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Copper-Catalyzed Asymmetric Alkynylation of Cyclic *N*-sulfonyl Ketimines

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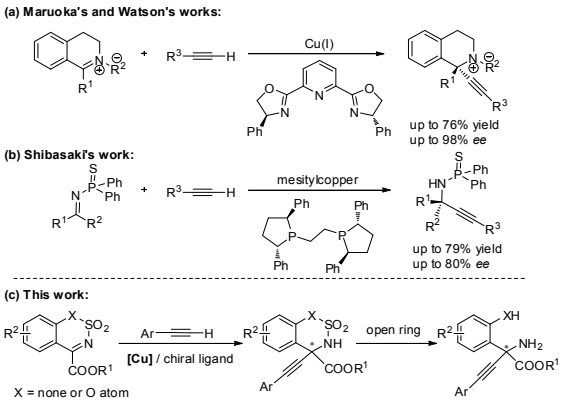
A Cu-catalyzed asymmetric alkynylation of cyclic *N*-sulfonyl ketimines was developed, providing the corresponding chiral *α*-tertiary amines with up to 98% *ee*. The method tolerates some variations in cyclic *N*-sulfonyl ketimine and alkyne scope. These products could be used in several transformations, in particular, the products of 6-membered cyclic *N*-sulfonyl ketimines could be easily converted to linear chiral *α*-tertiary amines. This asymmetric alkynylation provides an efficient, gram-scale, low-cost transition-metal catalyzed synthesis of chiral *α*-tetrasubstituted propargylamines.

The construction of chiral *α*-tertiary amines is still a subject of intensive research in organic chemistry.[1,2] Therein, chiral *α*-tetrasubstituted propargylamines are useful intermediates in organic synthesis and are versatile scaffolds for the preparation of natural products and bioactive compounds.[3] The metal-catalyzed asymmetric alkynylation of ketimines is one of the most direct, efficient and popular methods.[4] However, construction of *α*-tetrasubstituted propargylamines is still challenging due to the low reactivity of ketimines and poor stereocontrol. To date, there are only several reports concerning the catalytic enantioselective alkynylation of ketimines catalyzed by metals such as Cu,[5] Zn,[6] and Rh.[7]

The Cu-catalyzed alkynylation of ketimines is favored because of its low cost, operational simplicity and good stability of the copper reagent. In recent years, the Maruoka and Watson groups have reported asymmetric alkynylations for the preparation of isoquinolines with *α*-diaryl tetrasubstituted stereocenters, with yields in excess of 76% and 98% *ee,* respectively (Scheme 1, (a)).[5a,5d] On the other hand, the Shibasaki group reported a direct catalytic asymmetric addition of terminal alkynes to ketimines to give linear *α*-tetrasubstituted propargylamines with good yields (up to 79%) and moderate enantioselectivity (up to 80% *ee*) (Scheme 1, (b)).[5b,5c]

In general, for asymmetric addition reactions, a cyclic framework is preferred for the stereoselective synthesis of *α*-tetrasubstituted propargylamines. However, propargylamine products bearing a cyclic scaffold have limited use as synthetic building blocks or intermediates. We hypothesized that the asymmetric addition of ketimines possessing a cyclic scaffold, followed by a simple ring opening of the cyclic products, could be used to generate linear *α*-tertiary amines. These amines could then be implemented as synthetic building blocks for a wide range of natural products and bioactive compounds containing chiral *α*-tertiary amines.[8] Cyclic *N*-sulfonyl ketimines, which have been used in addition reactions with various nucleophiles, aza-Diels-Alder reactions and allylic substitution reactions,[2k,9] have been chosen as the preferred substrates because the SO_2 group can be easily removed (Scheme 1, (c)). It is also worth noting that chiral cyclic sulfonamides have found extensive use in a number of medicines[10] such as 5-HT2 receptor antagonists, HIV-1 inhibitors, HCV (Hepatitis C virus) NS5b inhibitors, and selective CRTh2 antagonists.[11] Additionally, to ensure good reactivity and better functionalization, we chose cyclic *N*-sulfonyl *α*-ketiminoesters



Scheme 1 Cu-catalyzed asymmetric alkynylation of ketimines.

with relatively high activity to generate the alkynylation products.[12] Herein we describe an efficient protocol for the preparation of amines containing a tetrasubstituted stereogenic centre using a direct Cu-catalyzed asymmetric addition of terminal alkynes to *N*-sulfonyl *α*-ketiminoesters.[13]

