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# Organocatalytic Enantioselective Hydroxymethylation of Oxindoles with Paraformaldehyde as C1 Unit

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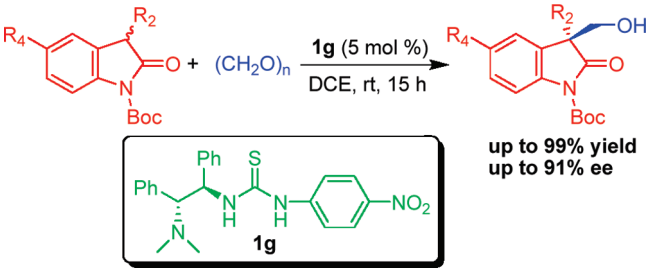


A bifunctional thiourea−tertiary amine-catalyzed asymmetric hydroxymethylation of 3-substituted oxindoles using paraformaldehyde as the C1 unit was developed. A wide scope of oxindoles, bearing C3 sterically congested quaternary carbon centers, were smoothly obtained in good to excellent yields (up to 99%) and high enantioselectivities (up to 91% ee) under mild reaction conditions. A more significant feature of this approach employs cheap and readily available paraformaldehyde as a hydroxymethylation C1 unit, which is activated by chiral bifunctional thiourea organocatalysts.

Chiral 3,3-disubstituted 2-oxindole substructures are present in many biologically active natural products and pharmaceutical compounds.[1,2] Recently, some progress has been described in the development of efficient methods to construct functionalized chiral 3,3-disubstituted 2-oxindole scaffolds.[3,4] In this regard, various electrophiles have been investigated for the asymmetric reactions with prochiral 3-substituted oxindoles as donors. However, to the best of our knowledge, only a single example, reported by Feng and co-workers, describes a direct asymmetric aldol-type reaction of 3-substituted oxindoles with aldehyde (phenylglyoxal derivatives) using *N*,*N*′-dioxide−$Sc(OTf)_3$ complex as catalyst.[3k] Thus, it is evident that there remains further need for synthetic approaches of oxindoles with aldehydes to access diversely structured 3,3-disubstituted 2-oxindoles.

Enantioselective hydroxymethylation of carbonyl compounds at their α-position with formaldehyde as the C1 unit is one useful method for constructing chiral building blocks in organic synthesis, and some progress has been obtained

(1) For selected reviews, see: (a) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66. (b) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (d) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (e) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(2) For selected examples, see: (a) Wearing, X. Z.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4237. (b) Albrecht, B. K.; Williams, R. M. *Org. Lett.* **2003**, *5*, 197. (c) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043. (d) Abadi, A. H.; Abou-Seri, S. M.; Abdel-Rahman, D. E.; Klein, C.; Lozach, O.; Meijer, L. *Eur. J. Med. Chem.* **2006**, *41*, 296. (e) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087. (f) Ruck, R. T.; Huffman, M. A.; Kim, M. M.; Shevlin, M.; Kandur, W. V.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4711.

(3) For the synthesis of 3,3-disubstituted oxindoles via transition-metal-catalyzed asymmetric reactions, see: (a) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164. (b) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027. (c) Toullec, P. Y.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2006**, *8*, 2715. (d) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (e) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488. (f) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040. (g) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946. (h) Hanhan, N. V.; Sahin, A. H.; Chang, W.; Fettinger, J. C.; Franz, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 744. (i) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548. (j) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308. (k) Shen, K.; Liu, X.; Zheng, K.; Li, W.; Hu, X.; Lin, L.; Feng, X. *Chem.−Eur. J.* **2010**, *16*, 3736.

