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COMMUNICATION

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tert-Butyl Hydroperoxide-Initiated Radical Cyclization of 1-(allyloxy)-2-(1-arylvinyl)benzenes with Sulfinic Acids to Access Sulfonated Benzoxepines

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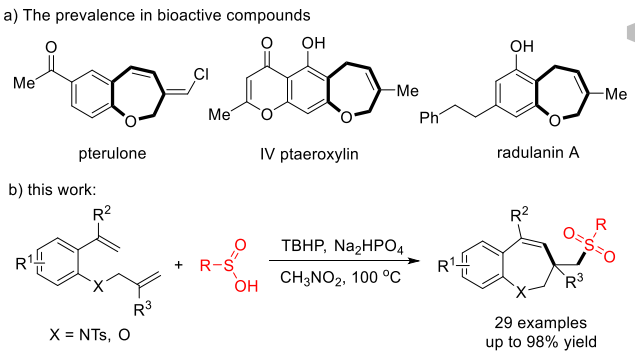
Abstract: A *tert*-butyl hydroperoxide-initiated radical cyclization of 1-(allyloxy)-2-(1-arylvinyl)benzenes with sulfinic acids for the construction of sulfonated benzoxepines is developed. This reaction involves a radical pathway and offers a straightforward route to the formation of seven-membered ring via sulfonylation/cyclization process. This methodology features mild reaction conditions, a broad substrate scope and good functional group tolerance.

Keywords:; radical reactions, cyclization, oxygen heterocycles, sulfonated benzoxepines, synthetic methods

Benzoxepine deriatives, as one of the important classes of oxygen-containing heterocycles, have been widely found in many natural compounds and synthetic bioactive molecules (Scheme 1a), which display diverse chemical and biological activities such as anti-inflammatory, antiproliferative and antifungal.[1] Therefore, the establishment of straightforward synthetic strategies to construct structurally important benzoxepine scaffolds has received substantial attention. In the past decade, transition-metal-catalyzed transformations for the synthesis of benzoxepine skeletons have become attractive strategies.[2,3] Among the selected elegant examples, Dong and co-workers reported a Rh-catalyzed intramolecular olefin hydroacylation to yield benzoxepine deriatives in 2009.[2b] Then, Chan et al developed an Au-catalyzed intramolecular cyclization of 2-(prop-2-ynyloxy)benzaldehydes to form various benzoxepines.[2d] In addition, Gulías group employed a Rh-catalyzed (5+2) cycloaddition of *o*-vinylphenols with alkynes, providing an efficient and practical route to a range of benzoxepines.[3c] It should be noted that Lautens and co-workers described a Pd-catalyzed sequential alkylation-alkenylation reactions for the synthesis of 2-substituted-4-benzoxepines.[3d] Very recently, many groups, for example, Jiang,[4a] Meng,[4c] Heo,[4d] and Reddy,[4e] have established efficient protocols for the construction of benzoxepine deriatives under transition-metal-free conditions. Although these advances have been achieved, the exploration of an efficient and ecofriendly approach to this biologically important class of seven membered cyclic ethers is still in demand.

It is known that organosulfone compounds are important synthetic intermediates in organic and medicinal chemistry.[5] Therefore, the development of green, efficient, and straightforward protocols to access sulfone-containing compounds has aroused the interest of chemists and pharmacologists.[6] Sulfinic acids are versatile, relatively stable, easily accessible,



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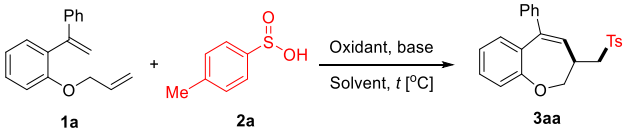
Scheme 1. a) Examples of biologically active compounds containing benzoxepine scaffold; b) Our work concept.

