Organocatalysis

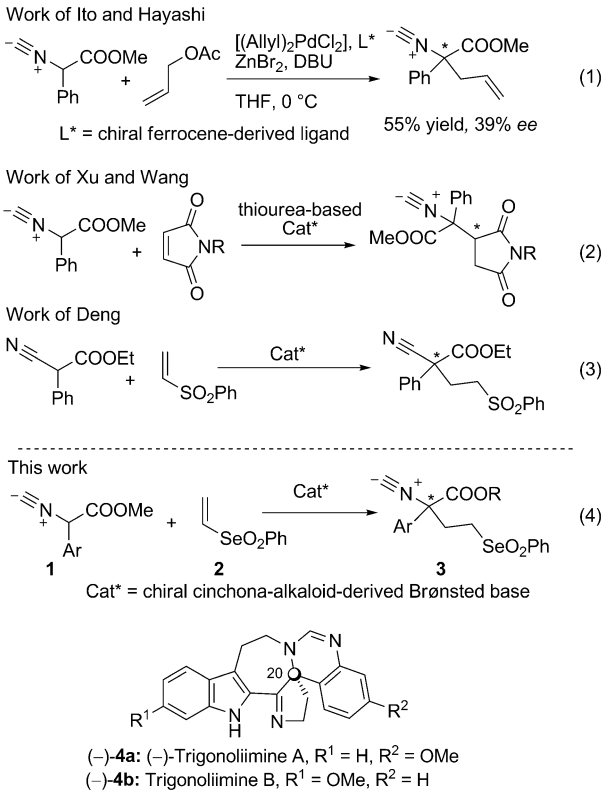
DOI: 10.1002/anie.201306663

Catalytic Enantioselective Michael Addition of α-Aryl-α-Isocyanoacetates to Vinyl Selenone: Synthesis of α,α-Disubstituted α-Amino Acids and (+)- and (−)-Trigonoliimine A**

*Thomas Buyck, Qian Wang, and Jieping Zhu**

α-Isocyanoacetates are well-known glycine templates for the synthesis of racemic α,α-disubstituted α-amino acids.[1] However, catalytic enantioselective alkylation of α-isocyanoacetates remains underexploited. Ito, Hayashi, and co-workers pioneered the field by discovering the first palladium-catalyzed enantioselective allylation of methyl α-phenyl-α-isocyanoacetate [Eq. (1), Scheme 1; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene].[2] The enantioselectivity of this reaction was, however, moderate (< 39% *ee*). In contrast, a number of Lewis-acid- and small-organomolecule-catalyzed enantioselective [2+3] cycloadditions of α-isocyanoacetates with aldehydes,[3] imines,[4] azodicarboxylates,[5] and polarized carbon–carbon double bonds, such as nitroalkenes,[6] α,β-unsaturated ketones,[7] and maleimides,[8] have been developed to access enantioenriched five-membered heterocycles. In contrast, catalytic enantioselective Michael addition of α-isocyanoacetates was met with only limited success. Indeed, it has been established that any Lewis acid catalyzed nucleophilic addition of α-isocyanoacetates to polarized double bonds inevitably provided the [2+3] cycloadducts. The same trend holds true for organocatalytic processes.[8] However, a recent paper from Xu, Wang, and co-workers[9] on a tertiary amine thiourea catalyzed enantioselective Michael addition of α-phenyl-α-isocyanoacetate to N-aryl maleimides demonstrated that the aforementioned reaction can be stopped at the Michael adduct stage under appropriate reaction conditions [Eq. (2), Scheme 1].

In connection with our ongoing total synthesis project, we needed rapid access to enantiomerically enriched α-aryl-α-(2′-FG-alkyl)-α-amino acids (FG = functional group).[10] We were aware of the seminal contributions of Deng and co-workers on the enantioselective Michael addition of α-phenyl-α-cyanoacetate to vinyl phenylsulfone and the subsequent conversion of the enantiomerically enriched adduct into α,α-disubstituted amino acids [Eq. (3), Scheme 1].[11] However, six steps were needed to convert both the cyano and sulfone groups into other organic residues. Stimulated by this observation, we became interested in examining the chiral Brønsted base catalyzed nucleophilic addition of α-aryl-α-isocyanoacetates (**1**) to vinyl phenyl selenone (**2**)[12–14] for the synthesis of the enantiomerically enriched α-aryl-α-(2′-FG-alkyl)-α-amino acids **3** [Eq. (4), Scheme 1].[15] The advantage of this approach is that the resulting adduct can be readily converted into an array of functionalized amino acids. Indeed, phenylselenonyl is an excellent leaving group,[16] while the isocyano group is easily hydrolyzed under mild acidic conditions into the free amino function. We report herein the successful development of an organocatalytic enantioselective Michael addition of **1** to **2** for the synthesis of the enantiomerically enriched α,α-disubstituted α-isocyanoacetates **3** and their subsequent transformations into the linear and the cyclic quaternary α-amino acids. Enantioselective total syntheses of both (+)- and (−)-trigonoliimine A [(+)-**4a** and (−)-**4a**][17] featuring this key transformation is also documented.



