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Enantioselective, Copper-Catalyzed Alkynylation of Ketimines To Deliver Isoquinolines with α-Diaryl Tetrasubstituted Stereocenters

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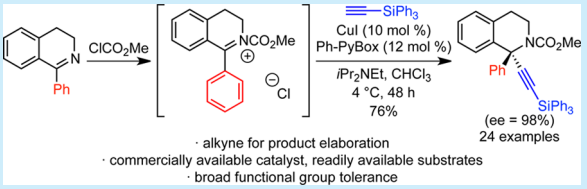
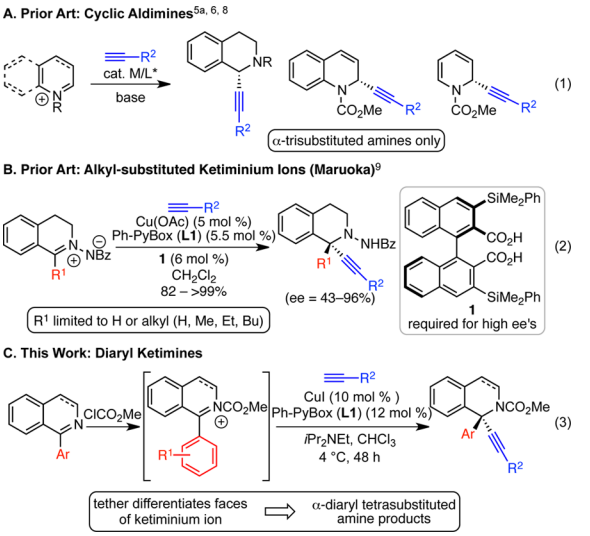
Supporting Information

ABSTRACT: An enantioselective, copper-catalyzed alkynylation of cyclic α,α-diaryl ketiminium ions has been developed to deliver isoquinoline products with diaryl, tetrasubstituted stereocenters. The success of this reaction relied on identification of Ph-PyBox as the optimal ligand, *i*-Pr$_2$NEt as the base, and $CHCl_3$ as the solvent. A broad scope and functional group tolerance were observed. Notably, the use of both aryl and silyl acetylenes results in high yields and enantioselectivities. Mechanistic experiments are consistent with a dimeric or higher order catalyst.



The prevalence of α-chiral cyclic amines in pharmaceuticals, natural products, and other bioactive molecules makes them enticing targets for synthesis.[1] In particular, cyclic α-tetrasubstituted amines are found in molecules possessing activity against a range of diseases, including breast cancer, seizures, thrombosis, and human immunodeficiency virus (HIV).[2] However, methods to prepare cyclic α-tetrasubstituted amines in high enantiopurity, a requirement for their biomedical use, are limited.[3] A powerful approach to these compounds would be enantioselective addition to a ketimine or ketiminium ion. Most substrates for such additions have been limited to those with electronically and/or sterically different substituents on the electrophilic carbon.[4] Enantioselective preparation of α-diaryl tetrasubstituted amines remains a challenge; only two classes of carbon nucleophiles (arenes, cyanide) have been delivered in high enantioselectivity to cyclic diaryl ketimines.[5−7] With an eye toward enantioselective addition of a versatile carbon nucleophile to cyclic diaryl ketimines, we envisioned enantioselective, copper-catalyzed alkynylation may provide a useful solution. Although enantioselective alkynylations of a variety of cyclic aldimines and aldiminium ions to deliver α-trisubstituted amines are known (Scheme 1, eq 1),[5a,6,8] only a single report of enantioselective alkynylation of a cyclic ketiminium ion exists. Maruoka has impressively shown that a Cu(Ph-PyBox)/Brønsted acid catalyst system enables alkynylation of *alkyl-substituted* isoquinolinium ions (Scheme 1, eq 2).[9,4] However, no methods exist for enantioselective alkynylation of *α,α-diaryl* ketimines or iminium ions with either cyclic or acyclic substrates. Given the similarity between Maruoka's conditions and our enantioselective, copper-catalyzed alkynylation of cyclic diaryl oxocarbenium ions,[10] we envisioned that an enantioselective alkynylation of diaryl iminium ions may enable synthesis of the challenging α-diaryl tetrasubstituted amine motif (Scheme 1, eq 3). Herein we report the successful development of this reaction, in which a tether enables differentiation of the faces of a diaryl ketiminium ion to allow synthesis of tetrahydroisoquinolines in excellent enantiomeric enrichment. This reaction relies on a commercially available copper precatalyst and chiral ligand, and boasts a broad scope in

Scheme 1. Enantioselective, Metal-Catalyzed Alkynylations of Cyclic Iminium Ions



the ketimine and alkyne. The alkyne provides a versatile functional group for further manipulation.

