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Isothiourea-Catalyzed Atroposelective N-Acylation of Sulfonamides

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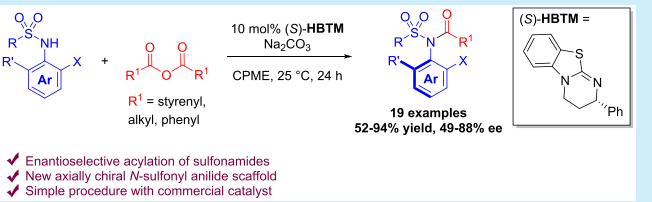
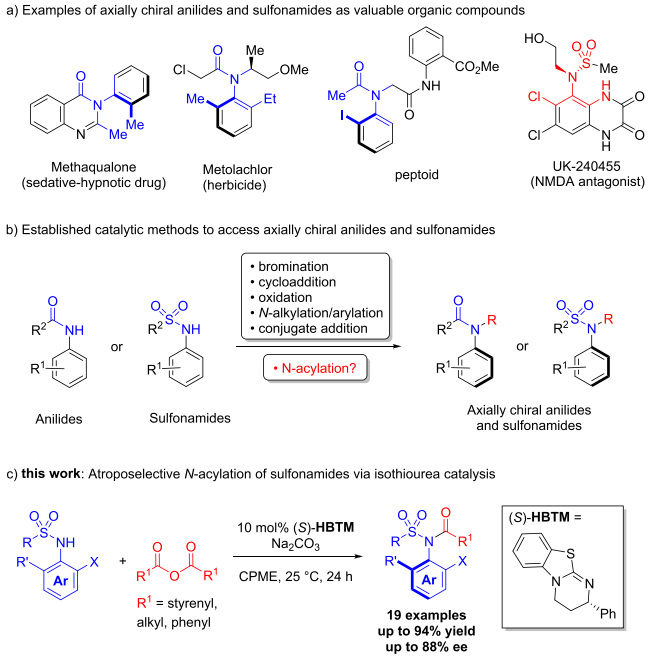
ABSTRACT: We report herein an atroposelective N-acylation of sulfonamides using a commercially available isothiourea catalyst, (*S*)-HBTM, with a simple procedure. The *N*-sulfonyl anilide products can be obtained in good to high enantiopurity, which represents a new axially chiral scaffold. The application of the product as a chiral iodine catalyst is also demonstrated for the asymmetric α-oxytosylation of propiophenone.



Atropoisomerism, a form of chirality arising from restricted rotation around a bond axis, has been a topic of great interest to chemists since its discovery in 1922.[1] One particular class of compounds containing atropoisomerism along a C−N bond axis, namely, tertiary anilides and sulfonamides, has received more attention in the past decades due to the discovery of their roles in medicinal and agricultural chemistry (Scheme 1a).[2] Because of their intrinsic value, many asymmetric catalytic reactions had been developed for the synthesis of these tertiary anilides and sulfonamides, including but not limited to conjugate addition,[3] oxidation,[4] cycloaddition,[5] bromination,[6] and N-alkylation or arylation[7] (Scheme 1b). However, the strategy of atroposelective N-acylation of these substrates remains elusive in the literature.

Scheme 1. Atropoisomeric Anilides and Sulfonamides



Enantioselective acylation of alcohols and phenols has been developed as a powerful tool in asymmetric catalysis.[8] In contrast, asymmetric acylation of amine-based nucleophiles is significantly more challenging due to the higher nucleophilicity of nitrogen, resulting in stronger background reactivity. In recent years, great advancement in this topic of research has been made by the groups of Fu,[9] Seidel,[10] and Bode[11] in the kinetic resolution of amines. The Birman group,[12] the Bolm group,[13] and the Miller group[14] also developed catalytic asymmetric N-acylation of lactams, sulfoximines, and (thio)-formamides, respectively. We report herein an unprecedented atroposelective N-acylation of sulfonamides by the use of a simple procedure catalyzed by commercially available isothiourea (*S*)-HBTM (Scheme 1c).[15] The chiral *N*-sulfonyl anilides accessed in this study represent a new axially chiral scaffold bearing a C−N bond axis. Notably, our products typically bear an iodine substituent, the utility of which for asymmetric iodine catalysis was demonstrated in an asymmeric α-oxytosylation of propiophenone.