Table 1. Optimization of reaction conditions.[a]



1a 2a 3aa

Entry	Oxidant	Base	Solvent	t[°C]	Yield (%)[b]
1	TBHP	-	CH_3CN	80	63
2	DTBP	-	CH_3CN	80	37
3	TBPB	-	CH_3CN	80	43
4	$K_2S_2O_8$	-	CH_3CN	80	21
5[c]	TBHP	-	CH_3CN	80	63
6	TBHP	-	DCM	80	60
7	TBHP	-	DMF	80	trace
8	TBHP	-	DMSO	80	43
9	TBHP	-	CH_3NO_2	80	70
10	TBHP	-	*tert*-Butanol	80	56
11	TBHP	NaOAc	CH_3NO_2	80	24
12	TBHP	K_2CO_3	CH_3NO_2	80	trace
13	TBHP	Na_2HPO_4	CH_3NO_2	80	80
14	TBHP	Pyridine	CH_3NO_2	80	45
15[d]	TBHP	Na_2HPO_4	CH_3NO_2	80	87
16[d]	TBHP	Na_2HPO_4	CH_3NO_2	70	78
17[d]	TBHP	Na_2HPO_4	CH_3NO_2	90	84
18[d]	TBHP	Na_2HPO_4	CH_3NO_2	100	93
19[d]	TBHP	Na_2HPO_4	CH_3NO_2	110	82
20[e]	TBHP	Na_2HPO_4	CH_3NO_2	100	43
21[d,f]	TBHP	Na_2HPO_4	CH_3NO_2	100	45
22[d,g]	TBHP	Na_2HPO_4	CH_3NO_2	100	74
23[d,h]	TBHP	Na_2HPO_4	CH_3NO_2	100	92
24[d,i]	TBHP	Na_2HPO_4	CH_3NO_2	100	75
25[d,j]	TBHP	Na_2HPO_4	CH_3NO_2	100	91

[a] Reaction condition: **1a** (0.1 mmol), **2a** (0.2 mmol), base (0.2 mmol), TBHP (70% in water, 0.3 mmol), solvent (1 mL), under Ar for 24 h.
[b] Isolated yield.
[c] TBHP (5-6 M in decane).
[d] **2a** (0.25 mmol).
[e] **2a** (0.1 mmol).
[f] Under air.
[g] TBHP (70% in water, 0.2 mmol).
[h] TBHP (70% in water, 0.4 mmol).
[i] Na_2HPO_4 (0.15 mmol).
[j] Na_2HPO_4 (0.25 mmol).

and numerous efforts have been devoted to the high-efficiency construction of organosulfones by using sulfinic acids as sulfonylation agents.[7] To date, the incorporation of a sulfonyl group into the benzoxepine skeleton through a radical-mediated cascade reaction was rarely scarce. With our continuing interest in the synthesis and application of sulfone-containing organic compound,[8] herein, we wish to report a *tert*-butyl hydroperoxide (TBHP) initiated radical cascade sulfonylation/cyclization of 1-(allyloxy)-2-(1-arylvinyl)benzenes with sulfinic acids for the synthesis of sulfonated benzoxepines (Scheme 1b).

Initially, we chose 1-(allyloxy)-2-(1-phenylvinyl)benzene **1a** and *p*-tolylsulfinic acid **2a** as model substrates to identify the optimal reaction conditions. When 3.0 equiv of TBHP (70% in water) was chosen as the oxidant with CH_3CN as the solvent, the expected (*R*)-5-phenyl-3-(tosylmethyl)-2,3-dihydrobenzo[*b*]oxepine **3aa** was obtained in 63% yield at 80 °C under argon (entry 1). Encouraged by this result, other peroxides such as di-*tert*-butylperoxide (DTBP), *tert*-butyl peroxybenzoate (TBPB), $K_2S_2O_8$ and TBHP in decane were examined, and no better results were observed (entries 2-5). Subsequently, a series of solvents such as DCM, DMF, DMSO, CH_3NO_2 and *tert*-Butanol were explored, and CH_3NO_2 was found to be the most efficient one (entries 6-10, see Supporting Information for details). To further improve the yield of this reaction, different bases were examined, of which Na_2HPO_4 provided the highest yield (entries 11−14). In addition, when 2.5 equiv of **2a** was added in this reaction, **3aa** was observed in 87% yield (entry 15). Besides, various the reaction temperature were also screened, and the desired product **3aa** was obtained in 93% yield at 100 °C (entries 16−19). When 1 equiv of **2a** was used in this reaction, **3aa** was observed in 23% yield (entry 20). Lower yield was obtained when the reaction was run in air (entry 21). The yield was decreased when the amount of TBHP and Na_2HPO_4 were reduced (entries 22 and 24), while the yield was not significantly improved when the amount of TBHP and Na_2HPO_4 were increased (entries 23 and 25).

