Asymmetric Catalysis

International Edition: DOI: 10.1002/anie.201506701
German Edition: DOI: 10.1002/ange.201506701

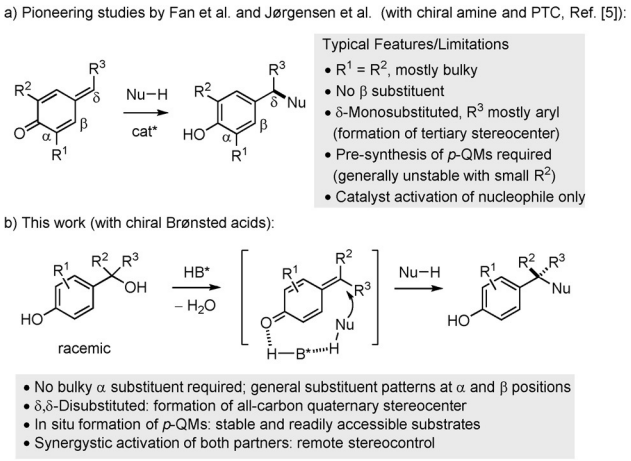
Catalytic Asymmetric 1,6-Conjugate Addition of *para*-Quinone Methides: Formation of All-Carbon Quaternary Stereocenters

*Zhaobin Wang, Yuk Fai Wong, and Jianwei Sun**

Abstract: *Described herein is a general and mild catalytic asymmetric 1,6-conjugate addition of para-quinone methides (p-QMs), a class of challenging reactions with previous limited success. Benefiting from chiral Brønsted acid catalysis, which allows in situ formation of p-QMs, our reaction expands the scope to general p-QMs with various substitution patterns. It also enables efficient intermolecular formation of all-carbon quaternary stereocenters with high enantioselectivity.*

para-Quinone methides (*p*-QMs) are important molecules, which are not only observed in various natural products and pharmaceuticals, but also involved in a number of biologically significant processes.[1–3] Owning to their intrinsic electrophilic nature, *p*-QMs are also versatile species in a wide range of useful organic reactions, particularly 1,6-conjugation additions.[1,4–6] However, for a long time, the exploration of their reactivity has been confined to the domain of non-asymmetric synthesis, which is in sharp contrast to *ortho*-quinone methides (*o*-QMs), whose asymmetric reactions have received considerable attention.[7] Indeed, asymmetric induction for *p*-QMs upon activation by a chiral catalyst is substantially more challenging than that for *o*-QMs because of the increased distance between the catalyst activation site (carbonyl) and the reaction center.[8] Consequently, the development of catalytic asymmetric reactions of *p*-QMs is still in its infancy.

Recently, the groups of Fan and Jørgensen sequentially reported their pioneering studies on asymmetric 1,6-conjugate addition of *p*-QMs employing enamine and phase-transfer catalysis, respectively (Scheme 1 a).[5] There are several features of these two examples. Mechanistically, their approaches do not involve the activation of *p*-QMs. Instead, a catalytically generated chiral nucleophile is responsible for the excellent facial selectivity on the *p*-QMs, thereby bypassing the above-mentioned challenging remote stereocontrol. Moreover, the *p*-QMs employed in these two reactions are pre-synthesized and mostly bear two of the same bulky α-substituents (e.g., *t*Bu) and no β-substituent. The δ-position is uniformly monosubstituted, mostly with an aryl group, to form a tertiary stereocenter. The structural limitation might be partly due to the general instability of *p*-QMs, particularly with small α-substituents. Nevertheless,



Scheme 1. Catalytic asymmetric 1,6-addition to *p*-QMs.

excellent efficiency and stereoselectivity have been achieved, and these examples represent significant advances in asymmetric reactions of *p*-QMs.