Our group has been interested in the enantioselective acylation of alcohols and phenols with the use of N-heterocyclic carbenes as the catalyst.[16] Very recently, together with the Kurti group, we have also successfully achieved the first atroposelective N-alkylation of sulfonamides (such as **1a** in Scheme 2) to prepare axially chiral *N*-alkyl sulfonamides.[7j] In an effort to access new variations of this intriguing axially chiral scaffold, we decided to examine asymmetric acylation of this sulfonamide instead, which was unprecedented for this class of N-based nucleophiles. Initial investigation involved the

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Scheme 2. Screening of Various Catalysts for Atroposelective N-Acylation of Sulfonamide 1

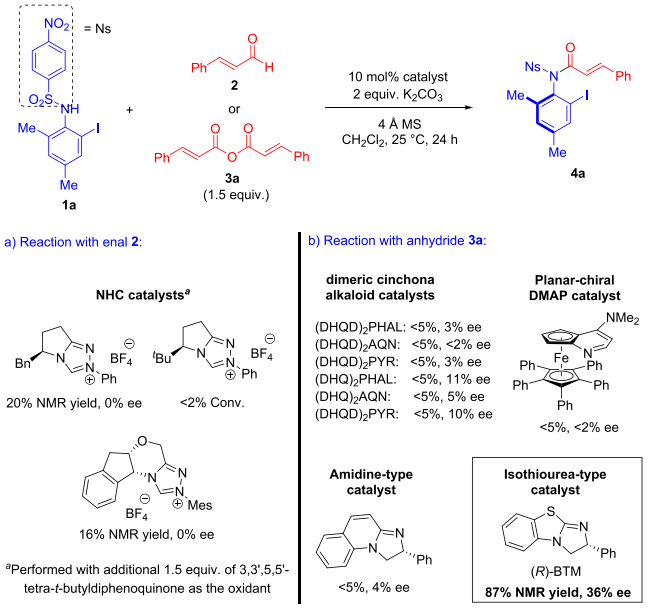
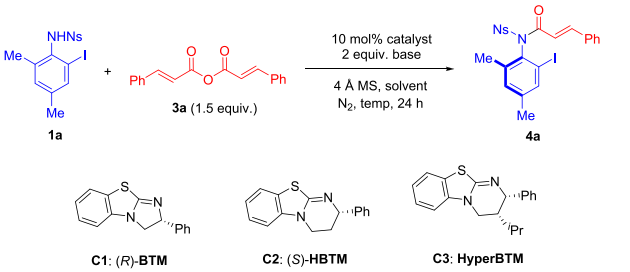


Table 1. Optimization of Atroposelective Acylation[a]



entry	catalyst	base	solvent	yield (%)[b]	ee (%)[c]
1	**C1**	K_2CO_3	CH_2Cl_2	87	36
2	**C2**	K_2CO_3	CH_2Cl_2	92	76
3	**C3**	K_2CO_3	CH_2Cl_2	97	36
4	**C2**	K_2CO_3	THF	53	80
5	**C2**	K_2CO_3	toluene	95	81
6	**C2**	K_2CO_3	MeCN	89	15
7	**C2**	K_2CO_3	CPME	83	84
8	**C2**	Na_2CO_3	CPME	85 (73[d])	85
9	**C2**	Cs_2CO_3	CPME	97	80
10	**C2**	KO^{t}Bu	CPME	97	62
11	**C2**	DIPEA	CPME	80	82
12	–	Na_2CO_3	CPME	3	–
13[e]	**C2**	Na_2CO_3	CPME	23	76

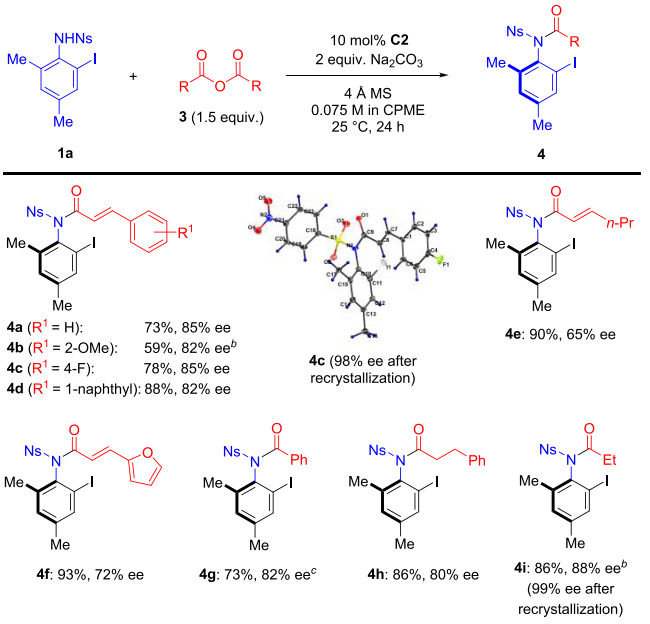
[a]The reaction was conducted using **1** (1.0 equiv), **3a** (1.5 equiv), a catalyst (10 mol %), a base (2.0 equiv), and 4 Å molecular sieves in solvent (0.075 M) under N_2 at 25 °C, unless stated otherwise. [b]^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c]Determined by HPLC with a chiral stationary phase. [d]Isolated yield. [e]Conducted at 0 °C instead.

