JOC The Journal of Organic Chemistry

pubs.acs.org/joc

Note

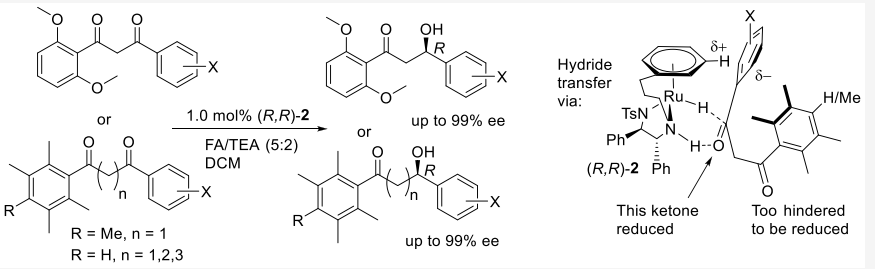
Regio- and Enantioselective Asymmetric Transfer Hydrogenation of One Carbonyl Group in a Diketone through Steric Hindrance

Noha Khamis, Ye Zheng, Marianna N. Diamantakis, Guy J. Clarkson, Jie Liu, and Martin Wills*

Cite This: J. Org. Chem. 2024, 89, 2759−2763

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: On the basis of steric hindrance, one carbonyl group in a diketone can be reduced in a regioselective manner, with high enantioselectivity. The methodology can be extended to ketones with varied length of hydrocarbon chain spacing, and the products can be converted by oxidation to hydroxy esters or lactones without loss of enantiopurity.

The asymmetric transfer hydrogenation (ATH) of ketones using ruthenium-based catalysts such as **1** and its tethered variants such as **2** or **3** (Figure 1A) has been widely applied in synthetic chemistry.[1] Acetophenone and its derivatives are known to be excellent substrates and give reduction products for which the major product enantiomer arises through the transition state model illustrated in Figure 1B.[1−3] Several classes of ketone have been shown to be highly compatible with ATH reduction using Ru-based catalysts such as **1**−**3**.[4,5]

Ikariya et al.[4a,b] reported the first ATH of 1,2-diketones using catalyst **1**, in a reaction which generated 1,2-diols in >99% ee and 98.6:1/4 dr. Reductions of symmetrical and unsymmetrical diketones were reported. In later examples, an extended series of diketones were reduced by ATH,[4c] and other Ru-based ATH catalysts have been successfully applied (Figure 1C).[4d,e] Although in the majority of diketone reductions, both ketones are reduced, sometimes just one ketone can be reduced (Figure 1D, 1E).[5] In an important precedent,[5b] an unsymmetrical diketone was reduced, under carefully controlled reaction conditions, to a 3-hydroxy ketone (Figure 1D). In this case the reactive ketone was adjacent to a trifluoromethyl group. Catalyst **1** was applied to the successful reduction of just one ketone of a diketone in high ee, on the basis of differing levels of steric hindrance.[5a] In other cases of selective keto reduction,[5b,e] a substituted carbon atom is generally found between the carbonyl groups (Figure 1E). Herein we report a systematic study of substrates containing

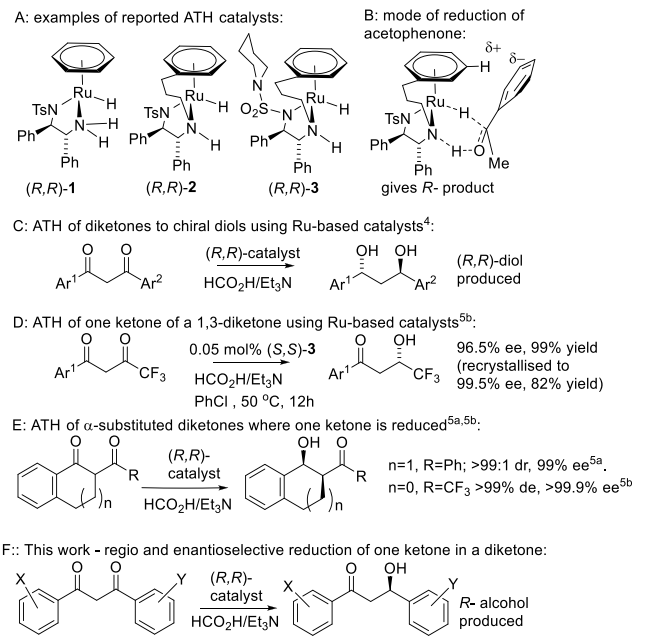


Figure 1. (A) Examples of Ru-based ATH catalysts, (B) mode of hydrogen transfer, (C−E) known precedents, (F) work reported here. In all cases, the descriptor '(*R*,*R*)-' refers to the configuration of the ligand in the complex.

