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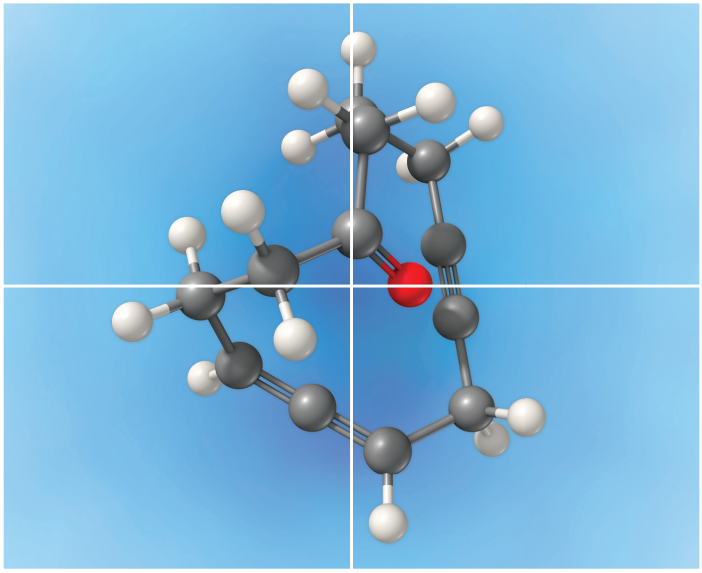

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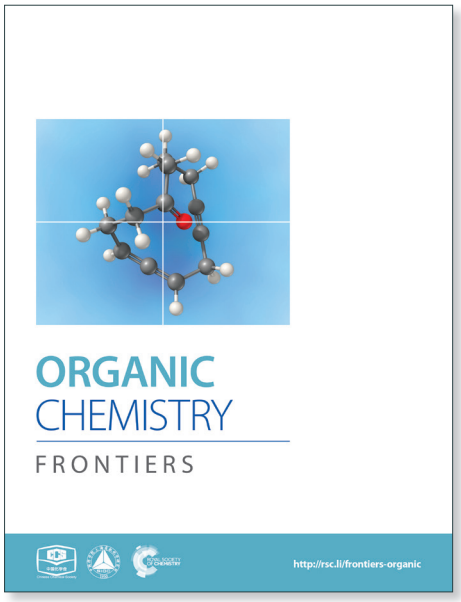

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COMMUNICATION

Enantioselective Synthesis of Bicyclo[2.2.2]octane-1-carboxylates under Metal Free Conditions

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A new tandem reaction was realized that permits rapid access to a wide range of bicyclo[2.2.2]octane-1-carboxylates in good to excellent yields with excellent enantioselectivities under metal free, mild, and operationally simple conditions. An *open* transition state was deemed operative in the highly enantioselective process mediated by the organic base.

Bicyclo[2.2.2]octane represents a privileged structure found in a myriad of natural products such as atisanes and *ent*-atisanes, atisine-, denudatine-, as well as daphmanidin-type alkaloids,[1,2] in addition to being the core unit of a type of molecular rotor.[3] Some biologically significant molecules such as platencin,[4] maoecrystal V,[5] crotogoudin and crotobarin,[6] are featured by this bicyclic structure (Figure 1). In particular, the antibiotic platencin (**1**) has become one of the most prominent natural products in recent years.[7] Platencin blocks FabF and FabH enzymes and exhibits broad-spectrum antibacterial activity against Gram-positive pathogens that show resistance to current antibiotics.[4,8,9] However, the poor in vivo efficacy has precluded platencin from being a clinical drug, thereby entailing procurement of analogues for further biological evaluations.[10] Tremendous efforts have been made to access platencin,[11a-s] synthetic analogues.[11t-w], as well as related natural products.[12]

