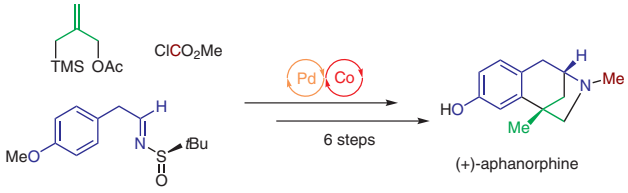
Synlett C. Wang, Y. Guan Letter

Concise Total Synthesis of (+)-Aphanorphine

Cheng Wang
Yukun Guan*

School of Pharmacy, Yantai University, Qingquan Road-30, Yantai 264005, P. R. of China
gyk@ytu.edu.cn



Received: 28.02.2021
Accepted after revision: 19.03.2021
Published online: 08.04.2021
DOI: 10.1055/s-0037-1610769; Art ID: st-2021-l0074-l

Abstract A concise total synthesis of (+)-aphanorphine is described. The key features of the strategy include a Pd-catalyzed intermolecular trimethylenemethane [3+2]-cycloaddition to form ring C and a Co-catalyzed radical cyclization through a hydrogen-atom transfer to close ring B. The synthesis was completed in six steps.

Key words aphanorphine, total synthesis, alkaloids, *tert*-butanesulfinimine, cycloaddition, hydrogen-atom transfer

In 1988, an alkaloid named aphanorphine (**1**) was isolated by Shimizu and Clardy and their co-workers during their studies on the biosynthesis of the neurotoxic alkaloid neosaxitoxin in the freshwater blue-green alga *Aphanizomenon flos-aquae*.[1] Aphanorphine has a tricyclic benzazepine core and is structurally similar to the natural and synthetic analgesic benzomorphan alkaloids morphine (**2**), pentazocine (**3**), and eptazocine (**4**) (Figure 1). Its intriguing structure and its potential analgesic biological activity made aphanorphine an attractive target for organic synthesis. Many elegant strategies have been developed to construct the tricyclic benzazepine motif, such as Lewis acid-promoted Friedel–Crafts or tin hydride-mediated radical cyclization of the 2-benzylpyrrolidine intermediate to construct the ring B,[2] transannular enolate or radical cyclization of 3-benzazepine derivatives to form both rings B and C,[3] or intramolecular nucleophilic cyclization of tetralin or dihydronaphthalene substrates to build ring C.[4] Grainger developed a unique approach including a carbamoyl-radical cyclization to close ring C and a late-stage formation of aromatic ring A through an inverse-electron-demand Diels–Alder reaction.[5] Here, we report a concise total synthesis of (+)-aphanorphine (**5**) based on transition metal-catalyzed cyclization reactions.

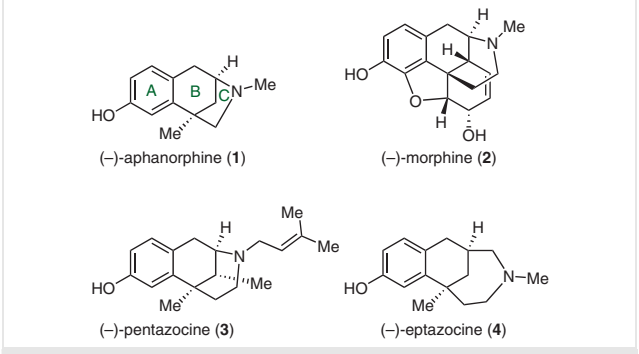
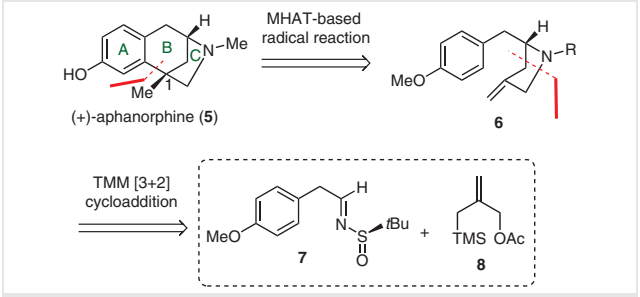


Figure 1 Representative benzomorphan alkaloids

The metal-catalyzed hydrogen-atom transfer (MHAT) reaction has emerged as a powerful tool in organic synthesis.[6,7] As shown in Scheme 1, we envisioned that the ring B and C1 quaternary carbon center of (+)-aphanorphine (**5**) might be obtained by a radical cyclization initiated by MHAT of the 2-benzylpyrrolidine **6**, which, in turn, could be assembled by intermolecular trimethylenemethane (TMM) [3+2]-cycloaddition[8] of the known chiral imine **7** with 2-[(trimethylsilyl)methyl]allyl acetate (**8**) (Scheme 1).

