OL | Organic Letters

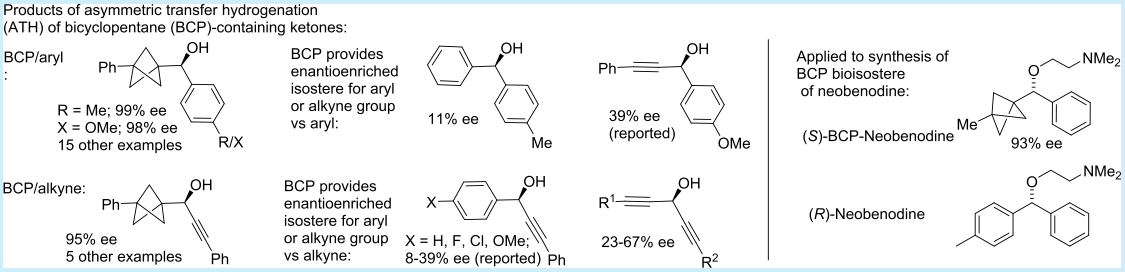
pubs.acs.org/OrgLett Letter

Enantioselective Synthesis of Bicyclopentane-Containing Alcohols via Asymmetric Transfer Hydrogenation

Vijyesh K. Vyas, Guy J. Clarkson, and Martin Wills*

Cite This: *Org. Lett.* 2021, 23, 3179–3183 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Compounds a containing bicyclo[1.1.1]pentane (BCP) adjacent to a chiral center can be prepared with high enantiomeric excess through asymmetric transfer hydrogenation (ATH) of adjacent ketones. In the reduction step, the BCP occupies the position distant from the η^6-arene of the catalyst. The reduction was applied to the synthesis of a BCP analogue of the antihistamine drug neobenodine.

Compounds that contain a bicyclo[1.1.1]pentane (BCP) are valuable structures for pharmaceutical research.[1,2] Examples include cases where a BCP is bioisosteric with a *para*-substituted aromatic ring,[1b−d] a tBu group,[1e,f] or an alkyne[2] (Figure 1a). Pellicciari et al. reported the asymmetric synthesis of an amino acid bearing a BCP, prepared via separation of diastereomeric cyanohydrins, that exhibited activity as an mGlu1 receptor antagonist.[1b] Compound **1** is a BCP analogue of a γ-secretase inhibitor that exhibits improved aqueous solubility and oral absorption characteristics.[1c] Compound **2** is a BCP analogue of darapladib, a cardiovascular disease drug, in which the isostere exhibited an improved physiochemical profile.[1d]

Knochel et al. described the formation of BCP isosteres of alkynes including tazarotene and MPEP (**3** and **4**, respectively) using coupling of Zn-BCP reagents (formed by the reaction of a Grignard reagent with [1.1.1]propellane) with aromatic and heteroaromatic halides (Figure 1a).[2,3]

Anderson et al. reported innovative routes to several BCP derivatives.[4] One example features a versatile synthesis of disubstituted BCP derivatives through the reaction of [1.1.1]-propellane with organic iodides under photochemical conditions, followed by an iron-catalyzed Kumada cross-coupling reaction with an aromatic or heteroaromatic Grignard reagent.[4a] Syntheses of BCP-flubiprofen **5** (where the BCP replaces a fluorinated aromatic ring in the anti-inflammatory drug) and BCP-brequinar **6** (where the BCP replaces a bridging aromatic ring) were reported (Figure 1b).

Aggarwal et al. reported the trapping of BCP-containing Grignard reagents with boronic esters to form BCP-boronate complexes (Figure 1b).[5a] The methodology was particularly effective for the synthesis of alkene-containing derivatives (e.g., **7**), and an example of an amine-containing derivative, **8**, was achieved using a procedure reported by Baran et al.[5b] Baran et al.[6a] and Qin et al.[6b] reported the selective synthesis of functionalized BCP derivatives.

