ORGANIC LETTERS

2010
Vol. 12, No. 24
5636−5639

Enantioselective Conjugate Addition of Oximes to Trisubstituted *β*-Nitroacrylates: An Organocatalytic Approach to $\beta^{2,2}$-Amino Acid Derivatives

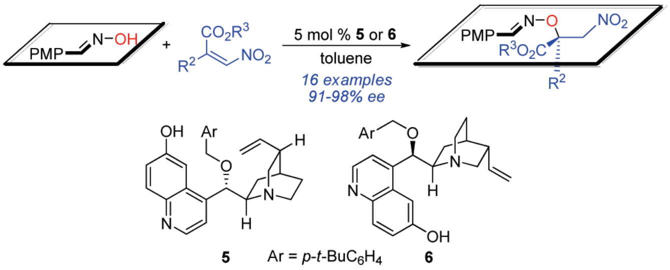
Fu-Gen Zhang, Qing-Qing Yang, Jun Xuan, Hai-Hua Lu, Shu-Wen Duan, Jia-Rong Chen,* and Wen-Jing Xiao*

Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China

wxiao@mail.ccnu.edu.cn; jiarongchen2003@yahoo.com.cn

Received September 30, 2010

ABSTRACT



A highly enantioselective organocatalytic intermolecular conjugate addition of oximes to *β*-nitroacrylates has been developed. The highly functionalized adducts obtained are valuable precursors for asymmetric synthesis, as demonstrated by the synthesis of $\beta^{2,2}$-amino acids and oxazolidin-2-ones.

One focal objective of contemporary organic synthesis is to develop catalytic asymmetric processes for the efficient formation of carbon−carbon and carbon-heteroatom bonds.[1] In this regard, the conjugate addition of *O*-nucleophiles to electron-deficient olefins has proven to be one of the most important but challenging methods for forming a carbon−oxygen bond, which is frequently encountered in biologically active natural products and pharmaceuticals.[2] However, the relative low reactivity of the *O*-nucleophiles and reaction reversibility have hampered the development of asymmetric variants of this reaction.[3] To our knowledge, there are only a few examples of highly enantioselective oxo-conjugate addition reactions documented to date.[4]

With the use of a chiral catalyst (either metallic or organic), the intramolecular conjugate addition becomes a powerful tool to construct carbon-heteroatom bonds, using a variety of heteroatom-based nucleophiles (S, O, P, N, etc.) and electron-deficient alkenes.[5] Surprisingly however, the analogous *intermolecular* variant of heteroatom-based nucleophiles to *β*,*β*-disubstituted α,*β*-unsaturated systems has not been

---

[1] (a) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vols. I−III. (b) Berkessel, H., Gröger, H., Eds. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (d) Adair, G.; Mukherjee, S.; List, B. *Aldrichim. Acta* **2008**, *41*, 31.

[2] For reviews on conjugate additions, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U. K., 1992. (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991.

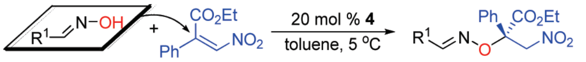
[3] For a recent review, see: (a) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218. For a phosphine-catalyzed conjugate addition of water and alcohols to variety of activated olefins, see: (b) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696. For a base-promoted addition of alcohols to enones, see: (c) Kisanga, P. B.; Ilankumaran, P.; Fetterly, B. M.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 3555.

10.1021/ol102580n

extensively explored.[4n,6] This presents an opportunity to develop a highly desirable stereoselective system, that in principle would provide an alternative synthetic technique to the corresponding Aldol or Mannich-type reaction protocols.

As a continuing effort to develop solutions to complex synthetic challenges, we herein describe a new approach to the construction of a tertiary alcohol[7] unit through organocatalytic intermolecular conjugate addition of oximes to β-nitro-acrylates.[8] This research describes the formation of optically active α-oxylated β-nitro esters (15 examples, 91−98% ee), which are useful building blocks[6b,9] for the synthesis of $\beta^{2,2}$-amino acids and oxazolidin-2-ones.

