Oxygen Heterocycles

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Enantioselective Copper(I)-Catalyzed Alkynylation of Oxocarbenium Ions to Set Diaryl Tetrasubstituted Stereocenters

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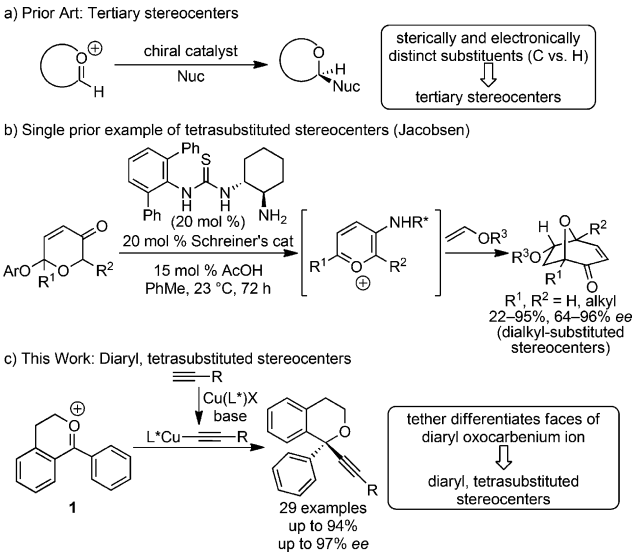
Abstract: *An enantioselective, copper(I)-catalyzed addition of terminal alkynes to isochroman ketals to set diaryl, tetrasubstituted stereocenters has been developed. The success of this reaction relies on identification of a Cu/PyBox catalyst capable of distinguishing the faces of the diaryl-substituted oxocarbenium ion. This challenging transformation enables efficient conversion of readily available, racemic ketals into high-value enantioenriched isochroman products with fully substituted stereogenic centers. High yields and enantiomeric excesses are observed for various isochroman ketals and an array of alkynes.*

Oxygen heterocycles with α-tetrasubstituted stereocenters possess biological activities against various targets, including as antioxidant, antidepressant, and anti-HIV agents.[1] A common strategy for asymmetric synthesis of these molecules is to first install the stereocenter, and then to perform a cyclization.[1a,e,2] This approach often relies on enantioselective additions to ketone substrates, which generally require significant differences in the electronic or steric character of their substituents to achieve high *ee* values.[[1e,3–5]] In particular, enantioselective additions to diaryl ketones are rare, and to our knowledge none enable addition of an acetylide.[6] We envisioned that enantioselective addition to a cyclic oxocarbenium ion might provide an opportunity for differentiating the faces of a diaryl-substituted oxocarbenium ion, thus providing an alternative strategy to set α-diaryl, tetrasubstituted stereocenters on oxygen heterocycles. By tethering one aryl group to the oxygen atom, the otherwise similar aryl substituents are differentiated by freedom of rotation and by their relationship to the oxygen substituents (alkyl versus lone pair). These factors make the geometry of the oxocarbenium ion similar to that of a trisubstituted olefin, which has been utilized in powerful enantioselective transformations.[7] Notably, however, the oxocarbenium ion reacts as an electrophile in contrast to its alkene analogue.

However, enantioselective additions of carbon nucleophiles to oxocarbenium ions remain challenging, and no known method enables formation of the proposed motif. Significant advances in enantioselective additions to cyclic oxocarbenium ions have been made by using organocatalysts and/or Lewis acid catalysts to deliver a number of different carbon nucleophiles.[8] We have developed a copper(I)-catalyzed method to enable enantioselective alkynylation by addition of a chiral organometallic nucleophile.[9] However, the vast majority of enantioselective additions of carbon nucleophiles are limited to the formation of tertiary stereocenters by additions to oxocarbenium ions with sterically and electronically distinct substituents on the cationic carbon atom (C versus H, Scheme 1 a).[10] Only a single method exists



