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Copper-Catalyzed Enantioselective Additions to Oxocarbenium Ions: Alkynylation of Isochroman Acetals

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Supporting Information

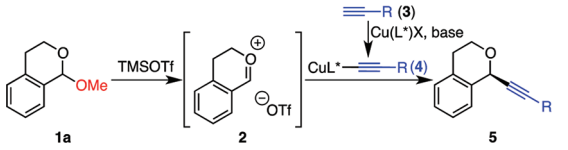
ABSTRACT: We have developed an enantioselective, copper(I)-catalyzed addition of terminal alkynes to racemic isochroman acetals. This method is one of the first transition-metal-catalyzed approaches to enantioselective additions to prochiral oxocarbenium ions. In this reaction, TMSOTf is used to form the oxocarbenium ion in situ under conditions compatible with simultaneous formation of the chiral copper acetylide. By using a bis(oxazoline) ligand, good yields and enantioselectivities are observed for a variety of enantioenriched 1-alkynyl isochromans.

Chiral substituted benzopyrans comprise a number of important molecular targets, including the natural products aposphaerin A and cytosporone C and synthetic U-101387, a selective dopamine D4 receptor agonist.[1] Nucleophilic addition to a prochiral, cyclic oxocarbenium ion intermediate would offer a highly efficient route to such bioactive molecules.[2] Li has reported the oxidative coupling of isochromans with alkynes and ketones, proposed to proceed via oxocarbenium ions.[3] In addition, achiral transition metal catalysts and Lewis acid promoters have been used for the addition of silyl and boronic carbon nucleophiles to acetals.[4] However, only a few enantioselective additions to such substrates have been achieved.[5] Jacobsen reported an impressive method for the catalytic enantioselective addition of silyl ketene acetals to 1-chloroisochromans using a chiral thiourea catalyst.[6] More recently, Schaus described the addition of vinyl- and arylboronic esters to chromene acetals using chiral diol catalysts with a Lewis acid cocatalyst.[7] Braun has also reported a Lewis acid-catalyzed allylation of a single dihydropyranyl acetal, but stoichiometric Lewis acid was required for high enantioselectivity.[8]

In contrast, enantioselective addition of chiral metal acetylides to aldehydes and ketones is a well-developed and powerful method for the preparation of chiral alcohols.[9] We envisioned that an analogous alkynylation of oxocarbenium ions would be possible if the metal acetylide could be catalytically generated under conditions compatible with oxocarbenium formation. Noting Downey's report that trimethylsilyl triflate (TMSOTf) can be used to enable catalytic turnover in the alkynylation of aldehydes,[10] we have developed an enantioselective, copper(I)-catalyzed addition of terminal alkynes to isochroman acetals in the presence of TMSOTf (Scheme 1). By using (−)-2,2′-isopropylidene-[(4*S*)-4-benzyl-2-oxazoline] (**6**) as ligand, high enantioselectivities in the formation of chiral benzopyrans **5** were obtained.

Isochroman acetal **1a**, readily prepared from isochroman,[6,11] and phenylacetylene **3a** were selected as model substrates for optimization of the alkynylation. We quickly found that both zinc(II) and copper(I) compounds are effective catalysts for the addition of phenylacetylene (**3a**) to isochroman acetals in the absence of chiral ligand (Table 1, entries 1−3). However, when chiral ligand is added, only Cu(I) catalysts provided ether **5aa** in good yields (entries 4 vs 5−7). Further, the copper counterion had a dramatic effect on the observed enantioselectivity with weakly coordinating PF_6^- being optimal (entries 5−7). Bis(oxazoline) ligands were quickly identified as promising chiral ligands, and ligand **6** was found to provide the highest selectivities (entries 6−15). By lowering the reaction temperature to −22 °C, the enantioselectivity increased to 89% ee (entry 16), but decreasing the reaction temperature further was detrimental to yield (entry 17). Reinvestigation of the Cu salt at these colder temperatures again showed $[Cu(MeCN)_4]PF_6$ gave the best enantioselectivities (entries 18−20). Notably, high enantioselectivities were only observed if the Cu salt and ligand were stirred in solvent for 1 h at rt prior to the addition of the other reagents.