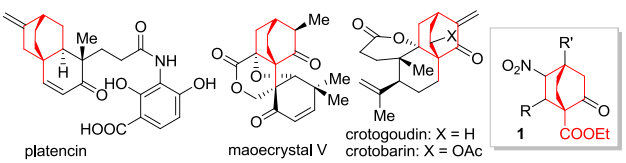
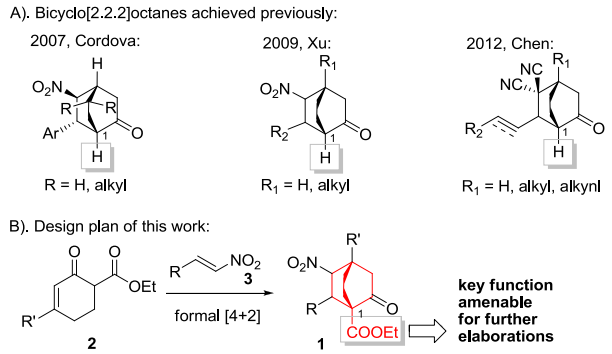


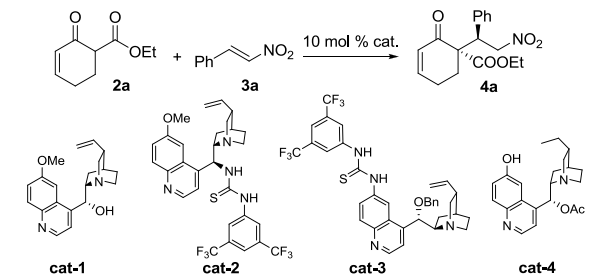
Fig. 1 Platencin and related natural products.

In our recent effort to realize a diversity-oriented synthesis of platencin and related natural products, bicyclo[2.2.2]octane-1-carboxylate **1** was selected as an early-stage key intermediate. Therefore, to explore a method that allows gram-scale preparation of **1** under operationally simple conditions is highly desirable. The development of enantioselective approaches to bicyclo[2.2.2]octanes has remained an attractive yet challenging arena, and to date only several methods have been successfully established.[13] Among these, Córdova,[13c] Xu,[13d] and Chen[13e] developed catalytic asymmetric [4+2] cycloaddition reactions of cyclohexenones with electron-deficient alkenes based on enamine/iminium catalysis.[14] However, only cyclohexenones devoid of α'-substituents were employed as substrates in these reactions, leading to [2.2.2] bicyclic products without substitution on the C1 bridgehead (Scheme 1 A). Based on our experiences in natural product synthesis,[15] an enantioselective approach to bicyclo[2.2.2]octane-1-carboxylate **1** could fill a significant gap in the current repertoire. We envisioned **1** to be assembled from α'-ethoxycarbonyl cyclohexenone **2** and nitroolefin **3** through a formal [4+2] cycloaddition reaction (Scheme 1 B). To the best of our knowledge, to date this formal [4+2] cycloaddition reaction has not been reported. Actually, under relevant circumstances, formation of the formal [4+2] products was not documented.[12d,16] In this paper, we delineate the highly enantioselective synthesis of **1** by employing metal free, mild, and operationally simple conditions.



Scheme 1. Conceptual formal [4+2] reaction leading to **1**.

Table 1. Conditions Screening for the Intermolecular Conjugate Addition.[a]

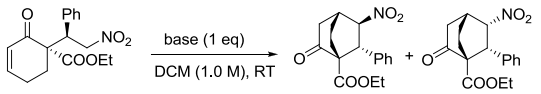


Entry	Substrate	Cat.	Conv.[b] [%]	dr[b]	ee[c] [%]
1	**3a**	**cat-1**	81	> 20/1	-31
2	**3a**	**cat-2**	94	> 20/1	87
3	**3a**	**cat-3**	88	> 20/1	-90
4	**3a**	**cat-4**	99	> 20/1	99
5	(*Z*)-**3a**	**cat-4**	84 [d]	19/1	97

[a] The reaction was conducted with 3a (0.40 mmol), 4a (0.20 mmol), catalyst (10 mol %), in DCM (1.0 mL) at RT. [b] Determined by ^{1}H NMR analysis of the crude products. [c] Determined by chiral HPLC analysis. [d] Isolated yield.

