DOI: 10.1002/ejoc.201403158

Organocatalyzed Asymmetric 1,4-Addition of Azlactones to α,β-Unsaturated Trichloromethyl Ketones: Synthesis of α,α-Disubstituted α-Amino Acid Derivatives

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Keywords: Organocatalysis / Amino acids / Alkaloids / Nitrogen heterocycles / Ketones

The first asymmetric 1,4-addition of azlactones to α,β-unsaturated trichloromethyl ketones catalyzed by cinchona alkaloid derived bifunctional thiourea catalysts was developed. A series of α,α-disubstituted α-amino acid derivatives bearing a quaternary stereocenter at the α-position were obtained in high yields with excellent diastereo- and enantioselectivities (up to >20:1 *dr* and 99 % *ee*). In addition, the trichloromethyl moiety in these adducts was identified as a good leaving group.

Introduction

The catalytic asymmetric synthesis of α,α-disubstituted α-amino acids and their derivatives has attracted considerable attention in bioorganic chemistry, as they constitute an important class of non-natural amino acids.[1] The properties of peptides and proteins possessing an α-quaternary amino acid component, for example, resistance against chemical and enzymatic degradation, can be dramatically enforced owing to the stability and restricted conformational flexibility of such a moiety.[2] Furthermore, α,α-disubstituted α-amino acids are also present in a variety of pharmaceuticals and antibiotics.[3] Owing to their significance from biological and medicinal points of view, intense effort has been focused on the development of various easy and efficient synthetic methods to gain access to a structurally diverse family of these optically active amino acids.[4] In recent years, as versatile masked and reactive amino acid equivalents, azlactones[5] ($pK_a \approx 9$) have been recognized to be one of the most valuable reagents for the asymmetric synthesis of α-amino acid derivatives containing a hetero-quaternary carbon stereocenter,[6] and a variety of catalytic transformations for their preparation have been established, including the Michael reaction,[7] Aldol-type reaction,[8] Mannich-type reaction,[9] cycloaddition,[10] Steglich rearrangement,[11] allylation,[12] benzylation,[13] and kinetic resolution.[14] Among these methodologies, the catalytic asymmetric conjugate addition to different α,β-unsaturated ketones could be regarded as a straightforward strategy, partially because organocatalysis can serve as a powerful tool for stereochemical control in the reaction process.[7a–7c,7e]

Peters and co-workers[7b,7c,7e] reported very elegant Michael additions of azlactones to enones with a mono- or bispalladiumcycle catalyst, and excellent results were obtained [Scheme 1, Equation (1)]. Thereafter, the Amarante group[7a] developed a (±)-camphorsulfonic acid catalyzed protocol for this transformation with high diastereoselectivity [Scheme 1, Equation (2)]. In the above two cases, the products were only *anti* isomers.

Given that part of our research program is directed at the asymmetric synthesis of bioactive chemical compounds, especially non-natural amino acid derivatives, we decided to conduct a reaction between azlactones and α,β-unsaturated ketones in the presence of a bifunctional organocatalyst. However, if the R^4 group was methyl or phenyl, the reaction did not take place. It was reasoned that the activation of unsaturated ketones by the catalyst was insufficient for this pathway, and more chemically reactive substrates were needed. In this respect, α,β-unsaturated trichloromethyl ketones[15] were synthesized, in which the trichloromethyl motif is a good electron-withdrawing group. Excitingly, after a series of optimization attempts, this reaction proceeded well with a quinine-derived bifunctional thiourea catalyst[16] and provided *syn* products in good yields with high to excellent diastereo- and enantioselectivities. More importantly, the trichloromethyl group turned out to be an attractive ester and amide synthetic equivalent.

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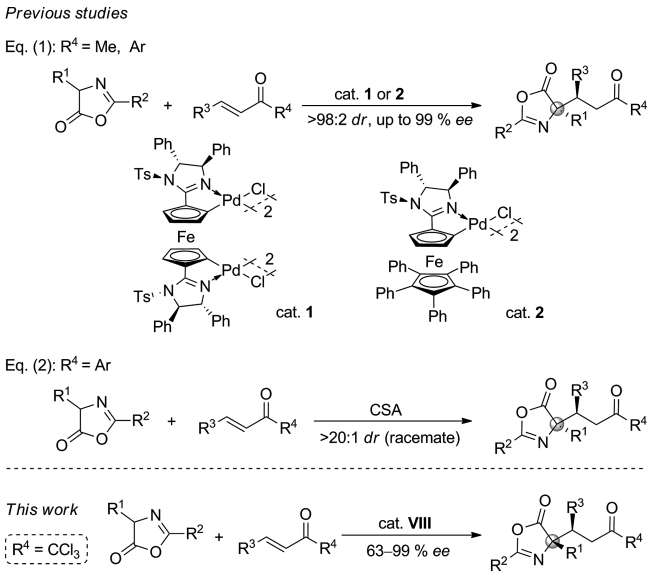
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403158.