(4) For the synthesis of 3,3-disubstituted oxindoles via organocatalytic asymmetric reactions, see: (a) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921. (b) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418. (c) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670. (d) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925. (e) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8666. (f) Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Chem.−Eur. J.* **2008**, *14*, 8079. (g) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157. (h) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583. (i) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593. (j) Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14. (k) Jiang, K.; Peng, J.; Cui, H.-L.; Chen, Y.-C. *Chem. Commun.* **2009**, 3955. (l) Cheng, L.; Liu, L.; Jia, H.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874. (m) Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou., J. *Chem. Commun.* **2009**, 6753. (n) Cheng, L.; Liu, L.; Jia, H.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2009**, *74*, 4650. (o) Galzerano, P.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Giannichi, B.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.−Eur. J.* **2009**, *15*, 7846. (p) He, R.; Ding, C.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4559. (q) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (r) Li, X.; Xi, Z.-G.; Luo, S.; Cheng, J.-P. *Org. Biomol. Chem.* **2010**, *8*, 77. (s) Li, X.; Zhang, B.; Xi, Z.-G.; Luo, S. Z.; Cheng, J.-P. *Adv. Synth. Catal.* **2010**, *352*, 416. (t) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368. (u) Bui, T.; Syed, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2009**, *131*, 8758. (v) Bui, T.; Candeias, N. R.; Barbas, C. F. *j. Am. Chem. Soc.* **2010**, *132*, 5574.

(5) For direct aldol reactions involving formaldehyde with transition-metal catalysts, see: (a) Kuwano, R.; Miyazaki, H.; Ito, Y. *Chem. Commun.* **1998**, 71. (b) Kuwano, R.; Miyazaki, H.; Ito, Y. *J. Organomet. Chem.* **2000**, *603*, 18. (c) Fukuchi, I.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2007**, *349*, 509. (d) Mouri, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2009**, 5138. (e) Kobayashi, S.; Kokubo, M.; Kawasumi, K.; Nagano, T. *Chem. Asian J.* **2010**, *5*, 490.

(6) For direct aldol reactions involving formaldehyde with organocatalysts, see: (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (b) Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 6117. (c) Fujii, M.; Sato, Y.; Aida, T.; Yoshihara, M. *Chem. Express* **1992**, *7*, 309. (d) Boeckman, R. K., Jr.; Miller, J. R. *Org. Lett.* **2009**, *11*, 4544.



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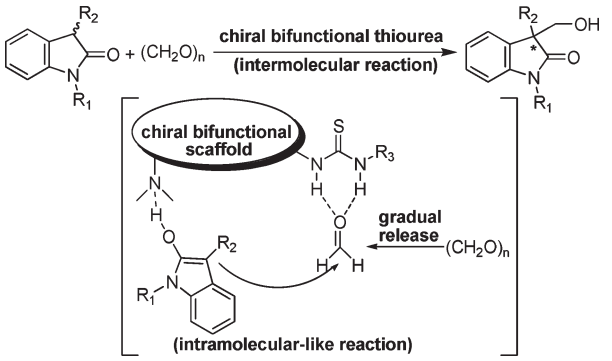
**SCHEME 1**




in this area.[5−7] However, the use of formaldehyde as a useful C1 unit in direct catalytic asymmetric aldol reactions is relatively limited.[5−7] Presumably, this limitation is due to the special chemical properties of formaldehyde, such as (i) high reactivity and (ii) the source of purely monomeric formaldehyde (*traditionally exists as aqueous formaldehyde solution, i.e., formalin*). On the other hand, Córdova and Boeckman independently reported the direct enantioselective hydroxymethylation of aldehydes utilizing organocatalysts.[6b,d] In this context, we envisioned that the widely available paraformaldehyde would serve as a C1 electrophile instead of formaldehyde because its polymeric structure allows the gradual release of monomeric formaldehyde under suitable reaction conditions. This gradual release is favorable for keeping a low concentration of formaldehyde monomer in the reaction system so as to control its high reactivity. On the other hand, inspired by the dramatic progress on organocatalysis over the past decade,[8] particularly about the chiral bifunctional urea and thiourea catalysts,[9] we supposed that these bifunctional catalysts were able to formally transform the intermolecular reaction into an intramolecular-like reaction due to their concurrently inducing and activating nucleophiles (3-substituted oxindoles) and electrophiles (formaldehyde) for favorable stereoselectivity (Scheme 1). As a continuation of our studies on organocatalysis,[10] herein we describe a