Scheme 1. Enantioselective alkylation of α-aryl-α-isocyanoacetates.

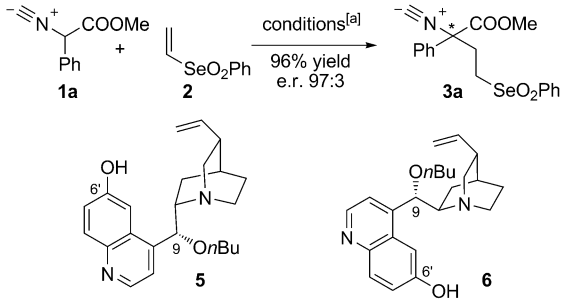
Various cinchona-derived bifunctional organocatalysts were screened for the reaction depicted in Equation (4)

[*] T. Buyck, Dr. Q. Wang, Prof. Dr. J. Zhu
Laboratory of Synthesis and Natural Products
Institute of Chemical Sciences and Engineering
Ecole Polytechnique Fédérale de Lausanne
EPFL-SB-ISIC-LSPN, CH-1015 Lausanne (Switzerland)
E-mail: jieping.zhu@epfl.ch

[**] Financial support from EPFL (Switzerland), Swiss National Science Foundation (SNSF), the COST action (CM0905), and Swiss State Secretariat for Education and Research (SER) are gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201306663.

(Ar = Ph). The results (for details, see the Supporting Information) allowed us to draw the following conclusions: a) The reaction is best carried out in a nonpolar aprotic solvent in the presence of 4 Å molecular sieves;[6–8] b) The alkyl residue of the ester impacted the *ee* value of the reaction with the following trend being clearly observable: methyl ester > ethyl ester > *tert*-butyl ester; c) The presence of an hydrogen-bond donor function at C6′ of the cinchona alkaloids is essential and quinine derivatives having an OH at C6′ displayed better enantiodiscriminating power than those bearing amido and thioureido groups at 6′.[18] However, β-ICD and its derivatives were ineffective;[19] d) The alkyl residue introduced to the C9 OH group of quinine also influenced the *ee* value of the reaction with an *n*Bu group being optimal. Overall, the optimum reaction conditions involve performing the reaction of **1a** (Ar = Ph) and **2** in toluene (*c* 0.25 M) in the presence of the catalyst **5** (0.1 equiv) and molecular sieves at −40 °C (Scheme 2). Under these



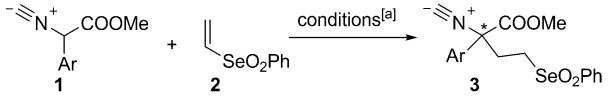
Scheme 2. Enantioselective Michael addition of **1a** to **2**. [a] **1** (1.5 equiv), **2** (1.0 equiv), **5** (0.1 equiv), 4 Å M.S., toluene, *c* = 0.25 M, −40 °C. M.S. = molecular sieves.

reaction conditions, the Michael adduct **3a** was isolated in 96% yield with an excellent enantioselectivity (e.r. 97:3). When the quinidine derivative **6**, a pseudoenantiomer of **5**, was used as a catalyst under otherwise identical reaction conditions, the reaction of **1a** and **2** afforded *ent*-**3a** in quantitative yield with an e.r. of 7.4:92.6.

The scope of the present catalytic enantioselective Michael addition was next examined by varying the aryl substituent of the methyl α-isocyanoacetate (Table 1). The presence of electron-donating and electron-withdrawing substituents at the *ortho*, *meta*, and *para* position of the phenyl ring is tolerated (entries 2–12). However, those bearing an electron-donating substituent (entries 2 and 3) afford, in general, the Michael adducts with a higher e.r. value than those having electron-withdrawing group (entries 4–12). The α-heteroaryl α-isocyanoacetates participated in the reaction efficiently to provide adducts in excellent yields and enantioselectivities (entries 13 and 14).

