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Copper-Catalyzed Enantioselective 1,2-Reduction of Cycloalkenones

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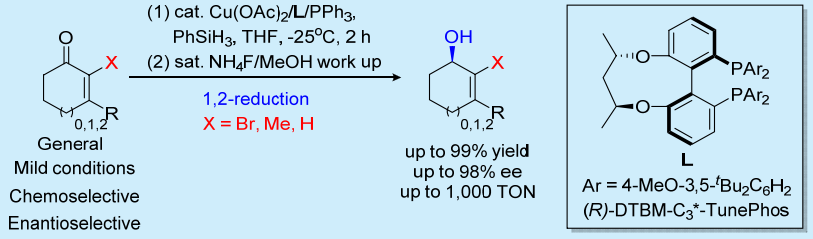

ABSTRACT: We report an asymmetric 1,2-reduction of cyclic α,β-unsaturated ketones to access various enantiomerically enriched cyclic allylic alcohols under mild conditions, catalyzed by in situ generated copper hydride ligated with (*R*)-DTBM-C_3*-TunePhos. α-Brominated cycloalkenones were reduced with excellent enantioselectivities of up to 98% ee, while substrates that were without α-substituents were reduced chemoselectively, with moderate enantioselectivities.

Many natural products and pharmaceuticals are chiral allylic alcohols (Figure 1A).[1] Besides being desirable targets in themselves, chiral allylic alcohols are versatile starting materials in organic synthesis for engaging in Claisen and Overman rearrangements,[2] directed epoxidations and reductions,[3] S_N2', and various stereospecific substitution reactions.[4] As such, allylic alcohols have been used as building blocks in many total syntheses.[1,5]

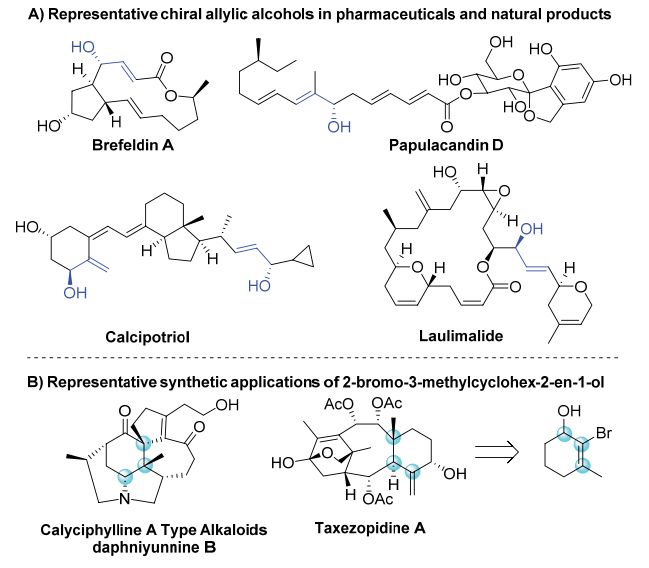

Figure 1. Representative chiral allylic alcohols.

Due to the importance of chiral allylic alcohols in synthesis, efficient benchtop catalytic processes to generate various structural types with high enantioselectivity are desirable. The asymmetric synthesis of allylic alcohols has been accomplished by many strategies, including dynamic kinetic resolution,[6] nucleophilic addition to enals,[7] and allylic substitution.[8] Asymmetric 1,2-reduction of α, β-unsaturated ketones is also a straightforward way to obtain chiral allylic alcohols from easily accessible enone substrates. The challenges of this transformation are the chemoselectivity for competitive 1,2- or 1,4-reduction processes, as well as high facial selectivity. Ru-catalyzed asymmetric high pressure catalytic hydrogenations of enones and Ru-catalyzed asymmetric transfer hydrogenations have reported considerable success.[9] Probably, the most used reduction, particularly for cyclic enones, is the Corey–Bakshi–Shibata (CBS) reduction, which offers a predictable asymmetric reduction.[10] However, besides requiring a relatively high catalyst loading, this reduction can be quite capricious in practice and needs to operate within extremely stringent reaction parameters for high enantiomeric induction.[5a,10]

Among the transition metals, copper is a base metal that has one of the lowest supply risks, even lower than that of iron.[11] It is much less expensive than Ru, Ir, and Pd, as well as being comparatively less toxic, and has a long history of promoting reactions both stoichiometrically and catalytically. Expanding the repertoire of copper-mediated reactions would have