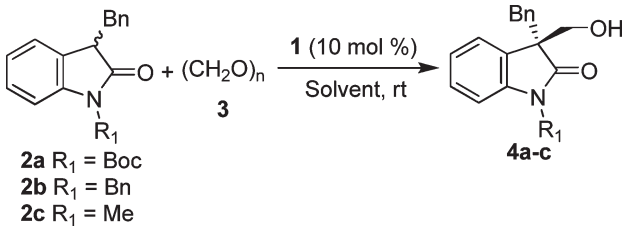
(7) For some selected examples of indirect asymmetric aldol reaction of formaldehyde with silyl enolates, see: (a) Ozawa, N.; Wadamoto, M.; Ishihara, K.; Yamamoto, H. *Synlett* **2003**, 2219. (b) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 12236. (c) Kobayashi, S.; Ogino, T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K. *Org. Lett.* **2005**, *7*, 4729. (d) Kokubo, M.; Ogawa, C.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6909.

(8) For selected reviews on organocatalytic asymmetric reactions, see: (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (d) Xu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.

(9) For selected reviews of bifunctional urea and thiourea catalysts, see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (c) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (e) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785. (f) Connon, S. J. *Synlett* **2009**, 354.

(10) (a) Zheng, H.-J.; Chen, W.-B.; Wu, Z.-J.; Deng, J.-G.; Lin, W.-Q.; Yuan, W.-C.; Zhang, X.-M. *Chem.—Eur. J.* **2008**, *14*, 9864. (b) Liao, Y.-H.; Zhang, H.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron: Asymmetry* **2009**, *20*, 2397. (c) Xue, Z.-Y.; Jiang, Y.; Yuan, W.-C.; Zhang, X.-M. *Eur. J. Org. Chem.* **2010**, 616. (d) Chen, W.-B.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2010**, *66*, 1441. (e) Liao, Y.-H.; Chen, W.-B.; Wu, Z.-J.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2010**, *352*, 827. (f) Zhang, H.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Lett. Org. Chem.* **2010**, *7*, 219. (g) Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 2896.

**TABLE 1. Optimization of Reaction Conditions**[a]




| entry | 1 | 2 | solvent | time (h) | yield (%) | ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | DCM | 24 | 84 (**4a**) | (+) 85 |
| 2 | **1b** | **2a** | DCM | 24 | 84 (**4a**) | (+) 74 |
| 3 | **1c** | **2a** | DCM | 24 | 85 (**4a**) | (−) 72 |
| 4 | **1d** | **2a** | DCM | 24 | 86 (**4a**) | (−) 74 |
| 5 | **1e** | **2a** | DCM | 15 | 87 (**4a**) | (−) 86 |
| 6 | **1f** | **2a** | DCM | 15 | 91 (**4a**) | (+) 88 |
| 7 | **1g** | **2a** | DCM | 15 | 91 (**4a**) | (+) 90 |
| 8 | **1h** | **2a** | DCM | 8 | 96 (**4a**) | (−) 33 |
| 9 | **1i** | **2a** | DCM | 8 | 95 (**4a**) | (+) 58 |
| 10 | **1j** | **2a** | DCM | 16 | 93 (**4a**) | 0 |
| 11 | **1g** | **2b** | DCM | 30 | 96 (**4b**) | (−) 10[c] |
| 12 | **1g** | **2c** | DCM | 30 | 88 (**4c**) | (−) 8[c] |
| 13 | **1g** | **2a** | DCE | 15 | 99 (**4a**) | (+) 90 |
| 14 | **1g** | **2a** | $CHCl_3$ | 15 | 99 (**4a**) | (+) 86 |
| 15 | **1g** | **2a** | toluene | 15 | 99 (**4a**) | (+) 83 |
| 16 | **1g** | **2a** | EtOAc | 15 | < 5 (**4a**) | nd[d] |
| 17 | **1g** | **2a** | $(C_2H_5)_2O$ | 15 | < 10 (**4a**) | nd[d] |
| 18 | **1g** | **2a** | $CH_3CN$ | 15 | 98 (**4a**) | (+)87 |
| 19 | **1g** | **2a** | DCE | 2 | 97 (**4a**) | (+)86[c] |
| 20 | **1g** | **2a** | DCE | 40 | < 10 (**4a**) | nd[d,e] |
| 21 | **1g** | **2a** | DCE | 15 | 99 (**4a**) | (+) 90[f] |
| 22 | **1g** | **2a** | DCE | 15 | 99 (**4a**) | (+) 91[g] |

