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LETTER

Enantioselective Synthesis of Functionalized 3,4-Disubstituted Dihydro-2(1*H*)-quinolinones via Michael-Hemiaminalization/Oxidation Reaction

Ai-Bao Xia, Xiao-Long Zhang, Tao Wang, Xiao-Hua Du, Dan-Qian Xu*   and Zhen-Yuan Xu*

A novel method is developed for the enantioselective synthesis of highly functionalized 3,4-disubstituted dihydro-2(1*H*)-quinolinones bearing two trans contiguous stereogenic centers with excellent diastereoselectivities (up to >99:1 dr) and high to excellent enantioselectivities (up to >99% ee). The process combines an enantioselective organocatalytic Michael–hemiaminalization reaction and a highly efficient oxidation reaction sequence with good yields and stereoselectivity.

Functionalized 3,4-dihydro-2(1*H*)-quinolinones are privileged scaffolds that can be found in a large number of clinical pharmaceuticals and natural products possessing various biological activities (Figure 1).[1] Considering the medicinal significance of this structural core, these compounds have drawn great attention from synthetic chemists and those in the medicinal field.[2] A number of catalyzed reactions such as transition metal-catalyzed[3,4],

photochemical[5], radical-mediated[6], and other[7] reactions have been carried out for the synthesis of 3,4-dihydro-2(1*H*)-quinolinones. However, to the best of our knowledge, only a few examples involve the asymmetric synthetic approach to construct functionalized 3,4-dihydro-2(1*H*)-quinolinone systems.[8] In most cases, stoichiometric chiral reagents are required. In 2011, Marinetti et al. reported only one example of (S,S)-FerroPHANE promoted [3+2] cyclization to construct chiral functionalized 3,4-dihydro-2(1*H*)-quinolinone.[8f] In 2014, Kim et al. reported one example of reaction to construct chiral functionalized tetrahydroquinoline with cis selectivity, promoted by diphenylprolinol TMS ether as an organocatalyst.[8g] Despite this remarkable progress, the exploration of efficient catalytic asymmetric methods of generating this architecture is still highly desired, particularly those using simple and readily available starting materials under mild organocatalytic conditions.[9]

In this communication, an unprecedented organocatalytic asymmetric method of constructing chiral functionalized 3,4-disubstituted dihydro-2(1*H*)-quinolinones bearing two contiguous stereogenic centers through a highly efficient asymmetric Michael–hemiaminalization/oxidation reaction is proposed.[10] The yields are moderate to high, and the diastereoselectivities and enantioselectivities are excellent, with anti selectivity (Scheme 1).

Figure 1. Examples of biologically active compounds containing functionalized 3,4-dihydro-2(1*H*)-quinolinone

Scheme 1. Design of an organocatalytic asymmetric strategy for synthesizing functionalized 3, 4-dihydro-2(1*H*)-quinolinone