We began by examining the alkynylation of 1-phenyl dihydroisoquinoline **2a** with phenyl acetylene. Dihydroisoquinoline **2a** is easily prepared via a two-step procedure from commercially available materials.[11] Following precedent with unsubstituted pyridines and isoquinolines,[8h,l−n] we acetylated in situ using methyl chloroformate to generate a ketiminium ion. We then added the mixture of ketiminium ion to the other reaction components (alkyne, copper salt, ligand, base). In the presence of an achiral copper(I) catalyst, alkynylation proceeded smoothly to give up to an 81% yield (Table 1, entries 1−3). When CuI was stirred with Ph-PyBox **L1** for 30 min before addition of the other

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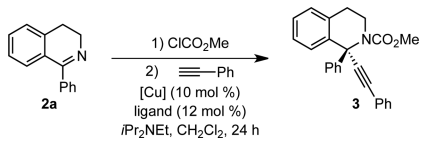
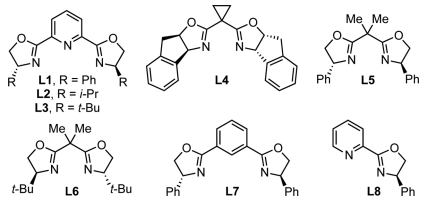
Table 1. Optimization of Alkynylation[a]



entry	[Cu]	ligand	temp (°C)	yield (%)	ee (%)
1	CuI	–	rt	81	–
2	$Cu(MeCN)_4PF_6$	–	rt	65	–
3	CuSPh	–	rt	50	–
4	CuI	**L1**	rt	85	37
5	CuI	**L1**	4	65	53
6	CuI	**L2**	4	89	20
7	CuI	**L3**	4	75	10
8	CuI	**L4**	4	39	11
9	CuI	**L5**	4	61	0
10	CuI	**L6**	4	76	0
11[b]	CuI	**L1**	4	72	19
12[c]	CuI	**L1**	4	60	0
13[d]	CuI	**L1**	4	80	89
14[d]	CuI	**L1**	−20	77	92
15[d,e]	CuI	**L1**	4	81	91
16[d,e,f]	CuI	**L1**	4	(64)	95
17[d,g]	CuI	**L1**	4	95	91
18[d,g]	CuBr	**L1**	4	95	35
19[d,g]	CuCl	**L1**	4	91	33

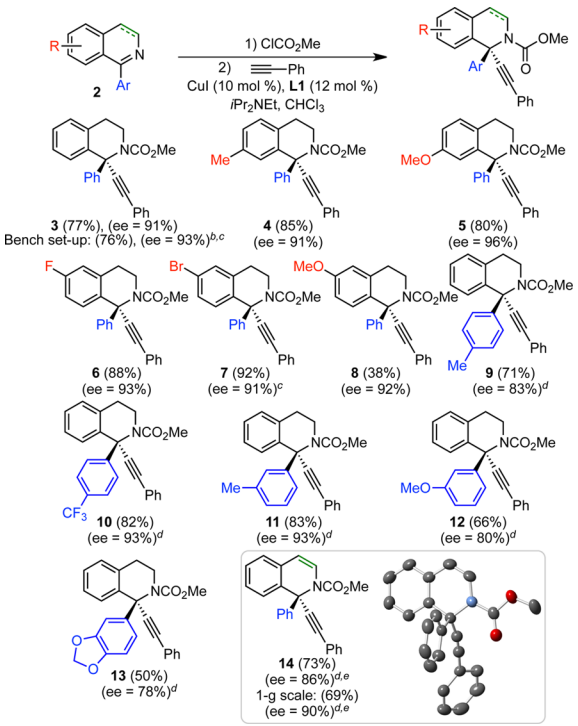
[a]Conditions: Ketimine **2a** (0.1 mmol), [Cu] (10 mol %), ligand (12 mol %), phenylacetylene (1.2 equiv), $ClCO_2Me$ (1.0 equiv), iPr_2NEt (1.5 equiv), CH_2Cl_2 (0.15 M), 24 h, unless otherwise noted. Yields determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard. Ee's determined by HPLC using a chiral stationary phase. [b]Et_3N as base. [c]MTBD (7-methyl-1,5,7-triazabiocyclo[4.4.0]dec-5-ene) as base. [d]$CHCl_3$ as solvent. [e][**2a**] = 0.1 M. [f]$ClCO_2Bn$ in place of $ClCO_2Me$. Isolated yield in parentheses. [g][**2a**] = 0.05 M. Iminium ion was not preformed; $ClCO_2Me$ added last.



