their most recent work described excellent enantioselectivity using aromatic amines.[8] However, they also found a tendency similar to that seen in our results, and the reaction with electron-rich amines did not achieve a synthetically useful level. We speculated that this phenomenon is due to the basic character of amines, causing deactivation of Lewis acid catalysts by coordination to the metal center, while amines of higher nucleophilicity react spontaneously, resulting in uncontrolled reactions (Scheme 1). Thus, a novel reaction

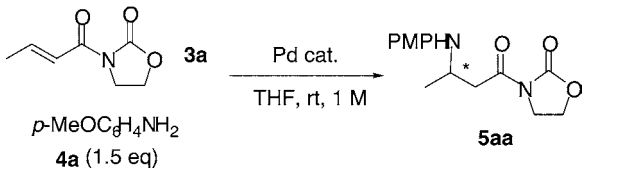
Scheme 1



system is required to realize a generally effective reaction using various amines. Herein, we report a novel reaction system for catalytic asymmetric conjugate addition of various amines to alkenoyl oxazolidinones **3**, in which the combined use of the Pd complex **2** and amine salt is the key to successful results. In addition, preliminary experiments on catalytic enantioselective protonation in the conjugate addition of amines are also described.

Initially, anisidine **4a** was chosen as a nucleophile because electron-rich amines gave poor results as described above. The reaction of **3a** with **4a** was carried out using 2 mol % Pd aqua complex **1** (Table 1, entry 1). Unfortunately, the reaction was sluggish, and the ee of the product **5aa** was only 2%. As we speculated, NMR experiments indicated that

Table 1. Optimization of Reaction Conditions



entry	catalyst (mol %)	TfOH (equiv to **4a**)	time (h)	yield (%)	ee (%)
1	**1** (2)	–	24	35	2
2	–	–	24	41	–
3[a]	**1** (2)	TfOH (1.0), **6a**	24	25	88
4	**1** (1)	TfOH (0.5)	24	98	4
5[a]	**2** (1)	TfOH (1.0), **6a**	12	92	98

[a] TfOH was added as a salt of **4a** (**6a**).

1 reacted with excess amine, and several less active palladium complexes were formed.

Furthermore, the control experiment revealed that spontaneous reaction proceeded at a comparable rate (entry 2). These may be the reasons poor results were obtained in entry 1. On the basis of our finding that the cationic Pd complexes **1** and **2** work well in the presence of a Brønsted acid,[6] we envisaged that the usage of a salt to block the lone pair of amines with a proton might be effective to suppress such unfavorable side reactions (Scheme 1). Among the protic acids examined, TfOH was found to be effective.[9,10] When the isolated salt **6a** (**4a**/TfOH) was used, the reaction of **3a** proceeded slowly (25% after 24 h), probably because the formation of **4a** from **6a** was not favorable (entry 3).[11] Encouragingly, however, the enantioselectivity was greatly improved to 88%. In entry 4, it was found that the addition of a 0.5 equiv of TfOH to **4a** accelerated the reaction, but only negligible asymmetric induction was observed.[12] Thus, we considered that the generation of an appropriate amount of free amine would be necessary. For this purpose, the Pd complex **2**, in which the hydroxyl group shows a basic character,[6f,g] was employed instead of **1** (entry 5). The reaction of **2** with **6a** adequately regulated the generation of free amine, thus avoiding unfavorable side reactions. As shown in entry 5, the reaction of **3a** with **6a** was carried out in THF using 1 mol % **2**. Gratifyingly, *the reaction proceeded smoothly, and the desired product was obtained in 92% yield and 98% ee (rt, 12 h).*

This method was also applicable to other starting materials, as depicted in Table 2.[13] The reaction with simple aniline or

(5) A recent example of the addition of Li amide of $BnNHSiMe_3$ using a chiral ether ligand: Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc*. **2003**, *125*, 2886−2887.

(6) (a) Sodeoka, M.; Ohrai, M.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648−2649. (b) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463−466. (c) Sodeoka, M.; Shibasaki, M. *Pure Appl. Chem*. **1998**, *70*, 411−414. (d) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc*. **1998**, *120*, 2474−2475. (e) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc*. **1999**, *121*, 5450−5458. (f) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc*. **2002**, *124*, 11240−11241. (g) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc*. **2002**, *124*, 14530−14531. (h) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett*. **2003**, *5*, 3225−3228.

(7) Unpublished results. See Supporting Information.

(8) Li, K.; Cheng, X.; Hii, K. K. *Eur. J. Org. Chem*. **2004**, 959−964. This paper appeared during the preparation of our manuscript.

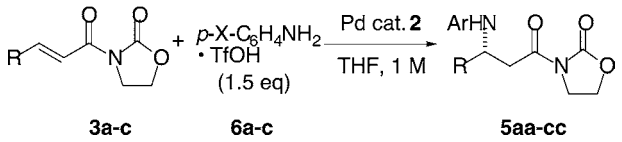
(9) AcOH, HCl, and MsOH gave less satisfactory results.

