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Silver-Catalyzed Enantioselective Propargylation Reactions of *N*-Sulfonylketimines

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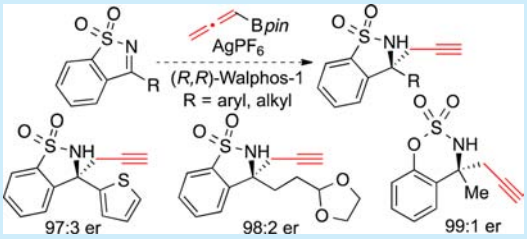
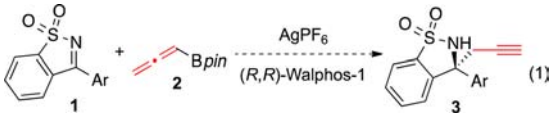
Supporting Information

ABSTRACT: The enantioselective silver-catalyzed propargylation of *N*-sulfonylketimines is described. This reaction proceeds in high yield and excellent enantiomeric ratio and is compatible with a wide variety of diaryl- and alkylketimines. Synthetic transformations of homopropargylic products via enyne ring-closing metathesis, Sonogashira cross-coupling, and reduction reactions proceed with high stereochemical fidelity. Both allenyl and propargyl borolane reagents can be used to obtain homopropargylic products, a distribution most consistent with a mechanism involving transmetalation of the silver catalyst with the borolane reagent.

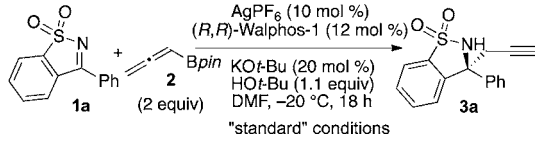


Nearly half of the top 200 pharmaceuticals in 2012 contain functional groups that can be prepared from α-chiral amines.[1] To access this moiety, numerous enantioselective methods for the synthesis of chiral amines have been developed, many of which involve addition of organometallic nucleophiles to aldimines.[2] Additions to ketimines pose specific challenges. For example, mixtures of *E* and *Z* isomers can lead to low levels of enantioinduction.[3] These obstacles have inspired creative approaches[4] including use of cyclic *N*-sulfonylketimines (e.g., **1**), which do not undergo *E*/*Z* isomerization and are synthesized in one step from saccharin.[5,6] Hayashi and co-workers have pioneered the rhodium-catalyzed enantioselective arylation reactions of *N*-sulfonylketimines; other elegant examples of arylation, allylation, and alkenylation reactions have also been reported.[5c,7] An enantioselective propargylation reaction would afford a chiral sultam with a pendant terminal alkyne, a valuable functional group handle that can be easily derivatized for further synthetic elaboration.[8] In this paper, we report the first enantioselective propargylation reaction of ketimines (eq 1).

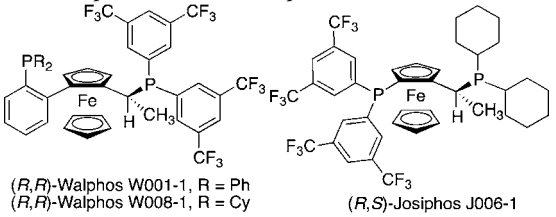


Building on early advances in enantioselective propargylation reactions of aldehydes, in the past five years there has been rapid development of enantioselective propargylation reactions of ketones and aldimines.[9−11] Our laboratory has reported the silver-catalyzed enantioselective propargylation reactions of aldimines and diaryl ketones.[10b,12,13] Using AgF and chiral phosphine ligands from the Walphos family provided a variety of homopropargylic amines and alcohols in good yield and high enantiomeric excess (ee). We reasoned that a Ag/Walphos catalyst would be able to differentiate between the *Re* and *Si* faces of diarylketimines, based on their structural similarity to diaryl ketones. Indeed, we found that employing $AgPF_6$ with Walphos-1 resulted in formation of homopropargylic amine **3a** in 99:1 enantiomeric ratio (er) and modest yield (Table 1, entry 1). In

Table 1. Optimization of Silver-Catalyzed Propargylation Reaction



entry	deviation from standard conditions	yield[a] (%)	er[b]
1	none	51	99:1
2[c]	catalyst preformed in MeOH and reaction run in THF	19	96:4
3	Walphos-8 instead of Walphos-1	35	76:24
4	Josiphos-6 instead of Walphos-1	70	74:26
5	(*S*)-BINAP instead of Walphos-1	55	40:60
6	reaction performed at 4 °C	54	99:1
7	reaction performed at rt	57	98:2
8	reaction performed at rt with 4 equiv **2**	76	99:1



[a]Determined using ^{1}H NMR by comparison to PhTMS as internal standard. [b]Determined using chiral SFC. [c]Preparation of Ag/Walphos catalyst performed according to ref 10b.