With the optimized conditions in hand, we then studied the scope of the reaction with various 1-(allyloxy)-2-(1-arylvinyl)benzenes, as shown in Table 2. First, we examined the substitution pattern on the aromatic ring of the phenol moiety. Both electron-donating (Me, MeO) and electron-withdrawing (Br) groups at the 5 position of phenyl ring provided the desired sulfonated benzoxepines **3ba-3da** in 69-75% yields. The halide substituents (F, Cl, Br) at the 4 position of the phenyl ring proceeded smoothly and gave the corresponding products **3ea-3ga** in 64-74% yields. The structure of **3ga** was confirmed by single-crystal X-ray analysis (Figure 1). [9] Furthermore, substrate bearing disubstituted *tert*-butyl group was viable in the transformation, producing **3ha** in 51% yield. It should be noted that 2-(allyloxy)-1-(1-phenylvinyl)naphthalene **1i** was also tolerated under this reaction conditions, delivering the desired product **3ia** in 88% yield. Subsequently, we

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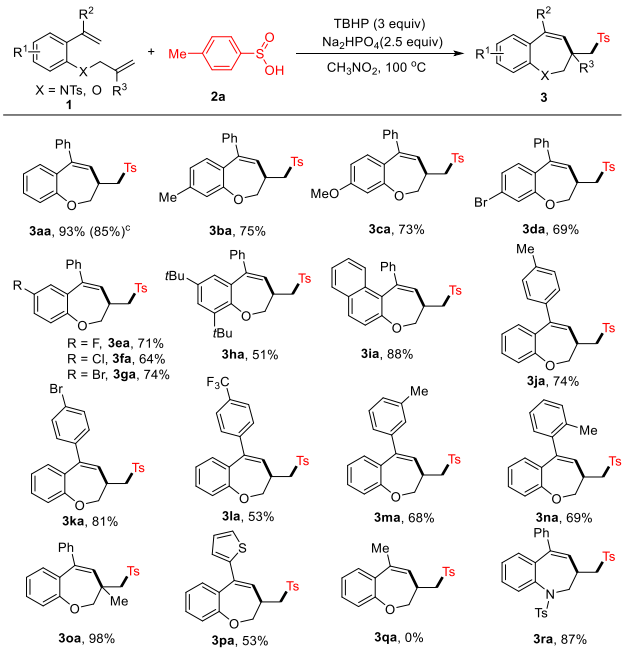
investigated the effect of substituents on the benzene ring tethered alkene. The functional groups such as *p*-Me, *p*-Br, *m*- Me, and *o*-Me on the phenyl ring gave the corresponding products **3ja-3na** in 53-81% yields.

Table2. Scope of 1-(allyloxy)-2-(1-arylvinyl)benzenes [a,b]



[a] Reaction condition: **1** (0.1 mmol), **2a** (0.25 mmol), Na_2HPO_4 (0.2 mmol), TBHP (0.3 mmol), CH_3NO_2 (1 mL), under Ar at 100 °C for 24 h. [b] Isolated yield. [c] **1a** (5 mmol) was used, and the corresponding product **3aa** was obtained in 1.65 g.

