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# Catalytic C—N Bond Alkynylation of *N*-Benzylic Sulfonamides with Terminal Alkynes

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A new cross-coupling reaction of *N*-benzylic sulfonamides with terminal alkynes for the synthesis of internal alkynes is reported. In the presence of 5 mol% of $(Tf)_2NH/Bi(OTf)_3$ (1∶1), a broad range of *N*-benzylic sulfonamides react smoothly with arylacetylenes to afford structurally diverse internal alkynes in moderate to excellent yields. We reasoned that vinyl cations could be formed by the regioselective attack of terminal alkynes with benzyl cations generated *in situ* from *N*-benzylic sulfonamides under acidic conditions, which then eliminated to form a carbon-carbon triple bond.

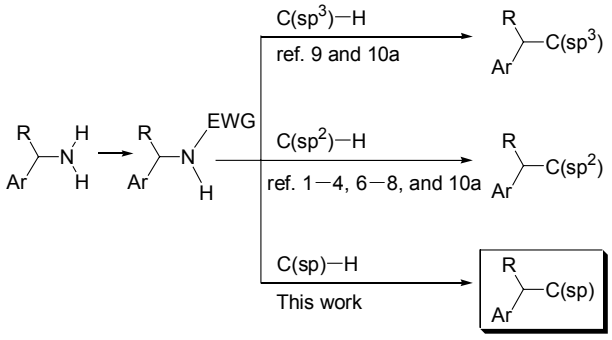
**Keywords** benzylic amines, alkynylation, internal alkynes, carbon nucleophiles, cross-coupling

## Introduction

While primary benzylic amines are readily accessible, they do not serve as useful carbon electrophiles in chemical synthesis owing to the poor leaving ability of their amino groups. In this regard, it is necessary to activate primary benzylic amines to enhance electrophilicity by modifying their amino groups. A number of studies show that the C($sp^3$)—N bonds of primary benzylic amines are significantly activated by introducing electron-withdrawing groups to the amine nitrogen atoms and undergo cleavage when further promoted with either Brønsted acids[1-5] or Lewis acids.[6-10] This double activation approach allows primary benzylic amines to emerge as useful carbon electrophiles to couple with C($sp^3$)—H bonds[9,10a] and C($sp^2$)—H bonds[1-4,6-8,10a] under various acidic conditions (Scheme 1). To our knowledge, there has been no report on the coupling of C(sp) — H bonds with activated primary benzylic amines.

Recently we discovered a $FeCl_3$-catalyzed [3+2] annulation reaction of sulfonyl-activated primary benzylic amines (*N*-benzylic sulfonamides) with disubstituted alkynes for the synthesis of indene derivatives.[10b] However, this protocol was not applicable at all to terminal alkynes. We reasoned that analogous vinyl cations could be formed by the regioselective attack of terminal alkynes with benzyl cations generated *in situ* from *N*-benzylic sulfonamides through C($sp^3$)—N bond cleavage under acidic conditions, but they would prefer to stay farther away from the internal aromatic rings and consequently, ring closure could not occur through an intramolecular Friedel-Crafts reaction (Scheme 2).[11] In this context, switching reaction conditions might result in deprotonation of the vinyl cations to give internal alkyne.[12]

**Scheme 1** Coupling of activated primary benzylic amines with different C—H bonds (EWG=electron-withdrawing group)




Herein, we wish to report a new coupling reaction of activated primary benzylic amines with terminal alkynes for the synthesis of internal alkynes through the cleavage of C($sp^3$)—N bonds and C(sp)—H bonds in the presence of acidic catalysts (Scheme 1).