Received: August 28, 2023
Revised: January 12, 2024
Accepted: January 23, 2024
Published: February 3, 2024

https://doi.org/10.1021/acs.joc.3c01950
J. Org. Chem. 2024, 89, 2759−2763

two ketones in which one is resistant to ATH due to a high level of steric hindrance from an adjacent aromatic ring. The less hindered ketone is reduced in high enantioselectivity, creating hydroxyketone products with a unique structure and which may form the basis for the synthesis of unusual target molecules.

We first aimed to establish which aromatic groups might present sufficient steric hindrance to prevent the ATH of an adjacent ketone. There are examples of ketones which are resistant to ATH due to steric hindrance;[6] however, we initially tested ketones **4**–**7** using catalyst (*R*,*R*)-**2** in formic acid/triethylamine 5:2 azeotrope (FA:TEA) and DCM at rt (Figure 2), which represents a catalyst/reductant system adopted for

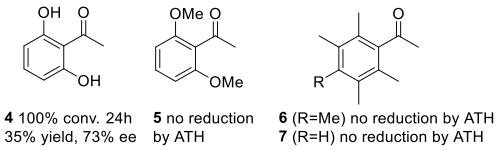


Figure 2. ATH and attempted ATH of ketones **4**–**7** using catalyst (*R*,*R*)-**2** in FA:TEA (5:2 azeotrope)/DCM at rt.

ATH reactions.[2] The *diortho*-hydroxy ketone **4** was completely converted to the corresponding alcohol with 73% ee in 24 h (*R* configuration tentatively assigned by analogy with acetophenone).

In contrast, the attempted ATH of ketone **5**, synthesized via O,O′-dimethylation of **4**, yielded no alcohol even after 7 days. In the ATH of a 1:1 mixture of ketone **5** and acetophenone under the same conditions, only acetophenone was reduced, thus ruling out catalyst inhibition by **5** and confirming that it was likely too hindered for reduction. Ketones **6** and **7**, prepared by acetylation of the penta- and tetramethylbenzene respectively, also provide resistance to ATH under the same conditions, even after 7 days. Considering these results, ketones **5**–**7** formed the basis of diketones in which one ketone was designed to be resistant to ATH, providing a potentially valuable element for directing selectivity.

Toward this end, a series of 1,3-diketones **8a**–**24a** were prepared by deprotonation of **5**–**7** with NaH to generate an enolate, followed by addition of the requisite ester (Figure 3, Supporting Information). The products, **8b**–**24b**, from the ATH of the diketones, using 1.0 mol % catalyst (*R*,*R*)-**2** in FA/TEA/DCM, are shown in Figure 4.

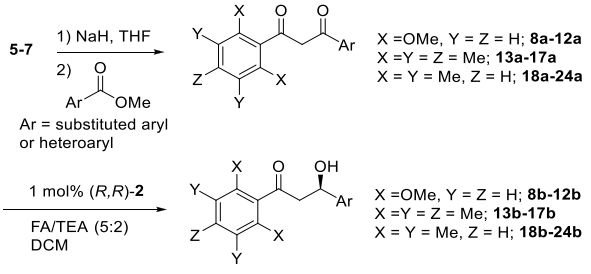


Figure 3. Synthetic route to 1,3-diketones **8a**–**24a** and subsequent ATH to alcohols **8b**–**24b**. The diketones were predominantly in the enol form (by NMR). Yields of **8a**–**12a** were 51–88%, those of **13a**–**17a** were 29–67%, and those of **18a**–**24a** were 48–86%. Racemic standards were prepared using a ca. 1:1 mixture of each enantiomer of the same catalyst.

