JOC*Note*

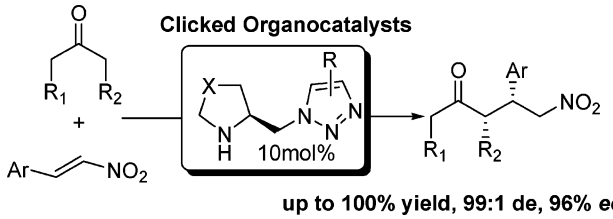
Evolution of Pyrrolidine-Type Asymmetric Organocatalysts by "Click" Chemistry

Sanzhong Luo,*[,†] Hui Xu,[†] Xueling Mi,[‡] Jiuyuan Li,[†] Xiaoxi Zheng,[†] and Jin-Pei Cheng*[,†,‡]

Beijing National Laboratory for Molecular Sciences, Center for Chemical Biology, Institute of Chemistry, Chinese Academy of Science, Beijing, 100080 China, and Department of Chemistry and State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, 300071 China

luosz@iccas.ac.cn; chengjp@mail.most.gov.cn

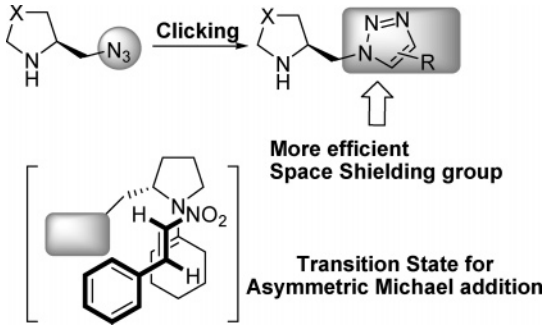
Received August 9, 2006



Click chemistry has been employed to construct a library of the pyrrolidine-type asymmetric organocatalysts. The clicked organocatalysts were evaluated in asymmetric Michael addition of ketones to nitroolefins, showing good catalytic activity and stereoselectivity (up to 100% yield, syn:anti = 99:1, 96% ee).

Ever since Gilbert Stork et al.'s seminal work in 1954,[1] enamine has become one of the most useful synthons in many organic transformations, and recently the enamine-based mechanism has also found many successful applications in a number of organocatalytic reactions.[2] Chiral pyrrolidine is now regarded as one of the best asymmetric organocatalysts of the type.[3] In 2000, List and co-workers reported that L-proline could catalyze an enantioselective direct Aldol reaction.[4] Later, many applications of the L-proline-catalyzed asymmetric organic synthesis were soon accumulated.[2] In some of the reactions, the natural catalysts such as L-proline failed to demonstrate good enantioselectivity and worked normally only for limited substrates.[5] Consequently, considerable efforts have been directed toward the development of a new type of asymmetric organocatalysts. Now, a sound improvement has already been achieved with chiral pyrrolidine-based catalytic systems. However, these pyrrolidine-type organocatalysts are generally more complex and therefore have to be prepared by multistep synthesis. In this context, a modular and more efficient approach for constructing a chiral pyrrolidine library with structural diversity to speed up the catalyst finding process is undoubtedly most desirable.[6]

SCHEME 1. Clicking Strategy for Asymmetric Organocatalysts



Because of its modularity, fidelity, and wide scopes, the so-called "click" chemistry has recently emerged as a powerful strategy for rapid assembly of organic molecules with diverse functionality.[7] Currently, click chemistry, represented by the 1,3-dipolar cycloaddition between azides and alkynes,[7b] has been applied in drug discovery for generating a drug-like library via the diversity-oriented approach,[8] in biological study as ligation chemistry, in material science, and so on.[9] In this work, we explored the utility of click chemistry as a modular approach for the construction of an organocatalyst-like library on the basis of the "privileged" chiral pyrrolidine skeletons (Scheme 1).