Scheme 1. Enantioselective Alkynylation of Acetals



Because $[Cu(MeCN)_4]PF_6$ is reported to oxidize in air, we set up these reactions in a N_2-atmosphere glovebox, removing the mixtures just before addition of TMSOTf to cool them to −22 °C. However, we found that setting up the alkynylation outside the glovebox, including weighing $[Cu(MeCN)_4]PF_6$ in air, resulted in 68% isolated yield of ether **5aa** in 88% ee. This benchtop procedure offers an alternative to our usual glovebox procedure.[12,13]

Under the optimized conditions (see Table 1, entry 16), a variety of aryl acetylenes react with acetal **1a** (Table 2). In some cases, we found that mixing the Cu salt and ligand at higher concentration resulted in higher enantioselectivites.[12] Increased steric bulk was well tolerated (entries 2−5). Good enantioslectivity was observed for aryl acetylenes with both electron-donating and -withdrawing groups at the para position (entries 4, 6−8), but a *p*-methoxy substituent led to diminished enantioselectivity (61% ee, entry 9), and a *p*-dimethylamino substituent resulted in racemic ether **5** (not shown). For substituents in the meta position, more strongly electron-withdrawing groups led to lower enantioselectivities (entries 10, 11), but the addition of *m*-fluorophenyl acetylene resulted in ether **5al** with 88% ee (entry 12). Notably, in contrast to the result with *p*-methoxyphenylacetylene, the

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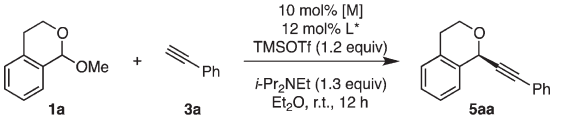
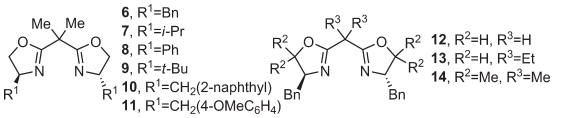
Table 1. Optimization of Alkynylation of Acetal 1a[a]



entry	[M]	L*	yield (%)[b]	ee (%)[c]
1[d,e]	$ZnBr_2$	–	84	–
2[d,e]	CuI	–	(95)	–
3	$[Cu(MeCN)_4]PF_6$	–	12	–
4	$ZnBr_2$	**6**	15	n.d.[f]
5[g]	CuI	**6**	78	26
6	$[Cu(MeCN)_4]BF_4$	**6**	57	60
7	$[Cu(MeCN)_4]PF_6$	**6**	(90)	80
8	$[Cu(MeCN)_4]PF_6$	**7**	81	50
9	$[Cu(MeCN)_4]PF_6$	**8**	70	7
10	$[Cu(MeCN)_4]PF_6$	**9**	60	2
11[h]	$[Cu(MeCN)_4]PF_6$	**10**	60	75
12[h]	$[Cu(MeCN)_4]PF_6$	**11**	30	78
13	$[Cu(MeCN)_4]PF_6$	**12**	70	36
14	$[Cu(MeCN)_4]PF_6$	**13**	85	50
15	$[Cu(MeCN)_4]PF_6$	**14**	65	34
16[h]	$[Cu(MeCN)_4]PF_6$	**6**	(90)	89
17[i]	$[Cu(MeCN)_4]PF_6$	**6**	<5	n.d.[f]
18[j]	$[CuOTf]_2 \cdot PhMe$	**6**	87	72
19[j]	$Cu(OTf)_2$	**6**	85	68
20[j]	CuO*t*-Bu	**6**	79	82