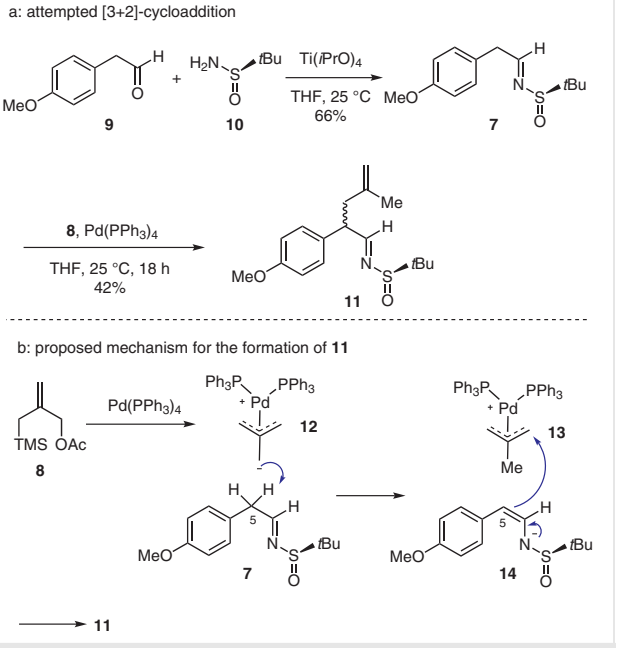


Scheme 1 Retrosynthetic analysis of (+)-aphanorphine (**5**)

Our total synthesis of (+)-aphanorphine (**5**) commenced with the TMM [3+2]-cycloaddition of 2-[(trimethylsilyl)methyl]allyl acetate (**8**) with the chiral imine **7** (Scheme 2),[9] which can be prepared from (4-methoxyphenyl)acetaldehyde (**9**) and (*R*)-(+)-*tert*-butylsulfinamide (**10**) in 66% yield by a known procedure.[10] Stockman and co-workers

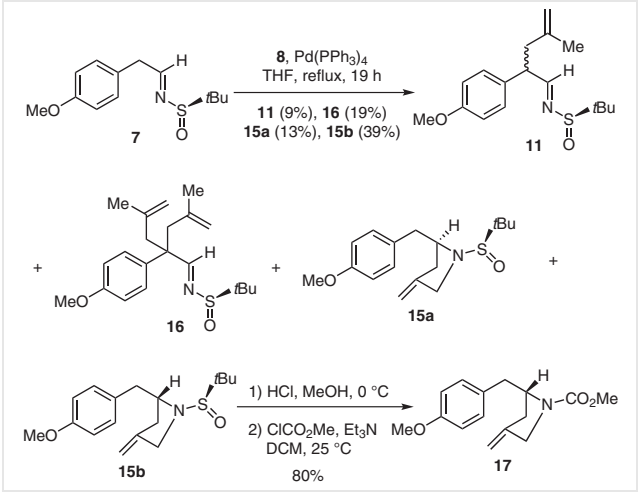
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

previously investigated the TMM [3+2]-cycloadditions of chiral aryl and alkyl *tert*-butanesulfinimines to yield enantiopure pyrrolidine products.[11] Unfortunately, when we followed Stockman's method, none of the desired cycloaddition product was detected when **7** and **8** were stirred with $Pd(PPh_3)_4$ in THF for 18 hours at 25 °C. Instead, the unexpected alkylation product **11** was isolated in 42% yield (Scheme 2a). We surmised that **11** might be formed by proton transfer from the C5 atom of **7** to the Pd–TMM intermediate **12**. The C5 position of **7** is activated by both an electron-withdrawing inductive effect of the imine group and by the conjugate effect of the phenyl group; consequently, instead of the expected cycloaddition of the TMM intermediate **12** with the imine, proton transfer from the C5 atom of **7** to the Pd-TMM intermediate **12** becomes the favored pathway to give methallyl complex **13**, which is attacked by the resulting anion **14** to deliver the alkylation product **11**.[12]