Additionally, substrate **1** with a methyl group on the alkene could also undergo the tandem reaction to generate the desired product **3oa** in 98% yield. Furthermore, when R^2 is a thienyl group, the desired product **3pa** was isolated in 53% yield. Unfortunately, when R^2 is a methyl group, no desired product **3qa** was obtained probably due to the unstable benzyl radical intermediate. It was found that N-allyl-4-methyl-N-(2-(1-phenylvinyl)phenyl)benzenesulfonamide **1r** could react with 4-methylbenzenesulfinic acid **2a** under the standard conditions to give the desired product **3ra** in 87% yield.

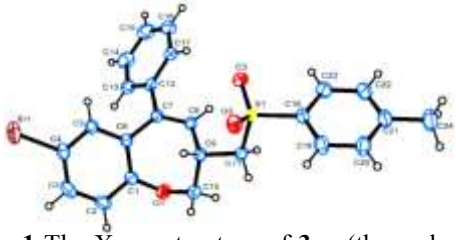
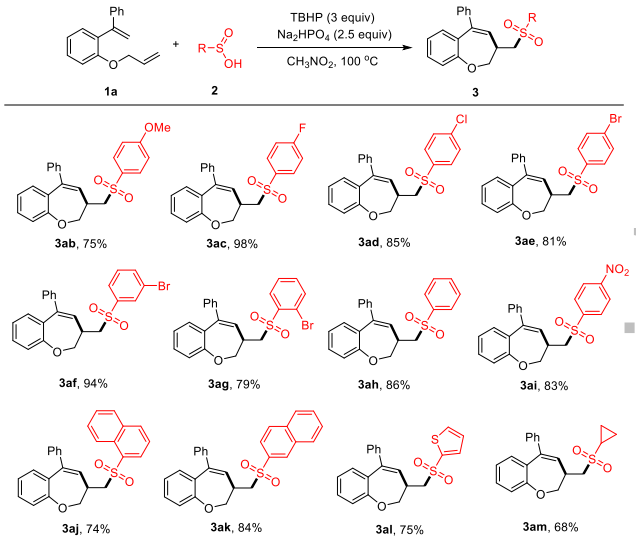


Figure 1 The X-ray structure of **3ga** (thermal ellipsoids are shown with 30% probability).

Next, the reaction of 1-(allyloxy)-2-(1-phenylvinyl)benzene **1a** with a wide range of sulfinic acids **2** were examined, as shown in Table 3. Arylsulfinic acids bearing either electron-donating (MeO) or electron-withdrawing (F, Cl, Br) groups at the *para*-position of the aromatic ring underwent this transformation smoothly, and the desired products **3ab-3ae** were obtained in 75-98% yields. Halide

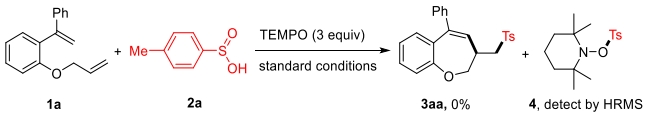
Table3. Substrate scope of sulfinic acids [a,b]



[a] Reaction condition: **1a** (0.1 mmol), **2** (0.25 mmol), Na_2HPO_4 (0.2 mmol), TBHP (0.3 mmol), CH_3NO_2 (1 mL), under Ar at 100 °C for 24 h. [b] Isolated yield.