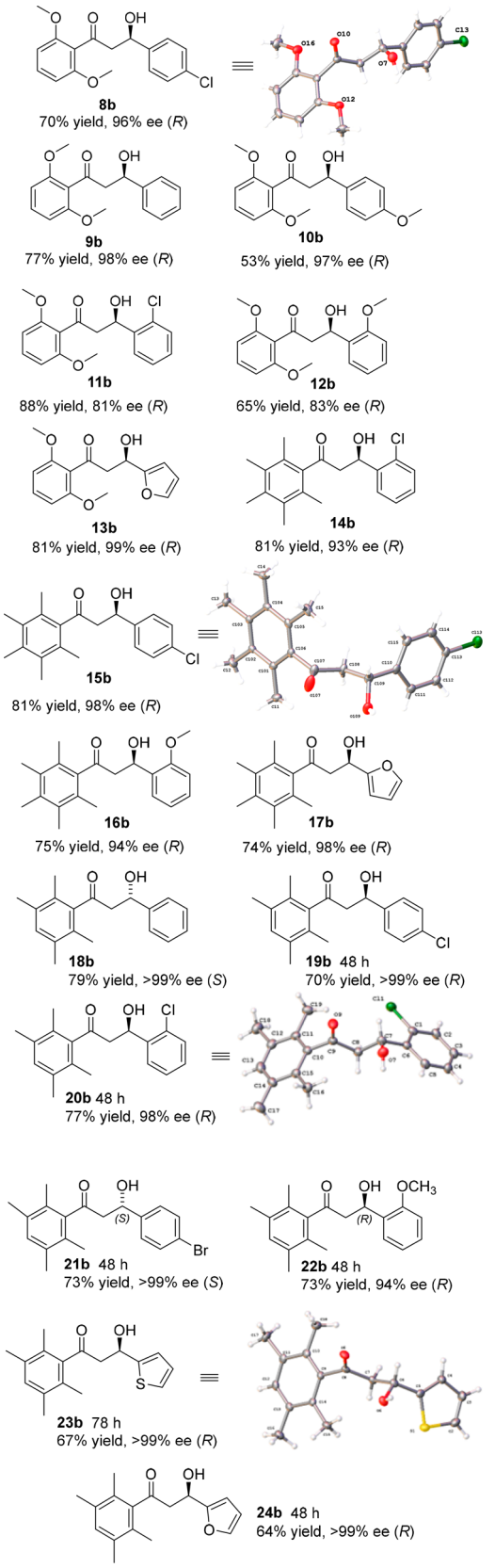


Figure 4. Products of ATH of diketones **8a**–**24a** using catalyst (*R*,*R*)-**2**, except for **18a** and **21a**, for which (*S*,*S*)-**2** was used. Reaction time is 24h unless a different time is listed. Full conversion was observed in all cases, isolated yields are listed. Where an X-ray structure was not obtained, the configuration was assigned by analogy.

https://doi.org/10.1021/acs.joc.3c01950
J. Org. Chem. 2024, 89, 2759–2763

In all cases, the less hindered ketone was reduced selectively, and in high ee. The *R* configuration of product **8b** was confirmed by an X-ray crystallographic structure analysis, indicating the preference for the *para*-chlorophenyl ring of the substrate to adopt the position adjacent to the η^6-arene ring of the catalyst, while the bulky *diortho*-methoxyphenyl ring prevented reduction of the adjacent ketone, as predicted. Unsubstituted product **9b** and *para*-methoxy substituted **10b** were formed in 98% and 97% ee, respectively. The configurations were assigned as *R* by analogy with **8b**. Introducing *ortho*-chloro and *ortho*-methoxy groups onto one phenyl ring of the 1,3-diketone substrates provided a route to products **11b** and **12b** in 81% and 83% ee, respectively, indicating that an *ortho*-substituent causes a slight decrease of preference for the aromatic ring to create a CH/π interaction with η^6-arene ring of the catalyst.[1] However, the electron-rich heterocyclic product **13b** was formed in 99% ee with an *R*-configuration assigned to it.

