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Copper-Catalyzed Enantioselective Synthesis of Bridged Bicyclic Ketals from 1,1-Disubstituted-4-methylene-1,6-hexanediols and Related Alkenols

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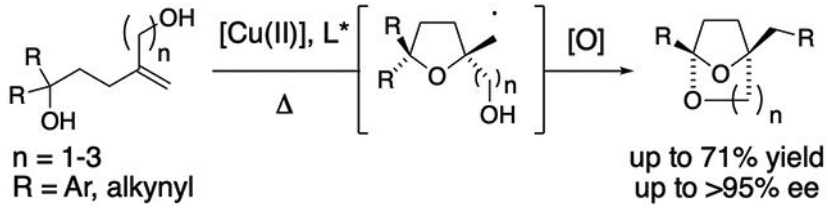
Abstract

Bridged bicyclic ketals display a range of bioactivities. Their catalytic enantioselective synthesis from achiral, acyclic 1,1-disubstituted alkene diols is disclosed. This reaction combines asymmetric catalysis with a distal radical migration. Alkynes and arenes undergo the group transfer. Product distribution depends on substrate and conditions and informs mechanistic analysis.

Graphical Abstract



Bicyclic ketals via copper-catalyzed enantioselective bis(cyclization) involving radical group transfer is disclosed.

Bridged bicyclic ketals (e.g. those in Figure 1) are rigid organic structures composed of saturated cyclic ethers that can place substituents in precise relative locations in three dimensions.[1] Bridged bicyclic ketal natural products include the zaragozic acids, a class of squalene synthesis inhibitors,[2] and the saliniketals, which have demonstrated inhibition of ornithine decarboxylase induction.[3] A bridged bicyclic ketal that inhibits sodium-dependent glucose cotransporter 2 has been developed to treat type 2 diabetes (e.g. Steglatro).[4] An alkyne-substituted bridged bicyclic ketal has demonstrated cytotoxicity toward leukemia cells.[5]

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/d0cc06404a

Conflicts of interest
There are no conflicts to declare.

Microbial production is a common route to complex bridged bicyclic ketals.[6–7] Considerable effort has also been put toward their de novo chemical synthesis.[1] A ketal stereocenter is frequently created via cyclization of two pendant alcohols onto a ketone, where the lowest energy diastereomer is typically favored.[1] The acid-catalyzed addition of an alcohol to an enol ether is a related approach.[8] Transition metal-catalyzed [including (Pt),[9] (Ag)[10] and (Au)[11]] additions of alcohols, carbonyls or carbenes [catalyzed by (Rh)[12]] to alkynes have also been applied.[1]

In recent years, excellent progress has also been made toward the catalytic enantioselective synthesis of spirocyclic ketals.[13–16] The catalytic enantioselective synthesis of bridged bicyclic ketals is less common, and all such methods reported to date involve catalytic enantioselective conjugate addition of various nucleophiles to enones, followed by diastereoselective addition of pendant alcohols to the resident carbonyl (Scheme 1a). Along these lines, Shi and co-workers have reported a [Pd]-catalyzed method.[17] Liu and co-workers have reported a Bronsted acid catalyzed method.[18] Related organocatalytic methods have been reported independently by Pan,[19] Jorgensen,[20] and Franzen.[21] A copper-catalyzed cyclization of a ketone onto an alkene in the presence of DMSO for the synthesis of (±)-benzobicyclo[3.2.1]octanes has also been disclosed.[22]

We report herein a strategy for the enantioselective synthesis of chiral bridged bicyclic spiroketals that involves a radical group transfer step (Scheme 1c). Radical migration reactions enable the scission and transfer of unsaturated carbon moieties within a molecule. A number of recent reports have highlighted the power of the distal radical migration strategy in organic synthesis (e.g. Scheme 1b).[23–26] Herein we report the first distal radical migration reaction to occur in the context of asymmetric catalysis.

