OL | Organic Letters

pubs.acs.org/OrgLett Letter

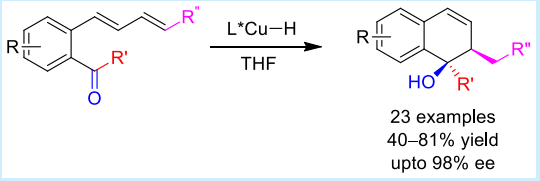
Asymmetric Synthesis of 1,2-Dihydronaphthalene-1-ols via Copper-Catalyzed Intramolecular Reductive Cyclization

Ranjan Kumar Acharyya, Soyoung Kim, Yeji Park, Jung Tae Han, and Jaesook Yun*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02829 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: We describe a copper-catalyzed intramolecular reductive cyclization of easily accessible benz-tethered 1,3-dienes containing a ketone moiety. This process provided biologically active 1,2-dihydronaphthalene-1-ol derivatives in good yields with excellent enantio- and diastereoselectivity. Mechanistic investigations using density functional theory revealed that (*Z*)- and (*E*)-allylcopper intermediates formed in situ from the diene and copper catalyst undergo isomerization and selective intramolecular allylation of the (*E*)-allylcopper form of the major product through a six-membered boatlike transition state. The resulting products were further transformed to fully saturated naphthalene-1-ols by reactions of the olefin moiety.



Optically active homoallylic tertiary alcohols and their derivatives are widely found in many natural products and pharmaceuticals.[1] In particular, 1,2-dihydronaphthalene alcohol derivatives are a very important class of framework present in a wide range of biologically active molecules[2] including oxytetracycline (antibiotic agent),[3] lacinilene C (antibacterial),[4] and active metabolite compound C[5] (Figure 1).

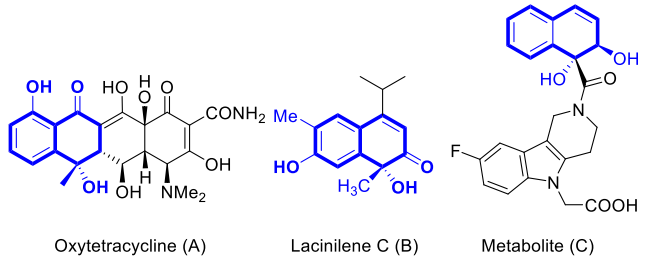
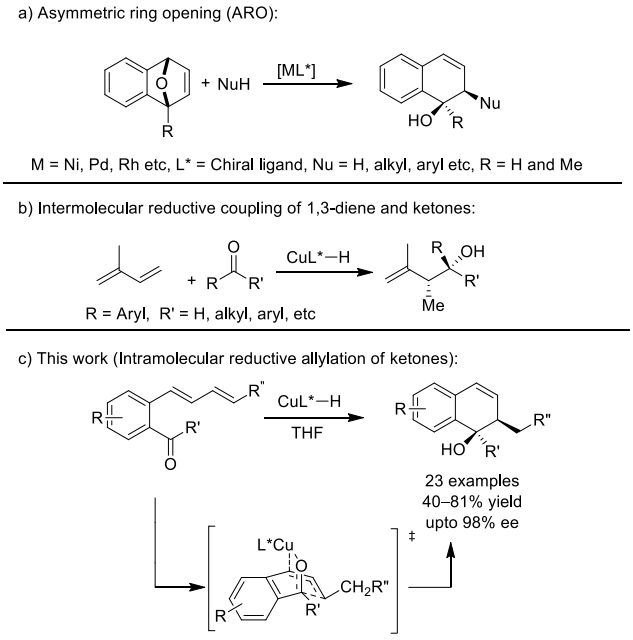


Figure 1. Representative examples of 1,2-dihydronaphthalene-containing natural products.

The enantioselective synthesis of cyclic homoallylic alcohols continues to attract attention, as these are highly useful intermediates in complex molecule synthesis and medicinal chemistry.[6] Established methods have been reported in the literature for the synthesis of 1,2-dihydronaphthalene-1-ols. All of these methods are based on the transition-metal-catalyzed asymmetric ring opening (ARO) reaction of oxa- and azabicyclic alkenes with carbon or heteroatom-containing nucleophiles (Scheme 1a).[7,8] ARO reactions have been widely modified using various transition metals including Ir,[9] Ni,[10] Pd,[11] Cu,[12] Rh,[13] and others.[14]

While the synthesis of dihydronaphthalenes having secondary homoallylic alcohols has been extensively explored through the ARO reaction, the synthesis of such compounds containing a tertiary alcohol is not well-defined yet. Indeed, a few research groups have reported the syntheses of such cyclic

Scheme 1. Previous Approaches and the Present Work



Received: August 23, 2020

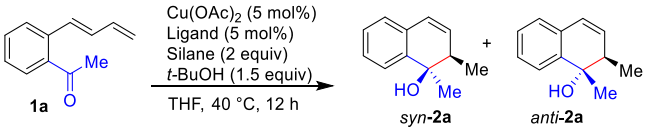
tertiary alcohols using ARO,[15] but the yields and enantioselectivities of those reactions were not satisfactory.[16] Therefore, the development of a versatile methodology to synthesize cyclic homoallylic tertiary alcohols from easily accessible starting materials with higher efficiency is much sought.