We began our studies by investigating the reaction of **2a** and **3a**. Surprisingly, under various examined conditions, **4a** was validated as the sole product. Therefore, optimization of this conjugate addition reaction[17,13c-i] was first conducted and the selected results are summarized in Table 1. The best results were obtained with **cat-4**, delivering **4a** in a quantitative yield with excellent stereoselectivity (entry 4). Importantly, when (*Z*)-**3a** instead of **3a** was employed as the electrophile, the same product **4a** was obtained with excellent selectivity (entry 5). This result could be attributed to the liability of (*Z*)-**3a** undergoing isomerization to **3a** in the presence of the catalyst, as evidenced by our ^{1}H NMR studies. Accordingly, use of geometrically pure nitroolefin was not necessary.

Table 2. Base Screening for the Intramolecular Conjugate Addition Reaction.[a]



4a **1a** ***epi*-1a**

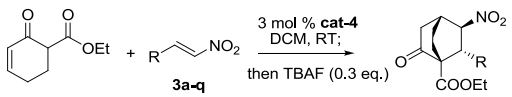
Entry	Base	Yield[b] [%]	dr[c] [**1a**/*epi*-**1a**]	ee[d] [%]
1	K_2CO_3	trace	-	-
2	Cs_2CO_3	26	1/2.2	71|15
3	CsOH	30	1.2/1	31|02
4	CsF	22	1/1.1	38|19
5	LiOH	35	1/12	0
6	NEt_3	trace	-	-
7	DIPEA	trace	-	-
8	DMAP	trace	-	-
9	DBU	61	> 20/1	94
10	TBAF $3H_2O$	78	> 20/1	96

[a] The reaction was conducted with **4a** (0.10 mmol) in DCM (1.0 M) at RT. [b] Isolated yield. [c] Determined by 1H NMR analysis of the crude products. [d] Determined by chiral HPLC analysis.

With enantiopure **4a** secured, we focused ourselves on the crucial intramolecular conjugate addition. Due to the reversibility of the previous step, it was critical to define suitable conditions for this step to proceed without invoking racemization. Various bases were scrutinized (Table 2). While K_2CO_3 gave no reaction, by switching to Cs_2CO_3, **1a** and *epi*-**1a** in a combined yield of 26% were obtained with poor selectivity (entry 2). Interestingly, with LiOH employed as the base, a high diastereoselectivity favoring *epi*-**1a** was observed, although the product was completely racemic (entry 5). These compelling evidences of racemization indicated that **4a** did revert to **2a** and **3a** to certain levels under these reaction conditions. To our delight, after the failure of several conventional amine bases (entries 6~8), DBU and TBAF were found to be efficient promoters for this reaction (entries 9, 10). Thus, by treatment of **4a** with 1.0 equiv TBAF, **1a** was isolated in 78% yield with >20/1 dr and 96% ee (entry 10).

With the two separate steps successfully established, the stage was now set for development of a one-pot tandem reaction. To this end, after the first conjugate addition catalyzed by **cat-4** was completed, TBAF was introduced to the reaction mixture to promote the second conjugate addition. Use of 0.3 equiv TBAF (1.0 M in THF) was determined optimal, wherein **1a** could be isolated in 84% yield with >20/1 dr and 97% ee (Table 3, entry 1). Under the optimized conditions, a broad scope of nitroolefins were found successful substrates for this tandem reaction, providing bicyclo[2.2.2]octane-1-carboxylates in good yields and mostly with excellent stereoselectivities. For nitrostyrene substrates, both electron donating and electron withdrawing substituents on the benzene ring are well tolerated (entries 2~11). In general, substrates with electron withdrawing groups gave better results than did with electron donating groups (entries 5~11 versus 2~4), presumably as a result of the higher reactivity of the former substrates than that of the latter ones. Of particular interest were nitrostyrenes with an *ortho* substituent wherein surprisingly high yields were obtained (entries 10 and 11 versus 5). This may be accounted for by resorting to the strain release effect in the reaction, considering that there is repulsive interaction between the vinyl proton and the *ortho* substituent coplanar in the substrates. This rationale is in agreement with the fact that **1k** was obtained in a higher yield than **1j** since the bromine atom, albeit with a less electronegativity, is more sterically demanding than the chlorine atom (entry 11 versus 10). Gratifyingly, other aryl, heteroaryl, as well as alkenyl and alkyl nitroolefins also proved suitable substrates for this reaction (entries 12~17). The relative as well as the absolute stereochemistry of the products were established unambiguously through the X-ray crystallographic analysis of enantiopure **1e**.[21]

