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Enantioselective Copper-Catalyzed Remote C(sp^3)−H Alkynylation of Linear Primary Sulfonamides

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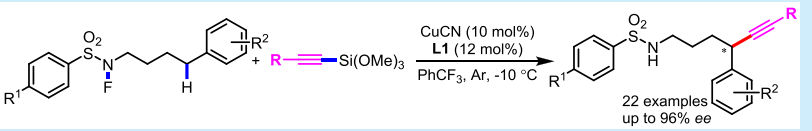
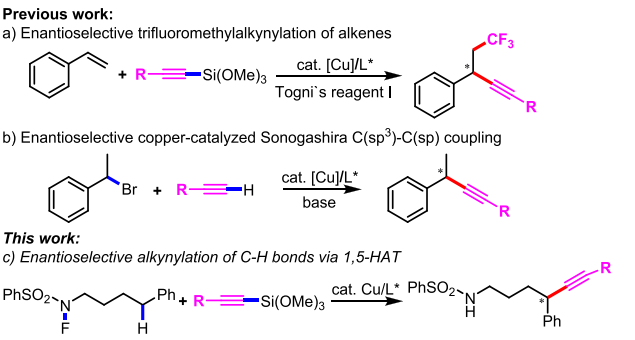


ABSTRACT: The highly efficient copper-catalyzed enantioselective alkynylation of the remote C(sp^3)−H bond on linear primary sulfonamides is presented here using a radical relay strategy. The chiral box−copper complex, which is used to recapture the *in-situ*-generated alkyl radical via a 1,5-HAT strategy, is the key to success, affording the chiral alkynes after a following reductive elimination. A general substrate scope, mild conditions, and excellent regio- and enantioselective control are demonstrated in this method.

Benefitting from their electronic properties and various methods for further transformations, alkynes have been found in multiple natural products, and they often serve as special material synthons and are widely used as pivotal intermediates for the total synthesis of complex biologically active or functional molecules. Accordingly, chiral alkynes have long attracted increasing attention as a vital building block in therapeutics and biological molecules and a useful chiral synthon in organic synthesis.[1] Therefore, many efforts have been dedicated to finding new methods for the concise and efficient synthesis of various optically active alkynes over the past several decades.[2] Although the catalytic enantioselective hydroalkynylation of alkene has been well established,[3,4] methods for the direct enantioselective alkynylation of remote C(sp^3)−H bonds are still very rare and remain a major issue to be solved. The first breakthrough was made by the Li group with an enantioselective copper-catalyzed alkynylation, which was limited only by its prerequisite that the later-functionalized C(sp^3)−H bonds must be positioned next to a nitrogen atom, and the method achieved only moderate *ee*.[5] Meanwhile, the Shi group recently demonstrated an enantioselective alkynylation of methylene C(sp^3)−H bonds under a Pd(II)-catalyzed system.[6] Despite such advances in this area, direct asymmetric C(sp^3)−H alkynylation is consistently a heated research area that should be addressed.

Given the intrinsic high activity and instability of radicals, the transition-metal-catalyzed asymmetric functionalization via the radical pathway has already shown its significance while being a huge challenge.[7] It must be said that this radial-involved enantioselective functionalization strategy has been successfully utilized for asymmetric alkynylation very recently. The Liu group described a copper-catalyzed enantioselective alkynylation in which a benzylic radical generated by the capture of the trifluoromethyl radical with styrenes was involved (Scheme 1a).[8] Very recently, the Liu group established a radical-involved asymmetric Sonogashira cross-coupling reaction (Scheme 1b).[9] However, although hydrogen-atom abstraction via the radical pathway has long been recognized as one of the most efficient methods to realize various functionalization of C(sp^3)−H bonds, the direct enantioselective alkynylation of C(sp^3)−H bonds through selective hydrogen-atom abstraction is worth establishing. Inspired by the well-established reaction pattern in 1,5-

Scheme 1. Radical-Involved Enantioselective Alkynylation



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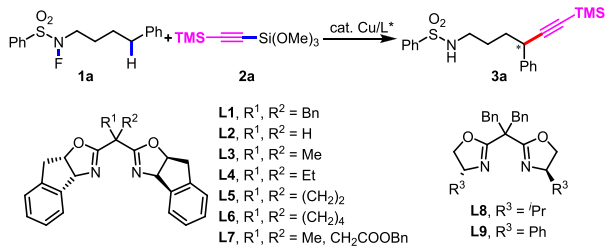
hydrogen atom transfer (1,5-HAT),[10−12] we reckoned that the selective cleavage of the δ-C(sp^3)−H bond on the aliphatic chain leading to the generation of a remote carbon radical via 1,5-HAT could be recaptured by a chiral alkynyl copper catalyst, which then furnished the desired optically pure alkynes after the following enantioselective reductive elimination from the resulting chiral copper complex.