Pioneered by Jacobsen and co-workers[4b] in the Al(III)-catalyzed highly enantioselective conjugate addition of oximes to α,β-unsaturated imides, and later in the unprecedented organocatalytic hydroxylation of enals and nitroalkenes by Jørgensen and co-workers,[4e,f] oximes proved to be a highly valuable class of "soft" oxygen nucleophiles. Due to the planar character of an oxime which has minimal steric hindrance, which we believe to be a key prerequisite for successful conjugate addition reactions with crowded tri- or tetrasubstituted electron-deficient alkenes.[10] Initially, we examined the reaction of ethyl glyoxylate oxime **1a**, which is an excellent Michael donor as shown by Jørgensen and co-workers for the hydroxylation of aliphatic nitroalkenes by thiourea catalysts,[4f] with β-nitroacrylate **2a** in the presence of 20 mol % of organocatalyst **4** (eq 1).



(1)

1a: $R^1 = CO_2Et$
1b: R^1 = *p*-MeOC$_6$H$_4$
2a
3a: 48 h, *trace*
3b: 26 h, *81% yield*

Although disappointed by the poor reaction outcome with only a trace amount of the desired product, this encouraged us to believe that this protocol should be achieved if the nucleophilicity of the oxime could be enhanced. Gratifyingly, by simply changing the oxime from **1a** to the relatively more nucleophilic *p*-methoxybenzaldehyde oxime **1b**, we obtained the desired product in 81% yield with 17% ee (Table 1, entry 1).[11] Interestingly, decreasing the catalyst loading greatly improved the stereoselectivity of the reaction (entries 2 vs 1).

We then embarked on optimizing the reaction conditions. For example, a solvent investigation revealed that nonploar solvents were superior to polar solvents in terms of yields and enantioselectivities (entries 1−10). Toluene was found to be the best solvent (entry 2, 75% yield and 50% ee). After screening a number of organocatalysts, cinchona alkaloids **5** and **6** bearing a C6′-hydroxy group developed by the Deng group,[12] were identified to be the best organocatalysts for this conjugate addition.[13] With 5 mol % **5** or **6**, the reaction

---

(4) (a) Sekino, E.; Kumamoto, T.; Tanaka, T.; Ikeda, T.; Ishikawa, T. *J. Org. Chem.* **2004**, *69*, 2760. (b) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724. (c) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007**, *63*, 8658. (d) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem.—Eur. J.* **2007**, *13*, 574. (e) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536. (f) Dinér, P.; Nielsen, M.; Bertelsen, S.; Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 3646. (g) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830. (h) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.-H.; Wang, W. *Chem. Commun.* **2007**, 507. (i) Wang, L.-J.; Liu, X.-H.; Dong, Z.-H.; Fu, X.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8670. (j) Zu, L.-S.; Zhang, S.-L.; Xie, H.-X.; Wang, W. *Org. Lett.* **2009**, *11*, 1627. (k) Reyes, E.; Talavera, G.; Vicario, J. L.; Badia, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 5701. (l) Wang, H.-F.; Cui, H.-F.; Chai, Z.; Li, P.; Zheng, C.-W.; Yang, Y.-Q.; Zhao, G. *Chem.—Eur. J.* **2009**, *15*, 13299. (m) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056. (n) Matoba, K.; Kawai, Hiroyuki; Furukawa, T.; Kusuda, A.; Tokunaga, E.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 5762.

(5) For selected reviews and examples on sulfa-Michael reactions, see: (a) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 8379. (b) Hui, Y.-H.; Jiang, J.; Wang, W.-T.; Chen, W.-L.; Cai, Y.-F.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4290. (c) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418. (d) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754. (e) Wang, J.; Xie, H.-X.; Li, H.; Zu, L.-S.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177. (f) Enders, D.; Luttgen, K.; Narine, A. *Synthesis* **2007**, 959. RAJIV(5) For recent phosphite addition reactions and reviews, see: (g) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew, Chem., Int. Ed.* **2010**, *49*, 153. (h) Wang, J.; Heikkinen, L. D.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1052. (i) Terada, M. T.; Ube, I. H. *J. Am. Chem. Soc.* **2007**, *129*, 14112. (j) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (k) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (l) Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, 2065. For recent aza-Michael reactions and review, see: (m) Roy, S. R.; Chakraborti, A. K. *Org. Lett.* **2010**, *12*, 3866. (n) Gogoi, S.; Zhao, C.-G.; Ding, D.-R. *Org. Lett.* **2009**, *11*, 2249. (o) Lin, Q.-Y.; Meloni, D.; Pan, Y.-C.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.-L.; Zhou, J.-C. *Org. Lett.* **2009**, *11*, 1999. (p) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058.

