OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Stereoselective Synthesis of Atropisomeric Bipyridine *N,N′*-Dioxides by Oxidative Coupling

Yasuaki Fukazawa,[†] Vladimir Yu. Vaganov,[‡] Sergei A. Shipilovskikh,[‡,§] Aleksandr E. Rubtsov,*[,‡] and Andrei V. Malkov*[,†]

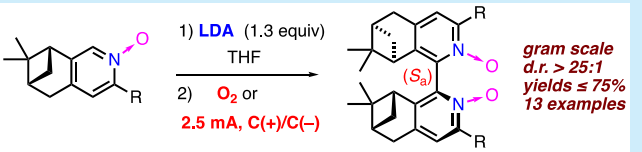
[†]Department of Chemistry, Loughborough University, Loughborough LE11 3TU, U.K.

[‡]Department of Chemistry, Perm State University, Bukireva 15, Perm 614990, Russia

[§]Institute of Chemical Technology, Ural Federal University, Mira 19, Yekaterinburg 620002, Russia

Supporting Information

ABSTRACT: Bipyridine *N,N′*-dioxide is a structural fragment found in many bioactive compounds. Furthermore, chiral analogues secured their place as powerful Lewis base catalysts. The scope of the existing methods for the synthesis of atropisomeric bipyridine *N,N′*-dioxides is limited. Herein, we present a practical, highly chemo- and stereoselective method for oxidative dimerization of chiral pyridine *N*-oxides using O_2 as a terminal oxidant. A series of 13 axially chiral bipyridine *N,N′*-dioxides were synthesized in up to 75% yield.



Heterocyclic *N*-oxides, including their bis-heterocyclic analogues, accrued an extensive record of applications in drug discovery and natural product chemistry,[1] while chiral mono-*N*-oxides and *N,N′*-dioxides become important players in asymmetric catalysis due to their distinct Lewis basic properties.[2] A selection of the most efficient *N,N′*-dioxide organocatalysts is shown in Figure 1. Except for some

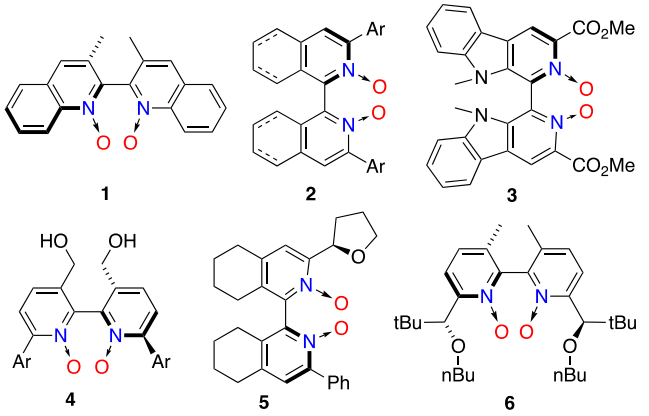
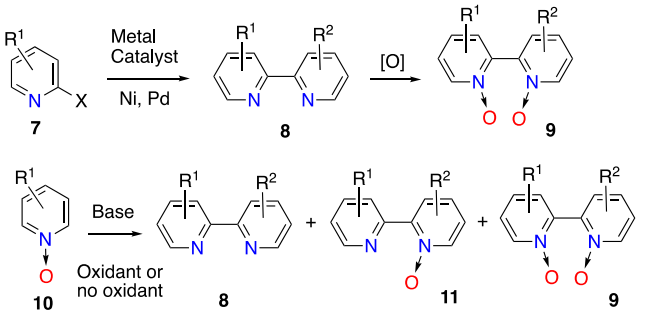


Figure 1. Axially chiral bipyridine-*N,N′*-dioxides.

derivatives of **2**,[3] **4**,[4] and **5**,[5] such compounds are obtained by coupling of the monomeric pyridine precursors. Typically, the synthesis of *N,N′*-dioxides relies on a transition-metal mediated coupling of 2-halopyridines **7** (Scheme 1) followed by *N*-oxidation and separation into enantiomers or diastereoisomers, as appropriate. Compounds **1**−**3** were synthesized by this route (Scheme 1, **7** → **8** → **9**).[6] Since the preparation of 2-halopyridines requires a synthetic detour, an alternative