Table 3. Substrate Scope of Nitroolefins for the Tandem Reaction.[a]



2a **3a-q** **1a-q**

Entry	R	Prod.	Yield[b] [%]	dr[c]	ee[d] [%]
1	Ph	**1a**	85	> 20/1	97
2	4-Me-C_6H_4	**1b**	80	19/1	95
3	4-MeO-C_6H_4	**1c**	70	13/1	95
4	3,4-$(MeO)_2$-C_6H_3	**1d**	72	13/1	96
5	4-Br-C_6H_4	**1e**	86	19/1	98
6	4-F-C_6H_4	**1f**	76	> 20/1	99
7	4-CF_3-C_6H_4	**1g**	87	> 20/1	98
8	4-NO_2-C_6H_4	**1h**	85	> 20/1	99
9	3-NO_2-C_6H_4	**1i**	96	> 20/1	97
10	2-Cl-C_6H_4	**1j**	93	> 20/1	97
11	2-Br-C_6H_4	**1k**	97	> 20/1	98
12	1-naphthyl	**1l**	88	7.3/1	96
13	2-furanyl	**1m**	69	12/1	90
14	styryl	**1n**	60	13/1	94
15	isobutyl	**1o**	93	19/1	97
16	phenethyl	**1p**	62	> 20/1	97
17	cyclohexyl	**1q**	53	19/1	99

[a] Conditions: **2a** (0.40 mmol), **3** (0.20 mmol), **cat-4** (3 mol %), CH_2Cl_2 (0.2 mL); then TBAF (1.0 M in THF, 60 uL), RT. [b] Isolated yield based on **3**. [c] Determined by ^1H NMR analysis of the crude products. [d] Determined by chiral HPLC analysis.

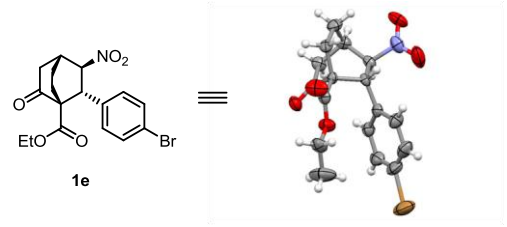
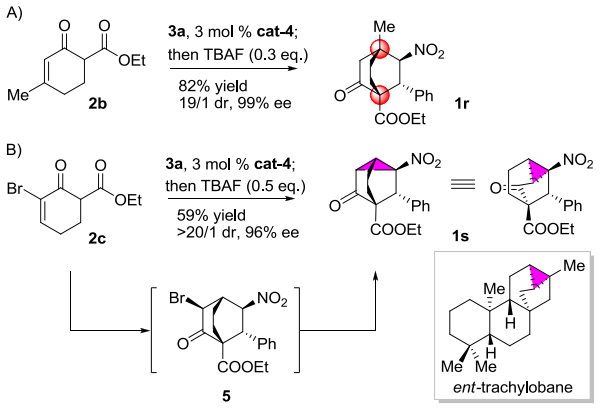
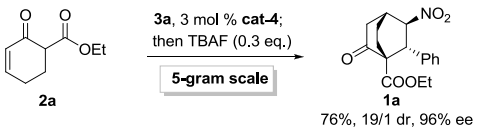


Fig. 2 X-ray structure of **1e**.