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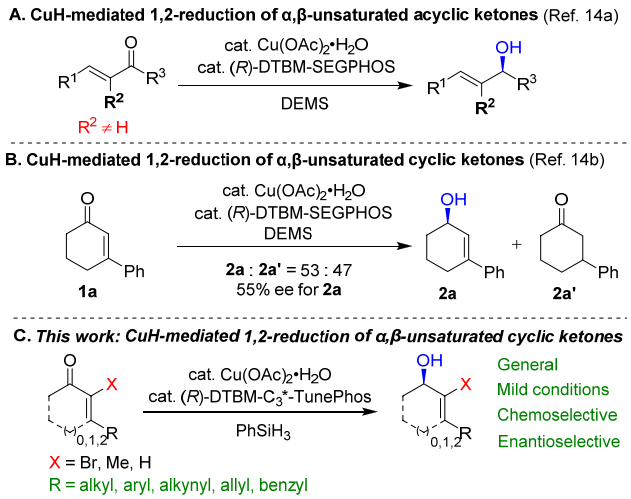
practical implications for laboratory-scale as well as industrial chemistry.

$[(Ph_3P)CuH]_6$ is a discrete copper hydride initially demonstrated to be a chemoselective reagent for 1,4-reduction of α, β-unsaturated ketones, and later as a catalyst in the presence of various stoichiometric reductants.[12] The use of alternative ligands, together with the in situ generation of copper hydride, modified the reduction to be chemoselective for 1,2-reduction and carbonyl reductions, making this a very versatile reducing system amenable to ligand tuning.[13]

In 2010, the Lipshutz group reported an asymmetric 1,2-reduction of acyclic conjugated ketones, mediated by copper(I) hydride generated in situ from $Cu(OAc)_2$, (*R*)-DTBM-SEGPHOS, and diethoxymethylsilane (DEMS) (Scheme 1A).

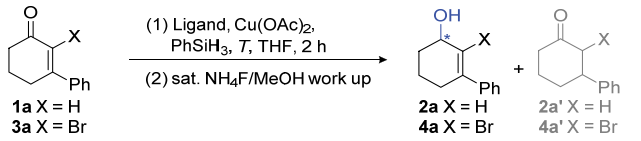
Scheme 1. Asymmetric 1,2-Reduction of Enones



Both the ligand used, as well as the α-substituents of the conjugated ketone, contributed to the high chemo- and enantioselectivity of the reduction.[14a] Many β,β-disubstituted enones were also reduced with excellent ee.[14b] However, as applied to cyclic enones such as **1a**, it was an unsatisfactory solution: the reduction was not chemoselective, and 1,2- and 1,4-reduction products **2a** and **2a′** in a 53:47 ratio, and with 55% ee for **2a**, were obtained under the optimized conditions (Scheme 1B).[14b] Using JOSIPHOS as ligand, the reduction was neither chemoselective nor enantioselective (**2a**:**2a′** = 75:25, **2a** = 2% ee).[14b] Probably this was due to the greater challenge for enantiodifferentiation of prochiral faces in these substrates. Based on our previous research on copper hydride chemistry[15] and continued interest in copper-mediated asymmetric reductions and ligand development,[16] we wondered whether the CuH-mediated reduction of enones could be developed to be a robust method to access structurally diverse cyclic allylic alcohols in particular (Scheme 1C). Herein, we report the use of DTBM-C_3*-TunePhos as a ligand,[17] to achieve an improved copper catalyzed asymmetric 1,2-reduction of cyclic enones and α-brominated cyclic enones, wherein excellent chemoselectivity and good to excellent enantioselectivities can be achieved.

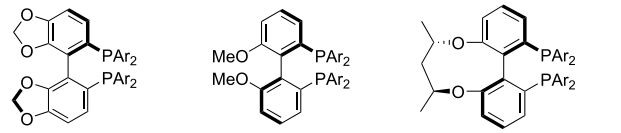
Our initial investigation began with studying whether different stoichiometric reductants could improve the reduction mediated by DTBM-SEGPHOS-ligated copper hydrides. However, the use of alternative silanes (Table S1), or PinBH (Table 1, entry 1), did not result in much improvement in the chemoselectivity or enantioselectivity.

