Asymmetric Synthesis

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Configurational Control of Benzyl Carbanion–Copper Complexes by Sulfinyl Groups: Synthesis of Optically Pure Allenes with Central and Axial Chirality**

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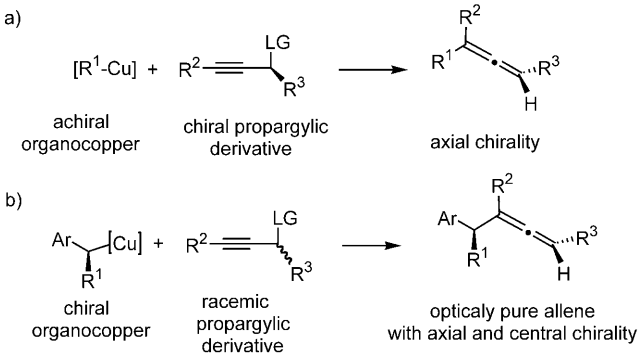
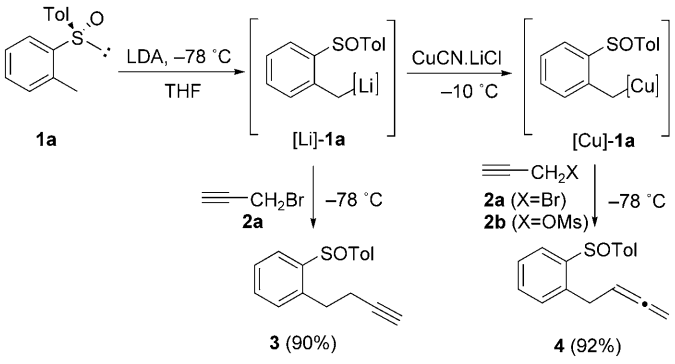
Allenes are unique compounds that exhibit axial chirality,[1] and they are present in a large number of medicinal and natural products.[2] One of the most used methods for the synthesis of optically pure allenes is based on the addition of organocopper reagents to optically pure propargylic derivatives (Scheme 1 a),[3] in which almost complete stereoselectivity is observed. The main limitation in the syntheses of these chiral allenes is the availability of the optically pure propargylic alcohols.[4] In this sense, the search for chiral organocopper reagents for the kinetic resolution of racemic propargylic esters is highly desirable. The use of optically pure organocopper reagents having a chiral center directly attached to the metal should presumably provide an efficient method for the kinetic resolution of racemic propargylic esters. The efficiency of this resolution is expected to be higher when the chiral elements involved in the asymmetric induction are close in proximity. To the best of our knowledge, there are no reports concerning the preparation and use of configurationally stable carbanion–copper complexes in these reactions despite the interest in the resulting allenes, which bear a chiral carbon center connected to the allenic system and exhibit central and axial chirality, for studies of asymmetric synthesis (Scheme 1 b).[5]



Scheme 1. Different approaches for asymmetric syntheses of allenes: a) classical approach, b) present work. LG = leaving group.

During the course of our studies on the reactivity of the lithium-chelated 2-*p*-tolylsulfinylbenzyl carbanions, we found that the sulfinyl group, which is attached to the lithium ion, can control the configuration of the benzylic carbon center. This reagent reacts with electrophiles such as carbonyl compounds,[6] *N*-sulfinylimines,[7] *N*-arylimines,[8] alkylating reagents,[9] and other reagents[10] to form of $C(sp^3)$–$C(sp^3)$ bonds connecting two chiral centers. These results prompted us to check the ability of the sulfinyl group to control the configuration of benzyl carbanion–copper complex by investigating the reaction of the 2-*p*-tolylsulfinylbenzyl carbanion–copper species with racemic propargylic derivatives. This approach could provide a new entry into the synthesis of allenes having chiral carbon centers directly attached to the allenic moieties ($C(sp^3)$–$C(sp^2)$ bond). The results obtained are reported herein.