Asymmetric catalytic methods for the synthesis of BCP derivatives have been reported,[7a−c] but not to our knowledge for the formation of adjacent α-oxo stereocenters.[7d] Therefore, we investigated the introduction of a chiral center adjacent to the group through asymmetric transfer hydrogenation (ATH) of a ketone. This would permit the synthesis of BCP compounds analogous to benzhydrols and their derivatives such as neobenodine, carbinoxamine, and levocetrizine (antihistamines) in enantiomerically pure form (Figure 2).[8] Benzhydrols and their imine derivatives are challenging substrates for ATH because of the often minimal differences in steric and/or electronic properties of the aryl rings in the precursor benzophenones, although a number of successful strategies have been reported.[8,9] We reasoned that BCP versus an aromatic or alkyne flanking the ketone in a substrate would offer a greater chance of differentiation due to their contrasting structural properties and therefore would be suitable for ATH.

Received: March 15, 2021
Published: April 5, 2021

https://doi.org/10.1021/acs.orglett.1c00889
Org. Lett. 2021, 23, 3179–3183

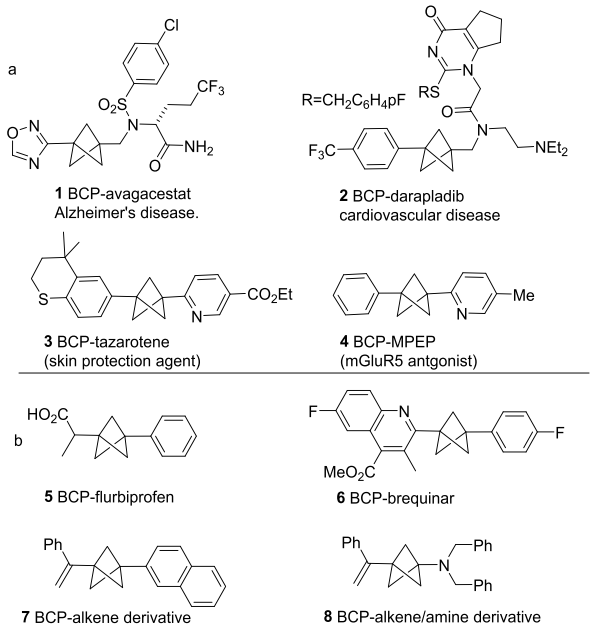


Figure 1. (a) BCP analogues of therapeutics where the BCP replaces either an aromatic ring (**1** and **2**) or an alkyne (**3** and **4**). (b) BCP analogues of therapeutics prepared by Anderson et al. (**5** and **6**) and BCP derivatives containing alkenes reported by Aggarwal et al. (**7** and **8**).

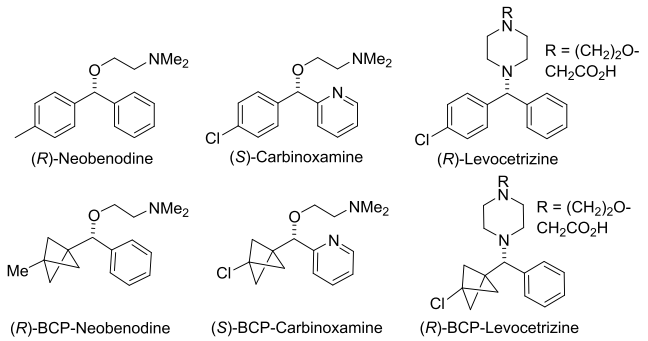


Figure 2. Potential BCP analogues of antihistamine therapeutics.

We prepared ketone precursors of the desired alcohols through the reaction of Grignard reagents with [1.1.1]-propellane[2,3] followed by trapping with an appropriate electrophile (as illustrated in Figure 3a for substrate **10**). For

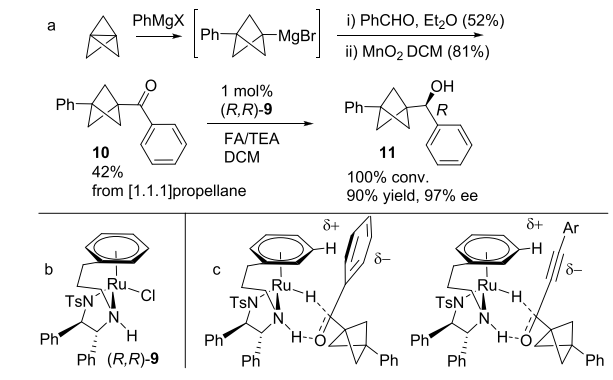


Figure 3. (a) Strategy for ATH of BCP ketones and their subsequent asymmetric reduction using ATH, as illustrated for alcohol **11**. (b) Catalyst used in this study. (c) Likely modes of ATH.