Similar results were obtained with the pentamethylphenyl series, with products **14b**−**17b** formed in consistently high ee, including the *ortho*-substituted examples, and an X-ray crystal structure of **15b** (formed in high ee of 98%) also confirming that an *R*- alcohol was formed, analogous to the previous series.[7] In the tetramethyl series, products **18b**−**24b** were formed in excellent ee, of >99% in several cases and only slighty lower for the two *ortho*-substituted examples. The ATH of **18a** was carried out on a 1 mmol scale. The X-ray structures of two derivatives (**20b** and **23b**) again served to confirm that the absolute stereochemistry of this series was consistent with the others. The conversion of the ATH products into esters via the Baeyer−Villiger reaction was explored. However, both the reaction of product **8b** and its TBS-protected derivative using mCPBA failed to give the anticipated products. Similar attempted oxidations of a pentamethyl derivative also failed (Supporting Information). Donohoe et al. have reported the conversion of pentamethylphenyl ketones to esters through reaction with bromine followed by an alcohol.[8] For the conversion of β-hydroxy ketones to esters, however, it was necessary to convert tetramethylketones to the *p*-hydroxy derivative first, followed by oxidation and trapping with an alcohol.[8b,c] Following Donohoe's protocol, (*S*)-**18b** (>99% ee) was reacted with phthaloyl peroxide to give **25**, followed by CAN oxidation to give ester **26** with retention of configuration in 98% ee (Figure 5). Apart from confirming the configuration of **18b**, this confirms that the Donohoe protocol works without significant decrease in ee.

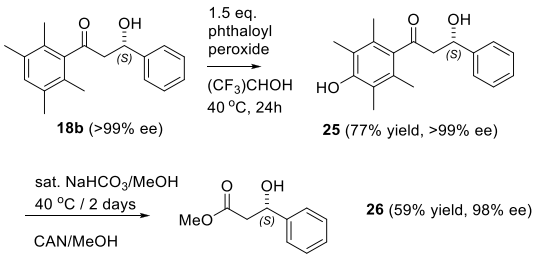


Figure 5. Synthetic route to methyl (*S*)-3-hydroxy-3-phenylpropanoate **24**.

1,4-Diketones **27a**−**30a**, the precursors to alcohols **27b**−**30b** were prepared by the reaction between unsaturated carboxylic acid **31** with the requisite aldehyde in the presence of thiazolium salt **32** (Supporting Information).[9] Two 1,5-diketones, **33a** and **33b**, the precursors to alcohols **33b** and **34b**, were prepared through the reaction of cyclopropane **35** with **36** and **37** respectively, following a reported method (Supporting Information).[10] Reduction of ketones **27a**−**30a**, **33a**, and **34a** using 1 mol % catalyst (*S*,*S*)-**2** again gave ATH products **27b**−**30b**, **33b**, and **34b** in high ee (Figure 6) in all

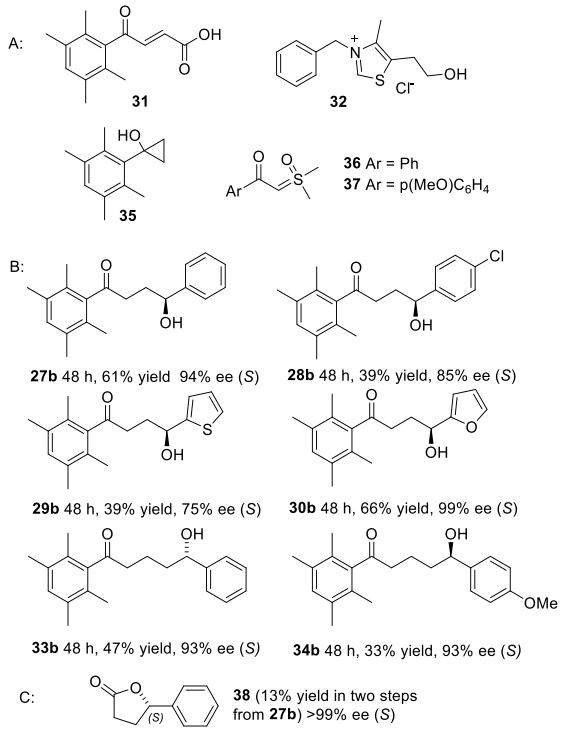


Figure 6. (A) Reagents used to prepare 1,4- and 1,5-diketones for this study. (B) ATH products of 1,4-diketones and 1,5-diketones rt. 1 mol % (*S*,*S*)-**2** was used in all cases except for **34b**. Isolated yields are listed. The configurations were assigned by analogy with the 1,3-series. (C) Oxidation product of **27b**.

cases other than the thiophene derivative **29b**. The oxidation of **27b** (97% ee) following the protocol in Figure 5 resulted in formation of lactone **38** in >99% ee,[11] although with only a 13% yield,[12] presumably the result of intramolecular trapping of the intermediate ester by the hydroxy group following the oxidation with CAN.