components, 85% yield and 37% ee were observed (Table 1, entry 4). By lowering the temperature to 4 °C, the ee was increased to 53%, albeit with a drop in yield (Table 1, entry 5). Other pyridine (bis)oxazoline and oxazoline ligands **L2**−**L6** provided no improvement in enantioselectivity (entries 6−10). In addition, the use of alternative bases, including MTBD, the optimal base for the alkynylation of diaryl oxocarbenium ions, also resulted in lower ee (Table 1, entries 11−12). However, by changing the solvent to $CHCl_3$, a dramatic increase in enantioselectivity was observed (Table 1, entry 13).[12] The enantioselectivity was increased further by reducing the temperature to −20 °C, but at the cost of yield (Table 1, entry 14). Decreasing the concentration was a more effective improvement, leading to an 81% yield and 91% ee (Table, 1 entry 15). Under these conditions, $ClCO_2Me$ can be replaced by $ClCO_2Bn$ to give product in 64% isolated yield and 95% ee (Table 1, entry 16). By decreasing the concentration further ([**2a**] = 0.05 M), we achieved high yield and ee without preforming the ketiminium ion in a separate reaction vessel (Table 1, entry 17). Under these conditions, replacing CuI with either CuBr or CuCl resulted in a dramatic decrease in ee (Table 1, entries 18, 19). This result is particularly surprising with CuCl, given that chloride is present due to the acylation with methyl chloroformate.

Under the optimized conditions (Table 1, entry 15), a broad range of 1-arylisoquinolines undergo enantioselective alkynylation (Scheme 2). Alkynylation of **2a** proceeded effectively, giving

Scheme 2. Scope in Isoqinoline[a]



[a]Conditions: **2** (0.3 mmol), $ClCO_2Me$ (1.0 equiv), alkyne (1.2 equiv), CuI (10 mol %), **L1** (12 mol %), *i*Pr2NEt (1.5 equiv), $CHCl_3$ (0.1 M), 4 °C, 48 h. Average isolated yields (±5%) and ee's (±2%) of duplicate experiments, unless noted otherwise. [b]Set up outside glovebox. [c]Single experiment. [d][**2**] = 0.05 M. [e]Iminium ion was not preformed; $ClCO_2Me$ added last.

a 77% isolated yield and 91% ee. If this reaction is set up on the benchtop, instead of the glovebox, a similar yield and ee are observed. Both electron-donating and -withdrawing groups were tolerated on the isoquinoline backbone (**4**−**8**), including an aryl bromide, which offers a useful handle for elaboration (**7**). The alkynylation also proceeded effectively for substrates with substitution on the 1-phenyl group (**9**−**13**). In some cases, reducing the concentration to 0.05 M led to increased enantioselectivity. The aromatic isoquinoline can also be employed to give product **14**. As expected, the reversible acylation of isoquinoline was less favorable than that for the dihydroisoquinolines, initially leading to lower yields with our original procedure. However, by following a one-pot procedure, in which methyl chloroformate is added last, and by using a reduced concentration ([**2**] = 0.05 M), a 69% yield and 90% ee were obtained in a 1 g scale reaction. The crystal structure of **3** indicates that the copper acetylide adds to the *re* face.[13] Interestingly, in the analogous alkynylation of 1-aryl isochroman oxocarbenium ions, addition to the *si* face is dominant.[10] We also examined 1-methyl isoquinoline. However, no reaction was observed, highlighting the benefit of Maruoka's conditions for 1-alkyl isoquinolines.[9a]