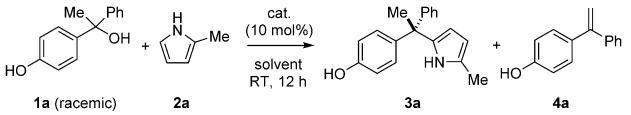
Intrigued by the recent success of chiral phosphoric acid catalyzed asymmetric reactions of *o*-QMs,[7d–p] as well as our preliminary efforts,[7i] we envisioned the possibility of further advancing the study of *p*-QMs with this approach (Scheme 1 b). The compatible in situ generation of *p*-QMs from stable *p*-hydroxybenzyl alcohols is expected to obviate pre-synthesis of unstable *p*-QMs, and can significantly expand the reaction scope and simplify operations. However, the remote stereocontrol by a catalyst in the 1,6-conjugate addition is necessary and substantially challenging. Herein we report the realization of such an efficient and mild protocol, which is not only amenable to various substitution patterns, but also capable of forming all-carbon quaternary stereocenters with excellent remote stereocontrol.[9]

We started the exploration with the racemic tertiary alcohol **1a** as the *p*-QM precursor (Table 1). 2-Methylpyrrole (**2a**) was used as a model nucleophile in view of its good nucleophilicity, as well as the wide utility of pyrroles.[10] Gratifyingly, various chiral phosphoric acids can smoothly catalyze the intermolecular C–C bond formation at room temperature. The desired triarylethane **3a**, bearing an all-carbon quaternary stereocenter, was formed as the major product,[11] together with minor dehydration product **4a**. Among all the evaluated acid catalysts (see the Supporting Information for more details), the catalyst **C3**, substituted with 9-anthryl groups, proved most effective (96% yield, 82% *ee*, entry 6).[12] Further solvent screening indicated that $CHCl_3$ can slightly improve the enantioselectivity (entry 7). The use

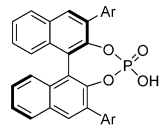
[*] Dr. Z. Wang, Y. F. Wong, Prof. J. Sun
Department of Chemistry
The Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, Hong Kong SAR (China)
E-mail: sunjw@ust.hk

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201506701.

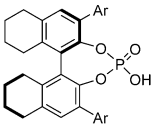
Table 1: Reaction optimization.[a]



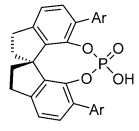
1a (racemic) **2a** **3a** **4a**



(*R*)-**A1**: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$
(*R*)-**A2**: Ar = 9-anthryl



(*R*)-**B1**: Ar = 9-anthryl



(*S*)-**C1**: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$
(*S*)-**C2**: Ar = 9-phenanthryl
(*S*)-**C3**: Ar = 9-anthryl

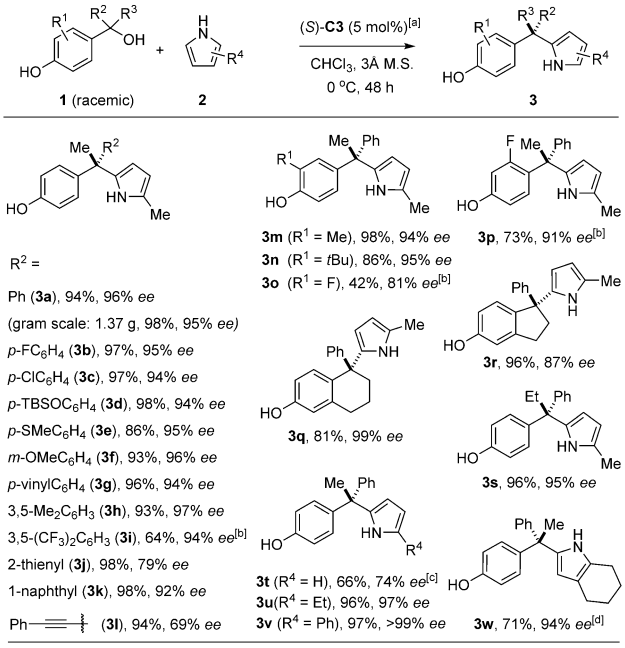
Entry	Cat.	Solvent	Yield [%][b]		*ee* [%][b]
			3a	**4a**	
1	(*R*)-**A1**	CH_2Cl_2	91	8	44
2	(*R*)-**A2**	CH_2Cl_2	96	3	48
3	(*R*)-**B1**	CH_2Cl_2	94	5	43
4	(*S*)-**C1**	CH_2Cl_2	58	28	33
5	(*S*)-**C2**	CH_2Cl_2	91	8	76
6	(*S*)-**C3**	CH_2Cl_2	96	4	82
7	(*S*)-**C3**	$CHCl_3$	96	4	86
8[c,d]	(*S*)-**C3**	$CHCl_3$	21	3	92
9[d,e]	(*S*)-**C3**	$CHCl_3$	95	4	92
10[e,f]	(*S*)-**C3**	$CHCl_3$	94	5	95