Scheme 1. Synthesis of Bipyridine *N,N′*-Dioxides by Dimerization of Mononuclear Precursors



direct oxidative coupling of *N*-oxides **10** (Scheme 1) was realized for making **6**[7] and its analogues.[8]

Synthesis of **6** involves low-temperature deprotonation of the monomeric pyridine *N*-oxide followed by oxidation with molecular iodine to trigger dimerization. In some instances, the atropisomers were formed with excellent diastereoselectivity; however, the yields suffered from the formation of substantial quantities of the respective 2-iodopyridine *N*-oxide as a byproduct. In addition to the diastereoselectivity issues, direct coupling of pyridine *N*-oxides **10**, depending on the reaction conditions, can afford up to three products: bipyridines **8**,[9] mono-*N*-oxides **11**,[9a,10] and *N,N′*-dioxides **9**[7b,c,10e,11] (Scheme 1). Therefore, demand for a robust and efficient method for coupling of pyridine *N*-oxides still has not been fulfilled.[12]

Herein, we present a practical, highly chemo- and diastereoselective method for oxidative dimerization of

Received: May 14, 2019

DOI: 10.1021/acs.orglett.9b01687
Org. Lett. XXXX, XXX, XXX−XXX

lithiated pyridine *N*-oxides employing oxygen as a terminal oxidant.

The chemoselectivity in the formation of mono-*N*-oxide **11** or *N,N′*-dioxide **9** from the deprotonated monomeric pyridine *N*-oxide **10** is controlled by the interplay between two different reaction manifolds. Thus, a nucleophilic addition of *α*-metalated *N*-oxide to a neutral **10** followed by elimination of metal hydroxide leads to **11**, whereas oxidation of the anion to radical species results in dimerization product **9**.[7c,10e]

Pursuing our longstanding interest in chiral *N,N′*-dioxide catalysts for asymmetric C−C bond formation,[11b,13] we focused on developing a simple and practical method for selective oxidative coupling of pyridine *N*-oxides.

Synthesis of chiral monomeric *N*-oxides **16a−o** was accomplished in three steps from commercially available ketones **12** by Kröhnke annulation of **13** and (1*R*)-myrtenal **14** to afford pyridines **15** that were further oxidized with *m*-CPBA to **16** (Scheme 2).[14] Next, *N*-oxide **16a** was selected as a model substrate for developing conditions for its oxidative dimerization into **17a** (Table 1).

Scheme 2. Synthesis of Atropisomeric Bipyridine *N,N′*-Dioxides

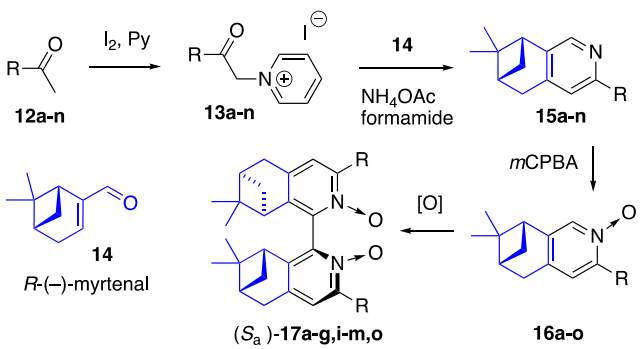


Table 1. Optimization of the Oxidative Dimerization Protocol (16a → 17a)[a]

entry	base	oxidant	*T* (°C)	time before addition of oxidant (h)	yield of **17a** (%)
1	LDA	I_2	−78	16	0 (80)[b]
2	LDA	I_2	−78	2	0 (85)[b]
3	LDA	I_2	−78	0	0 (81)[b]
4	LDA	O_2	−78	0.5	SM
5	LDA	O_2	−78	0	70[c] (81)[d]
6	LDA	O_2	0	0	60[e] (72)[d]
7	LDA	O_2	rt	0	55[f] (65)[d]
8	LDA, 12-crown-4	O_2	−78	0	SM
9	KHMDS	O_2	−78	0	SM

[a]The reactions were carried out in dry THF, and solution of **16a** was added to 1.3 equiv of base. Where *t* = 0, the oxidant was applied immediately after addition of **16a**. LDA = lithium diisopropylamide, KHMDS = potassium bis(trimethylsilyl)amide, SM = starting material. [b]Yield of 2-iodopyridine *N*-oxide. [c]dr > 25:1, no mono-*N*-oxide **11** formed. [d]Yield based on recovered starting material. [e]Mono-*N*-oxide **11** formed (5%). [f]Mono-*N*-oxide **11** formed (8%).