(6) For intermolecular conjugate addition of heteroatom-based nucleophiles with β,β-disubstituted α,β-unsaturated systems see: (a) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043. (b) Lu, H.-H.; Zhang, F.-G.; Meng, X.-G.; Duan, S.-W.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 3946. Other oxygen-nucleopiles take part in intermolecular conjugate addition, for examples, see: (c) Seagers, W. J.; Elving, P. J. *J. Am. Chem. Soc.* **1949**, *71*, 2947. (d) Fuer, H.; Markofsky, S. *J. Org. Chem.* **1964**, *29*, 929. (e) Duffy, J. L.; Kurth, J. A.; Kurth, M. J. *Tetrahedron Lett.* **1993**, *34*, 1259. (f) Dulcere, J. P.; Dumez, E. *Chem. Commun.* **1997**, 971. (g) Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Laine, D. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 4241. (h) Yi, C.-S.; Yun, S.-S.; He, Z.; Guzei, I. A. *Organometallics* **2003**, *22*, 3031. (i) Buchanan, D. J.; Dixon, D. J. *Org. Lett.* **2004**, *6*, 1357. (j) Xiong, X.; Ovens, C.; Pilling, A. W.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 565.

(7) For recent reviews on asymmetric synthesis of tertiary alcohols, see: (a) Hatano, M.; Ishihara, K. *Synthesis* **2008**, 1647. (b) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969.

(8) Reviews of asymmetric organocatalytic 1,4-conjugate additions: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299.

(9) (a) Liu, T.-Y.; Li, R.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem.—Eur. J.* **2006**, *13*, 319 For reviews, see. (b) Juaristi, E.; Soloshonok, V. *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Wiley-VCH: New York, 2005. (c) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1.

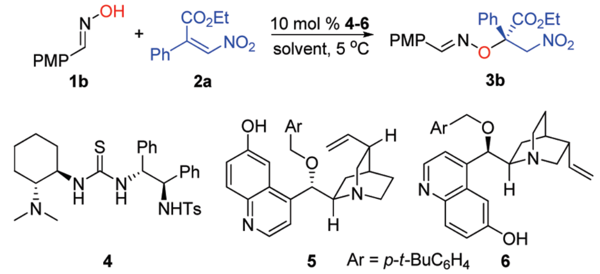
(10) Quite recently, Scheidt and coworkers developed an elegant *N*-heterocyclic carbene-catalyzed conjugate additions of alcohols to enones, see: Phillips, E. M.; Riedrich, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 13179.

(11) In our hands, the conjugate addition adducts are stable and could be directly subjected to silical gel chromatography. We believe that the electron-withdrawing ester group has a stabilizing effect as reversible conjugate addition was observed in the case of simple nitroalkenes by Jørgensen and coworkers, see ref 4f.

(12) (a) Li, H.-M.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (b) Li, H.-M.; Wang, Y.; Tang, L.; Wu, F.-H.; Liu, X.-F.; Guo, C.-Y.; Foxman, B.-M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105. (c) Liu, X.-F.; Li, H.-M.; Deng, L. *Org. Lett.* **2005**, *7*, 167. (d) Li, H.-M.; Wang, B.-M.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732. See also: (e) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. For reviews on cinchona alkaloid catalysis, see: (f) Chen, Y.-G.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965. (g) Tian, S.-K.; Chen, Y.-G.; Chen, J.-F.; Tang, L.; Mcdaid, P.; Deng, L. *Acc, Chem, Res.* **2004**, *37*, 621. (h) Chen, Y.-C. *Synlett* **2008**, 1919.

(13) Please view the Supporting Information for details.