(10) An interesting proton effect was reported previously: Seligson, A. L.; Trogler, W. C. *Organometallics* **1993**, *12*, 744−751.

(11) A trace amount of the product was formed in toluene, probably because the salt was not dissolved.

(12) Recently, Spencer et al. reported that the proton itself can be an active achiral catalyst for aza-Michael reaction. See: Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem. Eur. J*. **2004**, *10*, 484−493. In contrast, high enantioselectivity was observed under our optimized conditions even in the presence of a stoichiometric amount of proton source (Table 1, entry 5).

Table 2. Catalytic Asymmetric Conjugate Addition of Amines



3a-c 6a-c 5aa-cc

entry	R	X	catalyst (mol %)	temp (°C)	time (h)	yield (%)	ee (%)
1[a]	Me (**3a**)	H (**6b**)	1	20	36	83	96
2[b]	**3a**	CF_3 (**6c**)	2	40	24	77	97
3	Et (**3b**)	OMe (**6a**)	2	40	24	80	94
4	**3b**	**6b**	2	40	24	98	95
5[c]	**3b**	**6c**	4	20	72	49	85
6	$BnOCH_2$ (**3c**)	**6a**	2	20	6	98	97
7	**3c**	**6b**	2	20	12	76	96
8[c]	**3c**	**6c**	4	20	16	98	94
9	**3a**	**6a**	0.2	20	16	98	96

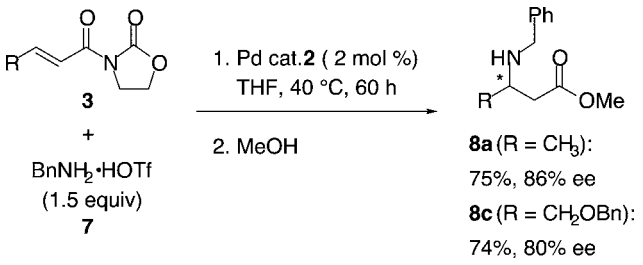
[a] Absolute configuration was determined to be *S* after conversion of the product to the known carboxylic acid.[14] [b] THF/toluene = 1/2. [c] **4c** (1 equiv to Pd) was added.

electron-deficient CF_3-substituted aniline (**6b**,**c**) gave the Michael adducts with high enantioselectivity (entries 1, 2). The absolute configuration of **5ab** was determined to be *S* after conversion to the known carboxylic acid.[14] The ethyl-substituted oxazolidinone **3b** reacted with **6a** and **6b**, affording the corresponding products in excellent yields and ees (entries 3, 4). Although the reaction of **3b** with **6c** was relatively slow, probably due to the lower nucleophilicity of the amine, the desired product was obtained in moderate yield and high ee by the addition of a catalytic amount of free amine **4c** (entry 5). In addition, substrate **3c** bearing the benzyloxymethyl group, which is useful for the later transformation, was also a good substrate. For all the amines tested, the conjugate addition proceeded smoothly, and excellent ees were obtained (94−97% ee, entries 6−8). For entry 9, the catalyst amount was reduced to 0.2 mol %, and comparable enantioselectivity was obtained (96% ee). In these reactions, no double addition product, which is a possible byproduct of the reaction with primary amine, was formed. Also, it is noteworthy that these reactions were not sensitive to either air or water and could be conducted without any particular precautions.[15]

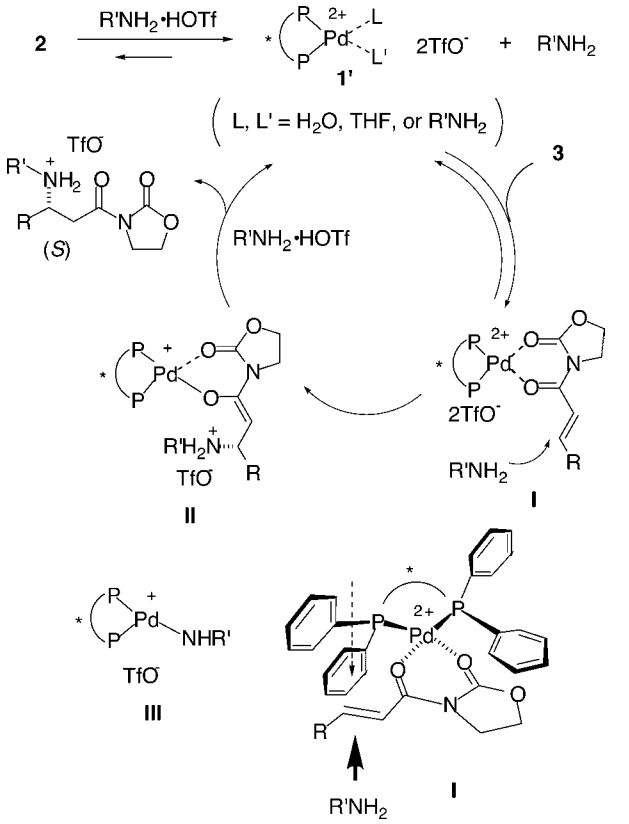
Further examples are as follows (Scheme 2). Benzylamine reacted with **3a** in the presence of 2 mol % Pd complex **2** in THF (40 °C, 60 h). Because the product was rather unstable, the corresponding methyl ester **8a** was isolated in 75% yield (two steps), with 86% ee. The reaction of **3c** afforded the desired β-benzylamino ester with good enantioselectivity (80% ee). Since the catalytic reaction with alkylamines is still an unsolved problem,[16] the considerable potential of this reaction system is indicated by these examples.