Deprotonation of **16a** was carried out with LDA (1.3 equiv) at −78 °C. Quenching with MeOD after 5 min revealed 78% D incorporation. For the oxidation of the anion, molecular iodine was assessed first following the literature methods.[7c,8b] However, only the respective 2-iodopyridine *N*-oxide was obtained in high yield (entry 1). The length of deprotonation had no effect on the reaction outcome (entries 2 and 3). Previously, we reported a single example of oxidative coupling of deprotonated **16b** in a modest yield in the presence of oxygen, but reproducibility was low.[11b,13] We now undertook a more detailed investigation of this reaction. Allowing the deprotonation to run for 30 min (or longer) and then introducing O_2 gave no coupling product, with starting material being quantitatively recovered (entry 4). However, when O_2 was applied immediately after addition of **16a** to LDA, dioxide **17a** formed as a single diastereoisomer (dr > 25:1) in 71% yield (81% based on the recovered starting material). The reaction was complete in under 15 min. At higher temperatures, the yield of **17a** dropped slightly (entries 6 and 7) due to competing nucleophilic addition route to give the respective bipyridine mono-*N*-oxide (see Scheme 1). Mechanistically, the reaction is likely to resemble oxidative coupling of lithium enolates and proceed through single-electron oxidation.[15] The key factor appears to be formation of highly ordered organolithium aggregates,[16] where two pyridine units are favorably aligned to form a C−C bond. Comparison of the results in entries 4 and 5 suggests that the kinetically formed complexes at the early stages adopt a correct geometry for coupling, whereas within 30 min they rearrange into more stable but nonreactive complexes. Lithium seems to play a crucial part in holding the heterocyclic units together. Thus, addition of 12-crown-4 to LDA disrupts formation of aggregates and shuts down the reaction (entry 8). Likewise, a less Lewis acidic potassium (KHMDS) was not competent either (entry 9).

With the optimal conditions identified (Table 1, entry 5), the scope and limitations of this protocol were explored next (Table 2). In most cases, the reactions were performed on a

Table 2. Scope of Oxidative Dimerization (16 → 17)[a]

entry	**16**, R	(S_a)-**17**	yield of **17** (brsm)[b] (%)
1	**16a**, Ph	**17a**	70 (81)
2	**16b**, 3,5-$(CF_3)_2$-C_6H_3	**17b**	45 (74)
3	**16c**, 3,5-Me_2-C_6H_3	**17c**	59 (70)
4	**16d**, 4-ClC_6H_4	**17d**	38 (89)
5	**16e**, 4-FC_6H_4	**17e**	65 (87)
6	**16f**, 3-$NO_2C_6H_4$	**17f**	48 (81)
7	**16g**, 4-$MeOC_6H_4$	**17g**	35 (82)
8	**16h**, 2-$MeOC_6H_4$	**17h**	SM
9	**16i**, 2-naphthyl	**17i**	40 (76)
10	**16j**, 2-furyl	**17j**	44 (63)
11	**16k**, 2-thienyl	**17k**	32 (88)
12	**16l**, CF_3	**17l**	75 (75)
13	**16m**, *t*Bu	**17m**	49 (68)
14	**16n**, *i*Pr	**17n**	SM
15	**16o**, CN	**17o**	23

[a]The reactions were carried out in dry THF on a 1−5 mmol scale using 1.3 equiv of LDA at −78 °C for deprotonation. A balloon with O_2 was attached immediately after combining the reactants. In all cases, the dr of **17** was >25:1. Configuration S_a was established for **17g** by X-ray analysis and was extrapolated to all other dioxides **17**. [b]Isolated yield; brsm = yield based on recovered starting material.