In recent years, our group has established that enantioenriched tetrahydrofurans can be synthesized from copper-catalyzed carboetherifications of 4-pentenols.[27–30] Enantioselective *cis*-oxycupration across the alkene,[26] followed by in situ homolysis of the resulting C-Cu(II) bond is proposed to result in carbon radical formation (Scheme 1c and Scheme 4, *vide infra*). Subsequent C-C bond formation can occur via addition of the carbon radical to styrenes[28–29] or pendant arenes,[27, 30] which, in prior reports, underwent subsequent oxidation under the conditions to form higher substituted alkenes or arenes (net C-H functionalization). We have also shown that copper(II)-promoted oxyamination and dioxygenation can occur in the absence of π-bond radical group acceptors,[31] where the carbon-heteroatom bond formation is thought to occur via a Cu(III) intermediate and a Kharash-Sosnovsky type mechanism.[32–33] Although we anticipated 1,1-diphenyl-4-methylene-1,6-hexanediol (**1a**) would undergo the oxycupration step, it was unclear if the resulting radical intermediate would favor 1,4-phenyl transfer, followed by cyclization to form bridged bicyclic ketal **2a**, or a Cu(III)-facilitated dioxygenation to form bis(ether) **3a** (Table 1). In the event, we found that the reaction conditions and the substrate structure both impact the course of the reaction and subsequently, product formation (*vide infra*).

Various reaction conditions for the oxidative transformation of **1a** are presented in Table 1. Bridged bicyclic ketal **2a** is formed in 64% yield, >10:1 selectivity of **2a** over **3a**, in 92% ee, using 20 mol% $Cu(OTf)_2$ and 25 mol% of (*S,S*)-*t*-BuBox (**L2**) as catalyst, MnO_2 (2.6 equiv)

as oxidant, with K_2CO_3 and 4 Å mol. sieves as additives, in $PhCF_3$ at 120 °C for 60 h (Table 1, entry 1). The first indication of the major product's identity as a ketal was its distinctive ^{13}C NMR signal at 106 ppm.

A ligand effect on product ratio was observed: when the reaction was run using the achiral bis(oxazoline) ligand (**L1**), a 5:1 ratio of racemic ketal **2a** and bis(ether) **3a** was obtained in a combined 61% yield (entry 2). When (*S,S*)-*i*-Pr-Box (**L3**) was applied, a 4:1 mixture of **2a** and **3a** was observed where **2a** was formed in 57% ee (entry 3). Catalyst loading had a more significant impact on the ratio of products. Increased catalyst loading decreased the ratio of **2a**:**3a**, tending to form more **3a** as the loading increased (entries 6-8). At 60 mol % [Cu] loading, the ratio of products was close to 1:1. At 25 mol% [Cu] loading, using (*S,S*)-*t*-Bu-Box (**L2**), the ratio of **2a** to **3a** was 5:1; bis(ether) **3a** was isolated and its enantiomeric excess was measured at 86% (entry 6). Changing the oxidant to Ag_2CO_3 did not strongly impact the reaction while addition of $KMnO_4$ (10 mol%) increased the amount of bis(ether) **3a** produced (entries 10 and 11). While the reaction worked in both toluene and DCE (1,2-dichloroethane, entries 12 and 13), neither reaction was superior to the reaction in α,α,α-trifluorotoluene. $Cu(NTf_2)_2$ was tried as an alternative source but was found to give lower **2a**:**3a** selectivity for substrate **1a** (entry 14). The ratio of **2a** and **3a** is kinetically controlled; both products were re-subjected to the reaction conditions and were not observed to interconvert.

1,1-Diaryl-4-methylene-1,6-hexanediols bearing various aryl substituents were next examined in the enantioselective [3.2.1]-bridged bicyclic ketal synthesis (Table 2). While the parent 1,1-diphenyl substrate gave ketal **2a** in 64% yield and 92% ee, 4- and 3-toluyl analogs gave ketals **2b** and **2c** in moderate yields (40-42%) but good enantioselectivities (87% and 92%, respectively, Table 2, entries 2 and 3). The remainder of the mass was attributed to oxepanes **4**, formed via a competing S_N1 process enabled by presumably more stabilized benzylic carbocations. Under the standard conditions, oxepane **4e** was the predominant product (61% yield) with bis(4-methoxyphenyl) hexanediol **1e** as substrate (Table 2, entry 6). By changing the catalyst to $Cu(NTf)_2$, we were able to obtain ketal **2e** in a modest 40% isolated yield and in 70% ee (Table 2, entry 7). Substrates with electron-withdrawing substituents fared better in the ketal synthesis reaction. 4-Trifluoromethylphenyl, 4-chlorophenyl, 3-chlorophenyl and 4-sulfonamidophenyl substituted hexane diols underwent the cyclization in 52-73% yield and with 88-97% ee (entries 4, 8, 9 and 10). Reaction of the 4-trifluoromethylphenyl substituted hexane diol was performed on 1 mmol scale (entry 5). Surprisingly, a 4-phenylbenzene substrate gave ketal **2i** in 59% yield but with only 20% ee under standard conditions (entry 11). The enantioselectivity was improved to 56% ee by changing to the less sterically demanding (*S,S*)-*i*-Pr-Box ligand (**L3**) (entry 12). Ketal **2i** was crystalline and its X-ray structure enabled its rigorous structural assignment (see Supporting Information for details). Reaction of 4-methylene-1,1-diphenylheptane-1,7-diol, whose more substituted alcohol chain is more conformationally pre-disposed toward cyclization, led to the [4.2.1]-bridged bicyclic ketal **2j**, (entry 13).