Table 1. Optimizations of Asymmetric 1,2-Reductions



Entry[a]	Ligand	T	Product	Conversion[b]	ee[c]
1[d]	**L3b**	0 °C	**2a**/**2a′** = 40:60	96%	53%
2[d]	**L4b**	0 °C	**2a**/**2a′** = 35:65	99%	58%
3[d]	**L5b**	0 °C	**2a**/**2a′** = 92:8	63%	68%
4[e,f]	**L5b**	−25 °C	**2a**	99% (98%)	73%
5	**L3a**	rt	**4a**	83%	51%
6	**L4a**	rt	**4a**	27%	54%
7	**L5a**	rt	**4a**	47%	56%
8	**L3b**	rt	**4a**	>99%	91%
9	**L4b**	rt	**4a**	>99%	89%
10	**L5b**	rt	**4a**	>99%	93%
11[d]	**L5b**	rt	**4a**	67%	93%
12[e]	**L5b**	−25 °C	**4a**	>99%	96%
13[e,f]	**L5b**	−25 °C	**4a**	99% (95%)	97%

[a]Reaction conditions: **1a**/**3a** (0.1 mmol), Ligand (5 mol %), $Cu(OAc)_2$ (5 mol %), $PhSiH_3$ (0.15 mmol), THF (0.5 mL). [b]Conversions determined by ^{1}H NMR analysis; isolated yields in brackets. [c]Ee determined by chiral HPLC. [d]PinBH used instead of $PhSiH_3$; 12 h instead of 2 h. [e]Ligand (3.3 mol %), $Cu(OAc)_2$ (3 mol %), $PhSiH_3$ (0.12 mmol). [f]PPh_3 (3 mol %) used as additive.



Next, we examined other ligands for this copper-mediated reduction. After screening various ligands (Table S1), the C_3*-TunePhos family of ligands was found to be the best ligands in terms of yield, chemo- and stereoselectivity. The C_n-TunePhos series of ligands were designed to be more rigid than the BIPHEP analogues by restricting the biaryl rotations through joining the aryl units using a linker.[17] In addition, through variation of the length of the linker (C_1 to C_6), the bite angle of the diphosphine could be systematically "tuned". Finally, the series of C_3*-TunePhos ligands incorporated chirality into the C_3-linker. The use of the more bulky (*R*)-DTBM-C_3*-TunePhos ligand with PinBH generated **2a** with an improved conversion as well as a much higher chemoselectivity, while maintaining an ee of 68% (Table 1, entry 3). Further optimizations found that the use of phenylsilane as a reductant led to a quantitative yield of (*R*)-**2a** of 73% ee at −25 °C (Table 1, entry 4), whereas conversions were quite acceptable with PinBH in the presence of the other ligands (Table 1, entries 1−3). A series of β-arylated α, β-unsaturated cyclic ketones were synthesized to be probed (**1b**−**1d**), and their reductions under these conditions similarly provided products **2b**−**2d** chemoselectively, and with an ee of up to 77% (Table 2). We surmise that the improved chemoselectivity and enantioselectivity are both mainly due to additional rigidity

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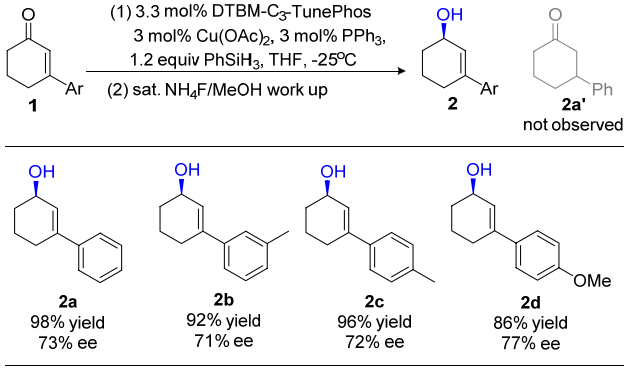
Table 2. Substrate Scope for Asymmetric 1,2-Reduction of β-Substituted Cyclohexenones[a]



[a]Isolated yields are shown.

of (*R*)-DTBM-C_3*-TunePhos over the (*R*)-DTBM-SEGPHOS and the (*R*)-MeO-BIPHEP, as the electronics of these ligands are relatively similar.

