Enantioselective Protonation in the Aza-Michael Reaction Using a Combination of Chiral Pd–μ-Hydroxo Complex with an Amine Salt

Yoshitaka Hamashima, Toshihiro Tamura, Shoko Suzuki, Mikiko Sodeoka*

Advanced Science Institute, RIKEN, 2-1 Hirosawa, Wako 351-0198, Japan
Fax +81(48)4624666; E-mail: sodeoka@riken.jp

Received 30 January 2009

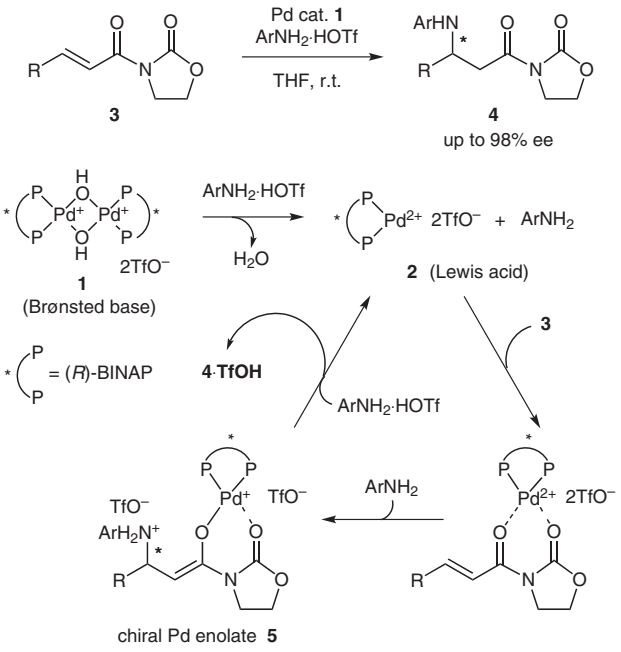
Abstract: A highly enantioselective protonation of enolate intermediates in aza-Michael reaction was achieved by using the combination of a bifunctional chiral Pd–μ-hydroxo complex with aromatic amine salts. The reaction proceeded smoothly to give the desired β-amino carbonyl compounds bearing a stereogenic carbon center at the α-position in good yield with excellent enantioselectivity (up to 97% ee). Although reactions with salts of electron-deficient amines were slow, the introduction of free amine as an additive promoted the reaction to a synthetically useful level.

Key words: asymmetric catalysis, protonations, palladium, aza-Michael additions, β-amino acids

Enantioselective protonation of enolates has been intensively investigated, because it is a useful method to construct a stereogenic carbon center at the α-position of carbonyl compounds.[1] The reaction of preformed metal enolates, including silyl enol ethers, with a chiral proton source has been a main focus,[2] but catalytic generation of chiral enolates in situ, followed by their enantioselective protonation, is also an attractive approach.[3] The conjugate addition of (pro)nucleophiles to α,β-unsaturated carbonyl compounds seems to be a closely related reaction. Indeed, excellent results were achieved in some tandem conjugate addition–protonation sequences. Such reactions involve the conjugate addition of sulfur,[4] phosphorus,[4c] and carbon nucleophiles, including aryl boronic acids[5] and substituted pyroles.[6]

As a part of our studies on synthetic methodologies for optically active β-amino acid derivatives,[7] which constitute an important class of chiral building blocks,[8] we previously reported a highly enantioselective aza-Michael reaction. We devised a novel strategy that combines chiral Pd–μ-hydroxo complex **1** and trifluoromethanesulfonic acid salt of aromatic and benzyl amines, and obtained the desired compounds having a stereogenic carbon center connected to a nitrogen atom in a highly enantioselective manner (Scheme 1).[7a] Also, several efficient conjugate addition reactions using hydroxylamine or azide as a nitrogen nucleophile were developed by other groups.[9]

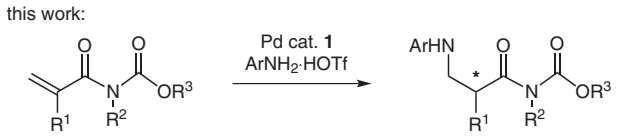
As shown in Scheme 1, the Pd complex **1** acted as a bifunctional catalyst.[10] First, the μ-hydroxo complex reacted with amine salts as a Brønsted base, and a catalytically active Lewis acidic Pd complex **2** was formed with concomitant generation of free amine. Then, the generated **2** activated the substrate **3** to promote conjugate addition of the free amine. This controlled generation of the nucleophilic amine was extremely effective to suppress undesired reactions, such as catalyst deactivation by coordination of the amine compounds and the uncatalyzed racemic pathway. Consequently, high chemical yield and excellent enantioselectivity were achieved even with highly nucleophilic amines, such as anisidine and benzylamine.