1,1-Diynyl-4-methylene-1,6-hexane diols readily underwent the cyclization and group transfer process to provide bridged bicyclic ketals **2k** and **2l** in moderate yield and very good

enantioselectivity (Scheme 2). The absolute configuration of **2l** was assigned by X-ray crystallography.

1,1-Diaryl-4-methylene-1,5-pentane diols **1m** and **1n** were investigated for their ability to form [2.2.1]-bridged bicyclic ketals (Scheme 3). Surprisingly, the 1,1-diphenyl substrate **1n** exclusively formed spirooxetane **3m**.

Conversely, bis(biaryl) allylic alcohol **1n** provided the [2.2.1]-bicyclic ketal exclusively. Ketal **2n** was not stable under enantiomeric excess measurement conditions (chiral HPLC or GC) and oxetane **3m** is achiral, so the reaction with the achiral bis(oxazoline) **L1** is shown for these examples.

A mechanistic analysis is illustrated in Scheme 4. Complexation of the [Cu(II)] catalyst to the tertiary alcohol leads to intermediate **I**, which can enter the oxycupration **TS-A**, generating tetrahydrofuran **II** enantioselectively. In this transition state, the alkene terminal carbon approaches the copper *anti* to the *t*-Bu group on the nearest oxazoline ring.[28] Organocopper intermediate **II** undergoes C-[Cu(II)] homolysis to give the carbon radical **III**. Carbon radical **III** can undergo *ipso* aryl addition, to give **IV**, which undergoes subsequent C-C bond cleavage/group transfer to give the alkoxy-stabilized carbon radical **V**. Oxidation of **V** then gives oxonium ion **VI** and subsequent ketalization provides bicyclic ketal **2** (Scheme 4A). A potential path for diminished enantioselectivity is ring opening of carbon radical **III** to give alkoxy radical **VII**, which could cyclize to give a racemic tetrahydrofuranyl carbon radical (±)-**III** (Scheme 4B).[27] Alternatively, homolysis of the RO-[Cu(II)] bond of intermediate **I** could also give alkoxy radical **VII**. Substrates with resonance-donating aryl substituents (e.g. **1d**, R = Ph and **1e**, R = OMe, Scheme 4) give products **2d** and **2e** in lower enantioselectivity (Table 2) compared to substrates with neutral or electron-withdrawing substituents (e.g. **1a**, R = H, **1d**, R = CF_3, Scheme 4 and Table 2). Electron-donating arene substituents could lower the oxidation potential of the nearby alcohol.[34]

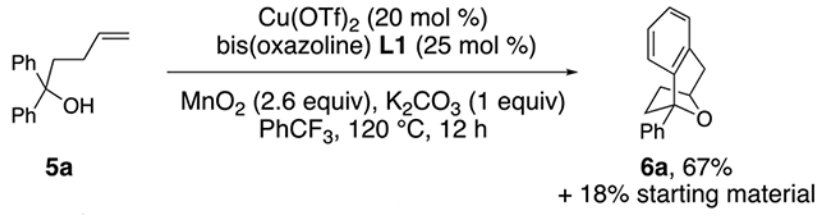
A route to bis(ether) **3a** involves carbon radical **III** combining with [Cu(II)] to give [Cu(III)] intermediate **VIII**. Coordination to the pendant alcohol then gives **IX**, and reductive elimination provides **3a**.[32–33] The rate of conversion of **VIII** to **IX** should increase with decreasing carbon tether length (forming 5- vs. 6-membered chelate) which could explain why allylic alcohol **1m** forms the bis(ether) **3m** (Scheme 3) while the homoallylic alcohol **1a** forms ketal **2a** (Tables 1 and 2).