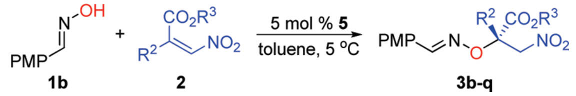
Table 1. Asymmetric Conjugate Addition of Oxime **1b** with β-Nitroacrylate **2a** under Various Conditions[a]

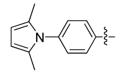
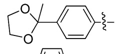
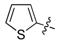


entry	solvent	catalyst	h	yield (%)[b]	ee (%)[c]
1	toluene	**4**	26	81	17[d]
2	toluene	**4**	30	75	50[e]
3	xylenes	**4**	36	91	35
4	benzene	**4**	36	71	50
5	DCM	**4**	24	82	40
6	DCE	**4**	24	86	33
7	$CHCl_3$	**4**	24	77	45
8	Et_2O	**4**	48	59	38
9	CH_3CN	**4**	48	47	15
10	EtOH	**4**	72	45	9
11	toluene	**5**	12	75	−95
12	toluene	**5**	20	77	−96[e]
13	toluene	**6**	24	75	94[e]

[a] Unless noted, reactions were carried out with **1b** (0.75 mmol), **2a** (0.25 mmol) and **4-6** (10 mol %) in 1.0 mL of solvent at 5 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Twenty mol % of catalyst was used. [e] Five mol % of catalyst was used.

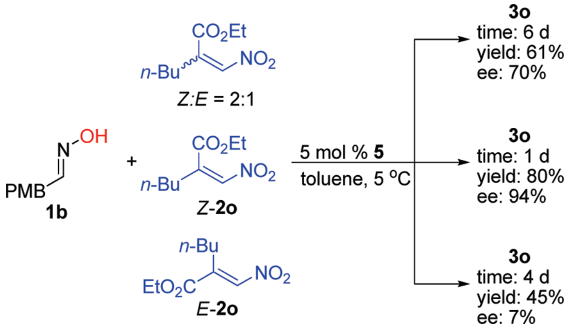
Table 2. Asymmetric Conjugate Addition of Oxime **1b** to Various β-Nitroacrylates **2** in the Presence of 5 mol % of Organocatalyst **5**[a]



entry	R^2	R^3	h	yield (%)[b]		ee (%)[c]
1	C_6H_5	Et	20	**3b**	77	96
2	C_6H_5	Bn	24	**3c**	84	96
3	C_6H_5	*i*-Pr	24	**3d**	93	96
4	C_6H_5	*t*-Bu	36	**3e**	72	98
5	3-$MeOC_6H_4$	Et	48	**3f**	79	95
6	4-$MeOC_6H_4$	Et	50	**3g**	61	91
7	4-MeC_6H_4	Et	30	**3h**	72	96
8	4-PhC_6H_4	Et	24	**3i**	89	93
9	4-ClC_6H_4	Et	12	**3j**	91	96[d]
10	3,5-$(CH_3)_2C_6H_3$	Et	36	**3k**	93	96
11		Et	24	**3l**	89	95
12		Et	36	**3m**	88	93[e]
13		Et	48	**3n**	79	96[f]
14	*n*-Bu	Et	24	**3o**	80	94[e]
15	*i*-Pr	Et	24	**3p**	87	96

[a] Unless noted, reactions were carried out with **1b** (0.75 mmol), **2** (0.25 mmol) and **5** (5 mol %) in 1.0 mL of toluene at 5 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Absolute configuration of **3j** was determined by X-ray analysis. [e] Conducted at 0 °C. [f] Conducted at −25 °C.

Scheme 1. Effect of the Olefin Geometry of β-Nitroacrylate



between oxime **1b** and β-nitroacrylate **2a** proceeded smoothly to produce the corresponding products in high yield and excellent enantioselectivities but with opposite stereochemistry (entries 12 and 13).

Under these optimized conditions, the synthetic scope of the conjugate addition was evaluated, and the results are presented in Table 2. Changing the ester group of the β-nitroacrylate component **2**, from ethyl to gradually more sterically hindered benzyl, *i*-propyl and *t*-butyl groups, had a minor effect on the yields and enantioselectivities (entries 1−4). Most importantly, with 5 mol % of catalyst **5** excellent enantioselectivities and high yields could be obtained for both aryl β-nitroacrylates (entries 1−13) and aliphatic β-nitroacrylates (94−96% ee, entries 14−15).

Furthermore, significant variation in the phenyl β-nitroacrylate **2** architecture can be realized, regardless of steric or electronic properties, to afford products in 91−98% ee (entries 4−12). Heteroaryl β-nitroacrylate could also be employed in this reaction to yield 96% ee (entry 13). The configuration of the electron-deficient olefins has significant influence on the stereoselectivity of the reaction. Control experiments (Scheme 1) afforded pure (*Z*)-**2o,** which reacted smoothly with **1b** and gave the corresponding product **3o** in 94% ee, while pure (*E*)-**2o** or the (*Z*)/(*E*)-mixture of **2o** (*Z*/*E* = 2:1) gave poor stereoinductions.