reaction of sulfonamide **1a** with *trans*-cinnamaldehyde **2** under oxidative NHC catalysis conditions (Scheme 2a), which unfortunately resulted in minimal reactivity with no enantioselectivity for product **4a**. We then switched to the more classical asymmetric acylation using an anhydride **3a** as the reagent (Scheme 2b). Early efforts using cinchona alkaloid-based nucleophilic amine catalysts, planar chiral DMAP, and amidine type all proved to be futile. To our delight, the promising reactivity and enantioselectivity for **4a** (87% yield and 36% ee) were finally obtained when an isothiourea catalyst,[17] (*R*)-BTM first developed by the Birman group,[18] was used.

We then proceeded with the screening of various parameters to further optimize the reaction (Table 1). The use of other commercially available isothiourea catalysts, (*S*)-HBTM and HyperBTM developed by the groups of Birman[19] and Smith,[20] respectively, afforded better yields (entries 2 and 3, respectively), but only (*S*)-HBTM could give an improved enantioselectivity of 76% (entry 2).[21] Screening of the solvents revealed that cyclopentyl methyl ether (CPME) was the optimal choice (entries 4−7), giving a slightly improved 84% ee. The use of Na_2CO_3 furnished the product in a good 85% yield (73% isolated yield) and 85% ee (entry 8), while the use of strong inorganic bases such as Cs_2CO_3 and KO^{t}Bu gave almost quantitative yields but decreased ee values (entries 9 and 10, respectively). The use of a weak organic base, DIPEA, did not improve the experimental results further (entry 11). A control reaction (entry 12) showed that background reaction, although low, is still present despite the use of a strongly electron-withdrawing nosyl protecting group, thus hindering our efforts to improve the enantioselectivity further. Finally, in an attempt to eliminate the background reaction, we tried to decrease the reaction temperature to 0 °C (entry 13), but that led to a drastic decrease in the yield of the product and a mild erosion of enantioselectivity, likely due to the decrease in the reactivity of the catalyst. We then decided to adopt the set of reaction conditions in entry 8 as the optimal conditions for further investigation.

With the optimal conditions in hand, the scope of various substituted anhydrides **3** for the reaction with **1a** was examined first (Scheme 3). Similar to model product **4a**, both electron-donating methoxy (OMe) and electron-withdrawing fluorine

Scheme 3. Substrate Scope for Various Anhydrides 3[a]



[a]See the Supporting Information for the detailed procedure. [b]Performed with 20 mol % catalyst. [c]Reaction time of 96 h.