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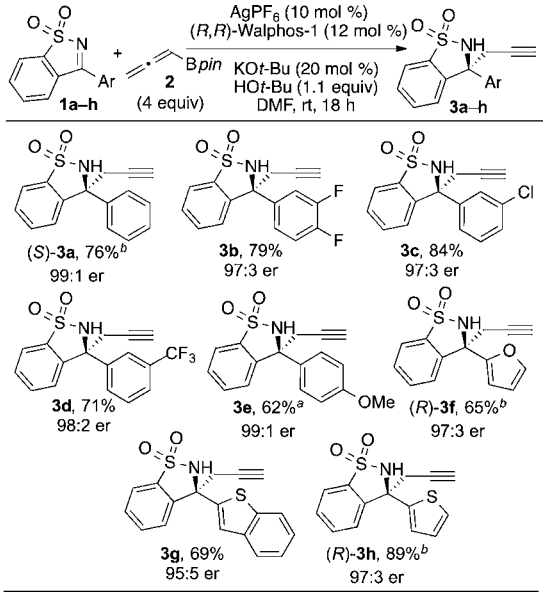
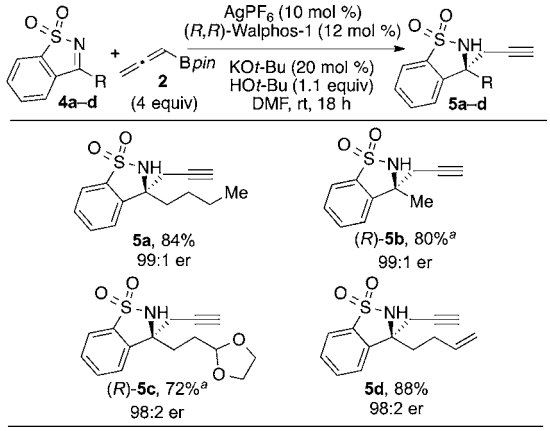
Scheme 1. Scope of Diaryl Sultams



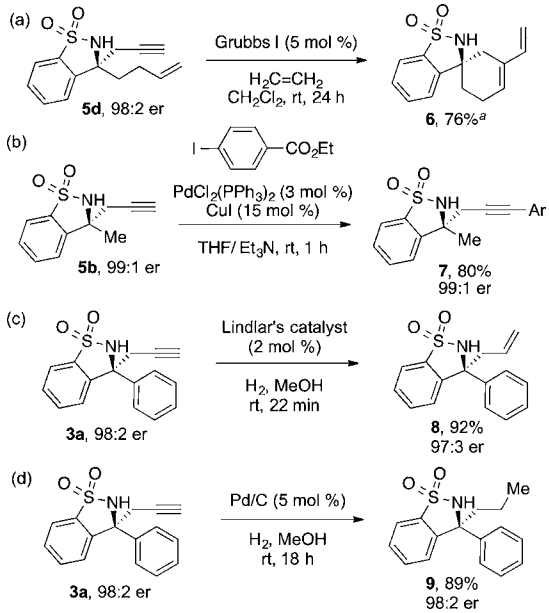
[a]6 equiv allenylboronic acid pinacol ester **2** were employed. [b]Absolute configuration assigned by X-ray crystallographic analysis.[16]

Scheme 2. Scope of Alkyl Sultams



[a]Absolute configuration assigned by X-ray crystallographic analysis.[17]

Scheme 3. Synthetic Transformations of Homopropargylic Sultams



[a]Enantiomeric ratio could not be determined using chiral SFC instrumentation.

comparison, preforming the catalyst in methanol and running the reaction in THF gave high er but only 19% product (entry 2).[14] Other chiral ferrocene-based ligands such as Walphos-8 and Josiphos-6 provided lower er (entries 3 and 4), as did (*S*)-BINAP (entry 5).

We further modified the reaction conditions to improve the yield. We found that at ambient temperature **3a** was still formed in a modest yield; fortunately, the er remained high (Table 1, entry 7). We hypothesized that protodeborylation of allenylboronic acid pinacol ester **2** to allene (C_3H_4) was competitive with the desired addition reaction and thus resulted in modest yields.[15] Use of an additional 2 equiv of allenylboronic acid pinacol ester **2** via slow addition increased the yield, providing **3a** in 76% yield and 99:1 er (entry 8).