In a final set of studies, diketones **39a**−**41a** were prepared in order to test the ATH of diketones in which the ketones are in different environments (Figure 7). The unhindered diketone **39a** was converted to diol **39b** in high dr and ee; following the reaction over time revealed that the internal α-alkoxy ketone was reduced ahead of the peripheral acetophenone, i.e. via **42**, likely due to the activating effect of the electron-withdrawing ArO group.[13] The ATH of **40a** and **41a** resulted in the reduction of only the unhindered ketone in **40b** and **41b**, in 97% and 99% ee respectively, again demonstrating the complete control of regioselectivity which can be achieved by strategically placed bulky 2,6-substituents flanking the ketone (Figure 7). The absolute configuration of **40b** was confirmed by an X-ray crystal analysis (see the Supporting Information).

In conclusion, we have demonstrated that certain bulky 2,6-disubstituted-aryls can prevent the ATH of adjacent ketones

https://doi.org/10.1021/acs.joc.3c01950
J. Org. Chem. 2024, 89, 2759−2763

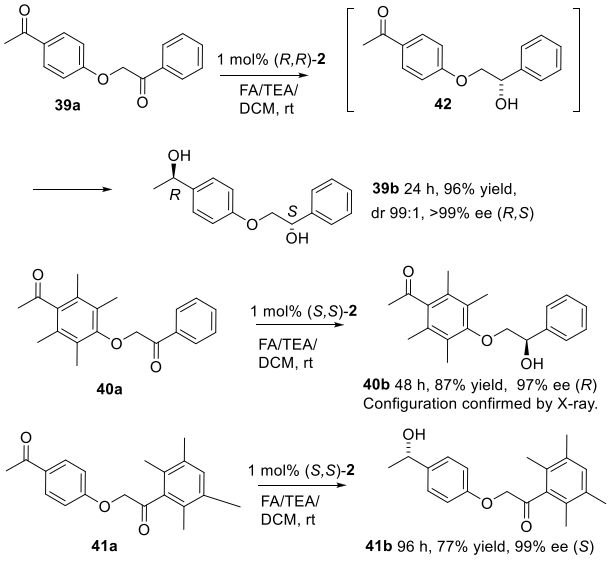


Figure 7. ATH of diketones with the ketones in nonsymmetrical positions. Diketone **39a** was also reduced with (*S,S*)-**2**, giving the product of opposite configuration.

and hence facilitate the selective reduction of one ketone in a diketone, with high enantioselectivity. The products can subsequently be elaborated to further derivatives. This application may be of value when a regioselective reduction of one carbonyl is required, leaving the others available for further transformation.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article, in its Supporting Information, and openly available in http://wrap.warwick.ac.uk/.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c01950.

Procedures, characterization data, NMR spectra and HPLC chromatograms relating to ee and dr determination, and X-ray data (CCDC 2276986−2276989 and 2324377) are available as Supporting Information (PDF)

Accession Codes

CCDC 2276986−2276989 and 2324377 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 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

Noha Khamis − *Department of Chemistry, The University of Warwick, Coventry CV4 7AL, U.K.; Department of Chemistry, Faculty of Science, University of Alexandria, Alexandria, Egypt*

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

Marianna N. Diamantakis − *Department of Chemistry, The University of Warwick, Coventry CV4 7AL, U.K.*

Guy J. Clarkson − *Department of Chemistry, The University of Warwick, Coventry CV4 7AL, U.K.;* orcid.org/0000-0003-3076-3191

Jie Liu − *Department of Physics, The University of Warwick, Coventry CV4 7AL, U.K.;* orcid.org/0000-0002-1301-057X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.3c01950

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Ministry of Higher Education of the Arab Republic of Egypt for support of N.K. through a fully funded Newton-Mosharafa scholarship [NMM4/20]. The X-ray diffraction instrument for CCDC 2276986−2276989 was obtained through the Science City Project with support from Advantage West Midlands (AWM) and partial funding by the European Regional Development Fund (ERDF). Single-crystal X-ray diffraction measurements for CCDC 2324377 were made using equipment housed within the X-ray Diffraction Research Technology Platform at Warwick University with funding from EPSRC grant EP/X034836/1. Catalysts (*R,R*)-**2** and (*S,S*)-**2** used in this project were a generous gift from Johnson Matthey CCT. The authors thank Professor Tim Donohoe for helpful discussions.