Scheme 1. Enantioselective additions to oxocarbenium ions.

for the formation of tetrasubstituted stereocenters by enantioselective addition to oxocarbenium ions, that is, the thiourea-catalyzed [5+2] cycloaddition of pyrilium ions for formation of α-dialkyl tetrasubstituted stereocenters on 8-oxabicylcooctanes as reported by Jacobsen and co-workers (Scheme 1 b).[8k,l] Beyond this report, there are no examples of setting tetrasubstituted stereocenters by additions of carbon nucleophiles to oxocarbenium ions, and no such additions enable formation of challenging diaryl tetrasubstituted stereocenters. We now report the first enantioselective addition to oxocarbenium ions to provide α-diaryl tetrasubstituted stereocenters. This alkynylation employs a Cu/PyBox catalyst to deliver chiral organometallic nucleophiles to diaryl-substituted oxocarbenium ions in high yields and enantioselectivities (Scheme 1 c).

We began by studying the alkynylation of the isochroman ketal **2a** (Table 1), which is readily synthesized by addition of phenyl lithium to isochromanone. Under reaction conditions similar to those used in the formation of tertiary stereocenters, low yields and enantioselectivities of the product **3** were

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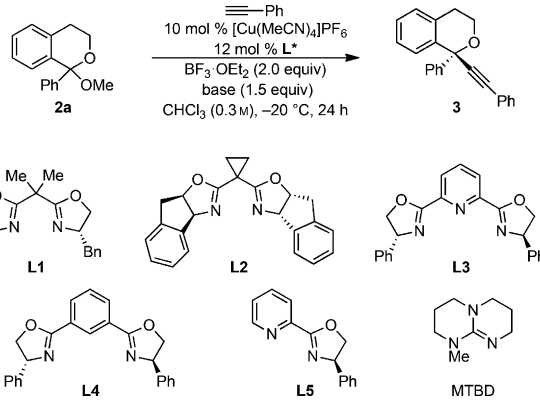
Table 1: Optimization of alkynylation of the acetal **2a**.[a]