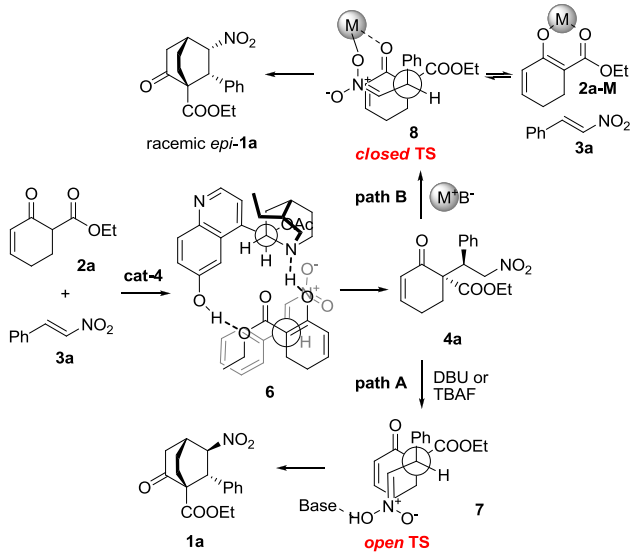
Scheme 2. Reaction of **3a** with **2b** (A) and **2c** (B).



Scheme 3. Five-gram-scale preparation of **1a**.

Gratifyingly, variations on the enone component proved viable (Scheme 2). Bicyclo[2.2.2]octane functions as the bridge in some molecular rotors,[18] and the synthetic challenge for such rotors resides in the construction of the bridgehead quaternary carbons.[19] As a proof of concept, the reaction of **2b** with **3a** was examined, and **1r** was isolated in 82% yield with 19/1 dr and 99% ee (Scheme 2 A). Another result of particular interest was obtained in the reaction of **2c** with **3a**, delivering **1s** harboring five contiguous stereocenters with >20/1 dr and 96% ee, probably through the intermediacy of **5** (Scheme 2 B). Notably, **1s** contains a tricyclo[3.2.1.$0^{2,7}$]octane core characteristic of trachylobanes.[20] Remarkably, this reaction could be readily scaled up, as exemplified by the five-gram scale preparation of **1a** (Scheme 3).

On the basis of the preceding results, the stereochemical outcome of the tandem reaction could be rationalized, as exemplified by the reaction of **2a** with **3a** (Scheme 4). In the first step, **2a** may form a complex with **cat-4** via hydrogen-bonding interactions, thereby discriminating the two faces of the reactive enol. The nitroolefin approaches the enol selectively from the less hindered α-face with the substituents of the two bond-forming carbons positioned in a staggered arrangement (**6**), delivering **4a**. In the second step, when DBU or TBAF is used as the base, the *open* transition state **7** might be operative to minimize the steric repulsion between the nitro and the phenyl groups, leading to the formation of **1a** as the major product (path A). In contrast, when metal-containing bases are employed, the *closed* transition state **8** could be operative owing to the coordinating ability of metal ion. Framework **8** may break down to **2a**-**M** and **3a** which recombine to afford **8** as a racemic form before further proceeding to racemic *epi*-**1a** (path B). This rationale is in agreement with the fact that metal-containing bases are detrimental for this enantioselective reaction.



Scheme 4. Proposed stereochemical course of the reaction in the presence of organic bases (path A) or metal-containing bases (path B).