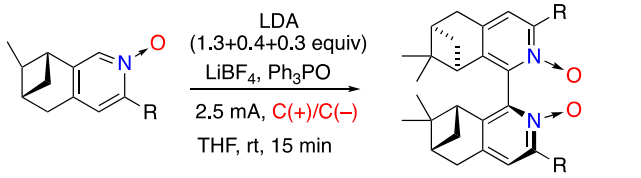
DOI: 10.1021/acs.orglett.9b01687
Org. Lett. XXXX, XXX, XXX−XXX

gram scale, and there was no noticeable difference in the product yields within the tested range of 1−5 mmol scale. For the substrates with aromatic substituents **16b−g,i**, the reaction followed the same trend as for the parent **16a**. Configuration of the chiral axis in **17g** was established as S_a by X-ray analysis (see the Supporting Information for details), which was extrapolated to all other *N,N′*-dioxides. However, *N*-oxide **16h**, with the methoxy group in the *o*-position capable of chelating Li, failed to produce the coupling product, which likely resulted from formation of complexes with unfavorable alignment of the pyridine units (entry 8). Substrates with heterocyclic substituents **16j** and **16k** mirrored reactivity of the aromatic analogues to furnish the respective *N,N′*-dioxides (entries 10 and 11). For *N*-oxides with aliphatic substituents, the reaction outcome depended on the presence of an *α*-C−H bond in the substituent. Thus, substrates **16l** (CF_3) and **16m** (*t*Bu) lacking any C−H bond reacted uneventfully (entries 12 and 13), whereas **16n** (*i*Pr) proved unreactive, even though a MeOD quench 5 min after deprotonation revealed 75% D incorporation in the 2-position of the pyridine ring and none in the *i*Pr group. The reason for such an anomalous behavior is not clear at the moment.

The coupling of 2-cyanopyridine **16o** resulted in a low yield of the *N,N′*-dioxide **17o**. In this instance, the starting material was fully consumed through competing side reactions.

The prerequisite to quickly intercept the kinetically formed complexes of 2-lithiopyridine *N*-oxides prompted us to briefly examine their electrochemical oxidation (Scheme 3). The

Scheme 3. Electrochemical Synthesis of Atropisomeric Bipyridine *N,N′*-Dioxides



16a,e,f

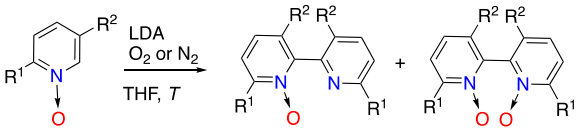
(S_a)-**17a**, yield 51% (82% brsm)
(S_a)-**17e**, yield 55% (89% brsm)
(S_a)-**17f**, yield 47% (78% brsm)

reaction was carried out in THF at ambient temperature employing $LiBF_4$ as an electrolyte. It was found essential to use Ph_3PO (1.5 equiv), presumably acting as a sacrificial electron acceptor to prevent reduction of pyridine *N*-oxide. The best yields were attained when LDA was added in three portions with 5 min intervals. In these cases, the yields were on par with those obtained under O_2 atmosphere. The *N,N′*-dioxides **17a**, **17e**, and **17f** were attained as single diastereoisomers. Furthermore, formation of bipyridine mono-*N*-oxides was not observed, thus making the electrochemical dimerization of 2-lithiopyridine *N*-oxides **16** a useful tool for synthesizing **17**.

Appearance of bipyridine mono-*N*-oxides alongside **16a** (Table 1, entries 6 and 7) raised questions regarding the factors influencing the competition between the two reaction manifolds: oxidative coupling vs nucleophilic addition/elimination sequence. Therefore, coupling of *N*-oxides **10a−c** with substituents in position 5 of differing sizes was examined (Table 3).

The least sterically congested 2-phenylpyridine *N*-oxide **10a** furnished only addition/elimination product **11a** under both oxidative and inert atmosphere (entries 1,2). The most

Table 3. Oxidative Coupling vs Nucleophilic Addition/Elimination Process[a]



