OL | Organic Letters

pubs.acs.org/OrgLett Letter

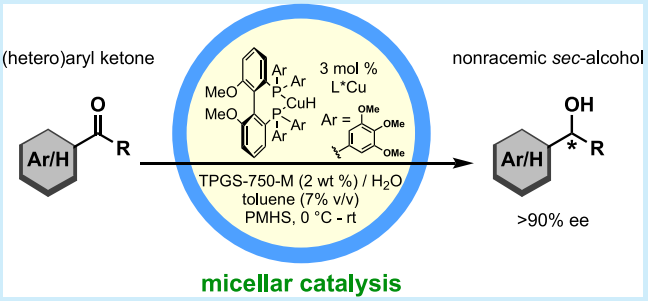
Copper-Catalyzed Asymmetric Reductions of Aryl/Heteroaryl Ketones under Mild Aqueous Micellar Conditions

David M. Fialho, Elham Etemadi-Davan, Olivia C. Langner, Balaram S. Takale, Amol Gadakh, Ganesh Sambasivam, and Bruce H. Lipshutz*

Cite This: *Org. Lett.* 2021, 23, 3282–3286 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Enantioselective syntheses of nonracemic secondary alcohols have been achieved in an aqueous micellar medium via copper-catalyzed ($Cu(OAc)_2 \cdot H_2O$/(*R*)-3,4,5-MeO-MeO-BIPHEP) reduction of aryl/heteroaryl ketones. This methodology serves as a green protocol to access enantio-enriched alcohols under mild conditions (0–22 °C) using a base metal catalyst, together with an inexpensive, innocuous, and convenient stoichiometric hydride source (PMHS). The secondary alcohol products are formed in good to excellent yields with ee values greater than 90%.



Enantio-enriched alcohols are important building blocks for the preparation of pharmaceuticals and agrochemicals,[1] including compounds such as anticancer agents (e.g., crizotinib),[2] antihistamines (e.g., orphenadrine),[3] antidepressants (e.g., duloxetine),[4] and several others.[5−9] Asymmetric hydrogenation (AH) of prochiral ketones is among the most common methods and is routinely achieved using transition-metal-based reagents (Figure 1).[10] Organocatalysis is yet another important option.[11] Biocatalysis, especially enzymatic reactions,[12] e.g., using a ketoreductase, now possible in tandem with chemo-catalysis in water,[12] represents a rapidly growing area of considerable potential in synthesis. Industrial processes tend to utilize hydrogen in the presence of expensive transition metal catalysts such as rhodium, iridium, and ruthenium.[13,14] Pioneering work by Noyori in 1987 showed the potential for $RuCl_2$[(*R*)-BINAP] to catalyze enantioselective reductions of ketones. These reactions are typically performed under 100 atm of H_2 and at 0.05 mol % catalyst loading in methanol.[14] Later, a variety of related Ru-based catalysts were developed for asymmetric transfer hydrogenation (ATH), utilizing hydride donors other than H_2.[15−19] Catalysts based on Ir have also been introduced for A(T)H of ketones, as have those based on Rh and Fe. However, these methodologies still typically require high pressures of H_2 and/or use of organic solvents as the reaction medium.[20−25] While methods exist for aqueous ATH with[26] or without[27] surfactant, these still require the precious metal ruthenium.

Several organocatalytic approaches, such as oxazaborolidine-based methods developed by Itsuno[11a] and Corey,[11b,c] lead to asymmetric ketone reductions without use of transition metals. In general, these organocatalytic approaches also rely on the use of organic solvents.

There have, likewise, been investigations into the viability of the base metal copper as a catalyst in ligated form to facilitate enantioselective transformations.[28−34] However, these procedures require such 1,2-additions be run in toluene at low temperatures for maximum ee's.[35] Clearly, new technology is needed that considers sustainability and environmental impact by (1) avoiding the energy input associated with low temperature reactions, (2) reducing costs associated with precious and/or endangered transition metal catalysts, and (3) minimizing waste creation from reactions run in non-recycled organic solvents.

We now disclose a new and general process that involves a copper hydride-catalyzed reduction in a recyclable aqueous medium. Reactions are run between 0 °C and room temperature and rely on a commercially available chiral ligand, leading to nonracemic alcohols, typically in useful isolated yields and with high ee's.

