Asymmetric Catalysis

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Direct Synthesis of Chiral Allenoates from the Asymmetric C–H Insertion of α-Diazoesters into Terminal Alkynes**

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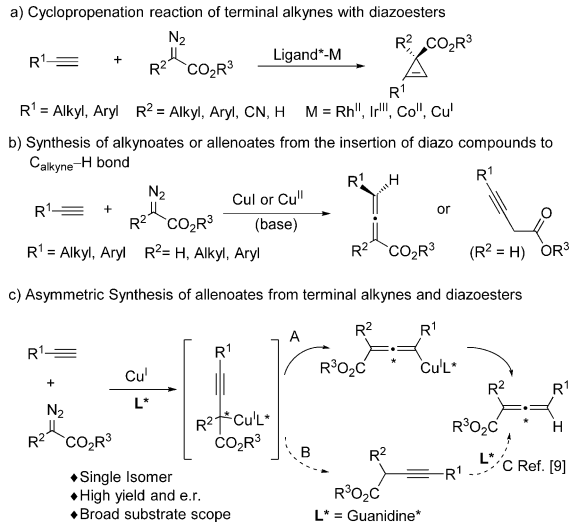
Abstract: *The asymmetric C–H insertion of α-diazoesters into 1-alkynes was achieved using chiral cationic guanidinium salts and copper(I) complexes. Optically active 2,4-disubstituted allenoates were generated under mild reaction conditions from various α-diazoesters and 1-alkynes in high yield (up to 99%) and enantioselectivity (up to 97:3 e.r.). Control experiments excluded the possibility of an asymmetric isomerization of alkynoates.*

The reaction of terminal alkynes with diazo compounds in the presence of metal complexes, such as Rh^{II}, Ir^{III}, and Co^{II}, typically leads to cyclopropenation.[1] The related asymmetric version has been well documented by several groups (Scheme 1a).[2] Aryl-, alkyl-, and cyano-substituted diazo reagents react with 1-alkynes to afford cyclopropenes with high enantiocontrol.[2] In the presence of copper salts, in contrast, 3-alkynoates can be generated from the insertion of a diazoester into the C_{alkyne}–H bond under mild reaction conditions (Scheme 1b; $R^2 = H$).[3a] The group of Fox attributed the initial observation to the presence of adventitious base (an azine), but in their optimized reaction conditions used potassium carbonate (Scheme 1b).[3b] The group of Wang also reported the synthesis of trisubstituted allenes from terminal alkynes and tosylhydrazones by a copper-carbene migratory insertion process.[3c] An enantioselective variant toward the synthesis of allenes involves the olefination of ketenes with diazoacetate employing a chiral phosphine and an iron porphyrin complex.[4]



Scheme 1. Reactions between terminal alkynes and diazo compounds.

Axially chiral allenes are useful synthons in synthetic organic chemistry.[5] They are also found in many natural products[6] and as backbones of chiral ligands in asymmetric catalysis.[7] Substantial efforts have been made toward the asymmetric synthesis of allenoates and other allenes.[8] Nevertheless, the catalytic asymmetric synthesis of axially chiral allenes, especially starting from prochiral substrates, is still in its infancy. The asymmetric isomerization of the FG-CH_2–C≡C moiety by chiral base catalysts, such as guanidines,[9] were among the early examples. Recently, some ingenious asymmetric protocols for the synthesis of chiral allenes, including the kinetic resolution of racemic allenoates,[10a] functionalization of 1-alkyl allene-1,3-dicarboxylates,[10b] β-hydride elimination of enoltriflates,[10c] carbonylation of propargylic carbonates,[10d] and addition to activated enynes,[10e] were reported by the groups of Gong, Maruoka, Frantz, Ma, and Zhang, respectively.