Herein we present an enantioselective alkynylation of the C(sp^3)−H bond under copper catalysis using the 1,5-HAT strategy with excellent enantioselectivity (up to 96% *ee*). Besides high reactivity, a broad substrate scope, and mild conditions, excellent regio- and enantioselective control have been revealed in our newly established method. The radical relay strategy presented here supplies an efficient solution to the construction of chiral alkynes by the functionalization of omnipresent inert C(sp^3)−H bonds with high regio- and enantioselective control.

Considering that the Thorpe−Ingold effect could enable the HAT process to minimize the entropy, the use of alkyl amides with substituents on the alkyl chain normally serves as an efficient strategy for remote C−H functionalization, whereas its synthetic utility is evidently constrained due to the scope limitation. Indeed, C(sp^3)−H bonds on N-sulfonylated linear primary amines are debatably the most difficult substrates in the selective functionalization via 1,5-HAT.[12d,13,14] To address this challenge, we commenced our initial investigation with **1a** as the starting material, disilyl-substituted acetylene (**2a**) as the alkynylating reagent, and a catalytic amount of CuCN (10 mol %) in $PhCF_3$ at 0 °C. To our great delight, the desired alkynylation product **3a** was obtained in 49% yield with 93% *ee* when using chiral bis(oxazoline) ligand **L1** (Table 1, entry 1). Next, we carefully performed experiments to identify optimal solvents and copper salts using **L1** as the ligand (Table 1, entries 2−9). Actually, the use of dichloromethane (DCM) as the solvent or CuSCN as the copper source could afford **3a** in similar yields with slightly lower *ee* (Table 1, entries 2 and 8). Guided by our previous research experience, determining the best chiral ligand for each reaction is a very important factor in the enantioselective reactions. Therefore, we tested a number of chiral bis(oxazoline) ligands (Table 1, entries 10−17) and found that compared with **L1**, all of the other ligands gave lower yields and *ee*. To further improve the yield, we then carefully analyzed this reaction system and found that a large amount of the H-abstraction byproduct of nitrogen was hard to suppress. It was conjectured that the rate of the enantioselective alkynylation step, where the benzyl radicals were trapped by the chiral copper complex to afford **3a**, might be slow and thus enabled the abstraction of the hydrogen atom of the nitrogen-centered radical then stopped the following remote functionalization. Therefore, we intended to slow down the rate of the generation of the nitrogen-centered radical and coordinated the trapping rate of the *in-situ*-generated carbon radical by the copper complex and thus improve the yields. Accordingly, the reduction of the reaction temperature to −10 °C slightly improved the yield to 58% (Table 1, entry 18). Considering that oxygen might be detrimental to the yields and *ee*, the yield was remarkably increased to 81% with slightly higher *ee* (94%) when degassed $PhCF_3$ was used as the solvent in a lower concentration (Table 1, entries 19 and 20).

After completing the optimization of reaction conditions, we set out to test the functional group compatibility of this catalytic asymmetric alkynylation. As shown in Scheme 2, a

Table 1. Optimization of Conditions[a]



entry	[Cu]	solvent	L	yield (%)[b]	*ee* (%)[c]
1	CuCN	$PhCF_3$	**L1**	49 (20[d])	93
2	CuCN	DCM	**L1**	46 (12[d])	90
3	CuCN	DCE	**L1**	46 (11[d])	83
4	CuCN	PhCl	**L1**	41 (24[d])	84
5	CuCN	MeCN	**L1**	43 (22[d])	74
6	$Cu(MeCN)_4PF_6$	$PhCF_3$	**L1**	trace	
7	CuI	$PhCF_3$	**L1**	68 (19[d])	84
8	CuSCN	$PhCF_3$	**L1**	58 (23[d])	90
9	$Cu(OAc)_2$	$PhCF_3$	**L1**	41 (25[d])	82
10	CuCN	$PhCF_3$	**L2**	34	31
11	CuCN	$PhCF_3$	**L3**	32	72
12	CuCN	$PhCF_3$	**L4**	23	77
13	CuCN	$PhCF_3$	**L5**	41	53
14	CuCN	$PhCF_3$	**L6**	36	57
15	CuCN	$PhCF_3$	**L7**	35	69
16	CuCN	$PhCF_3$	**L8**	35	82
17	CuCN	$PhCF_3$	**L9**	43	79
18[e]	CuCN	$PhCF_3$	**L1**	58 (24[d])	93
19[e,f]	CuCN	$PhCF_3$	**L1**	72 (23[d])	94
20[e,f,g]	CuCN	$PhCF_3$	**L1**	81 (19[d])	94

