A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202000860

Link to VoR: https://doi.org/10.1002/anie.202000860

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Copper-Catalyzed Enantioselective Sonogashira Type Coupling of Alkynes with α-Bromoamides

Xueling Mo, Bin Chen, Guozhu Zhang*

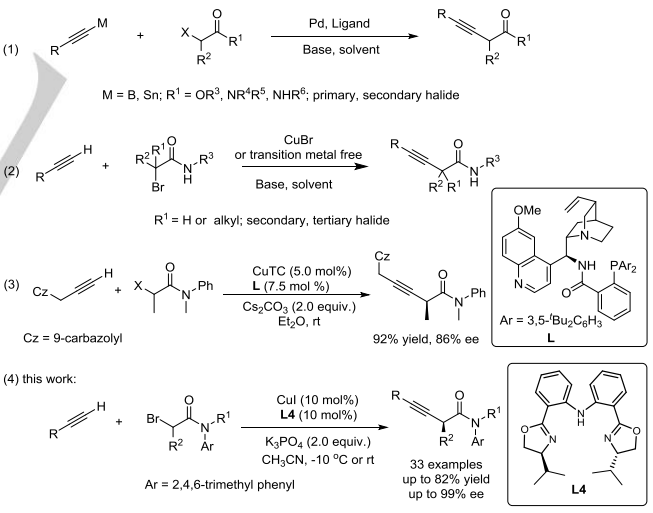
Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry

Abstract: An asymmetric copper-catalyzed Sonogashira type coupling between alkynes and α-bromoamides has been developed. This method represents a facile approach to synthetically useful β, γ-alkynyl amides from two readily available starting materials in a highly enantioselective manner. A bisoxazoline diphenylanaline (BOPA) serves as the effective chiral ligand. Preliminary mechanistic studies support the formation of alkyl radical species.

Transition-metal-catalyzed cross-coupling reactions between alkyl electrophiles and prefunctionalized nucleophiles, such as organozinc, organoboron, Grignard and organosilane reagents, with a nonsymmetrical ligands have been one of the most powerful tools for the synthesis of enantioenriched products. [1] Among these reactions, coupling of α-halocarbonyl and carbonyl-like compounds (such as nitriles, sulfonates, phosphates, amides and so forth) is noteworthy because the resulting α-functionalized carbonyl compounds are versatile building blocks in organic synthesis.[2] Although significant progresses have been made on the α-functionalization of carbonyl groups with both C(sp^3)[3] and C(sp^2)[4] coupling partners, relatively limited reports are available for the C(sp) ones, presumably due to the facile side reactions occurring on alkynes.[5] Given the fact that internal alkynes are important motifs in natural and bioactive molecules[6] as well as functional materials,[7] the methodology development of introduction of the C≡C moiety has been attracting continuous attention from the synthetic community.[8]

In 2003, Fu et al. pioneered a method of coupling terminal alkynes with unactivated primary bromides and iodides by using catalytic amounts of both palladium and copper salts combined with *N*-heterocyclic carbene ligands.[9] It inspired chemists to explore other metal/ligand systems to couple more challenging secondary alkyl halides, and α-carbonyl halides as well. Lei group and others reported the coupling of alkynylmetallic species (alkynylstannanes and alkynyltrifluoroborates) with α-halo carbonyl compounds through the Pd-catalyzed Stille and Suzuki reactions (Scheme 1, eq. 1).[10] Oshima and others realized the reaction of gallium or indium acetylides with α-halo carbonyl compounds through a tandem radical addition-fragmentation process.[11] Fu, Wang and others showed that the Cu could catalyze the reaction between alkynes and diazocarbonyl compounds via a carbenoid intermediate.[12] Nishikata group developed a Cu-catalyzed Sonogashira type coupling of α-bromoamide to construct quaternary carbons, in which alkynylated copper is a key intermediate.[13] Li's group recently reported light-mediated couplings with terminal alkynes and α-carbonyl halides (eq. 2).[14] Despite all those elegant progress, as far as we know, the asymmetric Sonogashira type coupling of terminal alkynes with α-carbonyl halides has been met with limited success. Liu recently reported an elegant copper-catalyzed stereoconvergent Sonogashira C(sp^3)–C(sp) cross-coupling of a broad range of terminal alkynes and racemic alkyl halides enabled by a chiral cinchona alkaloid-based P,N-ligand.[15] In their scope studies, they reported one example of α-bromoamide as substrate, a good yield and ee was obtained (eq. 3). Given the significance of α-alkynylcarbonyl functionality, alternative chiral catalyst system that can directly employ the commercially available compounds, such as alkynes and α-halo carbonyl compounds, leading to enantioenriched α-alkynylcarbonyls is still highly desired.

