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Synthesis of Spirocyclic Ethers Via Enantioselective Copper-Catalyzed Carboetherification of Alkenols**

Shuklendu D. Karyakarte, Chanchamnan Um, Ilyas A. Berhane and Sherry R. Chemler*

Abstract: Spirocyclic ethers can be found in bioactive compounds. This copper-catalyzed enantioselective alkene carboetherification provides 5,5-, 5,6- and 6,6-spirocyclic products containing fully substituted chiral carbons with up to 99% enantiomeric excess. This reaction features formation of two rings from acyclic substrates, 1,1-disubstituted alkenols functionalized with arenes, alkenes or alkynes and clearly constitutes a powerful way to synthesize chiral spirocyclic ethers.

Spirocyclic ethers are frequently found in bioactive small molecules including those exhibiting anti-viral,[1] antibiotic[2], anti-fungal,[3] anti-cancer[4] and analgesic activity (Figure 1).[5] Spirocycles are attractive scaffolds for medicinal chemistry as they allow precise placement of functional groups in three-dimensional space.[6]

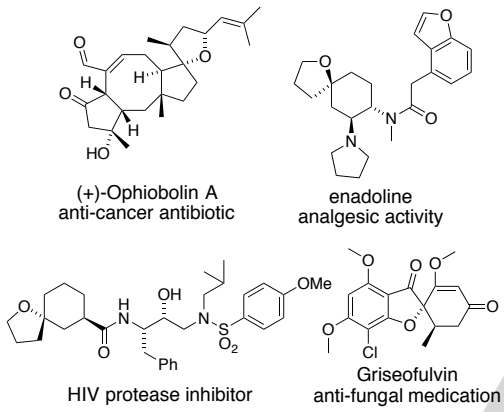
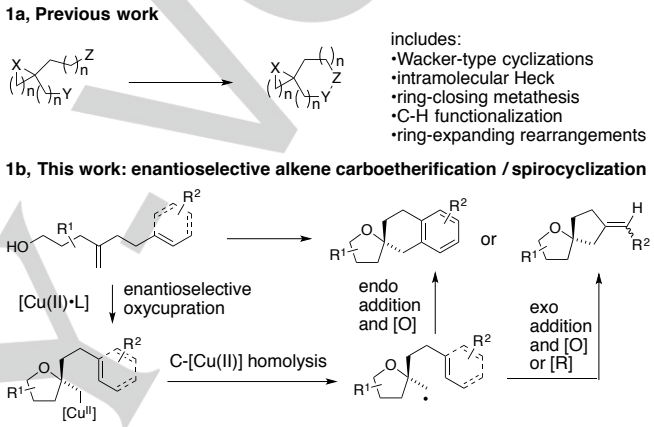


Figure 1. Bioactive spirocyclic ethers.

The attractive biological features of spirocyclic ethers have inspired the development of a number of strategies for their efficient synthesis,[6a, 7] including methods reliant on asymmetric catalysis as an efficient way to introduce chirality.[8] A common strategy for spirocycle synthesis involves cyclization of the ends of two substituents on a fully-substituted carbon that is already embedded in a ring (Scheme 1a).[7g,8a,8b,8d,8e] Aside from spiroketals, which can be made by intramolecular addition of two alcohols to a ketone,[8d] rarely are both rings of the spirocyclic ether formed in the same step,[7b, 9] and de novo formation of both rings of the spirocyclic ether with concomitant control of absolute stereochemistry at the quaternary carbon is even more rare.[10] The spirocyclic ether synthesis strategy disclosed herein enables the enantioselective doubly intramolecular 1,2-difunctionalization of unactivated 1,1-disubstituted alkenes using a copper-catalyzed alkene carboetherification (Scheme 1b). This strategy forms both rings of the spirocyclic ether in one step and forms the fully substituted tertiary ether carbon with control of absolute stereochemistry, thus expanding the repertoire of strategies available to the synthetic and medicinal chemist.



Scheme 1. Spirocycle synthesis strategy.