Initially, asymmetric reduction of 6′-methoxy-2′-acetonaphthone (**1a**) was selected for evaluation as a model system (Table 1). CuH was generated *in situ* starting with $Cu(OAc)_2 \cdot H_2O$ (3 mol %) in the presence of one of a variety of nonracemic *bis*-phosphine ligands in an aqueous solution of designer surfactant TPGS-750-M (2 wt %), using polymethylhydrosiloxane (PMHS), a convenient and inexpensive stoichiometric hydride source. Recognizing that the optimal

Received: March 3, 2021
Published: April 27, 2021

https://doi.org/10.1021/acs.orglett.1c00746
Org. Lett. 2021, 23, 3282–3286

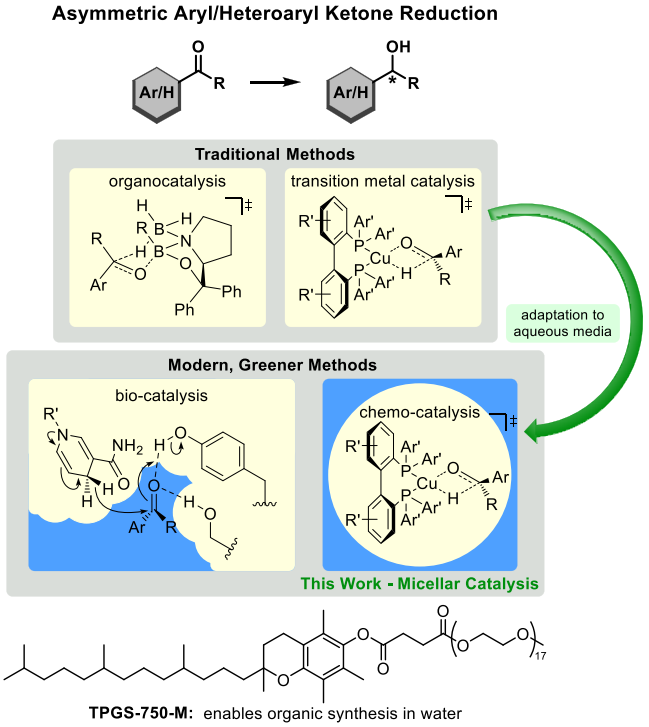


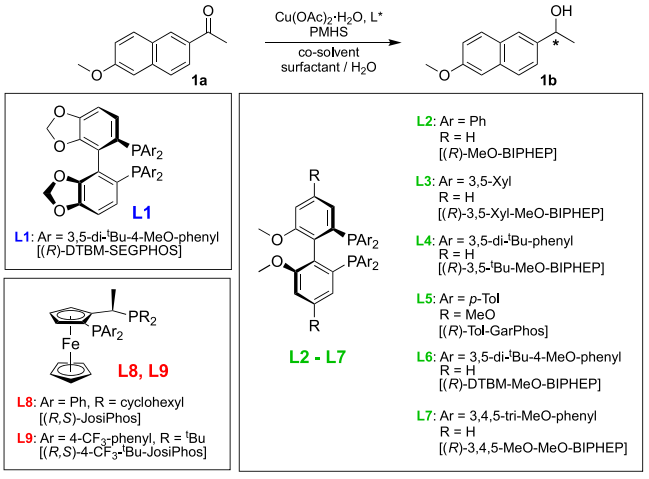
Figure 1. Various approaches to asymmetric ketone reduction: yellow-colored regions represent hydrophobic media, such as organic solvents, enzyme cores, or micellar cores; blue regions represent bulk water.

Roche (BIPHEP) and Takasago (SEGPHOS) ligands for asymmetric hydrosilylation in toluene at −78 to 0 °C[35] would not necessarily behave similarly in aqueous emulsions at room temperature, screening of ligands was required. It was, therefore, not surprising that chelated CuH derived from the previously successful ligand (*R*)-DTBM-SEGPHOS (**L1**),[33] while leading to an ee for product alcohol **1b** of 90% (Table 1; entry 9), was, indeed, not the best observed result (*vide infra*). Yields were also found to be compromised using several other *bis*-phosphine ligands that had previously been employed successfully in organic solvents, including those in the BIPHEP (**L2**−**L6**, Table 1; entry 3) and JosiPhos (**L8** and **L9**, Table 1; entries 5 and 6) series (see results in the Supporting Information).[33b] Synthetically useful results in terms of both ee's and isolated yields were eventually realized using 3 mol % CuH complexed by commercially available (*R*)-3,4,5-MeO-MeO-BIPHEP (**L7**), thus leading to its selection as the preferred ligand on copper for further optimization (entry 7). Conducting the reaction under the same conditions "on water" (i.e., in the absence of surfactant) gave poor results, emphasizing the key role being played by the micellar medium (entries 1 and 2).