the reduction,[10] we focused on the use of the "tethered"[11] catalyst (*R*,*R*)-**9** (Figure 3b), which we have previously found to be very versatile in ATH applications. [1.1.1]Propellane was initially converted to the ketone via reaction with PhMgBr followed by trapping of the Grignard reagent with PhCOCl. However, a significant amount of benzophenone was also formed, which could not be separated from **10**. We found that **10** could be made more cleanly through addition to an aldehyde followed by oxidation with MnO_2. ATH of BCP ketone **10** gave the desired alcohol **11** with 97% ee, which confirmed the sharp difference in directing effects between the two groups flanking the ketone. Subsequent X-ray crystallographic analysis of a chiral derivative (see the Supporting Information) confirmed that the product configuration was *R* using (*R*,*R*)-**9**. Applying the model previously proposed for ATH indicates that reduction likely proceeds with the BCP distal from the η^6-arene (Figure 3c).[12]

The methodology was successfully extended to a number of aromatic substrates and one enone (Figure 4). Alkyl substitution on the aromatic ring was tolerated, giving products with 99% ee for *para*-substituted substrates and slightly lower for the *m*-methyl substrate. Substrates containing electron-withdrawing groups such as *p*-CF_3 and *p*-F were reduced with lower ee, possibly reflecting a weaker η^6-arene interaction. Substrates containing electron-donating OMe groups were also generally highly enantioselective in reductions (88−98% ee), although a *p*-phenoxy substrate was reduced with a lower ee of just 85%.

A sharp contrast was exhibited by the formation of the product of ATH of the *o*-OMe derivative (i.e., **19**), which was reduced with just 2% ee. This result reflects the lower enantioselectivities observed for substrates such as 2-methoxyacetophenone.[11a] This can be attributed to disruption of the approach of the substrate to the catalyst due to a likely twist of the aromatic ring out of planarity with the ketone. A *p*-amino substrate was also tolerated, forming the alcohol with 97% ee, while a *p*-bromo substrate gave the alcohol with 81% ee. Heterocycle-containing substrates were also enantioselectively reduced by ATH, with furan (99% ee), thiophene (99% ee), and pyridine (91% ee) all being compatible with the conditions. The configurations were assigned by analogy with that of the unsubstituted example, but in the case of **28**, which was reduced with just 41% ee, the configuration was not established.

We also examined the reductions of ketones flanked by a combination of BCP and an alkyne (Figure 4).[13] We obtained products with high ee (95−99% for all of the examples tested). Hence, the reaction conditions were shown to be tolerant of groups such as *p*- and *o*-methoxy, an alkyl group, trimethylsilyl, and chloro. An X-ray crystal structure of **33** (see the Supporting Information) served to confirm the configuration as *R* when (*R*,*R*) **9** was used in the reductions. This outcome would correspond to the proposed mode of reduction of propargylic ketones by this class of catalyst (Figure 3c).

To highlight the value of the BCP as an isostere of aromatic rings and triple bonds that can facilitate the synthesis of highly enantiomerically enriched products via ATH, we examined the reduction of a range of comparator compounds (Figure 5); products were formed with only moderate ee. The combination of alkyne versus aromatic in ketones is also known to be challenging.[13b] However, known and important exceptions are provided by substrates containing *ortho*-substituted aromatic rings, which give products with high ee