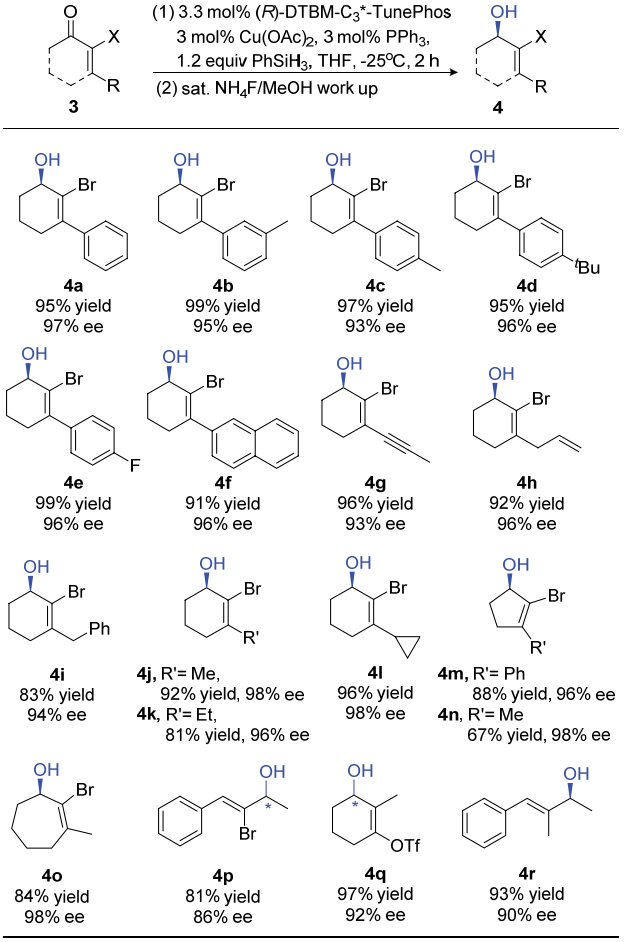
Although both the chemoselectivity and enantioselectivity of the reduction of cyclohexenones have been improved compared with the previous results,[14b] the absolute enantiomeric excess of 71−77% is moderate by today's standards. Thus, another solution for a more enantioselective reduction of cyclohexenones was still needed.

We next considered the installation of a bromo-substituent to the α, β-unsaturated cyclic ketones and to examine this reduction. α-Brominated enones have been reduced with higher enantioselectivities under various conditions, including the CBS reduction.[5c] The α-bromo allylic alcohols obtained upon reduction could be subsequently debrominated to access the parent allylic alcohols,[5b,c] or the vinylic bromide functional group can be exploited for functionalization in various ways, as in the synthetic studies of calyciphylline A or taxezopidine A (Figure 1B).[18] The confluence of reactivity over three contiguous functionalized carbons of α-bromo allylic alcohols facilitates elaborations to furnish densely functionalized molecular constructs.

Using **3a** as a standard substrate, of the chiral diphosphine ligands that were screened (Table S2), reduction in the presence of (*R*)-DTBM-SEGPHOS (**L3b**), (*R*)-DTBM-BIPHEP (**L4b**), and (*R*)-DTBM-C_3*-TunePhos (**L5b**), all proceeded to full conversion over 2 h with exclusive 1,2-reduction, and concurrently with good enantioselectivities (Table 1, entries 8−10). The reductions were both higher yielding and more enantioselective than those with their less hindered, non-DTBM analogues having the same backbones (**L3a**, **L4a**, **L5a**). The enantiocontrol achieved for **4a** in the presence of (*R*)-DTBM-C_3*-TunePhos was slightly superior (93% ee). Using HBPin as a stoichiometric reductant did not facilitate full conversion (Table 1, entries, 10, 11). The catalyst loading could be further decreased to 3 mol % along with 1.2 equiv of $PhSiH_3$, with no detriment to the yield or the enantioselectivity. The ee of the reduction was further enhanced when the temperature was decreased to −25 °C (Table 1, entry 12). The addition of 3 mol % PPh_3 increased the ee of the reduction to 97% (Table 1, entry 13).

With the optimized conditions in hand, we next evaluated the substrate scope. For 3-arylated or 3-naphthylated **3a−f** bearing various substituents on the aromatic ring, for which there is conjugation and potential electronic influence on the enone, they were all reduced to the corresponding optically enriched allylic alcohols with excellent enantioselectivities (93−97% ee) and yields of up to 99% (Table 3). Alkynylated

Table 3. Substrate Scope for Asymmetric 1,2-Reduction of α-Substituted Enones[a]



[a]Isolated yields are shown.

3g having a further extended conjugated system was chemoselectively reduced to alcohol **4g** in high yield and ee. Enone **3h** bearing a skipped diene and enone **3i** with a benzyl group were reduced to the corresponding alcohols in excellent yields and enantioselectivities. Various 3-alkyl substituted cyclohexenones (**3j−l**) were also reduced in high yields and with up to 98% ee.