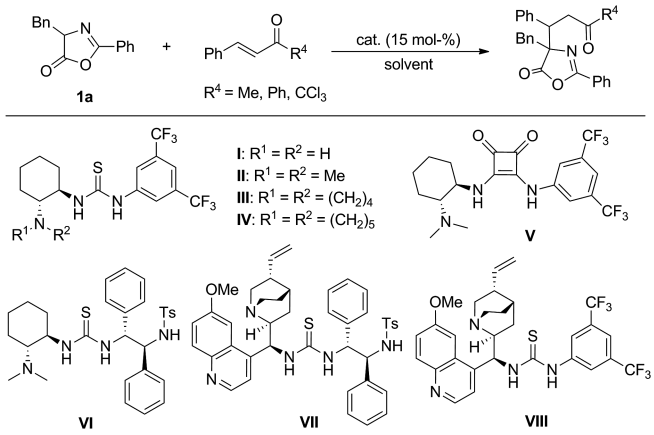
Scheme 1. Michael additions between azlactones and ketones; Ts = *p*-tolylsulfonyl, CSA = camphorsulfonic acid.

Results and Discussion

Initial investigation of the reaction conditions was set out for the model reaction between azlactone **1a** and α,β-unsaturated trichloromethyl ketone **2a** with cyclohexanediamine-derived thioureas **I**–**IV** in toluene at room temperature. Fortunately, C4 addition product **3a** was obtained with moderate yield albeit low diastereoselectivity (Table 1, entries 3–6). No improvement in the enantioselectivity was observed if cyclohexanediamine-derived organocatalysts **V**–**VI** were added to the reaction mixture (Table 1, entries 7 and 8). Next, quinine-derived catalysts were applied to the transformation, and the best result was gained by using thiourea **VIII** as a catalyst, with which the diastereo- and enantioselectivity were increased to 6:1 and 82%, respectively (Table 1, entries 9 and 10). A screening of the solvents indicated that aromatic solvents appeared to be the best reaction media, and xylene gave the products with 88%*ee* and 13:1 *dr* (Table 1, entries 11–13). Clearly, further optimization of the reaction conditions was still desired, and mesitylene was used to promote the process. As expected, a high yield and excellent chemical stereoselectivity were achieved (Table 1, entry 14). Finally, the influence of reaction temperature on this transformation was estimated, and 0 °C was selected for further studies in terms of both reactivity and selectivity (Table 1, entry 15).

With the optimized reaction conditions established, the substrate scope of the 1,4-addition between azlactone **1a** and different α,β-unsaturated trichloromethyl ketones was investigated in the presence of catalyst **VIII** (15 mol-%). As the results show (Table 2), both electron-donating and electron-withdrawing substituents in the *para* position of the phenyl ring in substrate **2** were adaptable to the optimal reaction conditions, and the products were obtained in high yields with excellent stereoselectivity (Table 2, see compounds **3a**–**f**). Moreover, we found that the reaction of an

Table 1. Screening of the reaction conditions.[a]