In addition, the absolute configuration of the conjugate addition product **3j** was unambiguously determined by X-ray crystallographic analysis, and the newly formed stereogenic center was assigned to be *S* accordingly.[14] Based on the experimental results and previous studies,[6b] we proposed possible transition state models for this transformation. As shown in Figure 1, the O−H group of the catalyst may activate the electrophile through hydrogen bonding interaction, and the oxime attack the *Si* face of the β-nitroacrylate to form the major stereoisomers.

---

(14) The configuration of **3j** was determined by X-ray crystallographic analysis. CCDC 784524 (**3j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/daa_request/cif.

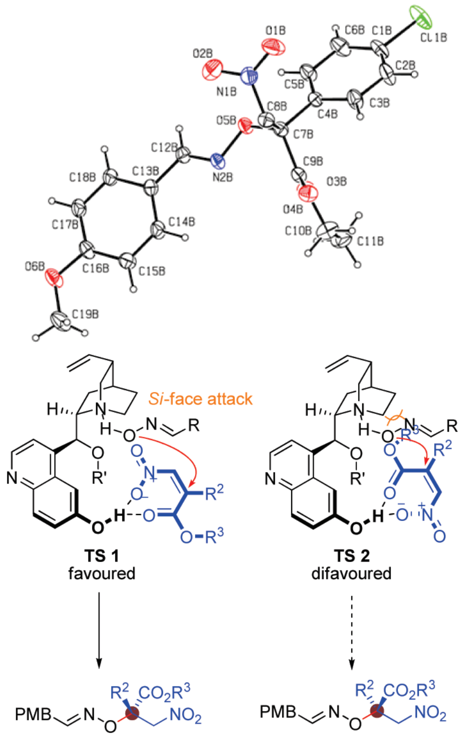
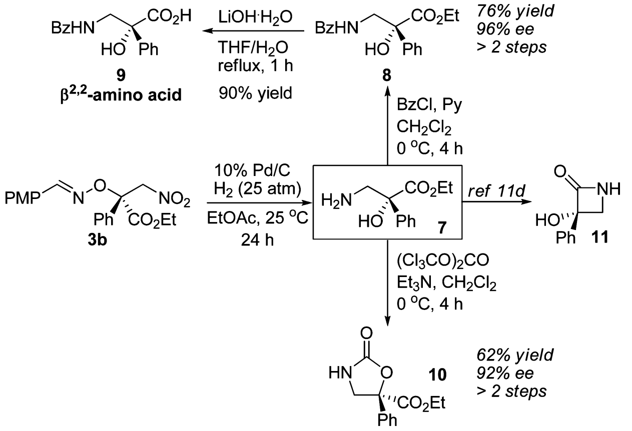


Figure 1. X-ray crystal structure of compound **3j** and proposed transition states (TS) of the conjugate addition reaction.

The addition adducts **3** from this protocol should be valuable building blocks for asymmetric synthesis, as they are highly functionalized with amenable nitro, ester and oxo groups. For example, cleavage of the weak N−O bond and simultaneous reduction of the nitro group under mild condition with 10% Pd/C/H_2 cleanly afforded an important α-hydroxy β-amino acid ester **7**. Subsequent protection with benzoyl chloride and hydrolysis of the ester group readily provided the highly desired a $\beta^{2,2}$-amino acid derivative **9**.

Scheme 2. Synthetic Applications of the Conjugate Addition Adducts



In addition, chiral oxazolidin-2-one **10**, and β-lactam **11**,[12d] could be conveniently accessed from **7** as well.

In conclusion, we have developed a rapid and efficient method for the catalytic enantioselective construction of tertiary alcohols through the intermolecular conjugate addition with synthetically useful enantioselectivities. The adducts produced by this technique are valuable precursors for accessing synthetically important chiral building blocks such as $\beta^{2,2}$-amino acids, oxazolidin-2-ones, β-lactams, etc.

Acknowledgment. We are grateful to the National Science Foundation of China (NO. 21072069 and 21002036) and the Program for Changjiang Scholars and Innovative Research Team in University (IRT0953) for support of this research.

Supporting Information Available: Experimental procedures and compound characterization data including X-ray crystal date (CIF file) for **3j**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102580N