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), solvent (1.0 mL). [b] Yield was determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. The *ee* value was determined by HPLC. [c] Run with 4 Å molecular sieves (M.S.; 20 mg). [d] Run for 24 h. [e] Run with 3 Å molecular sieves (20 mg). [f] Run at 0 °C for 48 h.

of either 3 Å or 4 Å molecular sieves as an additive further enhanced the enantioselectivity, but the latter significantly slows down the reaction (entries 8 and 9). Finally, the reaction proceeded with both excellent efficiency and enantioselectivity at 0 °C.

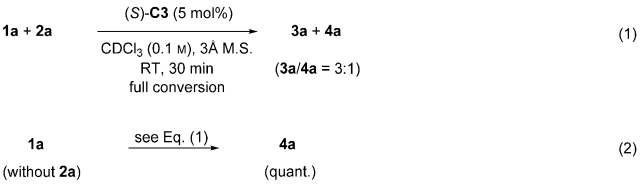
The optimal reaction conditions are applicable to a wide range of substrates (Scheme 2; **3a–s**). They all smoothly participated in the efficient C–C bond-forming process. Notably, various substituents at different positions on the substrates were tolerated. This excellent generality benefits largely from the compatible in situ formation of the unstable *p*-QMs. In addition to a δ-methyl group, larger alkyl groups in both acyclic and cyclic contexts do not affect the efficiency (**3q–s**). Other substituted pyrroles are also good nucleophiles (**3t–w**). The mild reaction conditions are compatible with various functional groups, such as silyl-protected alcohols, ethers, thioethers, alkenes, and alkynes. A gram-scale synthesis of **3a**, with the same protocol, also worked comparably well. Notably, the remote stereocontrol in establishing these acyclic all-carbon quaternary stereocenters is remarkable.[8,9]

To understand the competing dehydration process (formation of **4a**), the reaction progress was carefully monitored by ^{1}H NMR spectroscopy [Eq. (1)]. It was found that the reaction of **1a** and **2a** in $CDCl_3$ reached complete conversion within 30 minutes to form a mixture of **3a** and **4a**. The ratio of **3a**/**4a** gradually increased over time, thus indicating that **4a**

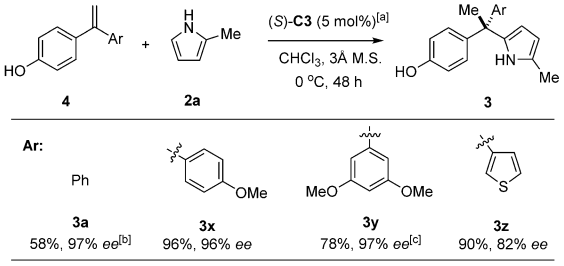


Scheme 2. Reaction scope. [a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), 3 Å M.S. (40 mg), solvent (2.0 mL). Yield of isolated product is given. [b] Run at 50 °C with 10 mol% of (*S*)-**C3**. [c] Run for 72 h. [d] Run at RT. TBS = *tert*-butyldimethylsilyl.

can be transformed into **3a**. The rapid dehydration was also confirmed in the absence of **2a** [Eq. (2)].



