Enantioselective Synthesis of Five-Membered-Ring Atropisomers with a Chiral Rh(III) Complex

Saad Shaaban, Houhua Li, Felix Otte, Carsten Strohmann, Andrey P. Antonchick,* and Herbert Waldmann*

ABSTRACT: Axially chiral atropisomeric compounds are widely applied in asymmetric catalysis and medicinal chemistry, and efficient methods for their synthesis are in high demand. This applies in particular to atropisomers derived from five-membered aromatic rings because their lower barrier for rotation among the biaryl axis limits their asymmetric synthesis. We report here an enantioselective C–H functionalization method using our chiral Rh Jas Cp complex for the synthesis of the biaryl atropisomer types that can be accessed from three different five-membered-ring heterocycles.

Axially chiral atropisomers have found widespread application in diverse areas of investigation, in particular asymmetric synthesis and medicinal chemistry, and consequently, methods for their efficient synthesis are in high demand.1 Attention has been mostly focused on six-membered-ring biaryl axis atropisomers,2 but atropisomers formed from five-membered rings have been infrequently explored (Scheme 1a). In these cases, the lower barrier for rotation among the biaryl axis limits both their asymmetric synthesis and their applicability.3 Carbazole-, indole-, and pyrrole-derived atropisomers with mostly a C–N axis, but also C–C axis, have been isolated from natural sources (Scheme 1b).4 A few synthesized chiral five-membered-ring atropisomer ligands have also been employed in asymmetric catalysis (Scheme 1b).5 Five-membered-ring atropisomers have been synthesized by means of transition metal-catalyzed cross coupling reactions5 (Scheme 1c, left), organo-catalyzed asymmetric arylation reactions6 (Scheme 1c, right), and the establishment of the biaryl axis via construction of one of the rings.7 In addition, enantioselective C–H functionalization using chiral Cp* ligands has been employed as an alternative strategy to access atropisomers.8 Thus, Heller et al. reported a Co-catalyzed enantioselective synthesis of axially chiral biaryls by means of [2+2+2] cycloaddition reactions.9 You et al. described an enantioselective dehydrogenative Heck coupling of biaryls with alkenes,10 and Cramer et al. achieved an Ir-catalyzed synthesis of axially chiral biaryl phosphines using diazonaphthoquinones.11 We have described an intramolecular C–H functionalization of aromatic compounds with alkynes forming axially chiral 4-arylisoquinolones catalyzed by chiral Rh Jas Cp complexes,12 and Li et al. recently reported the use of chiral Rh Cp* complexes in the synthesis of axially chiral biindylols.13 To the best of our knowledge, there is no general enantioselective method that enables the construction of atropisomers containing a five-membered aromatic ring (furans, thiophenes, and pyrroles). Herein, we report the Rh Jas Cp-catalyzed enantioselective synthesis of these five-membered-ring atropisomers via direct C–H functionalization with 1-diazonaphthoquinones (Scheme 1c, bottom).

To establish the methodology, we investigated coupling of 2-amido-benzothiophene 1a14 and 1-diazonaphthoquinone 2a as model substrates using various Rh Jas Cp catalysts. As shown in Table 1, Rh1 led to the formation of desired product 3a in low yield and poor enantiomeric ratio (entry 1), whereas Rh2 gave the corresponding product in higher yield and better enantiomeric ratio (entry 2). Screening of a variety of solvents demonstrated that 1,4-dioxane was the best (entries 2–7), and variation of the catalysts with strict temperature control (entries 8–12) showed that Rh3 gave the desired product in excellent...
yield and with very good enantiomeric ratio (entry 11). It should be noted that the temperature moderately influences the enantioselectivity (entries 8, 11, and 12).

After having identified suitable reaction conditions, we investigated the scope for the transformation of thiophenes and benzothiophenes (Scheme 2). A substituent at position C-4 of the benzothiophenes led to an increase in enantioselectivity. Thus, 4-fluoro and chloro substituents (3c−3g) afforded the corresponding biaryl derivatives in high yields and excellent enantiomeric ratios. In addition, the presence of electron-donating (3f) and electron-withdrawing (3b) groups was tolerated and the desired products were formed in good yields and very appreciable enantioselectivities. Thiophene (3i) was obtained in high yield; however, the compound racemized very quickly. We attributed this to the lack of steric hindrance allowing the rotation barrier to remain low. To overcome this problem, sterically demanding substituents were incorporated at position C-4 of the thiophene coupling partner, and the corresponding thiophene atropisomers were formed in very good yields and high enantiomeric excesses (3k−3p). We note that bromo derivative (3n) may open up further opportunities to elaborate structure, e.g., via Pd(0) chemistry. Slow evaporation of product 3p afforded crystals suitable for X-ray diffraction analysis, which allowed us to unambiguously confirm the structure. Measuring several crystals provided the same absolute configuration (aR) (CCDC 1994612; see the Supporting Information for more details).