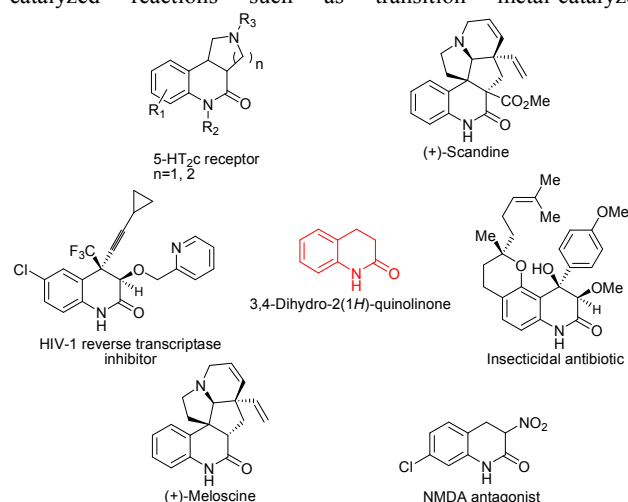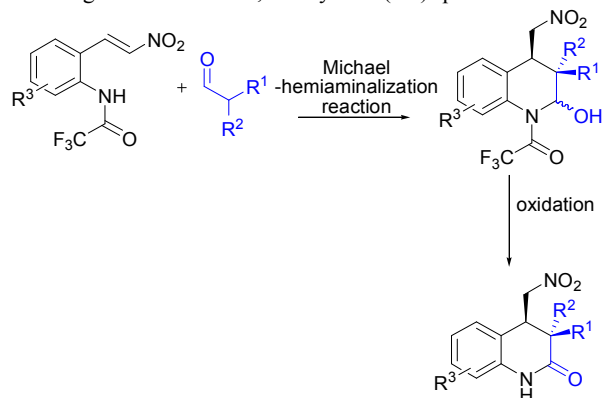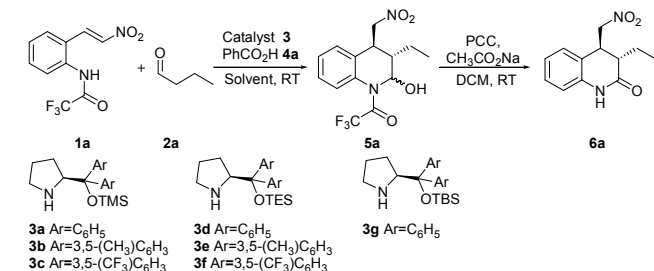In the initial investigation, several Jørgensen‑Hayashi catalysts were screened to evaluate their ability to promote a cascade reaction of N-COCF$_3$-2-(E)-(2-nitrovinyl)aniline **1a** and butyraldehyde **2a** in dichloromethane at room temperature (entries 1‑7 in Table 1). Among the tested Jørgensen‑Hayashi catalysts, **3d** was found to be the best catalyst for the reaction, providing **5a** in 96% yield after 24 h. After further oxidation and deprotection, **5a** with PCC and CH$_3$CO$_2$Na in CH$_2$Cl$_2$ at room temperature afforded 3, 4-dihydro-2(1*H*)-quinolinone 6a in >99:1 dr with corresponding 95% ee (entry 4).[11] Subsequent evaluation of solvent effects showed improved enantioselectivity of up to 99% ee when PhMe was used as solvent (entries 8‑17).

Table 1. Catalyst screening and reaction optimization[a]

3a Ar=C$_6$H$_5$
3b Ar=3,5-(CH$_3$)C$_6$H$_3$
3c Ar=3,5-(CF$_3$)C$_6$H$_3$

3d Ar=C$_6$H$_5$
3e Ar=3,5-(CH$_3$)C$_6$H$_3$
3f Ar=3,5-(CF$_3$)C$_6$H$_3$

3g Ar=C$_6$H$_5$

entry	catalyst **3**	solvent	**5a**/yield[b]	dr[c]	ee(%)[c]
1	**3a**	CH$_2$Cl$_2$	81	32 : 1	96
2	**3b**	CH$_2$Cl$_2$	66	85 : 1	88
3	**3c**	CH$_2$Cl$_2$	87	>99 : 1	50
4	**3d**	CH$_2$Cl$_2$	96	>99 : 1	95
5	**3e**	CH$_2$Cl$_2$	70	>99 : 1	89
6	**3f**	CH$_2$Cl$_2$	81	>99 : 1	96
7	**3g**	CH$_2$Cl$_2$	93	65 : 1	56
8	**3d**	DMF	88	>99 : 1	52
9	**3d**	MeCN	93	>99 : 1	96
10	**3d**	*i*PrOH	89	>99 : 1	97
11	**3d**	CHCl$_3$	91	>99 : 1	98
12	**3d**	THF	83	>99 : 1	97
13	**3d**	1,4-dioxane	89	>99 : 1	96
14	**3d**	Isopropether	95	>99 : 1	98
15	**3d**	PhMe	97	>99 : 1	99
16	**3d**	xylene	84	>99 : 1	97
17	**3d**	PhCF$_3$	92	>99 : 1	97