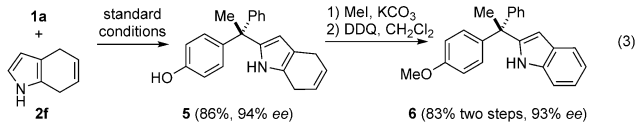
Inspired by these results, we further confirmed that the styrenes **4** are also competent substrates (Scheme 3). They can achieve equally high enantioselectivity in the asymmetric C–C bond-formation process, and is consistent with the involvement of common intermediates. However, the reac-



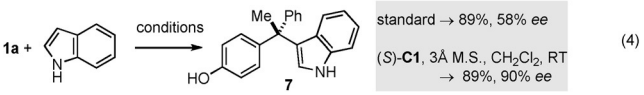
Scheme 3. Reaction with styrene-type substrates. [a] Reaction conditions: **4** (0.2 mmol), **2a** (0.4 mmol), 3 Å M.S. (40 mg), solvent (2.0 mL). Yield of isolated product is given. [b] Low but clean conversion (ca. 60%). [c] Run at RT.

tions of **4** proceed more slowly than those of the corresponding tertiary alcohols **1**. The long reaction time required with **1** is indeed to consume the rapidly in situ generated styrenes **4**.

To further expand the utility of our process, 4,7-dihydroindole (**2f**) was also employed as a nucleophile to synthesize the triarylethane **5** with high efficiency and enantioselectivity [Eq. (3); DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone]. After simple protection and oxidation, it can be easily transformed into the highly enantioenriched 2-substituted indole **6**.[13] Indole can also serve as a nucleophile to form the 3-subsituted product **7** in good yield, but with low enantioselectivity [Eq. (4)]. However, further optimization, inspired by our preliminary results, identified **C1** to be superior,[7i] thus furnishing the desired product with excellent efficiency and enantioselectivity at room temperature.

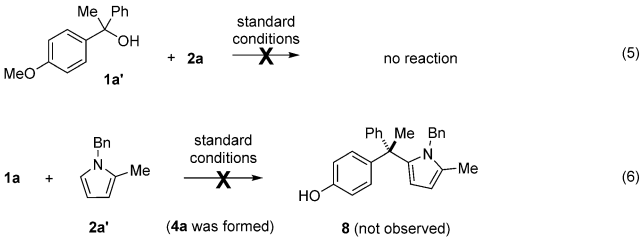


(3)



(4)

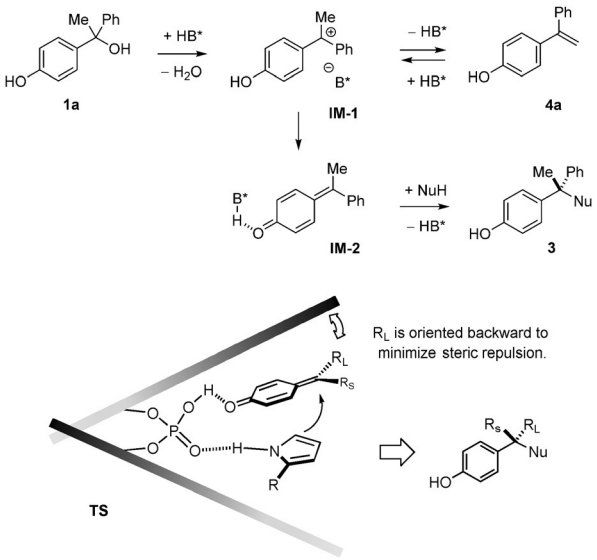
We carried out some control experiments to gain further insights into the mechanism. The methyl-protected substrate **1a′** is not reactive [Eq. (5)], thus suggesting that successful formation of the *p*-QM intermediate is key to the process. Furthermore, the N-protected pyrrole **2a′** is not reactive either, thus indicating the important role of the N–H moiety, presumably as a hydrogen bond donor [Eq. (6)].