We extended the substrate scope to other cycloalkenones. Reduction under the optimized conditions provided both β-aryl and β-alkyl substituted cyclopent-2-en-1-ols **4m, 4n** and cyclohept-2-en-1-ol **4o** with excellent ee (96%−98% ee). Finally, while these studies were mainly focused on cyclic substrates in connection with our total synthesis work, we also considered the reduction of the only brominated enone, (*Z*)-3-bromo-4-phenylbut-3-en-2-one **3p**, examined in the previous report.[14a] Asymmetric reduction using (*R*)-DTBM-C_3*-TunePhos (**L5b**) as ligand provided **4p** in 81% yield and 86% ee, compared with 77% ee and 91% yield using (*R*)-DTBM-SEGPHOS (**L3b**) in the Lipshutz work. The reduction of two α-methylated enones afforded **4q**, **4r** with comparable or slightly improved enantioselectivities.[14a]

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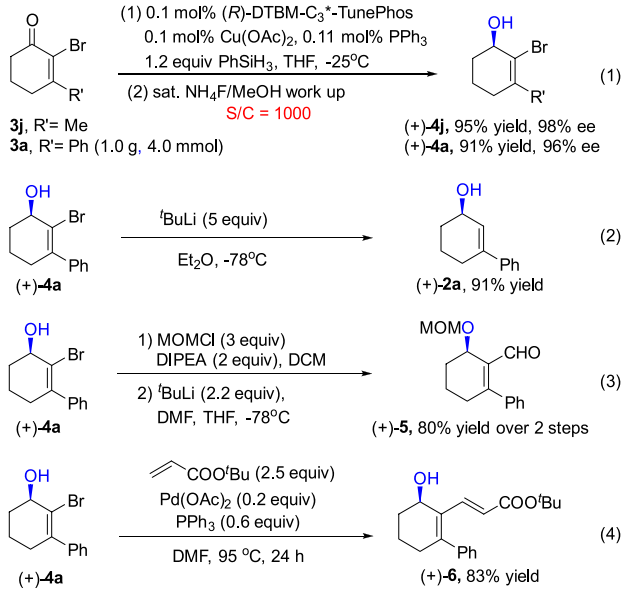
We evaluated the limits of this reduction separately in larger scale TON experiments. It was found that, with S/C as high as 1000, enone **3j** was reduced to **4j** with full conversion and 98% ee without any loss of enantioselectivity or yield (Scheme 2, Table S3). Such a high TON represents economies for both the amount of metal and ligand required for the asymmetric reduction. To demonstrate the practicality of this reduction, a gram-scale synthesis was accomplished using 0.1% catalyst, to convert **3a** to **4a** in 91% yield and 96% ee (Scheme 2). This reduction can be readily operated as a benchtop synthesis without requiring the use of a glovebox. It was also possible to work up the reaction such that most of the THF solvent could be recovered or, alternatively, 2-MeTHF from renewable resources could be used instead as solvent.

Scheme 2. TON Experiments and Derivatizations



The α-bromo-substituted allylic alcohols are versatile intermediates in organic synthesis, and several derivatizations are shown using **4a** (Scheme 2). Metalation and protonation resulted in debromination to generate **2a** in high yield with retention of optical purity.[5b] Alternatively, after MOM protection, metalation and then treatment with DMF provided aldehyde **5** in 80% yield over 2 steps.[18b] Finally, the vinylic bromide can be a handle to engage in cross-coupling reactions, such as a palladium-catalyzed Heck reaction, providing dienoate **6** in 83% yield.

In summary, we have developed a convenient and effective asymmetric reduction catalyzed by a base metal, copper, to provide α-substituted allylic alcohols with excellent enantioselectivities. A TON of at least 1000 was observed, and the reduction is robust and reliable. The optimized reaction conditions tolerated a fairly broad substrate scope, and various β-aryl, alkyl, allyl, alkynyl-substituted brominated cyclohexenones, and bromo-cyclopentenones and cycloheptenones were reduced with good enantioselectivities. For cyclohexenones that are α-protonated, a highly chemoselective 1,2-reduction occurred, with improved, albeit moderate, enantiomeric excesses over other chiral ligands thus far studied. This also represents the first application of the C_n-Tunephos ligands in copper-mediated chemistry. The reduction is readily scalable for multigram-scale preparations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01744.