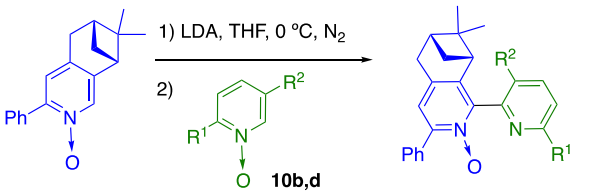
10a-c **a**: R^1 = Ph, R^2 = H; **b**: R^1 = Ph, R^2 = Br; **c**: R^1 = Ph, R^2 = Ph — **11a-c** — **9a-c**

entry	**10**, R^1, R^2	*T* (°C)	N_2 or O_2	yield of **11**[b] (%)	yield of **9** (%)
1	**10a**, Ph, H	−78	O_2	92	0
2	**10a**, Ph, H	−78	N_2	93	0
3	**10b**, Ph, Br	−78	O_2	0	69[c]
4	**10b**, Ph, Br	0	O_2	30[c]	47[c]
5	**10b**, Ph, Br	−78	N_2	80	0
6	**10c**, Ph, Ph	−78	O_2	0	60[c]
7	**10c**, Ph, Ph	0	N_2	0	0

[a]The reactions were carried out in dry THF on a 0.4−0.6 mmol scale, unless stated otherwise, using 1.3 equiv of LDA at −78 °C for deprotonation. A balloon with O_2 was attached immediately after combining the reactants. [b]Isolated yield. [c]Yield based on recovered starting material.

sterically hindered 2,5-diphenylpyridine *N*-oxide **10c** in the presence of O_2 gave only *N,N′*-dioxide **9c**, while no product was formed under inert atmosphere (entries 6, 7). Bromide in position 5 appears to mark a borderline case. Under O_2 at −78 °C, only *N,N′*-dioxide **9b** was formed (entry 3); at 0 °C, both reaction manifolds exhibited similar rates slightly favoring oxidative dimerization (entry 4). Naturally, under N_2, only mono-*N*-oxide **11b** was attained (entry 5). The results indicate that the steric size of the substituent in position 5, along with the reaction temperature and the reaction atmosphere, strongly influence the preferred pathway. As a follow up, cross-coupling of two different pyridine *N*-oxides was examined under conditions favoring a nucleophilic addition/elimination route (Scheme 4).[10c] Pyridine *N*-oxides **10b** or **10d** were added to a

Scheme 4. Cross-Coupling of Two Different Pyridine *N*-Oxides



16a — **10b,d** **b**: R^1 = Ph, R^2 = Br; **d**: R^1 = Cl, R^2 = Cl

18ab, yield 75%, d.r. 2:1
18ad, yield 68%, d.r. 1.6:1

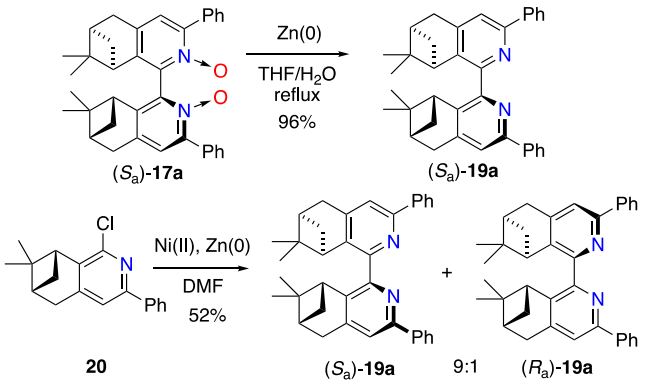
solution of deprotonated *N*-oxide **16a** at 0 °C under N_2 atmosphere. Mono-*N*-oxides **18ab** and **18ad** were obtained in good yield, though with low diastereoselectivity.

To illustrate the advantage of the oxidative dimerization over the existing metal-mediated coupling of 2-halopyridines, the two sequences in the synthesis of atropisomeric (S_a)-**19a** were compared (Scheme 5).

Thus, pure (S_a)-**17a** obtained by oxidative coupling of **16a** was readily converted to (S_a)-**19a** by heating with metallic Zn in aqueous THF with no erosion of the stereochemical integrity. On the other hand, a Ni-catalyzed coupling of 2-

DOI: 10.1021/acs.orglett.9b01687
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Synthesis of Atropisomeric Bipyridines



chloropyridine **20**, synthesized from **16a** and $POCl_3$, furnished a 9:1 mixture of atropisomeric (S_a)-**19a** and (R_a)-**19a**, which required chromatographic separation, making this route less attractive from the practical viewpoint.[17] Configuration of the chiral axis in the major isomer was confirmed as (S_a)-**19a** by X-ray crystallography.