(5)

(6)

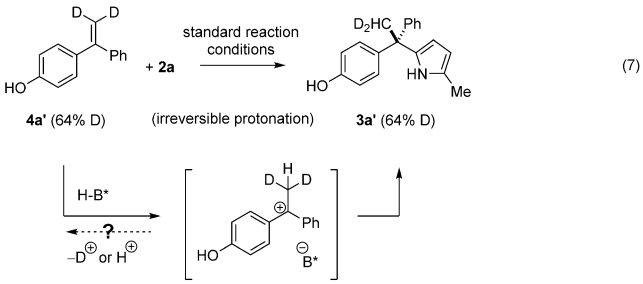
A possible mechanism is proposed in Scheme 4 using **1a** as the representative substrate. Initial protonation of the tertiary alcohol followed by H_2O extrusion forms the ion pair **IM-1**. Next, the phosphate anion may approach the phenolic proton to form the activated *p*-QM **IM-2**. Subsequent nucleophilic 1,6-conjugate addition takes places to complete the process. We also proposed the stereodetermining transition state **TS**, in which the phosphoryl oxygen atom interacts with the nucleophile N–H through hydrogen bonding. We did not observe obvious nonlinear effects, which is consistent with



Scheme 4. Proposed mechanism and transition state.

only one catalyst molecule responsible for the bifunctional activation of both substrates. In the **TS**, the larger δ substituent is oriented towards the back to minimize steric repulsion with the top-front anthryl substituent, and is in agreement with the observed product stereochemistry.

In the above mechanism, the styrene **4a** can be formed as a byproduct via **IM-1** by E1 elimination (Scheme 4). Since **4a** is a reactive substrate, we also studied the kinetics of this C–C bond-forming process. The reaction is first-order in catalyst (see the Supporting Information for details). Furthermore, the deuterated styrene **4a′** was subjected to the standard reaction conditions. No deuterium content loss on the product methyl group was observed [Eq. (7)], thus suggesting that the protonation step is irreversible and might be rate-limiting.[14] Indeed, these results are consistent with the observed slow reaction rate with **4** (vs. **1**) because protonation of **4** has a relatively high barrier.



(7)

In conclusion, we have developed a new general and mild catalytic asymmetric 1,6-conjugate addition process of *p*-QMs. It represents not only a new member of the small family of asymmetric reactions of *p*-QMs, but also the first of such processes with general scope enabling efficient and mild formation of all-carbon quaternary stereocenters. Benefiting from the in situ formation of *p*-QMs, our process does not

require substrates with bulky α-substituents or δ-monosubstitution. The remote stereocontrol for the intermolecular C–C bond formation is remarkably efficient. Mechanistic studies involving control reactions, kinetics, isotopic labeling, and nonlinear effects provided important insights into the reaction mechanism. The phosphoric acid molecule serves as a bifunctional catalyst to synergistically activate both reaction partners. This model will shed light on future development of more asymmetric reactions of *p*-QMs.

Acknowledgements

Financial support was provided by HKUST, Hong Kong RGC (GRF 604513, ECS605812, and M-HKUST607/12).

Keywords: asymmetric catalysis · heterocycles · nucleophilic addition · organocatalysis · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 13711 – 13714
Angew. Chem. **2015**, *127*, 13915 – 13918

[1] a) A. B. Turner, *Q. Rev. Chem. Soc.* **1964**, *18*, 347 – 360; b) H.-U. Wagner, R. Gompper in *The Chemistry of the Quinonoid Compounds*, *Vol. 2* (Ed.: S. Patai), Wiley, New York, **1974**, chap. 18, pp. 1145 – 1178; c) M. G. Peter, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 555 – 570; *Angew. Chem.* **1989**, *101*, 572 – 587; d) T. Itoh, *Prog. Polym. Sci.* **2001**, *26*, 1019 – 1059; e) *Quinone Methides* (Ed.: S. E. Rokita), Wiley, Hoboken, **2009**; f) M. M. Toteva, J. P. Richard, *Adv. Phys. Org. Chem.* **2011**, *45*, 39 – 91; g) A. Parra, M. Tortosa, *ChemCatChem* **2015**, *7*, 1524 – 1544.