Experimental procedures, spectral and analytical data, copies of ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Lumbroso, A.; Cooke, M. L.; Breit, B. Catalytic Asymmetric Synthesis of Allylic Alcohols and Derivatives and their Applications in Organic Synthesis. *Angew. Chem., Int. Ed.* **2013**, *52*, 1890−1932. (b) Fischer, J.; Ganellin, C. R. *Analogue-based Drug Discovery*; John Wiley & Sons: 2006; p 452. ISBN: 9783527607495.

(2) (a) Beaulieu, P.; Ogilvie, W. W. A sequential Claisen/ring-closing metathesis approach to the synthesis of spirocyclic cyclopentanes and cyclohexanes. *Tetrahedron Lett.* **2003**, *44*, 8883−8885. (b) Anderson, C. E.; Overman, L. E. Catalytic Asymmetric Rearrangement of Allylic Trichloroacetimidates. A Practical Method

for Preparing Allylic Amines and Congeners of High Enantiomeric Purity. *J. Am. Chem. Soc.* **2003**, *125*, 12412−124133.
(3) For directed epoxidations, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Substrate-directable chemical reactions. *Chem. Rev.* **1993**, *93*, 1307−1370. For reductions, see: (b) Brown, J. M. Directed Homogeneous Hydrogenation. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190−203.
(4) For examples. see: (a) Stork, G.; Schoofs, A. R. Concerted Intramolecular Displacement with Rearrangement in Allylic Systems. Displacement of an Allylic Ester with a Carbanion. *J. Am. Chem. Soc.* **1979**, *101*, 5081−5082. (b) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855−1969.
(5) (a) Zhou, Y.-G.; Wong, H. N. C.; Peng, X.-S. Total Syntheses of (−)-Deoxoapodine, (−)-Kopsifoline D, and (−)-Beninine. *J. Org. Chem.* **2020**, *85*, 967−976. (b) Wada, K.; Sakai, M.; Kawashima, H.; Ogawa, N.; Kobayashi, Y. Efficient Synthesis of Anastrephin via the Allylic Substitution for Quaternary Carbon Construction. *Synlett* **2016**, *27*, 1428−1432. (c) Khatua, A.; Niyogi, S.; Bisai, V. Total Synthesis Of (+)-ar-Macrocarpene. *Org. Biomol. Chem.* **2019**, *17*, 7140−7143. (d) Paterson, I.; Xuan, M.; Dalby, S. M. Total Synthesis of Jiadifenolide. *Angew. Chem., Int. Ed.* **2014**, *53*, 7286−7289.
(6) Pàmies, O.; Bäckvall, J.-E. Combination of Enzymes and Metal Catalysts. A Powerful Approach in Asymmetric Catalysis. *Chem. Rev.* **2003**, *103*, 3247−3262.
(7) Nowotny, S.; Vettel, S.; Knochel, P. Dramatic titanium alkoxide effect in the catalytic enantioselective addition of dialkylzincs to aldehydes. *Tetrahedron Lett.* **1994**, *35*, 4539−4540.
(8) Lussem, B. J.; Gais, H.-J. Palladium-Catalyzed Deracemization of Allylic Carbonates in Water with Formation of Allylic Alcohols: Hydrogen Carbonate Ion as Nucleophile in the Palladium-Catalyzed Allylic Substitution and Kinetic Resolution. *J. Am. Chem. Soc.* **2003**, *125*, 6066.
(9) (a) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. Preferential Hydrogenation of Aldehydes and Ketones. *J. Am. Chem. Soc.* **1995**, *117*, 10417. (b) Ohkuma, T.; Doucet, H.; Pham, T.; Mikami, K.; Korenaga, T.; Terada, M.; Noyori, R. Asymmetric Activation of Racemic Ruthenium(II) Complexes for Enantioselective Hydrogenation. *J. Am. Chem. Soc.* **1998**, *120*, 1086−1087. (c) Zhang, Q.-Q.; Xie, J.-H.; Yang, X.-H.; Xie, J.-B.; Zhou, Q.-L. Iridium-Catalyzed Asymmetric Hydrogenation of α-Substituted α,β-Unsaturated Acyclic Ketones: Enantioselective Total Synthesis of (−)-Mesembrine. *Org. Lett.* **2012**, *14*, 6158−6161. (d) Arai, N.; Azuma, K.; Nii, N.; Ohkuma, T. Highly Enantioselective Hydrogenation of Aryl Vinyl Ketones to Allylic Alcohols Catalyzed by the Tol-Binap/Dmapen Ruthenium (II) Complex. *Angew. Chem., Int. Ed.* **2008**, *47*, 7457−7460.