Employing (*S*)-**L7** on the reduction of **1a** gave the opposite enantiomer of **1b** as expected (see the Supporting Information). Further screening explored the effect of the order of addition of reactants, the rate and temperature of PMHS addition, the impact of varying the cosolvent and additive, and the concentration of both the catalyst and starting materials (see the Supporting Information).

Addition of PMHS to the aqueous reaction mixture at ice bath temperatures was found to be beneficial in terms of both resulting alcohol yields and ee's. This may be due to the avoidance of heat associated with an initial "on water"

Table 1. Optimization of Asymmetric Ketone Reductions[a]



entry	ligand	*T* (°C)	(co)solvent	yield (%)	ee (%)
1[b]	**L1**	22	THF	18	ND
2[b,c]	**L1**	22		<10	ND
3[b]	**L6**	22	THF	78	87
4[b]	**L7**	22	THF	65	93
5[b]	**L8**	22	THF	0	ND
6	**L9**	22	THF	25	18
7	**L7**	22	toluene	83	95
8[d]	**L7**	22	toluene	80	95
9	**L1**	0−22	toluene	28	90
10	**L7**	0−22	toluene	92	97
11[e]	**L7**	0−22	toluene	95	96

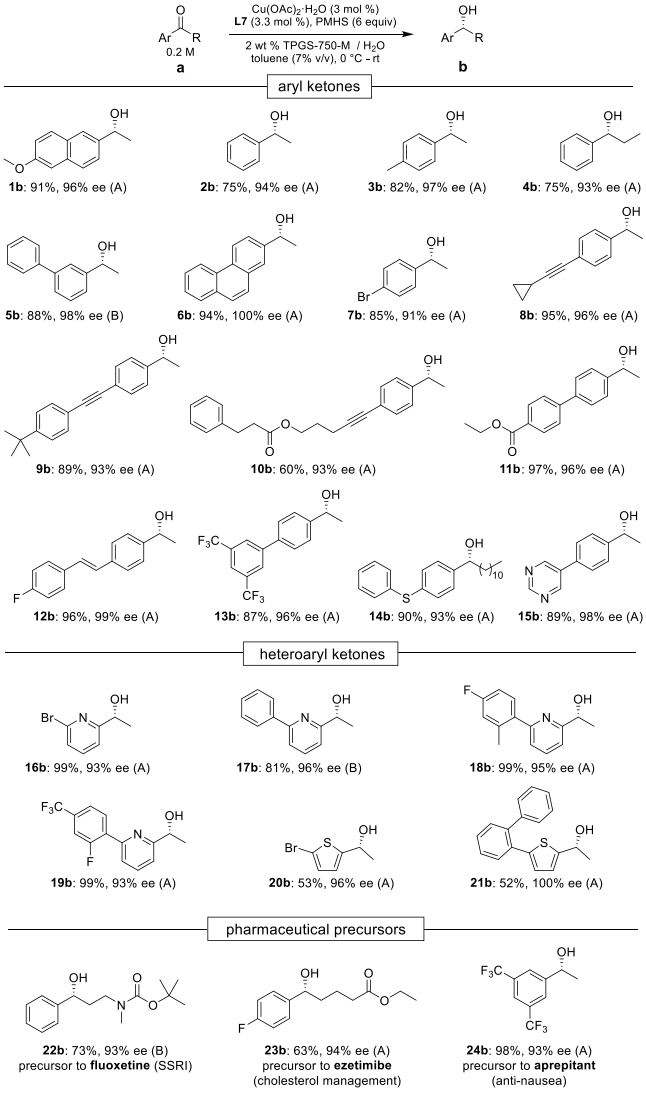
[a]Unless otherwise noted, all reactions were carried out using 0.1 mmol of **1a**, 3 mol % catalyst (5 mol % for trials 1 and 2), 3.3 mol % ligand, 0.5 mL of solvent, 35 μL of cosolvent, 0.6 mmol of PMHS (added 0.1 mmol every 25 min), and TPGS-750-M at 2 wt %. All reactions were carried out under an inert atmosphere. Yields refer to isolated material and were determined by weight; ee's were determined by chiral HPLC. The remaining mass was starting material. [b]PMHS added in one portion. [c]Performed in pure water with no surfactant or cosolvent. [d]Performed with 8 mol % catalyst. [e]Performed in pure toluene.