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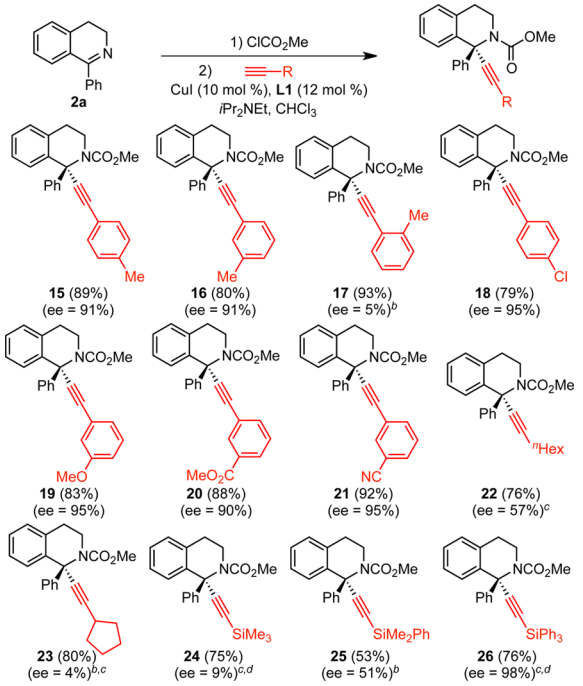
A range of alkynes can also be used (Scheme 3). Both *para* and *meta* substitution of aryl acetylenes are tolerated (**15**, **16**).

Scheme 3. Scope in Alkyne[a]

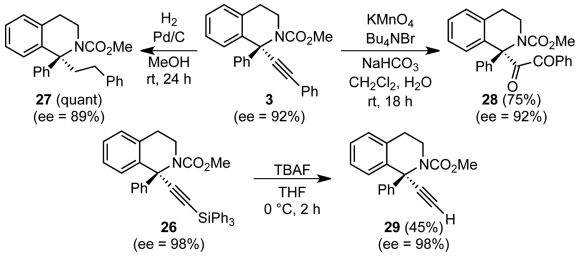


[a]Conditions: **2a** (0.3 mmol), $ClCO_2Me$ (1.0 equiv), alkyne (1.2 equiv), CuI (10 mol %), **L1** (12 mol %), iPr_2NEt (1.5 equiv), $CHCl_3$ (0.1 M), 4 °C, 48 h. Average isolated yields (±6%) and ee's (±1%) of duplicate experiments, unless noted otherwise. [b]Single experiment. [c][**2a**] = 0.05 M. [d]Iminium ion was not preformed; $ClCO_2Me$ added last.

However, *o*-methyl phenylacetylene resulted in a nearly racemic product, albeit with an excellent yield (**17**). Alkynes with aryl chloride **18**, ether **19**, ester **20**, and nitrile **21** groups participated effectively. For alkyl acetylenes, high yields, but low enantioselectivities, were observed, with lower ee's when a branched alkyl group is used (**22**, **23**). We also examined silyl acetylenes. We observed only a 9% ee in the addition of trimethylsilyl acetylene **24**. However, by increasing the phenyl groups on silicon, steadily higher ee's were seen. Triphenylsilyl acetylene **26** was formed in good yield and 98% ee. A rationale for the low ee's observed with alkyl and trimethylsilyl acetylenes currently eludes us. One possibility is that these alkynes or their decomposition products (e.g., allenes for alkyl acetylenes) react with the copper catalyst to generate a less enantioselective catalyst. However, addition of trimethylsilylacetylene, 1-octyne, or 1,2-octadiene to the model reaction (addition of phenyl acetylene to **2a**) resulted in only minor decreases in yield and ee.[11] This vague outcome suggests further studies are necessary to understand the low enantioselectivity observed with these substrates.

To demonstrate the utility of the alkyne, we performed several elaborations (Scheme 4). Alkyne **3** was reduced to (*S*)-**27** in quantitative yield with only a slight decrease in ee. Hydrogenation of **14** also led to (*S*)-**27**, showing that the *re* face of the iminium ion is attacked for both dihyroisoquinolines and aromatic isoquinolines.[11] The alkyne can also be oxidized to diketone **28** in good yield and 100% conservation of ee. Deprotection of triphenylsilane **26** proceeded in an unoptimized 45% yield, again with no loss in enantiomeric enrichment.