We have previously reported the synthesis of bicyclic fused-ring and bridged-ring ethers as well as monocyclic tetrahydrofurans using copper(II)-catalyzed alkene carboetherification.[11] The present methodology examines the much less studied reactions of 1,1-disubstituted alkenes, whose enantioselective carboetherifications produce enantiomerically enriched fully-substituted chiral carbons and new rings connected in a spirocycle (Scheme 1). The enantioselective alkene carboetherification strategy has been explored by our group[11b] and others[12] for the synthesis of chiral oxygen heterocycles. We hypothesized that the 1,1-disubstituted alkenols would undergo enantioselective *cis*-oxycupration with the chiral [Cu(II)] catalyst and that the resulting C-[Cu(II)] bond would homolyze to produce a carbon radical intermediate (Scheme 1b). Addition of the intermediate to its pendant unsaturated carbon would then produce the desired spirocycle via either *endo* or *exo* cyclization and subsequent oxidation or reduction of the resulting carbon radical (Scheme 1b). Herein is disclosed the results of this study.

The majority of the 1,1-disubstituted alkenols investigated were synthesized via a Mannich / Claisen / nucleophilic addition route (see Supporting Information).[13] The copper(II)-catalyzed oxidative cyclization of 1,1-disubstituted alkenol **1a** was first investigated (Table 1). In the event, we found that 1,1-disubstituted alkenol **1a** could readily undergo the desired alkene difunctionalization/oxidative cyclization to form racemic spirocyclic ether **2a** using catalytic $Cu(OTf)_2$ in the presence of

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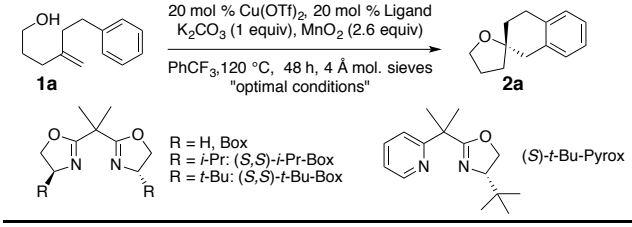
an unsubstituted, achiral bis(oxazoline) ligand, K_2CO_3, and MnO_2 as the stoichiometric oxidant, in $PhCF_3$ at 120 °C (Table 1, entry 1).[11b] The observed product **2a** is the result of formal *endo* addition of the presumed carbon radical (Scheme 1) onto the pendant phenyl (as opposed to *ipso* addition). This carboetherification reaction was optimized for efficiency, isolated yield and enantioselectivity by varying ligand structure, catalyst and ligand loading, solvent and reaction time (Table 1). The use of the (*S,S*)-*t*-Bu-Box ligand in $PhCF_3$ proved critical to obtaining spirocycle **2a** with respectable enantioselectivity (Table 1, entries 3, 5 and 7). Toluene was not used due to the potential for H-atom abstraction side reactivity.[14] While a catalyst loading of 20 mol% $Cu(OTf)_2$ proved efficient (Table 1, entry 5, optimal conditions), reducing the loading to 15 mol % diminished the isolated yield (Table 1, entry 7). Conducting the reaction for 48 h rather than 24 h maximized isolated yield (compare entries 3 and 5, Table 1).

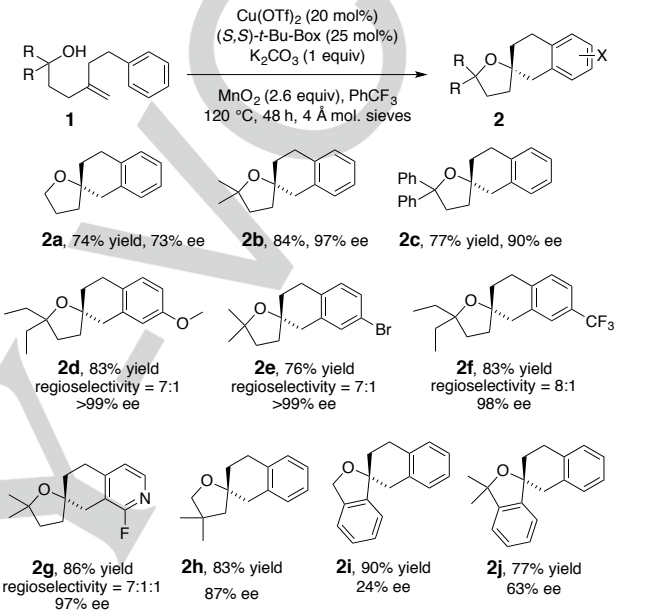
Table 1. Optimization of the enantioselective carboetherification.