formation of ligated CuH, given the insolubilities of both the silane and ligated copper(II) salt in an aqueous medium (Table 1; entries 7 and 10). Attempting the reaction at higher substrate concentrations proved difficult due to clumping which inhibited stirring, notwithstanding the presence of toluene as a cosolvent. Higher catalyst loadings proved not to be beneficial (entry 7 vs 8). Similar yields and ee's were obtained when the reaction was performed in pure toluene, indicating that the transition to an aqueous medium at the same temperature leads to results that are as good or better as those seen in organic solvents (entry 10 vs 11). Scaling the **1a** to **1b** reduction employing 20 mg (0.1 mmol) up to 1 g (5 mmol) at 0−5 °C afforded the product in 70% isolated yield without significant loss of ee (96%).

Following identification of the optimized ligand and conditions for asymmetric 1,2-addition to model educt 6′-methoxy-2′-acetonaphthone, other aryl and heteroaryl ketones were then assessed in 2 wt % aqueous TPGS-750-M (Scheme 1). Various acetophenone derivatives were efficiently reduced with excellent enantioselectivities. Isolated yields were in the range 52−99%, while ee's were between 91 and 100%. Ketones were chemoselectively converted to their corresponding

https://doi.org/10.1021/acs.orglett.1c00746
Org. Lett. 2021, 23, 3282−3286

Scheme 1. CuH-Catalyzed Asymmetric Reductions of Aryl/Heteroaryl Ketones[a]



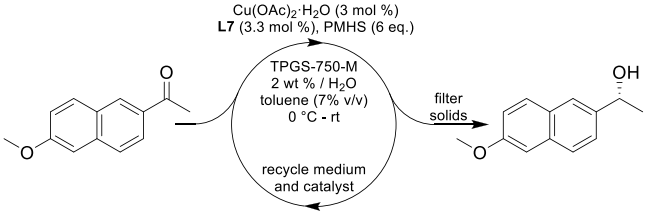
[a]Reactions were either (A) performed in sealed vials or (B) set up from a stock solution of the catalyst complex and run under argon.

alcohols in the presence of other reducible functional groups, such as alkenes (**12b**), alkynes (**8b**–**10b**), and esters (**10b**, **23b**). Heteroaryl ketones, including 2-acetylpyridines and 2-acetylthiophenes are also amenable, leading to products **16b**–**19b** and **20b**–**21b**, respectively. However, while the former could be reduced efficiently, 2-acetylthiophenes gave only moderate yields of secondary alcohols. This may be due to electronic effects: 2-acetylpyridines are electron-deficient, whereas 2-acetylthiophenes are comparatively electron-rich. In cases leading to low isolated yields, most of the remaining mass was recovered as starting material, perhaps indicative of a far slower reduction.

To demonstrate utility of this methodology, syntheses of several intermediates associated with pharmaceuticals were undertaken. Compounds **22b**, **23b**, and **24b**, precursors to fluoxetine/atomoxetine,[36] ezetimibe,[37] and aprepitant,[5] respectively, could all be formed in good yields and excellent ee's from their respective aryl ketones.

Once the initial reduction was complete, recycling studies were performed to determine the extent to which the entire reaction medium could be reused, including not only the surfactant solution but also the catalyst/ligand (Table 2).

Table 2. Recycling Study

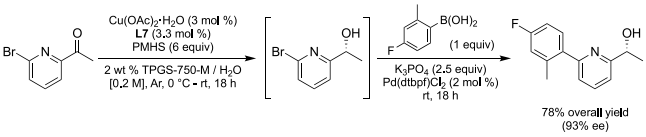


reaction cycle	yield (%)	ee (%)
initial reaction	75	96
first recycling	79	96
second recycling	54	96

Recycling was performed by filtering the reaction under argon after completion to remove the solid product, oxidized PMHS, and remaining starting material. The filtrate was then reused for the subsequent reaction. Good to moderate yields could be obtained for three cycles of the same reaction medium without any loss of ee. By recycling the reaction medium, the loading of Cu/reaction drops to 1 mol % while the amount of organic waste created is minimized, as quantified by the associated low *E* factor (7.6; see the Supporting Information for calculations).[38]

Sequential reactions run in a one-pot operation are easily accommodated given the commonality of water as a reaction medium, thereby dramatically reducing both the time invested per reaction and waste being generated (associated with individual workups). As illustrated in Scheme 2, following an initial CuH-catalyzed asymmetric reduction, a Suzuki–Miyaura coupling on the derived bromopyridine led to the anticipated biaryl product in good isolated yield, generated in 93% ee.