Scheme 1 Catalytic asymmetric aza-Michael reaction using Pd catalyst **1** and amine salts

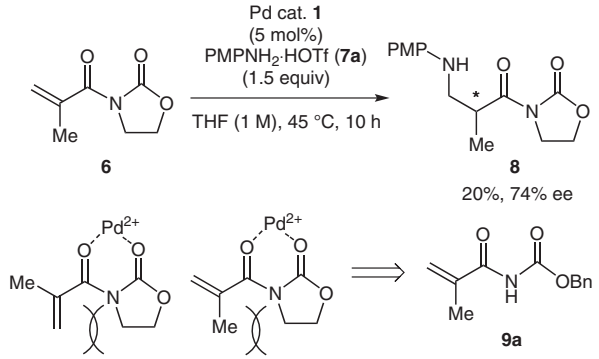
Since the putative Pd enolate **5** is generated in a chiral environment, it is anticipated that the final protonation of **5** should also occur stereoselectively. To examine this hypothesis, we planned the reaction of α-substituted acrylate derivatives under our standard reaction conditions (Scheme 2). Although tandem protonation reactions initiated by the conjugate addition of nitrogen nucleophiles are extremely useful to prepare optically active α-substituted β-amino acids, quite few such reactions are known.[11] Herein we wish to describe the catalytic enantioselective protonation of chiral Pd enolates accompanied with aza-Michael reaction.

SYNLETT 2009, No. 10, pp 1631–1634
Advanced online publication: 02.06.2009
DOI: 10.1055/s-0029-1217347; Art ID: Y00509ST



Scheme 2 Enantioselective protonation in aza-Michael reaction

Based on our previous results,[7a] we initially examined the reaction of oxazolidinone **6** with anisidine salt **7a** in the presence of 5 mol% of the Pd complex **1** (Scheme 3). Although a promising enantioselectivity was observed, the reaction was slow and afforded the product **8** in only 20% yield. When **6** coordinates to the catalyst in a bidentate fashion, intramolecular steric interactions would occur, so that the carbonyl group and the olefin of the substrate are prevented from being co-planar. This may be the main reason for the low chemical yield in this reaction. Therefore, we expected that the reaction rate would be increased if such steric interaction was minimized. Consequently, we selected *N*-benzyloxycarbonyl-protected methacrylamide **9a** as a model substrate.[12]

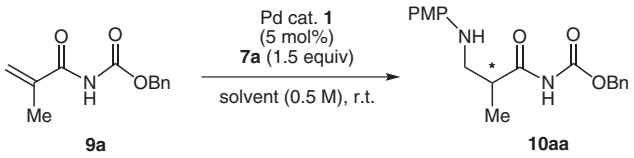


Scheme 3 An initial attempt using **6** as a substrate

As we had hoped, the reaction of **9a** with **7a** proceeded smoothly in THF at room temperature (Table 1, entry 1). The desired product **10aa** was obtained in 80% yield after basic aqueous workup.[13] To our delight, the ee was determined to be 94% by chiral HPLC analysis. Reaction temperature affected the reaction rate, and the reaction at 0 °C resulted in low chemical yield even after 12 hours (entry 2). Among the solvents tested, THF was found to be the best. Less polar solvents such as CH_2Cl_2 and toluene gave decreased enantioselectivity (entries 3 and 4). In the case of polar solvents, such as EtOH and DMF, the reactions did not proceed well (entries 5 and 6). As shown in entry 7, it was possible to reduce the catalyst amount to as little as 1 mol%. Although the reaction did not go to completion after 12 hours, results comparable to those in entry 1 were obtained after 24 hours. Hii and co-workers reported that the slow addition of anisidine was effective to improve the enantioselectivity in their reactions.[11] In contrast, this was not necessary in the present reaction. Since our catalytic system can keep the concentration of the nucleophilic free amine low during the reaction, high catalytic activity and stereoselectivity were achieved.