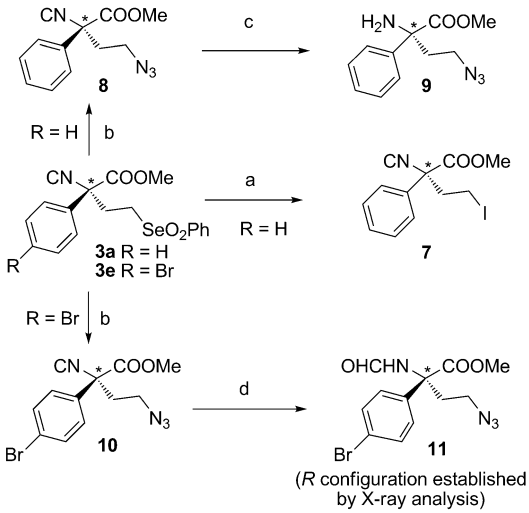
Some basic transformations taking advantage of the reactivity of the isocyano and phenylselenonyl groups were undertaken (Scheme 3). Treatment of **3a** with sodium iodide in acetone at room temperature or with sodium azide in DMF at 40 °C afforded the iodide **7** (99%) and azide **8** (86%), respectively. The compound **8** was further hydrolyzed under

Table 1: Scope of catalytic enantioselective Michael addition of α-aryl-α-isocyanoacetate to vinyl phenylselenone.



Entry	Ar	Product	Yield [%]	e.r.[b]
1	Ph	**3a**	96	97:3
2	4-MeC_6H_4	**3b**	95	97.9:2.1
3	4-$MeOC_6H_4$	**3c**	96	96.9:3.1
4	4-FC_6H_4	**3d**	92	95.8:4.2
5	4-BrC_6H_4	**3e**	92	94.5:5.5
6	3-BrC_6H_4	**3f**	93	90.5:9.5
7	4-$CF_3C_6H_4$	**3g**	96	92.8:7.2
8	4-$NO_2C_6H_4$	**3h**	95	87.3:12.7
9	2-NO_2-4-$OMeC_6H_4$	**3i**	62	93.5:6.5[c]
10	2-FC_6H_4	**3j**	96	93.7:6.3[d]
11	2-NO_2	**3k**	90	89.5:10.5[d]
12	2,4-diFC_6H_3	**3l**	90	91.1:8.9[d]
13	3-furanyl	**3m**	94	97.3:2.7
14	2-furanyl	**3n**	96	97.1:2.9

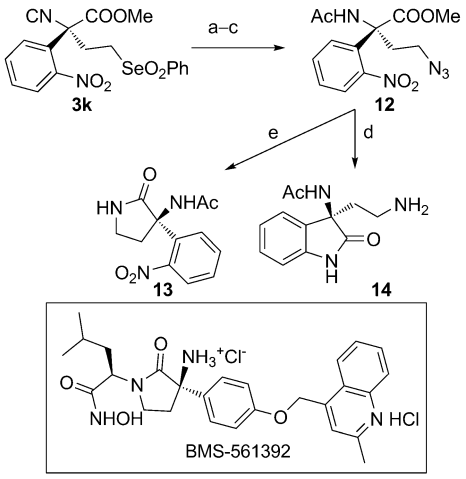
[a] **1** (1.5 equiv), **2** (1.0 equiv), **5** (0.1 equiv), 4 Å M.S., toluene, *c* = 0.25 M, −40 °C. [b] Determined by SFC analysis on a chiral stationary phase. [c] Reaction performed at −10 °C. [d] Reaction performed at −20 °C.



Scheme 3. Transformations and determination of absolute configuration of **11**. Conditions: a) NaI, acetone, RT, 99%; b) NaN_3, DMF, 40 °C, 86% for **8**; 76% for **10**; c) 1 N HCl, in MeOH, 81%; d) 1 N HCl in Et_2O, 70%. DMF = *N*,*N*-dimethylformamide.

mild reaction conditions (1N HCl in MeOH) to the methyl α-phenyl-α-(2-azidoethyl)-α-aminoester (**9**) in 81% yield. As it can be expected, no racemization was observed during these transformations (see the Supporting Information). To determine the absolute configuration of these adducts, **3e**, bearing a 4-bromophenyl substituent, was converted into the more crystalline N-formamide derivative **11** via the azido intermediate **10**. X-ray crystallographic analysis allowed assignment of the absolute configuration of **11**, and hence that of **3e**, to be *R* (Scheme 3). Consequently, the absolute configuration of all adducts shown in Table 1 was tentatively assigned to be *R* by analogy.