Entry[a]	Ligand	Variation from optimal conditions	Yield (%)[b]	ee (%)[c]
1	Box	30 mol% [Cu], 35 mol% ligand, 24 h	46	—
2	(*S,S*)-*i*-Pr-Box	24 h	60	<5
3	(*S,S*)-*t*-Bu-Box	24 h	60	67
4	(*S,S*)-*t*-Bu-Box	1,2-dichloroethane, 105 °C	57	47
5	(*S,S*)-*t*-Bu-Box	None	74	73
6	(*S*)-*t*-Bu-Pyrox	None	79	<5
7	(*S,S*)-*t*-Bu-Box	15 mol % [Cu], 18 mol % ligand	46	76

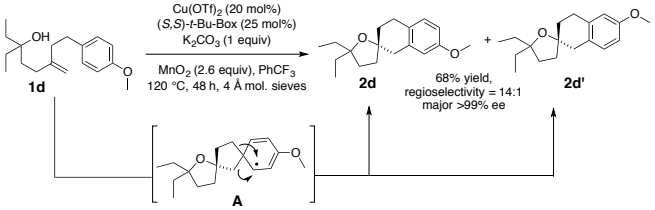
[a] Optimal conditions: Reaction was run on 0.13 mmol scale **1a** with 20 mol% $Cu(OTf)_2$ and 25 mol% Ligand, 260 mol % MnO_2 (85%, <5 μ), 100 mol % K_2CO_3, 4 Å mol. sieves (flame-dried, 20 mg/mL) in $PhCF_3$ at 120 °C for 48 h unless otherwise noted. [b] Isolated yield after flash chromatography on SiO_2. [c] Enantioselectivity measured by chiral GC analysis (CP-Chirasil-Dex CB column).

The reactivity and selectivity of a range of 1,1-disubstituted alkenols were examined in this enantioselective carboetherification reaction (Scheme 3). In general, tertiary alcohol substrates such as **1b** react with higher enantioselectivity than primary alcohol substrates such as **1a**. Increasing backbone substitution, however, did provide increased enantioselectivity for the primary alcohol substrate leading to **2h**. Functional groups on the arene, such as Br, OMe and CF_3 were compatible, and a 2-fluoropyridyl substrate also underwent productive spirocyclization to give **2g**. Minor regioisomers were observed with *para*-substituted substrates (*vide infra*, Scheme 4). Spirophthalanes **2i** and **2j** could also be formed using this alkene carboetherification (Scheme 1). Unfortunately, neither spirophthalane was formed in high enantioselectivity, but the tertiary ether substrate reacted more selectively. In the case of the primary benzylic alcohol substrate leading to **2i**, Ag_2CO_3 was used as terminal oxidant as it proved milder than MnO_2, where oxidation of the benzylic alcohol to its corresponding benzaldehyde was competitive.



Scheme 3. Scope of the enantioselective carboetherification. Conditions from Table 1, entry 5 were used. In the reaction leading to **2i**, Ag_2CO_3 was used as oxidant instead of MnO_2.

The reaction of **1d** was run on 1.8 mmol scale. The minor isomer **2d'**, isolated as a mixture with **2d**, appears to be the result of *exo* (*ipso*) addition to the arene followed by rearrangement and rearomatization (Scheme 4).[15]



Scheme 4. Scale-up (1.8 mmol **1d**) and regioisomer rationale.

In addition to aryl ring radical acceptors, the alkenols **3** and the alkynol **5** were examined (Scheme 5). In both cases, 5-exo cyclization was favored over 6-endo cyclization. Alkenol **3a** formed oxaspiro[4.4]nonane **4a** both in the presence and absence of H-atom donor 1,4-cyclohexadiene, indicating that oxidation of the intermediate benzylic radical to the alkene is faster than H-atom transfer. In the case of alkynol **5**, a vinyl radical is the projected intermediate (not shown). While formation of a vinyl copper(II) and subsequent protonation to