This reaction was found to be applicable to other α-substituted substrates (Table 2).[13] Ethyl-substituted compound **9b** underwent the reaction under the standard conditions, affording **10ba** in 54% yield with 88% ee (entry 1). Further optimization revealed that a better chemical yield was obtained in a mixed solvent system of THF–CPME (1:1; CPME = cyclopentyl methyl ether; entry 2). The reaction of bulkier phenyl-substituted compound **9c** proceeded without difficulty to give the corresponding product **10ca** in good yield with excellent enantioselectivity (79%, 93% ee; entry 3). In addition to **7a**, aniline salt **7b** was also available, and the corresponding product **10ab** was formed in 65% yield with 97% ee (entry 4).

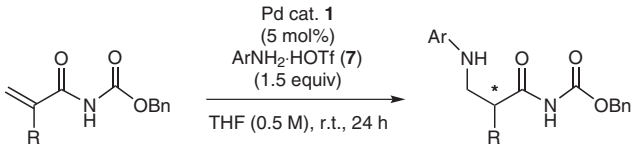
Table 1 Optimization of Aza-Michael–Protonation Reaction



Entry	Solvent	Time (h)	Yield (%)	ee (%)
1	THF	8	80	94
2[a]	THF	12	31	93
3[a]	CH_2Cl_2	24	79	77
4	toluene	3.5	82	88
5	EtOH	24	18	65
6	DMF	24	n.r.	–
7[b]	THF	24	79	94

[a] Temp: 0 °C.
[b] 1 mol% of the Pd complex **1**; n.r. = no reaction.

Table 2 Catalytic Enantioselective Protonation in Aza-Michael Reaction



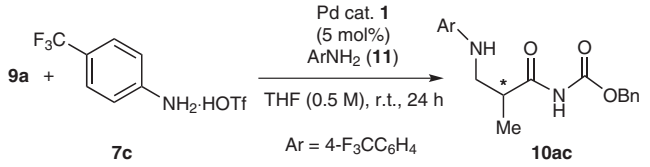
Entry	Acceptor **9**	Salt **7**	Product	Yield (%)	ee (%)
1	**9b**	**7a**	**10ba**	54	88
2[a]	**9b**	**7a**	**10ba**	78	84
3	**9c**	**7a**	**10ca**	79	93
4	**9a**	**7b**	**10ab**	65	97

[a] Solvent: THF–CPME = 1:1.

Unfortunately, however, aromatic amines substituted with electron-withdrawing groups, such as CF_3 and Br, failed

to react smoothly. For example, even though the reaction of **9a** with amine salt **7c** was carried out at higher temperature (40 °C) for a prolonged reaction time (50 h), the adduct **10ac** was obtained in only 11% yield (Table 3, entry 1). We speculated that the low chemical yield might be due to insufficient nucleophilicity of the parent 4-$F_3CC_6H_4NH_2$ (**11**). To address this issue, we next examined the addition of **11** as an additive with the expectation that the first aza-Michael reaction might be accelerated. As we had hoped, the chemical yield was improved to 55%, as the amount of **11** was increased to 0.5 equivalents (entries 2 and 3). But further addition of **11** was not effective, and the chemical yield was only 20%, when 1 equivalent of **11** was employed (entry 4). Interestingly, the ee was in the range of 96–97% in these reactions.

Table 3 Reactions in the Presence of Additional Amine

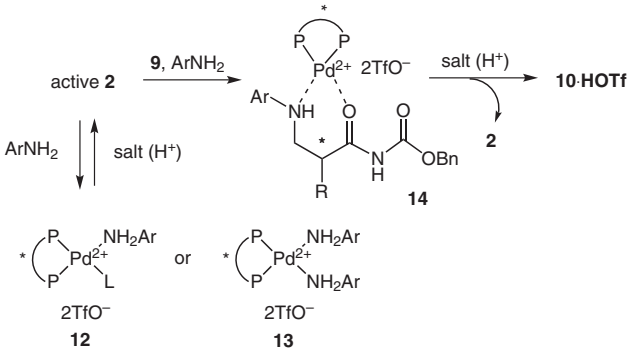


7c 10ac

Entry	Salt **7** (equiv)	Amine **11** (equiv)	Yield (%)	ee (%)
1[a]	1.5	–	11	n.d.
2	1.5	0.25	35	97
3	1.5	0.5	55	96
4	1.5	1.0	20	97
5	3.0	1.0	76	95
6[b]	1.5	0.5	64	94

[a] Conditions: 40 °C, 50 h.
[b] Concentration: 1 M; n.d. = not determined.