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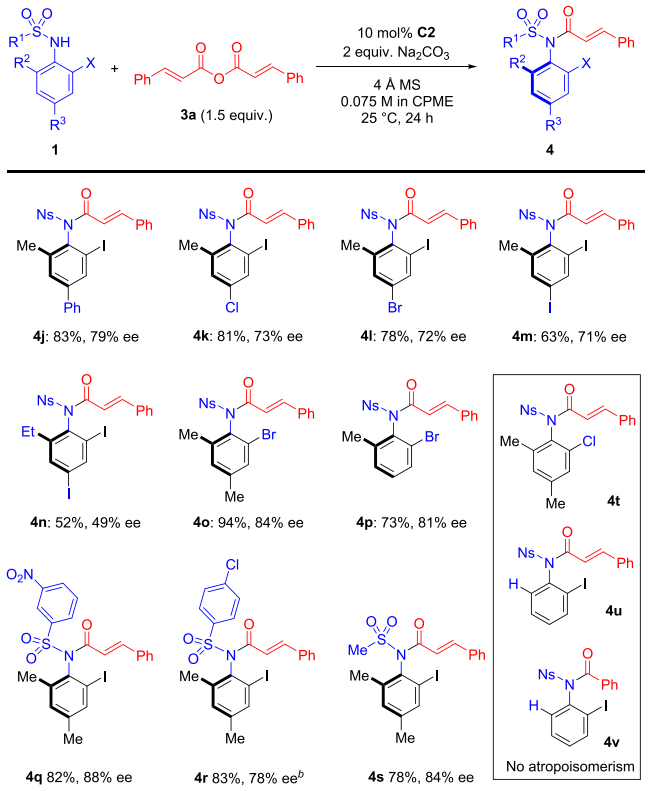
substituents on the phenyl ring were well tolerated to yield **4b** and **4c** with similar levels of enantioselectivities. Fused 1-naphthyl-substituted **4d** was also accessed with high efficiency and enantioselectivity. Anhydrides with an alkyl chain or heteroaromatic ring at the β position also participated in the reaction with an excellent level of reactivity but suffered an erosion in enantioselectivity to 65% and 72% for **4e** and **4f**, respectively. Reaction with benzoic anhydride produced **4g** with a good level of enantioselectivity, but the reaction was sluggish and required a reaction time of 96 h, possibly due to the greater steric bulk of the phenyl ring. Alkyl anhydrides were also tested, which successfully yielded **4h** and **4i** with good levels of reactivity and enantioselectivity (80−88% ee). The desired products could be obtained in an enantiopure form after recrystallization as demonstrated by **4c** and **4i** (Scheme 3). The absolute configuration of **4c** was unambiguously assigned by single-crystal X-ray analysis. The configurations of other products in Scheme 3 were assigned by analogy.

We then turned our attention to the scope of substituted sulfonamides **1** (Scheme 4). By changing the *para* substituent

Scheme 4. Substrate Scope for Various Sulfonamides 1[a]



[a]See the Supporting Information for the detailed procedure. [b]Performed with 20 mol % catalyst.

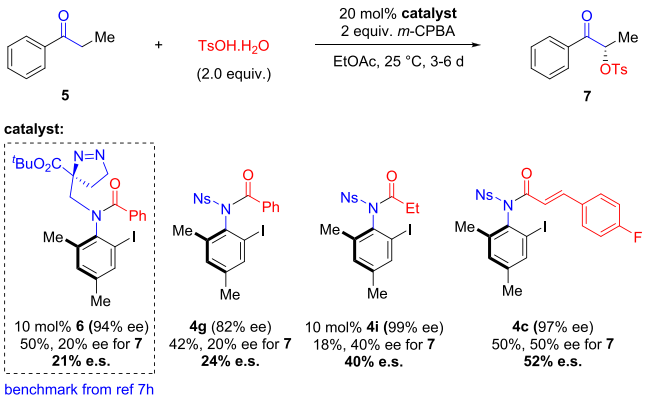
of the aryl unit to either phenyl or other halogens, we produced products **4j**−**4m** with good to high efficiency. The level of enantioselectivities for this series of products, however, decreased to 71−79%. Not surprisingly, keeping one of the *ortho* substituents on the aryl unit as a small methyl gorup was needed for the good enantioselectivity. For ethyl-substituted product **4n**, a much lower ee of 49% was obtained, which was probably due to the diminished size difference between the two *ortho* substituents in this substrate (Me/I vs Et/I). To our gratification, changing the *ortho* iodine substituent to bromine worked out well to deliver **4o** and **4p** in high yield and good ee's of 81−84%. These compounds can serve as a versatile springboard for accessing other valuable analogues by cross coupling. Finally, when the nosyl protecting group on the nitrogen atom was changed to one with either the *meta*-nitro or the *para*-chloro substituent, the reaction proceeded with similar levels of reactivity and selectivity for **4q** and **4r**. Additionally, we were happy to observe that a substrate with a small mesyl protecting group also worked well in this reaction to yield **4s** in 84% ee.

To demonstrate the practical utility of the method, the reaction of **1a** and **3a** was carried out at a larger scale of 0.5 mmol. To our satisfaction, **4a** was isolated with an improved ee of 90% albeit in a slightly lower yield of 60%.

It is noteworthy that during the investigation of the substrate scope, several limitations were discovered (Scheme 4). First, changing the iodine to a small chlorine atom yielded the desired product **4t** that has no stable atropoisomerism, suggesting that the chlorine atom is too small to provide a sufficient rotation barrier along the C−N axis. Second, we discovered by achiral **4u** and **4v** that both the *ortho* positions of the substrate are needed to provide a rotation barrier that is sufficiently high for both atropoisomers to exist.