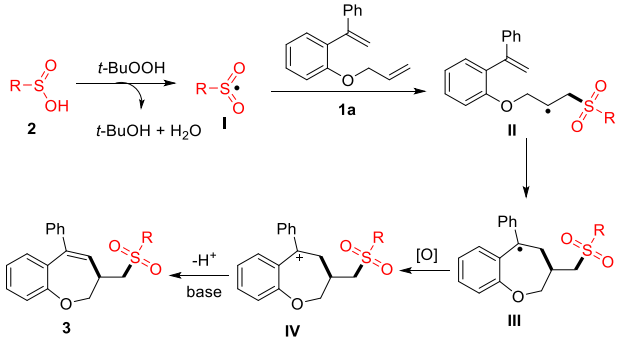
substituents such as Br at the 2 or 3 positions of the phenyl rings afforded the desired products **3af** and **3ag** in 94% and 79% yields, respectively. Benzenesulfinic acid also proved to be a viable substrate and gave the desired product **3ah** in 86% yield. In addition, the arylsulfinic acid with a strong electron withdrawing group such as NO_2 substituent at the *para* position produced **3ai** in 83% yield. Moreover, naphthalene-1-sulfinic acid and naphthalene-2-sulfinic acid were good sulfonating agents, providing **3aj** and **3ak** in 74% and 84% yields, respectively. Furthermore, thiophene-2-sulfinic acid was also compatible with this conversion to give the corresponding desired product **3al** in 75% yield. Remarkably, the aliphatic sulfinic acid, such as cyclopropanesulfinic acid, was also suitable for this conversion, rendering the desired product **3am** in 68% yield.

To understand the reaction mechanism, a radical trapping experiment was conducted as shown in Scheme 2. When a radical scavenger such as TEMPO (3.0 equiv) was added to the reaction, the reaction was completely inhibited and the TEMPO-Ts adduct **4** was detected by HRMS-ESI. This result suggested that a radical processe might be involved in this transformation.



Scheme 2 Control experiment.

Based on the above results and previous reports,[7] a possible reaction mechanism was proposed as shown in Scheme 3. Initially, sulfinic acid **2** reacts with TBHP resulted in the formation of the sulfonyl radical **I**. Then radical **I** chemoselective adds to the C=C bond to afford the intermediate **II**, which undergoes intramolecular cyclization to give the benzyl radical intermediate **III**. Finally, intermediate **III** undergoes oxidation to produce the cation **IV**, which affords the desired product **3** via deprotonation.



Scheme 3. Proposed mechanism.

In summary, we have successfully developed a protocol for access to various sulfonated benzoxepines via a *tert*-butyl hydroperoxide-mediated sulfonylation/cyclization process of various 1-(allyloxy)-2-(1-arylvinyl)benzenes with sulfinic acids. This protocol featured with wide substrate scope and mild reaction conditions, providing a general approach toward sulfonated benzoxepines. Further studies on the application of 1-(allyloxy)-2-(1-arylvinyl)ben-zenes are underway in our laboratory.

Experimental Section

General Procedure for Synthesis of Products 3: An oven-dried Schlenk tube (10 mL) was equipped with a magnetic stir bar, **1** (0.1 mmol), sulfinic acids **2** (2.5 equiv, 0.25 mmol), Na_2HPO_4 (2 equiv, 0.2 mmol). The flask was evacuated and backfilled with Ar for 3 times. Then 1 mL CH_3NO_2 was added followed by TBHP (3 equiv, 0.3 mmol). The tube was then sealed and the mixture was stirred for 24 h at 100 °C under Argon (1 atm). After the reaction was finished, the organic solvent was removed under the reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 5:1) to afford the desired products **3**.

Acknowledgements

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References

[1] a) M. Engler, T. Anke, O. Sterner, *J. Antibiot.* **1997**, *50*, 330–333; b) D. G. Lloyd, R. B. Hughes, D. M. Zisterer, D. C. Williams, C. Fattorusso, B. Catalanotti, G. Campiani, M. J. Meegan, *J. Med. Chem.* **2004**, *47*, 5612–5615; c) S. Kim, B.-N. Su, S. Riswan, L. B. S. Kardono, J. J. Afriastini, J. C. Galluci, H. Chai, N. R. Farnswerth, G. A. Cordell, S. M. Swanson, A. D. Kinghorn, *Tetrahedron Lett.* **2005**, *46*, 9021–9024; d) I. Barrett, M. J. Meegan, R. B. Hughes, M. Carr, A. J. Knox, N. Artemenko, G. Golfis, D. M. Zisterer, D. G. Lloyd, *Bioorg. Med. Chem.* **2008**, *16*, 9554–9573; e) B. W. T. Gruijters, A. Van Veldhuizen, C. A. G. M. Weijers, J. B. P. A. Wijnberg, *J. Nat. Prod.* **2002**, *65*, 558–561; f) J. R. Vyvyan, R. E. Looper, *Tetrahedron Lett.* **2000**, *41*, 1151–1154; g) W. Wang, A. Clay, R. Krishnan, N. J. Lajkiewicz, L. E. Brown, J. Sivaguru, J. A., Jr. Porco, *Angew. Chem. Int. Ed.* **2017**, *56*, 14479-14482.