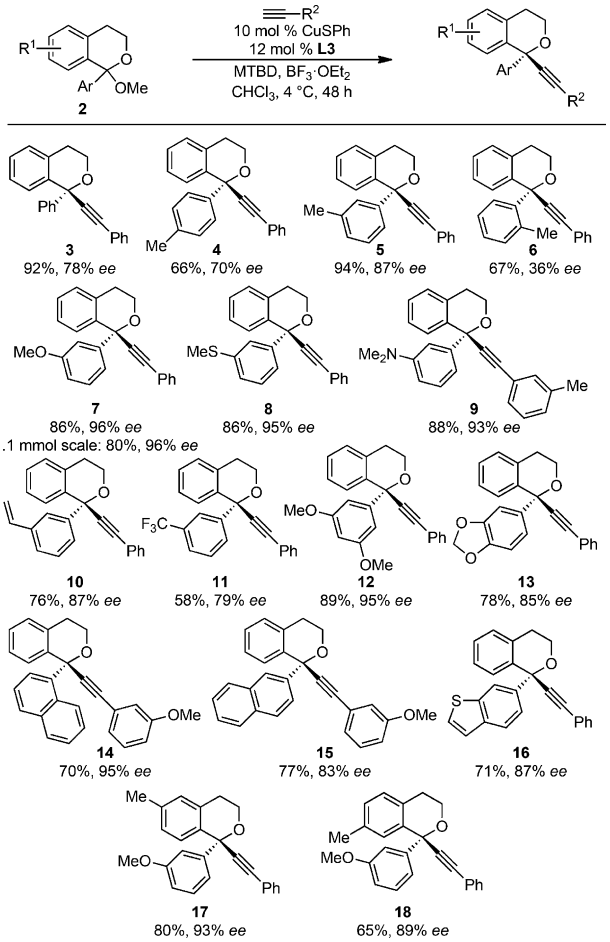


Entry	L*	Base	Yield [%][b]	*ee* [%][c]
1[d,e]	**L1**	*i*Pr$_2$NEt	21	8
2[e]	**L1**	*i*Pr$_2$NEt	20	0
3	**L1**	*i*Pr$_2$NEt	83	4
4	**L2**	*i*Pr$_2$NEt	83	37
5	**L3**	*i*Pr$_2$NEt	24	27
6	**L2**	DBU	16	36
7	**L3**	DBU	32	81
8	**L3**	MTBD	22	84
9[f]	**L3**	MTBD	12	87
10[f,g,h]	**L3**	MTBD	87	78

[a] Reaction conditions: Acetal **2a** (0.08 mmol, 1.0 equiv), [Cu(MeCN)$_4$]PF$_6$ (0.008 mmol, 10 mol%), **L***(0.01 mmol, 12 mol%), phenylacetylene (0.096 mmol, 1.2 equiv), BF$_3$·Et$_2$O (0.16 mmol, 2.0 equiv), base (0.12 mmol, 1.5 equiv), $CHCl_3$ (0.3 M), −20°C, 24 h, unless otherwise noted. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC analysis using a chiral stationary phase. [d] TMSOTf (1.2 equiv) replaced BF$_3$·Et$_2$O. [e] Et$_2$O instead of $CHCl_3$. [f] CuSPh instead of [Cu(MeCN)$_4$]PF$_6$. [g] MTBD (1.55 equiv), $CHCl_3$ (0.15 M). [h] 4°C. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

observed (entries 1 and 2).[9a] Higher yield was observed when $CHCl_3$ was employed as the solvent, but the product was nearly racemic (entry 3). However, when the benzyl-substituted **L1** was replaced with either the phenyl-substituted bis(oxazoline) **L2** or phenyl-substituted pyridine (bis)oxazoline (PyBox) **L3**, promising enantioselectivities were obtained (entries 4 and 5). Base also affected the enantioselectivity (entries 5–8). With the use of **L3** and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 84% *ee* was obtained, albeit in 22% yield (entry 8). Optimization of the copper salt, equivalents of base, concentration, and temperature led to an optimized 87% yield and 78% *ee* (entries 9 and 10). Other pyridine bis(oxazoline) ligands did not provide higher enantioselectivities.[11]

Under the optimized reaction conditions (Table 1, entry 10), a variety of isochroman ketals successfully underwent alkynylation (Scheme 2). The product **3** was isolated in 92% yield and 78% *ee*, which we deemed to be impressive selectivity given the challenging nature of this highly substituted stereocenter. With this success, we explored other ketals. As discussed below, even higher enantioselectivities, up to 97% *ee*, were realized with substituted substrates.