Scheme 2. One-Pot L*CuH-Catalyzed Reduction Followed by a Suzuki–Miyaura Coupling in Water at rt

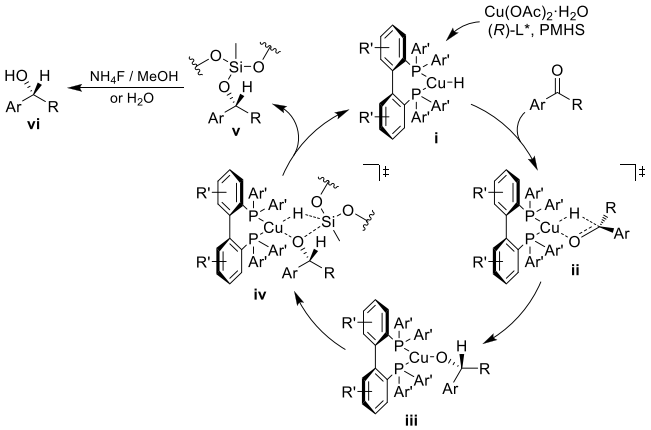


The mechanism of these copper-catalyzed ketone reductions in water most likely follows that of analogous copper-catalyzed 1,2-additions in organic solvents (Scheme 3).[33b] Nonracemically ligated copper(I) hydride (L-CuH; **i**) is first generated in situ. Hydride transfer then occurs in a 4-centered transition state **ii**, with oxygen binding to copper to afford the copper alkoxide, complex **iii**. Through another 4-membered transition state **iv** involving PMHS, the initially formed product silyl ether (**v**) is generated in concert with regeneration of the ligated copper hydride catalyst (**i**). By either hydrolysis or quenching with fluoride, the silyl ether **v** is cleaved to give the *sec*-alcohol (**vi**).

In summary, a new protocol has been developed that transforms prochiral aryl and heteroaryl ketones to enantioenriched secondary alcohols, making use of mild, environmentally responsible conditions, as well as a readily available copper pre-catalyst and inexpensive PMHS. A previously underutilized ligand as part of a copper hydride catalyst has

https://doi.org/10.1021/acs.orglett.1c00746
Org. Lett. 2021, 23, 3282–3286

Scheme 3. Proposed Mechanism of L*CuH-Catalyzed Asymmetric Ketone Reduction



been identified that is "matched" to the enabling aqueous micellar medium, which smoothly effects these asymmetric reductions in substrates bearing either electron-donating or electron-withdrawing groups. Syntheses of known nonracemic precursors to biologically active compounds are of particular note, utilizing an environmentally responsible route, thereby providing access to a wide variety of benzylic and α-heteroaryl nonracemic secondary alcohols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00746.

Experimental procedures, analytical data, and copies of NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Bruce H. Lipshutz − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States;* orcid.org/0000-0001-9116-7049; Email: lipshutz@chem.ucsb.edu

Authors

David M. Fialho − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States*

Elham Etemadi-Davan − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States*

Olivia C. Langner − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States*

Balaram S. Takale − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States;* orcid.org/0000-0001-8279-944X

Amol Gadakh − *Anthem Biosciences Private Limited, Bommasandra, Bangalore 560 099, India*

Ganesh Sambasivam − *Anthem Biosciences Private Limited, Bommasandra, Bangalore 560 099, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00746

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support provided by Anthem Biosciences, PHT International, and the NSF (CHE 18-56406) is warmly acknowledged with thanks.

■ REFERENCES

(1) (a) Ikariya, T.; Murata, K.; Noyori, R. Bifunctional transition metal-based molecular catalysts for asymmetric syntheses. *Org. Biomol. Chem.* **2006**, *4*, 393. (b) Gladiali, S.; Alberico, E. Asymmetric transfer hydrogenation: chiral ligands and applications. *Chem. Soc. Rev.* **2006**, *35*, 226. (c) Ohkuma, T.; Noyori, R. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007; Vol. 3, pp 1105−1163. (d) Arai, N.; Ohkuma, T. In *Science of Synthesis: Stereoselective Synthesis 2; Stereoselective Reactions of Carbonyl and Imino Groups*; Molander, G. A., Ed.; Thieme: Stuttgart, Germany, 2010; pp 9−57. (e) Ohkuma, T.; Arai, N. In *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H., Maruoka, K., Eds.; Elsevier: Amsterdam, The Netherlands, 2012; Vol. 5, pp 270−300.