[2] For recent examples of transition-metal-catalyzed intramolecular cyclization reactions, see: a) A. Varela-Fernández, C. García-Yebra, J. A. Varela, M. A. Esteruelas, C. Saá, *Angew. Chem. Int. Ed.* **2010**, *49*, 4278–4281; b) M. M. Coulter, P. K. Dornan, V. M. Dong, *J. Am. Chem. Soc.* **2009**, ***131***, 6932–6933; c) E. D. D. Calder, S. A. I. Sharif, F. I. McGonagle, A. Sutherland, *J. Org. Chem.* **2015**, *80*, 4683–4696; d) E. M. L. Sze, W. Rao, M. J. Koh, P. W. H. Chan, *Chem.-Eur. J.* **2011**, *17*, 1437–1441; e) J. Liu, Y. Liu, *Org. Lett.* **2012**, *14*, 4742–4745.

[3] For recent examples of transition-metal catalyzed intermolecular [m + n] cyclization reacions, see: a) Liu, G.; Lu, X. *Adv. Synth. Catal.* **2007**, *349*, 2247–2252; b) X. Yu, X. Lu, *J. Org. Chem.* **2011**, *76*, 6350–6355; c) A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas, M. Gulías, *J. Am. Chem. Soc.* **2014**, *136*, 834–837; d) A. A. Friedman, J. Panteleev, J. Tsoung, V. Huynh, M. Lautens, *Angew. Chem. Int. Ed.* **2013**, *52*, 9755–9758.

[4] a) L. Ouyang, C. Qi, H. He, Y. Peng, W. Xiong, Y. Ren, H. Jiang, *J. Org. Chem.* **2016**, *81*, 912–919; b) J. Xu, S. Yuan, J. Peng, M. Miao, Z. Chen, H. Ren, *Org. Biomol. Chem.* **2017**, ***15***, 7513–7517; c) Y. Zhang, A. Yu, J. Jia, S. Ma, K. Li, Y. Wei, X. Meng, *Chem. Commun.* **2017**, *53*, 10672–10675; d) Y. L. Choi, H. S. Lim, H. J. Lim, J.-N. Heo, *Org. Lett.* **2012**, *14*, 5102–5105; e) S. J.

Gharpure, S. R. B. Reddy, *Eur. J. Org. Chem.* **2013**, *2013*, 2981–2984.

[5] a) J. Drews, *Science*, **2000**, *287*, 1960–1964; b) A. EI-Awa, M. N. Noshi, X. M. du Jourdin, P. L. Fuchs, *Chem. Rev.* **2009**, *109*, 2315–2349; c) B. A. Frankel, M. Bentley, R. G. Kruger, D. G. McCafferty, *J. Am. Chem. Soc.* **2004**, *126*, 3404–3405; d) V. P. Sandanayaka, A. S. Prashad, Y.-J. Yang, R. T. Williamson, Y.-I. Lin, T. S. Mansour, *J. Med. Chem.* **2003**, *46*, 2569–2571; e) J. N. Desrosiers, A. B. Charette, *Angew. Chem., Int. Ed.* **2007**, *46*, 5955–5957; f) R. Ettari, E. Nizi, M. E. Di Francesco, M.-A. Dude, G. Pradel, R. Vicik, T. Schirmeister, N. Micale, S. Grasso, M. Zappala, *J. Med. Chem.* **2008**, *51*, 988–996; g) T. Ai, Y. Xu, L. Qiu, R. J. Geraghty, L. Chen, *J. Med. Chem.* **2015**, *58*, 785–800.