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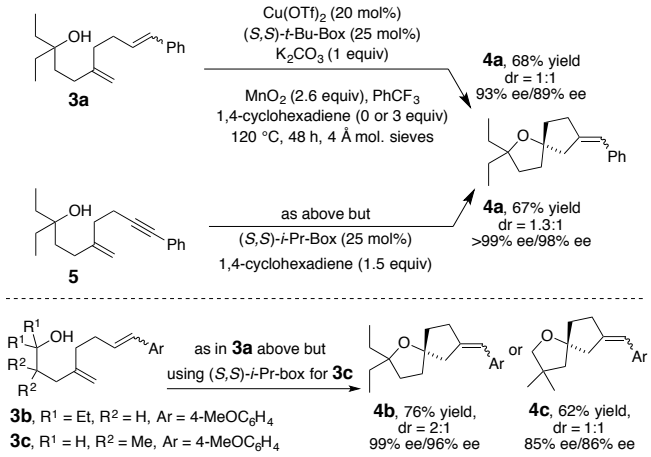
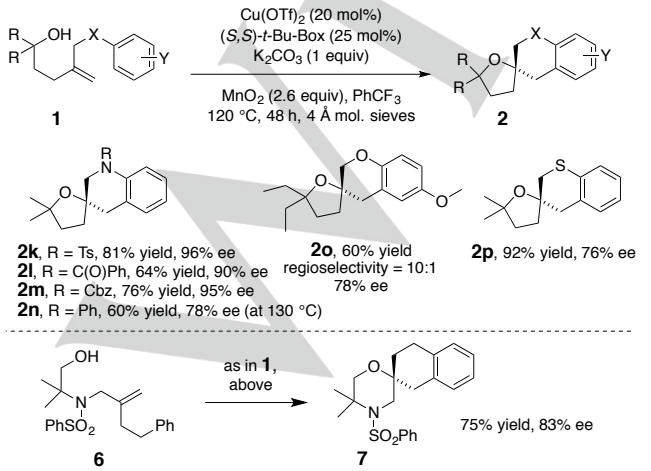
give **4a** is possible, it was noted that a more complex reaction mixture was obtained when 1,4-cyclohexadiene was omitted, indicating H-atom transfer to the vinyl radical could be a major pathway to the formation of **4a**. Similarly, cyclization of alkenols **3b** and **3c** led to oxaspiro[4.4]nonanes **4b** and **4c**, respectively. In the case of **3c**, the isolated yield was higher when the less hindered (*S,S*)-*i*-Pr-box ligand was used (62% versus 35% when (*S,S*)-*t*-Bu-box was used). Substrate **3d** (R^1 = R^2 = H, not shown) did not give the desired spirocycle in this reaction.



Scheme 5. Substrates with pendant alkenes and alkyne.

When an ether, amine or thioether (the X group on **1**) links the alkenol to the arene, an additional heterocycle is formed upon cyclization (Scheme 6). In these reactions, the nature of the heteroatom, X, was observed to have an impact on the enantioselectivity. Specifically, for products **2k**-**2p** it appears electron-deficient allylic X groups like NTs, NC(O)Ph and NCbz give higher levels of enantioinduction than more electron-rich allylic X groups like NPh, O and S. It is possible the more electron-rich groups can coordinate, to some extent, with the [Cu] center in the transition state leading to a change in relative transition state (major versus minor enantiomer) energy. Such spirocyclic bis-heterocycles have enjoyed significant interest in pharmaceutical applications.[16]

The synthesis of a spirocyclic morpholine, where the additional heteroatom resides in the cyclic ether ring, is also possible as demonstrated in the conversion of **6** to **7** (Scheme 6). This example also illustrates the possibility of 6-membered ring formation in the initial cyclization step to form a 6,6-spirocycle.



Scheme 6. Conditions from Table 1, entry 5 were used unless otherwise noted. The reaction to give **2o** was run using (*S,S*)-*i*-Pr-Box instead of (*S,S*)-*t*-Bu-Box.

The absolute configuration of **2k** was assigned (*S*) by X-ray crystallography (Figure 2). The *S*-enantiomer is consistent with major transition state **A**.[11b] All other 5,6-spirocyclic products were assigned analogous absolute stereochemistry although group priorities dictate if they are designated *R* or *S*. An X-ray structure of **7** was obtained to assign its configuration as *R* (see Supporting Information).