The synthetic potential of the α-aryl-α-(2′-phenylselenonylethyl)-α-isocyanoacetates **3** was further demonstrated by their transformations into important heterocycles as shown in Scheme 4. Treatment of **3k** with sodium azide and subsequent



Scheme 4. Derivatization to chiral 3,3-disubstituted oxindole and pyrrolidinone: a) NaN_3, DMF, 40 °C, 69%; b) HCl in MeOH, RT, 81%; c) Ac_2O, CH_2Cl_2, RT, quant; d) Raney nickel, H_2, MeOH, RT, 72%; e) PPh_3, THF/H_2O (5:1), 50 °C, 77%. THF = tetrahydrofuran.

hydrolysis of the isocyano group and N acetylation of the resulting primary amine afforded the compound **12**. Hydrogenation of **12** in the presence of Raney nickel directly afforded the 3-acetamido-3′-(2-aminoethyl) oxindole **14** in 72% yield. In contrast, selective reduction of azido group under Staudinger conditions (PPh_3, THF/H_2O, 50 °C) provided the 2,2-disubstituted pyrrolidinone **13**, which is the core structure of BMS-561392, a potent and selective TNF-α-convertase enzyme inhibitor.[20]

The key role played by the OH group at C6′ of **5** in the enantioselective addition implied that it might be involved in the hydrogen bonding with the substrate. Since the divalent carbon atom of the isocyano group has a strong tendency to form hydrogen bonds with even a slightly acidic proton,[21] a stereochemical model (Figure 1) implicating a *Z* enolate of methyl α-isocyanoacetate[3e] was proposed based on previous observations that protonated cinchona alkaloids adopted, in nonpolar solvent, an *anti* open conformer.[22] The OH group at C6′ formed hydrogen bonds with both the ester and the selenone groups, thus defining the positioning of the two reactants. A pseudo-intramolecular *Si*-face attack of enolate to the vinyl selenone would deliver, after protonation, the Michael adduct with an absolute configuration of *R*. In this working model, the ester moiety has a steric interaction with the quinoline subunit of the catalyst. Therefore, increasing the size of the R group would destabilize this transition state, thus leading to a diminished enantioselectivity. This trend was indeed observed as the reaction involving *tert*-butyl α-isocyanoacetate gave the product with a much lower e.r. value than that obtained with the methyl counterpart.

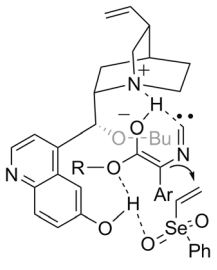
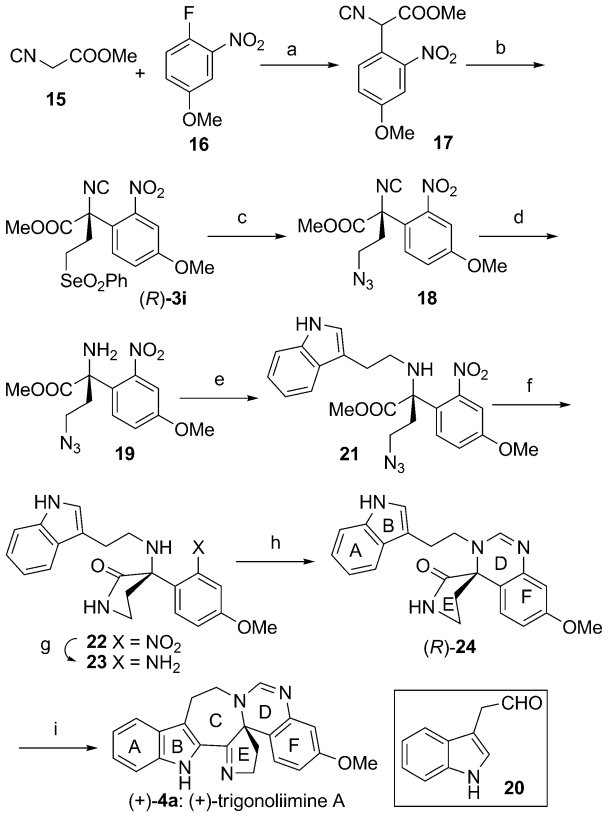


Figure 1. Possible transition-state model consistent with the observed stereoselectivity.