Scheme 2 Investigation of the [3+2]-cycloaddition

Reports by Trost and co-workers[12a,c] suggested that increasing the temperature might enhance the nucleophilicity of TMM. Pleasingly, when the reaction mixture was stirred under reflux for 19 hours, our desired cycloaddition products **15a** and **15b** were obtained in 1:3 dr with a combined yield of 52%, along with the mono- and dialkylation products **11** and **16**, respectively, in yields of 9 and 19%. For the synthesis of (+)-aphanorphine (**5**), the *tert*-butylsulfinyl group of **15b** was removed by treatment with 2 M HCl in MeOH, and the resulting secondary amine was treated with $ClCO_2Me$ in the presence of NEt_3 to give the methyl carbamate **17** in 80% yield over the two steps (Scheme 3).



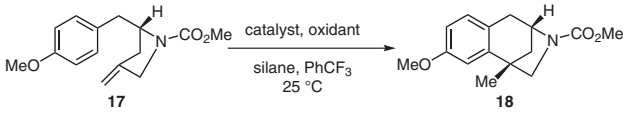
Scheme 3 Synthesis of benzylpyrrolidine **17**

According to our synthetic plan, the next work was to construct the tricyclic benzazepine core of (+)-aphanorphine (**5**) through MHAT-based radical cycloaddition. We began our study by evaluating a catalytic system previously used by Shigehisa et al. for the hydroarylation of nonactivated alkenes (Table 1).[13] Treatment of **17** with 1,1,3,3-tetramethyldisiloxane (TMDSO), *N*-fluoro-2,4,6-trimethylpyridinium triflate (**O1**, Figure 2), and the ethylenediamine-containing salen Co-catalyst **C1** in $PhCF_3$ gave the desired tricyclic benzazepine **18** in only 6% yield (Table 1, entry 1). To our delight, the use of the 1,3-diaminopropane-containing catalyst **C2** (Figure 2) improved the yield to 72% (entry 2). The longer 1,4-butanediamine gave a much lower yield (entry 3). Replacing the *tert*-butyl group on the 5-position of the aromatic ring of **C2** with H, Me, or OMe (**C4**–**C6**) led to no conversion (entries 4–6). Further catalyst screening showed that **C7** was the best catalyst, affording a 76% yield of the desired product (entries 7 and 8). Next, a series of oxidants including *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**O2**), *N*-fluoropyridinium triflate (**O3**), *N*-fluoropyridinium tetrafluoroborate (**O4**), and (diacetoxyiodo)benzene (**O5**) were evaluated, but all proved inferior to *N*-fluoro-2,4,6-trimethylpyridinium triflate (**O1**) (entries 9–12). Finally, we examined various silanes and we found that poly(methylhydrosiloxane) (PMHS) was superior to TMDSO, $PhSiH_3$, or Ph(*i*-PrO)SiH_2,[14] giving an improved yield of 83%[15] (entries 13–15).

With **18** in hand, the remaining transformations of the synthesis were N-methylation and O-demethylation. Reduction of **18** with excess $LiAlH_4$ afforded (–)-8-*O*-methylaphanorphine (**19**) in 88% yield. On following the procedure of Fuchs and Funk,[3a] treatment of **19** with BBr_3 in DCM at a low temperature effected the expected O-demethylation, giving (+)-aphanorphine (**5**) in 50% yield (Scheme 4).

The physical and spectroscopic data of the synthetic (+)-aphanorphine (**5**) {$[\alpha]_D^{25}$ +20.8 (*c* 0.4, MeOH)} agreed with those reported previously.[1,2l]

Table 1 Optimization of the MHAT-Based Radical Cycloaddition



Entry	Catalyst[a]	Silane	Oxidant[a]	Yield[b] (%)
1	**C1**	TMDSO	**O1**	6
2	**C2**	TMDSO	**O1**	72
3	**C3**	TMDSO	**O1**	12
4	**C4**	TMDSO	**O1**	ND[c]
5	**C5**	TMDSO	**O1**	ND
6	**C6**	TMDSO	**O1**	ND
7	**C7**	TMDSO	**O1**	76
8	**C8**	TMDSO	**O1**	13
9	**C7**	TMDSO	**O2**	58
10	**C7**	TMDSO	**O3**	ND
11	**C7**	TMDSO	**O4**	36
12	**C7**	TMDSO	**O5**	38
13	**C7**	$PhSiH_3$	**O1**	32
14	**C7**	PMHS	**O1**	83
15	**C7**	$PhSiH_2$(O-*i*-Pr)	**O1**	27

[a] For catalyst and oxidant structures, see Figure 2.
[b] Isolated yield.
[c] ND = not detected.