Conclusions

We have realized a formal [4+2] reaction that permits rapid access to a wide range of functionalized [2.2.2] bicyclic octanes in a highly enantioselective manner from simple starting materials. The reaction features metal free, mild, and operationally simple conditions, providing synthetically useful bicyclo[2.2.2]octane-1-carboxylates in good yields with excellent enantioselectivity. Notably, only 3 mol % of the organocatalyst is used for the enantioselective reaction. Importantly, this method is amenable to large scale preparation, thus facilitating relevant synthetic studies of natural products. Moreover, this work has also laid the basis for access to bicyclo[2.2.1]heptane-1-carboxylates. Endeavors along these lines are currently underway and will be reported in due course.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 (a) P.-J. Zhao, S. Gao, L.-M. Fan, J.-L. Nie, H.-P. He, Y. Zeng, Y.-M. Shen, X.-J. Hao, *J. Nat. Prod.*, 2009, **72**, 645; (b) F.-P. Wang, Q.-H. Chen, X.-Y. Liu, *Nat. Prod. Rep.*, 2010, **27**, 529.

2 (a) J. Kobayashi, T. Kubota, *Nat. Prod. Rep.*, 2009, **26**, 936; (b) M. E. Weiss, E. M. Carreira, *Angew. Chem. Int. Ed.*, 2011, **50**, 11501.

3 B. Rodríguez-Molina, S. Pérez-Estrada, M. A. Garcia-Garibay, *J. Am. Chem. Soc.*, 2013, **135**, 10388.

4 J. Wang, S. Kodali, S. H. Lee, A. Galgoci, R. Painter, K. Dorso, F. Racine, M. Motyl, L. Hernandez, E. Tinney, S. Colletti, K. Herath, R. Cummings, O. Salazar, I. Gonzalez, A. Basilio, F. Vicente, O. Genilloud, F. Pelaez, H. Jayasuriya, K. Young, D. Cully, S. B. Singh, *Proc. Natl. Acad. Sci. U.S.A.*, 2007, **104**, 7612.

5 (a) S. H. Li, J. Wang, X. M. Niu, Y. H. Shen, H. J. Zhang, H. D. Sun, M. L. Li, Q. E. Tian, Y. Lu, P. Cao, Q. T. Zheng, *Org. Lett.*, 2004, **6**, 4327; (b) J. Gong, G. Lin, W. Sun, C.-C. Li, Z. Yang, *J. Am. Chem. Soc.*, 2010, **132**, 16745; (c) F. Peng, S. J. Danishefsky, *J. Am. Chem. Soc.*, 2012, **134**, 18860; (d) P. Lu, Z. Gu, A. Zakarian, *J. Am. Chem. Soc.*, 2013, **135**, 14552.

6 (a) O. L. Rakotonandrasana, F. H. Raharinjato, M. Rajaonarivelo, V. Dumontet, M.-T. Martin, J. Bignon, P. Rasoanaivo, *J. Nat. Prod.* 2010, **73**, 1730; (b) S. Breitler, E. M. Carreira, *Angew. Chem. Int. Ed.* 2013, **52**, 11168.

7 (a) E. Martens, A. L. Demain, *J. Antibiot.*, 2011, **64**, 705; (b) G. I. Moustafa, S. Nojima, Y. Yamano, A. Aono, M. Arai, S. Mitarai, T. Tanaka, T. Yoshimitsu, *Med. Chem. Commun.*, 2013, **4**, 720; (c) M, J. Smanski, R. M. Peterson, S. R. Rajski, B. Shen, *Antimicrob. Agents Chemother.*, 2009, **53**, 1299.

8 R. M. Peterson, T. Huang, J. D. Rudolf, M. J. Smanski, B. Shen, *Chemistry & Biology*, 2014, **21**, 389.

9 G. A. I. Moustafa, S. Nojima, Y. Yamano, A. Aono, M. Arai, S. Mitarai, T. Tanaka, T. Yoshimitsu, *Med. Chem. Commun.*, 2013, **4**, 720.

10 (a) S. Brinster, G. Lamberet, B. Staels, P. Trieu-Cuot, A. Gruss, C. Poyart, *Nature*, 2009, **458**, 83. (b) E. Martens, A. L. Demain, *J. Antibiot.*, 2011, **64**, 705.