Trigonoliimines A and B (**4**, Scheme 1) were isolated by Hao in 2010 from the leaves of *Trigonostemon lii* Y. T. Chang collected in the Yunnan Province of China.[17] Structurally, trigonoliimines A and B contain a quaternary carbon atom whose four substituents are crosslinked to form five-, six-, and seven-membered tricyclic cores of the hexacyclic structure. The fascinating molecular architecture of trigonoliimines has attracted the attention of synthetic chemists.[23,24]

An asymmetric total synthesis of (+)-trigonoliimine A [(+)-**4a**] by applying the so-developed enantioselective Michael addition as a key element is depicted in Scheme 5. The S_NAr reaction between methyl α-isocyanoacetate (**15**) and 4-methoxy-2-nitrofluorobenzene (**16**)[25] afforded the desired methyl α-(4′-methoxy-2′-nitro)phenyl-α-isocyanoacetate (**17**) in 74% yield. Catalytic enantioselective Michael addition of **17** to vinyl phenylselenone (**2**) under the standard reaction conditions afforded the adduct **3i** in 62% yield (e.r. 93.5:6.5). Nucleophilic displacement of the phenylselenone by sodium azide afforded **18**, which was converted, upon acidic treatment, into the quaternary α-amino ester **19** in 94%



Scheme 5. Reagents and conditions: a) Cs_2CO_3 (1.5 equiv), DMSO, 76%; b) **2**, **5** (0.1 equiv), toluene, 4 Å M.S., −10 °C, 62%, e.r. 93.5:6.5; c) NaN_3, DMF, RT, 94%; d) HCl, MeOH, quantitative; e) **20**, $NaBH(OAc)_3$, CH_2Cl_2, 73%; f) PPh_3, THF/H_2O, 60 °C, 78%; g) H_2, Raney Ni, MeOH, RT, 84%; h) PPTS, $HC(OMe)_3$, 60 °C, 66%; i) $POCl_3$, sulfolane, 80 °C, 54%. DMSO = dimethylsulfoxide, PPTS = pyridinium *para*-toluenesulfonate.

yield over two steps. Reductive alkylation of **19** with 2-(1*H*-indol-3-yl)acetaldehydealdehyde (**20**) provided **21**. Staudinger reduction of the azide was followed by spontaneous lactamization to furnish the γ-lactam **22** in 78% yield. Reduction of nitro group followed by the treatment of resulting diamine **23** with trimethyl orthoformate (PPTS, 60°C) yielded the spirocycle **24** without event.

To complete the synthesis, the Bischler–Napieralski reaction was envisioned to close the remaining seven-membered ring.[26] To the best of our knowledge, there was no example, prior to our work on the synthesis of trigonoliimine B, in the literature dealing with the formation of a hexahydroazepino[4,5-*b*]indole skeleton with the concurrent formation of an exo-imine function.[23c] Application of our previously developed conditions to **24** afforded the desired product in only 20% yield, and was accompanied by degradation. Therefore, the reaction conditions were reoptimized by varying the stoichiometry and concentration of the reaction. Gratefully, under optimum reaction conditions (sulfolane, $c = 0.025$ M, $POCl_3$ (40.0 equiv), 80°C, 70 h), the (+)-**4a** was isolated in 54% yield. All spectroscopic data for our synthetic product are in perfect agreement with those reported in the literature. The sign of specific rotation of our synthetic sample ($[\alpha]_D = +225$ ($c = 0.3$, $CHCl_3$, e.r. 92:8) is opposite to that of Movassaghi's synthetic compound ($[\alpha]_D = -294$ ($c = 0.24$, $CHCl_3$, e.r. 97:3), thus indicating the *R* configuration at C20 for our synthetic sample. Following exactly the same synthetic sequence using quinidine derivative **6** as a bifunctional catalyst, (−)-trigonoliimine A [(+)-**4a**] ($[\alpha]_D = -189$, $c = 0.29$, $CHCl_3$, e.r. 86.5:13.5) was synthesized in 6.8% overall yield.