In recent years, a number of research groups, including this one, have reported approaches for copper-catalyzed reductive functionalization of unsaturated substrates through in situ-generated alkylcopper nucleophiles.[17] Various activated pronucleophiles such as alkenes,[18] enynes,[19] allenes,[20] and enones[21] were successfully used in nucleophilic addition reactions to ketones. Recently, the Buchwald,[22a] Xiong,[22b] and Oestreich[22d] groups independently reported copper-catalyzed intermolecular reductive couplings of 1,3-dienes with ketones as well as aldehydes[22c] (Scheme 1b). In their proposed mechanism, the intermolecular allylation reaction proceeded via a stable well-organized six-membered chairlike transition state to yield the major product.

Herein we report an asymmetric intramolecular copper-catalyzed reductive coupling of 1,3-dienes with benz-tethered ketones for the easy acquisition of substituted dihydronaphthalene-1-ol derivatives (Scheme 1c). Attaining a favorable transition state and controlling the diastereo- and enantioselectivity in an intramolecular allylation reaction, especially in a benz-tethered system, are envisioned to be difficult because of a low level of flexibility and high ring strain for the cyclization and thus are considered the primary challenges.

We started our investigation by taking the simple 1,3-diene-containing acetophenone substrate **1a** as our model substrate (Table 1 and Figure 2). At first, we performed the reaction in the presence of BenzP* (**L1**) as the ligand, $Cu(OAc)_2$ as the catalyst, and 2.0 equiv of diethoxy(methyl)silane (DEMS) as the hydride source in THF solvent at 40 °C, which yielded the

Table 1. Optimization of the Copper-Catalyzed Reductive Cyclization Reaction[a]



entry	ligand	silane	yield (%)[b]	dr (*syn*:*anti*)[c]	*syn*-**2a** ee (%)[d]
1	**L1**	DEMS	69	15:1	45
2	**L2**	DEMS	30	16:1	47
3	**L3**	DEMS	70	19:1	89
4	**L4**	DEMS	72	14:1	37
5	**L5**	DEMS	45	16:2	57
6	**L6**	DEMS	70	10:1	22
7	**L3**	TMDSO	75	20:1	90
8[e]	**L3**	TMDSO	72	18:1	89
9[f]	**L3**	TMDSO	70	17:1	85
10[g]	**L3**	TMDSO	65	17:1	88
11[h]	**L3**	TMDSO	73	19:1	89
12[i]	**L3**	**TMDSO**	**78**	**20:1**	**93**

[a]Reactions were conducted on a 0.2 mmol scale of **1a**. [b]Isolated yields of *syn*-**2a**. [c]Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures using dimethylformamide as an internal standard. [d]The ee values for *syn*-**2a** were determined by chiral HPLC analysis. [e]MTBE was used as the solvent. [f]Diethyl ether was used as the solvent. [g]1,2-Dichloroethane was used as the solvent. [h]Toluene was used as the solvent. [i]The reaction was performed on a 2 mmol scale at 60 °C.

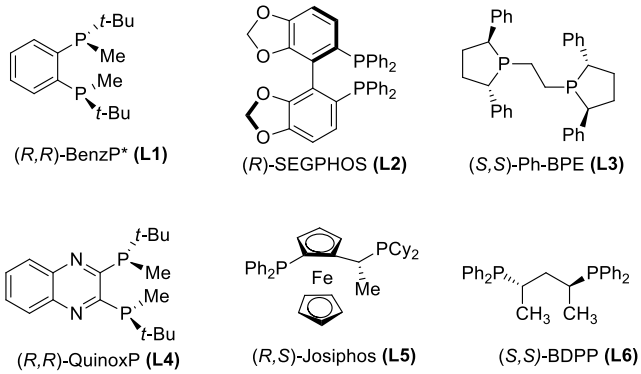


Figure 2. Structures of the chiral ligands.