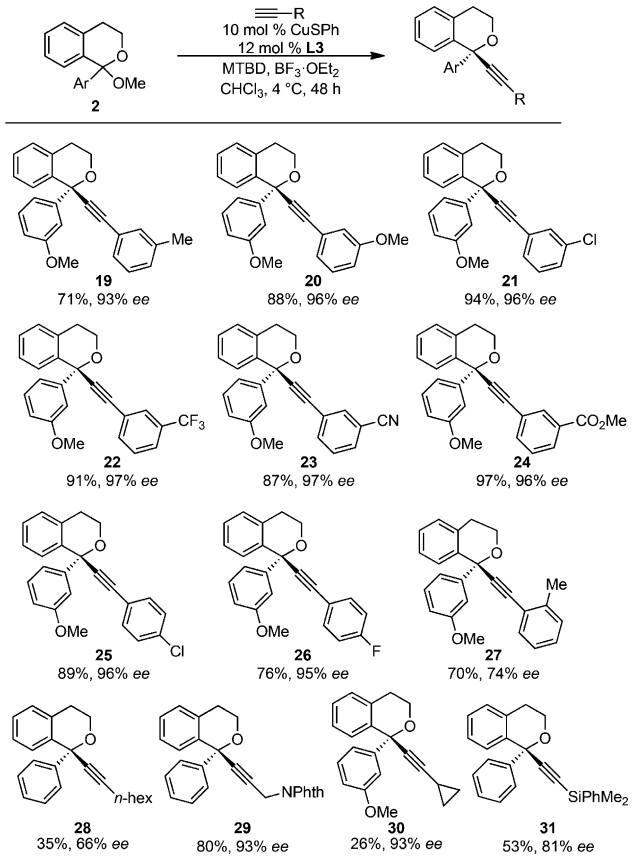


Scheme 2. Scope with respect to the isochroman acetals. Reaction conditions: acetal **2** (0.2 mmol, 1.0 equiv), CuSPh (0.02 mmol, 10 mol%), **L3** (0.024 mmol, 12 mol%), alkyne (0.24 mmol, 1.2 equiv), BF$_3$·Et$_2$O (0.4 mmol, 2.0 equiv), MTBD (0.31 mmol, 1.55 equiv), $CHCl_3$ (0.15 M), 4°C, 48 h. Average yield of the isolated product from duplicate experiments (±5%) and average *ee* value from duplicate experiments as determined by HPLC analysis using a chiral stationary phase (±2%), unless otherwise noted. Results for **8**, **10**, and **17** are for a single experiment.

Investigation of substituent effects on the 1-aryl group (Ar) showed that useful yields are observed in the formation *ortho*-, *meta*-, and *para*-tolyl-substituted products (**4**–**6**). However, low enantioselectivity is observed for the *ortho*-tolyl-substituted **6**, thus indicating the limit of steric hindrance. Higher enantioselectivities are obtained with *meta* substituents. The *meta*-heteroatom substituents led to the best enantioselectivities (up to 97% *ee*; **7**–**9**, **12**). A range of functional groups was well tolerated, including ethers (**7**, **12**, **17**, **18**), thioethers (**8**), anilines (**9**), alkenes (**10**), trifluoromethyls (**11**), and acetals (**13**). Although the *ortho*-tolyl substituent led to low *ee* values, the 1-naphthyl-substituted **14** was formed in 95% *ee*. Substrates with 2-naphthyl and heteroaryl substituents also underwent alkynylation (**15** and **16**). Substitution on the benzopyranyl core was also well tolerated (**17** and **18**). Importantly, increasing the scale of the reaction results in similar yield with no change in enantioselectivity (see **7**). The absolute configuration of **14** was

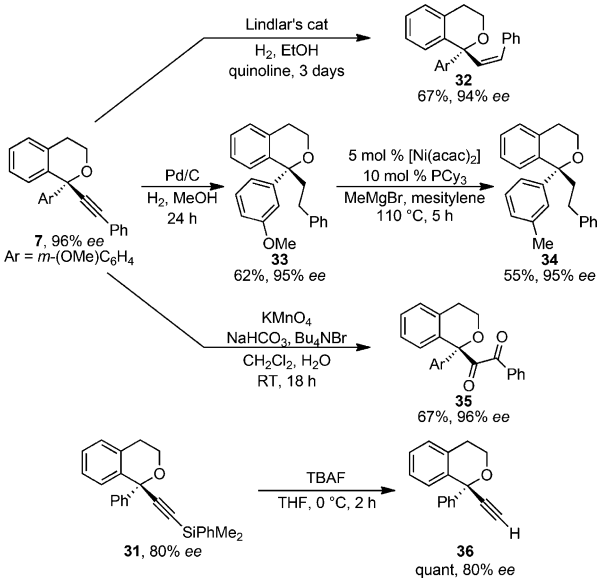
determined by X-ray crystallography.[12] The configurations of other products were assigned by analogy. Unfortunately, 1-alkylisochroman acetals are poor substrates under these reaction conditions. No desired product was observed in the reaction of 1-methoxy-1-methylisochromane with phenyl acetylene.[13]