After trying different copper sources and reaction conditions, we found that the best transmetalation conditions involved the addition of CuCN/LiCl (2.5 equiv) in THF at −10 °C to the optically pure lithium-chelated 2-*p*-tolylsulfinylbenzyl carbanion ([Li]–**1a**) at −78 °C (Scheme 2). Under these conditions, [Cu]–**1a** reacts with propargyl bromide (**2a**) in a regioselective way to exclusively afford allene **4** in 92 % yield by an S_N2' process. A similar result was obtained by using the corresponding propargyl mesylate (**2b**) instead of bromide **2a** as the starting material. The reaction of the [Li]–**1a** with **2a** at −78 °C yields the alkyne **3** in 90 % yield, through an S_N2 process.



Scheme 2. S_N2 versus S_N2' selectivity with lithium- and copper-chelated benzyl carbanions.

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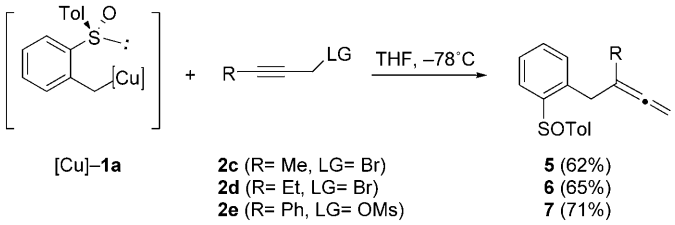
Reactions of [Cu]–**1a** with C3-substituted propargylic systems **2c**–**2e** under similar conditions to afford 1,1-disubstituted allenes **5**–**7** with complete regioselectivity and in good yields (Scheme 3). The reaction was performed on a larger scale (up to 5.0 mmol) without loss in yield or selectivity.

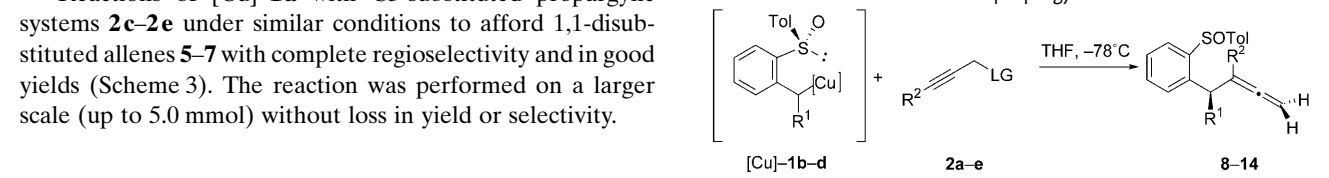


Scheme 3. Reactions of C3-substituted propargylic systems.

We then studied reactions of the prochiral benzyl carbanion–copper complex, derived from 2-*p*-tolylsulfinyl ethylbenzene (**1b**), with propargyl derivatives. Reaction of [Cu]–**1b** with **2a** is completely regioselective, giving the S_N2' products as a 94:6 mixture of diastereoisomers **8** and **8′**, which are epimeric at the benzylic position (Table 1, entry 1). Identical results were obtained by using the propargyl mesylate (**2b**), which indicated the lack of influence of the leaving group on the stereoselective control (Table 2, entry 2). After confirming that the sulfinyl group was efficient in controlling the configuration at the benzylic position, we studied the scope of this reaction with respect to **2**. Accessing different 1,1-disubstituted allenes, having a chiral center connected to the allenic system, is important in for the asymmetric syntheses of allenes. Reaction of **1b** with **2c** afforded an 88:12 mixture of **9** and **9′** (Table 1, entry 3). Interestingly, the reaction of **1b** with **2e** was completely stereoselective, yielding **10** with a *de* value greater than 96% (Table 1, entry 4). Complete stereoselective control was also achieved in reactions of **1c** with **2a** and **2c**, which afforded **11** and **12**, respectively, as single diastereoisomers (Table 1, entries 5 and 6). Reactions of allyl derivative [Cu]–**1d** with propargylic bromides **2a** and **2c** gave the corresponding 1,2,6-trienes **13** and **14**, respectively, with good diastereomeric ratios and high yields (Table 1, entries 7 and 8). These results indicate that the configurational control of benzyl carbanion–copper species can be achieved by having the 2-*p*-tolylsulfinyl group act as a remote chiral inducer.