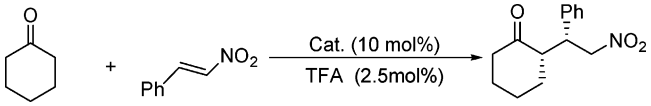
Asymmetric Michael addition was selected as the targeted model reaction for the clicked pyrrolidine library. Michael reaction is one of the basic C−C bond-forming reactions, and its versatile utility in organic synthesis has stimulated tremendous research interests in the development of asymmetric Michael catalysts, especially metal-free organocatalysts.[10] A variety of asymmetric organocatalysts have been explored for the Michael addition of ketones or aldehydes to nitroolefins, of which a few chiral pyrrolidinyl derivatives show high enantioselectivity.[11] In general, the pyrrolidine-catalyzed Michael addition occurs via an enamine intermediate, wherein efficient space shielding would be a key factor for stereo-control as suggested by literature[12] and our recent studies[13] (Scheme 1). On the basis of these observations, we envisioned that elaboration of chiral azido pyrrolidines (like that in pyrrolidine **CP-1**) into their triazole derivatives by click chemistry would provide a viable strategy for the discovery of better catalysts because the polar and planar triazole ring should be more efficient for space shielding than the small azido group (Scheme 1).

[†] Chinese Academy of Sciences.
[‡] Nankai University.

(1) Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029.
(2) For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (b) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley−VCH: Weinheim, 2005.
(3) List, B. *Chem. Commun.* **2006**, 819−824.
(4) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.
(5) (a) List, B. *Tetrahedron* **2002**, *58*, 5573−5590. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580−591.
(6) (a) Fonseca, M. H.; List, B. *Curr. Opin. Chem. Biol.* **2004**, *8*, 319−326. (b) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrehedron* **2002**, *58*, 8167−8177. (c) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 4369−4372.
(7) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
(8) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128−1137.
(9) For a review, see: Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200−1205.
(10) For a review, see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877−1894.

10.1021/jo061657r CCC: $33.50
Published on Web 11/04/2006

TABLE 1. Screening of Clicked Catalysts



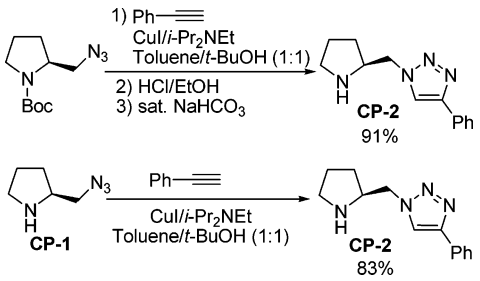
entry	catalyst (mol %)	time (h)	yield[a] (%)	dr[b]	ee[c] (%)	entry	catalyst (mol %)	time (h)	yield[a] (%)	dr[b]	ee[c] (%)
Initial Catalyst Discovery						12	**CP-10**	18	74	9:1	33
1[d]	L-proline	24	94	>20:1	23	13	**CP-11**	18	92	19:1	40
2	L-prolinol	24	23	20:1	78						
3	**CP-1**	24	34	20:1	80	Clicked Library II					
4	**CP-2**	18	99	49:1	92	14	**CP-12**	18	99	49:1	91
Clicked Library I						15	**CP-13**	20	56	49:1	91
5	**CP-3**	24	25	10:1	87	16	**CP-14**	18	97	19:1	90
6	**CP-4**	36	7	n.d.[e]	n.d.	17	**CP-15**	18	95	49:1	90
7	**CP-5**	70	trace	n.d.	n.d.	18	**CP-16**	18	99	49:1	89
8	**CP-6**	24	44	17:1	79	19	**CP-17**	18	99	49:1	92
9	**CP-7**	18	95	24:1	93	20	**CP-18**	18	90	49:1	90
10	**CP-8**	18	51	19:1	92	21	**CP-19**	18	87	49:1	91
11	**CP-9**	24	59	49:1	94	22	**CP-20**	24	90	49:1	87

[a] Isolated yields. [b] Syn/anti as determined by ^{1}H NMR. [c] Determined by HPLC (chiral pak AD-H column). [d] 15 mol % of L-proline was employed, see ref 14a. [e] Abbreviation n.d.= not determined.

Previously, L-proline has been shown to be a viable catalyst for Michael addition of ketones to nitroolefins but with low enantioselectivity (Table 1, entry 1).[14] We found that simple proline derivatives such as L-prolinol and azido-pyrrolidine **CP-1** were able to promote the same reaction with improved enantioselectivity, albeit in low yields (Table 1, entries 2 and 3). On the basis of these observations, we thought to further improve the catalyst by click chemistry based on the clicking hypothesis (Scheme 1). The pyrrolidine−triazole conjugate **CP-2** was easily accessed by reaction of azido-pyrrolidine **CP-1** or Boc-protected **CP-1** with phenylacetylene in high yields (Scheme 2).