[a]Unless otherwise stated, the reaction was conducted by stirring in solvent (0.5 mL) using **1a** (0.1 mmol) and **2a** (0.3 mmol) with 20 mol% catalyst **3** and 20 mol% PhCO$_2$H **4a** at room temperature for 24 h. After purification, **5a** and DCM (2 mL) were added to a mixture of PCC (3 equiv.) with CH$_3$CO$_2$Na (3 equiv.) at room temperature under vigorous stirring. [b]Yield of isolated **1a**. [c]The dr ratio of trans-**6** to cis-**6** or ee value of trans-**6**, determined by HPLC analysis on a Chiralcel AS-H.

Under optimized reaction conditions, a series of experiments was performed to investigate the substrate scope for this reaction. N-COCF$_3$-2-(E)-(2-nitrovinyl)aniline **1a** smoothly reacted with a wide array of aldehydes **2** to afford the expected adducts **5** (**5a**–**5p**) in high to excellent yields (70% to >99%) (Table 2). After further oxidation and deprotection at room temperature, the desired chiral products 3, 4-dihydro-2(1*H*)-quinolinones **6a**–**6p** were smoothly obtained in moderate to good yields (50% to 87%), excellent diastereoselectivities (>99:1 dr), and excellent enantioselectivities (92% to >99% ee). Structural variations in the (**2i**), alkene (**2j**), trifluoromethyl (**2k**), cyano (**2l**), and ester (**2m**–**2o**) are possible. Interestingly, the sterically demanding branched aldehyde
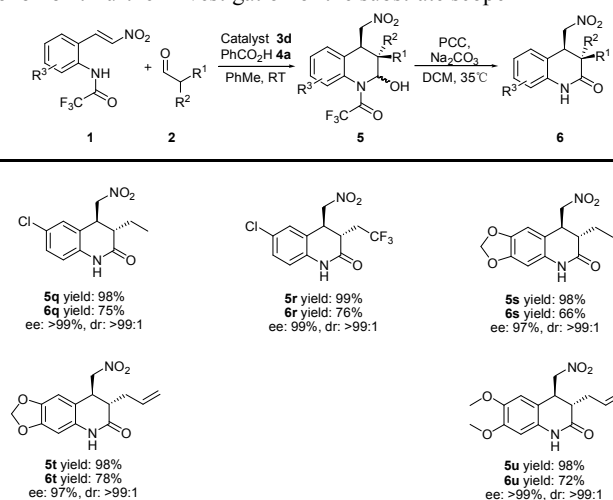
Table 2. Scope of the asymmetric Michael-hemiaminalization/oxidation reaction[a]
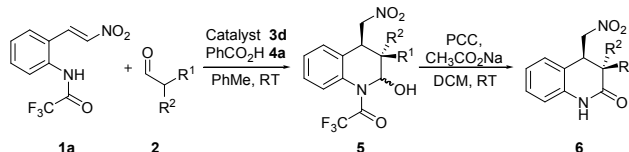
entry	R^1/R^2/**2**	**5**/yield (%)[b]	**6**/yield (%)[b]	dr[c]	ee (%)[c]
1	H/CH$_2$CH$_3$/**2a**	**5a**/97	**6a**/87	>99:1	99
2	H/CH$_3$/**2b**	**5b**/81	**6b**/61	>99:1	>99
3	H/(CH$_2$)$_2$CH$_3$/**2c**	**5c**/86	**6c**/63	>99:1	98
4	H/(CH$_2$)$_3$CH$_3$/**2d**	**5d**/98	**6d**/78	>99:1	>99
5	H/(CH$_2$)$_4$CH$_3$/**2e**	**5e**/87	**6e**/74	>99:1	>99
6	H/(CH$_2$)$_5$CH$_3$/**2f**	**5f**/99	**6f**/76	>99:1	98
7	H/CH(CH$_3$)$_2$/**2g**	**5g**/96	**6g**/77	>99:1	95
8	H/CHCH$_3$(CH$_2$)$_2$CHC(CH$_3$)$_2$/**2h**	**5h**/91	**6h**/73	>99:1	>99
9	H/CH$_2$C$_6$H$_5$/**2i**	**5i**/92	**6i**/75	>99:1	95
10	H/CH$_2$CH=CH$_2$/**2j**	**5j**/94	**6j**/73	>99:1	98
11	H/CH$_2$CF$_3$/**2k**	**5k**/93	**6k**/70	>99:1	92
12	H/CN/**2l**	**5l**/85	**6l**/67	>99:1	>99
13	H/CH$_2$CO$_2$CH$_3$/**2m**	**5m**/97	**6m**/68	>99:1	95
14	H/(CH$_2$)$_2$CO$_2$CH$_3$/**2n**	**5n**/>99	**6n**/66	>99:1	>99
15	H/(CH$_2$)$_3$CO$_2$CH$_3$/**2o**	**5o**/>99	**6o**/70	>99:1	96
16	CH$_3$/CH$_3$/**2p**	**5p**/70	**6p**/50	--	>99