That the bis(biaryl) allylic alcohol **1n** forms ketal **2n**, while the diphenyl allylic alcohol **1m** forms oxetane **3m** may be due to a faster rate of *ipso* addition to the phenyl-substituted arene, generating a more stabilized aryl radical intermediate.[25]

Substrates **5** that lack the second alcohol form bridged bicyclic [3.2.1] heterocycles **6**. Terminal alkene **5a** provides adduct **6a** in 67% yield (Eq. 1).[27] The 1,1-disubstituted alkene **5b**, differing from **5a** only in alkene substitution, provided adduct **6b** and 14% of ketone **7** (Eq. 2). Ketone **7** is likely formed via group transfer and subsequent hydrolysis of the resulting intermediate. The higher substitution of **5b** results in greater bond angle

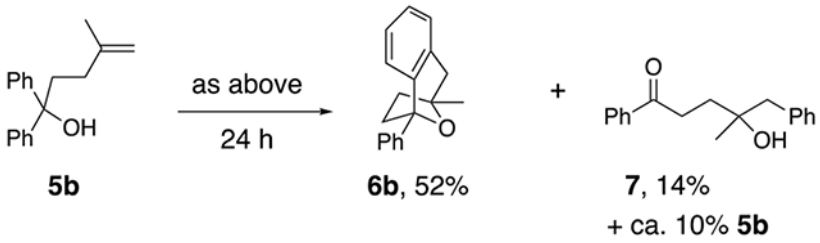
compression of its carbon radical intermediate, placing the radial closer to the arene *ipso* carbon, leading to **7**.

In conclusion, a new route to enantioenriched bridged bicyclic ketals from achiral, acyclic alkenols has been developed. The polar / radical cross-over mechanistic abilities of copper (II) catalysis enable both polar enantioselective alkene addition and radical-based group transfer reactivity. Some reactivity trends associated with radical stability have been identified; these observations can be used to guide new reaction design.



5a **6a**, 67% + 18% starting material

(1)



5b **6b**, 52% **7**, 14% + ca. 10% **5b**

(2)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Notes and references

Crystal structures of **2i** and **2l** have been deposited in the Cambridge Database, CCDC 2020673 and 1978089.