We herein report the copper-catalyzed asymmetric Sonogashira cross-coupling to generate β, γ-alkynyl amides (eq. 4). This reaction enables the enantioselective coupling of α-halo amides with unfunctionalized terminal alkynes. We demonstrate this coupling's utilities as many manipulations can be applied to the alkyne functionalities. Preliminary mechanistic investigations suggest the formation of alkyl radical species.



Scheme 1. The synthesis of α-alkynyl carbonyl compounds

Adopted the conditions from our previous study on enantioselective arylalkynylation of alkenes,[16] our investigations began with reaction of commercially available racemic *N*-benzyl-2-bromo-*N*-phenylpropionamide and ethynylbenzene to make β, γ-alkynyl amide **c1** using a variety of chiral ligands in the presence of copper salt and base (Table 1, entries 1-8). We tested a variety of Cbzbox with different substituents (**L1–L3**). However, no better results in terms of ee were obtained (Table 1, entries 1–3). Surprisingly, we were pleased to find that the reaction using CuI as catalyst, *i*Pr-BOPA **L4** as ligand and

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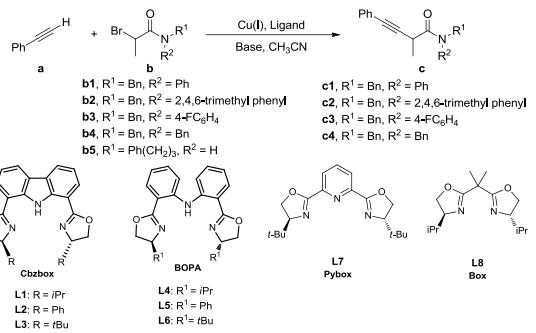
10.1002/anie.202000860

K_3PO_4 as base provided the desired product **c1** with 76% ee, in 80% yield (Table 1, entry 4). [17]

Table 1. Optimization of the reaction conditions.



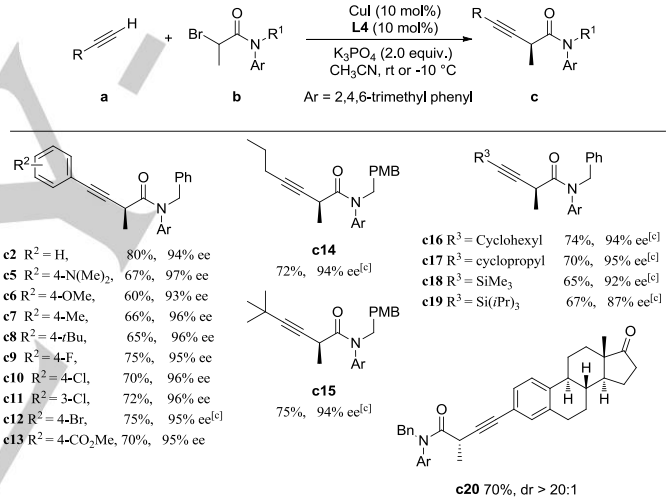
entry[a]	R^1, R^2	catalyst	ligand	ee%	yield%[b]
1	Bn, Ph (**b1**)	CuI	**L1**	13	67 (**c1**)
2	Bn, Ph (**b1**)	CuI	**L2**	13	86 (**c1**)
3	Bn, Ph (**b1**)	CuI	**L3**	3	55 (**c1**)
4	Bn, Ph (**b1**)	CuI	**L4**	76	80 (**c1**)
5	Bn, Ph (**b1**)	CuI	**L5**	40	60 (**c1**)
6	Bn, Ph (**b1**)	CuI	**L6**	-	0
7	Bn, Ph (**b1**)	CuI	**L7**	-	0
8	Bn, Ph (**b1**)	CuI	**L8**	-	0
9[c]	Bn, Ph (**b1**)	CuI	**L4**	87	76 (**c1**)
10[d]	Bn, Ph (**b1**)	CuI	**L4**	89	45 (**c1**)
11[c]	Bn, Mes (**b2**)	CuI	**L4**	94	84 (**c2**)
12[c]	Bn, 4-FC_6H_4 (**b3**)	CuI	**L4**	83	80 (**c3**)
13[c]	Bn, Bn (**b4**)	CuI	**L4**	41	70 (**c4**)
14[c]	$Ph(CH_2)_3$, H (**b5**)	CuI	**L4**	0	0