[2] a) K.-i. Takao, T. Sasaki, T. Kozaki, Y. Yanagisawa, K.-i. Tadano, A. Kawashima, H. Shinonaga, *Org. Lett.* **2001**, *3*, 4291 – 4294; b) B. E. Barragán-Huerta, J. Peralta-Cruz, R. F. González-Laredo, J. Karchesy, *Phytochemistry* **2004**, *65*, 925 – 928; c) H. J. Martin, T. Magauer, J. Mulzer, *Angew. Chem. Int. Ed.* **2010**, *49*, 5614 – 5626; *Angew. Chem.* **2010**, *122*, 5746 – 5758; d) R. Jansen, K. Gerth, H. Steinmetz, S. Reinecke, W. Kessler, A. Kirschning, R. Müller, *Chem. Eur. J.* **2011**, *17*, 7739 – 7744.

[3] a) A. A. Larsen, *Nature* **1969**, *224*, 25 – 27; b) D. Hamels, P. M. Dansette, E. A. Hillard, S. Top, A. Vessières, P. Herson, G. Jaouen, D. Mansuy, *Angew. Chem. Int. Ed.* **2009**, *48*, 9124 – 9126; *Angew. Chem.* **2009**, *121*, 9288 – 9290; c) G. B. Messiano, T. da Silva, I. R. Nascimento, L. M. X. Lopes, *Phytochemistry* **2009**, *70*, 590 – 596; d) R. Dehn, Y. Katsuyama, A. Weber, K. Gerth, R. Jansen, H. Steinmetz, G. Höfle, R. Müller, A. Kirschning, *Angew. Chem. Int. Ed.* **2011**, *50*, 3882 – 3887; *Angew. Chem.* **2011**, *123*, 3968 – 3973; e) C. Sridar, J. D'Agostino, P. F. Hollenberg, *Drug Metab. Dispos.* **2012**, *40*, 2280 – 2288.

[4] Selected non-asymmetric reactions: a) S. R. Angle, K. D. Turnbull, *J. Am. Chem. Soc.* **1989**, *111*, 1136 – 1138; b) S. R. Angle, D. O. Arnaiz, *J. Org. Chem.* **1990**, *55*, 3708 – 3710; c) S. R. Angle, D. O. Arnaiz, J. P. Boyce, R. P. Frutos, M. S. Louie, H. L. Mattson-Arnaiz, J. D. Rainier, K. D. Turnbull, W. Yang, *J. Org. Chem.* **1994**, *59*, 6322 – 6337; d) W. Baik, H. J. Lee, J. M. Jang, S. Koo, B. H. Kim, *J. Org. Chem.* **2000**, *65*, 108 – 115; e) V. Reddy, R. V. Anand, *Org. Lett.* **2015**, *17*, 3390 – 3393.

[5] Catalytic asymmetric 1,6-addition of *p*-QMs: a) W. D. Chu, L. F. Zhang, X. Bao, X. H. Zhao, C. Zeng, J. Y. Du, G. B. Zhang, F. X. Wang, X. Y. Ma, C. A. Fan, *Angew. Chem. Int. Ed.* **2013**, *52*, 9229 – 9233; *Angew. Chem.* **2013**, *125*, 9399 – 9403; b) L. Caruana, F. Kniep, T. K. Johansen, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2014**, *136*, 15929 – 15932.

[6] Asymmetric anionic polymerization of *p*-QMs (all with very low enantioselectivity, < 10 % *ee*): a) N. Nakagaki, T. Uno, M. Kubo, T. Itoh, *J. Polym. Sci. Part A* **2009**, *47*, 5923 – 5927; b) R. Nakagawa, T. Uno, M. Kubo, T. Itoh, *Polym. Bull.* **2012**, *68*, 1831 – 1844.