To demonstrate the synthetic utility of our methodology, we tested products **4** as a potential enantioselective iodine catalyst for the asymmetric α-oxytosylation of propiophenone,[22] which was previously attempted as an application from the group of Li and Cheng.[7h] As illustrated by selected data in Scheme 5,

Scheme 5. Use of Product 4 as an Iodine Catalyst



compared to the benchmark of 21% enantiospecificity (e.s.) from the use of iodine **6**, a simple switch of the *N*-alkyl substituent to nosyl as in **4g** led to a similar level of 24% e.s. More attempts showed that the identity of the *N*-acyl unit had an important influence on enantioselectivity. The use of **4i** and **4c** bearing an ethyl or a styrenyl group improved the enantioselectivity of **7** to 40% and 52% e.s., respectively. This serves as an important proof of concept that our product could be used as an iodine catalyst with catalytic turnover and moderate enantioselectivity.

In conclusion, we have developed an efficient and atroposelective acylation of sulfonamides to yield *N*-sulfonyl anilides with a novel axially chiral scaffold. The reaction was facilitated by a commercially available isothiourea catalyst, (*S*)-HBTM, and the potential of the product as an iodine catalyst was also demonstrated. The development of other novel axially chiral entities is currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02266.

Experimental details, characterization data, NMR and HPLC spectra, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 2015027 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

⊥J.-Y.O. and X.Q.N. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For a general review of atroposelective synthesis of axially chiral biaryls, see: (a) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384−5427. (b) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193−3207. (c) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563−639. (d) Bencivenni, G. *Synlett* **2015**, *26*, 1915−1922. (e) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. *Chem. Soc. Rev.* **2015**, *44*, 3418−3430. (f) Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. *Coord. Chem. Rev.* **2016**, *308*, 131−190. (g) Wang, Y.-B.; Tan, B. *Acc. Chem. Res.* **2018**, *51*, 534−547.

(2) (a) Webster, R.; Cole, S.; Gedge, J.; Roffey, S.; Walker, D.; Wild, W. *Xenobiotica* **2003**, *33*, 541−560. (b) Takahashi, I.; Suzuki, Y.; Kitagawa, O. *Org. Prep. Proced. Int.* **2014**, *46*, 1−23.

(3) (a) Duan, W.-L.; Imazaki, Y.; Shintani, R.; Hayashi, T. *Tetrahedron* **2007**, *63*, 8529−8536. (b) Lin, S.; Leow, D.; Huang, K. W.; Tan, C. H. *Chem. - Asian J.* **2009**, *4*, 1741−1744.

(4) Clayden, J.; Turner, H. *Tetrahedron Lett.* **2009**, *50*, 3216−3219.

(5) (a) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586−4587. (b) Oppenheimer, J.; Hsung, R. P.; Figueroa, R.; Johnson, W. L. *Org. Lett.* **2007**, *9*, 3969−3972. (c) Oppenheimer, J.; Johnson, W. L.; Figueroa, R.; Hayashi, R.; Hsung, R. P. *Tetrahedron* **2009**, *65*, 5001−5012.

(6) (a) Diener, M. E.; Metrano, A. J.; Kusano, S.; Miller, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 12369−12377. (b) Metrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Miller, S. J. *Chem. Commun.* **2016**, *52*, 4816−4819. (c) Crawford, J. M.; Stone, E. A.; Metrano, A. J.; Miller, S. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2018**, *140*, 868−871. (d) Yan, X. C.; Metrano, A. J.; Robertson, M. J.; Abascal, N. C.; Tirado-Rives, J.; Miller, S. J.; Jorgensen, W. L. *ACS Catal.* **2018**, *8*, 9968−9979.

(7) (a) Kitagawa, O.; Kohriyama, M.; Taguchi, T. *J. Org. Chem.* **2002**, *67*, 8682−8684. (b) Terauchi, J.; Curran, D. P. *Tetrahedron: Asymmetry* **2003**, *14*, 587−592. (c) Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 3676−3677. (d) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923−12931. (e) Liu, H.; Feng, W.; Kee, C. W.; Leow, D.; Loh, W.-T.; Tan, C.-H. *Adv. Synth. Catal.* **2010**, *352*, 3373−3379. (f) Shirakawa, S.; Liu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 916−919. (g) Liu, Y.; Feng, X.; Du, H. *Org. Biomol. Chem.* **2015**, *13*, 125−132. (h) Li, S. L.; Yang, C.; Wu, Q.; Zheng, H. L.; Li, X.; Cheng, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 12836−12843. (i) Kikuchi, Y.; Nakamura, C.; Matsuoka, M.; Asami, R.; Kitagawa, O. *J. Org. Chem.* **2019**, *84*, 8112−8120. (j) Lu, S.; Ng, S. V. H.; Lovato, K.; Ong, J. Y.; Poh, S. B.; Ng, X. Q.; Kurti, L.; Zhao, Y. *Nat. Commun.* **2019**, *10*, 3061.