11 (a) K. C. Nicolaou, G. S. Tria, D. J. Edmonds, *Angew. Chem. Int. Ed.*, 2008, **47**, 1780; (b) J. Hayashida, V. H. Rawal, *Angew. Chem. Int. Ed.*, 2008, **47**, 4373; (c) K. Tiefenbacher, J. Mulzer, *Angew. Chem. Int. Ed.*, 2008, **47**, 6199; (d) S. Y. Yun, J.-C. Zheng, D. Lee, *Angew. Chem. Int. Ed.*, 2008, **47**, 6201; (e) D. C. J. Waalboer, M. C. Schaapman, F. L. van Delft, F. P. J. T. Rutjes, *Angew. Chem. Int. Ed.*, 2008, **47**, 6576; (f) K. C. Nicolaou, Q.-Y. Toh, D. Y.-K. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 11292; (g) K. A. B. Austin, M. G. Banwell, A. C. Willis, *Org. Lett.*, 2008, **10**, 4465. (h) K. Tiefenbacher, J. Mulzer, *J. Org. Chem.*, 2009, **74**, 2937; (i) G. N. Varseev, M. E. Maier, *Angew. Chem. Int. Ed.*, 2009, **48**, 3685; (j) A. K. Ghosh, K. Xi, *Angew. Chem. Int. Ed.*, 2009, **48**, 5372; (k) K. C. Nicolaou, G. S. Tria, D. J. Edmonds, M. Kar, *J. Am. Chem. Soc.*, 2009, **131**, 15909; (l) P. Li, H. Yamamoto, *Chem. Commun.*, 2010, **46**, 6294; (m) V. Singh, B. C. Sahu, V. Bansal, S. M. Mobin, *Org. Biomol. Chem.*, 2010, **8**, 4472; (n) S. Hirai, M. Nakada,*Tetrahedron Lett.*, 2010, **51**, 5076; (o) K. Palanichamy, A. V. Subrahmanyam, K. P. Kaliappan, *Org. Biomol. Chem.*, 2011, **9**, 7877; (p) T. Yoshimitsu, S. Nojima, M. Hashimoto, T. Tanaka, *Org. Lett.*, 2011, **13**, 3698; (q) S. Hirai, M. Nakada,*Tetrahedron*, 2011, **67**, 518; (r) L. Zhu, C. Zhou, W. Yang, S. He, G.-J. Cheng, X. Zhang, C.-S. Lee, *J. Org. Chem.*, 2013, **78**, 7912; (s) J. S. Yadav, R. Goreti, S. Pabbaraja, B. Sridhar, *Org. Lett.*, 2013, **15**, 3782; (t) O. V. Barykina, K. Rossi, L. M. J. Rybak, B. B. Snider, *Org. Lett.*, 2009, **11**, 5334; (u) K. Tiefenbacher, A. Gollner, J. Mulzer, *Chem. Eur. J.*, 2010, **16**, 9616; (v) D. C. J. Waalboer, S. H. A. M. Leenders, T. Schuelin-Casonato, F. L. van Delft, F. P. J. T. Rutjes, *Chem. Eur. J.*, 2010, **16**, 11233; (w) G. Y. C. Leung, H. Li, Q.-Y. Toh, A. M.-Y. Ng, R. J. Sum, J. E. Bandow, D. Y.-K. Chen, *Eur. J. Org. Chem.*, **2011**, 183.

12 (a) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, Y. Hayase, *J. Am. Chem. Soc.*, 1963, **85**, 2342; (b) W. A. Ayer, C. E. McDonald, G. G. Iverach, *Tetrahedron Lett.*, 1963, **4**, 1095; (c) R. A. Bell, R. E. Ireland, *Tetrahedron Lett.*, 1963, **4**, 269; (d) A. Abad, C. Agulló, A. C. Cuñat, I. de Alfonso Marzal, I. Navarro, A. Gris, *Tetrahedron*, 2006, **62**, 3266; (e) X.-Y. Liu, H. Cheng, X.-H. Li, Q.-H. Chen, L. Xu, F.-P. Wang, *Org. Biomol. Chem.*, 2012, **10**, 1411.