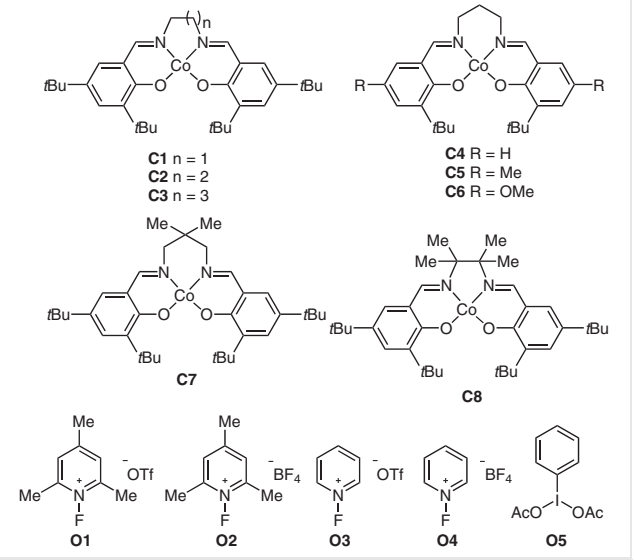
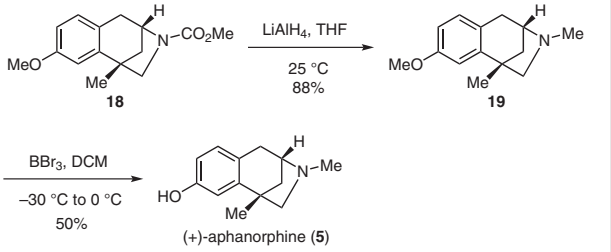


Figure 2 Catalyst structures **C1**–**C8** and oxidants **O1**–**O5**



Scheme 4 Completion of the total synthesis of (+)-aphanorphine (**5**)

In summary, a concise total synthesis of (+)-aphanorphine (**5**) was achieved, starting from the known chiral *tert*-butanesulfinimine **7**, in six steps and 11% overall yield. The transition-metal-catalyzed intermolecular TMM [3+2]-cycloaddition and a MHAT-based radical cyclization were used in a rapid construction of the tricyclic benzazepine core of the natural product. In addition, methyl carbamate was used as a latent methylamine, avoiding additional steps involving manipulation of N-substituent group, as required in the previous synthesis, thereby improving the overall synthetic efficiency.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

This work was financially supported by the Natural Science Foundation of Shandong Province (ZR2018PB006).

Acknowledgment

We thank Prof. Chun-An Fan (Lanzhou University) for assistance in measuring the optical rotations.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610769.

References and Notes

(1) Gulavita, N.; Hori, A.; Shimizu, Y.; Laszlo, P.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 4381.
(2) (a) Tamura, O.; Yanagimachi, T.; Kobayashi, T.; Ishibashi, H. *Org. Lett.* **2001**, *3*, 2427. (b) Zhai, H.; Luo, S.; Ye, C.; Ma, Y. *J. Org. Chem.* **2003**, *68*, 8268. (c) Hu, H.; Zhai, H. *Synlett* **2003**, 2129. (d) Tamura, O.; Yanagimachi, T.; Ishibashi, H. *Tetrahedron: Asymmetry* **2003**, *14*, 3033. (e) Bower, J. F.; Szeto, P.; Gallagher, T. *Chem. Commun.* **2005**, 5793. (f) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Biomol. Chem.* **2007**, *5*, 143. (g) Ma, Z.; Zhai, H. *Synlett* **2007**, 161. (h) Ma, Z.; Hu, H.; Xiong, W.; Zhai, H. *Tetrahedron* **2007**, *63*, 7523. (i) Yang, X.; Zhai, H.; Li, Z. *Org. Lett.* **2008**, *10*, 2457. (j) Yang, X.; Cheng, B.; Li, Z.; Zhai, H. *Synlett* **2008**,

2821. (k) Yoshimitsu, T.; Atsumi, C.; Iimori, E.; Nagaoka, H.; Tanaka, T. *Tetrahedron Lett.* **2008**, *49*, 4473. (l) Mai, D. N.; Rosen, B. R.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2932. (m) Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2011**, 2230. (n) Pansare, S. V.; Kulkarni, K. G. *RSC Adv.* **2013**, *3*, 19127. (o) Wang, Z.; Zheng, H.; Yang, J.; Xie, X.; She, X. *Adv. Synth. Catal.* **2015**, *357*, 2082. (p) Peterson, L. J.; Wolfe, J. P. *Adv. Synth. Catal.* **2015**, *357*, 2339.