[a] The reaction conditions were α-halo amides (0.1 mmol), alkyne (0.2 mmol), Cu(I) (10 mol%), ligand (10 mol%), base (0.2 mmol), in CH_3CN(1.0 mL) at 25 °C for 24 h unless noted otherwise. [b] The yields were measured by ^1H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase. [c] Reactions were performed in CH_3CN (0.1 M) at -10 °C. [d] Reactions were performed in CH_3CN (0.1 M) at -20 °C.

L5 and **L6** exhibited lower enantioselectivities (entries 5 and 6). Further examination of chiral ligands revealed that Pybox **L7** and privileged box **L8** were not effective for current reaction (entries 7 and 8). Lowering the reaction temperature to -10 °C further improved the ee to 90% with no compromise in product yield (entry 9). Further adjustment of the reaction parameters showed that the steric demand of R^2 plays an important role in improving the efficiency of the cross-coupling process. The reaction of **b2** with a mesitylene subsititution at -10 °C provide **c2** in 84% yield and 94% ee (entry 11). Dialkyl tertiary amide and secondary amide are less efficient substrates for this reaction (entries 13 and 14). The tuning of other parameters such as changing the solvent to something other than acetonitrile, using other bases in place of K_3PO_4 and other Cu-catalysts instead of CuI was elaborated in Tables S1 to S5 (see the Supporting Information). The optimized reaction conditions was thus determined to be 1.0 equiv of *N*-benzyl-2-bromo-*N*-mesitylpropanamide and 2.0 equiv of ethynylbenzene at -10 °C in CH_3CN, catalyzed by 10 mol% CuI and 10 mol% *i*Pr-BOPA **L4** (Table 1, entry 11).

Under the optimized conditions, the coupling reactions between racemic α-bromoamide with various alkynes were examined (Table 2). Firstly, a range of substituted aryl alkynes were evaluated to identify the generality of the method with respect to this substrate. In this regard, α-alkynylation proceeded smoothly with *N,N*-dimethylamino-, methoxy-, alkyl-, and halogen-substituted arylalkynes (products **c5**-**c13**). In addition to aromatic alkynes, a number of alkyl-substituted alkynes (products **c14**, **c15**) and cycloalkyl- (products **c16**, **c17**) proved to be good substrates for the coupling reaction. Silyl subsituted alkynes (**c18**, **c19**) were also tolerated, and the corresponding products were obtained in good yields with excellent enantioselectivities. Notably, 3-ethynylestrone containing carbonyl group and four continuous chiral centers resulted in the desired product in 70% yield and > 20:1 dr by this method (**c20**).