[a]Unless otherwise noted, reactions were carried out with **2** (0.1 mmol), **3** (3.0 equiv), and catalyst **1** (10 mol %) in 4.0 mL of solvent at rt. [b]Determined by chiral-HPLC analysis. [c]Run at 45 °C. [d]Not determined. [e]Run at 0 °C. [f]5 mol % of **1g** was used. [g]This reaction was carried out with **2a** (0.2 mmol), **3** (3.0 equiv), and catalyst **1g** (5 mol %) in 4.0 mL of DCE at rt for 15 h.

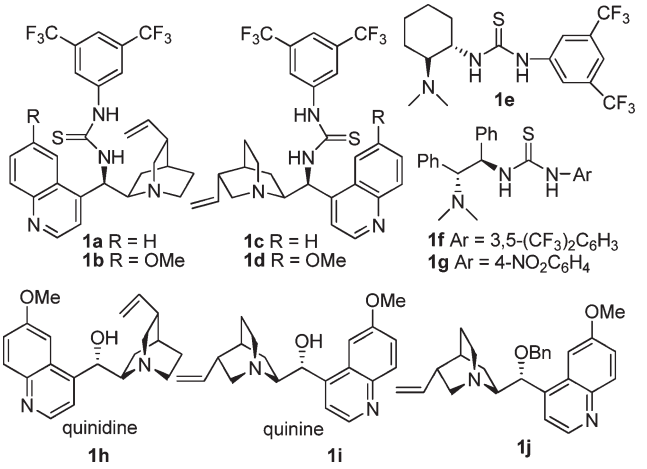



**FIGURE 1.** Chiral organocatalysts evaluated in this study.

bifunctional thiourea-catalyzed direct asymmetric aldol reaction of 3-substituted oxindoles and paraformaldehyde for the synthesis of diversely structured 3,3-disubstituted 2-oxindoles in high yields (up to 99%) and high ee (up to 91%).

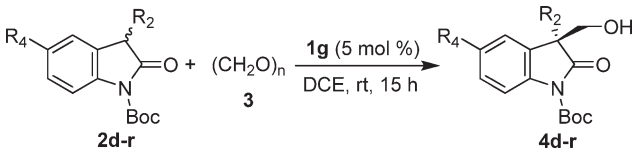
To demonstrate the working hypothesis, our initial studies focused on the reaction of *N*-Boc-oxindole **2a** and paraformaldehyde (**3**) in dichloromethane (DCM). As shown in Table 1,