To our delight, **CP-2** demonstrated high activity (18 h, 99% yield) and high stereoselectivity (Table 1, entry 4, syn/anti = 49:1, 92% ee). The Michael adduct obtained has the (1′S,2R) absolute stereochemistry by optical comparison with published results.[12,13] Therefore, the stereoselectivity can be explained by the transition state shown in Scheme 1, which is consistent with our initial hypothesis (Scheme 1). Next, libraries of the clicked pyrrolidines were successively constructed using the clicking protocol (see Supporting Information for details)[15] from the corresponding azido cores in order to identify more potent catalysts and to better understand the structure−activity relationships (Figure 1).

SCHEME 2. Synthesis of CP-2 by Click Reaction



First, we explored clicked catalysts with different chiral skeletons (Clicked Library I). As shown in Table 1, the performance of clicked catalysts vary dramatically with different skeletons where several features are evident: (1) The thiozolidine-type catalysts (**CP-3**−**5**) are ineffective in catalyzing the reaction (Table 1, entries 5−7). The reason for the failure of this type of catalysts is unclear presently, but warrants further theoretical study. (2) 4-*cis*-Substituted pyrrolidines (**CP-6**−**9**, Table 1, entries 8−11) showed better enantioselectivity than the 4-*trans*-substituted catalysts (**CP-10** and **CP-11**, Table 1, entries 12 and 13). The clicked catalyst **CP-10** with a bulky 4-*trans*-BnO group gave lower activity and enantioselectivity than its analogue **CP-11** (bearing a less bulky 4-OH group), suggesting the space-shielding effect is working in the reaction.

(11) For examples, see: (a) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737−3740. (b) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527. (c) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808−1809. (d) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84−96. (e) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611−3614. (f) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559−2561. (g) Mosse, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559−2562. (h) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (i) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem.−Eur. J.* **2006**, *12*, 4321−4332. (j) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077−3079. (k) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901−2904. (l) Xu, Y.; Cordova, A. *Chem. Commun.* **2006**, 1451−1453. (m) Xu, Y.; Zou, W.; Sunden, H.; Ibrahem, I.; Cordova, A. *Adv. Synth. Catal.* **2006**, *348*, 418−424. (n) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451−1453. (o) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170−7171. (p) Zhu, M.-L.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491−493. (q) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966−4967. (r) Terakado, D.; Takano, M.; Oriyama, T. *Chem. Lett.* **2005**, *34*, 962−963. (s) Enders, D.; Huttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861−863.

(12) (a) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558−9559. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212−4215. (c) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147−1168. (d) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611−614. (e) Betancort, J. M.; Sakthivel, K.; Thayumanava, R.; Tanaka, F.; Barbas, C. F., III. *Synthesis* **2004**, 1509−1521.

(13) (a) Luo, S. Z.; Mi, X. L.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093−3097. (b) Luo, S. Z.; Mi, X. L.; Liu, S.; Xu, H.; Cheng, J.-P. *Chem. Commun.* **2006**, 3687.

(14) (a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423−2425. (b) Enders, D.; Seki, A. *Synlett* **2002**, 26.

(15) For "click" reaction, that is, 1,3-dipolar cycloaddition between azides and alkynes with 1,4-regioselectivity, see ref 7b and (a) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. For 1,5-regioselectivity, see (b) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998−15999. (c) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237.