The data from the enantioselective synthesis of five-membered-ring atropoisomeric benzothiophene 3a are presented in Table 1.

| Entry | Catalyst | Solvent     | Temp (°C) | Yield (%) | Enantiomeric Ratio (er) |
|-------|----------|-------------|-----------|-----------|-------------------------|
| 1     | Rh1      | 1,4-dioxane | 23        | 64        | 76:24                   |
| 2     | Rh2      | 1,4-dioxane | 23        | 85        | 90.5:9.5                |
| 3     | Rh2      | MeOH        | 23        | 39        | 72:28                   |
| 4     | Rh2      | DCM         | 23        | 75        | 87.13                   |
| 5     | Rh2      | toluene     | 23        | 69        | 85.5:14.5               |
| 6     | Rh2      | MeCN        | 23        | 41        | 79.5:21.5               |
| 7     | Rh2      | THF         | 23        | 85        | 71.29                   |
| 8     | Rh3      | 1,4-dioxane | 23        | 92        | 91.9                    |
| 9     | Rh4      | 1,4-dioxane | 23        | 79        | 87.5:12.5               |
| 10    | Rh5      | 1,4-dioxane | 23        | 85        | 90.5:9.5                |
| 11    | Rh3      | 1,4-dioxane | 17        | 90        | 92.5:7.5                |
| 12    | Rh3      | 1,4-dioxane | 0         | 35        | 91.9                    |

*Reactions were run for 36 h. Yields were determined for isolated products. Values of ee were determined using chiral HPLC.
To further explore the applicability of the method, the scope for analogous transformations employing benzofurans and furans was investigated (Scheme 3). Benzofuran afforded desired product 3q in good yield albeit with lower enantioselectivity. Increasing the steric bulk at position C-4 led to formation of the desired benzofuran biaryl atropisomers in good yields and high enantioselectivities (3t−3w). We note that high reactivity with good enantioselectivity was also observed with a bromo-substituted furan derivative (3x).

The orienting exploration of indoles and pyrroles in this transformation revealed that indoles with an unprotected NH-group and a directing group at position C-2 are not reactive under the employed conditions. Introduction of a variety of substituents at the nitrogen atom did not substantially improve this situation (see the Supporting Information for more details). Fortunately, installation of the directing group on the nitrogen afforded the desired products in very good yield and moderate to high ee values under the optimized reaction conditions. Exploration of the reaction scope revealed that indoles bearing both electron-donating and electron-withdrawing groups were tolerated and yielded the desired 2-indolo-naphthaline atropisomers (4b−4h) in good yields and good enantioselectivities (Scheme 4).

On the basis of previous studies, the mechanism shown in Scheme 5 for rationalizing the observed transformation appears to be plausible. The reaction begins with an oxidative addition of active Rh(III) complex I to give five-membered-ring rhodacycle II. Insertion of the diazonaphthoquinone affords intermediate III, which upon loss of nitrogen (N2) yields Rh−carbene intermediate IV. This intermediate undergoes 1,2-migration, followed by subsequent reductive elimination yielding chiral compound VI. Finally, aromatization (point to axis chirality transfer) furnishes final biaryl atropisomer 3.

In conclusion, we have developed an enantioselective C−H functionalization method giving access to the biaryl atropisomer types that can be accessed from three different five-membered-ring heterocycle classes. The method enabled a straightforward synthesis of (benzo)furano, (benzo)thiopheno, and indolo atropoisomers in high yields and high enantioselectivity. In light of the challenging synthesis of these five-membered-ring atropoisomeric products in general, we anticipate that this practical, enantioselective direct C−H functionalization methodology may find widespread interest and application in various areas of science.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03355.