[a]Unless otherwise stated, the reaction was conducted by stirring in PhMe (0.5 mL) using **1a** (0.1 mmol) and **2** (0.3 mmol) with 20 mol% catalyst **3d** and 20 mol% PhCO$_2$H **4a** at room temperature for 24 h. After purification, **5** and DCM (2 mL) was added to a mixture of PCC (3 equiv.) with CH$_3$CO$_2$Na (3 equiv.) at room temperature under vigorous stirring. In the case of racemic samples, 50 mol% DL-proline were used in DMSO. [b]Yield of isolated **1a**. [c]The dr ratio of trans-**6** to cis-**6** or ee value of trans-**6**, determined by chiral-phase HPLC. [d]For 48 h.

Scheme 2. Further investigation of the substrate scope[a, b, c]

5q yield: 98%
6q yield: 75%
ee: >99%, dr: >99:1

5r yield: 99%
6r yield: 76%
ee: 99%, dr: >99:1

5s yield: 98%
6s yield: 66%
ee: 97%, dr: >99:1

5t yield: 98%
6t yield: 78%
ee: 97%, dr: >99:1

5u yield: 98%
6u yield: 72%
ee: >99%, dr: >99:1

[a]The reaction was conducted by stirring in PhMe (0.5 mL) using **1** (0.1 mmol) and **2** (0.3 mmol) with 20 mol% catalyst **3d** and 20 mol% PhCO$_2$H **4a** at room temperature for 24 h. After purification, then **5** and DCM (2 mL) was added to a mixture of PCC (3 equiv.) with Na$_2$CO$_3$ (3 equiv.) at room temperature with vigorous stirring. In the case of racemic samples, 50 mol% DL-proline were used in DMSO. [b]Yield of isolated **1**. [c] The dr ratio of trans-**6** to cis-**6** or ee value of trans-**6**, determined by chiral-phase HPLC.

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component including long-chain alkyl (**2a–2f**), branched alkyl (**2g–2h**), as well as functionalized aromatic ring alkyl (**2p**) was accommodated with little effect on diastereoselectivity or enantioselectivity but high effect on yield (entry 16).

Further studies showed that various electrophiles 1 with different substituents on phenyl were effective substrates (Scheme 2). Results showed that nucleophiles **2** can be used to form **5** in excellent yields (up to >99%). After further oxidation and deprotection with PCC and Na_2CO_3 in CH_2Cl_2 at room temperature, the desired products 6q–6u were furnished in excellent diastereoselectivities (up to >99:1 dr) and enantioselectivities (up to >99% ee) with good yield (66% to 78%).[11] And the proposed structure of the products, including the absolute configuration, could be assigned by X-ray crystal structure analysis of **6q**.[12]
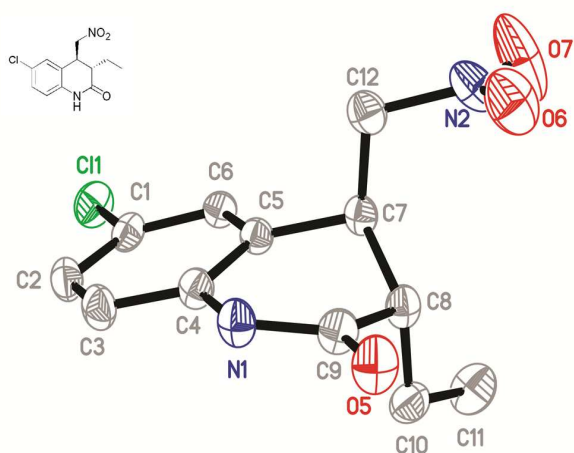