Table 2. Scope studies with alkynes. [a][b]



[a] Unless noted otherwise, reactions were performed in CH_3CN (0.1 M) at -10 °C; [b] Yields of isolated products are given. The ee values were determined by HPLC analysis on a chiral stationary phase. [c] Reactions at rt. Ar = 2,4,6-trimethyl phenyl; PMB = *p*-Methoxbenzyl.

According to the condition studies, disubsituted α-bromoamide with a sterically demanding aryl group (2,4,6-trimethyl phenyl in this case) are critical for good stereocontrol. Thus, fixing of the aryl substitution, the substituent on the nitrogen of the amide can be an electron-rich or an electron-poor benzyl groups (**c21** to **c26**), or it can be an alkyl group (**c27** and **c28**). Based on single crystal X-Ray analysis of **c24**, the absolute configuration of the cross-coupling product was (*S*). Thiophene and naphylnene could be tolerated as well (**c29** and **c30**). We next explored the use of different alkyl groups attached to the α-carbon of the bromo amide substrates. When the α-alkyl was Et or *n*Bu, 72–75% yields with the ee up to 99% were obtained (**c31** and **c32**). However, the current catalytic process was unsatisfactory with other α-bromocarbonyl compounds. Reactions of α-bromo ester and ketone didn't provide the desired products, homocoupling products dominated with small amount of allenyl derivative. [18] Reaction of α-bromo nitrile provide the vinyl bromide as the major product which is derived from atom transfer radical addition pathway.

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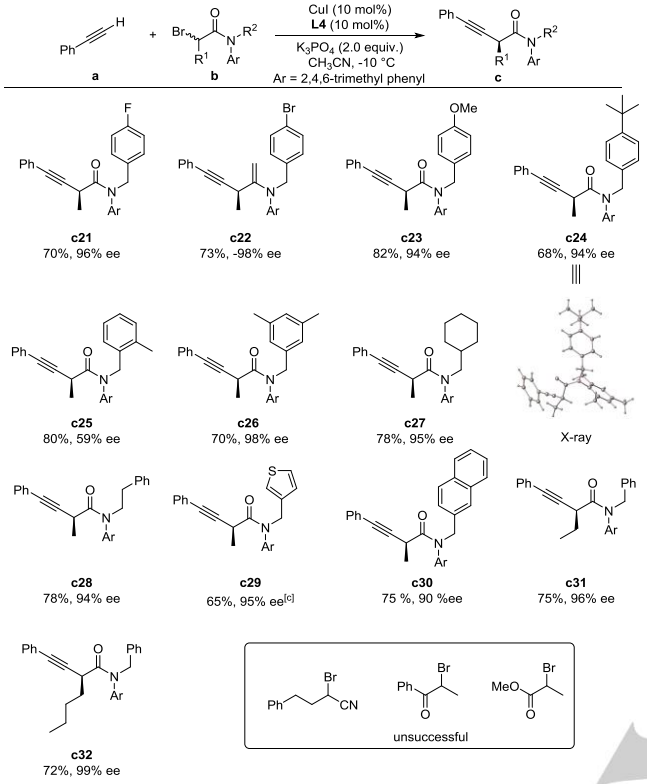
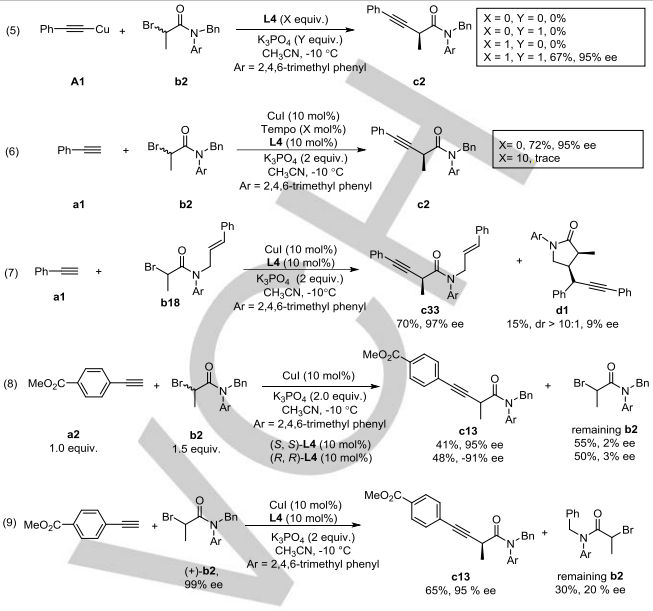
Table 3. Scope studies with α-carbonyl compounds. [a][b]