[a] Conditions: Acetal **1** (0.12 mmol, 1.0 equiv), [M] (0.012 mmol, 10 mol %), L* (0.014 mmol, 12 mol %), alkyne **3** (0.13 mmol, 1.1 equiv), *i*-Pr_2NEt (0.16 mmol, 1.3 equiv), TMSOTf (0.15 mmol, 1.2 equiv), Et_2O, rt, 12 h, unless otherwise noted. [b] Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. Numbers in parentheses are isolated yields. [c] Determined by chiral HPLC analysis. [d] NEt_3 replaced *i*-Pr_2NEt. [e] CH_2Cl_2 replaced Et_2O. [f] n.d. = Not determined. [g] 1.1 equiv of TMSOTf, 1.2 of equiv *i*-Pr_2NEt. [h] Reaction was cooled to −22 °C. [i] Reaction was cooled to −30 °C. [j] Reaction was cooled to −20 °C.

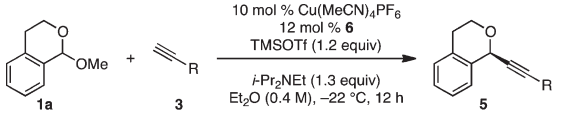


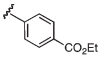
reaction of *m*-methoxyphenylacetylene proceeded in much better enantioselectivity (entry 9 vs 13). Alkynes with nonaromatic substituents were less successful. Using 20 mol % Cu catalyst, cyclohexenyl- and cyclopropylacetylene reacted, but with lower yields and selectivities (entries 14, 15). Under the optimized conditions, the addition of 1-octyne proceeded in poor yield (entry 16).

Good yields and high enantioselectivies were achieved in the alkynylation of a variety of acetal substrates (Table 3). In particular, the alkynylation of naphthopyranyl acetals provided ether products in high enantioselectivites (entires 1−3). Both electron-donating and -withdrawing substituents were tolerated on the acetal, although bromoether **5gc** was formed in somewhat reduced enantioselectivity (entry 8).

Some of the ether products slowly decompose under ambient conditions to give lactone and benzoic acid,[14] but most products are fairly stable when stored as solutions in Et_2O at −26 °C. However, dimethoxybenzopyran **5hc** decomposes quickly even with these precautions. Reduction of unpurified alkyne **5hc**

Table 2. Scope of Alkyne[a]



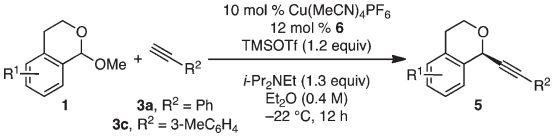
entry	R	3	5	yield (%)[b]	ee (%)[c]
1	Ph	**3a**	**5aa**	89	89
2		**3b**	**5ab**	83	91
3		**3c**	**5ac**	81	92
4		**3d**	**5ad**	72	85
5		**3e**	**5ae**	69	85
6		**3f**	**5af**	77	87
7[d,e]		**3g**	**5ag**	78	81
8		**3h**	**5ah**	78	88
9		**3i**	**5ai**	64	61
10[e,f]		**3j**	**5aj**	80	84
11[e]		**3k**	**5ak**	73	85
12		**3l**	**5al**	79	88
13[g]		**3m**	**5am**	73	87
14[h]		**3n**	**5an**	64	67
15[h]		**3o**	**5ao**	28	42
16[g,h,i]	$(CH_2)_5CH_3$	**3p**	**5ap**	15	n.d.[j]

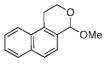
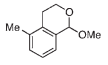
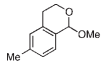
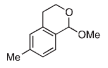
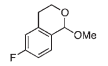
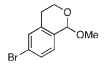
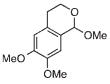
[a] Conditions: Acetal **1** (0.30 mmol, 1.0 equiv), $[Cu(MeCN)]_4PF_6$ (0.030 mmol, 10 mol %), (*S,S*)-**6** (0.036 mmol, 12 mol %), alkyne **3** (0.34 mmol, 1.1 equiv), *i*-Pr_2NEt (0.396 mmol, 1.3 equiv), TMSOTf (0.365 mmol, 1.2 equiv), Et_2O, −22 °C, 12 h, unless otherwise noted. [b] Average isolated yield from duplicate experiments (±3%). [c] Average ee from duplicate experiments as determined by chiral HPLC analysis (±2%). [d] 20 mol % [Cu] and 23 mol % **6**, 0 °C. [e] (*R,R*)-**6** was used as ligand, forming (*S*)-**5** as product. [f] 12 mol % [Cu], 14 mol % **6**. [g] Results of a single experiment. [h] 20 mol % [Cu] and 23 mol % **6**, PhMe, 0 °C. [i] Performed on 0.1 mmol scale. [j] n.d. = not determined.