(10) (a) Corey, E. J.; Helal, C. J. Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a Powerful New Synthetic Method. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. (b) Velasco-Rubio, Á.; Alexy, E. J.; Yoritate, M.; Wright, A. C.; Stoltz, B. M. Stereospecific Overman Rearrangement of Substituted Cyclic Vinyl Bromides: Access to Fully Substituted α-Amino Ketones. *Org. Lett.* **2019**, *21*, 8962−8965. (c) Kuang, L.; Liu, L. L.; Chiu, P. Formal Total Synthesis of (+)-Cortistatins A and. *Chem. - Eur. J.* **2015**, *21*, 14287−14291.
(11) Wen, J.; Wang, F.; Zhang, X. Asymmetric hydrogenation catalyzed by first-row transition metal complexes. *Chem. Soc. Rev.* **2021**, *50*, 3211−3237.
(12) (a) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. Simplified, "one-pot" procedure for the synthesis of $[(Ph_3P)CuH]_6$, a stable copper hydride for conjugate reductions. *Tetrahedron Lett.* **1988**, *29*, 3749−3752. (b) Baker, B. A.; Bošković, Ž. V.; Lipshutz, B. H. (BDP)CuH: A "Hot" Stryker's Reagent for Use in Achiral Conjugate Reductions. *Org. Lett.* **2008**, *10*, 289−292. For reviews, see: (c) Rendler, S.; Oestreich, M. Polishing a Diamond in the Rough: "Cu−H" Catalysis with Silanes. *Angew. Chem., Int. Ed.* **2007**, *46*, 498−504. (d) Deutsch, C.; Krause, N.; Lipshutz, B. H. CuH-Catalyzed Reactions. *Chem. Rev.* **2008**, *108*, 2916−2927. (e) Lipshutz, B. H. Rediscovering Organocopper Chemistry Through Copper Hydride. It's All About the Ligand. *Synlett* **2009**, *2009*, 509−524. Representative CuH catalyzed asymmetric 1,4-reductions: (f) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. Synthesis of α-Alkyl Cyclopentanones in High Enantiomeric Excess via Copper-Catalyzed Asymmetric Conjugate Reduction. *J. Am. Chem. Soc.* **2000**, *122*, 6797−6798. (g) Lipshutz, B. H.; Servesko, J. M. CuH-Catalyzed Asymmetric Conjugate Reductions of Acyclic Enones. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789−4792. (h) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. Asymmetric 1,4-Hydrosilylations of α,β-Unsaturated Esters. *J. Am. Chem. Soc.* **2004**, *126*, 8352−8353. (i) Lee, D.; Yang, Y.; Yun, J. Copper-Catalyzed Asymmetric Reduction of 3,3-Diarylacrylonitriles. *Org. Lett.* **2007**, *9*, 2749−2751. (j) Rupnicki, L.; Saxena, A.; Lam, H. W. Aromatic Heterocycles as Activating Groups for Asymmetric Conjugate Addition Reactions. Enantioselective Copper-Catalyzed Reduction of 2-Alkenylheteroarenes. *J. Am. Chem. Soc.* **2009**, *131*, 10386−10387.
(13) (a) Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. Highly Chemoselective Catalytic Hydrogenation of Unsaturated Ketones and Aldehydes to Unsaturated Alcohols Using Phosphine-Stabilized Copper(I) Hydride Complexes. *Tetrahedron* **2000**, *56*, 2153−2166. (b) Lipshutz, B. H.; Noson, K.; Chrisman, W. Ligand-Accelerated, Copper-Catalyzed Asymmetric Hydrosilylations of Aryl Ketones. *J. Am. Chem. Soc.* **2001**, *123*, 12917−12918.
(14) (a) Moser, R.; Bošković, Ž. V.; Crowe, C. S.; Lipshutz, B. H. CuH-Catalyzed Enantioselective 1,2-Reductions of $\alpha\,\beta$−Unsaturated Ketones. *J. Am. Chem. Soc.* **2010**, *132*, 7852−7853. (b) Voigtritter, K. R.; Isley, N. A.; Moser, R.; Aue, D. H.; Lipshutz, B. H. Regioselective reductions of β,β-disubstituted enones catalyzed by nonracemically ligated copper hydride. *Tetrahedron* **2012**, *68*, 3410−3416.