Good yields and high enantioselectivities were observed across a range of acetylenes (Scheme 3). In particular, electron-poor to moderately electron-rich aryl groups were well tolerated, including various *meta*-substituents (**19**–**24**) and electron-poor *para*-substituents (**25** and **26**). Functional groups including ethers (**20**), trifluoromethyls (**22**), nitriles (**23**), esters (**24**), and halides (**21**, **25**, **26**) can be incorporated. The *ortho*-tolyl **27** was also formed in 75% yield, albeit 73% *ee*. However, the use of aryl acetylenes with electron-rich *para*-substituents, such as *para*-(dimethylamino) or *para*-methyl, led to low or irreproducible enantioselectivities (0 and 20–90% *ee*, respectively). We hypothesize that electron-rich isochroman products may undergo epimerization by Lewis-acid-induced ionization of the benzylic C–O bond, thus leading to a trityl-like cation. With respect to alkyl-substituted alkynes, 1-octyne gave low yield and modest enantioselectivity (**28**). However, addition of propargyl phthalimide resulted in 80% yield of the product **29** in 93% *ee*. High enantioselectivity was also observed in the addition of cyclopropyl acetylene (**30**). Silyl acetylenes also underwent addition. The addition of (trimethylsilyl)acetylene resulted in modest yield (40% by ^{1}H NMR spectroscopy), but relatively high enantioselectivity (82% *ee*; not shown). (Dimethylphenylsilyl)acetylene showed greater reactivity, thus giving 53% yield and 80% *ee* of the silyl-protected acetylene **31**.



Scheme 3. Scope with respect to the alkynes. Reaction conditions: Acetal **2** (0.2 mmol, 1.0 equiv), CuSPh (0.02 mmol, 10 mol%), **L3** (0.024 mmol, 12 mol%), alkyne (0.24 mmol, 1.2 equiv), $BF_3{\cdot}Et_2O$ (0.4 mmol, 2.0 equiv), MTBD (0.31 mmol, 1.55 equiv), $CHCl_3$ (0.15 M), 4 °C, 48 h. Average yield of isolated product from duplicate experiments (±5%) and average *ee* value from duplicate experiments as determined by HPLC analysis using a chiral stationary phase (±2%), unless otherwise noted. Results for **26**, **28**, and **30** are for a single experiment.

The products can be easily elaborated. Reduction of the alkyne **7** gives the vinyl- and alkyl-substituted isochromans **32** and **33**, respectively, in good yields and high enantiopurities (Scheme 4). Oxidation to the diketone **35** was accomplished



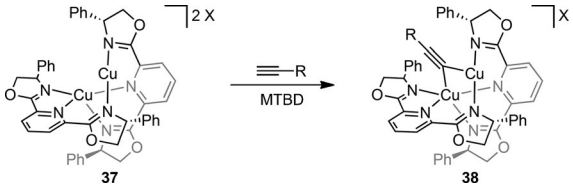
Scheme 4. Elaboration of products. acac = acetylacetonoate, TBAF = tetra-*n*-butylammonium fluoride.

in 67% yield and with perfect stereochemical fidelity.[14] As noted above, *meta*-methoxyphenyl-substituted isochroman products are formed in the highest enantioselectivities. This *meta*-methoxy substituent is easily functionalized by cross coupling. It can be converted into a *meta*-methyl group without loss in *ee* (**34**).[15] Finally, deprotection of silyl acetylene **31** was accomplished in quantitative yield and perfect stereochemical fidelity to deliver the terminal alkyne **36**.