In conclusion, we developed a highly chemo- and stereoselective method for oxidative dimerization of monomeric chiral pyridine *N*-oxides enabling gram-scale synthesis of atropisomeric *N,N′*-dioxides. The oxidative coupling manifold uses O_2 as a terminal oxidant and relies on the capture of kinetically formed organolithium complexes. The oxidation can be carried out in an electrochemical cell. The alternative nucleophilic addition pathway is less stereoselective but allows for the synthesis of nonsymmetrical biaryls. Application of bipyridine *N,N′*-dioxides **17** and bipyridines **19** in asymmetric catalysis is currently under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01687.

Experimental procedures; ^1H and ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 1905937 and 1909215 contain 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.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: a.malkov@lboro.ac.uk.
*E-mail: rubtsov@psu.ru.

ORCID

Sergei A. Shipilovskikh: 0000-0002-8917-2583
Aleksandr E. Rubtsov: 0000-0002-4299-3464
Andrei V. Malkov: 0000-0001-6072-2353

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Russian Science Foundation for Grant No. 18-73-10156. Y.F. and A.V.M. thank the Leverhulme Trust for the research grant (RGP-2015-351). Y.F. also thanks the Japanese Government and Loughborough University for a studentship.

■ REFERENCES

(1) (a) Antkowiak, W. Z.; Gessner, W. P. *Tetrahedron Lett.* **1979**, *20*, 1931. (b) Mfuh, A. M.; Larionov, O. V. *Curr. Med. Chem.* **2015**, *22*, 2819. (c) O'Donnell, G.; Poeschl, R.; Zimhony, O.; Gunaratnam, M.; Moreira, J. B. C.; Neidle, S.; Evangelopoulos, D.; Bhakta, S.; Malkinson, J. P.; Boshoff, H. I.; Lenaerts, A.; Gibbons, S. *J. Nat. Prod.* **2009**, *72*, 360.

(2) (a) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129. (b) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (c) Denmark, S. E.; Fu, J. P. *Chem. Rev.* **2003**, *103*, 2763. (d) Koukal, P.; Ulč, J.; Nečas, D.; Kotora, M. Pyridine N-Oxides and Derivatives Thereof in Organocatalysis. In *Heterocyclic N-Oxides*; Springer: Cham, 2017; p 29. (e) Liu, B.; Feng, X.; Chen, F.; Zhang, G.; Cui, X.; Jiang, Y. *Synlett* **2001**, *2001*, 1551. (f) Jiao, Z.; Feng, X.; Liu, B.; Chen, F.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* **2003**, *2003*, 3818. (g) Liu, X. H.; Lin, L. L.; Feng, X. M. *Acc. Chem. Res.* **2011**, *44*, 574. (h) Liu, X.; Lin, L.; Feng, X. *Org. Chem. Front.* **2014**, *1*, 298. (i) Liu, X.; Zheng, H.; Xia, Y.; Lin, L.; Feng, X. *Acc. Chem. Res.* **2017**, *50*, 2621. (j) Liu, X.; Dong, S.; Lin, L.; Feng, X. *Chin. J. Chem.* **2018**, *36*, 791. (k) Malkov, A. V.; Kočovský, P. *Curr. Org. Chem.* **2003**, *7*, 1737. (l) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, *2007*, 29.

(3) (a) Hrdina, R.; Dračinský, M.; Valterová, I.; Hodačová, J.; Císařová, I.; Kotora, M. *Adv. Synth. Catal.* **2008**, *350*, 1449. (b) Reep, C.; Morgante, P.; Peverati, R.; Takenaka, N. *Org. Lett.* **2018**, *20*, 5757.

(4) (a) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799. (b) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329. (c) Kina, A.; Shimada, T.; Hayashi, T. *Adv. Synth. Catal.* **2004**, *346*, 1169.

(5) Kadlčíková, A.; Hrdina, R.; Valterová, I.; Kotora, M. *Adv. Synth. Catal.* **2009**, *351*, 1279.

(6) (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (b) Malkov, A. V.; Westwater, M. M.; Gutnov, A.; Ramírez-López, P.; Friscourt, F.; Kadlčiková, A.; Hodačová, J.; Rankovic, Z.; Kotora, M.; Kočovský, P. *Tetrahedron* **2008**, *64*, 11335. (c) Bai, B.; Shen, L.; Ren, J.; Zhu, H. J. *Adv. Synth. Catal.* **2012**, *354*, 354. (d) Bai, B.; Zhu, H. J.; Pan, W. *Tetrahedron* **2012**, *68*, 6829.