desired product **2a** in 69% yield but with a low level of enantioselectivity (45%) (entry 1). Next, SEGphos (**L2**) as the ligand furnished the product in a poor yield with similar enantioselectivity (entry 2). Switching to (*S*,*S*)-Ph-BPE (**L3**) showed better results and provided product **2a** in an increased yield of 70% with a dramatic increase in enantioselectivity (89%) (entry 3). Other bisphosphine ligands such as QuinoxP (**L4**), Josiphos (**L5**), and BDPP (**L6**) furnished the product in low yields and low to moderate dr and ee (entries 4−6). After evaluation of the ligand efficiency, we focused on optimizing the silane reactivity in the reaction. The use of more stable and less flammable dimeric 1,1,3,3-tetramethyldisiloxane (TMDSO) resulted in a slightly increased yield of 75% with 90% ee (entry 7). Ethereal solvents such as MTBE and diethyl ether provided results similar to those with THF (entries 8 and 9). The halogenated solvent 1,2-DCE gave the product in lower yield (65%) but with similar ee (88%) (entry 10), whereas toluene furnished the product in good yield (73%) and ee (89%) (entry 11). The reaction showed better performance at 60 °C in THF as the solvent, providing the product in 78% yield with 93% ee and 20:1 dr (entry 12). These were chosen as the optimal reaction conditions for the intramolecular cyclization.

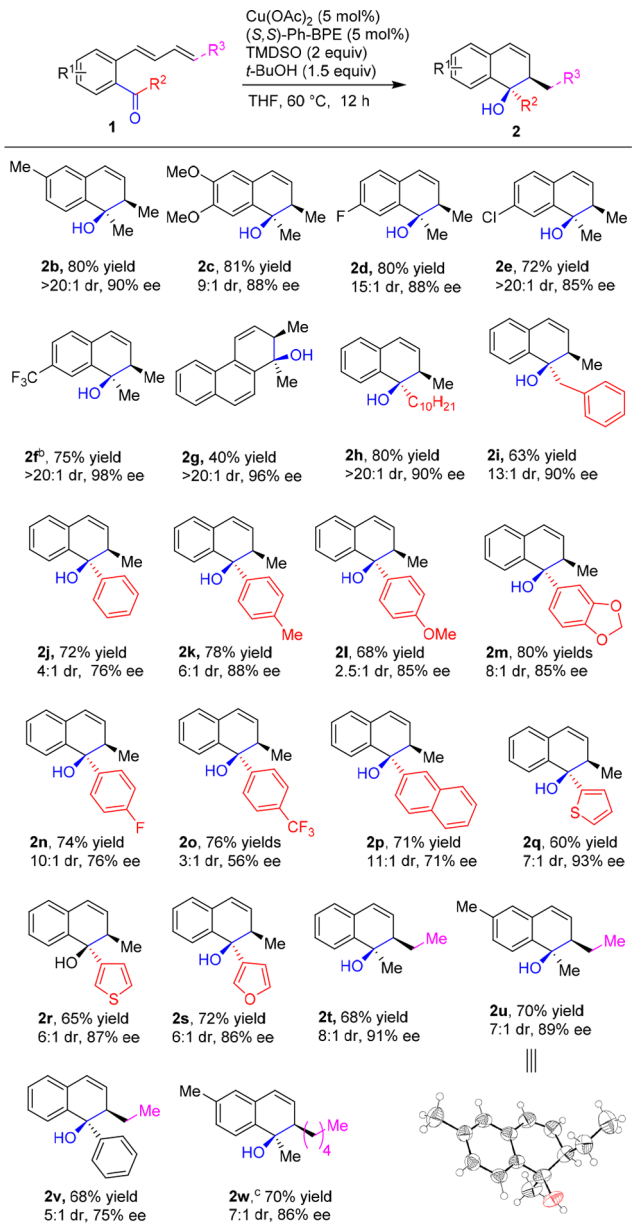
With the optimized conditions established, we proceeded to examine the substrate scope of the reductive intramolecular ketone allylation. As summarized in Table 2, a wide range of substituted dienes containing aryl ketones **1** were found to be suitable substrates under mild conditions and furnished the corresponding homoallylic cyclic tertiary alcohols **2** in good to excellent yields and enantioselectivities as well as high diastereoselectivities.

Variation of the substituent of the aromatic ring (R^1) was first investigated. Substrates containing an electron-donating substituent (Me, OMe) reacted smoothly to afford the corresponding products **2b** and **2c** in good yields with excellent ee and dr. Substrates bearing electron-withdrawing substituents such as −F, −Cl, and $-CF_3$ were also valid substrates for the reductive cyclization reaction, providing products **2d**, **2e**, and **2f** with good efficiency. Naphthalene-tethered substrate **1g** provided the corresponding cyclized 1,2-dihydrophenanthrene product **2g** in alower yield (40%), but excellent enantioselectivity (96%) and dr (20:1) were observed.