Regarding a mechanism, this reaction likely proceeds by addition of a chiral copper acetylide to an oxocarbenium ion intermediate (Scheme 1c). Two equivalents of $BF_3{\cdot}OEt_2$ are required; less leads to lower yields and *ee* values, and is likely due to incomplete ionization to the oxocarbenium ion. However, the isolated isochroman products racemize when subjected to $BF_3{\cdot}OEt_2$.[11] As with other acetals,[16] BF_4^- was detected in the reaction of the ketal **2a** with BF_3 (2 equiv) by ^{19}F NMR spectroscopy and mass spectrometry. This observation suggests that the second equivalent of BF_3 reacts with $F_3B(OMe)^-$, which forms upon ionization of the ketal. This

disproportionation results in the less Lewis acidic $BF_2(OMe)$, which seems incapable of epimerizing most products.

We are also interested in understanding the structure of the putative chiral copper acetylide. Although PyBox ligands often enforce a square-planar geometry on a M–X fragment, there is no electronic benefit for copper(I) complexes to adopt this more sterically crowded geometry. We considered that **L3** may act instead as a bidentate ligand, with either the pyridine or one oxazoline arm dissociating, but models for these types of coordination geometries resulted in much lower enantioselectivities (**L4**: 4% *ee*; **L5**: 28% *ee*).[17] Another possibility is a dimeric (or other higher order) copper/**L3** catalyst. $[Cu_2(\mathbf{L3})_2X_2]$ complexes [**37**; Eq (1)] have



(1)

been previously observed,[18] and these dinuclear copper catalysts have been proposed to proceed by dicopper acetylide intermediates (**38**) in related reactions.[18c,19] Consistent with the presence of higher-order copper/**L3** species, a positive nonlinear correlation is observed between the *ee* value of **L3** and the *ee* value of product (Figure 1).[20]

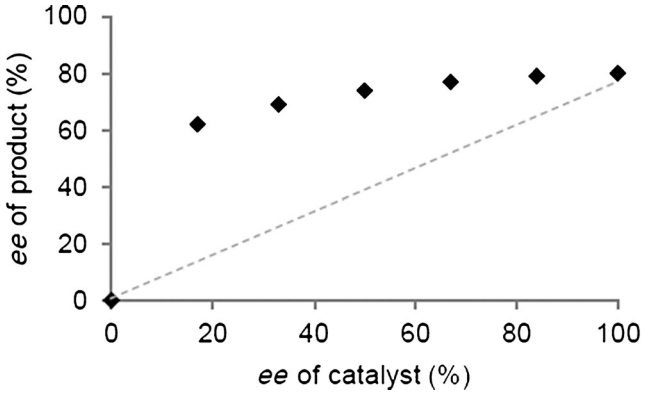


Figure 1. Positive nonlinear effect in formation of the isochroman **3**.

Although this data does not exclude the possibility that these higher-order copper species may exist in an off-cycle reservoir, we currently favor a dicopper acetylide intermediate, given their importance in other copper acetylide chemistry. Because of the many possible catalyst structures, we cannot yet propose a detailed rationale for the observed stereochemistry. However, we hypothesize that the role of the phenyl substituents on (*R*)-Ph-PyBox (**L3**) is largely steric in nature, because (*R*)-*t*Bu-PyBox results in the same major enantiomer.[11]

In conclusion, we developed a copper-catalyzed alkynylation of 1-aryl isochroman ketals and it enables efficient formation of diaryl, tetrasubstituted stereocenters in high enantioselectivities. Application of this strategy to the preparation of other diaryl, tetrasubstituted stereocenters, as well as mechanistic investigations of these reactions, are currently underway.

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Keywords: alkynes · asymmetric catalysis · enantioselectivity · oxocarbenium ion · oxygen heterocycles

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[10] Oxocarbenium ions derived from acetals may also impose less steric hindrance in the approach of a nucleophile than their fully substituted counterparts derived from ketals.

[11] See the Supporting Information.

[12] CCDC 973167 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[13] 19% yield of the isolated product was obtained with an achiral catalyst (12 mol% $[Cu(MeCN)_4]PF_6$, Et_3N, TMSOTf, Et_2O, RT, 24 h).

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