Experimental procedures and characterization data for all new compounds and computational details (PDF)

#### Accession Codes

CCDC 1994612 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.
AUTHOR INFORMATION

Corresponding Authors
Andrey P. Antonchick – Max-Planck-Institute of Molecular Physiology, Department of Chemical Biology, 44227 Dortmund, Germany; Technical University Dortmund, Faculty of Chemical Biology, 44227 Dortmund, Germany;
  orcid.org/0000-0003-0435-9443;
  Email: andrey.antonchick@mpi-dortmund.mpg.de
Herbert Waldmann – Max-Planck-Institute of Molecular Physiology, Department of Chemical Biology, 44227 Dortmund, Germany; Technical University Dortmund, Faculty of Chemical Biology, 44227 Dortmund, Germany;
  orcid.org/0000-0002-9606-7247;
  Email: herbert.waldmann@mpi-dortmund.mpg.de

Authors
Saad Shaaban – Max-Planck-Institute of Molecular Physiology, Department of Chemical Biology, 44227 Dortmund, Germany
Houhua Li – Max-Planck-Institute of Molecular Physiology, Department of Chemical Biology, 44227 Dortmund, Germany
Felix Otte – Technical University Dortmund, Department of Inorganic Chemistry, 44227 Dortmund, Germany
Carsten Strohmann – Technical University Dortmund, Department of Inorganic Chemistry, 44227 Dortmund, Germany

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.0c03355

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the Max-Planck-Gesellschaft. S.S. thanks the Alexander von Humboldt Foundation for funding. H.L. is grateful to the Swiss National Science Foundation (SNSF) for an Early Postdoc. Mobility fellowship (P2GEP2_168250).

REFERENCES

(1) (a) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Angew. Chem., Int. Ed. 2005, 44, 5384.
  (b) LaPlante, S. R.; Fader, L. D.; Fendrick, K. R.; Fendrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. Med. Chem. 2011, 54, 7005.
  (c) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Chem. Rev. 2015, 115, 11239.

(2) (a) Loqzq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. Coord. Chem. Rev. 2016, 308, 131.
  (b) Wang, Y.; Tan, B. Acc. Chem. Res. 2018, 51, 534.
  (c) Mancinelli, M.; Bencivieni, G.; Pecorari, D.; Mazzanti, A. Eur. J. Org. Chem. 2020, 2020, 4070.

(3) (a) Bonne, D.; Rodriguez, J. Chem. Commun. 2017, 53, 12385.
  (b) Bonne, D.; Rodriguez, J. Eur. J. Org. Chem. 2018, 2018, 2417.
  (c) Li, T.-Z.; Liu, S.-J.; Tan, W.; Shi, F. Chem. - Eur. J. 2020, DOI: 10.1002/chem.202001397.

(4) (a) Norton, R. S.; Wells, R. J. J. Am. Chem. Soc. 1982, 104, 3628.
  (b) Hughes, C. S.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. Org. Lett. 2008, 10, 629.
  (c) Schneider, P.; Schneider, G. Chem. Commun. 2017, 53, 2272.

(5) (a) He, C.; Hou, M.; Zhu, Z.; Gu, Z. ACS Catal. 2017, 7, 5316.
  (b) Yamaguchi, K.; Yamaguchi, J.; Studer, A.; Itami, K. Chem. Sci. 2012, 3, 2165.
  (c) Nishimoto, Y.; Kondo, H.; Yamaguchi, K.; Yokogawa, D.; Yamaguchi, J.; Itami, K.; Irle, S. J. Org. Chem. 2017, 82, 4900.
  (d) Zhang, S.; Yao, Q.-J.; Liao, G.; Li, X.; Li, H.; Chen, H.-M.; Hong, X.; Shi, B.-F. ACS Catal. 2019, 9, 1956.
  (e) Nguyen, Q.; Guo, S.; Royal, T.; Baudo, O.; Cramer, N. J. Am. Chem. Soc. 2020, 142, 2161.