Substrates having a different R^2 substitution of the keto functionality were examined. Cyclization of primary-alkyl-substituted keto substrates (R^2 = alkyl) provided the corresponding cyclized products (**2h** and **2i**) in excellent yields and ee. Aryl-substituted substrates (R^2 = aryl) were also

https://dx.doi.org/10.1021/acs.orglett.0c02829
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Substrate Scope for the Synthesis of 1,2-Dihydronaphthalene-1-ols[a]



[a]The reactions were carried out on a 0.2 mmol scale. The dr is the ratio of *syn*-**2** to *anti*-**2**. Isolated yields and ee values for *syn*-**2** as a single isomer are shown; the ee values for *syn*-**2** were determined by chiral HPLC analysis. [b]The reaction was performed at 0 °C and was complete within 30 min. [c]0.1 mmol scale.

suitable for the cyclization reaction. Substrates containing electron-donating substituents (−Me, −OMe, dioxolane) furnished the corresponding cyclized products (**2k**, **2l**, and **2m**) with excellent performance, but substrates **1n** and **1o** containing electron-deficient substituents (−F, $-CF_3$) provided the desired products with moderate ee. Naphthalene-substituted substrate **1p** also provided the desired cyclized product in good yield with moderate ee. Heteroaromatic-substituted substrates furnished the desired cyclized products **2q**, **2r**, and **2s** with excellent performance. Furthermore, variation of substituents on the diene part (R^3) was also examined. Notably, challenging the internal 1,3-diene substrates with a methyl or *n*-pentyl substituent provided the desired products **2t**, **2u**, **2v**, and **2w** in good yields (68−70%) and ee (75−91%). The reaction was also applied to aldehydes to get secondary cyclic homoallylic alcohols, but unfortunately, the reduced primary alcohol was obtained as the major product rather than the cyclized product. Finally, the absolute configuration of compound (1*R*,2*R*)-**2u** was unambiguously confirmed by X-ray crystal analysis, and the stereochemistries of the other products were assigned by analogy.

To obtain a detailed understanding of the reaction mechanism, we performed density functional theory (DFT) calculations. Taking **1a** as our model substrate, we hypothesized that hydrocupration of 1,3-butadiene with an active Cu−H catalyst might proceed either via direct 1,4-hydrocupration or via 1,2-hydrocupration followed by 1,3-allylic migration. Detailed analysis of the hydrocupration step revealed that the process strongly prefers to occur through 1,2-addition to form secondary allylcopper intermediates **3** and **3′** over 1,4-hydrocupration.[22a,23] The initial 1,2-hydrocupration proceeds with good π-facial selectivity leading to (*S*)-allylcopper intermediate **3** as the major product and (*R*)-allylcopper intermediate **3′** via **TS1a** and **TS1b**, respectively. Intermediate **3** rapidly undergoes facile isomerization via either **TS2**-*cis* or **TS2**-*trans* to form stable benzylic allylcopper intermediates **4**-*cis* and **4**-*trans* (Figure 3).

Extensive DFT calculations of the intramolecular cyclization of the allylcopper species identified **TS3a** and **TS3b** as the most favorable pathways for each allylation. The activation energy from (*E*)-allylcopper intermediate **4**-*trans* to **TS3a** is 8.9 kcal/mol, whereas the activation energy for **4**-*cis* to **TS3b** is 20.6 kcal/mol. In **TS3a**, the methyl groups on the ketone and the allylcopper are placed in an equatorial orientation of a six-membered boat-type transition state, whereas **TS3b** suffers from steric congestion, meaning that **TS3b** requires a higher-energy transition state. Because of the low activation energy of the **4**-*trans* intermediate, it immediately cyclizes to provide copper−alkoxide intermediate **6**, whereas (*Z*)-allylcopper (**4**-*cis*) isomerizes back to **3**. In previous reports, (*Z*)-allylcopper intermediates were responsible for the major product formation in intermolecular[22a] and intramolecular[24] allylation of ketones and imines. In contrast, the (*E*)-allylcopper intermediate plays a vital role in furnishing the major six-membered cyclized product in this intramolecular ketone allylation.

On the basis of the DFT calculations, the preferred catalytic cycle for the intramolecular ketone allylation is shown in Figure 4. The cycle consists of 1,2-hydrocupration, 1,3-allylic migration of copper, and cyclization through the six-membered boat-type transition state **TS3a** leading to *syn*-alkoxycopper intermediate **6**. Subsequent protonation furnishes the product *syn*-**2a** and regenerates the active Cu−H catalyst.