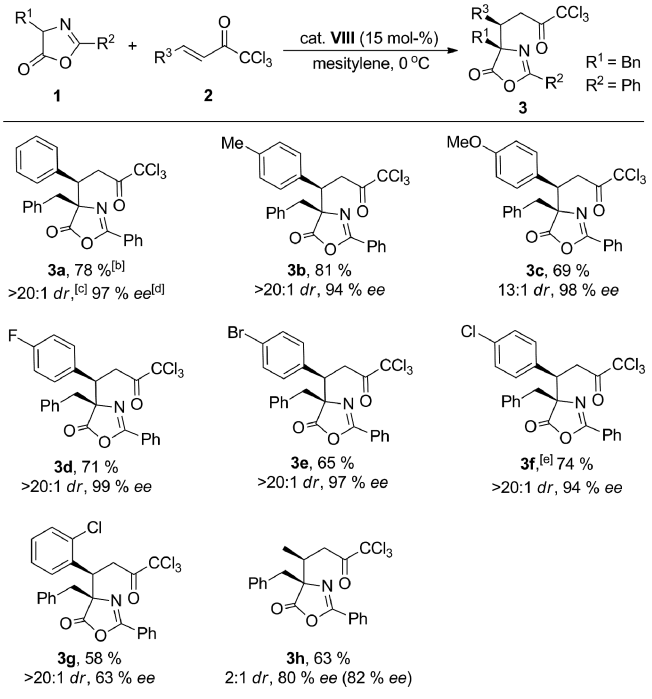
Entry	Cat.	R^4	Solvent	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	**II**	Me	toluene	–	–	–
2	**II**	Ph	toluene	–	–	–
3	**II**	CCl_3	toluene	75	6:1	50
4	**I**	CCl_3	toluene	32	5:1	43
5	**III**	CCl_3	toluene	76	8:1	61
6	**IV**	CCl_3	toluene	69	5:1	47
7	**V**	CCl_3	toluene	51	4:1	80
8	**VI**	CCl_3	toluene	80	5:1	60
9	**VII**	CCl_3	toluene	78	15:1	20
10	**VIII**	CCl_3	toluene	72	6:1	82
11	**VIII**	CCl_3	CH_2Cl_2	85	11:1	35
12	**VIII**	CCl_3	MTBE[e]	62	>20:1	80
13	**VIII**	CCl_3	xylene	74	13:1	88
14	**VIII**	CCl_3	mesitylene	81	>20:1	90
15	**VIII**	CCl_3	mesitylene	78	>20:1	97[f]

[a] Performed with **1a** (0.13 mmol), ketone (0.10 mmol), and catalyst (15 mol-%) in solvent (0.3 mL) at room temperature for 10 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. [e] MTBE = methyl *tert*-butyl ether. [f] Conducted at 0 °C.

α,β-unsaturated trichloromethyl ketone with a chloro substituent in the *ortho* position of the aromatic ring proceeded smoothly to provide the product in moderate yield with high diastereoselectivity (up to >20:1) but with low enantiomeric excess (Table 2, see compound **3g**). However, starting material methylated at the β-position of **2** could also be applied, and both diastereomers were obtained as a mixture with 80 and 82%*ee*, respectively (Table 2, see compound **3h**).

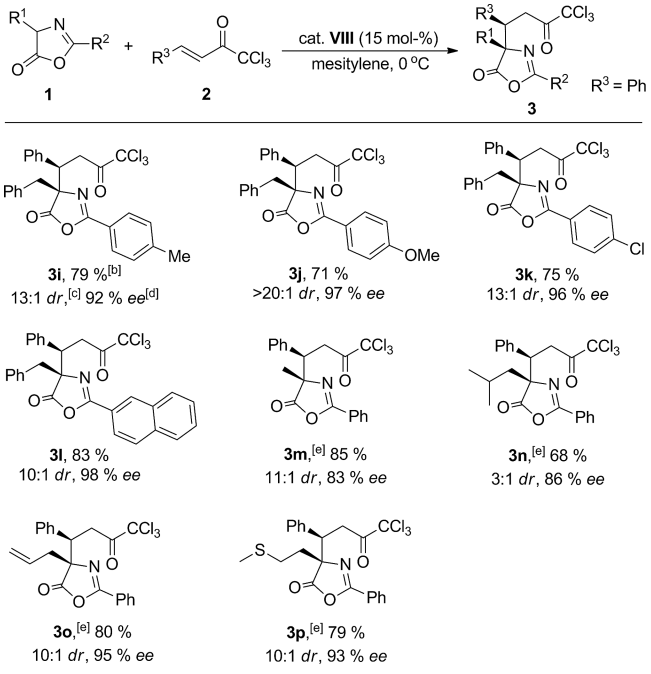
The reaction scope of the Michael addition between **2a** and various azlactones under the optimized conditions was also studied, and the results are shown in Table 3. The reaction was performed with a substituted aromatic group at R^2, and the high yields and excellent stereoselectivities were similar to those obtained with a phenyl substituent (Table 3, see compounds **3i**–**l**). Subsequently, azlactones derived from alanine, leucine, allylglycine, and methionine were tested in this reaction, and their additions to α,β-unsaturated trichloromethyl ketone **2a** took place in good yields, and the enantioselectivities ranged from 83 to 95% (Table 3, see compounds **3m**–**p**). Only in the case of isoleucine-derived azlactone **2n** was a low 3:1 diastereomeric ratio afforded.