In conclusion, a catalytic enantioselective cinchona-alkaloid-catalyzed Michael addition between methyl α-aryl-α-isocyanoacetates and vinyl phenylselenone has been developed. The resulting enantioenriched α-aryl-α-(2′-phenylselenonylethyl)-α-isocyanoacetates **3** were subsequently converted into α-aryl-α-(2′-FG-alkyl)-α-amino acids and medicinally important heterocycles such as oxindoles and pyrrolidinones. A concise total synthesis of (+)- and (−)-trigonoliimine A(nine steps, overall yield 7.5% and 6.8%, respectively) was completed using the Michael adduct **3i** as a starting material.[27] The successful cyclization of **24** into the natural product **4a** further illustrates the power of the Bischler–Napieralski reaction for the formation of a seven-membered ring with concurrent creation of an exo-imine function, a hitherto unknown transformation.

Experimental Section

Typical procedure: A solution of methyl α-phenyl-α-isocyanoacetate (**1a**; 18.3 mg, 1.0 mmol) in toluene (0.2 mL) was added to a solution of vinyl phenylselenone (**2**; 15.0 mg, 0.07 mmol), **5** (2.6 mg, 10 mol%), 4 Å molecular sieves (8.0 mg) in toluene (0.1 mL) at −40°C . After being stirred at −40°C for 20 h, the reaction mixture was directly submitted to column chromatography (petroleum ether/ethyl acetate 7:3 to 3:7) to afford **3a** (26.1 mg, 96%, e.r. 97:3). ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 7.99$–7.92 (m, 2H), 7.79–7.72 (m, 1H), 7.70–7.63 (m, 2H), 7.50–7.39 (m, 5H), 3.79 (s, 3H), 3.51 (ddd, $J = 12.2$, 11.9, 5.7 Hz, 1H), 3.30 (ddd, $J = 12.2$, 11.5, 5.4 Hz, 1H), 2.99–2.83 ppm (m, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$): $\delta = 166.9$, 163.6, 141.0, 134.9, 132.8, 130.7, 130.0, 129.7, 127.1, 124.9, 69.5, 54.6, 54.1, 32.3 ppm. ATR-IR $\tilde{\nu}$ =3063 (w), 2958 (w), 2135 (m), 1748 (s), 1447 (m), 1254 (s), 1165 (w), 1065 (w), 941 (s), 886 (s), 731 (s), 697 (m), 687 (s); HRMS (ESI) calcd for $C_{18}H_{18}NO_4Se^+$ $[M+H]^+$ 392.0396; found 392.0409.

Received: July 30, 2013
Published online: October 11, 2013

Keywords: asymmetric synthesis · heterocycles · natural products · organocatalysis · selenium