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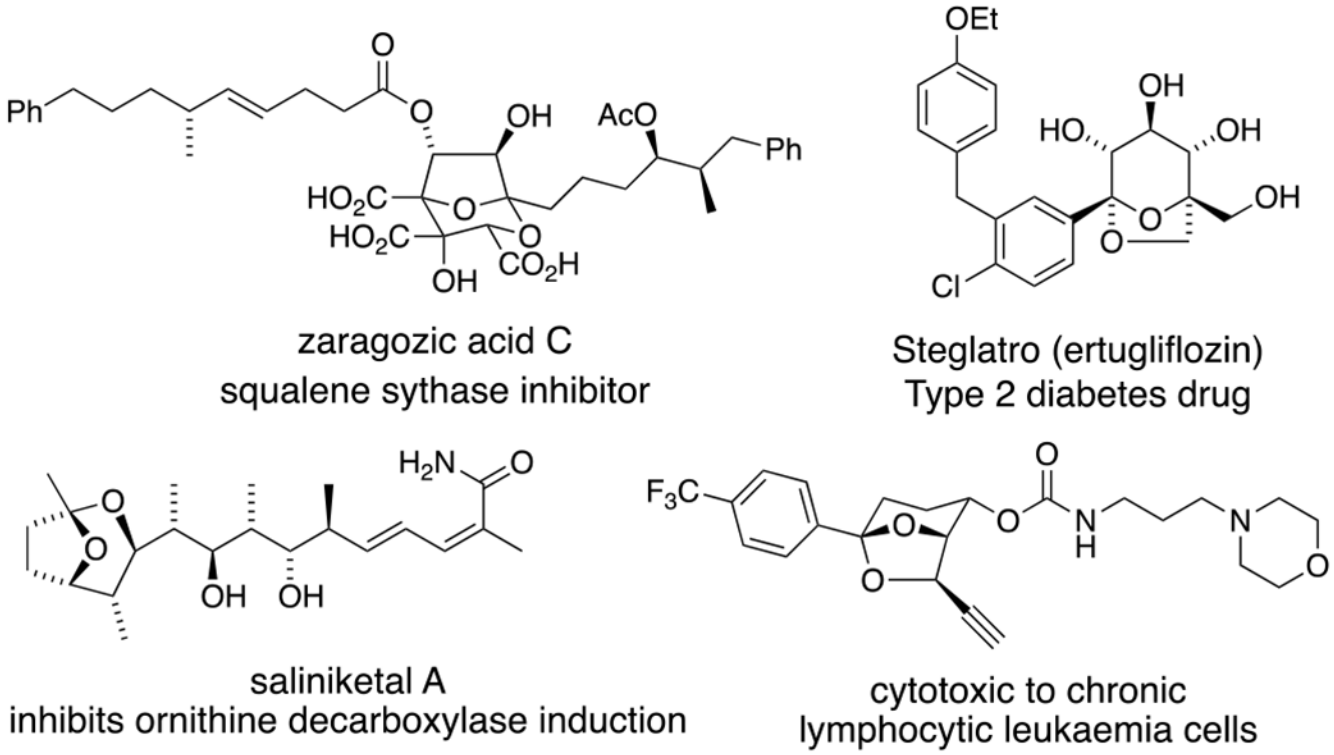
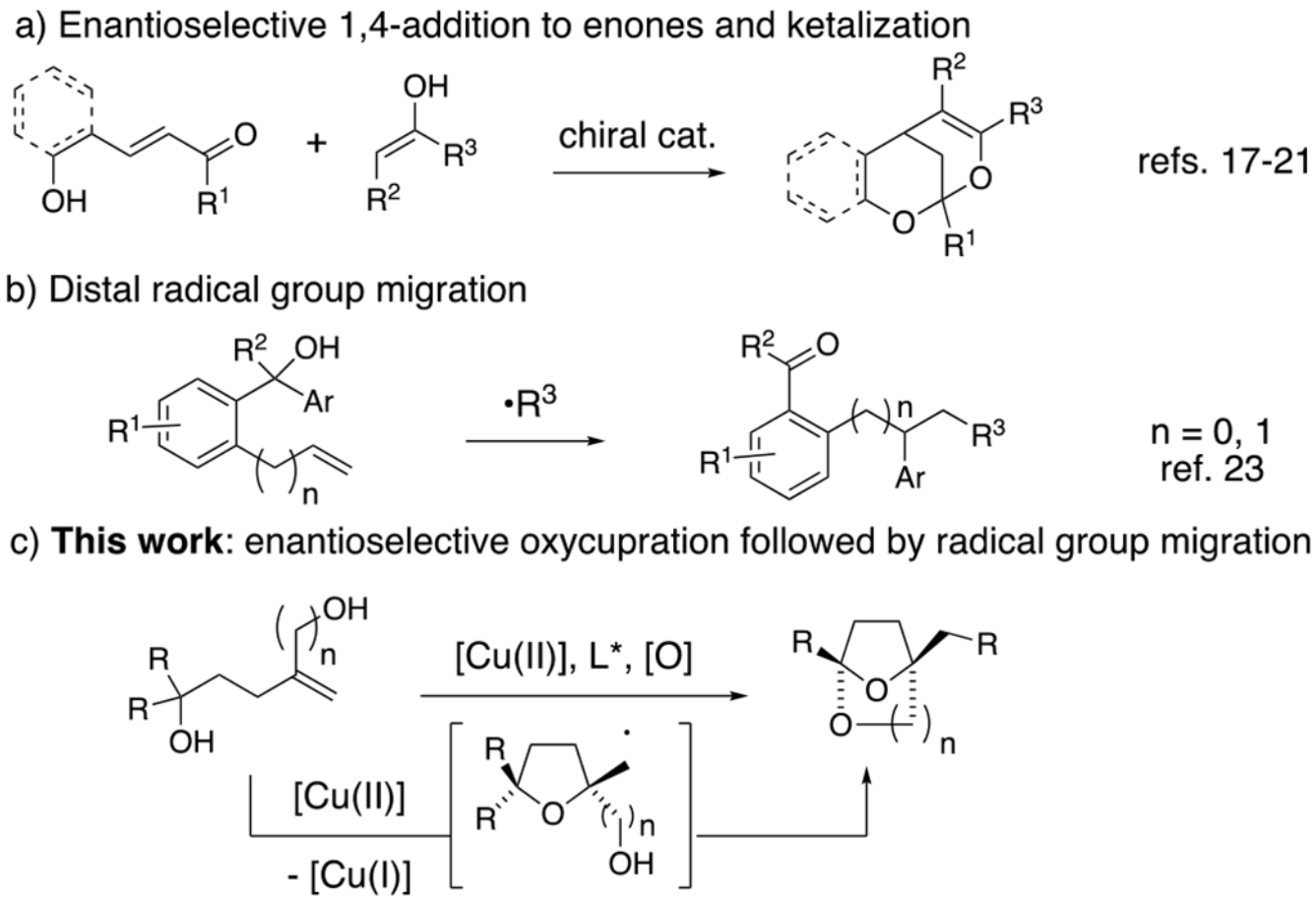
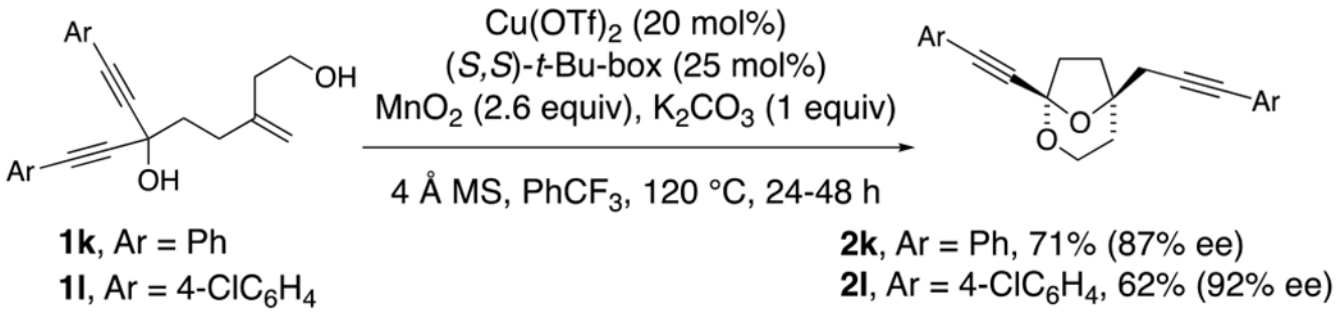