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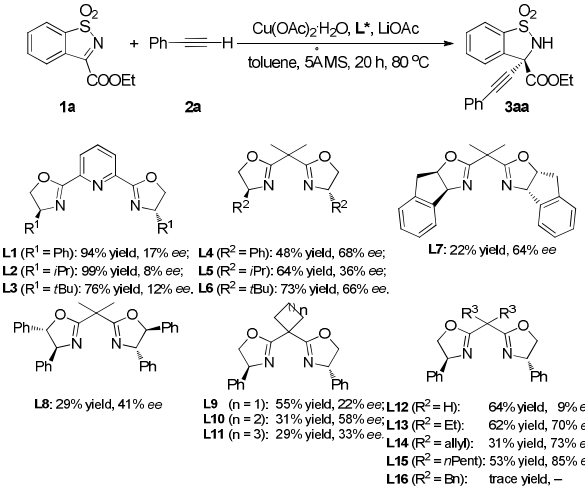
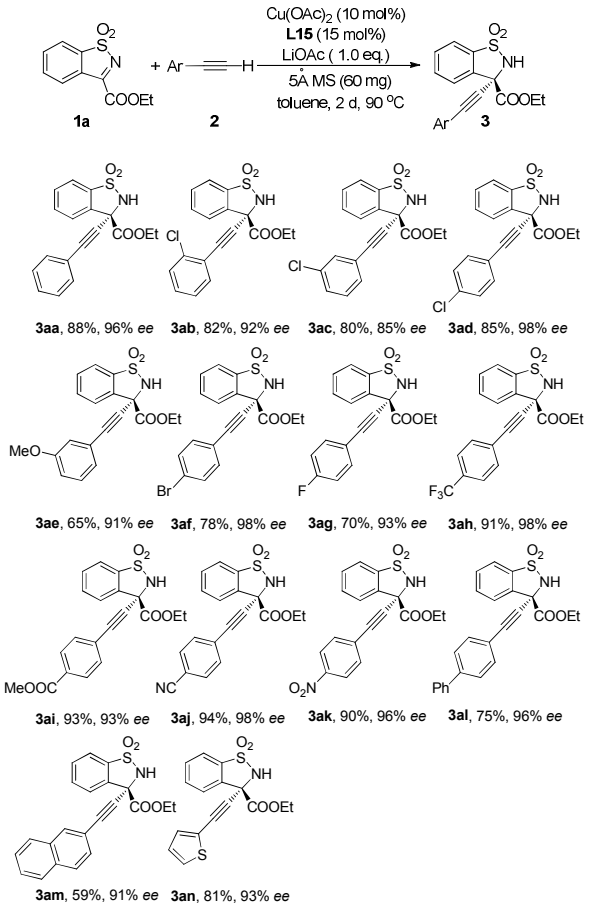
At the beginning of this study, the Cu-catalyzed addition of terminal alkyne **2a** to cyclic *N*-sulfonyl *α*-ketiminoester **1a** was carried out in the absence of ligand (Scheme 2). Unsurprisingly, no reaction occurred. Pyridine-bis(oxazolines) (PyBox) ligand **L1** was then tested in this catalytic system. To our delight, the reaction proceeded well, giving the desired product in 94% isolated yield and 17% *ee*. Subsequent screenings using PyBox ligands with different substituents on the oxazoline rings (**L2, L3**) were carried out (Scheme 2), however, no acceptable results were obtained. Using bisoxazoline (Box) ligand **L4** greatly improved the enantioselectivity to 68%. Changing the substituents on the oxazoline rings of the Box ligands (**L5-L8**) showed that phenyl-substituted groups (**L4**) afforded better results. Subsequently, the effect of substituents at the carbon atom connecting the two oxazoline rings was investigated. Low to moderate enantioselectivities were provided when substituents were cyclic groups (**L9-L11**). The substituent (R^3) was then changed to H, ethyl, allyl, *n*-pentyl and benzyl groups for screening (**L12-L16**). As a result, **L15** exhibited the best catalytic efficiency, providing the desired product with 85% *ee* and in 53% isolated yield.



[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.01 mmol), **L*** (0.012 mmol), LiOAc (0.10 mmol) and 5Å MS (60 mg) at 80 °C in toluene (1 mL) for 20 h. [b] Isolated yield. [c] The *ee* was determined by HPLC analysis. [d] The absolute configuration of **3aa** was determined as *R* according to ref. 7b.
Scheme 2 Screen of chiral ligands[a,b,c,d].