The previously described $C_{alkynyl}$–H insertion of diazoesters implied to us that an accessible one-pot construction of enantiomerically enriched allenoates was within reach.[3] The most pressing challenges were to address the chemo- and enantioselectivity of this reaction to make it more practical. Previous reports[3b,c] showed that ligands could accelerate the reaction. Encouraged by our recent success with chiral guanidine amides as both organocatalysts[11] and ligands[12] in asymmetric reactions, we explored their use in the copper-mediated asymmetric reaction between terminal alkynes and α-diazoesters. We envisioned two possible pathways for the desired asymmetric method (Scheme 1c). Path A would involve C–H insertion to form a chiral organocopper intermediate, which could be protonated enantioselectively to give the chiral allenoates. Alternatively, the reaction could proceed by cooperative catalysis. Copper salts could accelerate the formation of an alkynoate precursor (path B), followed by the guanidine catalyst serving as a chiral base to facilitate the enantioselective isomerization to the final

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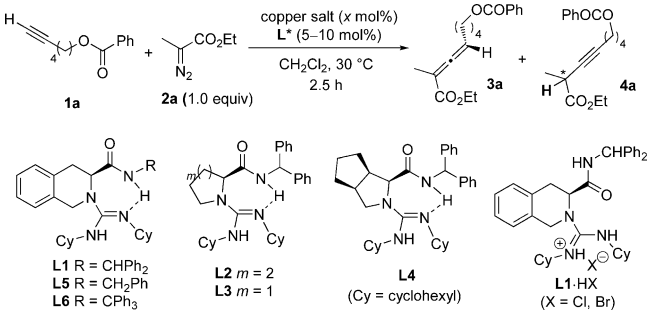
allenoates (path C). The latter possibility is a well-known process.[9] Herein, we report the first asymmetric C–H insertion between terminal alkynes and α-diazoesters in the presence of cost-efficient copper(I) salts and chiral guanidinium salts. Various trisubstituted chiral allenoates were afforded directly in high yield and enantioselectivity under mild reaction conditions. Some experiments were carried out to probe into the reaction mechanism.

Initial studies focused on the reaction between the 1-alkyne **1a** and ethyl 2-diazopropanoate (**2a**) in CH_2Cl_2 at 30 °C with 20 mol % of a copper salt and 10 mol % of the chiral guanidine **L1**, derived from (*S*)-tetrahydroisoquinoline-3-carboxylic acid (Table 1). The 2,3-allenoate **3a** was obtained

Table 1: Optimization of the reaction conditions.[a]



Entry	L	Copper salt (*x* mol %)	Yield [%][b] (**3a**/**4a**)[c]	e.r. [%][d] **3a**
1	**L1**	$CuCl_2$ (20)	< 5 (97:3)	94:6
2	**L1**	CuCl (20)	< 5 (96:4)	93:7
3	**L1**	CuI (20)	18 (90:10)	88:12
4	**L1**	$CuCl_2$ (50)	30 (> 20:1)	94:6
5	**L1**	CuCl (100)	43 (> 20:1)	98:2
6	**L2**	CuCl (100)	6 (91:9)	78:22
7	**L3**	CuCl (100)	68 (90:10)	90:10
8	**L4**	CuCl (100)	73 (41:59)	68:32
9	**L1**·HCl	CuCl (100)	55 (> 20:1)	97:3
10	**L5**·HCl	CuCl (100)	23 (> 20:1)	91:9
11	**L6**·HCl	CuCl (100)	62 (> 20:1)	94:6
12	**L1**	CuBr (60)	99 (> 20:1)	96:4
13[e]	**L1**·HBr	CuBr (50)	99 (> 20:1)	96:4
14[e]	**L1**·HBr	CuBr·Me_2S (15)	99 (> 20:1)	97:3

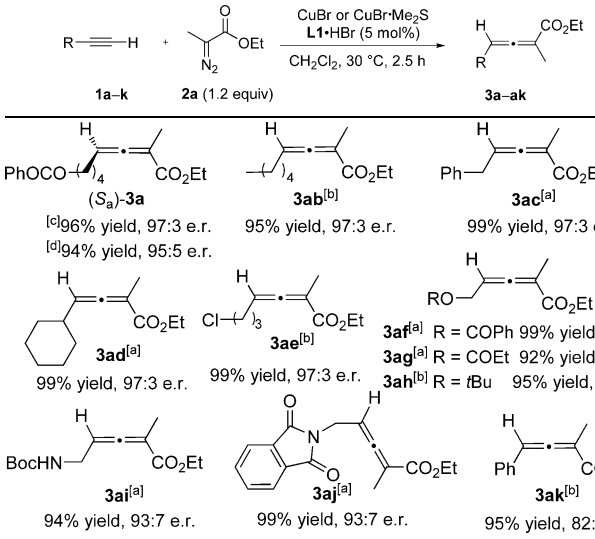
[a] Unless otherwise noted, all reactions were carried out with **L** (10 mol %), copper salt, **1a** (0.10 mmol), and **2a** (0.10 mmol) in CH_2Cl_2 (0.5 mL) at 30 °C for 2.5 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC, and the predominant enantiomer was pure. [e] **L**·HBr (5 mol %) and **2a** (1.2 equiv).