(3) (a) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923. (b) Katoh, M.; Inoue, H.; Suzuki, A.; Honda, T. *Synlett* **2005**, 2820. (c) Honda, T.; Katoh, M.; Inoue, H. *Heterocycles* **2007**, *72*, 497. (d) Donets, P. A.; Goeman, J. L.; Van der Eycken, J.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, E. V. *Eur. J. Org. Chem.* **2009**, 793.

(4) (a) Takano, S.; Inomata, K.; Sato, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1591. (b) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 290. (c) Honda, T.; Yamamoto, A.; Cui, Y.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 531. (d) Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265. (e) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 893. (f) Hallinan, K. O.; Honda, T. *Tetrahedron* **1995**, *51*, 12211. (g) Meyers, A. I.; Schmidt, W.; Santiago, B. *Heterocycles* **1995**, *40*, 525. (h) Shiotani, S.; Okada, H.; Nakamata, K.; Yamamoto, T.; Sekino, F. *Heterocycles* **1996**, *43*, 1031. (i) Node, M.; Imazato, H.; Kurosaki, R.; Kawano, Y.; Inoue, T.; Nishide, K.; Fuji, K. *Heterocycles* **1996**, *42*, 811. (j) Ogasawara, K.; Shimizu, M.; Kamikubo, T. *Heterocycles* **1997**, *46*, 21. (k) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 283. (l) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 371. (m) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049. (n) ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Heterocycles* **2002**, *56*, 39. (o) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *J. Org. Chem.* **2003**, *68*, 5917. (p) Taylor, S. K.; Ivanovic, M.; Simons, L. J.; Davis, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 743. (q) Li, M.; Zhou, P.; Roth, H. F. *Synthesis* **2007**, 55. (r) Zhu, D.-Y.; Xu, M.-H.; Tu, Y.-Q.; Zhang, F.-M.; Wang, S.-H. *Chem. Eur. J.* **2015**, *21*, 15502. (s) Chiou, W.-H.; Chen, P.-C. *J. Org. Chem.* **2017**, *82*, 8213.

(5) Grainger, R. S.; Welsh, E. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 5377.

(6) For reviews about MHAT reaction, see: (a) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. *Chem. Rev.* **2016**, *116*, 8912. (b) Green, S. A.; Crossley, S. W. M.; Matos, J. L. M.; Vásquez-Céspedes, S.; Shevick, S. L.; Shenvi, R. A. *Acc. Chem. Res.* **2018**, *51*, 2628.

(7) For selected applications MHAT reaction in natural product synthesis, see: (a) Zhang, B.; Zheng, W.; Wang, X.; Sun, D.; Li, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 10435. (b) Xu, G.; Elkin, M.; Tantillo, D. J.; Newhouse, T. R.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 12498. (c) Deng, H.; Cao, W.; Liu, R.; Zhang, Y.; Liu, B. *Angew. Chem. Int. Ed.* **2017**, *56*, 5849. (d) Godfrey, N. A.; Schatz, D. J.; Pronin, S. V. *J. Am. Chem. Soc.* **2018**, *140*, 12770. (e) Lu, Z.; Zhang, X.; Guo, Z.; Chen, Y.; Mu, T.; Li, A. *J. Am. Chem. Soc.* **2018**, *140*, 9211. (f) Farney, E. P.; Feng, S. S.; Schäfers, F.; Reisman, S. E. *J. Am. Chem. Soc.* **2018**, *140*, 1267. (g) Ji, Y.; Xin, Z.; He, H.; Gao, S. *J. Am. Chem. Soc.* **2019**, *141*, 16208. (h) Xu, G.; Wu, J.; Li, L.; Lu, Y.; Li, C. *J. Am. Chem. Soc.* **2020**, *142*, 15240. (i) Chen, P.; Wang, C.; Yang, R.; Xu, H.; Wu, J.; Jiang, H.; Chen, K.; Ma, Z. *Angew. Chem. Int. Ed.* **2021**, *60*, 5512.