Finally, we investigated the synthesis of allenes having axial chirality. We synthesized optically pure mesylates (*R*)-**2f** and (*S*)-**2f**, derived from 4-phenyl-3-butyn-2-ol by an enzymatic resolution of the racemic alcohol.[4b] The reactions of [Cu]–**1a** with (*S*)-**2f** and (*R*)-**2f** are completely stereoselective and afford optically pure (S_S, *aS*)-**15′** and (S_S, *aR*)-**15**, respectfully; the yields of the isolated products were 73% and 76%, respectively

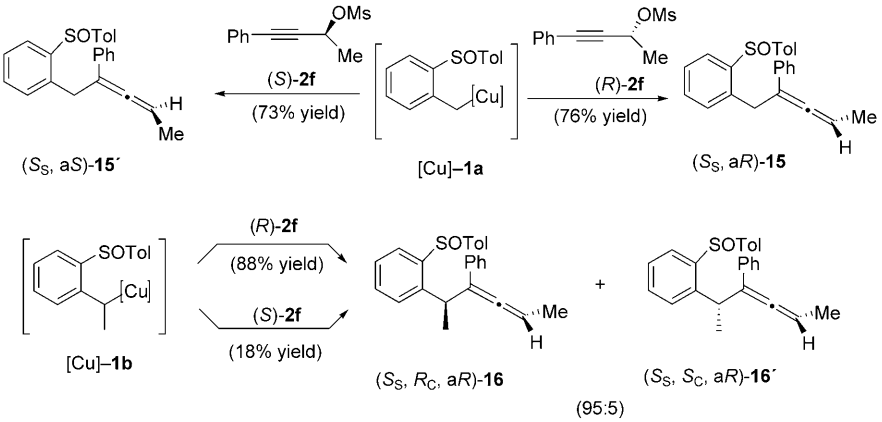
Table 1: Reactions of **1b**–**1d** with propargylic derivatives **2a**–**2e**.[a]



Entry	Reagent (R^1)	Electrophile (R^2/LG)	Product	Yield [%][b]	d.r.[c]
1	[Cu]–**1b** (Me)	**2a** (H/Br)	**8**	76	94:6
2	[Cu]–**1b** (Me)	**2a** (H/OMs)	**8**	72	94:6
3	[Cu]–**1b** (Me)	**2c** (Me/Br)	**9**	51	88:12
4	[Cu]–**1b** (Me)	**2e** (Ph/OMs)	**10**	69	>98:<2
5	[Cu]–**1c** (Bn)	**2a** (H/Br)	**11**	40[d]	>98:<2
6	[Cu]–**1c** (Bn)	**2c** (Me/Br)	**12**	68	>98:<2
7	[Cu]–**1d** (allyl)	**2a** (H/Br)	**13**	64	85:15
8	[Cu]–**1d** (allyl)	**2c** (Me/Br)	**14**	75	95:5

[a] All reactions were performed in a 0.2 mmol scale. LG = leaving group. [b] Yield of isolated product as mixture of stereoisomers. [c] Determined by ^{1}H NMR spectroscopy of the crude mixture. [d] Conversion measured by ^{1}H NMR spectroscopy, in which allene **11** was inseparable from sulfoxide **1c**.

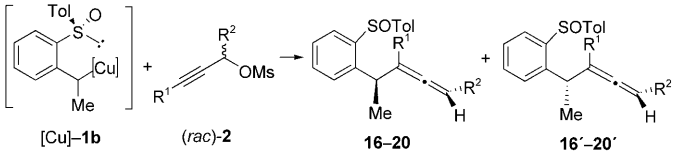
(Scheme 4). The axial chirality of the products was assigned by assuming the predominance of the *anti* attack observed in most of the reactions of the anion–copper reactant with the propargylic esters.[3] The reaction of [Cu]–**1b** with (*R*)-**2f** under mild conditions (−78°C) almost instantaneously afforded a 95:5 mixture of diastereoisomers **16** and **16′** in 88% yield (Scheme 4). This result provides evidence that control of one of the two chiral elements (carbon center or axis) can be achieved efficiently. On the basis of the complete *anti* stereoselectivity observed in the reactions of [Cu]–**1a**, we initially assumed that **16** and **16′** were epimers at the benzylic position; this was additionally confirmed (see analysis for **17** below). Reaction of [Cu]–**1b** with (*S*)-**2f** also gave a 95:5 mixture of **16** and **16′**, however, the reaction times were longer and the yield was much lower (18%) than those obtained from (*R*)-**2f**. Unreacted (*S*)-**2f** was recovered as a mixture of enantiomers. These results suggested that reaction of [Cu]–**1b** with (*S*)-**2f** did not take place and that mesylate **2f** was racemized under the reaction conditions.[11]



Scheme 4. Asymmetric syntheses of allenes with axial chirality.