Biologically important tetrahydronaphthalene-1-ol derivatives[25] can be easily accessed by organic transformations of our resulting 1,2-dihydronaphthalene-1-ol products (Scheme 2). Catalytic hydrogenation of compound **2a** yielded tetrahydronaphthalene compound **7** in 80% yield with retention of the ee. The absolute configuration of compound **2a** was confirmed by comparing its optical rotation data with the literature value.[26] Hydroxyl-group-directed epoxidation of **2a** furnished epoxide **8** in 90% yield without a change in enantiomeric excess and with a 5:1 diasteromeric ratio. Epoxide ring opening of **8** in the presence of NaN_3 provided fully saturated naphthalene product **9** containing four consecutive stereogenic centers in 80% yield.

https://dx.doi.org/10.1021/acs.orglett.0c02829
Org. Lett. XXXX, XXX, XXX−XXX

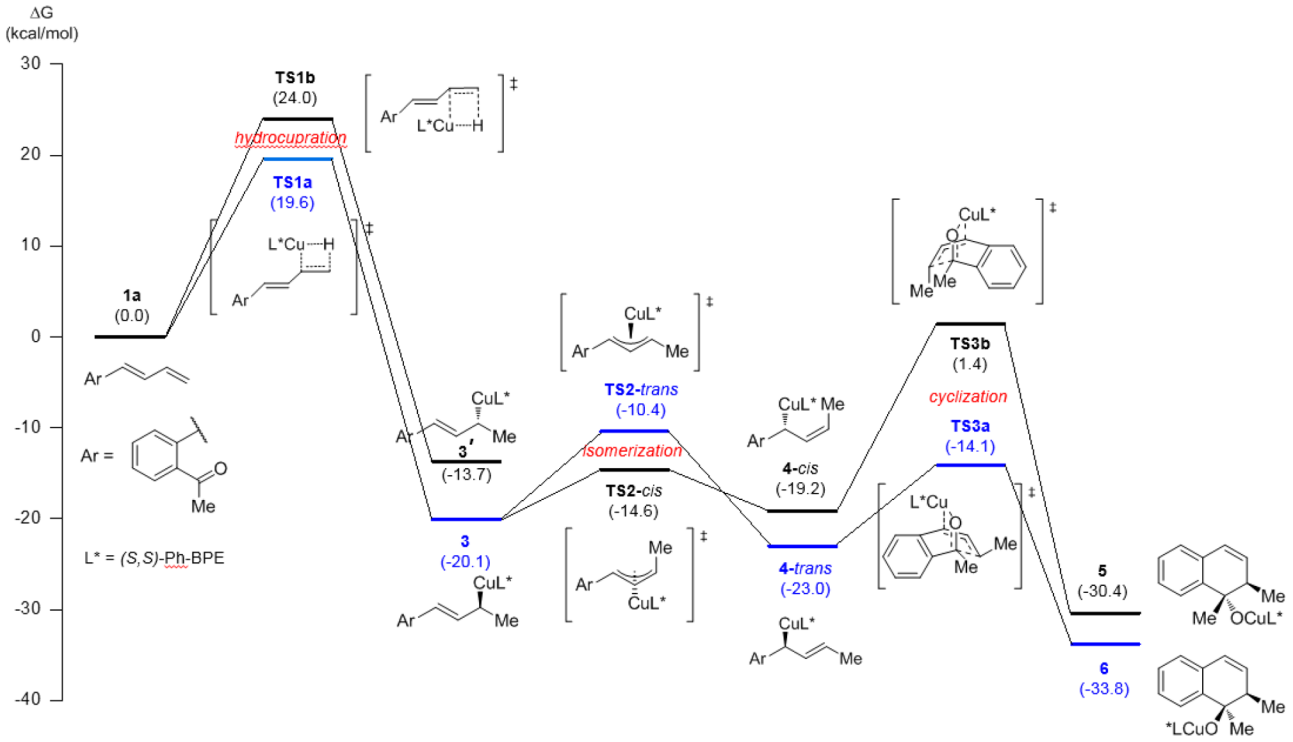


Figure 3. Computed energy profiles of the CuH-catalyzed reductive cyclization of **1a**. All energies are reported with respect to diene **1a** (the Gaussian 09 program was used for calculations in the gas phase at the M06-2X/6-13G* level).