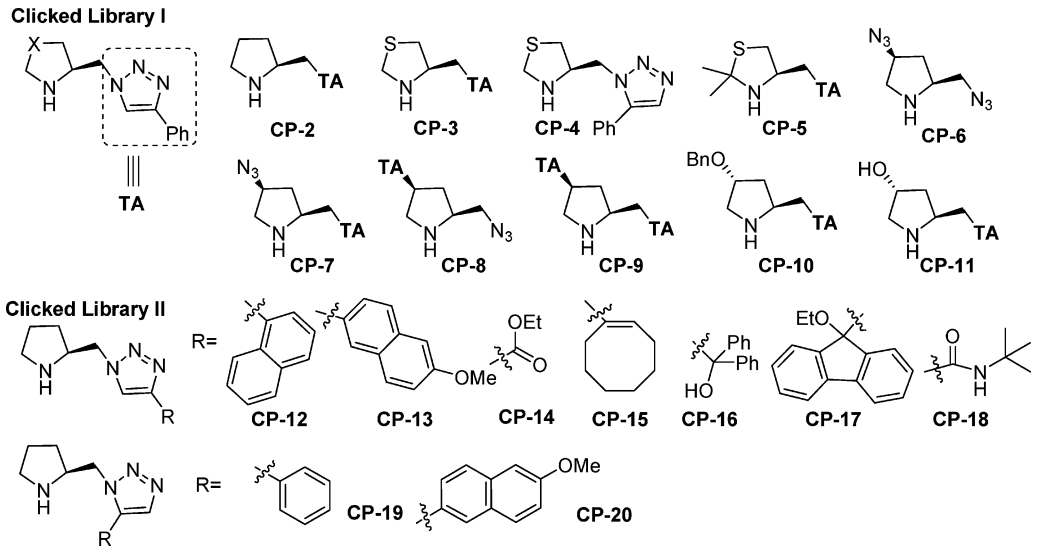


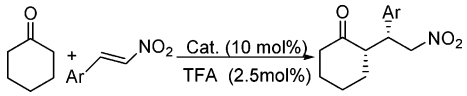
FIGURE 1. Library of clicked organocatalysts.

(3) And again, the clicked catalysts were found to exhibit superior performance to their azido precursors (**CP-7**−**9** vs **CP-6**, Table 1, entries 9−11 vs entry 8), validating our clicking strategy.

With the identified chiral pyrrolidinyl core, we next examined the substitute effect of the triazole rings. The Clicked Library II with variations on triazole rings were readily constructed by click reactions between **CP-1** and a variety of alkynes (Table 1). As revealed in Table 1, there is only a modest influence of the substitute patterns of triazole rings on the reaction (Table 1, entries 14−22). Most of the clicked catalysts demonstrated a similar performance to **CP-2**, but none of them were found to exceed the level of **CP-2** (9 representative catalysts out of 30 were shown in Figure 1). For example, clicked catalysts **CP-12**−**20** with varied substituents on the triazole rings gave comparable stereoselectivities (syn/anti = 19:1−49:1, 87%−92% ee) in the reactions (Table 1, entries 14−22). Both the position (**CP-2** vs **CP-19**, **CP-13** vs **CP-20**) and the nature of the substituents (**CP-12**−**18**) were shown to have little impact on the stereoselectivities. These results suggest that the substituents on the triazole rings might be oriented too far from the enamine intermediate to affect stereocontrol in the reaction. Overall, several clicked catalysts such as **CP-2**, **CP-7**, and **CP-17** gave the best outcomes in terms of both the activity and the selectivity. **CP-2** and **CP-7** were selected for further experiments since they were easily accessible.

With **CP-2** and **CP-7** as the selected catalysts, the scope of the Michael reaction was briefly explored (Table 2). In general, the reaction worked quite well with cyclohexanone to give the desired Michael adducts in high yields and excellent diaselectivity and enantioselectivity. Both electron-rich and electron-deficient nitrostyrenes were excellent Michael acceptors for cyclohexanone. A value of 10 mol % of the clicked catalyst was sufficient to promote the reactions, giving the desired Michael adducts in nearly quantitative yields. It was found that catalyst **CP-7** and **CP-2** worked equally well for the cases examined (Table 2, entries 1−6). The reactions of other Michael donors such as cyclopentanone, acetone, and *iso*-valeraldehyde were also attempted with **CP-2** (20 mol %) as the catalyst (Scheme 3). The reactions gave the desired Michael adducts in high yields but low enantioselectivities. The absolute configurations of the Michael adducts obtained were determined to be (1′S,2R) by comparison with the known products.[12,13] Therefore, the transition state shown in Scheme 1 should be applicable to all of these cases except to the reaction of *iso*-valeraldehyde.[16]