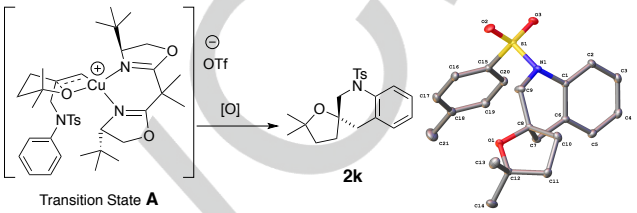
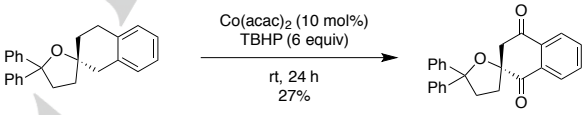


Figure 2. Proposed transition state consistent with the crystal structure of **2k**.

Further functionalization of spirocycle **2c** was performed by benzylic C-H oxidation with $Co(acac)_2$ in the presence of *tert*-butylhydroperoxide (TBHP) (Eq. 1). Oxidation of **2c**, **2h** and **2j** (see Supporting Information for **2h** and **2j**) were required to measure enantiomeric excess as we were unable to separate the enantiomers using a number of chiral HPLC columns.



(1)

In summary, a new catalytic enantioselective route to spirocyclic ethers from acyclic alkenols has been developed. Key features involve good functional group compatibility, the installation of a fully substituted chiral carbon, direct C-H functionalization of arenes with good levels of regioselectivity and the synthesis of both spirocyclic tetrahydrofurans and spirophthalanes. While aryl-substituted alkenols favor formation of the net *endo* addition product, to give 5,6- and 6,6-spirocycles, alkenyl and alkynyl-substituted alkenols favor formation of the *exo* addition product and provide the 5,5-spirocycles. Given the significant interest in bioactive spirocyclic ether compounds, it is possible this method will find use in drug discovery endeavors.

Acknowledgements

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Keywords: copper • catalysis • spirocycle • enantioselective • alkenol

[1] A. K. Ghosh, D. Shin, L. Swanson, K. Krishnan, H. Cho, K. A. Hussain, D. E. Walters, L. Holland, J. Buthod, *IL Farmaco* **2001**, *56*, 29-32.

[2] I. A. Katsoulis, G. Kythreoti, A. Papakyriakou, K. Koltsida, P. Anastasopoulou, C. I. Stathakis, I. Mavridis, T. Cottin, E. Saridakis, D. Vourloumis, *ChemBioChem* **2011**, *12*, 1188-1192.

[3] D. W. Anderson, *Annals of Allergy* **1965**, *23*, 103.

[4] N. Noguchi, M. Nakada, *Org. Lett.* **2006**, *8*, 2039-2042.

[5] P. R. Halfpenny, D. C. Horwell, J. Hughes, J. C. Hunter, D. C. Rees, *J. Med. Chem.* **1990**, *33*, 286-291.

[6] a) S. Kumar, P. D. Thornton, T. O. Painter, P. Jain, J. Downard, J. T. Douglas, C. Santini, *J. Org. Chem.* **2013**, *78*, 6529-6539; b) Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. & Med. Chem. Lett.* **2014**, *24*, 3673-3682.

[7] a) M.-E. Sinibaldi, I. Canet, *Eur. J. Org. Chem.* **2008**, 4391-4399; b) F. Alonso, B. Dacunha, J. Melendez, M. Yus, *Tetrahedron* **2005**, *61*, 3437-3450; c) T. Xu, N. A. Savage, G. Dong, *Angew. Chem. Int. Ed.* **2014**, *53*, 1891-1895; d) K. Itami, A. Palmgren, J. E. Backvall, *Tetrahedron Lett.* **1998**, *39*, 1223-1226; e) L. I. Palmer, J. R. de Alaniz, *Org. Lett.* **2013**, 476-479; f) N. Noto, T. Koike, M. Akita, *J. Org. Chem.* **2016**, *81*, 7064-7071; g) S. Rosenberg, R. Leino, *Synthesis* **2009**, 2651-2673.