Our original conditions using the combination of the Pd complex **1** and amine salts were optimized for the reactions with electron-rich amines, such as anisidine, where the concentration of the free amine must be kept low to avoid uncatalyzed racemic reaction. However, such a process is likely to be negligible in the case of a less nucleophilic amine such as **11**, and a much higher concentration of the free amine is required for smooth reaction. Nevertheless, too much free amine would deactivate the catalyst through the formation of unreactive complexes, such as **12**–**14**, for example (Scheme 4). We considered that these complexes were responsible for the decrease in the catalyst turnover observed in entry 4 and that a precise balance between the salt (proton source) and the amine would be important to keep the Pd complex catalytically active by decomposing inactive complexes via proton-exchange reactions. Our reaction requires both the Lewis acidic complex **2** and a free amine, and the optimum amine/salt ratio would vary depending on the nature of the amine.



Scheme 4 Critical roles of amine salt

Finally, to improve the chemical yield, we examined the reaction using twice the amount of the reagents (3 equiv of **7c** and 1 equiv of **11**) with their ratio being the same as in the case of entry 3. In accordance with our speculation, deactivation of the catalyst was effectively suppressed, and the desired product was formed in a better chemical yield with high enantioselectivity (76% yield, 95% ee; entry 5). Furthermore, when the concentration of the reaction mixture was increased to 1 M, satisfactory results were also obtained under the same conditions as shown in entry 3 (entry 6).

In summary, we have succeeded in developing a tandem aza-Michael reaction–enantioselective protonation reaction. Our novel strategy using the bifunctional Pd–μ-hydroxo complex and amine salts was the key to success. The obtained chiral β-amino acid derivatives with a chiral center at the α-position are expected to be useful in the field of medicinal chemistry. Because catalytic enantioselective aminomethylation, namely classical Mannich reaction, is still difficult to achieve, the present work provides an important alternative method.[14,15] Further studies on the scope of the reaction and the reaction mechanism will be reported in due course.

Acknowledgment

This work was supported by a Grant-in-Aid for the Encouragement of Young Scientists (B) (No. 18790005) and a Grant-in-Aid for Scientific Research on Priority Areas (No. 19028065, 'Chemistry of Concerto Catalysis'), and Special Project Funding for Basic Science. We also thank to NIPPON ZEON Corporation for the generous gift of CPME.

References and Notes

(1) (a) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653. (b) Yanagisawa, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis*, Vol. 3; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**, 1295. (c) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*, Suppl. 2; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **2004**, 125.

(2) For recent examples of protonation of preformed enolates, see: (a) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120. (b) Vedejs, E.; Kruger, A. W.; Lee, N.; Sakata, S. T.; Stec, M.; Suna, E. *J. Am. Chem. Soc.* **2000**, *122*, 4602. (c) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246. (d) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 1546. (e) Poisson, T.; Dalla, V.; Marsais, F.; Dupas, G.; Oudeyer, S.; Levacher, V. *Angew. Chem. Int. Ed.* **2007**, *46*, 7090. (f) Fehr, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 7119; added in revision: after submission of our manuscript, the paper cited in ref. 2g was reported. (g) Morita, M.; Drouin, L.; Motoki, R.; Kimura, Y.; Fujimori, I.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3858.

(3) Reactions starting from ketenes: (a) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006. (b) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176. (c) Schaefer, C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2005**, *44*, 4606. Decarboxylative protonation starting from β-keto esters: (d) Baur, M. A.; Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron: Asymmetry* **2003**, *14*, 2755. (e) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039. Reactions using a chiral carbene catalyst: (f) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406.

(4) (a) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043. (b) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 440. (c) Leow, D.; Lin, S.; Chittimalla, S. K.; Fu, X.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5641.