(8) (a) Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, Y.; Yang, X.; Birman, V. B. *J. Org. Chem.* **2012**, *77*, 1722−1737. (b) Taylor, J. E.; Bull, S. D.; Williams, J. M. *Chem. Soc. Rev.* **2012**, *41*, 2109−2121. (c) Zell, D.; Schreiner, P. R. In *Comprehensive Organic Synthesis II*; 2014; pp 296−354. (d) Lu, S.; Poh, S. B.; Ong, J. Y.; Zhao, Y. In *N-Heterocyclic Carbenes in Organocatalysis*; Biju, A. T., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2019; pp 287−308.

(9) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234−236.

(10) (a) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060−17061. (b) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624−13626. (c) De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 14538−14541. (d) Klauber, E. G.; Mittal, N.; Shah, T. K.; Seidel, D. *Org. Lett.* **2011**, *13*, 2464−2467. (e) Min, C.; Mittal, N.; De, C. K.; Seidel, D. *Chem. Commun.* **2012**, *48*, 10853−10855. (f) Mittal, N.; Sun, D. X.; Seidel, D. *Org. Lett.* **2012**, *14*, 3084−3087. (g) Seidel, D. *Synlett* **2014**, *25*, 783−794.

(11) (a) Binanzer, M.; Hsieh, S. Y.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 19698−19701. (b) Kreituss, I.; Murakami, Y.; Binanzer, M.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10660−10663. (c) Allen, S. E.; Hsieh, S. Y.; Gutierrez, O.; Bode, J. W.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 11783−11791.

(12) (a) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536−6537. (b) Yang, X.; Bumbu, V. D.; Birman, V. B. *Org. Lett.* **2011**, *13*, 4755−4757. (c) Yang, X.; Bumbu, V. D.; Liu, P.; Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, W.; Jiang, X.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2012**, *134*, 17605−17612.

(13) Dong, S.; Frings, M.; Cheng, H.; Wen, J.; Zhang, D.; Raabe, G.; Bolm, C. *J. Am. Chem. Soc.* **2016**, *138*, 2166−2169.
(14) Fowler, B. S.; Mikochik, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 2870−2871.
(15) During the preparation of the manuscript, a closely related elegant work was published by Dong and co-workers: Li, D.; Wang, S.; Ge, S.; Dong, S.; Feng, X. *Org. Lett.* **2020**, *22*, 5331−5336. It is noteworthy that we have a complementary scope of substrates from their studies despite the use of the same chiral catalyst.
(16) (a) Lu, S.; Poh, S. B.; Siau, W. Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1731−1734. (b) Lu, S.; Poh, S. B.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 11041−11045. (c) Lu, S.; Song, X.; Poh, S. B.; Yang, H.; Wong, M. W.; Zhao, Y. *Chem. - Eur. J.* **2017**, *23*, 2275−2281. (d) Lu, S.; Poh, S. B.; Rong, Z. Q.; Zhao, Y. *Org. Lett.* **2019**, *21*, 6169−6172.
(17) Merad, J.; Pons, J.-M.; Chuzel, O.; Bressy, C. *Eur. J. Org. Chem.* **2016**, *2016*, 5589−5610.
(18) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351−1354.
(19) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115−1118.
(20) Joannesse, C.; Johnston, C. P.; Concellon, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8914−8918.
(21) The tosyl (Ts)-protected sulfonamide was also tested with the catalyst (*S*)-HBTM (C2), which gave a NMR yield of 72% and an ee of 59%. The more promising substrate **1a** was thus chosen as the model substrate.
(22) Flores, A.; Cots, E.; Bergès, J.; Muñiz, K. *Adv. Synth. Catal.* **2019**, *361*, 2−25.

https://dx.doi.org/10.1021/acs.orglett.0c02266
Org. Lett. XXXX, XXX, XXX−XXX