As expected, the reaction of [Cu]–**1b** with (*rac*)-**2f** also gave a 95:5 mixture of **16** and **16′** (58%), as well as unreacted **1b** (33%) and an alcohol resulting from the hydrolysis of (*rac*)-**2f** (42%), which can be reused in additional reactions (Table 2, entry 1). A complete kinetic resolution and a deficient dynamic kinetic resolution can be observed in this reaction, and the main advantage derives from the lack of reactivity of the *S* enantiomer. The synthesis of allenes with axial and central chirality in high optical purity can be carried out starting from racemic propargyl derivatives, thus avoiding the tedious synthesis of optically pure propargylic alcohols.

Table 2: Reactions of **1b** with racemic propargylic derivatives.[a]



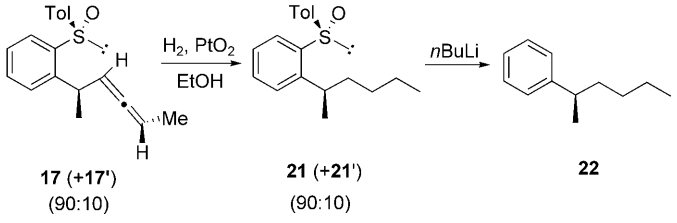
[Cu]–**1b** (*rac*)-**2** **16–20** **16′–20′**

Entry	Electrophile (R^1/R^2)	Product	Yield [%][b]	d.r.[c]
1	**2f** (Me/Ph)	**16**	58	95:5[d]
2	**2g** (H/Me)	**17**	53	90:10
3	**2h** (Me/*p*-BrPh)	**18**	56	85:15
4	**2i** (Me/*n*Bu)	**19**	53	93:7[d]
5	**2j** (Et/Ph)	**20**	56	96:4[d]

[a] All reactions were performed in a 0.2 mmol scale. [b] Yield of isolated product as a mixture of stereoisomers. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy of the crude reaction. [d] Diastereomeric ratio was also determined by chiral HPLC analysis.

Similar behavior was observed in the reactions of [Cu]–**1b** with different racemic mesylates (*rac*)-**2g–j**; only the *R* enantiomers reacted to yield optically pure allenes **17–20** (Table 2), which exhibited the *aR* configuration of the chiral axis. The yields of the isolated products are slightly higher than 50% in all the cases, suggesting that a dynamic kinetic resolution has occurred to some extent.

The unequivocal configurational assignment of compound **17** was performed by hydrogenation of the 90:10 mixture of **17** and **17′** (Table 2, entry 2) with the Adam's catalyst. A 90:10 mixture of two diastereoisomers, **21** and **21′**, respectively, was obtained (Scheme 5), demonstrating that **17** and **17′** were epimers at the benzylic position and not along the chiral axis. Desulfinylation of the mixture of **21** and **21′** afforded (*R*)-2-phenylhexane,[12] which allowed the unequivocal assignment of the *R* configuration to the benzylic carbon atom (see the Supporting Information for additional details).



17 (**+17′**) (90:10) **21** (**+21′**) (90:10) **22**

Scheme 5. Chemical correlation of compounds **17** and (*R*)-**22**.

In summary, we have demonstrated that the reactions of optically pure 2-*p*-tolylsulfinylbenzyl carbanion–copper reagents with propargyl bromides and mesylates take place in a completely regioselective way by a S_N2' process with complete *anti* stereoselectivity in the formation of a chiral axis. The sulfinyl group is very efficient in controlling the configuration of the α-alkylbenzyl carbanion–copper reagent, thus providing the first method to obtain optically pure allenes having a chiral center directly attached to the allenic system, which can also have a defined configuration of its chiral axis. Additionally, complete kinetic resolution of racemic propargylic mesylates can be achieved with sulfinylated α-alkylbenzyl carbanion–copper reagents, which in turn are moderately efficient for the dynamic kinetic resolution of the mesylates. Additional studies for establishing the mechanism of these reactions are in progress and will be reported at a later date.

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