Figure 1.
Bioactive bridged bicyclic ketals



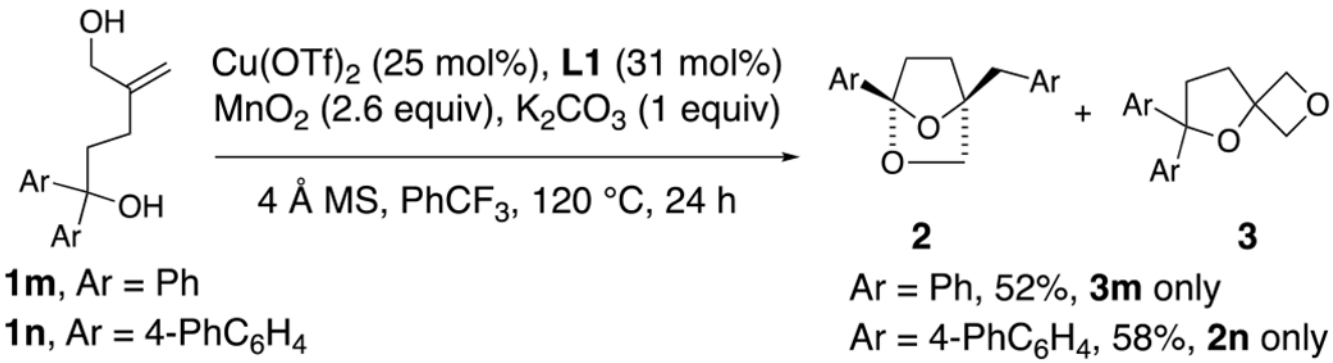
Scheme 1.
Bridged bicyclic ketals and distal group migration