Table 2. Scope for the asymmetric addition of azlactone **1a** to trichloromethyl ketones.[a]



[a] Performed with **1** (0.26 mmol), **2** (0.20 mmol), and catalyst **VIII** (15 mol-%) in mesitylene (0.6 mL) for 10 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. [e] Absolute stereochemistry of **3f** was determined by X-ray crystallography and that of the other products was assigned by analogy.

Table 3. Scope for the asymmetric addition of azlactones to trichloromethyl ketone **2a**.[a]

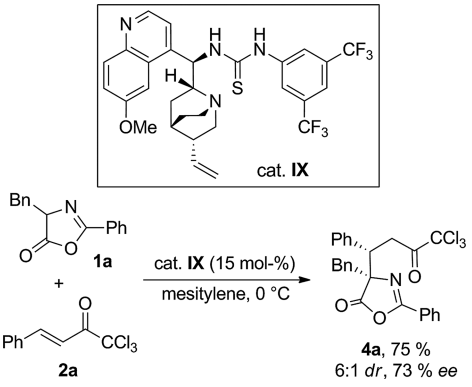


[a] Performed with **1** (0.26 mmol), **2** (0.20 mmol), and catalyst **VIII** (15 mol-%) in mesitylene (0.6 mL) for 10 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. [e] Conducted with **1** (0.20 mmol), **2** (0.30 mmol), and catalyst **VIII** (20 mol-%) in mesitylene (0.6 mL) for 30 h.

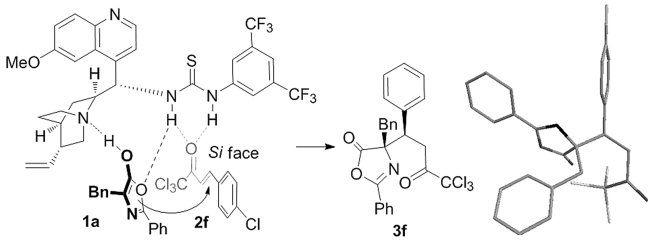
Encouraged by these results, quinidine-derived thiourea **IX** was synthesized and used to catalyze this reaction under the same conditions. Adduct **4a** was obtained in 75% yield with acceptable 73%*ee* and 6:1*dr*; this adduct is the enantiomer of compound **3a** (Scheme 2).

The absolute configuration of the two sequential stereocenters of **3f** was determined as (*S*,*R*) by X-ray crystallography and that of the other products was assigned by analogy.[17] On the basis of the absolute configuration, a plausible mechanism is outlined in Scheme 3. The activation of two substrates through hydrogen bonds attached to the catalyst followed by nucleophilic addition of the enolized electrophilic partner to α,β-unsaturated ketone **2f** from the *Si* face gives rise to 1,2-*syn* isomer **3f**.

The practical utility of this reaction was demonstrated in a further step by the transformation shown in Scheme 4. Highly optically active **3a** was easily converted into esterified products **3aa** and **3ab** in a THF/MeOH mixed solvent with the addition of $NaHCO_3$ and TMSCl, respectively. Upon using a strong nucleophile such as NaOMe, the reaction was complete within 30 min and afforded diesterified ring-opened product **3ac**. Amide **4ab** was also easily obtained from the corresponding amine in acetonitrile. Furthermore, reduction of the trichloromethyl group to a dichloromethyl group was achieved by using Pt/C as a cata-

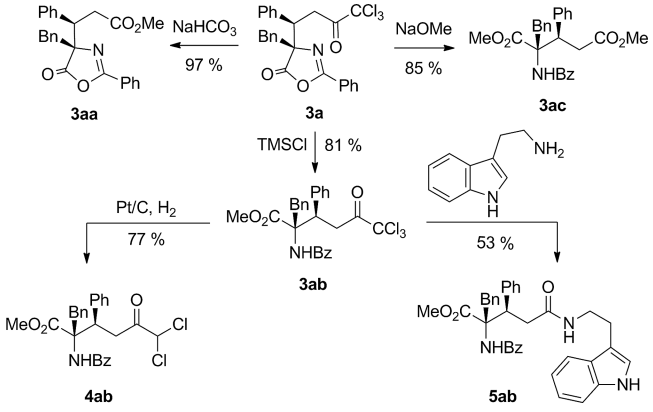


Scheme 2. Synthesis of enantiomer **4a** with a quinidine-derived thiourea.