■ REFERENCES

(1) (a) Arai, N.; Ohkuma, T. In *Asymmetric Hydrogenation and Transfer Hydrogenation*; Ratovelomanana-Vidal, V., Phansavath, P., Eds.; Wiley: 2021; ISBN 978-3-527-82230-0. (b) Wang, D.; Astruc, D. The Golden Age of Transfer Hydrogenation. *Chem. Rev.* **2015**, *115*, 6621−6686. (c) Noyori, R.; Hashiguchi, S. Asymmetric Transfer Hydrogenation Catalyzed by Chiral Ruthenium Complexes. *Acc. Chem. Res.* **1997**, *30*, 97−102. (d) 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.

(2) (a) 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. (b) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid−Triethylamine Mixture. *J. Am. Chem. Soc.* **1995**, *117*, 7562−7563. (c) Touge, T.; Nara, H.; Fujiwhara, M.; Kayaki, Y.; Ikariya, T. Efficient Access to Chiral Benzhydrols via Asymmetric Transfer Hydrogena-tion of Unsymmetrical Benzophenones with Bifunctional Oxo-Tethered Ruthenium Catalysts. *J. Am. Chem. Soc.* **2016**, *138*, 10084−10087.

(3) (a) 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. (b) 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. (c) Dub, P. A.; Tkachenko, N. V.; Vyas, V. K.; Wills, M.; Smith, J. S.; Tretiak, S. Enantioselectivity in the Noyori-