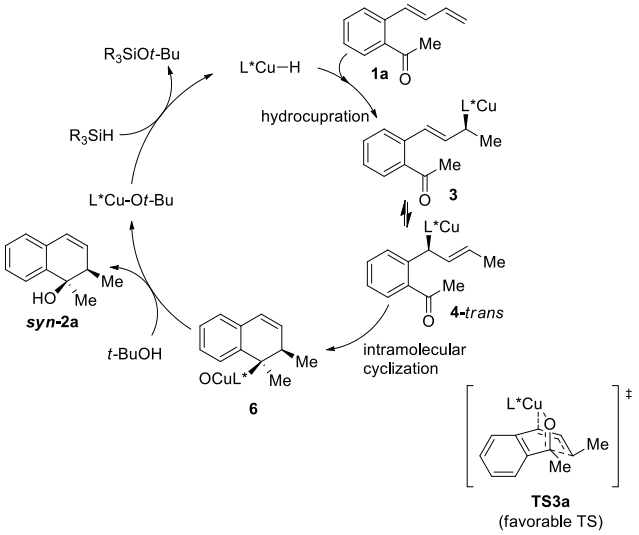
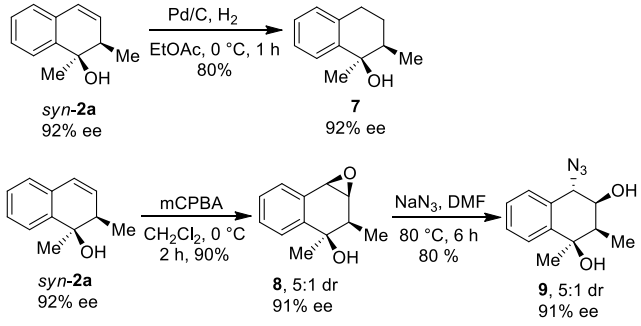


Figure 4. Proposed catalytic cycle and transition state.

In summary, we have developed an efficient and straightforward approach for the synthesis of enantioenriched substituted 1,2-dihydronaphthalene-1-ols through copper-catalyzed asymmetric intramolecular reductive coupling of (*E*)-dienylarenes with a benz-tethered ketone moiety. The (*S*,*S*)-Ph-BPE* (**L3**)–copper catalyst was suitable for this intramolecular process, furnishing cyclic tertiary alcohols containing two adjacent stereocenters in good to high yields with excellent enantioselectivity of up to 98%. DFT calculations explained the selectivity-determining factor for this strained intramolecular cyclization. From an isomerizable mixture of (*E*)- and (*Z*)-allylcopper intermediates, selective cyclization of the (*E*)-allylcopper complex generates the observed products. Additionally, our products can also be transformed to fully functionalized tetrahydronaphthalene moieties.

Scheme 2. Application of Enantioenriched 1,2-Dihydronaphthalene Derivatives



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02829.

Experimental procedures, characterization data, copies of ^{1}H and ^{13}C spectra for all new compounds, and X-ray data for compound **2u** (PDF)

Accession Codes

CCDC 2017520 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

https://dx.doi.org/10.1021/acs.orglett.0c02829
Org. Lett. XXXX, XXX, XXX–XXX

AUTHOR INFORMATION

Corresponding Author

Jaesook Yun − *Department of Chemistry, Sungkyunkwan University, Suwon 16419, Korea*; orcid.org/0000-0003-4380-7878; Email: jaesook@skku.edu

Authors

Ranjan Kumar Acharyya − *Department of Chemistry, Sungkyunkwan University, Suwon 16419, Korea*

Soyoung Kim − *Department of Chemistry, Sungkyunkwan University, Suwon 16419, Korea*

Yeji Park − *Department of Chemistry, Sungkyunkwan University, Suwon 16419, Korea*

Jung Tae Han − *Department of Chemistry, Sungkyunkwan University, Suwon 16419, Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02829

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the National Research Foundation of Korea (Grants 2019R1A2C2005706 and 2019R1A4A2001440).

REFERENCES

(1) (a) Liu, Y.-L.; Lin, X.-T. *Adv. Synth. Catal.* **2019**, *361*, 876−918. (b) Hatano, M.; Ishihara, K. *Synthesis* **2008**, *2008*, 1647−1675. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793.

(2) (a) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Ghiglieri, A.; Govoni, S. *J. Med. Chem.* **1995**, *38*, 942−949. (b) Snyder, S. E.; Aviles-Garay, F. A.; Chakraborti, R.; Nichols, D. E.; Watts, V. J.; Mailman, R. B. *J. Med. Chem.* **1995**, *38*, 2395−2409. (c) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246−5247. (d) Lautens, T.; Rovis, M. *J. Am. Chem. Soc.* **1997**, *119*, 11090−11091. (e) Lautens, M.; Fagnou, K.; Taylor, M.; Rovis, T. *J. Organomet. Chem.* **2001**, *624*, 259−270. (f) Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465−3468. (g) McManus, H. A.; Fleming, M. J.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 433−436. (h) Tsoung, J.; Krämer, K.; Zajdlik, A.; Liébert, C.; Lautens, M. *J. Org. Chem.* **2011**, *76*, 9031−9045.

