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Synthesis of Spirocyclic Ethers by Enantioselective Copper-Catalyzed Carboetherification of Alkenols

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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 carbon centers with up to 99% enantiomeric excess. This reaction features the formation of two rings from acyclic substrates, 1,1-disubstituted alkenols functionalized with either arenes, alkenes, or alkynes, and clearly constitutes a powerful way to synthesize chiral spirocyclic ethers.

Keywords

copper; cyclizations; enantioselectivity; spiro-compounds; synthetic methods

Spirocyclic ethers are frequently found in bioactive small molecules including those exhibiting antiviral,^[1] antibiotic,^[2] antifungal,^[3] anticancer,^[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]

The attractive biological features of spirocyclic ethers have inspired the development of a number of strategies for their efficient syntheses,^[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 center that is already embedded in a ring (Scheme 1a).^[7g, 8a, b, d, e] 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 center is even more rare.^[10] The spirocyclic ether synthesis strategy disclosed herein enables the enantioselective double 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

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Conflict of interest

The authors declare no conflict of interest.

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one step and forms the fully substituted tertiary ether carbon center with control of absolute stereochemistry, thus expanding the repertoire of strategies available to the synthetic and medicinal chemist.

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 carbon centers 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 center would then produce the desired spirocycle by either *endo* or *exo* cyclization and subsequent oxidation or reduction of the resulting carbon radical (Scheme 1b). Herein disclosed are the results of this study.

The majority of the 1,1-disubstituted alkenols investigated were synthesized by a Mannich/Claisen/nucleophilic addition route (see the Supporting Information).^[13] The copper(II)-catalyzed oxidative cyclization of the 1,1-disubstituted alkenol **1a** was first investigated (Table 1). In the event, we found that **1a** could readily undergo the desired alkene difunctionalization/oxidative cyclization to form the racemic spirocyclic ether **2a** using catalytic Cu(OTf)₂ in the presence of an unsubstituted, achiral bis(oxazoline) ligand, K₂CO₃, and MnO₂ as the stoichiometric oxidant, in PhCF₃ at 120 °C (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, 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 PhCF₃ proved critical to obtaining **2a** with respectable enantioselectivity (entries 3, 5, and 7). Toluene was not used because of the potential for H-atom abstraction side reactivity.^[14] While a catalyst loading of 20 mol% Cu(OTf)₂ proved efficient (entry 5; optimal reaction conditions), reducing the loading to 15 mol% diminished the yield of the isolated product (entry 7). Conducting the reaction for 48 hours rather than 24 hours maximized the yield (compare entries 3 and 5).

The reactivity and selectivity of a range of 1,1-disubstituted alkenols were examined in this enantioselective carboetherification reaction (Scheme 2). In general, tertiary alcohol substrates such as **1b–g** 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 CF₃ were compatible, and a 2-fluoropyridyl substrate also underwent productive spirocyclization to give **2g**. Minor regioisomers were observed with *para*-substituted substrates (see Scheme 3). The spirophthalanes **2i** and **2j** were also formed using this alkene carboetherification (Scheme 2). 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**, Ag₂CO₃ was used as terminal oxidant as it proved milder than MnO₂, where oxidation of the benzylic alcohol to its corresponding benzaldehyde was competitive.

The reaction of **1d** was run on 1.8 mmol scale (Scheme 3). 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.^[15]

In addition to aryl ring radical acceptors, the alkenols **3** and the alkynol **5** were examined (Scheme 4). In both cases, 5-*exo* cyclization was favored over 6-*endo* cyclization. The alkenol **3a** formed the oxaspiro[4.4]nonane **4a** both in the presence and absence of the 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 **5**, a vinyl radical is the projected intermediate (not shown). While formation of a vinyl copper(II) and subsequent protonation to 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 the alkenols **3b** and **3c** led to oxaspiro[4.4]nonanes **4b** and **4c**, respectively. In the case of **3c**, the yield of the isolated product was higher when the less hindered (*S,S*)-*t*Pr-box ligand was used (62% versus 35% when (*S,S*)-*t*Bu-box was used). The substrate **3d** (R¹=R²=H, not shown) did not give the desired spirocycle in this reaction.

When either an ether, amine, or thioether (the X group on **1**) links the alkenol to the arene, an additional heterocycle is formed upon cyclization (Scheme 5). In these reactions, the nature of the heteroatom X was observed to have an impact on the enantioselectivity. Specifically, for products **2k–p** 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** into **7** (Scheme 5). This example also illustrates the possibility of six-membered ring formation in the initial cyclization step to form a 6,6-spirocycle.

The absolute configuration of **2k** was assigned *S* by X-ray crystallography (Figure 2).^[17] 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 the Supporting Information).^[17]

Further functionalization of the spirocycle **2c** was performed by benzylic C—H oxidation with Co(acac)₂ in the presence of *tert*-butylhydroperoxide (TBHP) [Eq. (1); acac=acetylacetonate]. Oxidation of **2c**, **2h**, and **2j** (see the Supporting Information for **2h**

and **2j**) were required to measure enantiomeric excess as we were unable to separate the enantiomers even after using a number of chiral-phase 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 center, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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- [17]. CCDC 1572209 and 1858280 (**2k**, **7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Figure 2.
Proposed transition state consistent with the crystal structure of **2k**.^[17]

a) Previous work

includes:

- Wacker-type cyclizations
- intramolecular Heck
- ring-closing metathesis
- C-H functionalization
- ring-expanding rearrangements

b) This work: enantioselective alkene carboetherification / spirocyclization

Scheme 1.
Spirocycle synthesis strategy.

Scheme 2.

Scope of the enantioselective carboetherification. Reaction conditions from Table 1, entry 5 were used. In the reaction leading to **2i**, Ag₂CO₃ was used as oxidant instead of MnO₂.

Scheme 3.

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

Scheme 4.

Substrates with pendant alkenes and alkyne.

Scheme 5.

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. Cbz=benzyloxycarbonyl, Ts=4-toluenesulfonyl.

Table 1:

Optimization of the enantioselective carboetherification.

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

^[a]Optimal reaction conditions: Reaction was run on 0.13 mmol scale **1a** with 20 mol% Cu(OTf)₂ and 25 mol% ligand, 260 mol% MnO₂ (85%, <5 μ), 100 mol% K₂CO₃, and 4 Å mol. sieves (flame-dried, 20 mgmL⁻¹) in PhCF₃ at 120°C for 48 h unless otherwise noted.

^[b]Yield of product isolated after flash chromatography on SiO₂.

^[c]Enantioselectivity measured by chiral-phase GC analysis (CP-Chirasil-Dex CB column). Tf=trifluoromethanesulfonyl.