[7] Reviews on *o*-QMs (Ref [7a–c]) and examples of chiral phosphoric acid catalysis (Ref [7d–p]): a) R. W. Van De Water, T. R. R. Pettus, *Tetrahedron* **2002**, *58*, 5367 – 5405; b) T. P. Pathak, M. S. Sigman, *J. Org. Chem.* **2011**, *76*, 9210 – 9215; c) N. J. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160 – 9173; d) D. Wilcke, E. Herdtweck, T. Bach, *Synlett* **2011**, 1235 – 1238; e) M. Rueping, U. Uria, M.-Y. Lin, I. Atodiresei, *J. Am. Chem. Soc.* **2011**, *133*, 3732 – 3735; f) O. El-Sepelgy, S. Haseloff, S. K. Alamsetti, C. Schneider, *Angew. Chem. Int. Ed.* **2014**, *53*, 7923 – 7927; *Angew. Chem.* **2014**, *126*, 8057 – 8061; g) C.-C. Hsiao, H.-H. Liao, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 13258 – 13263; *Angew. Chem.* **2014**, *126*, 13474 – 13479; h) W. Zhao, Z. Wang, B. Chu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 1910 – 1913; *Angew. Chem.* **2015**, *127*, 1930 – 1933; i) Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin, J. Sun, *J. Am. Chem. Soc.* **2015**, *137*, 383 – 389; j) R.-Y. Zhu, C.-S. Wang, J. Zheng, F. Shi, S.-J. Tu, *J. Org. Chem.* **2014**, *79*, 9305 – 9312; k) C.-C. Hsiao, S. Raja, H.-H. Liao, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, *54*, 5762 – 5765; *Angew. Chem.* **2015**, *127*, 5854 – 5857; l) S. Saha, S. K. Alamsetti, C. Schneider, *Chem. Commun.* **2015**, *51*, 1461 – 1464; m) S. Saha, C. Schneider, *Chem. Eur. J.* **2015**, *21*, 2348 – 2352; n) S. Saha, C. Schneider, *Org. Lett.* **2015**, *17*, 648 – 651; o) G. C. Tsui, L. Liu, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 7703 – 7706; *Angew. Chem.* **2015**, *127*, 7814 – 7818; p) J.-J. Zhao, S.-B. Sun, S.-H. He, Q. Wu, F. Shi, *Angew. Chem. Int. Ed.* **2015**, *54*, 5460 – 5464; *Angew. Chem.* **2015**, *127*, 5550 – 5554.

[8] Reviews and examples of asymmetric 1,6-addition reactions: a) A. G. Csákÿ, G. de La Herrán, M. C. Murcia, *Chem. Soc. Rev.* **2010**, *39*, 4080 – 4102; b) A. T. Biju, *ChemCatChem* **2011**, *3*, 1847 – 1849; c) E. M. P. Silva, A. M. S. Silva, *Synthesis* **2012**, 3109 – 3128; d) L. Dell'Amico, Ł. Albrecht, T. Naicker, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 8063 – 8070.

[9] a) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593 – 4623; b) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295 – 7306.

[10] Reviews of pyrroles: a) B. A. Trofimov, A. I. Mikhaleva, E. Y. Schmidt, L. N. Sobenina, *Chemistry of Pyrroles*, CRC, Boca Raton, FL, **2015**; b) J. T. Gupton, *Top. Heterocycl. Chem.* **2006**, *2*, 53 – 92; c) H. Fan, J. Peng, M. T. Hamann, J.-F. Hu, *Chem. Rev.* **2008**, *108*, 264 – 287.

[11] Reviews and examples on the utility of 1,1,1-triarylalkanes: a) M. S. Shchepinov, V. A. Korshun, *Chem. Soc. Rev.* **2003**, *32*, 170 – 180; b) V. Nair, S. Thomas, S. C. Mathew, K. G. Abhilash, *Tetrahedron* **2006**, *62*, 6731 – 6747; c) R. Palchaudhuri, V. Nesterenko, P. J. Hergenrother, *J. Am. Chem. Soc.* **2008**, *130*, 10274 – 10281; d) M. K. Parai, G. Panda, V. Chaturvedi, Y. K. Manju, S. Sinha, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289 – 292.

[12] The catalyst **C3** was first reported by List and co-workers: S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534 – 18537.

[13] a) R. J. Sundberg, *Indoles*; Academic Press: London, **1996**; b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489 – 4497; c) M. Zeng, S.-L. You, *Synlett* **2010**, 1289 – 1301.

[14] If the protonation step is reversible, the reverse deprotonation may eliminate D^+, which can scramble with the phenolic H^+. It would ultimately cause D content loss at the methyl group of the product.

Received: July 20, 2015
Published online: September 22, 2015