(6) (a) Zhang, H.-H.; Wang, C.-S.; Li, C.; Mei, G.-J.; Li, Y.; Shi, F. Angew. Chem., Int. Ed. 2017, 56, 116.
  (b) Qi, L.; Mao, J.; Zhang, J.; Tan, B. Nat. Chem. 2018, 10, 58.
  (c) Zhu, S.; Chen, Y.-H.; Wang, Y.-B.; Yu, P.; Li, S.-Y.; Xiang, S.-H.; Wang, J.-Q.; Xiao, J.; Tan, B. Nat. Commun. 2019, 10, 4268.
  (d) Chatterjee, S.; Bhatattacharjee, P.; Butterfoss, G. L.; Achari, A.; Jaisankar, P. RSC Adv. 2019, 9, 22384.
  (e) Zheng, S.; Wang, Q.; Zhu, J. Angew. Chem., Int. Ed. 2019, 58, 1494.
  (f) Zheng, S.; Wang, Q.; Zhu, J. Angew. Chem., Int. Ed. 2019, 58, 9215.
  (g) Jiang, F.; Chen, K.; Wu, P.; Zhang, Y.-C.; Jiao, Y.; Shi, F. Angew. Chem., Int. Ed. 2019, 58, 15104.
  (h) Lu, S.; Ong, J.-Y.; Yang, H.; Poh, S.-B.; Liew, X.; Seow, C. S.; Wong, M.; Zhao, Y. J. Am. Chem. Soc. 2019, 141, 17062.

(7) (a) Wang, D.; Tong, X. Org. Lett. 2017, 19, 6392.
  (b) Raut, V. S.; Jean, M.; Vanthuyne, N.; Roussel, C.; Constantieux, T.; Bressy, C.; Bugaut, X.; Bonne, D.; Rodriguez, J. J. Am. Chem. Soc. 2017, 139, 2140.

(8) (a) Newton, C. G.; Kossler, D.; Cramer, N. J. Am. Chem. Soc. 2016, 138, 3935.
  (b) Yoshino, T.; Satake, S.; Matsunaga, S. Chem. - Eur. J. 2015, 2020, 26, 7346.
  (c) Shaaban, S.; Davies, C.; Waldmann, H. Eur. J. Org. Chem. 2020, 6512 DOI: 10.1002/ejoc.202000752.

(9) (a) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. Angew. Chem., Int. Ed. 2004, 43, 3795.
  (b) Hapke, M.; Kral, K.; Fischer, C.; Spannenberg, A.; Gutnov, A.; Redkin, D.; Heller, B. Org. Chem. 2010, 75, 3993.

(10) (a) Zheng, J.; You, S.-L. Angew. Chem., Int. Ed. 2014, 53, 13244.
  (b) Zheng, J.; Cui, W.-J.; Zheng, C.; You, S.-L. J. Am. Chem. Soc. 2016, 138, 5242.

(11) Jang, Y.-S.; Woźniak, Ł.; Pedroni, J.; Cramer, N. Angew. Chem., Int. Ed. 2018, 57, 12901.

(12) (a) Jia, Z.-J.; Merten, C.; Gonzal, R.; Daniluc, C. G.; Antonchick, A. P.; Waldmann, H. Angew. Chem., Int. Ed. 2017, 56, 2429.
  (b) Shan, G.; Flegel, J.; Li, H.; Merten, C.; Ziegler, S.; Antonchick, A. P.; Waldmann, H. Angew. Chem., Int. Ed. 2018, 57, 14250.
  (c) Li, H.; Yan, X.; Zhang, J.; Guo, W.; Jiang, J.; Wang, J. Angew. Chem. Int. Ed. 2019, 58, 6732.

(13) (a) Tian, M.; Bai, D.; Zheng, G.; Chang, J.; Li, X. J. Am. Chem. Soc. 2019, 141, 9527.
  (b) Wang, F.; Qi, Z.; Zhao, Y.; Zhai, S.; Zheng, G.; Mi, R.; Huang, Z.; Zhu, X.; He, X.; Li, X. Angew. Chem., Int. Ed. 2020, 59, 13288.

(14) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. J. Am. Chem. Soc. 2008, 130, 7190.

(15) Chen, X.; Yang, S.; Li, H.; Wang, B.; Song, G. ACS Catal. 2017, 7, 2392.

(16) (a) Chan, W.; Lo, S.; Zhou, Z.; Yu, W. J. Am. Chem. Soc. 2012, 134, 13565.
  (b) Liu, Z.; Wu, J.; Yang, S. Org. Lett. 2017, 19, 5434.
  (c) Ghosh, B.; Biswas, A.; Chakraborty, S.; Samanta, R. Chem. - Asian J. 2018, 13, 2388.