predominately, with the alkynoate **4a** also detected as a minor product, when using either $CuCl_2$, CuCl, or CuI as the metal source (entries 1–3). Although promising enantioselectivity for **3a** was given, the total yield was extremely low. To our delight, when the amount of the metal salt was increased, the yield, the ratio of **3a** to **4a**, and the enantioselectivity all improved (entries 4 and 5). The reaction conditions led to the isolation of **3a** as a single product. CuCl performed better than $CuCl_2$, thus providing **3a** in 43 % yield and 98:2 e.r. (entry 5). Encouraged by these results, we next identified the best structure for the chiral guanidine ligand. The yield and enantioselectivity dropped dramatically when the L-pipecolic-acid-derived **L2** was used (entry 6). In spite of an improvement in yield when either the L-proline-derived **L3** or L-ramipril-derived guanidine **L4** was used, the enantioselectivity decreased (versus **L1**) and the by-product **4a** was detected in higher quantities (entries 7 and 8). Previous reports showed that copper(I) acetylide could be formed from terminal alkynes and copper salts.[13] These reactions generally required base, which also acted as a ligand to assist the process. With this in mind, we wondered whether in situ protonation of the imine unit of the guanidine ligand could affect the outcome of the reaction. Accordingly, we sought to exploit the guanidinium hydrochloride salts **L**·HCl as prospective ligands. Fortuitously, **L1**·HCl improved the yield slightly while the chemo- and enantioselectivity remained unchanged (entry 9). Varying the amide unit of guanidinium salts in **L5**·HCl or **L6**·HCl gave no improved outcomes in terms of both yield and enantioselectivity (entries 10 and 11). CuBr exhibited significantly increased reactivity, and even decreasing the amount of copper salt to 60 mol % provided an almost quantitative yield at the cost of a slight deterioration in enantioselectivity (entry 12 versus entry 5). The ligand **L1**·HBr performed just as well as the neutral ligand (entry 13). Considering the poor solubility of CuBr in organic solvents, the soluble copper salt CuBr·Me_2S was tested (see the Supporting Information). In this case, the use of the copper(I) salt could be reduced to 15 mol % in the presence of 5 mol % of **L1**·HBr, thus resulting in a comparable yield and enantioselectivity (entry 14). After an extensive screen of the reaction conditions, our optimal reaction conditions involved 5 mol % of **L1**·HBr, either 50 mol % of CuBr or 15 mol % CuBr·Me_2S, and 1.2 equivalence of α-alkyl-α-diazoesters (conditions A; see the Supporting Information), or 5 mol % of **L1**·HCl, 90 mol % of CuCl, and 1.2 equivalents of α-aryl-α-diazoesters (conditions B; see the Supporting Information).

The applicability of this process to a broad range of terminal alkynes with **2a** is shown in Table 2. Straight chain alkyl substituted 1-alkynes gave slightly lower e.r. values compared to cyclohexyl- and benzyl-substituted ones (**3aa**–**ad**). Pleasingly, important functional groups, such as esters, ethers, amides, and halogens, were tolerated, thus providing the corresponding functionalized allenoates in up to 92–99 % yield and 89:11–97:3 e.r. (**3af**–**aj**). Moderate enantioselectivity was obtained with ethynyl benzene (**1k**), thus representing a limitation of the current reaction conditions. Finally, it is interesting to note that a gram-scale asymmetric synthesis of **3a** could also be accommodated with either 15 mol % of CuBr·Me_2S or 50 mol % of CuBr. The absolute configuration of **3a** was established to be S_a by X-ray diffraction study of the corresponding lactone derivative[10d,14] (see the Supporting Information).