(2) Nishii, H.; Chiba, T.; Morikami, K.; Fukami, T. A.; Sakamoto, H.; Kwangseok, K.; Koyano, H. Discovery of 6benzyloxyquinolines as c-Met selective kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1405.

(3) van der Stelt, C.; Heus, W. J.; Nauta, W. T. Resolution in optical isomers of orphenadrine, 4-methyldiphenhydramine and their Ndemethyl derivatives. *Arzneim. Forsch.* **1969**, *19*, 2010.

(4) (a) Wong, D. T.; Robertson, D. W.; Bymaster, F. P.; Krushinski, J. H.; Reid, L. R. LY227942, an inhibitor of serotonin and norepinephrine uptake: Biochemical pharmacology of a potential antidepressant drug. *Life Sci.* **1988**, *43*, 2049. (b) Hems, W.; Rossen, K.; Reichert, D.; Kohler, K.; Perea, J. J. Process for the preparation of 3-hydroxy-(2-thienyl)propanamines. US20050272930A1, December 8, 2005.

(5) (a) Wan, W.-L.; He, Y.; Guan, M.; Li, X.-L.; Cheng, X.; Wu, Y. Synthesis of the major isomers of Aprepitant and Fosaprepitant. *Chin. Chem. Lett.* **2013**, *24*, 1118. (b) Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N.; McNamara, J. M.; Reider, P. J. Efficient Synthesis of NK1 Receptor Antagonist Aprepitant Using a Crystallization-Induced Diastereoselective Transformation. *J. Am. Chem. Soc.* **2003**, *125*, 2129.

(6) (a) Klingler, F. D.; Wolter, L.; Dietrich, W. Method for preparing of L-phenylephrine hydrochloride. US6187956B1, February 13, 2001. (b) Brober, E. A.; Hofneinz, W.; Meili, A. Asymmetric Hydrogenation. EP0553778A1, August 4, 1993. (c) Klingler, F. D. Asymmetric hydrogenation of prochiral amino ketones to amino alcohols for pharmaceutical use. *Acc. Chem. Res.* **2007**, *40*, 1367.

(7) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. New developments in enantioselective hydrogenation. *Pure Appl. Chem.* **1996**, *68*, 131.

(8) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. Asymmetric Hydrogenation of Amino Ketones Using Chiral $RuCl_2$(diphophine)-(1,2-diamine) Complexes. *J. Am. Chem. Soc.* **2000**, *122*, 6510.

(9) Wenthur, C. J.; Bennett, M. R.; Lindsley, C. W. Classics in Chemical Neuroscience: Fluoxetine (Prozac). *ACS Chem. Neurosci.* **2014**, *5*, 14.

(10) Zhang, Z.; Butt, N. A.; Zhang, W. Asymmetric Hydrogenation of Nonaromatic Cyclic Substrates. *Chem. Rev.* **2016**, *116*, 14769.

(11) (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. Asymmetric Reduction of Aromatic Ketones with Chiral Alkoxy-amine-borane Complexes. *J. Chem. Soc., Chem. Commun.* **1981**, *7*, 315. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. Highly Enantioselective

Borane Reduction of Ketones Catalyzed by Chiral Oxazaborolidines. Mechanism and Synthetic Implications. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. A stable and easily prepared catalyst for the enantioselective reduction of ketones. Applications to multistep syntheses. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (d) Shende, V. S.; Singh, P.; Bhanage, B. M. Recent trends in organocatalyzed asymmetric reduction of prochiral ketones. *Catal. Sci. Technol.* **2018**, *8*, 955.

(12) Gröger, H.; Borchert, S.; Kraußer, M.; Hummel, W. Enzyme-Catalyzed Asymmetric Reduction of Ketones. *Encyclopedia of Industrial Biotechnology* 2010, DOI: 10.1002/9780470054581.eib294.