Having determined optimized conditions for this reaction, we proceeded to evaluate the substrate scope. A wide range of arylketimines underwent enantioselective propargylation in high yield and >95:5 er (Scheme 1). Ketimines containing electron-withdrawing groups formed products in excellent er (**3b–d**). We were gratified to find that substrates with electron-donating groups participated in this reaction, as the starting ketimines are generally less reactive. 4-Methoxyphenyl-substituted sultam **3e** was generated in good yield and excellent er upon using 6 equiv of allenylboronic acid pinacol ester **2**. In addition, several heterocycles were tolerated in the reaction. Ketimines containing furan, thiophene, and benzothiophene functional groups reacted smoothly to provide the corresponding homopropargylic sulfonamides (**3f–h**) in high er. The absolute configurations of **3a**, **3f**, and **3h** were determined by X-ray crystallographic analysis.[16]

We were pleased to find that alkylketimines were also well tolerated in the reaction (Scheme 2), since we were concerned that these substrates would tautomerize to enamines in the presence of potassium *tert*-butoxide. Several alkylketimines reacted to give homopropargylic products in excellent er (**5a–d**). Furthermore, we found that other functional groups are compatible with this method: sultam **5c**, containing an acetal protecting group, was formed in high yield. The absolute configurations of **5b** and **5c** were determined by X-ray crystallographic analysis.[17]

To emphasize the utility of the pendant terminal alkyne, we synthesized derivatives of several alkyl and aryl homopropargylic sulfonamides (Scheme 3). We prepared compound **5d** for an enyne ring-closing metathesis (Scheme 3a).[18] In the presence of 5 mol % of Grubbs I catalyst and under an atmosphere of ethylene, the desired spirocycle **6** was obtained in 76% yield. The Sonogashira cross-coupling reaction of compound **5b** with ethyl 4-iodobenzoate proceeded in high yield (Scheme 3b). Lindlar reduction of **3a** provided the corresponding enantioenriched diaryl allyl sultam **8**, a moiety that has not been previously reported (Scheme 3c).[7e,19] We further highlighted the versatility of the alkyne moiety by fully reducing **3a** to alkane **9** in 89% yield using palladium on carbon, without reduction of the cyclic benzylic sulfonamide (Scheme 3d).

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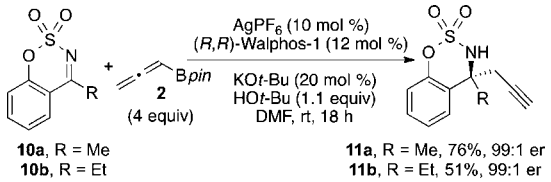
Scheme 4. Scope of Alkyl Sulfamidates



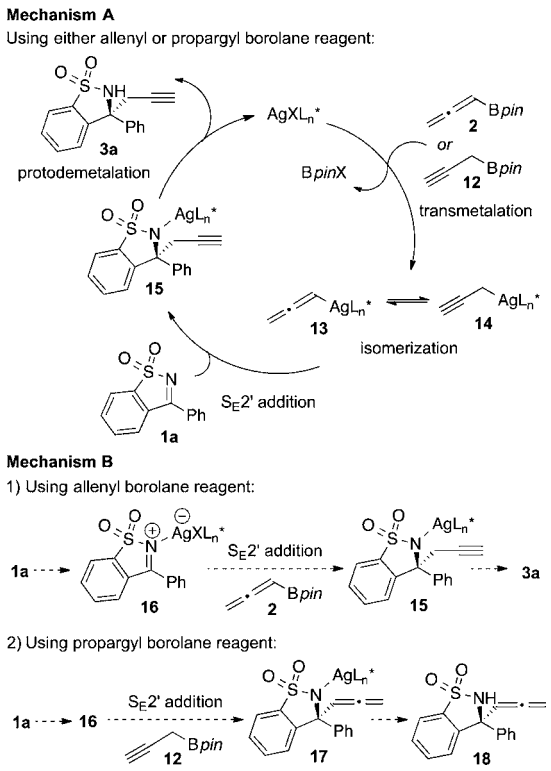


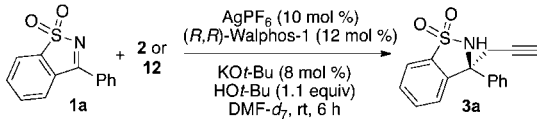
Figure 1. Possible mechanisms for silver-catalyzed propargylation reaction. (a) Proposed catalytic cycle involving transmetalation of silver catalyst with borolane reagent. (b) Lewis acid catalysis.