we were pleased to discover that all of the diversely structured thiourea−tertiary amine catalysts[11] **1a**−**g** (Figure 1) could catalyze the direct aldol reaction, providing **4a** with a quaternary stereocenter through the hydroxymethylation of prochiral 3-substituted oxindole (Table 1, entries 1−7). In particular, catalyst **1g** was superior to other catalysts **1a**−**f** in reactivity, yield, and ee value (Table 1, entries 7 vs 1−6). On the other hand, the catalytic performance of quinidine (**1h**) and quinine (**1i**) was also surveyed in the model reaction, and the desired product was obtained in high yield but with poor enantioselectivity (Table 1, entries 8 and 9). Furthermore, in sharp contrast, catalyst **1j**, derived from quinine with C-9 alcohol-protected by a benzyl group, provided racemic product in high yield (Table 1, entry 10). Therefore, these results indicate that the bifunctionality of chiral thiourea−tertiary amines is crucial for high levels of stereocontrol. Subsequently, we explored the effects of the *N*-protection group of oxindole with **1g** as catalyst. It revealed that *N*-protection with the Boc group in oxindoles is crucial for the enantioselectivity (Table 1, entries 7 vs 11−12).

Afterward, with **1g** as catalyst, screening of solvents revealed that excellent yields and very high ee's were obtained when the reaction was conducted in 1,2-dichloroethane (DCE) (Table 1, entry 13), $CHCl_3$ (Table 1, entry 14), toluene (Table 1, entry 15), and $CH_3CN$ (Table 1, entry 18). However, the process proceeded sluggishly and only gave a trace amount of the desired product in EtOAc (Table 1, entry 16) and diethyl ether (Table 1, entry 17). As a result, among the solvents surveyed, the best result was obtained in DCE (Table 1, entry 13). A further survey of reaction temperature revealed that the reaction proceeded quickly (2 h) and gave the product **4a** in 97% yield and with 86% ee at 45 °C (Table 1, entry 19). On the contrary, lowering the reaction temperature to 0 °C showed a severe adverse effect on the reaction outcome, as only trace amount of product was observed even with prolonged reaction times from 15 to 40 h (Table 1, entry 20), presumably due to the lower temperature, which inhibited the gradual release of monomeric formaldehyde. As to catalyst loading, to our delight, 5 mol % of **1g** made the reaction proceed cleanly after 15 h with 99% yield and a high enantioselectivity of 90% ee (Table 1, entry 21). Finally, when we performed the reaction with a slightly higher concentration of substrate **2a** (0.05 M), almost the same results were obtained as with a lower concentration (Table 1, entry 22 vs 21).

Having established a set of optimal reaction conditions, we sought to examine the scope of the reaction. Then, a number of different 3-substitiuted oxindoles were prepared[2c,3a,e] and subjected to the optimal conditions. As shown in Table 2, significant structural variation in the oxindole system could be accommodated in this reaction. For example, electron-poor (Table 2, entries 1 and 2) and electron-rich (Table 2, entries 3−6) substituent incorporation to the benzyl group were tolerated to the conditions. It is noteworthy that an *o*-methoxy group was well tolerated (Table 2, entry 5), and the sterically demanding product was obtained in excellent yield (98%) with high enantioselectivity (84% ee). In addition, the method was compatible with the modification of the benzo moiety of oxindole core (Table 2, entries 7 and 8). Otherwise, oxindole **2l** bearing a bulky 1-naphtylmethyl group also provided its product in good yield (87%) and enantioselectivity (79% ee) (Table 2, entry 9). At the same time, oxindoles containing a heterocycle group, 2-thienylmethyl (Table 2, entry 10), and 2-pyridylmethyl (Table 2, entry 11), could also be employed as substrates furnishing very high yields and ee values. Gratifyingly, C-3 aliphatic substituents led to almost no deleterious effects on the reactivity and enantioselectivity (Table 2, entries 12−14). Unfortunately, in the case of 3-phenyloxindole **2r** as substrate, the corresponding adduct was obtained in high to 95% yield but with lower than 5% ee value (Table 2, entry 15). However, as for this case, when the reaction was performed under catalyst-free conditions, after 20 h after stirring, we found that the starting material **2r** had completely disappeared by thin-layer chromatography (Table 2, entry 16). Thus, we assume that this competing background, nonasymmetric reaction maybe one of the reasons for the racemic product.