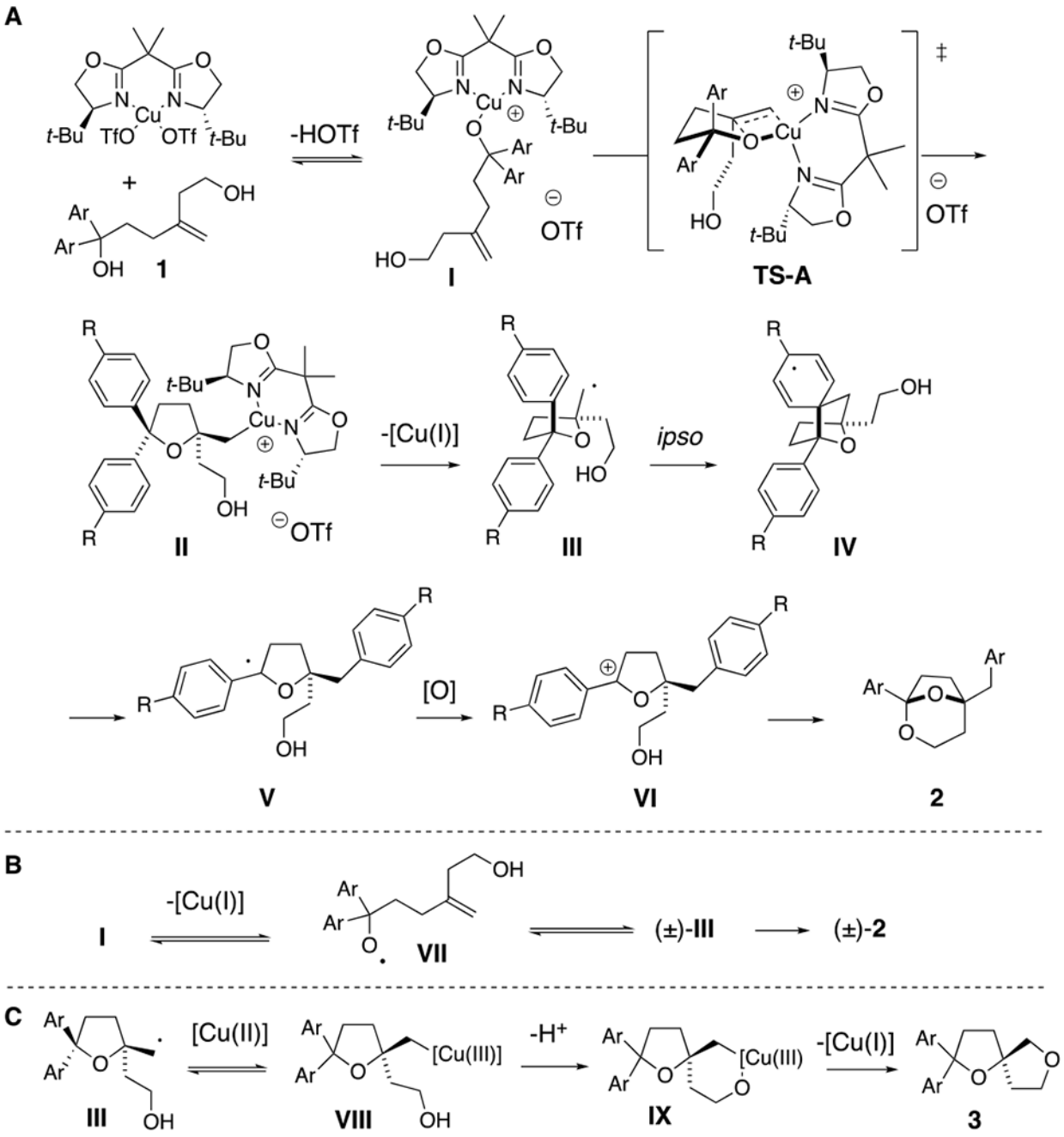
1k, Ar = Ph
1l, Ar = 4-ClC$_6$H$_4$

2k, Ar = Ph, 71% (87% ee)
2l, Ar = 4-ClC$_6$H$_4$, 62% (92% ee)

Scheme 2.
Alkyne-substituted examples



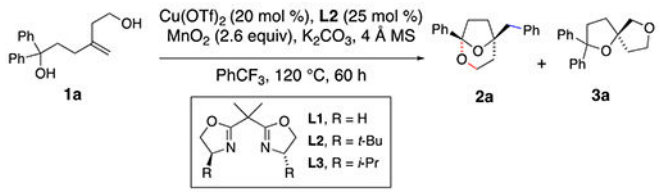
Scheme 3.
Reactions of allylic alcohols



Scheme 4.
Proposed mechanism to 2 and 3

Table 1.