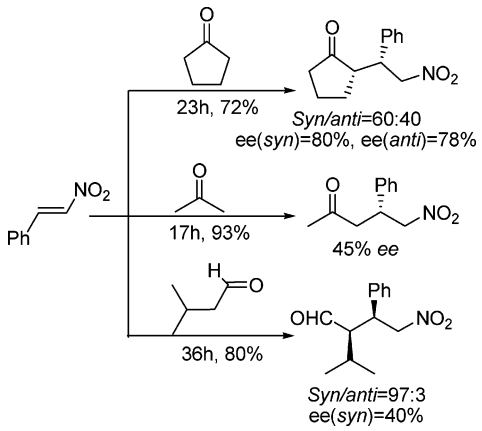
TABLE 2. Substrate Scope of the Clicked Catalysts



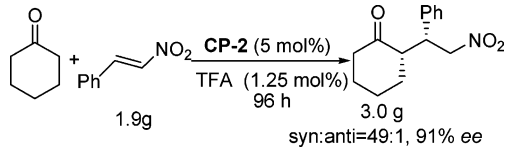
entry	Ar	catalyst	time (h)	yield[a] (%)	dr[b]	ee[c] (%)
1	Ph	**CP-2**	18	99	49:1	92
2	Ph	**CP-7**	17	95	24:1	93
3	4-ClPh	**CP-2**	18	93	49:1	93
4	4-ClPh	**CP-7**	18	>99	99:1	94
5	2-ClPh	**CP-2**	16	98	49:1	95
6	2-ClPh	**CP-7**	19	97	49:1	96
7	2-BrPh	**CP-2**	16	99	99:1	94
8	4-MePh	**CP-2**	22	99	49:1	93
9	4-MeOPh	**CP-7**	38	95	49:1	90
10	Piperal	**CP-2**	24	98	49:1	94
11	2,4-(MeO)2Ph	**CP-2**	24	93	99:1	93
12	2-Naphth	**CP-2**	22	99	99:1	93

[a] Isolated yields. [b] Syn/anti as determined by ^{1}H NMR. [c] Determined by HPLC (chiral pak AD-H column).

SCHEME 3. CP-2 Catalyzed Michael Addition to Nitrostyrene



SCHEME 4. Gram-Scale Synthesis Catalyzed by CP-2



Finally, the practical application of clicked asymmetric organocatalyst was demonstrated in a gram-scale synthesis using only 5 mol % of **CP-2** as the catalyst (Scheme 4). The reaction afforded the chiral Michael product in a nearly quantitative yield and high stereoselectivity.

In conclusion, we have developed a clicking strategy for the discovery of new asymmetric organocatalysts. The modular and versatile nature of the click chemistry allows for a rapid synthesis of a library of organocatalysts that should largely facilitate catalyst discovery and structure−activity study. Using the clicking strategy, we proved pyrrolidine−triazole conjugates to be a modular skeleton for the asymmetric Michael addition of cyclohexanone to nitrostyrenes. **CP-2** and **CP-7** were found to catalyze the reaction with high reactivity (up to 100% yield) and excellent stereoselectivity (syn/anti up to 99:1, ee up to 96%). Works are currently underway to further optimize the current clicked asymmetric organocatalysts and to apply the clicking strategy to other asymmetric organocatalytic processes.