Although the exact reaction mechanism has not been established, we speculate that the following catalytic cycle may occur (Scheme 3). NMR experiments suggested that the reaction of **2** with excess salt **6** would afford the monomeric Pd complex **1′**. The generated **1′** could activate

Scheme 2. Catalytic Asymmetric Conjugate Addition of Benzylamine



Scheme 3. Proposed Catalytic Cycle



3 in a bidentate fashion (**I**). Then, the concomitantly formed free amine would attack the activated double bond. Because the *re*-face of the double bond was blocked preferentially by one of the phenyl groups of (*R*)-BINAP, the addition of

(13) **Representative Procedure** (entry 9, Table 2): The palladium complex **2** (1.8 mg, 1 μmol), **3a** (77.6 mg, 0.5 mmol), and amine salt **6a** (205 mg, 0.75 mmol) were placed in a reaction vessel. THF (0.5 mL) was added, and the reaction mixture was stirred at room temperature. After 16 h, saturated aqueous $NaHCO_3$ was added on an ice bath for quenching. Extraction with EtOAc, followed by flash column chromatography on SiO_2, gave the pure product **5aa**. The ee of the product was determined by chiral HPLC.

(14) See Supporting Information for details.

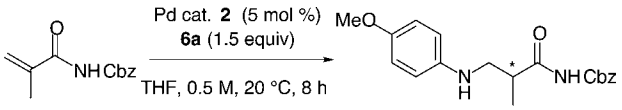
(15) Generally, a tedious anhydrous condition is required to avoid hydrolysis of the metal catalyst. See ref 12.

(16) In ref 5, a catalytic amount of chiral ether ligand (0.3 equiv) afforded the product in 75% yield and 70% ee (−78 °C, 17 h). For substoichiometric reaction (50 mol %): Sundararajan, G.; Prabagaran, N. *Org. Lett.* **2001**, *3*, 389−392.

amine proceeded from the *si*-face in a highly enantioselective manner, and the Pd enolate was formed (**II**). Subsequent protonation of this Pd enolate, followed by dissociation of the product as the salt, would complete the catalytic cycle. In this step, protonation of the product might contribute to preventing the product from coordinating to the metal center. The observed absolute stereochemistry of the product was in accord with the transition state model depicted in Scheme 3. Even though this mechanism seems to be plausible, we should also consider a second possibility, which involves the generation of Pd amide **III** as a nucleophile. Studies to clarify the mechanism are under way.

In this catalytic cycle, it is expected that protonation of the intermediate **II** should occur stereoselectively. To examine this hypothesis, we next planned the catalytic enantioselective protonation of Pd enolate accompanied with the conjugate addition of amines (Scheme 4).[17,18] Thus, the

Scheme 4. Catalytic Asymmetric Protonation in the Conjugate Addition of Anisidine



9 (Cbz = benzyloxy carbonyl) **10**: 80%, 94% ee

methacrylate derivative **9** was treated with **6a** in the presence of Pd complex **2** (5 mol %). The reaction was completed after 8 h, and the desired β-amino acid derivative **10** with a newly formed chirality at the α-position of the carbonyl group was isolated in 80% yield. *To our surprise, the ee of the product was determined to be 94% by chiral HPLC.* It is noteworthy that the small proton approached the transient Pd enolate with high enantioselectivity. The scope of this reaction and the basis of this significantly controlled reaction path will be described in detail elsewhere.

In conclusion, we have developed a novel and highly enantioselective catalytic conjugate addition of various amines to α,β-unsaturated carbonyl compounds. In this reaction, appropriate regulation of the amino functionality was achieved by the combined use of **2** and salt. As a result, both decomposition of the catalyst by amine and uncontrolled spontaneous reaction were considerably suppressed. This reaction, with both aromatic and alkylamines, should be extremely useful in synthetic organic chemistry. In addition, highly enantioselective protonation was also achieved using this novel reaction system. Further details and extension of this work will be reported in due course. Finally, we believe that this salt effect in metal catalysis may allow the development of other catalytic asymmetric reactions involving amine participation.

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Supporting Information Available: Experimental details of the reactions and results of spectroscopic characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) A partially successful example was reported in ref 4b. The reaction of methacrylonitrile with morpholine afforded the corresponding product in 69% ee.

(18) Recent examples of catalytic enantioselctive protonation of transient metal enolate in Michael addition: (a) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043−4044. (b) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 440−442. (c) Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719−723. Radical-based reaction: (d) Sibi, M.; Patil, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1235−1238.