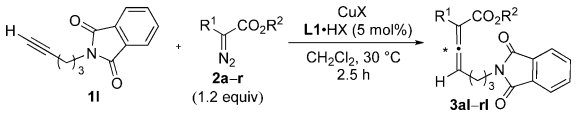
The scope of such an enantioselective strategy was then explored by conducting the reaction with various α-diazoesters. To facilitate the determination of e.r. values by HPLC, **1l** was selected as the representative 1-alkyne (Table 3). A series of 2-diazopropanoates reacted smoothly with **1l**, thus delivering the desired allenoates in excellent yield and enantioselectivity regardless of the steric hindrance of the ester substituent (entries 1–5). The α-alkyl-diazoesters **2f**–**h**

Table 2: Substrate scope for terminal alkynes.



[a] **L1**·HBr (5 mol%), and CuBr (50 mol%) at 0.2 mmol scale. [b] **L1**·HBr (5 mol%), CuBr·Me_2S (15 mol%). [c] Table 1, entry 14 at 4.0 mmol scale. [d] Table 1, entry 13 at 5.0 mmol scale. Yields are those of the isolated products. The e.r. values were determined by HPLC. Boc = *tert*-butoxycarbonyl.

Table 3: Substrate scope for α-diazoesters.

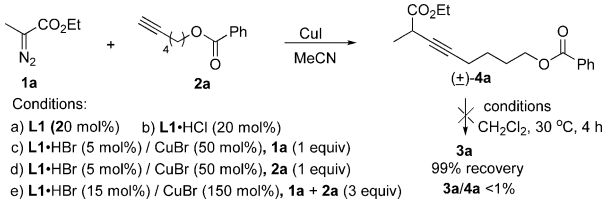


Entry	R^1	R^2	Yield [%][c]	e.r. [%][d]
1[a]	Me	Et	96 (**3al**)	96:4
2[a]	Me	Me	90 (**3bl**)	96:4
3[b]	Me	*t*Bu	99 (**3cl**)	97:3
4[a]	Me	1-adamantyl	98 (**3dl**)	97:3
5[b]	Me	Bn	99 (**3el**)	96:4
6[a]	Et	*t*Bu	72 (**3fl**)	94:6
7[a]	*n*-Pr	*t*Bu	70 (**3gl**)	94:6
8[a,f]	*n*-decyl	*t*Bu	48 (**3hl**)	93:7
9[c]	C_6H_5	Me	99 (**3il**)	94:6
10[c]	C_6H_5	Et	97 (**3jl**)	95:5
11[c]	C_6H_5	*t*Bu	87 (**3kl**)	97:3
12[c]	C_6H_5	1-adamantyl	85 (**3ll**)	96:4
13[c]	2-FC_6H_4	*t*Bu	94 (**3ml**)	97:3
14[c]	3-FC_6H_4	*t*Bu	73 (**3nl**)	96:4
15[c]	4-FC_6H_4	*t*Bu	93 (**3ol**)	97:3
16[c]	2-MeC_6H_4	*t*Bu	78 (**3pl**)	94:6
17[c]	3-MeC_6H_4	*t*Bu	75 (**3ql**)	94:6
18[c]	4-MeC_6H_4	*t*Bu	54 (**3rl**)	95:5

[a] **L1**·HBr (5 mol%), CuBr·Me_2S (15 mol%). [b] **L1**·HBr (5 mol%), CuBr (50 mol%). [c] **L1**·HCl (5 mol%), CuCl (90 mol%). [d] Yield of the isolated product. [e] Determined by HPLC. [f] The by-product alkene was determined by NMR spectroscopy.

with longer aliphatic chains underwent the reaction in moderate yield and 93:7–94:6 e.r. (entries 6–8). The decrease in yield was mainly a result of the formation of alkenes by H migration of α-alkyl-carbene intermediates.[15] Moreover, when 2-diazo-2-phenylacetate esters were employed (conditions B), there was no significant difference in enantioselectivity upon increasing the steric hindrance of the ester group (entries 9–12). Both the reactivity and the enantioselectivity were found to be dependent upon the electronic nature of the substituent on the α-aryl-diazoesters **2m–r**. The electron-deficient ones (**2m–o**) gave higher e.r. values and yields in comparison with the electron-rich ones (**2p–r**; entries 13–15 versus entries 16–18). It is noteworthy that the reactions completed rapidly within 2.5 hours at a mild reaction temperature and the alkynoates **4** were not isolated in these cases.