(3) (a) *Analogue-Based Drug Discovery*; Fischer, J., Ganellin, C. R. Wiley-VCH: Weinheim, Germany, 2006. (b) Shang, Z.; Salim, A. A.; Khalil, Z.; Bernhardt, P. V.; Capon, R. J. *J. Org. Chem.* **2016**, *81*, 6186−6194.

(4) (a) Krohn, K.; Zimmermann, G. *J. Org. Chem.* **1998**, *63*, 4140−4142. (b) Zhang, Y.; Liao, Y.; Liu, X.; Xu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2017**, *8*, 6645−6649.

(5) Risch, P.; Pfeifer, T.; Segrestaa, J.; Fretz, H.; Pothier, J. *J. Med. Chem.* **2015**, *58*, 8011−8035.

(6) Yus, M.; Gonźalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595−5698.

(7) For reviews, see: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844. (c) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58. (d) Lautens, M.; Fagnou, K. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5455−5460. (e) Rayabarapu, D. K.; Cheng, C.-H. *Acc. Chem. Res.* **2007**, *40*, 971−983.

(8) For recent works, see: (a) Tan, Y.; Yao, Y.; Yang, W.; Lin, Q.; Huang, G.; Tan, M.; Chen, S.; Chen, D.; Yang, D. *Adv. Synth. Catal.* **2020**, *362*, 139−145. (b) Koh, S.; Pounder, A.; Brown, E.; Tam, W. *Org. Lett.* **2020**, *22*, 3433−3437. (c) Diallo, A. G.; Roy, D.; Gaillard, S.; Lautens, M.; Renaud, J.-L. *Org. Lett.* **2020**, *22*, 2442−2447. (d) Chen, D.; Yao, Y.; Yang, W.; Lin, Q.; Li, H.; Wang, L.; Chen, S.; Tan, Y.; Yang, D. *J. Org. Chem.* **2019**, *84*, 12481−12489. (e) Endo, K.; Tanaka, K.; Ogawa, M.; Shibata, T. *Org. Lett.* **2011**, *13*, 868−871.

(9) (a) Yang, D.; Long, Y.; Wang, H.; Zhang, Z. *Org. Lett.* **2008**, *10*, 4723−4726. (b) Yang, X.; Yang, W.; Yao, Y.; Deng, Y.; Yang, D. *Org. Chem. Front.* **2019**, *6*, 1151−1156.

(10) (a) Rayabarapu, D. K.; Chiou, C.-F.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 1679−1682. (b) Li, L.-P.; Rayabarapu, D. K.; Nandi, M.; Cheng, C.-H. *Org. Lett.* **2003**, *5*, 1621−1624. (c) Mannathan, S.; Cheng, C.-H. *Adv. Synth. Catal.* **2014**, *356*, 2239−2246. (d) Shukla, P.; Sharma, A.; Pallavi, B.; Cheng, C.-H. *Tetrahedron* **2015**, *71*, 2260−2266. (e) Deng, Y.; Yang, W.; Yao, Y.; Yang, X.; Zuo, X.; Yang, D. *Org. Biomol. Chem.* **2019**, *17*, 703−711.

(11) (a) Cabrera, S.; Gómez Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3944−3947. (b) Zhang, T.-K.; Mo, D.-L.; Dai, L.-X.; Hou, X.-L. *Org. Lett.* **2008**, *10*, 3689−3692. (c) Liu, S.; Li, S.; Chen, H.; Yang, Q.; Xu, J.; Zhou, Y.; Yuan, M.; Zeng, W.; Fan, B. *Adv. Synth. Catal.* **2014**, *356*, 2960−2964. (d) Yamamoto, T.; Akai, Y.; Suginome, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 12785−12788. (e) Li, S.; Xu, J.; Fan, B.; Lu, Z.; Zeng, C.; Bian, Z.; Zhou, Y.; Wang, J. *Chem. - Eur. J.* **2015**, *21*, 9003−9007. (f) Lu, Z.; Wang, J.; Han, B.; Li, S.; Zhou, Y.; Fan, B. *Adv. Synth. Catal.* **2015**, *357*, 3121−3125. (g) Zhou, H.; Li, J.; Yang, H.; Xia, C.; Jiang, G. *Org. Lett.* **2015**, *17*, 4628−4631.

(12) (a) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2002**, *4*, 2703−2705. (b) Arrayas, R. G.; Cabrera, S. J.; Carretero, C. *Org. Lett.* **2005**, *7*, 219−221. (c) Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 3734−3736. (d) Zhang, W.; Zhu, S.-F.; Qiao, X.-C.; Zhou, Q.-L. *Chem. - Asian J.* **2008**, *3*, 2105−2111. (e) Millet, R.; Bernardez, T.; Palais, L.; Alexakis, A. *Tetrahedron Lett.* **2009**, *50*, 3474−3477. (f) Millet, R.; Gremaud, L.; Bernardez, T.; Palais, L.; Alexakis, A. *Synthesis* **2009**, *2009*, 2101−2112. (g) Bos, P. H.; Rudolph, A.; Pérez, M.; Fañanás-Mastral, M.; Harutyunyan, S. R.; Feringa, B. L. *Chem. Commun.* **2012**, *48*, 1748−1750.