(15) (a) Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. Tandem Conjugate Reduction-Aldol Cyclizations Using Stryker's Reagent. *Org. Lett.* **2001**, *3*, 1901−1903. (b) Chiu, P.; Leung, S. K. Reductive and Catalytic Reductive Aldol Cyclizations of Alkynediones Induced by Stryker's Reagent. *Chem. Commun.* **2004**, 2308−2309. (c) Chiu, P.; Chung, W. K. Reductive Intramolecular Henry Reactions Induced by Stryker's Reagent. *Synlett* **2005**, *2005*, 55−58. (d) Leung, L. T.; Leung, S. K.; Chiu, P. Copper-catalyzed hydrostannation of activated alkynes. *Org. Lett.* **2005**, *7*, 5249−5252. (e) Li, N.; Ou, J.; Miesch, M.; Chiu, P. Conjugate Reductions and Reductive Aldol Cyclizations of α,β−Unsaturated Thioesters Catalyzed by (BDP)CuH. *Org. Biomol. Chem.* **2011**, *9*, 6143−6147. (f) Wong, K. C.; Ng, E.; Wong, W. T.; Chiu, P. Copper Hydride-Catalyzed Reductive Claisen Rearrangements. *Chem. - Eur. J.* **2016**, *22*, 3709−3712.
(16) (a) Ou, J.; Wong, W.-T.; Chiu, P. Reductive aldol cyclizations of unsaturated thioester derivatives of 1,3-cyclopentanedione catalyzed by chiral copper hydrides. *Tetrahedron* **2012**, *68*, 3450−3456. (b) Ou, J.; Wong, W. T.; Chiu, P. Desymmetrizing reductive aldol cyclizations of enethioate derivatives of 1,3-diones catalyzed by a chiral copper hydride. *Org. Biomol. Chem.* **2012**, *10*, 5971−8. (c) Hu, L.; Zhang, Y.; Chen, G.-Q.; Lin, B.-J.; Zhang, Q.-W.; Yin, Q.; Zhang, X. CuH-Catalyzed Atropoenantioselective Reduction of Bringmann's Lactones via Dynamic Kinetic Resolution. *Org. Lett.* **2019**, *21*, 5575−5580. (d) Zeng, W.; Tan, X.; Yu, Y.; Chen, G.-Q.; Zhang, X. Copper-Catalyzed Asymmetric Hydrosilylation of β-Nitroethyl Aryl Ketones. *Org. Lett.* **2020**, *22*, 858−862.
(17) (a) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. Synthesis of Chiral Bisphosphines with Tunable Bite Angles and Their Applications in Asymmetric Hydrogenation of β-Ketoesters. *J. Org. Chem.* **2000**, *65*, 6223. (b) Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.; Zhou, Z.; Chan, A. S. C. A New Class of Versatile Chiral-Bridged Atropisomeric Diphosphine Ligands: Remarkably Efficient Ligand Syntheses and Their Applications in Highly Enantioselective Hydrogenation Reactions. *J. Am. Chem. Soc.* **2006**, *128*, 5955−5965. (c) Sun, X.; Zhou, L.; Li, W.; Zhang, X. Convenient Divergent Strategy for the Synthesis of TunePhos-Type Chiral Diphosphine Ligands and Their Applications in Highly Enantioselective Ru-Catalyzed Hydrogenations. *J. Org. Chem.* **2008**, *73*, 1143−1146.

https://doi.org/10.1021/acs.orglett.1c01744
Org. Lett. 2021, 23, 5658−5663

(18) (a) Jackson, R. W.; Shea, K. J. Synthesis Of A C-1 Epi Taxinine Intermediate Using The Type 2 Intramolecular Diels-Alder Approach. *Tetrahedron Lett.* **1994**, *35*, 1317−1320. (b) Shao, H.; Bao, W.; Jing, Z.-R.; Wang, Y.-P.; Zhang, F.-M.; Wang, S.-H.; Tu, Y.-Q. Construction of the [6,5,7,5] Tetracyclic Core of Calyciphylline A Type Alkaloids via a Tandem Semipinacol Rearrangement/ Nicholas Reaction. *Org. Lett.* **2017**, *19*, 4648−4651. (c) Hu, Y.-J.; Fan, J.-H.; Li, S.; Zhao, J.; Li, C.-C. Synthetic Study toward the Total Synthesis of Taxezopidines A and B. *Org. Lett.* **2018**, *20*, 5905−5909.

https://doi.org/10.1021/acs.orglett.1c01744
Org. Lett. 2021, 23, 5658−5663