Scheme 3. Stereochemical structure of enantiopure **3f** and mechanistic consideration for the approach.

lyst under a hydrogen atmosphere. These compounds are important protected non-natural quaternary α-amino acids.



Scheme 4. Different transformations of product **3a**; Bz = benzoyl.

Conclusions

In summary, we developed the first catalytic asymmetric Michael addition of azlactones to α,β-unsaturated trichloromethyl ketones in high yields with excellent stereoselectivities by using a commercially available quinine-derived thiourea catalyst. Alkyl and aromatic substituents on both substrates were explored under the optimized reaction conditions, and the corresponding products were obtained in all cases. More importantly, quinidine-derived thiourea was able to catalyze this reaction, by which the enantiomer of the former adduct was obtained with moderate stereoselectivity. Additional derivations for protected non-natural amino acids were also presented.

Experimental Section

General Procedure for the Addition of Azlactones to α,β-Unsaturated Trichloromethyl Ketones: Azlactone **1** (0.26 mmol) and α,β-unsaturated trichloromethyl ketone **2** (0.2 mmol) were added to a flask and cooled to 0 °C. After 10 min, a solution of catalyst **VIII** (15 mol-%) in mesitylene (0.6 mL, cooled to 0 °C) was added in one portion. The mixture was then stirred for another 10 h at this temperature (monitored by TLC). The crude residue was purified by column chromatography to afford compound **3**.

Procedure for the Addition of Azlactones to α,β-Unsaturated Trichloromethyl Ketones: Azlactone **1** (0.20 mmol) and α,β-unsaturated trichloromethyl ketone **2** (0.30 mmol) were added to a flask and cooled to 0 °C. After 10 min, a solution of catalyst **VIII** (15 mol-%) in mesitylene (0.6 mL, cooled to 0 °C) was added in one portion. The mixture was then stirred for another 30 h at this temperature (monitored by TLC). The crude residue was purified by column chromatography to afford compound **3**.

Supporting Information (see footnote on the first page of this article): Experimental details, analytical data, and copies of the ^{1}H NMR and ^{13}C NMR spectra of all key intermediates and final products.

Acknowledgments

The authors are grateful for grants from the National Natural Science Foundation of China (NSFC) (grant numbers 91213302 and 21272102), the Key National S&T Program "Major New Drug Development" of the Ministry of Science and Technology of China (2012ZX09504001-003), and the Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT1137).

[1] a) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406–430; b) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569–632; c) J. Venkatraman, S. C. Shankaramma, P. Balaram, *Chem. Rev.* **2001**, *101*, 3131–3152.

[2] a) M. Tanaka, *Chem. Pharm. Bull.* **2007**, *55*, 349–358; b) S. J. O'Connor, Z. Liu, *Synlett* **2003**, 2135–2138; c) A. Giannis, T. Kolter, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244–1267; *Angew. Chem.* **1993**, *105*, 1303–1326; d) M. C. Khosla, K. Stachowiak, R. R. Smeby, F. Piriou, K. Lintner, S. Fermandjian, *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 757–760.

[3] a) T. Kan, Y. Kawamoto, T. Asakawa, T. Furuta, T. Fukuyama, *Org. Lett.* **2008**, *10*, 169–171; b) A. Takahashi, H. Naganawa, D. Ikeda, Y. Okami, *Tetrahedron* **1991**, *47*, 3621–3632.

[4] For reviews on the synthesis of α,α-disubstituted α-amino acids, see: a) R. A. Mosey, J. S. Fisk, J. J. Tepe, *Tetrahedron: Asymmetry* **2008**, *19*, 2765–2762; b) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569–623; c) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4581–4671; d) Y. Ohfune, T. Shinada, *Eur. J. Org. Chem.* **2005**, 5127–5143; e) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406–430; f) M. Tanaka, *Chem. Pharm. Bull.* **2007**, *55*, 349–358; g) J. Venkatraman, S. C. Shankaramma, P. Balaram, *Chem. Rev.* **2001**, *101*, 3131–3152; h) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2000**, *11*, 645–732; i) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; j) M. C. Khosla, K. Stachowiak, R. R. Smeby, F. Piriou, K. Lintner, S. Fermandjian, *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 757–760.