In light of the previously reported chiral-guanidine-accelerated isomerization of the alkynoates,[9] we wondered whether the chiral products **3** formed following a similar process. However, when the racemic alkynoate **4a** was subjected to the catalytic conditions, such as the guanidine **L1**, **L1**·HCl, **L1**·HCl/CuCl, and others, none of **4a** converted into **3a**, and **4a** was recovered as a racemate (Scheme 2). This



Scheme 2. Control experiments.

observation implies that the enantiomerically enriched allenoate is not generated by isomerization of the corresponding alkynoate (path C; Scheme 1c).

The reaction rate and product distribution depend crucially on the ligand. This dependence is reinforced by the fact that a 20% total yield of racemic **3a**/**4a** (1:1) was afforded in the presence of 50 mol% of CuBr without any ligand. The interaction between either the ligand **L1** or **L1**·HCl and copper(I) was confirmed by NMR spectroscopy (see the Supporting Information). Although we have not isolated the complexes of copper(I) with the guanidine or guanidinium salt, we postulate that guanidine could act as a neutral ligand[16] and coordinate with the copper salts. More importantly, the guanidinium salts could act as a cationic ligand, and is uncommon in coordination chemistry.[17] The electron-withdrawing quaternized nitrogen atom of the guanidinium would render coordinated metal centers highly electrophilic. The presence of copper clusters in the $CuCl_2$/**L1**·HCl solution were substantiated by negative-mode ESI-MS (see the Supporting Information). The main observed anions are $[Cu_2Cl_5]^-$ and $[\mathbf{L1}\cdot HCl\text{-}Cu_2Cl_5]^-$. This observation indicates coordination of the guanidinium salt with the copper cluster, and to some extent interprets the role of excessive copper salt.

Plausible mechanisms accounting for either the copper(II)- or copper(I)-catalyzed formation of allenoates from terminal alkynes were proposed by the groups of Fox[3b] and Wang,[3c] respectively. This asymmetric catalytic system seems somewhat different given that no additional base was present. To assign the possible species and oxidation state of the copper center, we performed X-band EPR measurements on $CuCl_2$ in the presence of **L1** (and with other reactants) in THF

(see the Supporting Information). The X-band EPR spectrum of **L1**·HCl/$CuCl_2$ revealed an axial pattern, which is consistent with a Cu^{II} ($S = 1/2$) center. Once **2a** was added, the peak disappeared within 10 minutes, thus indicating rapid reduction of Cu^{II} to Cu^{I} by **2a** and suggesting the formation of a Cu^{I}–carbene intermediate. The spectrum of the reaction mixture which includes the 1-alkyne was identical. Additionally, the reduction of Cu^{II} to Cu^{I} by **1a** was observed[13] in the presence of two equivalents of guanidine, but the rate was much lower than that observed for the reduction by the α-diazoester. This outcome is not surprising as copper acetylide formation typically requires excess base. These observations suggest that the reaction begins with the formation of a ligand/copper carbenoid. The excess copper salt required in the process indicates that the effect of Cu^{I} is not exclusive to the formation of a copper carbenoid species. The mechanistic studies for the copper-catalyzed CuAAC reaction[13a,b] suggest that the reaction mechanism of our C–H insertion is more complicated than our initial speculation.

In summary, the asymmetric C–H insertion of 1-alkynes with α-diazoesters was realized for the first time. The reactions produced chiral 2,4-disubstituted allenoates directly and exclusively under mild reaction conditions. A variety of 1-alkynes and α-diazoesters were well tolerated, thus affording the corresponding allenoates in excellent yield and enantioselectivity. The successful use of chiral guanidinium salts suggests the potential to use these species as cationic chiral ligands in asymmetric catalysis. Current efforts are underway to discover the structures of guanidine-based metal complexes and a detailed mechanism, and develop other novel asymmetric reactions.

Experimental Section

C–H insertion of α-diazoesters to terminal alkynes: A mixture of copper salt (15–90 mol%) and the guanidinium salt **L1**·HX (0.01 mmol, 5 mol%) was weighed into a test tube under an inert atmosphere. Subsequently, 1.0 mL of CH_2Cl_2 was added, followed by the addition of the alkyne **2** (0.2 mmol) and α-diazoester **1** (0.24 mmol). The resulting mixture was stirred for 2.5 h at 30 °C and the product **3** was purified by flash chromatography (petroleum ether/EtOAc = 20:1).

Keywords: allenes · asymmetric catalysis · copper · diazo compounds · synthetic methods

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