[8] a) A. K. Franz, N. V. Hanhan, N. R. Ball-Jones, *ACS Catalysis* **2013**, *3*, 540-553; b) R. Rios, *Chem. Soc. Rev.* **2012**, *41*, 1060-1074; c) Z.-W. Jiao, S.-Y. Zhang, C. He, Y.-Q. Tu, S.-H. Wang, F.-M. Zhang, Y.-Q. Zhang, H. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 8811-8815; d) J. A. Palmes, A. Aponick, *Synthesis* **2012**, *44*, 3699-3721; e) N. R. Ball-Jones, J. J. Badillo, N. T. Tran, A. K. Franz, *Angew. Chem. Int. Ed.* **2014**, *53*, 9462-9465; f) J. Xie, J. Wang, G. Dong, *Org. Lett.* **2017**, *19*, 3017-3020.

[9] a) R. Grigg, V. Sridharan, *Tetrahedron Lett.* **1993**, *34*, 7471-7474; b) H. Yoon, M. Rolz, F. Landau, M. Lautens, *Angew. Chem. Int. Ed.* **2017**, *56*, 10920-10923. c) D. Lankri, Y. Mostinski, D. Tsvelikhovsky, *J. Org. Chem.* **2017**, *82*, 9452-9463.

[10] T. Shibata, Y.-k. Tahara, K. Tamura, K. Endo, *J. Am. Chem. Soc.* **2008**, *130*, 3451-3457.

[11] a) Y. Miller, L. Miao, A. S. Hosseini, S. R. Chemler, *J. Am. Chem. Soc.* **2012**, *134*, 12149-12156; b) M. T. Bovino, T. W. Liwosz, N. E. Kendel, Y. Miller, N. Tyminska, E. Zurek, S. R. Chemler, *Angew. Chem. Int. Ed.* **2014**, *53*, 6383-6387.

[12] a) B. A. Hopkins, Z. J. Garlets, J. P. Wolfe, *Angew. Chem. Int. Ed.* **2015**, *54*, 13390-13392; b) R. Zhu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 12655-12658; c) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 8069-8077; d) N. Hu, K. Li, Z. Wang, W. Tang, *Angew. Chem. Int. Ed.* **2016**, *55*, 5044-5048; e) G. M. Borrajo-Calleja, V. Bizet, C. Mazet, *J. Am. Chem. Soc.* **2016**, *138*, 4014-4017; f) Y. F. Cheng, X. Y. Dong, Q. S. Gu, Z. L. Yu, X. Y. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 8883-8886.

[13] K. Basu, J. Richards, L. A. Paquette, *Synthesis* **2004**, 2841-2844.

[14] W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948-12949.

[15] L. Miao, I. Haque, M. R. Manzoni, W. S. Tham, S. R. Chemler, *Org. Lett.* **2010**, *12*, 4739-4741.

[16] a) R. J. Hargreaves, N. M. Rupniak, *Use of a NK-1 receptor antagonist for treating or preventing abnormal bone resorption,* 2000, WO 2000007598 A1; b) Y. Zhang, S. T. Waddell, T. Yu, J. A. McCauley, A. Stamford, *Spirocyclic quinolizine derivatives useful as HIV integrase inhibitors,* 2017, WO 2017106071; c) R. Munakata, M. Inoue, H. Tominaga, S. Yamasaki, Y. Shiina, K. Samizu, H. Hamaguchi, L. Hong, *Chromane compounds as BACE inhibitors and their preparation,* 2013, WO 2013181202; c) C. Almansa-Rosales, C. Alegret-Molina, *Preparation of oxa-azaspiro compounds having activity against pain*, 2017, WO 2017067663A1.

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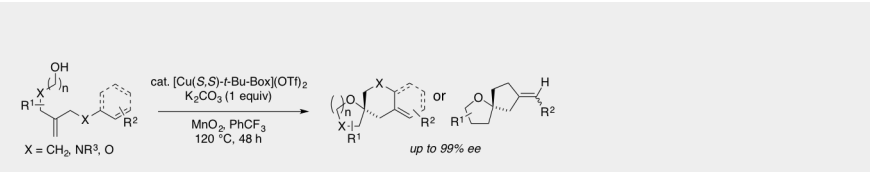

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A copper-catalyzed enantioselective alkene carboetherification that provides 5,5-, 5,6-, and 6,6-spirocyclic products containing fully substituted chiral carbons with up to 99% enantiomeric excess is disclosed. This reaction features formation of two rings from acyclic 1,1-disubstituted alkenols functionalized with arenes, alkenes or alkynes and is a powerful approach to the synthesis of chiral spirocyclic ethers.