[1] S. Kotha, S. Halder, *Synlett* **2010**, 337–354.
[2] Y. Ito, M. Sawamura, M. Matsuoka, Y. Matsumoto, T. Hayashi, *Tetrahedron Lett.* **1987**, *28*, 4849–4852.
[3] a) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406; b) S. D. Pastor, A. Togni, *J. Am. Chem. Soc.* **1989**, *111*, 2333–2334; c) A. V. Soloshonok, T. Hayashi, K. Ishikawa, N. Nagashima, *Tetrahedron Lett.* **1994**, *35*, 1055–1058; d) M.-X. Xue, C. Guo, L.-Z. Gong, *Synlett* **2009**, 2191–2197; e) H. Y. Kim, K. Oh, *Org. Lett.* **2011**, *13*, 1306–1309; f) F. Sladojevich, A. Trabocchi, A. Guarna, D. J. Dixon, *J. Am. Chem. Soc.* **2011**, *133*, 1710–1713; g) M.-X. Zhao, H. Zhou, W.-H. Tang, W.-S. Qu, M. Shi, *Adv. Synth. Catal.* **2013**, *355*, 1277–1283.
[4] a) T. Hayashi, E. Kishi, V. A. Soloshonok, Y. Uozumi, *Tetrahedron Lett.* **1996**, *37*, 4969–4972; b) X.-T. Zhou, Y.-R. Lin, L.-X. Dai, J. Sun, L.-J. Xia, M.-H. Tang, *J. Org. Chem.* **1999**, *64*, 1331–1334; c) J. Aydin, A. Ryden, K. J. Szabo, *Tetrahedron: Asymmetry* **2008**, *19*, 1867–1870; d) Z.-W. Zhang, G. Lu, M.-M. Chen, N. Lin, Y.-B. Li, T. Hayashi, A. S. C. Chan, *Tetrahedron: Asymmetry* **2010**, *21*, 1715–1721; e) S. Nakamura, Y. Maeno, M. Ohara, A. Yamamura, Y. Funahashi, N. Shibata, *Org. Lett.* **2012**, *14*, 2960–2963.
[5] D. Monge, K. L. Jensen, I. Marin, K. A. Jørgensen, *Org. Lett.* **2011**, *13*, 328–331.
[6] C. Guo, M.-X. Xue, M.-K. Zhu, L.-Z. Gong, *Angew. Chem.* **2008**, *120*, 3462–3465; *Angew. Chem. Int. Ed.* **2008**, *47*, 3414–3417.
[7] a) C. Arróniz, A. Gil-González, V. Semak, C. Escolano, J. Bosch, M. Amat, *Eur. J. Org. Chem.* **2011**, 3755–3760; b) J. Song, C. Guo, P.-H. Chen, J. Yu, S.-W. Luo, L.-Z. Gong, *Chem. Eur. J.* **2011**, *17*, 7786–7790; c) L.-L. Wang, J.-F. Bai, L. Peng, L.-W. Qi, L.-N. Jia, Y.-L. Guo, X.-Y. Luo, X.-Y. Xu, L.-X. Wang, *Chem. Commun.* **2012**, *48*, 5175–5177.
[8] a) M.-X. Zhao, D.-K. Wei, F.-H. Ji, X.-L. Zhao, M. Shi, *Chem. Asian J.* **2012**, *7*, 2777–2781; b) S. Padilla, J. Adrio, J. C. Carretero, *J. Org. Chem.* **2012**, *77*, 4161–4166.
[9] J.-F. Bai, L.-L. Wang, L. Peng, Y.-L. Guo, L.-N. Jia, F. Tian, G.-Y. He, X.-Y. Xu, L.-X. Wang, *J. Org. Chem.* **2012**, *77*, 2947–2953.
[10] Recent reviews on α,α-disubstituted amino acids: a) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569–623; b) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406–430.
[11] a) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949; b) H. Li, J. Song, L. Deng, *Tetrahedron* **2009**, *65*, 3139–3148.
[12] a) S. Sternativo, A. Calandriello, F. Costantino, L. Testaferri, M. Tiecco, F. Marini, *Angew. Chem.* **2011**, *123*, 9554–9557; *Angew. Chem. Int. Ed.* **2011**, *50*, 9382–9385; b) S. Sternativo, O. Walczak, B. Battistelli, L. Testaferri, F. Marini, *Tetrahedron* **2012**, *68*, 10536–10541.
[13] a) F. Marini, S. Sternativo, F. Del Verme, L. Testaferri, M. Tiecco, *Adv. Synth. Catal.* **2009**, *351*, 103–110; b) F. Marini, S. Sternativo, F. Del Verme, L. Testaferri, M. Tiecco, *Adv. Synth. Catal.* **2009**, *351*, 1801–1806.
[14] a) T. Zhang, L. Cheng, S. Hameed, L. Liu, D. Wang, Y.-J. Chen, *Chem. Commun.* **2011**, *47*, 6644–6646; b) M.-X. Zhao, W.-H.