[5] For reviews on the diverse chemistry of azlactones, see: a) A.-N. R. Alba, R. Rios, *Chem. Asian J.* **2011**, *6*, 720–734; b) J. S. Fisk, R. A. Mosey, J. J. Tepe, *Chem. Soc. Rev.* **2007**, *36*, 1432–1440.

[6] For reviews on the synthesis of quaternary stereocenters, see: a) B. Wang, Y.-Q. Tu, *Acc. Chem. Res.* **2011**, *44*, 1207–1222; b) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969–5994; c) J. T. Mohr, B. M. Stoltz, *Chem. Asian J.* **2007**, *2*, 1476–1491; d) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396; e) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482; f) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367; g) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105–10146.

[7] For selected examples of Michael additions of azlactones, see: a) E. P. Ávila, A. C. de Mello, R. Diniz, G. W. Amarante, *Eur. J. Org. Chem.* **2013**, 1881–1883; b) M. Weber, S. Jautze, W. Frey, R. Peters, *Chem. Eur. J.* **2012**, *18*, 14792–14804; c) M. Weber, R. Peters, *J. Org. Chem.* **2012**, *77*, 10846–10855; d) H. Jiang, M. W. Paixão, D. Monge, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 2775–2783; e) M. Weber, S. Jautze, W. Frey, R. Peters, *J. Am. Chem. Soc.* **2010**, *132*, 12222–12225; f) A.-N. R. Alba, G. Valero, T. Calbet, M. Font-Bardía, A. Moyano, R. Rios, *Chem. Eur. J.* **2010**, *16*, 9884–9889; g) S. Cabrera, E. Reyes, J. Alemán, A. Milelli, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037; h) J. Alemán, A. Milelli, S. Cabrera, E. Reyes, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 10958–10966; i) D. Uraguchi, Y. Ueki, T. Ooi, *Science* **2009**, *326*, 120–123; j) A.-N. R. Alba, X. Companyó, G. Valero, A. Moyano, R. Rios, *Chem. Eur. J.* **2010**, *16*, 5354–5361; for examples of additions to alkynyl carbonyl substrates, see: k) D. Uraguchi, Y. Ueki, A. Sugiyama, T. Ooi, *Chem. Sci.* **2013**, *4*,

1308–1311; l) T. Misaki, K. Kawano, T. Sugimura, *J. Am. Chem. Soc.* **2011**, *133*, 5695–5697.

[8] M. Terada, H. Tanaka, K. Sorimachi, *J. Am. Chem. Soc.* **2009**, *131*, 3430–3431.

[9] a) W.-Q. Zhang, L.-F. Cheng, J. Yu, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 4085–4088; *Angew. Chem.* **2012**, *124*, 4161–4164; b) D. Uraguchi, K. Koshimoto, T. Ooi, *Chem. Commun.* **2010**, *46*, 300–302; c) D. Uraguchi, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 14088–14089; d) X. Liu, L. Deng, X. Jiang, W. Yan, C. Liu, R. Wang, *Org. Lett.* **2010**, *12*, 876–879.

[10] a) F. Esteban, R. Alfaro, F. Yuste, A. Parra, J. L. G. Ruano, J. Alemán, *Eur. J. Org. Chem.* **2014**, 1395–1400; b) W. Sun, G. Zhu, C. Wu, G. Li, L. Hong, R. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 8633–8637; *Angew. Chem.* **2013**, *125*, 8795–8799; c) M. Weber, W. Frey, R. Peters, *Angew. Chem. Int. Ed.* **2013**, *52*, 13223–13227; *Angew. Chem.* **2013**, *125*, 13465–13469; d) M. Martín-Rodríguez, C. Nájera, J. M. Sansano, *Synlett* **2012**, *23*, 62–65; e) M. Terada, H. Nii, *Chem. Eur. J.* **2011**, *17*, 1760–1763; f) A. D. Melhado, G. W. Amarante, Z. J. Wang, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 3517–3527; g) Y. Ying, Z. Chai, H.-F. Wang, P. Li, C.-W. Zheng, G. Zhou, Y.-P. Cai, *Tetrahedron* **2011**, *67*, 3337–3342; h) S. Dong, X. Liu, X. Chen, F. Mei, Y. Zhang, B. Gao, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 10650–10651; i) J. Jiang, J. Qing, L.-Z. Gong, *Chem. Eur. J.* **2009**, *15*, 7031–7034; j) S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369.