Cyclic sulfamate ketimines (e.g., **10**) are a related class of *N*-sulfonylketimines that react with nucleophiles to provide sulfamidates that can be easily transformed to 2-hydroxyphenylmethylamines.[7] However, these ketimines are typically less reactive in addition reactions. We wanted to challenge our method and found that homopropargylic sulfamidates **11a** and **11b** were formed in good yield and >99:1 er (Scheme 4).

We sought to establish a reasonable mechanism for this propargylation reaction; two of the most likely possibilities are presented in Figure 1.[20] Our approach to distinguish between these mechanisms was to compare product distributions from reactions employing isomeric borolane reagents, allenyl borolane **2** and propargyl borolane **12**. Importantly, both mechanisms take into account our experimental observation that allenyl borolane **2** and propargyl borolane **12** are not in equilibrium under the reaction conditions during the time frame of the reaction (vide infra).[21]

Mechanism A involves transmetalation and isomerization of the allenylmetal intermediates.[22] Transmetalation of the silver catalyst with the borolane reagent forms the key nucleophilic allenylsilver complex (**13**) in situ. Allenylsilver complex **13** is in equilibrium with propargylsilver complex **14**.[23,24] Addition of allenylsilver complex **13** to the ketimine via S_E2' mechanism is favored to form alkyne **3a**. Therefore, if mechanism A is operative, using either allenyl borolane **2** or propargyl borolane **12** would result in formation of alkyne **3a** via equilibration of **13** and **14** (Figure 1a).

Table 2. Silver-Catalyzed Propargylation Reaction Using Allenylboronic Acid Pinacol Ester 2 or Propargylboronic Acid Pinacol Ester 12



borolane reagent	ratio **2**:**12** before rxn[a]	ratio **2**:**12** after rxn[a]	recovered **1a** (%)[b]	yield **3a** (%)[b]	er **3a**[c]	yield **18** (%)[d]
Bpin (**2**)	98:2	94:6	28	68	98:2	< 2
Bpin (**12**)	4:96	6:94	32	64	93:7	< 2

[a]Determined by ^{1}H NMR. [b]Isolated yield. [c]Determined using chiral SFC. [d]Determined using ^{1}H NMR by comparison to PhTMS as internal standard.

An alternative pathway is mechanism B, involving direct addition of the borolane reagent to the ketimine.[20] In this scenario, the silver catalyst acts as a chiral Lewis acid in the reaction (Figure 1b (1)). Coordination of the silver catalyst to form intermediate **16** followed by S_E2' addition of allenyl borolane **2** results in formation of alkyne **3a**. In this possible mechanism, isomerization of the allenyl- and propargylboron species is slower than attack on the activated electrophile (**16**).[21] Therefore, using propargyl borolane **12** would provide a different product, allene **18** (Figure 1b (2)).

To rule out one of these two possible mechanisms, we set out to examine reactions employing propargyl borolane **12**.[25] We synthesized **12** using a procedure recently published by Fandrick and co-workers.[22c] Using propargyl borolane **12** in the reaction yielded alkyne **3a** in 64% (Table 2).[26] We found that the er of the product remained high, with a slight decrease when using propargyl borolane **12**. To determine whether or not propargyl borolane **12** is in equilibrium with allenyl borolane **2** under the reaction conditions, the reaction was performed in deuterated DMF and the ratio of propargyl to allenyl borolane was analyzed by ^{1}H NMR before workup. The ratio of propargyl borolane **12** to allenyl borolane **2** remained similar before and after the reaction, most consistent with negligible equilibration of **12** and **2** over the time course of the propargylation reactions. While other mechanistic possibilities exist, these results are most consistent with mechanism A, where the silver catalyst undergoes transmetalation with the borolane reagent.

In summary, we have developed an enantioselective silver-catalyzed propargylation reaction of cyclic *N*-sulfonylketimines. Using a catalyst prepared from $AgPF_6$ and Walphos-1, we found that many aryl and alkyl homopropargylic amines were formed in high yield and excellent er. Derivatization of the terminal alkyne yielded spirocyclic, alkenyl, or alkyl products. Mechanistic experiments employing propargyl borolane reagent are most consistent with a mechanism in which the silver catalyst undergoes transmetalation with the borolane reagent to generate a nucleophilic allenylboron reagent.

■ ASSOCIATED CONTENT

Supporting Information

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X-ray crystallographic data for **3a** (CIF)
X-ray crystallographic data for **3f** (CIF)
X-ray crystallographic data for **3h** (CIF)
X-ray crystallographic data for **5b** (CIF)
X-ray crystallographic data for **5c** (CIF)
Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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