**TABLE 2. Catalytic Asymmetric Hydroxymethylation of Various 3-Substituted Oxindoles with Paraformaldehyde by 1g**[a]



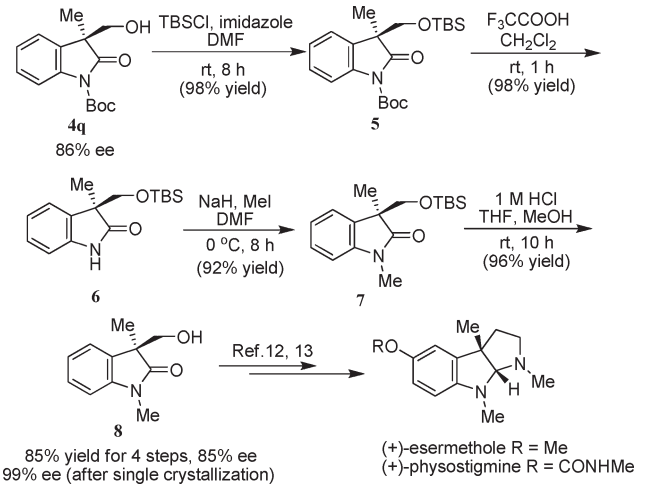

| entry | 2 | yield (%) | ee[b] (%) |
|---|---|---|---|
| 1 | $R_2$ = 4-ClPhCH$_2$, $R_4$ = H (**2d**) | 89 (**4d**) | 90 |
| 2 | $R_2$ = 4-FPhCH$_2$, $R_4$ = H (**2e**) | 93 (**4e**) | 90 |
| 3 | $R_2$ = 4-MePhCH$_2$, $R_4$ = H (**2f**) | 90 (**4f**) | 90 |
| 4 | $R_2$ = 4-MeOPhCH$_2$, $R_4$ = H (**2g**) | 94 (**4g**) | 90 |
| 5 | $R_2$ = 2-MeOPhCH$_2$, $R_4$ = H (**2h**) | 98 (**4h**) | 84 |
| 6 | $R_2$ = 3,4-(MeO)$_2$PhCH$_2$, $R_4$ = H (**2i**) | 96 (**4i**) | 89 |
| 7 | $R_2$ = Bn, $R_4$ = Br (**2j**) | 85 (**4j**) | 86 |
| 8 | $R_2$ = Bn, $R_4$ = Me (**2k**) | 95 (**4k**) | 90 |
| 9 | $R_2$ = 1-naphthylmethyl, $R_4$ = H (**2l**) | 87 (**4l**) | 79 |
| 10 | $R_2$ = 2-thienylmethyl, $R_4$ = H (**2m**) | 93 (**4m**) | 89 |
| 11 | $R_2$ = 2-pyridylmethyl, $R_4$ = H (**2n**) | 92 (**4n**) | 85 |
| 12 | $R_2$ = *n*-C$_4$H$_9$, $R_4$ = H (**2o**) | 92 (**4o**) | 90 |
| 13 | $R_2$ = *n*-C$_3$H$_7$, $R_4$ = H (**2p**) | 92 (**4p**) | 87 |
| 14 | $R_2$ = Me, $R_4$ = H (**2q**) | 80 (**4q**) | 85 |
| 15 | $R_2$ = Ph, $R_4$ = H (**2r**) | 95 (**4r**) | < 5 |
| 16 | $R_2$ = Ph, $R_4$ = H (**2r**) | 90 (**4r**) | -[c] |

[a]Unless otherwise noted, reactions were carried out with **2** (0.2 mmol), **3** (3.0 equiv), and catalyst **1g** (5 mol %) in 4.0 mL of solvent at room temperature for 15 h. [b]Determined by chiral-HPLC analysis. [c]The reaction was allowed to run for 20 h in DCE with no catalyst.