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (2.0 equiv), [Cu] (10 mol %), L (12 mol %), $PhCF_3$ (2.0 mL), 0 °C, Ar. [b]Isolated yields. [c]*ee* values were determined by HPLC analysis on a chiral stationary phase. [d]NMR yields for H-abstraction side products. [e]−10 °C. [f]Degassed $PhCF_3$. [g]$PhCF_3$ (3.0 mL).

number of *N*-fluorosulfonamides installed with various types of substituted benzenesulfonyl protecting groups ($ArSO_2$) were first examined. Various substrates with a para-substituted (R^1) functional group, such as Me (**1b**), MeO (**1c**), Cl (**1d**), and CF_3 (**1e**), were all greatly tolerated, and the desired alkynes **3** could be afforded in good to excellent yield along with excellent *ee*. Furthermore, we studied the substituent effect (R^2) of the aromatic ring that was linked to the aliphatic chain. To our satisfaction, both electron-donating groups, such as Me (**1f**, **1n**), $^nC_5H_{11}$ (**1g**), and OMe (**1g**), and electron-withdrawing groups like Cl (**1j**, **1o**), Br (**1k**), and CF_3 (**1l**, **1p**), were also well tolerated under our copper-catalyzed system, giving a good yield of desired products **3** with excellent *ee*. Notably, Br (**1k**) as well as Cl (**1j**, **1o**) on the aromatic ring provided a solution for further derivatizations of these chiral alkynes via different kinds of transition-metal-catalyzed cross-coupling reactions. Moreover, *ortho*-F (**1q**) substrate gave a moderate yield (30%) and satisfactory enantioselectivity (76% *ee*). However, when bulkier substituents like −Me or $-CF_3$ were introduced at ortho position, such transformations failed to perform with good reactivity. Furthermore, a heteroaromatic ring (**1r**) linked to the alkyl chain was also well tolerant, giving the product of **2r** with high *ee* in moderate yield. At last, to inspect the structural variations in the alkynylating reagents **2**, some other alkynylating reagents loading with aryl and alkyl groups at the terminal position (**2b**, **2c**) were also studied and

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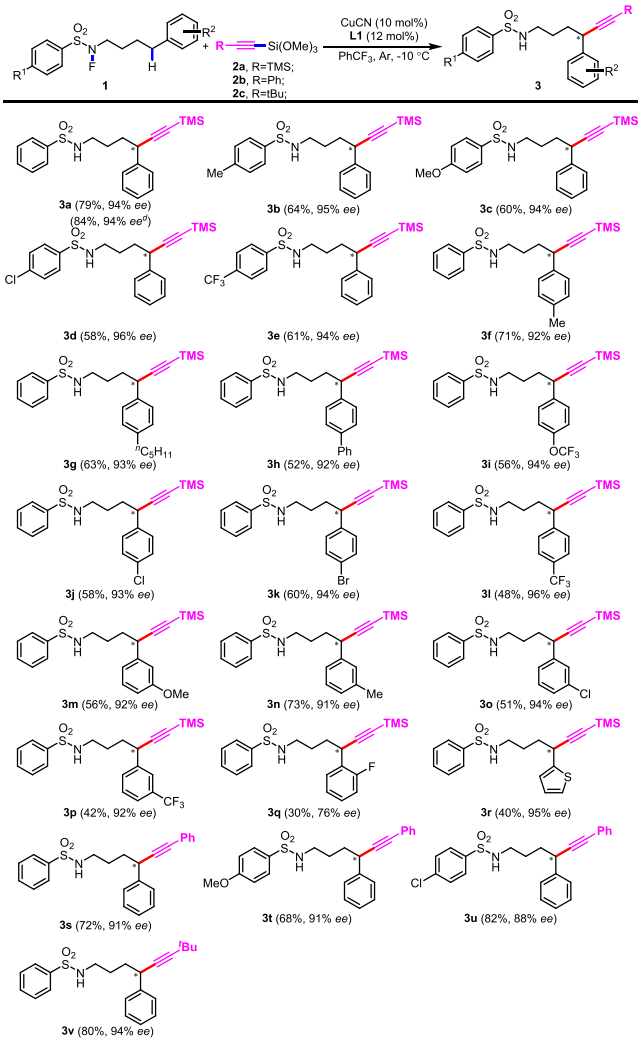
Scheme 2. Substrate Scope[a,b,c]