provided stable ether **15hc** in 85% ee and 50% yield from acetal **1h** (Scheme 2). The analogous reduction of alkyne **5aa** proceeded with minimal loss of enantioselectivity, showing that the preparation of enantioenriched alkyl-substituted ethers is also possible via a two-step alkynylation/hydrogenation procedure. Reduction of **5aa** also allowed assignment of the absolute configuration by comparison to ether **15aa** independently prepared with known absolute configuration.[12] The absolute configurations of the other propargylic ether products were assigned by analogy.

Preliminary results suggest that this strategy will also enable the preparation of other classes of enantioenriched ethers. Under

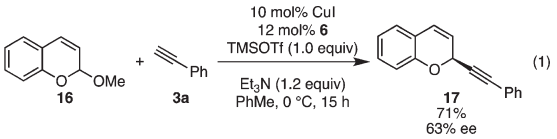
Table 3. Scope of Acetal Substrate[a]



entry	1		3	5	yield (%)[b]	ee (%)[c]
1		1b	3a	5ba	73	94
2		1b	3c	5bc	73	91
3		1c	3c	5cc	70	91
4		1d	3c	5dc	83	91
5		1e	3a	5ea	88	87
6		1e	3c	5ec	81	92
7		1f	3c	5fc	78	88
8		1g	3c	5gc	73	81
9[d]		1h	3c	5hc	50[e]	85[e]

[a] Conditions: Acetal **1** (0.30 mmol, 1.0 equiv), $[Cu(MeCN)]_4PF_6$ (0.030 mmol, 10 mol %), (*S,S*)-**6** (0.036 mmol, 12 mol %), alkyne **3** (0.34 mmol, 1.1 equiv), *i*-Pr_2NEt (0.396 mmol, 1.3 equiv), TMSOTf (0.365 mmol, 1.2 equiv), Et_2O, −22 °C, 12 h, unless otherwise noted. [b] Average isolated yield from duplicate experiments (±3%). [c] Average ee from duplicate experiments as determined by chiral HPLC analysis (±2%). [d] Results of a single experiment. [e] Yield (over two steps) and ee of **15hc**.

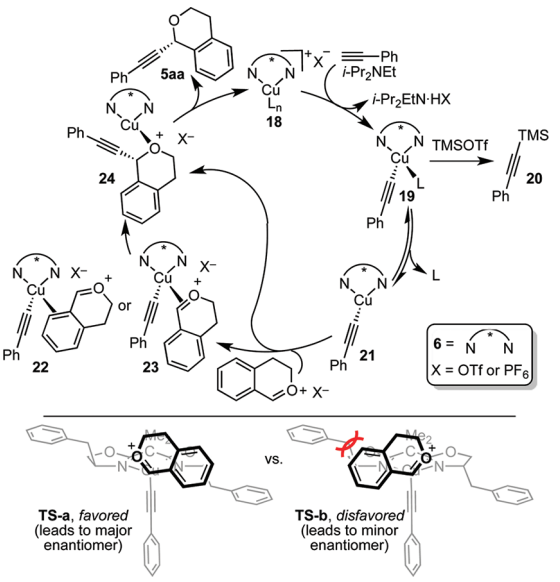
modified conditions, the Cu-catalyzed alkynylation of acetal **16**[7] resulted in efficient formation of benzopyran **17** in 71% yield and 63% ee (eq 1).[12,15]