https://doi.org/10.1021/acs.orglett.1c00889
Org. Lett. 2021, 23, 3179−3183

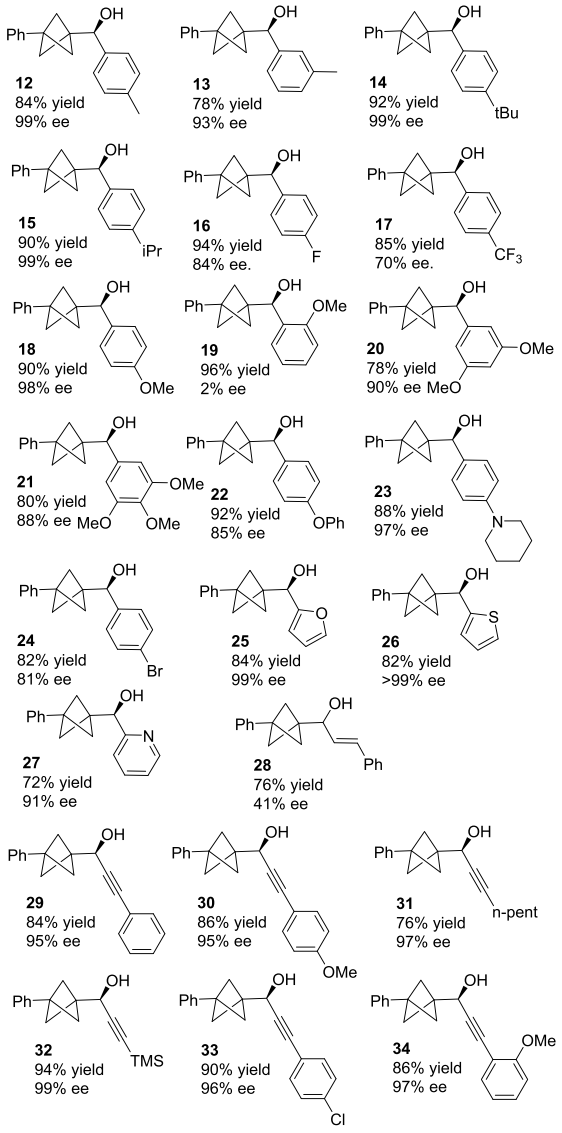


Figure 4. Products of ATH of BCP derivatives of aromatic and alkyne derivatives using a 1 mol % loading of catalyst (*R*,*R*)-**9**. Conditions are as in Figure 3. Isolated yields are given; conversions were 100% unless otherwise stated. Configurations other than that of **28** were assigned by analogy with (*R*)-**11** or (*R*)-**33**.

due to steric hindrance and electronic differentials between groups.[8,9,13b]

To illustrate the value of the methodology, its application to the synthesis of BCP- neobenodine was undertaken (Figure 6). Intermediate **35**[3a] was prepared via the BCP iodide (not isolated). ATH of **35** was undertaken on a 1 mmol scale and gave alcohol **36** with 94% ee in 90% isolated yield. Conversion to the BCP analogue of neobenodine following the procedure for neobenodine via the amide intermediate[8a,b] was successfully completed with minimal loss of ee. In this example, the *S*,*S* enantiomer of catalyst **9** was used in order to form the BCP with the analogous configuration to neobenodine.[15]

In conclusion, we have reported a highly enantioselective reduction of BCP-ketones to alcohols using ATH, which we believe represents the first example of a catalytic asymmetric synthesis of BCP derivatives. Since the BCP group is a known bioisostere of alkynes and aromatic groups, the methodology provides an asymmetric route to analogues of structures that

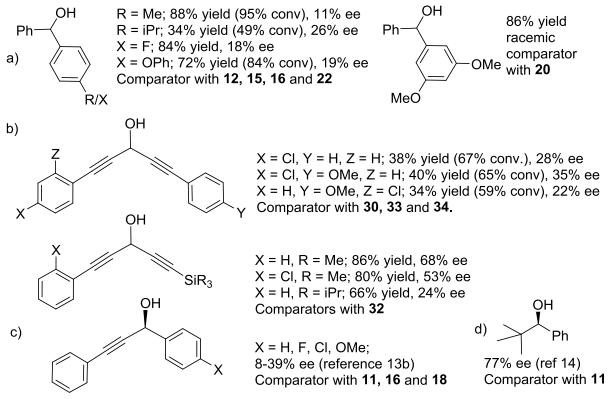


Figure 5. ATH products of non-BCP comparator compounds. (a) Benzhydrols (configuration not determined). (b) Dialkynyl ketone reduction products (configuration not determined). (c) Reported aromatic/alkenyl reduction products. (d) Reported Ph/tBu ketone.[14] Conversions were 100% unless otherwise stated.