13 (a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 4243; (b) B. M. Trost, K. L. Sacchi, G. M. Schroeder, N. Asakawa, *Org. Lett.*, 2002, **4**, 3427; (c) H. Sundén, R. Rios, Y. Xu, L. Eriksson, A. Córdova, *Adv. Synth. Catal.*, 2007, **349**, 2549; (d) D.-Q. Xu, A.-B. Xia, S.-P. Luo, J. Tang, S. Zhang, J.-R. Jiang, Z.-Y. Xu, *Angew. Chem. Int. Ed.*, 2009, **48**, 3821; (e) X. Feng, Z. Zhou, R. Zhou, Q.-Q. Zhou, L. Dong, Y.-C. Chen, *J. Am. Chem. Soc.*, 2012, **134**, 19942; (f) H. Yang, R. G. Carter, *J. Org. Chem.*, 2009, **74**, 5151; (g) H. Yang, R. G. Carter, *Tetrahedron*, 2010, **66**, 4854; (h) M. Bella, D. M. S. Schietroma, P. P. Cusella, T. Gasperi, V. Visca, *Chem. Commun.*, 2009, 597; (i) D. M. S. Schietroma, M. R. Monaco, V. Visca, S. Insogna, J. Overgaard, M. Bella, *Adv. Synth. Catal.*, 2011, **353**, 2648.

14 S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.*, 2007, **107**, 5471.

15 (a) J. Wang, S.-G. Chen, B.-F. Sun, G.-Q. Lin, Y.-J. Shang, *Chem. Eur. J.*, 2013, **19**, 2539. (b) R. Ding, B.-F. Sun, G.-Q. Lin, *Org. Lett.*, 2012, **14**, 4446. (c) R. Ding, J.-G. Fu, G.-Q. Xu, B.-F. Sun, G.-Q. Lin, *J. Org. Chem.*, 2014, **79**, 240. (d) X.-L. Wang, Y.-Y. Lu, J. Wang, X. Wang, H.-Q. Yao, G.-Q. Lin, B.-F. Sun, *Org. Biomol. Chem.*, 2014, **12**, 3562.

16 (a) L. Duroure, T. Jousseaume, R. Araoz, E. Barre, P. Retailleau, L. Chabaud, J. Molgo, C. Guillou, *Org. Biomol. Chem.*, 2011, **9**, 8112; (b) P. Elsner, L. Bernardi, G. D. Salla, J. Overgaard, K. A. Jørgensen, *J. Am. Chem. Soc.*, 2008, **130**, 4897.

17 For selected examples of catalytic enantioselective conjugate addition reactions, see: (a) M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.*, 2004, **126**, 5672. (b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119; (c) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906; (d) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed.*, 2005, **44**, 105; (e) Y. Chi, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.*, 2008, **130**, 5608.

18 (a) G. S. Kottas, L. I. Clarke, D. Horinek, J. Michl, *Chem. Rev.*, 2005, **105**, 1281; (b) T. M. Neubauer, T. van Leeuvan, D. Zhao, A. S. Lubbe, J. C. M. Kistemaker, B. L. Feringa, *Org. Lett.*, 2014, **16**, 4220.

19 (a) J. D. Roberts, W. T. Moreland, W. Frazer, *J. Am. Chem. Soc.*, 1953, **75**, 637; (b) H. D. Holtz, L. M. Stock, *J. Am. Chem. Soc.*, 1964, **86**, 5183; (c) K. Kumar, S. S. Wang, C. N. Sukenik, *J. Org. Chem.*, 1984, **49**, 665.

20 (a) Y. J. Hong, D. J. Tantillo, *J. Am. Chem. Soc.*, 2010, **132**, 5375; (b) L.-S. Shi, M. V. B. Reddy, H.-J. Yan, W.-L. Chang, H.-C. Lin, *J. Chin. Chem. Soc.*, 2006, **53**, 751.

21 CCDC-1024512 (**1e**) contains the supplementary crystallographic data for this paper.