As a working mechanistic hypothesis, we propose the catalytic cycle shown in Scheme 3.[16] The reaction likely proceeds via initial formation of Cu acetylide **19**. Although silylacetylene **20** is observed as a minor byproduct under certain conditions, we have determined that it is not a competent nucleophile in the alkynylation. In the presence of 10 mol % $[Cu(MeCN)_4]PF_6$, 12 mol % **6**, *i*-Pr_2NEt, and TMSOTf in Et_2O at rt, only 3% yield of **5aa** was observed when phenyl acetylene was replaced with trimethylsilyl acetylene **20**. Further, the addition of copper phenylacetylide[17] (1 equiv) to acetal **1a** and TMSOTf resulted in 92% yield (determined by ^1H NMR analysis), showing that Cu acetylide is a competent nucleophile.[18] From the 18-electron Cu acetylide complex **19**, dissociation of neutral ligand (L) likely occurs to allow approach of the oxocarbenium ion. Formation of the C−C bond may then occur either directly from trivalent **21** or via π-complexation of the oxocarbenium to Cu.[19]

Scheme 2. Reduction of Alkynes

Scheme 3. Proposed Mechanistic Hypothesis and Stereochemical Rationale



Because π-backbonding is significant in such Cu−olefin structures, we propose that the Cu may bind either the arene (**22**) or the C=O (**23**), or slip between these binding modes. At this point, it is unclear whether the C−C bond formation occurs via initial single-electron transfer or nucleophilic attack.

Analysis of the C−C bond forming step suggests a preliminary model for enantioinduction. Approach of Cu acetylene to the re face of the oxocarbenium ion minimizes steric interactions between the benzyl group of ligand **6** and the aromatic ring of the oxocarbenium ion (**TS-a**, Scheme 3). Significant steric hindrance between the aromatic ring of the oxocarbenium ion and the benzyl group destabilizes the diastereomeric transition state (**TS-b**). This model is consistent with the observed absolute stereochemistry of the major enantiomer and also explains the lack of enantioselectivity in the alkynylation of acyclic oxocarbenium ions (Scheme 4). For an *E*-configured acyclic oxocarbenium ion, there appears little difference in the stability of **TS-c** and **TS-d**. However, we must note that this steric-hindrance model does not explain why benzyl-substituted **6** is better than ligands **7** and **9** with *i*-Pr and *t*-Bu substituents, respectively. We have ruled out cation−π interactions as a possible explanation; increasing the π-donating capacity of the Bn group does not increase enantioselectivity (Table 1, entry 16 vs 11 and 12), suggesting that this group does not participate in cation−π interactions with the oxocarbenium ion.[20] Further, we do not observe a linear free-energy relationship between enantioselectivity and either the electronic or steric nature of substituents on the acetal or alkyne.[12] Mechanistic investigations to explain these details are underway and will be reported in due course.

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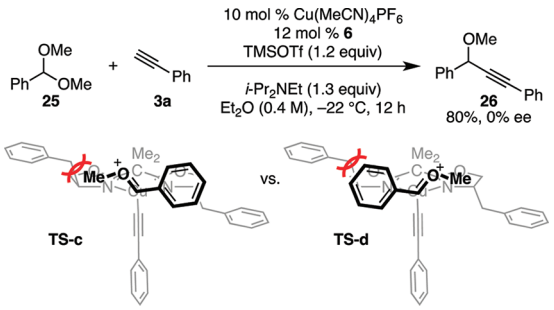
Scheme 4. Alkynylation of Acyclic Oxocarbenium Ion



As described above, we have developed a highly enantioselective method for the direct alkynylation of benzopyranyl acetals to form chiral cyclic ethers. This method allows facile access to a variety of 1-alkynyl isochromans, as well as 1-alkyl isochromans via reduction. Promising results with chromene acetals suggest that this Cu-catalyzed strategy may enable efficient enantioselective alkynylation of a variety of cyclic oxocarbenium ion intermediates. Efforts to expand the scope of this alkynylation to other acetal and alkyne substrates and to determine the reaction mechanism are underway.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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