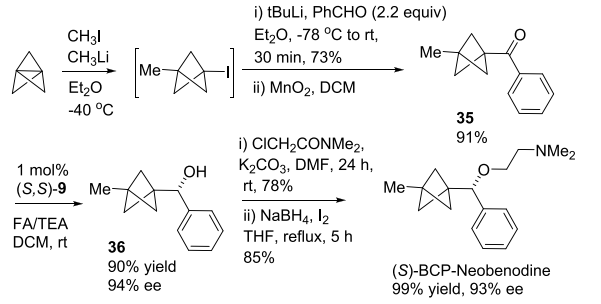


Figure 6. Asymmetric synthesis of a BCP-containing derivative of neobenodine. The conversion of **35** to (*S*)-**36** was conducted on a 1 mmol scale.

would be challenging to prepare with high ee. The methodology was applied to an efficient asymmetric synthesis of the BCP derivative of neobenodine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00889.

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

Accession Codes

CCDC 2067283 and 2067284 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, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Martin Wills − *Department of Chemistry, The University of Warwick, Coventry CV4 7AL, U.K.*; orcid.org/0000-0002-1646-2379; Email: m.wills@warwick.ac.uk

Authors

Vijyesh K. Vyas − *Department of Chemistry, The University of Warwick, Coventry CV4 7AL, U.K.*

https://doi.org/10.1021/acs.orglett.1c00889
Org. Lett. 2021, 23, 3179−3183

Guy J. Clarkson − *Department of Chemistry, The University of Warwick, Coventry CV4 7AL, U.K.*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00889

Notes

The authors declare no competing financial interest.
The research data (and/or materials) supporting this publication can be accessed at http://wrap.warwick.ac.uk/.

■ ACKNOWLEDGMENTS

We thank The Royal Society (U.K.) and the Science and Engineering Research Board (SERB, India) for funding V.K.V. through an SERB−Newton International Fellowship (ref NIF \R1\180142). Crystallographic data were collected using an instrument (described in the Supporting Information) purchased through support from Advantage West Midlands (AWM) and the European Regional Development Fund (ERDF). The authors thank Johnson Matthey (Cambridge, U.K.) for a donation of catalyst **9** and Shweta Gediya (University of Warwick) for assistance with the preparation of [1.1.1]propellane.

■ REFERENCES

(1) (a) Brown, N.; Mannhold, R. *Bioisosteres in Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2012. (b) Costantino, G.; Maltoni, K.; Marinozzi, M.; Camaioni, E.; Prezeau, L.; Pin, J. P.; Pellicciari, R. Synthesis and biological evaluation of 2-(3′-(1H-tetrazol-5-yl) bicyclo [1.1.1] pent-1-yl) glycine (S-TBPG), a novel mGlu1 receptor antagonist. *Bioorg. Med. Chem.* **2001**, *9*, 221−227. (c) Stepan, A. F.; Subramanyam, C.; Efremov, I. V.; Dutra, J. K.; O'Sullivan, T. J.; Dirico, K. J.; McDonald, W. S.; Won, A.; Dorff, P. H.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Riddell, D. R.; Kauffman, G. W.; Kormos, B. L.; Zhang, L.; Lu, Y.; Capetta, S. H.; Green, M. E.; Karki, K.; Sibley, E.; Atchison, K. P.; Hallgren, A. J.; Oborski, C. E.; Robshaw, A. E.; Sneed, B.; O'Donnell, C. J. Application of the Bicyclo[1.1.1]pentane Motif as a Nonclassical Phenyl Ring Bioisostere in the Design of a Potent and Orally Active γ-Secretase Inhibitor. *J. Med. Chem.* **2012**, *55*, 3414−3424. (d) Measom, N. D.; Down, K. D.; Hirst, D. J.; Jamieson, C.; Manas, E. S.; Patel, V. K.; Somers, D. O. Investigation of a Bicyclo[1.1.1]pentane as a Phenyl Replacement within an LpPLA2 Inhibitor. *ACS Med. Chem. Lett.* **2017**, *8*, 43−48. (e) Auberson, Y. P.; Brocklehurst, C.; Furegati, M.; Fessard, T. C.; Koch, G.; Decker, A.; La Vecchia, L.; Briard, E. Improving Nonspecific Binding and Solubility: Bicycloalkyl Groups and Cubanes as *para*-Phenyl Bioisosteres. *ChemMedChem* **2017**, *12*, 590−598. (f) Westphal, M. V.; Wolfstädter, B. T.; Plancher, J.-M.; Gatfield, J.; Carreira, E. M. Evaluation of *tert*-Butyl Isosteres: Case Studies of Physicochemical and Pharmacokinetic Properties, Efficacies, and Activities. *ChemMedChem* **2015**, *10*, 461−469. (g) Pellicciari, P.; Raimondo, M.; Marinozzi, M.; Natalini, B.; Costantino, G.; Thomsen, C. (*S*)-(+)-2-(3′-Carboxybicyclo[1.1.1]-pentyl)- glycine, a Structurally New Group I Metabotropic Glutamate Receptor Antagonist. *J. Med. Chem.* **1996**, *39*, 2874−2876.