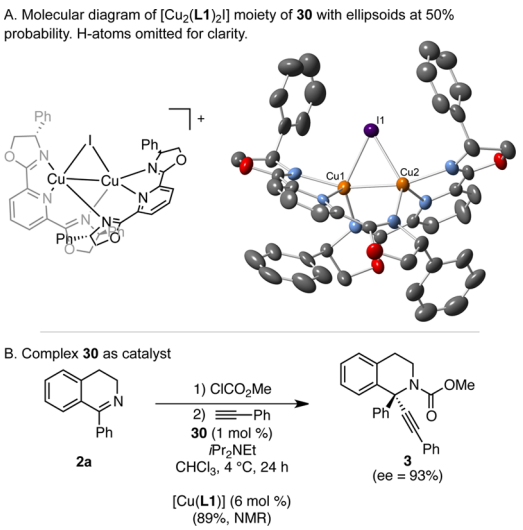
Scheme 4. Elaboration of Products



This reaction likely proceeds via a chiral copper acetylide, which adds to the isoquinolinium ion. We are very interested in understanding how the Cu/Ph-PyBox catalyst imparts enantioselectivity. As a first step, we need to understand the structure of the catalyst. Although PyBox ligands often enforce a square planar geometry on four-coordinate metals, there is no electronic benefit to forcing four ligands into the same plane for Cu(I), making this geometry unlikely. Bidentate coordination of the ligand is possible, but the use of model ligands for bidentate coordination (**L7**, **L8**) leads to racemic product **3** (**L7**: 67% yield by ^1H NMR. **L8**: 58% yield by ^1H NMR). In addition, we observe a moderate (+)-nonlinear effect under the optimized two-pot procedure.[14,15] These results are similar to our observations in the alkynylation of oxocarbenium ions catalyzed by a Cu/Ph-PyBox catalyst and suggest that catalyst aggregation may occur.[10]

In addition, the reaction of CuI (1 equiv) and **L1** (1 equiv) in CH_2Cl_2 resulted in complex **30**, $[Cu_2(\mathbf{L1})_2I]_3[Cu_4I_7]$, which has been characterized by ^1H and ^{13}C NMR, as well as X-ray crystallography.[12] Notably, $[Cu_2(PyBox)_2X_2]$ complexes with noncoordinating counteranions (PF_6, OTf) have been observed,[16] but this is the first crystal structure with a bridging halide counteranion.[17] Complex **30** is catalytically competent, delivering a high yield and 93% ee (Scheme 5B). Although these

Scheme 5. Structure and Reactivity of Complex 30



results do not exclude the possibility that a higher-order complex is simply an off-cycle reservoir for an active monomeric catalyst, we currently favor a dicopper acetylide as the catalytic intermediate. This mechanism is consistent with the well-recognized importance of such dicopper acetylides in copper acetylide chemistry.[16,18] Ongoing mechanistic studies are directed toward developing a stereochemical model based on

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such an intermediate, as well as understanding the effects of concentration and base on the enantioselectivity.

In summary, we developed a copper-catalyzed alkynylation of 1-aryl isoquinolinium ions that delivers cyclic α-diaryl tetrasubstituted amines in good yields and high enantioselectivities. This reaction employs a catalyst with commercially available components, and a wide range of isoquinolines and alkynes can be used. Notably, the addition of triphenylsilylacetylene is effective, providing the potential for elaboration of the silyl-protected alkyne. Our mechanistic studies are consistent with an aggregated Cu/**L1** complex as the active catalyst, consistent with the recognized importance of dicopper species in copper acetylide chemistry. Efforts are ongoing to expand the scope and more deeply understand the mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02787.

Experimental details and data (PDF)
Crystal structures (CIF, CIF)

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Notes

The authors declare no competing financial interest.

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(11) See the Supporting Information.

(12) We do not yet understand this dramatic solvent effect. See the Supporting Information for discussions and further experiments.

(13) CCDC 1499232 (**14**) and CCDC 1499233 (**30**) contain the supplementary crystallographic data for this paper. These can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(14) In contrast, no nonlinear effect was observed under the one-pot procedure. See the Supporting Information.

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