Next, optimization of the reaction conditions was carried out using **L15** as a ligand. After screening of various inorganic bases, solvents, copper salts, temperature and adjustment of the ligand and copper ratio, the desired product was obtained in 88% yield and 96% *ee* under the optimal reaction conditions (**1a** (0.10 mmol), **2** (0.15 mmol), $Cu(OAc)_2$ (0.01 mmol), **L15** (0.015 mmol), LiOAc (0.10 mmol) and 5Å MS (60 mg) at 90 °C in toluene (1 mL) for 2 days.).[14]

With the optimal reaction conditions in hand, a range of terminal alkynes were then investigated with this catalytic system (Scheme 3). Electron-withdrawing groups at the ortho or para-position of the phenyl group, such as, Cl, Br, CF_3, COOMe, CN, NO_2 and Ph, were all amenable to the reaction conditions, giving the corresponding products with good to excellent enantioselectivities (92-98% *ee*) and good yields (70-94%) (**3ab**, **3ad and 3af-3al**). Electron-withdrawing and electron-donating substituents (e.g. Cl and OMe) at the meta position of the phenyl ring resulted in a relative decrease in yields (65-80%) and enantioselectivities (85-91% *ee*) (**3ac**, **3ae**). Changing the phenyl group to a *β*-naphthyl group gave the expected product (**3am**) with excellent enantioselectivity (91% *ee*) and moderate yield (59%). Furthermore, even in the case of 2-ethynylthiophene, the expected product (**3an**) was afforded with excellent enantioselectivity (93% *ee*) and good yield (81%). Hex-1-yne, ethynylcyclopropane and ethynyltrimethylsilane were also applied to this reaction system but no reaction occurred.



[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.15 mmol), $Cu(OAc)_2$ (0.01 mmol), **L15** (0.015 mmol), LiOAc (0.10 mmol) and 5Å MS (60 mg) at 90 °C in toluene (1 mL) for 2 days. [b] Isolated yield. [c] The *ee* was determined by HPLC analysis. [d] The absolute configuration of **3aa** was determined as *R* according to ref. 7b.
Scheme 3 Scope of alkyne substrates[a,b,c,d].

The scope of substrate **1** was then explored (Scheme 4). Good to excellent enantioselectivities (89-95% *ee*) were obtained for substrates bearing a variety of ester groups (COOMe, COO*i*Pr, and COO*n*Bu) (**3ba-3da**). In addition, a series of fused 5-membered cyclic *N*-sulfonyl *α*-ketiminoesters possessing electron-donating or electron-withdrawing

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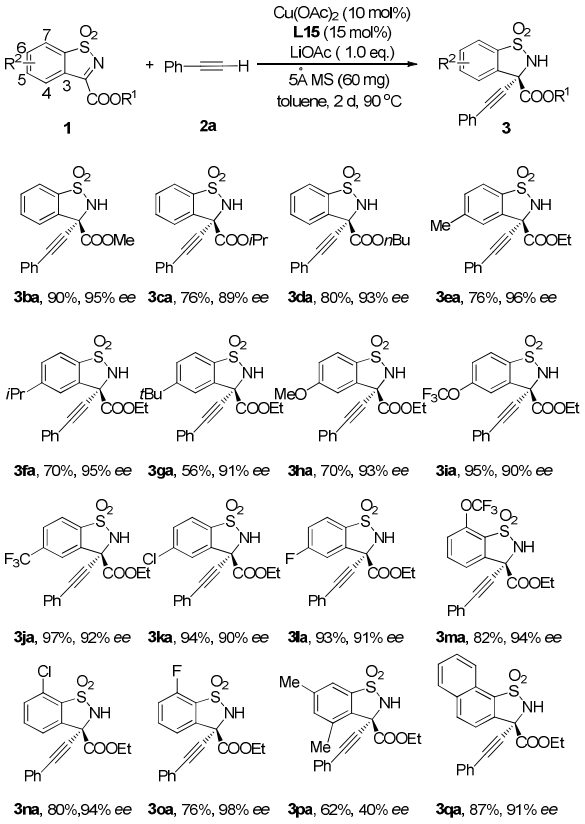
substituents at the 5- or 7-position of the phenyl groups proceeded smoothly to afford the desired products **3** with excellent enantioselectivities (90-98% *ee*) and good to excellent yields (56-97%) (**3ea-3oa**). A substrate bearing 4,6-dimethyl-substituted phenyl group provided its corresponding product with only 40% *ee* and 62% yield (**3pa**). Notably, naphtha-fused *N*-sulfonyl *α*-ketiminoester also gave the desired product with 91% *ee* and in 87% yield (**3qa**).