(2) Makarov, I. S.; Brocklehurst, C. E.; Karaghiosoff, K.; Koch, G.; Knochel, P. Synthesis of Bicyclo[1.1.1]pentane Bioisosteres of Internal Alkynes and para-Disubstituted Benzenes from [1.1.1]-Propellane. *Angew. Chem., Int. Ed.* **2017**, *56*, 12774−12777.

(3) (a) Messner, M.; Kozhushkov, S. I.; de Meijere, A. Nickel- and Palladium-Catalyzed Cross-Coupling Reactions at the Bridgehead of Bicyclo[1.1.1]pentane Derivatives - A Convenient Access to Liquid Crystalline Compounds Containing Bicyclo[1.1.1]pentane Moieties. *Eur. J. Org. Chem.* **2000**, *2000*, 1137−1155. (b) Rehm, J. D. D.; Ziemer, B.; Szeimies, G. A Facile Route to Bridgehead Disubstituted Bicyclo[1.1.1]pentanes Involving Palladium-Catalyzed Cross-Coupling Reactions. *Eur. J. Org. Chem.* **1999**, *1999*, 2079−2085.

(4) (a) Nugent, J.; Shire, B. R.; Caputo, D. F. J.; Pickford, H. D.; Nightingale, F.; Houlsby, I. T. T.; Mousseau, J. J.; Anderson, E. A. Synthesis of All-Carbon Disubstituted Bicyclo[1.1.1]pentanes by Iron-Catalyzed Kumada Cross-Coupling. *Angew. Chem., Int. Ed.* **2020**, *59*, 11866−11870. (b) Nugent, J.; Arroniz, C.; Shire, B. R.; Sterling, A. J.; Pickford, H. D.; Wong, M. L. J.; Mansfield, S. J.; Caputo, D. F. J.; Owen, B.; Mousseau, J. J.; Duarte, F.; Anderson, E. A. A General Route to Bicyclo[1.1.1]pentanes through Photoredox Catalysis. *ACS Catal.* **2019**, *9*, 9568−9574. (c) Caputo, D. F. J.; Arroniz, C.; Dürr, A. B.; Mousseau, J. J.; Stepan, A. F.; Mansfield, S. J.; Anderson, E. A. Synthesis and applications of highly functionalized 1-halo-3-substituted bicyclo[1.1.1]pentanes. *Chem. Sci.* **2018**, *9*, 5295−5300.

(5) (a) Yu, S.; Jing, C.; Noble, A.; Aggarwal, V. K. 1,3-Difunctionalizations of [1.1.1]Propellane via 1,2-Metallate Rearrangements of Boronate Complexes. *Angew. Chem., Int. Ed.* **2020**, *59*, 3917−3921. (b) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-release amination. *Science* **2016**, *351*, 241−246.

(6) (a) Zhao, J.-X.; Chang, Y.; Elleraas, J.; Montgomery, T. P.; Spangler, J. E.; Nair, S. K.; Del Bel, M.; Gallego, G. M.; Mousseau, J. J.; Perry, M. A.; Collins, M. R.; Vantourout, J.; Baran, P. 1,2-Difunctionalized bicyclo[1.1.1]pentanes to potentially mimic ortho/meta-substituted arenes. *ChemRxiv.* **2020**, DOI: 10.26434/chemrxiv.13120283.v1. (b) Yang, Y.; Tsien, J.; Hughes, J.; Peters, P.; Merchant, R.; Qin, T. Synthesis of Multi-Substituted Bicycloalkyl Boronates: An Intramolecular Coupling Approach to Alkyl Bioisosteres. *ChemRxiv* **2021**, DOI: 10.26434/chemrxiv.13724827.v1.