Ikariya Asymmetric Transfer Hydrogenation of Ketones. *Organometallics* **2021**, *40*, 1402−1410.
(4) (a) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. A Practical Stereoselective Synthesis of Chiral Hydrobenzoins via Asymmetric Transfer Hydrogenation of Benzils. *Org. Lett.* **1999**, *1*, 1119−1121. (b) Koike, T.; Murata, K.; Ikariya, T. Stereoselective Synthesis of Optically Active α-Hydroxy Ketones and anti-1,2-Diols via Asymmetric Transfer Hydrogenation of Unsymmetrically Substituted 1,2-Diketones. *Org. Lett.* **2000**, *2*, 3833−3836. (c) Chen, Y.-C.; Deng, J.-G.; Wu, T.-F.; Cui, X.; Jiang, Y.-Z.; Choi, M. C. K.; Chan, A. S. C. Facile Preparation of Chiral 1, 3-Diols via Stereoselective Transfer Hydrogenation of 1, 3-Diones. *Chin. J. Chem.* **2001**, *19*, 807−810. (d) 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 H2 Hydrogenation. *J. Am. Chem. Soc.* **2011**, *133*, 14960−14963. (e) Kišić, A.; Stephan, M.; Mohar, B. *ansa*-Ruthenium(II) Complexes of DPEN-SO_2N(Me)-$(CH_2)_n$(η^6-aryl) Conjugate Ligands for Asymmetric Transfer Hydrogenation of Aryl Ketones. *Adv. Synth. Catal.* **2014**, *356*, 3193−3198. (f) Fang, Z.; Wills, M. Asymmetric Transfer Hydrogenation of Functionalized Acetylenic Ketones. *J. Org. Chem.* **2013**, *78*, 8594−8605. (g) Zhang, H.; Feng, D.; Sheng, H.; Ma, X.; Wan, J.; Tang, Q. Asymmetric transfer hydrogenation of unsymmetrical benzils. *RSC Adv.* **2014**, *4*, 6417−6423.
(5) (a) Wu, Y.; Geng, Z.; Bai, J.; Zhang, Y. Synthesis of Chiral 2-Aroyl-1-tetralols: Asymmetric Transfer Hydrogenation of 2-Aroyl-1-tetralones via Dynamic Kinetic Resolution. *Chin. J. Chem.* **2011**, *29*, 1467−1472. (b) Cotman, A. E.; Cahard, D.; Mohar, B. Stereoarrayed CF_3-Substituted 1,3-Diols by Dynamic Kinetic Resolution: Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation. *Angew. Chem., Int. Ed.* **2016**, *55*, 5294−5298. (c) Ding, Y.-X.; Zhu, Z.-H.; Wang, H.; Yu, C.-B.; Zhou, Y.-G. Construction of three stereocenters via hydrogenative desymmetrization of 2,2,5-trisubstituted cyclohexane-1,3-diones. *Science China Chemistry* **2021**, *64*, 232−237. (d) Shi, B.; Merten, S.; Wong, D. K. Y.; Chu, J. C. K.; Liu, L. L.; Lam, S. K.; Jäger, A.; Wong, W.-T.; Chiu, P.; Metz, P. The Rhodium-Catalyzed Carbene Cyclization Cycloaddition Cascade Reaction of Vinylsulfonates. *Adv. Synth. Catal.* **2009**, *351*, 3128−3132. (e) Kuang, L.; Liu, L. L.; Chiu, P. Formal Total Synthesis of (+)-Cortistatins A and J. *Chem. - Eur. J.* **2015**, *21*, 14287−14291.
(6) (a) Kisic, A.; Stephan, M.; Mohar, B. Asymmetric Transfer Hydrogenation of 1-Naphthyl Ketones by an ansa-Ru(II) Complex of a DPEN-SO_2N(Me)-$(CH_2)_2$ (η^6-p-Tol) Combined Ligand. *Org. Lett.* **2013**, *15*, 1614−1617. (b) Kisic, A.; Stephan, M.; Mohar, B. *ansa*-Ruthenium(II) Complexes of DPEN-SO_2N(Me)$(CH_2)_n$(η^6-aryl) Conjugate Ligands for Asymmetric Transfer Hydrogenation of Aryl Ketones. *Adv. Synth. Catal.* **2014**, *356*, 3193−3198.
(7) The unsubstituted derivative (i.e., Ar = Ph) of the pentamethyl, 1,3-dicarbonyl series was prepared, but the ATH product could not be resolved by HPLC and the ee is unknown (see the Supporting Information).
(8) (a) Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F. J.; Christensen, K. E.; Stevenson, N. J.; Donohoe, T. J. Hydrogen borrowing catalysis using 1° and 2° alcohols: Investigation and scope leading to α and β branched products. *Tetrahedron* **2021**, *86*, 132051. (b) Cheong, C. B.; Frost, J. R.; Donohoe, T. J. Pentamethylphenyl (Ph*) and Related Derivatives as Useful Acyl Protecting Groups for Organic Synthesis: A Preliminary Study. *Synlett* **2020**, *31*, 1828−1832. (c) Crompton, J. L.; Frost, J. R.; Rowe, S. M.; Christensen, K. E.; Donohoe, T. J. Synthesis of Cyclopropanes via Hydrogen-Borrowing Catalysis. *Org. Lett.* **2023**, *25*, 5253−5257.
(9) Song, J.; Shao, P.-L.; Wang, J.; Huang, F.; Zhang, X. Asymmetric hydrogenation of 1,4-diketones: facile synthesis of enantiopure 1,4-diarylbutane-1,4-diols. *Chem. Commun.* **2021**, *58*, 262−265.
(10) Huang, X.; Li, J.; He, H.; Yan, K.; Lai, R.; Luo, Y.; Guan, M.; Wu, Y. Ruthenium-Catalyzed Alkylation of Cyclopropanols with Sulfoxonium Ylides via C-C Bond Cleavage: Formation of Diverse 1,5-Diketones. *Synthesis* **2022**, *54*, 779−787.
(11) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. Chiral Synthesis via Organoboranes. 39. A Facile Synthesis of γ-Substituted-γ-butyrolactones in Exceptionally High Enantiomeric Purity. *J. Org. Chem.* **1994**, *59*, 365−369.
(12) The intermediate *p*-hydroxyketone in the conversion of **27b** to **38** (i.e., the analogue of **25**) was found to have a lower ee than either **27b** or **38**. See the Supporting Information.
(13) Soni, R.; Hall, T. H.; Mitchell, B. P.; Owen, M. R.; Wills, M. Electron-withdrawing groups are known to increase the rate of ATH reactions; Asymmetric reduction of electron-rich ketones with tethered Ru(II)/TsDPEN catalysts using formic acid/triethylamine or aqueous sodium formate. *J. Org. Chem.* **2015**, *80*, 6784−6793.

https://doi.org/10.1021/acs.joc.3c01950
J. Org. Chem. 2024, 89, 2759−2763