[11] a) C. K. De, N. Mittal, D. Seidel, *J. Am. Chem. Soc.* **2011**, *133*, 16802–16805; b) D. Uraguchi, K. Koshimoto, S. Miyake, T. Ooi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5567–5569; *Angew. Chem.* **2010**, *122*, 5699–5710; c) C. Joannesse, C. P. Johnston, C. Concellón, C. Simal, D. Philp, A. D. Smith, *Angew. Chem. Int. Ed.* **2009**, *48*, 8914–8918; *Angew. Chem.* **2009**, *121*, 9076–9080; d) S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va, E. Vedejs, *J. Am. Chem. Soc.* **2006**, *128*, 925–934; e) H. V. Nguyen, D. C. D. Butler, C. J. Richards, *Org. Lett.* **2006**, *8*, 769–772; f) J. G. Seitzberg, C. Dissing, I. Søtofte, P.-O. Norrby, M. Johannsen, *J. Org. Chem.* **2005**, *70*, 8332–8337; g) S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369; h) J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.

[12] a) B. M. Trost, C. Jäkel, B. Plietker, *J. Am. Chem. Soc.* **2003**, *125*, 4438–4439; b) B. M. Trost, K. Dogra, *J. Am. Chem. Soc.* **2002**, *124*, 7256–7257; c) B. M. Trost, X. Ariza, *J. Am. Chem. Soc.* **1999**, *121*, 10727–10737.

[13] B. M. Trost, L. C. Czabaniuk, *Chem. Eur. J.* **2013**, *19*, 15210–15218.

[14] For selected examples of dynamic kinetic resolutions, see: a) C. Quigley, Z. Rodríguez-Docampo, S. J. Connon, *Chem. Commun.* **2012**, *48*, 1443–1445; b) J.-S. Oh, J.-W. Lee, T. H. Ryu, J. H. Lee, C. E. Song, *Org. Biomol. Chem.* **2012**, *10*, 1052–1055; c) G. Lu, V. B. Birman, *Org. Lett.* **2011**, *13*, 356–358; d) D. G. Blackmond, N. S. Hodnett, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2006**, *128*, 7450–7451; e) A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Müller, J. Lex, *Chem. Commun.* **2005**, 1898–1900; for other selected examples, see: f) B. Qiao, X. Liu, S. Duan, L. Yan, Z. Jiang, *Org. Lett.* **2014**, *16*, 672–675; g) P. Finkbeiner, N. M. Weckenmann, B. J. Nachtsheim, *Org. Lett.* **2014**, *16*, 1326–1329; h) Y.-L. Yang, C.-K. Pei, M. Shi, *Org. Biomol. Chem.* **2011**, *9*, 3349–3358; i) M. Terada, K. Moriya, K. Kanomata, K. Sorimachi, *Angew. Chem. Int. Ed.* **2011**, *50*, 12586–12590; *Angew. Chem.* **2011**, *123*, 12794–12798; j) D. Uraguchi, Y. Asai, T. Ooi, *Angew. Chem. Int. Ed.* **2009**, *48*, 733–737; *Angew. Chem.* **2009**, *121*, 747–751; k) E. Busto, V. Gotor-Fernández, V. Gotor, *Adv. Synth. Catal.* **2006**, *348*, 2626–2632.

[15] For the direct use of α,β-unsaturated trichloromethyl ketones in Michael reactions, see: a) C. Zheng, Y. Li, Y. Yang, H. Wang, H. Cui, J. Zhang, G. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 1685–1691; b) H. Morimoto, S. H. Wiedemann, A. Yamaguchi, S. Harada, Z. Chen, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2006**, *45*, 3146–3150; *Angew. Chem.* **2006**, *118*, 3218–3222.

[16] For reviews on cinchona alkaloids, see: a) H. Martin, R. Hoffmann, J. Frackenpohl, *Eur. J. Org. Chem.* **2004**, 4293–4312; b) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. Mcdaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621–631; c) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985–3012; for reviews on bifunctional thiourea catalysis, see: d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; e) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1243; *Angew. Chem.* **2006**, *118*, 1550–1573; f) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; g) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306.

[17] CCDC-1014388 (for **3f**) 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/data_request/cif. See the Supporting Information for details.

Received: September 2, 2014
Published Online: October 9, 2014