(7) (a) Garlets, Z. J.; Sanders, J. N.; Malik, H.; Gampe, C.; Houk, K. N.; Davies, H. M. L. Enantioselective C−H functionalization of bicyclo[1.1.1]pentanes. *Nat. Catal.* **2020**, *3*, 351−357. (b) Yu, S.; Jing, C.; Noble, A.; Aggarwal, V. K. Iridium-Catalyzed Enantioselective Synthesis of α-Chiral Bicyclo[1.1.1]pentanes by 1,3-Difunctionalization of [1.1.1]Propellane. *Org. Lett.* **2020**, *22*, 5650−5655. (c) Wong, M. L. J.; Sterling, A. J.; Mousseau, J. J.; Duarte, F.; Anderson, E. A. Direct catalytic asymmetric synthesis of α-chiral bicyclo[1.1.1]-pentanes. *Nat. Commun.* **2021**, *12*, 1644. (d) Wong, M. L. J.; Mousseau, J. J.; Mansfield, S. J.; Anderson, E. A. Synthesis of Enantioenriched α-Chiral Bicyclo[1.1.1]pentanes. *Org. Lett.* **2019**, *21*, 2408−2411.

(8) (a) Sui, Y.-Z.; Zhang, X.-C.; Wu, J.-W.; Li, S.; Zhou, J.-N.; Li, M.; Fang, W.; Chan, A. S. C.; Wu, J. Cu(II)-Catalyzed Asymmetric Hydrosilylation of Diaryl- and Aryl Heteroaryl Ketones: Application in the Enantioselective Synthesis of Orphenadrine and Neobenodine. *Chem. - Eur. J.* **2012**, *18*, 7486−7492. (b) Liu, W.; Guo, J.; Xing, S.; Lu, Z. Highly Enantioselective Cobalt-catalysed Hydroboration of Diaryl Ketones. Liu, W.; Guo, J.; Xing, S.; Lu, Z. *Org. Lett.* **2020**, *22*, 2532−2536. (c) Wang, B.; Zhou, H.; Lu, G.; Liu, Q.; Jiang, X. Bifunctional Oxo-Tethered Ruthenium Complex Catalyzed Asymmetric Transfer Hydrogenation of Aryl N-Heteroaryl Ketones. *Org. Lett.* **2017**, *19*, 2094−2097. (d) Spencer, C. M.; Faulds, D.; Peters, D. H. Cetrizine. *Drugs* **1993**, *46*, 1055−1080.

(9) (a) Touge, T.; Nara, H.; Fujiwhara, M.; Kayaki, Y.; Ikariya, T. Efficient Access to Chiral Benzhydrols via Asymmetric Transfer Hydrogenation of Unsymmetrical Benzophenones with Bifunctional Oxo-Tethered Ruthenium Catalysts. *J. Am. Chem. Soc.* **2016**, *138*, 10084−10087. (b) Zheng, Y.; Clarkson, G. C.; Wills, M. Asymmetric Transfer Hydrogenation of alpha-Hydroxyphenyl Ketones: Utilizing Directing Effects That Optimize the Asymmetric Synthesis of Challenging Alcohols. *Org. Lett.* **2020**, *22*, 3717−3721. (c) Wang, H.; Zhang, Y.; Yang, T.; Guo, X.; Gong, Q.; Wen, J.; Zhang, X. Chiral Electron-Rich PNP Ligand with a Phospholane Motif: Structural Features and Application in Asymmetric Hydrogenation. *Org. Lett.* **2020**, *22*, 8796−8801. (d) Murayama, H.; Heike, Y.; Higashida, K.; Shimizu, Y.; Yodsin, N.; Wongnongwa, Y.; Jungsuttiwong, S.; Mori, S.; Sawamura, M. Iridium-Catalyzed Enantioselective Transfer Hydrogenation of Ketones Controlled by Alcohol Hydrogen-Bonding and sp^3-C−H Noncovalent Interactions. *Adv. Synth. Catal.* **2020**, *362*, 4655−4661. (e) Hu, L.; Zhang, Y.; Zhang, Q.-W.; Yin, Q.; Zhang, X.