Figure 2. X-ray crystal structure of **6q**.

A one-pot operation was further investigated. Considering that the first Michael–hemiaminalization reaction and second oxidation reaction systems are both alkaline, these systems should not interfere with each other if the proper reaction conditions are used. Thus, the one-pot procedure followed. The Michael–hemiaminalization reaction of **1a** and **2a** proceeded in the presence of 20 mol% of **3d** and **4a** in toluene over 24 h. The toluene solvent was then replaced with DCM, and PCC with CH_3CO_2Na was added at room temperature under vigorous stirring. Compound **6a** was obtained in 81% yield with trans selectivity in excellent diastereoselectivity (>99:1 dr) and enantioselectivity (99% ee) (Scheme 3). The operation can also be performed successfully on gram-scale to obtain 1.9 g of **6a** (81% yield) with the same diastereoselectivity and enantioselectivity under modified conditions (Scheme 3).

Scheme 3. One-pot preparation of **6a**
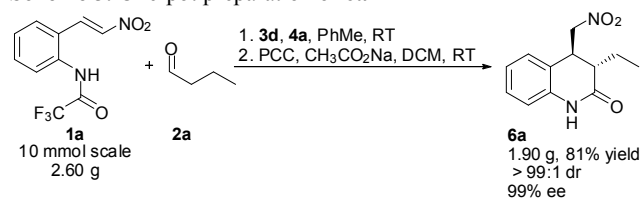
In summary, we described a concise synthesis of highly functionalized 3,4-disubstituted dihydro-2(1*H*)-quinolinones with excellent diastereoselectivities (up to >99:1 dr) and high to excellent enantioselectivities (up to >99% ee) by sequential organocatalytic Michael–hemiaminalization/oxidation reactions under mild reaction conditions. Notably, functionalized 3,4-disubstituted dihydro-2(1*H*)-quinolinones bearing two trans contiguous stereogenic centers were obtained with good yields and stereoselectivity. Further studies on the expansion of the substrate scope and the application of this methodology to other heterocycle syntheses are currently underway in our laboratory and will be reported in due course.

Acknowledgements

Experimental

Solvent (0.5 mL) was added to a mixture of nitroolefins **1** (0.1 mmol) with aldehydes **2** (0.3 mmol) in the presence of 20 mol% catalyst **3d** and 20 mol% $PhCO_2H$ **4a** at room temperature under vigorous stirring. After 1 day, the reaction mixture was extracted with DCM, washed with water, dried, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl ether/petroleum ether = 1:4 as eluent) to yield products **5**. Then, **5** and DCM (2 mL) was added to a mixture of PCC (3 equiv.) with CH_3CO_2Na (3 equiv.) or Na_2CO_3 (3 equiv.) at room temperature under vigorous stirring. After reaction completion, the residue was purified by flash chromatography on silica gel (ethyl ether/petroleum ether = 1:2 as eluent) to yield products **6**. Enantiomeric ratio was determined by HPLC analysis on a chiral column.