[a] All reactions were performed in CH_3CN (0.1 M) at -10 °C. [b] Yields of isolated products are given. The ee values were determined by HPLC analysis on a chiral stationary phase. [c] Reactions were at rt.

Control experiments were conducted to probe the possible mechanism of this copper catalysed coupling reaction (Scheme 2). The reaction of CuX and ethynylbenzene in the presence of a base readily give copper acetylide **A1**.[19a] **A1** did not react with **b2** in the absence of BOPA ligand or base, suggesting both factors are crucial for the coupling reaction taking place (Scheme 2, eq. 5). In the presence of K_3PO_4 (1.0 equiv) with ligand (1.0 equiv), **c2** was generated in 67% yield and 95% ee. This result suggests that **A1** is likely the key intermediate in this reaction. We also added TEMPO to these reaction mixtures, 10 mol% of TEMPO was enough to shut down the reaction (eq. 6). Reaction of **b18** provide the cyclized product **d1** in *cis* selectivity (eq. 7), a typical reactivity and stereoselectivity that have been reported for the cyclization of the derived secondary alkyl radical.[20] Those results implied that free-radical species may be generated during the reaction, which is in sharp contrast to the 1,10-phen and copper catalyzed alkynylation of tertiary α-bromoamide.[13][18] Consistent with our hypothesis that an enantioconvergent process is involved, the choice of either (*S*,*S*)-**L4** or (*R*,*R*)-**L4** as the chiral ligand leads to the formation of opposite enantiomers of the desired product with the stereochemical outcome determined entirely by the configuration of the ligand (eq. 8). Enantiomericaly pure *ent*-**b2** reacted well, analysis of the remaining bromide revealed a significant erosion of the enantiopurity, suggesting a fast racemization of an alkyl bromide (eq. 9). To gain more insight into the mechanism, we monitored the ee of the product as a function of the ee of the ligand (see the Supporting Information). The near linear relationship may indicate only one chiral ligand is involved in the enantiodetermining step.



Scheme 2. Mechanistic investigation.

Based on the literature [13], [15] and these findings, we proposed a reaction mechanism (Fig. 1). The Cu(I)X undergoes ligand exchange with **L** in the presence of base leading to tridentate complex Cu(I)**L**.[19] [21] A subsequent interaction with RC≡CH in the presence of K_3PO_4 yields [**L**Cu(I)(C≡CR)]$^-$ K^+ (**A**), which could reduce the α-bromoamide to provide a copper(II) species **L**Cu(II)(C≡CR) with a simultaneous formation of an alkyl radical (**B**). The cyclic voltammogram of **L**Cu(I) C≡CPh show a reversible wave at -2.58V versus the saturated calomel electrode (SCE) corresponding to the Cu (I)/Cu (II) redox couple.[22a, 22b] The alkyl bromides ($MeO_2CCH(CH_3)Br$) have reduction potential $E_{1/2}$ = -0.68V versus SCE.[22c] Those results suggest that the SET process form copper acetylide to α-bromoamide may be viable, an halogen atom abstraction is also possible. [23] [24] Two possible pathways[13] might be as follows: In path a, the alkyl radical reacts with copper(II), delivering a copper(III) complex (**C**), which undergoes reductive elimination to generate the product, with regeneration of the catalyst. Alternatively, in path b, the alkyl radical could undergo direct out-of-cage bond formation with the copper(II) species to provide the same result.