(13) (a) Knowles, W. S.; Sabacky, M. J. Catalytic asymmetric hydrogenation employing a soluble, optically active, rhodium complex. *Chem. Commun.* **1968**, *22*, 1445. (b) Ruthenium Prices and Ruthenium Price Charts - InvestmentMine. https://www.infomine.com/investment/metal-prices/ruthenium/ (accessed Aug 5, 2020). (c) Church, T. L.; Andersson, P. G. Iridium catalysts for the asymmetric hydrogenation of olefins with nontraditional functional substituents. *Coord. Chem. Rev.* **2008**, *252*, 513.

(14) Noyori, R.; Okhuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akuragawa, S. Asymmetric hydrogenation of β-keto carboxylic esters. A practical, purely chemical access to beta-hydroxy esters in high enantiomeric purity. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

(15) Faller, J. W.; Lavoie, A. R. Catalysts for the Asymmetric Transfer Hydrogenation of Ketones Derived from l-Prolinamide and $(p\text{-CymeneRuCl}_2)_2$ or $(Cp^*RhCl_2)_2$. *Organometallics* **2001**, *20*, 5245.

(16) Wan, K. Y.; Sung, M. M. H.; Lough, A. J.; Morris, R. H. Half-Sandwich Ruthenium Catalyst Bearing an Enantiopure Primary Amine Tethered to an N-Heterocyclic Carbene for Ketone Hydrogenation. *ACS Catal.* **2017**, *7*, 6827.

(17) Ohkuma, T.; Takeno, H.; Honda, Y.; Noyori, R. Asymmetric Hydrogenation of Ketones with Polymer-Bound BINAP/Diamine Ruthenium Catalysts. *Adv. Synth. Catal.* **2001**, *343*, 369.

(18) Jing, Q.; Zhang, X.; Sun, J.; Ding, K. Bulky Achiral Triarylphosphines Mimic BINAP in Ru(II)- Catalyzed Asymmetric Hydrogenation of Ketones. *Adv. Synth. Catal.* **2005**, *347*, 1193.

(19) 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.

(20) Yu, J.; Long, J.; Yang, Y.; Wu, W.; Xue, P.; Chung, L. W.; Dong, X.; Zhang, X. Iridium-Catalyzed Asymmetric Hydrogenation of Ketones with Accessible and Modular Ferrocene-Based Aminophosphine Acid (f-Ampha) Ligands. *Org. Lett.* **2017**, *19*, 690.

(21) Wang, Y.; Yang, G.; Xie, F.; Zhang, W. A Ferrocene-Based NH-Free Phosphine-Oxazoline Ligand for Iridium-Catalyzed Asymmetric Hydrogenation of Ketones. *Org. Lett.* **2018**, *20*, 6135.

(22) Ling, F.; Nian, S.; Chen, J.; Luo, W.; Wang, Z.; Lv, Y.; Zhong, W. Development of Ferrocene-Based Diamine-Phosphine-Sulfonamide Ligands for Iridium-Catalyzed Asymmetric Hydrogenation of Ketones. *J. Org. Chem.* **2018**, *83*, 10749.

(23) Liu, W.; Yuan, M.; Yang, X.; Li, K.; Xie, J.; Zhou, Q. Efficient asymmetric transfer hydrogenation of ketones in ethanol with chiral iridium complexes of spiroPAP ligands as catalysts. *Chem. Commun.* **2015**, *51*, 6123.

(24) (a) Stefane, B.; Pozgan, F. Metal-Catalysed Transfer Hydrogenation of Ketones. *Top. Curr, Chem.* **2016**, *374*, 1. (b) Yang, H. L.; Huo, N. N.; Yang, P.; Pei, H.; Lv, H.; Zhang, X. M. Rhodium Catalyzed Asymmetric Hydrogenation of 2-Pyridine Ketones. *Org. Lett.* **2015**, *17*, 4144.

(25) Li, Y.; Yu, S.; Wu, X.; Xiao, J.; Shen, W.; Dong, Z.; Gao, J. Iron Catalyzed Asymmetric Hydrogenation of Ketones. *J. Am. Chem. Soc.* **2014**, *136*, 4031.