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/c000000x/

1   (a) K. Bernauer, G. Enplert, W. Vetter and E. Weiss, *Helv. Chim. Acta* **1969**, *52*, 1886-1905; (b) W. E. Oberhänsli, *Helv. Chim. Acta* **1969**, *52*, 1905-1911; (c) H. Hayashi, Y. Miwa, I. Miki, S. Ichikawa, N. Yoda, A. Ishii, M. Kono and F. Suzuki, *J. Med. Chem.* **1992**, *35*, 4893-4902; (d) R. W. Carling, P. D. Leeson, K. W. Moore, J. D. Smith, C. R. Moyes, I. M. Mawer, S. Thomas, T. Chan, R. Baker, A. C. Foster, S. Grimwood, J. A. Kemp, G. R. Marshall, M. D. Tricklebank and K. L. Saywell, *J. Med. Chem.* **1993**, *36*, **2011**, *50*, 3605; (e) M. Patel, R. J. McHugh, B. C. Cordova, R. M. Klabe, L. T. Bacheler, S. Erickson-Viitanen and J. D. Rodgers, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1943-1945; (f) J. He, U. Lion, I. Sattler, F. A. Gollmick, S. Grabley, J. Cai, M. Meiners, H. Schünke, K. Schaumann, U. Dechert and M. Krohn, *J. Nat. Prod.* **2005**, *68*, 1397-1399; (g) R. Uchida, R. Imasato, K. Shiomi, H. Tomoda and S. ōmura, *Org. Lett.* **2005**, *7*, 5701-5704; (h) S. A. Neff, S. U. Lee, Y. Asami, J. S. Ahn, H. Oh, J. Baltrusaitis, J. B. Gloer and D. T.

Wicklow, *J. Nat. Prod.* **2012**, *75*, 464-472; (i) J. M. Fevig, J. Feng, K. A. Rossi, K. J. Miller, G. Wu, C.-P. Hung, T. Ung, S. E. Malmstrom, G. Zhang, W. J. Keim, M. J. Cullen, K. W. Rohrbach, Q. Qu, J. Gan, M. A. Pelleymounter and J. A. Robl, *Bioorg. Med. Chem. Lett.* **2013**, 23, 330-335.

2   (a) J. P. Michael, *Nat. Prod. Rep.* **1992**, 9, 25-35; (b) J. Michael, P. *Nat. Prod. Rep.* **1995**, 12, 465-475; (c) M. Mąkosza and K. Wojciechowski, *Chem. Rev.* **2004**, 104, 2631-2666; (d) J. P. Michael, *Nat. Prod. Rep.* **2008**, 25, 166-187; (e) V. V. Kouznetsov, *Tetrahedron* **2009**, 65, 2721-2750; (f) W. A. Loughlin, *Mini-Rev. Med. Chem.* **2010**, 10, 1139-1155.

3   Palladium-catalyzed reactions: (a) J. P. Wolfe, R. A. Rennels and S. L. Buchwald, *Tetrahedron* **1996**, *52*, 7525-7546; (b) B. E. Ali, K. Okuro, G. Vasapollo and H. Alper, *J. Am. Chem. Soc.* **1996**, *118*, 4264-4270; (c) B. H. Yang, and S. L. Buchwald, *Org. Lett.* **1999**, *1*, 35-37; (d) F. Ye and H. Alper, *Adv. Synth. Catal.* **2006**, *348*, 1855-1861; (e) T. Tsuritani, Y. Yamamoto, M. Kawasaki and T. Mase, *Org. Lett.* **2009**, *11*, 1043-1045; (f) X. F. François, C. Jérôme, Z. Cécile and F. Eric, *Chem. -Eur. J.* **2009**, *15*, 7238-7245.

4   Rhodium-catalyzed reactions: (a) K. -i. Fujita, Y. Takahashi, M. Owaki, K. Yamamoto and R. Yamaguchi, *Org. Lett.* **2004**, *6*, 2785-2788; (b) J. Horn, H. Y. Li, S. P. Marsden, A. Nelson, R. J. Shearer, A. J. Campbell, D. House and G. G. Weingarten, *Tetrahedron* **2009**, *65*, 9002-9007; (c) J. O. Park and S. W. Youn, *Org. Lett.* **2010**, *12*, 2258-2261.