(5) (a) Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem. Int. Ed.* **2004**, *43*, 719. (b) Moss, R. J.; Wadsworth, K. J.; Chapman, C. J.; Frost, C. G. *Chem. Commun.* **2004**, 1984. (c) Sibi, M. P.; Tatamidani, H.; Patil, K. *Org. Lett.* **2005**, *7*, 2571. (d) Nishimura, T.; Hirabayashi, S.; Yasuhara, Y.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 2556. (e) Frost, C. G.; Penrose, S. D.; Lambshead, K.; Raithby, P. R.; Warren, J. E.; Gleave, R. *Org. Lett.* **2007**, *9*, 2119. (f) Navarre, L.; Martinez, R.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159.

(6) Sibi, M. P.; Coulomb, J.; Stanley, L. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 9913.

(7) (a) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, *6*, 1861. (b) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1525. (c) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010.

(8) (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (c) Ma, J.-A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4290.

(9) A short review: (a) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633. For more recent examples: (b) Yamagiwa, N.; Qin, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419. (c) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328. (d) Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc.* **2007**, *129*, 8064. (e) Lu, X.; Deng, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 7710.

(10) (a) Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941. (b) Sodeoka, M.; Hamashima, Y. *Pure Appl. Chem.* **2006**, *78*, 477.

(11) We previously reported one example (entry 1, Table 1) in ref. 7a. Recently, Hii et al. also reported partially successful results related to our reaction using a chiral cationic Pd complex. See: Phua, P. H.; Mathew, S. P.; White, A. J. P.; de Vries, J. G.; Blackmond, D. G.; Hii, K. K. (Mimi) *Chem. Eur. J.* **2007**, *13*, 4602.

(12) The synthesis of the starting material was carried out based on the reported procedure. See: Liu, X.; Hu, X. E.; Tian, X.; Mazur, A.; Ebetino, F. H. *J. Organomet. Chem.* **2002**, *646*, 212.

(13) **General Procedure**
The starting material **9** (0.1 mmol), amine salts **7** (0.15 mmol), and the Pd complex **1** (5 mol%) were dissolved in THF (0.2 mL). In the case of **7c**, the additive **15** (0.05 mmol) was included. The resulting solution was stirred at ambient temperature for the time shown in Tables 1– 3. For quenching, cold sat. aq $NaHCO_3$ (2 mL) was added under ice-bath cooling. Usual workup, followed by flash column chromatography (Si_2O, hexane–EtOAc system) gave the pure products.
Analytical Data of 10ca
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (dd, *J* = 5.5, 13.0 Hz, 1 H), 3.74 (s, 3 H), 3.84 (dd, *J* = 8.7, 13.0 Hz, 1 H), 4.48 (br s, 1 H), 5.08 (s, 2 H), 6.58 (d, *J* = 8.8 Hz, 2 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 7.26–7.39 (m, 10 H), 7.55 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.0, 51.2, 55.7, 67.9, 114.7, 115.0, 128.0, 128.4, 128.5, 128.6, 128.7, 129.1, 134.7, 136.0, 141.2, 150.6, 152.5, 172.4. LRMS–FAB (*m*NBA): *m/z* = 404 [M^+], 405 [M + H]$^+$. HRMS (PEG 400/*m*NBA): *m/z* calcd for $C_{24}H_{24}N_2O_4$ [M]$^+$ 404.1736; found: 404.1739. $[\alpha]_D^{25}$ +64.6 (*c* 0.82, $CHCl_3$; 93% ee). HPLC (DAICEL CHIRALPAK AD-H, hexane–2-PrOH = 3:1, 1.0 mL/min, 254 mn): t_R(minor) = 17.2 min, t_R(major) = 20.9 min.

(14) Several practical aminomethylation reactions of aldehydes using organocatalysts have been reported. See: (a) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804. (b) Ibrahem, I.; Dziedzic, P.; Córdova, A. *Synthesis* **2006**, 4060.

(15) Asymmetric three-component classical Mannich reactions: (a) Ibrahem, I.; Casa, J.; Córdova, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 6528. (b) Hamashima, Y.; Sasamoto, N.; Umebayashi, N.; Sodeoka, M. *Chem. Asian J.* **2008**, *3*, 1443.