(26) (a) Rhyoo, H. Y.; Park, H. J.; Suh, W. H.; Chung, Y. K. Use of surfactants in water-soluble ruthenium(II) complex-catalyzed asymmetric hydrogen-transfer reduction of aromatic ketones. *Tetrahedron Lett.* **2002**, *43*, 269. (b) Liu, P. N.; Deng, J. G.; Tu, Y. Q.; Wang, S. H. Highly efficient and recyclable heterogeneous asymmetric transfer hydrogenation of ketones in water. *Chem. Commun.* **2004**, 2070. (c) Li, J.; Li, X.; Ma, Y.; Wu, J.; Wang, F.; Xiang, J.; Zhu, J.; Wang, Q.; Deng, J. Surfactant-accelerated asymmetric transfer hydrogenation with recyclable water-soluble catalyst in aqueous media. *RSC Adv.* **2013**, *3*, 1825. (d) Ma, Y.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J. Asymmetric transfer hydrogenation of prochiral ketones in aqueous media with new water-soluble chiral vicinal diamine as ligand. *Org. Lett.* **2003**, *5*, 2103.

(27) Rhyoo, H. Y.; Park, H. J.; Chung, Y. K. The first Ru(II)-catalysed asymmetric hydrogen transfer reduction of aromatic ketones in aqueous media. *Chem. Commun.* **2001**, 2064.

(28) Shimizu, H.; Igarashi, D.; Kuriyama, W.; Yusa, Y.; Sayo, N.; Salto, T. Asymmetric Hydrogenation of Aryl Ketones Mediated by a Copper Catalyst. *Org. Lett.* **2007**, *9*, 1655.

(29) Junge, K.; Wendt, B.; Addis, D.; Zhou, S.; Das, S.; Fleischer, S.; Beller, M. Copper-Catalyzed Enantioselective Hydrogenation of Ketones. *Chem. - Eur. J.* **2011**, *17*, 101.

(30) Krabbe, S. W.; Hatcher, M. A.; Bowman, R. K.; Mitchell, M. B.; McClure, M. S.; Johnson, J. S. Copper-catalyzed asymmetric hydrogenation of aryl and heteroaryl ketones. *Org. Lett.* **2013**, *15*, 4560.

(31) Li, W. J.; Qiu, S. X. A Novel D2-Symmetrical Chiral Tetraoxazoline Ligand for Highly Enantioselective Hydrosilylation of Aromatic Ketones. *Adv. Synth. Catal.* **2010**, *352*, 1119.

(32) Yu, F.; Zhou, J.; Zhang, X.; Sui, Y.; Wu, F.; Xie, L.; Chan, A. S. C.; Wu, J. Copper(II)-Catalyzed Hydrosilylation of Ketones Using Chiral Dipyridylphosphane Ligands: Highly Enantioselective Synthesis of Valuable Alcohols. *Chem. - Eur. J.* **2011**, *17*, 14234.

(33) (a) Lipshutz, B. H.; Lower, A.; Noson, K. Copper(I) Hydride-Catalyzed Asymmetric Hydrosilylation of Heteroaromatic Ketones. *Org. Lett.* **2002**, *4*, 4045. (b) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. Asymmetric Hydrosilylation of Aryl Ketones Catalyzed by Copper Hydride Complexed by Nonracemic Biphenyl Bisphosphine Ligands. *J. Am. Chem. Soc.* **2003**, *125*, 8779.

(34) Zatolochnaya, O. V.; Rodríguez, S.; Zhang, Y.; Lao, K. S.; Tcyrulnikov, S.; Li, G.; Wang, X.; Qu, B.; Biswas, S.; Mangunuru, H. P. R.; Rivalti, D.; Sieber, J. D.; Desrosiers, J.; Leung, J. C.; Grinberg, N.; Lee, H.; Haddad, N.; Yee, N. K.; Song, J. J.; Kozlowski, M. C.; Senanayake, C. H. Copper-catalyzed asymmetric hydrogenation of 2-substituted ketones via dynamic kinetic resolution. *Chem. Sci.* **2018**, *9*, 4505.

(35) Lee, C.-T.; Lipshutz, B. H. Nonracemic Diarylmethanols From CuH-Catalyzed Hydrosilylation of Diaryl Ketones. *Org. Lett.* **2008**, *10*, 4187.

(36) Vardanyan, R.; Hruby, V. *Synthesis of Best-Seller Drugs*; Elsevier: Amsterdam, The Netherlands, 2016.

(37) Dongmei, Z.; Shuai, S.; Jianzhuang, M.; Wenyan, L.; Luhua, G. Ezetimibe synthesis method. CN103086938A, May 8, 2013.

(38) Sheldon, R. A. The E Factor 25 years on: The rise of green chemistry and sustainability. *Green Chem.* **2017**, *19*, 18.

https://doi.org/10.1021/acs.orglett.1c00746
Org. Lett. 2021, 23, 3282−3286