To determine the absolute configuration of the products, and to further illustrate the potential utility of this methodology, the chiral product **4q** was readily converted to compound **8** in 85% overall yield and with complete retention of the stereochemistry over a four-step transformation (Scheme 2). Gratifyingly, the enantiopurity of compound **8** could be easily enhanced up to 99% ee via single crystallization (Scheme 2). The configuration of **8** was assigned as *S* by comparing the optical rotation of the synthesized compound with the

(11) For the synthesis of chiral bifunctional thiourea−tertiary amine catalysts, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (d) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7466. (e) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (f) Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097. (g) Kaik, M.; Gawronask, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1559. (h) Berkessel, A.; Mukherjee, S.; Nuller, T. N.; Cleemann, F.; Roland, K.; Brandenburg, M.; Neudor, J. M.; Lex, J. *Org. Biomol. Chem.* **2006**, *4*, 4319.

**SCHEME 2**




literature data.[12] As no reactions occurred at the stereogenic center of **4q** during the conversion of **4q** to **8** (Scheme 2), **4q** was thus also assigned the *S* configuration. The configurations of all other products were assigned by analogy with this product. In addition, it is worth emphasizing that (*S*)-**8** may be convert to (+)-esermethole and (+)-physostigmine in light of other developed methods.[12,13]

In conclusion, we have developed a bifunctional thiourea−tertiary amine-catalyzed asymmetric hydroxymethylation of 3-substituted oxindoles using readily available paraformaldehyde as the C1 unit. The significant features of this approach are as follows: (1) mild reaction conditions, (2) broad substrate scope, (3) good to excellent yields and high enantioselectivites in the construction of sterically congested quaternary carbon centers through hydroxymethylation of oxindole, and (4) use of cheap and readily available paraformaldehyde as a useful hydroxymethylation C1 unit, which is activated by chiral bifunctional thiourea organocatalysts.

(12) Akai, S.; Tsujino, T.; Akiyama, E.; Tanimoto, K.; Naka, T.; Kita, Y. *J. Org. Chem.* **2004**, *69*, 2478.
(13) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.

## Experimental Section

**Representative Procedure for the Hydroxymethylation of 3-Substituted Oxindoles with Paraformaldehyde as C1 Unit (Table 1, Entry 19).** In an ordinary vial equipped with a magnetic stirring bar, to the mixture of **2a** (0.2 mmol) and **1g** (0.01 mmol) in 4.0 mL of freshly distilled DCE was added paraformaldehyde solid (18.0 mg). The reaction mixture was stirred at room temperature for 15 h and was directly loaded onto silica gel and purified by flash chromatography to give the desired products **4a** as a white solid (99% yield, 91% ee): $[\alpha]^{20}_{D} = +25.7$ (*c* 1.26, $CHCl_3$); mp 109.1−109.9 °C; the ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/$^i$-PrOH; flow rate 1.0 mL/min; $\lambda$ = 254 nm; $t_{major}$ = 5.53 min, $t_{minor}$ = 5.02 min); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.57 (s, 9H), 2.45 (br s, 1H), 3.13 (d, $J$ = 13.2 Hz, 1H), 3.22 (d, $J$ = 13.2 Hz, 1H), 3.88 (d, $J$ = 11.1 Hz, 1H), 4.04 (d, $J$ = 11.1 Hz, 1H), 6.87−6.90 (m, 2H), 7.07−7.17 (m, 5H), 7.22−7.27 (m, 1H), 7.65 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.0, 40.0, 56.0, 66.3, 84.2, 115.0, 123.5, 124.1, 126.8, 127.8, 128.6, 130.0, 134.7, 140.1, 148.6, 178.0; IR (KBr) $\nu$ 3482, 2931, 1739, 1359, 1290, 1150, 1072, 749 cm$^{-1}$; HRMS (ESI) calcd for $C_{21}H_{23}NNaO_4$ $[M + Na]^+$ 376.1519, found 376.1536.

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**Supporting Information Available:** Experimental procedures and spectra data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.