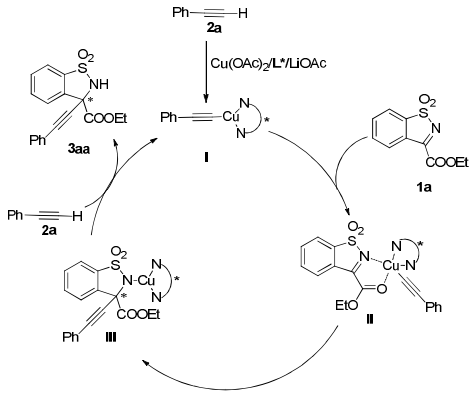


[a] Reaction conditions, please see Scheme 3.

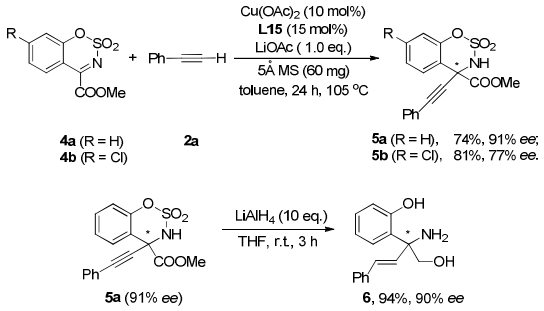
Scheme 4 Scope of *N*-sulfonyl *α*-ketiminoesters[a].

A possible mechanism for the current transformation is illustrated in Scheme 5. Initially, the Cu(II) salt can be reduced to (phenylethynyl)copper(I) using phenyl acetylene and LiOAc.[15] *N*-Sulfonyl *α*-ketiminoesters **1a** undergoes coordination with (phenylethynyl)copper (**I**) to generate the addition intermediate **III** via complex **II**.[16] Protonation of intermediate **III** furnishes the target product **3aa** and regenerates (phenylethynyl)copper (**I**) which can take part in next catalytic cycle.

Additionally, to further explore the scope of the reaction, two fused 6-membered cyclic *N*-sulfonyl *α*-ketiminoesters **4a** and **4b** were also examined in this catalytic system (Scheme 6). A substrate bearing a methyl ester group **4a** gave its corresponding product **5a** with 91% *ee* and 74% yield. The ring opening reaction of **5a** went smoothly to afford linear chiral *α*-tertiary amino alcohol **6** with 94% yield and 90% *ee*.



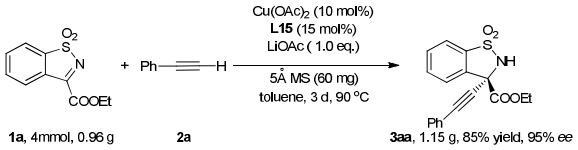
Scheme 5 Possible mechanism.



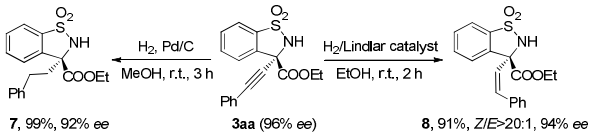
[a] Reaction conditions: **4** (0.10 mmol), **2a** (0.15 mmol), $Cu(OAc)_2$ (0.01 mmol), **L15** (0.015 mmol), LiOAc (0.10 mmol) and 5Å MS (60 mg) at 105 °C in toluene (1 mL) for 24 hours. [b] Isolated yield. [c] The *ee* was determined by HPLC analysis.

Scheme 6 Asymmetric alkynylation of 6-membered cyclic *N*-sulfonyl *α*-ketiminoesters[a,b,c] and its ring opening reactions.

Considering the importance of the structural skeleton of the alkynylation products, we explored the practicality of our methodology. A gram-scale reaction using substrate **1a** and alkyne **2a** was carried out (Scheme 7). The product **3aa** was obtained with results comparable to those shown in Scheme 3. In addition, **3aa** could be converted to alkyl and alkenyl compounds (**7**, **8**) via hydrogenation (Scheme 8).



Scheme 7 Gram-scale reaction.



Scheme 8 Transformations of **3aa**.

In conclusion, we have demonstrated a direct Cu-catalyzed asymmetric alkynylation of 5-membered cyclic *N*-sulfonyl *α*-ketiminoesters with good to excellent yields and enantioselectivities. A relatively wide substrate scope of

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terminal alkynes and cyclic ketimines are compatible with our conditions. In particular, this asymmetric alkynylation could also be applied to 6-membered cyclic *N*-sulfonyl α-ketiminoesters, whose products can be converted easily to linear chiral α-tertiary amines via simple ring opening reactions.

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