[6] a) Q.-Q. Lu, J. Zhang, G.-L. Zhao, Y. Qi, H.-M. Wang, A.-W. Lei, *J. Am. Chem. Soc.* **2013**, *135*, 11481–11484; b) K.-D. Zhou, H.-G. Xia, J. Wu, *Org. Chem. Front.* **2017**, *4*, 1121–1124; c) T.-Y. Shang, L.-H. Lu, Z. Cao, Y. Liu, W.-M. He, B. Yu, *Chem. Commun.* **2019**, *55*, 5408–5419; d) Y. Liu, Q. Wang, Z. Chen, H. Li, B. Xiong, P. Zhang, K.-W. Tang, *Chem. Commun.* **2020**, *56*, 3011–3014; e) L. Zhang, S. Chen, Y. Gao, P. Zhang, Y. Wu, G. Tang, Y. Zhao, *Org. Lett.* **2016**, *18*, 1286–1289; f) D. Zhang, J. Cai, J. Du, X. Wang, W. He, Z. Yang, C. Liu, Z. Fang, K. Guo, *J. Org. Chem.* **2021**, *86*, 2593–2601; g) M. Y. Ansari, N. Kumar, A. Kumar, *Org. Lett.* **2019**, *21*, 3931–3936; h) W.-J. Hao, Y. Du, D. Wang, B. Jiang, Q. Gao, S.-J. Tu, G. Li, *Org. Lett.* **2016**, *18*, 1884–1887; i) Y.-Z. Zhang, Z.-Y. Mo, H.-S. Wang, X.-A. Wen, H.-T. Tang, Y.-M. Pan, *Green Chem.* **2019**, *21*, 3807-3811; j) S. K. Pagire, A. Hossain and O. Reiser, *Org. Lett.* **2018**, *20*, 648–651; k) O. M. Mulina, A. I. Ilovaisky, V. D. Parshin, A. O. Terent'ev, *Adv. Synth. Catal.* **2020**, *362*, 4579–4654; l) Y.-N. Wu, T.-S. Zhang, W.-J. Hao, S.-J. Tu, B, Jiang, *Asian J. Org. Chem.* **2020**, 9, 1040-1044; m) T.-S. Zhang, W.-J. Hao, R. Wang, S.-C. Wang, S.-J. Tu, B, Jiang, *Green Chem.* **2020**, *22*, 4259-4269; n) H.-D. Zuo, W.-J. Hao, C.-F. Zhu, C. Guo, S.-J. Tu, B, Jiang, *Org. Lett.* **2020**, *22*, 4471–4477.

[7] a) F. Chen, Q. Meng, S.-Q. Han, B. Han, *Org. Lett.* **2016**, *18*, 3330-3333; b) J. Xu, X. Yu, J. Yan, Q. Song, *Org. Lett.* **2017**, *19*, 6292–6295; c) F.-H. Xiao, H. Chen, H. Xie, S.-Q. Chen, L. Yang, G.-J. Deng, *Org. Lett.* **2014**, *16*, 50–53; d) W. Wei, J.-W. Wen, D.-S. Yang, J. Du, J.-M. You, H. Wang, *Green Chem.* **2014**, *16*, 2988–2991; e) W. Yang, S. Yang, P. Li, L. Wang, *Chem. Commun.* **2015**, *51*, 7520-7523; f) Q. Liu, Y. Mei, L. Wang, Y. Ma, P. Li, *Adv. Synth. Catal.* **2020**, *362*, 5669–5680.

[8] a) N. Zhou, M. Wu, K. Kuang, S. Wu, M. Zhang, *Adv. Synth. Catal.* **2020**, *362*, 5391–5397; b) N. Zhou, M. Wu, M. Zhang, X. Zhou, W Zhou, *Org. Biomol. Chem.* **2020**, *18*, 1733–1737.

[9] CCDC-2074239 (**3ga**) 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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