(7) (a) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233. (b) Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235. (c) Denmark, S. E.; Fan, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 687.

(8) (a) Ulč, J.; Nečas, D.; Koukal, P.; Havlíček, V.; Tošner, Z.; Hybelbauerova, S.; Kotora, M. *Eur. J. Org. Chem.* **2018**, *2018*, 5109. (b) Bednářová, E.; Nečas, D.; Císařová, I.; Dušek, M.; Lamaty, F.; Kotora, M. *Monatsh. Chem.* **2019**, *150*, 29.

(9) (a) Inamoto, K.; Araki, Y.; Kikkawa, S.; Yonemoto, M.; Tanaka, Y.; Kondo, Y. *Org. Biomol. Chem.* **2013**, *11*, 4438. (b) Stephens, D. E.; Lakey-Beitia, J.; Burch, J. E.; Arman, H. D.; Larionov, O. V. *Chem. Commun.* **2016**, *52*, 9945.

(10) (a) Tagawa, Y.; Hama, K.; Goto, Y.; Hamana, M. *Heterocycles* **1992**, *34*, 2243. (b) Tagawa, Y.; Hama, K.; Goto, Y.; Hamana, M. *Heterocycles* **1995**, *40*, 809. (c) Kovalev, I. S.; Rusinov, V. L.; Chupakhin, O. N. *Chem. Heterocycl. Compd.* **2009**, *45*, 176. (d) Wang, H.; Pei, Y.; Bai, J.; Zhang, J.; Wu, Y.; Cui, X. *RSC Adv.* **2014**, *4*, 26244. (e) Jha, A. K.; Jain, N. *Eur. J. Org. Chem.* **2017**, *2017*, 4765.

(11) (a) Gronowitz, S.; Timari, G. *J. Heterocycl. Chem.* **1990**, *27*, 1501. (b) O'Hora, P. S.; Incerti-Pradillos, C. A.; Kabeshov, M. A.; Shipilovskikh, S. A.; Rubtsov, A. E.; Elsegood, M. R. J.; Malkov, A. V. *Chem. - Eur. J.* **2015**, *21*, 4551. (c) Peng, X. J.; Huang, P. P.; Jiang, L. L.; Zhu, J. Y.; Liu, L. X. *Tetrahedron Lett.* **2016**, *57*, 5223.

DOI: 10.1021/acs.orglett.9b01687
Org. Lett. XXXX, XXX, XXX−XXX

(12) (a) Yamada, S.; Kaneda, T.; Steib, P.; Murakami, K.; Itami, K. *Angew. Chem., Int. Ed.* **2019**, DOI: 10.1002/anie.201814701. (b) Hilton, M. C.; Zhang, X.; Boyle, B. T.; Alegre-Requena, J. V.; Paton, R. S.; McNally, A. *Science* **2018**, *362*, 799.
(13) Incerti-Pradillos, C. A.; Kabeshov, M. A.; O'Hora, P. S.; Shipilovskikh, S. A.; Rubtsov, A. E.; Drobkova, V. A.; Balandina, S. Y.; Malkov, A. V. *Chem. - Eur. J.* **2016**, *22*, 14390.
(14) Shipilovskikh, S. A.; Vaganov, V. Y.; Denisova, E. I.; Rubtsov, A. E.; Malkov, A. V. *Org. Lett.* **2018**, *20*, 728.
(15) Casey, B. M.; Flowers, R. A. *J. Am. Chem. Soc.* **2011**, *133*, 11492.
(16) Reich, H. J. *Chem. Rev.* **2013**, *113*, 7130.
(17) Furthermore, oxidation of (S_a)-**19a** with *m*-CPBA gave a mere 3:1 mixture of atropisomeric (S_a)-**17a** and (R_a)-**17a** (see the Supporting Information). No racemization of (S_a)-**19a** was observed after heating for 1 h at 100 °C in DMSO.

DOI: 10.1021/acs.orglett.9b01687
Org. Lett. XXXX, XXX, XXX−XXX