(8) Yamago, S.; Nakamura, E. *Org. React. (Hoboken, NJ, U. S.)* **2002**, *61*, 1.

(9) For selected applications of *N*-*tert*-butanesulfinimines in natural-product synthesis, see: (a) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Angew. Chem. Int. Ed.* **2011**, *50*, 9447. (b) Zhao, S.; Andrade, R. B. *J. Am. Chem. Soc.* **2013**, *135*, 13334. (c) Chogii, I.; Njardarson, J. T. *Angew. Chem. Int. Ed.* **2015**, *54*, 13706. (d) Tian, M.; Yan, M.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 14234. (e) Hugelshofer, C. L.; Palani, V.; Sarpong, R. *J. Am. Chem. Soc.* **2019**, *141*, 8431. (f) Li, Y.; Wang, C.; Ma, Z.; Zhang, K.; Xu, X.-T. *Org. Lett.* **2020**, *22*, 8589.

(10) Yao, Q.; Yuan, C. *J. Org. Chem.* **2013**, *78*, 6962.

(11) Procopiou, G.; Lewis, W.; Harbottle, G.; Stockman, R. A. *Org. Lett.* **2013**, *15*, 2030.

(12) (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6432. (b) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2326. (c) Trost, B. M.; Bringley, D. A.; O'Keefe, B. M. *Org. Lett.* **2013**, *15*, 5630.

(13) Shigehisa, H.; Ano, T.; Honma, H.; Ebisawa, K.; Hiroya, K. *Org. Lett.* **2016**, *18*, 3622.

(14) Obradors, C.; Martinez, R. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 4962.

(15) **Methyl (1S,4S)-8-methoxy-1-methyl-1,2,4,5-tetrahydro-3H-1,4-methanobenzo[d]azepine-3-carboxylate (18)**

A 4 mL vial was charged with sulfinimine **17** (13 mg, 0.05 mmol, 1.0 equiv), catalyst **C7** (1.5 mg, 0.0025 mmol, 0.05 equiv), and oxidant **O1** (29 mg, 0.1 mmol, 2.0 equiv). $PhCF_3$ (0.5 mL), previously dried in vacuo for 0.5 h, was then added and the solution was bubbled with N_2 for 10 min. PMHS (22 µL, 0.1 mmol, 2.0 equiv) was added, and the resulting mixture was stirred at 25 °C for 20 h then diluted with EtOAc (2 mL). The solution was washed with H_2O (0.5 mL) and brine (3 × 0.5 mL), then dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative TLC (PE–EtOAc, 5:1) to give a yellow solid: yield; 10.8 mg (83%); mp 89–92 °C; $[\alpha]_D^{25}$ +167.3 (*c* 0.55, $CHCl_3$).

IR (KBr): 3795, 2957, 1701, 1612, 1495, 1453, 1389, 863, 805, 769, 741, 698 cm^{-1}. Rotamer ^1H NMR (500 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.4 Hz, 0.5 H), 6.99 (d, *J* = 8.3 Hz, 0.5 H), 6.85–6.80 (m, 1 H), 6.72 (td, *J* = 8.3, 2.5 Hz, 1 H), 4.50–4.43 (m, 0.6 H), 4.39–4.32 (m, 0.4 H), 3.82–3.74 (m, 3 H), 3.72–3.66 (m, 1.3 H), 3.63–3.58 (m, 1.7 H), 3.42 (d, *J* = 10.1 Hz, 0.5 H), 3.36 (d, *J* = 9.9 Hz, 0.5 H), 3.28 (d, *J* = 10.0 Hz, 0.5 H), 3.22 (d, *J* = 9.9 Hz, 0.5 H), 3.18 (d, *J* = 16.6 Hz, 0.5 H), 3.04 (d, *J* = 16.6 Hz, 0.5 H), 2.90 (d, *J* = 16.6 Hz, 1 H), 2.02–1.86 (m, 2 H), 1.57–1.45 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.9, 157.8, 155.1, 154.9, 145.8, 145.7, 130.5, 130.3, 125.7, 125.4, 111.6, 111.4, 109.89, 109.86, 61.6, 61.2, 55.29, 55.27, 54.8, 54.6, 52.2, 52.0, 42.2, 41.7, 41.6, 40.8, 36.4, 35.7, 20.8. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}NO_3$: 262.1443; found: 262.1437.