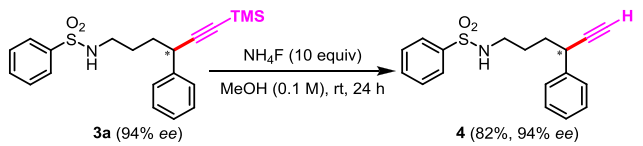


[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), CuCN (10 mol %), **L1** (12 mol %), $PhCF_3$ (6.0 mL), −10 °C, Ar. [b]Isolated yields. [c]*ee* values were determined by HPLC analysis on a chiral stationary phase. [d]Reactions carried out on a 1 mmol scale.

exhibited good reactivity, furnishing the corresponding products (**3s**, **3t**, **3u**, **3v**) in excellent yield with excellent *ee* (88−94%). A millimole-scale experiment was carried out as well with no decrease in yield or enantioselectivity (84% yield, 94% *ee*).

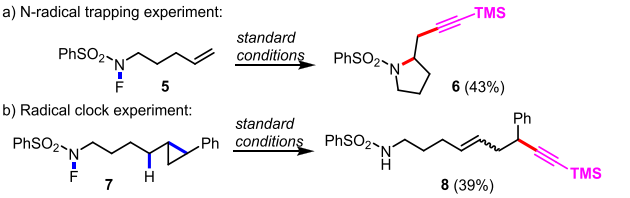
Next, we performed the derivatization study and successfully obtained the desired transformation product. Excitingly, the treatment of **3a** with ammonium fluoride successfully removed the trimethylsilyl (TMS) group and generated the terminal alkyne **4** in 82% yield without any decline of *ee* value (Scheme 3). This result showed that our method had the synthetic potential for the further construction of biologically active chiral molecules using the Sonogashira cross-coupling strategy.

Scheme 3. Further Transformation



To gain some insight into the enantioselective alkynation system, a series of mechanistic studies were also performed. The 5-exo cyclization product **6** was afforded in 43% yield when adding alkene **5** into the reaction; this experiment confirmed that a nitrogen-centered radical was produced by copper catalysis (Scheme 4a). Moreover, in the radical clock experiment, we obtained the ring-opening product **8** in 39% yield with **7**, and this suggested that, initiated by a N-radical, an *in-situ*-generated carbon-centered radical via 1,5-HAT was involved in this catalytic cycle (Scheme 4b).

Scheme 4. Mechanistic Study



On the basis of the above results and previous reports,[10−12] a radical relay pathway under a Cu(I)/Cu(II)-catalyzed catalytic cycle is proposed. (For more details, see the Supporting Information.) Initiating from the L*Cu(I) catalyst, a single electron transfer (SET) between the Cu(I) species and N-fluorosulfonamide **1** affords a higher valency chiral copper complex and a nitrogen-centered radical **A**. Futhermore, **A** undergoes an intramolecular hydrogen atom transfer and furnishes an *in-situ*-generated carbon radical **B**; meanwhile, the L*Cu(II)F complex generates an L*Cu(II)-alkynyl species with **2**. The final enantioselective trapping of **B** with the L*Cu(II)−alkynyl species, which is utterly crucial for constructing the propargylic stereocenter, gives the chiral *δ*-alkynylated sulfonamides **3** and regenerates the L*Cu(I) catalyst to enter the next catalytic cycle.

In conclusion, we have established an enantioselective alkynylation of remote C(sp^3)−H bonds in linear primary sulfonamides under copper catalysis. Excellent regio- and enantioselective control, mild conditions, and a general substrate scope are demonstrated in our system. This radical relay strategy has offered an efficient solution to remote enantioselective alkynylation producing *δ*-alkynated amines and their pharmaceutical derivatives. Further investigations on novel radial-involved enantioselective remote functionalization via 1,5-HAT are still in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01325.

Experimental procedure and characterization of all new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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