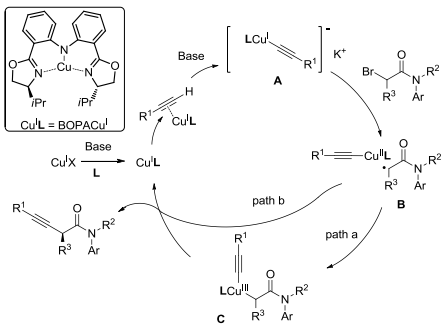
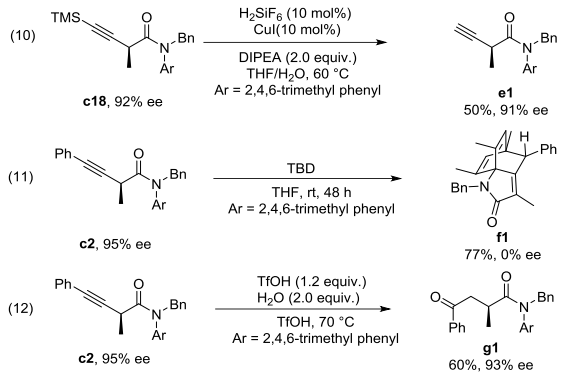


Figure 1. Proposed reaction mechanism.

β, γ-alkynyl amides are a particularly interesting class as the two functional groups have widely orthogonal reactivity, making them highly versatile intermediates in complex molecule synthesis. To illustrate the synthetic utility of the β, γ-alkynyl amide products, several derivatization reactions of product were

pursued. As shown in Scheme 3 (eq. 10), the desilylation[25] by catalytic H_2SiF_6 occurred smoothly to give free terminal alkyne **e1** with maintenance of enantiopurity. Treatment of **c2** with catalytic TBD led to a strained bridged polycyclic lactam **f1**, [26] however, in racemic form (eq. 11). The 1,4-diketone **g1** could be readily obtained by acidic hydration (eq. 12).[27]



Scheme 3. Synthetic utilities of β, γ-alkynyl amide

In conclusion, a general and highly effective, Cu-catalyzed enantioselective alkynylation of α-bromo amide have been achieved. This reaction can be applied to a variety of amides and a broad range of terminal alkynes. An unusual mono-anionic *NNN* pincer ligand (BOPA) accounts for the high efficiency and stereoselectivity. Owing to the ready availability of starting material, mild reaction conditions, the significance of resulting functionalities, and high enantioselectivity, the application of this novel strategy established here in synthetic and medicinal chemistry is positively expected.

-Acknowledgements

We are grateful to NSFC-21772218, 21421091, XDB20000000, the "Thousand Plan" Youth program, State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, and the Chinese Academy of Sciences.

Keywords: Copper-catalysed • Sonogashira reaction •Enantioselective • α-Bromoamide • Terminal alkyne

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10.1002/anie.202000860

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Layout 2:

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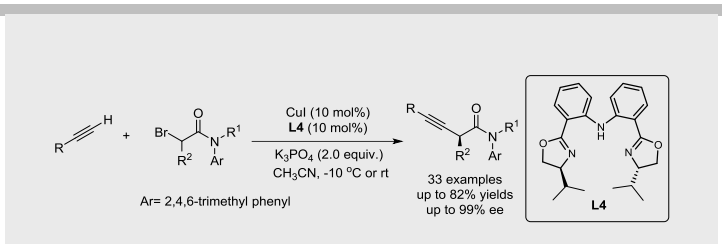

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Copper-Catalyzed Enantioselective Sonogashira Type Coupling of Alkynes with α-Bromoamides

An asymmetric copper-catalyzed Sonogashira type coupling between alkynes and α-bromo amide compounds has been developed. This method represents a facile approach to synthetically useful β,γ-alkynyl amides from two readily available starting materials in a highly enantioselective manner. A bisoxazoline diphenylanaline(BOPA) serve as the effective chiral ligand. Preliminary mechanistic investigations suggest the formation of alkyl radical species.