Experimental Section

Representative Procedure for the Click Reaction (Scheme 2): Method A. To a solution of Boc-protected **CP-1** (226 mg, 1 mmol) in toluene and *tert*-butanol (4 mL and 1 mL, respectively) were added phenylacetylene (122 mg, 1.2 mmol), CuI (10 mg, 0.05 mmol), and *N*,*N*′-diisopropylethylamine (DIPEA) (170 μL, 2 mmol). The reaction mixture was stirred at rt overnight. After removal of the solvent under vacuo, the residue was purified by flash chromatography on silica gel to afford a Boc-protected product as a white solid (314 mg, yield of 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37−1.65 (10H, m), 1.67−1.83 (1H, m), 1.89−2.07 (2H, m), 3.08−3.50 (2H, m), 4.15 (1H, s), 4.37−4.79 (2H, m), 7.29−7.38 (1H, m), 7.38−7.48 (2H, m), 7.62−7.90 (3H, m). The clicked product was deprotected in 5 M HCl in ethanol to give the hydrogen chloride salts and was subsequently dissolved in CH_2Cl_2 (5 mL) and then treated with a saturated $NaHCO_3$ solution (15 mL). This mixture was stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo after filtration to give essentially pure **CP-2** as pale yellow solid (301 mg, 96%). $[\alpha]_D^{rt}$ +41° (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35−1.52 (1H, m), 1.58−1.83 (3H, m), 1.85−1.99 (1H, m), 2.89 (2H, t, J = 6.6 Hz), 3.51−3.64 (1H, m), 4.11−4.21 (1H, dd, J = 7.9 Hz, 7.7 Hz, 13.8 Hz), 4.35−4.44 (1H, dd, J = 4.5 Hz, 4.3 Hz, 13.4 Hz), 7.21−7.30 (1H, t, J = 7.5 Hz), 7.35 (2H, t, J = 7.4 Hz), 7.77 (2H, t, J = 7.3), 7.86 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.5, 29.1, 46.6, 55.5, 58.0, 120.5, 125.7, 128.0, 128.8, 130.7, 147.5; HRMS for $C_{13}H_{17}N_4^+$ (M + 1$^+$) calcd, 229.1448; found, 229.1446.

Method B. To a solution of Boc-protected **CP-1** (452 mg, 2 mmol) in CH_2Cl_2 (5 mL) was added dropwise TFA (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight. After removal of the organic solvents under vacuo, the residue was dissolved in CH_2Cl_2 (5 mL) and then treated with a saturated $NaHCO_3$ solution (15 mL) for 1 h at rt. The aqueous layer was extracted with CH_2Cl_2 three times (5 mL × 3), and the combined extracts were dried over anhydrous Na_2SO_4. Concentration in vacuo after filtration gave **CP-1** as yellow oil (438 mg, 97%). $[\alpha]_D^{rt}$ −32° (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35−1.50 (1H, m), 1.66−2.00 (3H, m), 2.44−2.61 (1H, m), 2.86−3.04 (2H, m), 3.17−3.39 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.5, 29.0, 46.6, 56.2, 57.7; HRMS for $C_5H_{11}N_4^+$ (M + 1$^+$) calcd, 127.0984; found, 127.0982.

To a solution of **CP-1** (438 mg) and phenylacetylene (245 mg, 2.4 mmol) in a mixed solvent of toluene (8 mL) and *tert*-butanol (2 mL) were added CuI (20 mg, 10 mmol) and DIPEA (500 μL, 6 mmol). The reaction mixture was stirred at room temperature overnight. After removal of the solvents, the resulting residue was purified by flash chromatography on silica gel to give **CP-2** as a yellow solid (365 mg, 83%).

Procedure for the Michael Reaction. Nitrostyrene (37 mg, 0.25 mmol) and **CP-2** (12 mg, 10 mol %) were mixed with cyclohexanone (0.5 mL, 5 mmol) in the presence of TFA (0.00625 mmol) at room temperature (bulk solution of TFA in cyclohexanone was freshly prepared and employed in the reaction, 20 μL of TFA in 50 mL of cyclohexanone). The homogeneous reaction mixture was stirred at room temperature for 18 h. The reaction mixture was directly loaded onto a silica gel column to afford the Michael adduct **1** (61 mg, 99%) as a white solid:[11−13] $[\alpha]_D^{rt}$ −15.2° (*c* 0.5, CH_3OH), syn/anti = 49:1 (by ^{1}H NMR), 92% ee (by HPLC on a chiral phase chiralpak AD-H column, λ = 254 nm, *i*PrOH/hexane 10:90, 20 °C, 0.5 mL min^{-1}; t_R = 22.7 min (minor), 29.4 min (major)).

Acknowledgment. This work was supported by the Natural Science Foundation of China (NSFC 20452001, 20421202, and 20542007), the Ministry of Science and Technology (MoST), and the Institute of Chemistry, Chinese Academy of Sciences (ICCAS). We thank Prof. Mei-Xiang Wang and Prof. Dong Wang for HPLC analysis.

Supporting Information Available: Synthesis of **CP-1**−**20**, general experimental procedures, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061657R

(16) The Michael adduct of *iso*-valeraldehyde has (1′R,2S) absolute configuration, and an *anti*-enamine intermediate would be formed in the reaction.