5   Photochemical-mediated reaction: I. Akritopoulou-Zanze, A. Whitehead, J. E. Waters, R. F. Henry and S. W. Djuric, *Tetrahedron Lett.* **2007**, *48*, 3549-3552.

6   Radical-mediated reactions: (a) K. Jones, J. Wilkinson and R. Ewin, *Tetrahedron Lett.* **1994**, *35*, 7673-7676; (b) W. Zhou, L. Zhang and N. Jiao, *Tetrahedron* **2009**, *65*, 1982-1987; (c) T. Tsubusaki, H. Nishino, *Tetrahedron* **2009**, *65*, 9448-9459; (d) W.-P. Mai, J.-T. Wang, L.-R. Yang, J.-W. Yuan, Y.-M. Xiao, P. Mao and L.-B. Qu, *Org. Lett.* **2014**, *16*, 204-207.

7   Other reactions: (a) M. Cherest and X. Lusinchi, *Tetrahedron Lett.* **1989**, *30*, 715-718; (b) K. Li, L. N. Foresee and J. A. Tunge, *J. Org. Chem.* **2005**, *70*, 2881-2883; (c) K. L. Turner, T. M. Baker, S. Islam, D. J. Procter and M. Stefaniak, *Org. Lett.* **2006**, *8*, 329-332.

8   Asymmetric examples: (a) T. W. Johnson and E. J. Corey, *J. Am. Chem. Soc.* **2001**, *123*, 4475-4479; (b) T. Bach, B. Grosch, T. Strassner and E. Herdtweck, *J. Org. Chem.* **2003**, *68*, 1107-1116; (c) M. Dressel and T. Bach, *Org. Lett.* **2006**, *8*, 3145-3147; (d) M. Harmata and X. Hong, *Org. Lett.* **2007**, *9*, 2701-2704; (e) A. Bakowski, M. Dressel, A. Bauer and T. Bach, *Org. Biomol. Chem.* **2011**, *9*, 3516-3529; (f) M. Neel, J. Gouin, A. Voituriez and A. Marinetti, *Synthesis* **2011**, 2003-2009; (g) Y. Lee and S. -G. Kim, *J. Org. Chem.* **2014**, *79*, 8234-8243.

9   For selected books and reviews on organocatalysis, see: (a) Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis (Eds: A. Berkessel, H. Gröger), Wiley-VCH, Weinheim, **2004**; (b) Enantioselective Organocatalysis (Eds: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; (c) B. List and J. W. Yang, *Science* **2006**, *313*, 1584-1586; (d) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. C. Vo, *Drug Discovery Today* **2007**, *12*, 8-27; (e) D. W. C. MacMillan, *Nature* **2008**, *455*, 304-308; (f) A. Dondoni and A. Massi, *Angew. Chem.*

2008, *120*, 4716-4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638-4660; (g) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232-6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138-6171; (h) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178-2189; (i) E. Marqués-López, R. P. Herrera and M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138-1167; (j) C. Vaxelaire, P. Winter and M. Christmann, *Angew. Chem.* **2011**, *123*, 3685-3687; *Angew. Chem. Int. Ed.* **2011**, *50*, 3605-3607; (k) J. Alemán and S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774-793.

10 (a) D. Enders, C. Wang, X. N. Yang and G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 2869-2874; (b) D. -F. Lu, Y. -J. Li and Y. -F. Gong, *J. Org. Chem.* **2010**, *75*, 6900-6907; (c) B. -C. Hong, P. Kotame and J. -H. Liao, *Org. Biomol. Chem.* **2011**, 9, 382-386; (d) D. B. Ramachary, M. S. Prasad and R. Madhavachary, *Org. Biomol. Chem.* **2011**, *9*, 2715-2721; (e) D. Enders, G. Urbanietz, R. Hahn, G. Raabe, *Synthesis* **2012**, 773-782; (f) G. Urbanietz, I. Atodiresei, D. Enders, *Synthesis* **2014**, 1261-1269.

11 Please see the Supporting Information.

12 CCDC 1027104 (for **6q**) 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.

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