Effect of Reaction Conditions[a]



entry	change from standard conditions	2a + 3a (%)	2a:3a[b]	ee (%) 2a[c]
1	None	64	>10:1	92
2	**L1**, 48 h	61	5:1	--
3	**L3**	68	4:1	57
4	24 h	55	>10:1	92
5	15 mol % [Cu], 48 h	46	>20:1	nd
6	25 mol % [Cu], 72 h	72	5:1	92 (**3a**: 86)
7	30 mol % [Cu], 48 h	62	3:1	nd
8	60 mol % [Cu], 48 h	70	1.7:1	nd
9[d]	50 mol % [Cu], **L1,** 48 h	ca. 90	2:1	nd
10	Ag_2CO_3 (1.5 equiv) instead of MnO_2	76	5:1	nd
11	25 mol % [Cu], 10 % $KMnO_4$ combined with the MnO_2	68	1.4:1	nd
12	25 mol % [Cu], $PhCH_3$ instead of $PhCF_3$, 48 h	51	4:1	78
13	DCE instead of $PhCF_3$, 48 h	38	>10:1	50
14[d]	$Cu(NTf_2)_2$ instead of $Cu(OTf)_2$, 48 h	53	1.5:1	nd

[a]Reactions run on 0.1 mmol of **1a** in 1 mL of $PhCF_3$ with a [Cu]:**L** ratio of 1:1.25 in a sealed tube (heated in 120 °C oil bath). Isolated yield following chromatography on silica gel, unless otherwise noted.

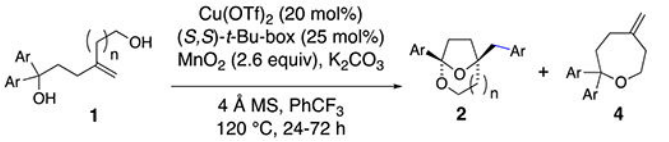
[b]Ratio obtained from analysis of the crude ^1H NMR.

[c]Enantiomeric excess measured by chiral HPLC.

[d]Estimated crude ^1H NMR yield. Nd = not determined.

Table 2.

Arene substituent scope and variable tether length[a]



Entry	Ar	n	Product	yield (%)[b]	ee (%)[c]
1	Ph	1	**2a**	64	92
2[d]	4-MeC_6H_4	1	**2b**	40	87
3[d]	3-MeC_6H_4	1	**2c**	42	92
4[e]	4-$CF_3C_6H_4$	1	**2d**	71	>95
5[f]	4-$CF_3C_6H_4$	1	**2d**	51	>95
6	4-$MeOC_6H_4$	1	**4e**	61	--
7[d,g]	4-$MeOC_6H_4$	1	**2e**	40	70
8	4-ClC_6H_4	1	**2f**	53	88
9[g]	3-ClC_6H_4	1	**2g**	58	94
10	4-TsMeNC_6H_4	1	**2h**	73	90
11	4-PhC_6H_4	1	**2i**	59	20
12[h]	4-PhC_6H_4	1	**2i**	64	56
13	Ph	2	**2j**	68	93

[a] Table 1, entry 1 conditions were applied with 0.1 mmol of substrate **1**.

[b] Isolated yield of major product following chromatography on silica gel.

[c] Enantiomeric excess measured by chiral HPLC.

[d] 30-40% of an S_N1 product **4** was also formed.

[e] 25 mol% $Cu(OTf)_2$ and 31 mol% (*S,S*)-*t*-Bu-Box was used.

[f] 1 mmol of **1d** was used. 34% of starting **1d** was recovered.

[g] $Cu(NTf_2)_2$ was used.

[h] (*S,S*)-*i*-Pr-Box was used, reaction temperature was 105 °C (at 120 °C, 58% of **2i** was obtained in 50% ee).