(13) (a) Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194−2196. (b) Cho, Y.-H.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837−6846. (c) Nishimura, T.; Tsurumaki, E.; Kawamoto, T.; Guo, X.-X.; Hayashi, T. *Org. Lett.* **2008**, *10*, 4057−4060. (d) Tsui, G. C.; Lautens, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 5400−5404. (e) Zhu, J.; Tsui, G. C.; Lautens, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 12353−12356. (f) Tsui, G. C.; Ninnemann, N. M.; Hosotani, A.; Lautens, M. *Org. Lett.* **2013**, *15*, 1064−1067. (g) Zhang, L.; Le, C. M.; Lautens, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 5951−5954.

(14) (a) Sawama, Y.; Kawamoto, K.; Satake, H.; Krause, N.; Kita, Y. *Synlett* **2010**, *2010*, 2151−2155. (b) Huang, Y.; Ma, C.; Lee, Y.; Huang, R.-Z.; Zhao, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 13696−13700.

(15) (a) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834−6839. (b) Luo, Y.; Gutierrez-Bonet, Á.; Matsui, J. K.; Rotella, M. E.; Dykstra, R.; Gutierrez, O.; Molander, G. A. *ACS Catal.* **2019**, *9*, 8835−8842.

(16) (a) Deng, Y.; Yang, W.; Yao, Y.; Yang, X.; Zuo, X.; Yang, D. *Org. Biomol. Chem.* **2019**, *17*, 703−711. (b) Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 3734−3736.

(17) For selected reviews, see: (a) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 48−57. (b) Mohr, J.; Oestreich, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 12148−12149 For selected reports, see:. (c) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746−15749. (d) Yang, Y.; Shi, S.-S.; Niu, D.-W.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62−66. (e) Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 15620−15623. (f) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10830−10834. (g) Xi, Y.; Butcher, T. W.; Zhang, J.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 776−780.

(18) Saxena, A.; Choi, B.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 8428−8431.

(19) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016**, *353*, 144−150.

(20) (a) Tsai, E. Y.; Liu, R. Y.; Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018**, *140*, 2007−2011. (b) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440−14441.
(21) (a) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292−1297. (b) Deschamp, J.; Riant, O. *Org. Lett.* **2009**, *11*, 1217−1220. (c) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225−4228. (d) Lipshutz, B. H.; Amorelli, B.; Unger, J. B. *J. Am. Chem. Soc.* **2008**, *130*, 14378−14379.
(22) (a) Li, C.; Liu, R. Y.; Jesikiewicz, L. T.; Yang, Y.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2019**, *141*, 5062−5070. (b) Fu, B.; Yuan, X.; Li, Y.; Wang, Y.; Zhang, Q.; Xiong, T.; Zhang, Q. *Org. Lett.* **2019**, *21*, 3576−3580. (c) Li, C.; Shin, K. R.; Liu, Y.; Buchwald, S. L. *Angew. Chem.* **2019**, *131*, 17230−17236. (d) Feng, J.-J.; Xu, Y.; Oestreich, M. *Chem. Sci.* **2019**, *10*, 9679−9683.
(23) See the Supporting Information for detailed DFT calculations.
(24) Li, D.; Park, Y.; Yoon, W.; Yun, H.; Yun, J. *Org. Lett.* **2019**, *21*, 9699−9703.
(25) (a) Sellars, D. J.; Steel, P. G. *Eur. J. Org. Chem.* **2007**, *2007*, 3815−3828. (b) Kaithal, A.; van Bonn, P.; Hölscher, M.; Leitner, W. *Angew. Chem., Int. Ed.* **2020**, *59*, 215−220. (c) Li, H.; Wang, Y.; Lai, Z.; Huang, K.-W. *ACS Catal.* **2017**, *7*, 4446−4450. (d) Makowski, P.; Demir Cakan, R.; Antonietti, M.; Goettmann, F.; Titirici, M.-M. *Chem. Commun.* **2008**, 999−1001. (e) Kisic, A.; Stephan, M.; Mohar, B. *Adv. Synth. Catal.* **2015**, *357*, 2540−2546.
(26) Jaouen, G.; Meyer, A. *J. Am. Chem. Soc.* **1975**, *97*, 4667−4672.

https://dx.doi.org/10.1021/acs.orglett.0c02829
Org. Lett. XXXX, XXX, XXX−XXX