Tang, M.-X. Chen, D.-K. Wei, T.-L. Dai, M. Shi, *Eur. J. Org. Chem.* **2011**, 6078 – 6084.
[15] Enantioselective alkylation of an aldimine glycine template: a) M. J. O'Donnell, S. Wu, *Tetrahedron: Asymmetry* **1992**, *3*, 591 – 594; b) B. Lygo, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **1999**, *40*, 8671 – 8674; c) T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228 – 5229.
[16] a) M. Tiecco, L. Testaferri, A. Temperini, R. Terlizzi, L. Bagnoli, F. Marini, C. Santi, *Org. Biomol. Chem.* **2007**, *5*, 3510 – 3351; b) M. Tiecco, A. Carlone, S. Sternativo, F. Marini, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2007**, *119*, 7006 – 7009; *Angew. Chem. Int. Ed.* **2007**, *46*, 6882 – 6885; c) for a review, see: F. Marini, S. Sternativo, *Synlett* **2013**, 11 – 19.
[17] C.-J. Tan, Y.-T. Di, Y.-H. Wang, Y. Zhang, Y.-K. Si, Q. Zhang, S. Gao, X.-J. Hu, X. Fang, S.-F. Li, X.-J. Hao, *Org. Lett.* **2010**, *12*, 2370 – 2373.
[18] Pioneering work on the OH functional group at C6′ of the cinchona-alkaloid-derived bifunctional catalysts: a) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906 – 9907; b) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107 – 110; *Angew. Chem. Int. Ed.* **2005**, *44*, 105 – 108; c) F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem.* **2006**, *118*, 961 – 964; *Angew. Chem. Int. Ed.* **2006**, *45*, 947 – 950; d) H. Li, B. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732 – 733; e) Y. Wu, R. P. Singh, L. Deng, *J. Am. Chem. Soc.* **2011**, *133*, 12458 – 11246; f) X. Xiao, Y. Xie, C. Su, M. Liu, Y. Shi, *J. Am. Chem. Soc.* **2011**, *133*, 12914 – 11291; g) Y. Wu, L. Deng, *J. Am. Chem. Soc.* **2012**, *134*, 14334 – 14337.
[19] a) Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219 – 10220; b) N. Abermil, G. Masson, J. Zhu, *J. Am. Chem. Soc.* **2008**, *130*, 12596 – 11259; c) N. Abermil, G. Masson, J. Zhu, *Org. Lett.* **2009**, *11*, 4648 – 465; d) N. Abermil, G. Masson, J. Zhu, *Adv. Synth. Catal.* **2010**, *352*, 656 – 666; e) J.-B. Denis, G. Masson, P. Retailleau, J. Zhu, *Angew. Chem.* **2011**, *123*, 5468 – 5472; *Angew. Chem. Int. Ed.* **2011**, *50*, 5356 – 5360.
[20] S. A. Savage, R. E. Waltermire, S. Campagna, S. Bordawekar, J. D. R. Toma, *Org. Process Res. Dev.* **2009**, *13*, 510 – 518.
[21] a) P. von R. Schleyer, A. Allerhand, *J. Am. Chem. Soc.* **1962**, *84*, 1322 – 1132; b) L. L. Ferstandig, *J. Am. Chem. Soc.* **1962**, *84*, 1323 – 1324; c) L. L. Ferstandig, *J. Am. Chem. Soc.* **1962**, *84*, 3553 – 3557; d) A. Allerhand, P. V. R. Schleyer, *J. Am. Chem. Soc.* **1963**, *85*, 866 – 870.
[22] G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Marko, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 8069 – 8076.
[23] Total synthesis of trigonoliimines A, B, and C. Enantioselective: a) S. Han, M. Movassaghi, *J. Am. Chem. Soc.* **2011**, *133*, 10768 – 10771; racemic: b) X. Qi, H. Bao, U. K. Tambar, *J. Am. Chem. Soc.* **2011**, *133*, 10050 – 10053; c) T. Buyck, Q. Wang, J. Zhu, *Org. Lett.* **2012**, *14*, 1338 – 1341; d) B. Zhao, X.-Y. Hao, J.-X. Zhang, S. Liu, X.-J. Hao, *Org. Lett.* **2013**, *15*, 528 – 530.
[24] Synthetic studies: a) S. Liu, X.-J. Hao, *Tetrahedron Lett.* **2011**, *52*, 5640 – 5642; b) P. Feng, Y. Fan, F. Xue, W. Liu, S. Li, Y. Shi, *Org. Lett.* **2011**, *13*, 5827 – 5829; c) J. Qiu, J.-X. Zhang, S. Liu, X.-J. Hao, *Tetrahedron Lett.* **2013**, *54*, 300 – 302.
[25] a) D. Bonne, M. Dekhane, J. Zhu, *Angew. Chem.* **2007**, *119*, 2537 – 2540; *Angew. Chem. Int. Ed.* **2007**, *46*, 2485 – 2488; b) C. Lalli, M. J. Bouma, D. Bonne, G. Masson, J. Zhu, *Chem. Eur. J.* **2011**, *17*, 880 – 889.
[26] W. M. Whaley, T. R. Govindachari, *Org. React.* **1951**, *6*, 74 – 150.
[27] Recent reviews dealing with the organocatalysis in total synthesis: a) E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138 – 1167; b) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167 – 178; c) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2012**, *475*, 183 – 188; d) G. Coulthard, W. Erb, V. K. Aggarwal, *Nature* **2012**, *489*, 278 – 281.