Ruthenium-Catalyzed Direct Asymmetric Reductive Amination of Diaryl and Sterically Hindered Ketones with Ammonium Salts and H_2. *Angew. Chem., Int. Ed.* **2020**, *59*, 5321−5325.
(10) (a) Wang, D.; Astruc, D. The Golden Age of Transfer Hydrogenation. *Chem. Rev.* **2015**, *115*, 6621−6686. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid−Triethylamine Mixture. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522. (c) Cotman, A. E. Escaping from Flatland: Stereoconvergent Synthesis of Three-Dimensional Scaffolds via Ruthenium-(II)-Catalysed Noyori-Ikariya Transfer Hydrogenation. *Chem. - Eur. J.* **2021**, *27*, 39−53. (d) Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. Transition-Metal-Catalyzed Asymmetric Hydrogenation and Transfer Hydrogenation: Sustainable Chemistry to Access Bioactive Molecules. *Chem. Rec.* **2016**, *16*, 2754−2771.
(11) (a) Nedden, H. G.; Zanotti-Gerosa, A.; Wills, M. The Development of Phosphine-Free Tethered Ruthenium(II) Catalysts for the Asymmetric Reduction of Ketones and Imines. *Chem. Rec.* **2016**, *16*, 2623−2643. (b) Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. Oxo-Tethered Ruthenium(II) Complex as a Bifunctional Catalyst for Asymmetric Transfer Hydrogenation and H_2 Hydrogenation. *J. Am. Chem. Soc.* **2011**, *133*, 14960−14963. (c) Cotman, A. E.; Modec, B.; Mohar, B. Stereoarrayed 2,3-Disubstituted 1-Indanols via Ruthenium-(II)-Catalyzed Dynamic Kinetic Resolution−Asymmetric Transfer Hydrogenation. *Org. Lett.* **2018**, *20*, 2921−2924. (d) Zheng, L.-S.; Férard, C.; Phansavath, P.; Ratovelomanana-Vidal, V. Rhodium-mediated asymmetric transfer hydrogenation: a diastereo- and enantioselective synthesis of syn-α-amido β-hydroxy esters. *Chem. Commun.* **2018**, *54*, 283−286.
(12) (a) Dub, P. A.; Ikariya, T. Quantum chemical calculations with the inclusion of nonspecific and specific solvation: asymmetric transfer hydrogenation with bifunctional ruthenium catalysts. *J. Am. Chem. Soc.* **2013**, *135*, 2604−2619. (b) Dub, P. A.; Gordon, J. C. The mechanism of enantioselective ketone reduction with Noyori and Noyori−Ikariya bifunctional catalysts. *Dalton Trans.* **2016**, *45*, 6756−6781. (c) Dub, P. A.; Gordon, J. C. Metal−ligand bifunctional catalysis: the "accepted" mechanism, the issue of concertedness, and the function of the ligand in catalytic cycles involving hydrogen atoms. *ACS Catal.* **2017**, *7*, 6635−6655.
(13) (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. Asymmetric Transfer Hydrogenation of α, β-Acetylenic Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739. (b) Vyas, V. K.; Knighton, R. C.; Bhanage, B. M.; Wills, M. Combining Electronic and Steric Effects To Generate Hindered Propargylic Alcohols in High Enantiomeric Excess. *Org. Lett.* **2018**, *20*, 975−978. (c) Arai, N.; Satoh, H.; Utsumi, N.; Murata, K.; Tsutsumi, K.; Ohkuma, T. Asymmetric Hydrogenation of Alkynyl Ketones with the η^6-Arene/TsDPEN−Ruthenium(II) Catalyst. *Org. Lett.* **2013**, *15*, 3030−3033. (d) Zhang, Y.-M.; Yuan, M.-L.; Liu, W.-P.; Xie, J.-H.; Zhou, Q.-L. Iridium-Catalyzed Asymmetric Transfer Hydrogenation of Alkynyl Ketones Using Sodium Formate and Ethanol as Hydrogen Sources. *Org. Lett.* **2018**, *20*, 4486−4489.
(14) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills. A Class of Ruthenium(II) Catalyst for Asymmetric Transfer Hydrogenations of Ketones. M. *J. Am. Chem. Soc.* **2005**, *127*, 7318−7319.
(15) A change in priority rules means that (*S*)-BCP-neobenodine is analogous in configuration to (*R*)-neobenidine.

https://doi.org/10.1021/acs.orglett.1c00889
Org. Lett. 2021, 23, 3179−3183