To test our hypothesis, we evaluated a number of Brønsted acids and Lewis acids (5 mol%) in the model reaction of *p*-toluenesulfonyl-activated benzhydrylamine (sulfonamide **1aa**) with phenylacetylene (**2a**) in 1, 2-dichloroethane at 90 ℃ (Table 1, Entries 1—8). The best catalytic activity was observed with $(Tf)_2NH$, which promoted the reaction to afford internal alkyne **3a**

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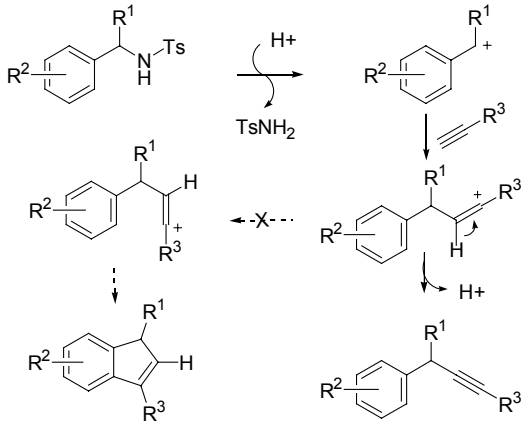
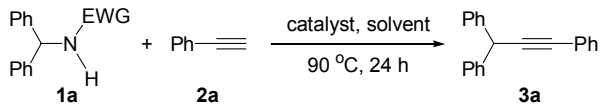
**Scheme 2** Possible reaction pathway for the formation of internal alkynes (for simplicity, proton represents an acidic catalyst)



in 54% yield (Table 1, Entry 4). Doubling the amount of $(Tf)_2NH$ improved the yield to 70% (Table 1, Entry 8) and more excitingly, significantly higher yield (85%) was obtained by combined use of $(Tf)_2NH$ and $Bi(OTf)_3$ in a 1∶1 ratio (Table 1, Entry 9). The yield was found to decrease dramatically when replacig 1,2-dichloroethane with a few other organic solvents (Table 1, Entries 10—12). Moreover, the efforts to enhance yield proved fruitless by activating benzhydrylamine with several other electron-withdrawing groups such as Ms, $POPh_2$, COPh, and Cbz (Table 1, Entries 13—16).

The substrate scope is broad with respect to

**Table 1** Optimization of reaction conditions[a]

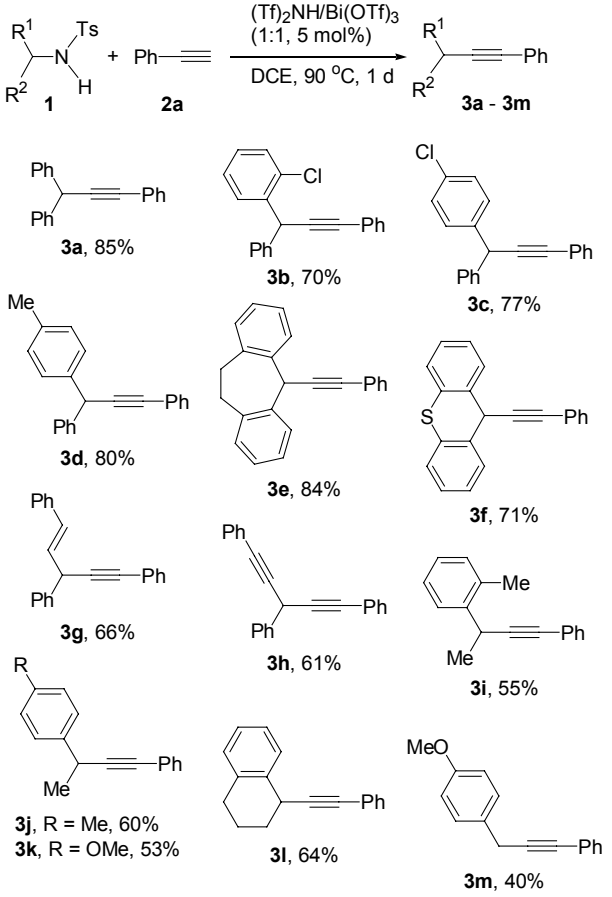



| Entry | a | EWG | Catalyst/mol% | Solvent | Yield[b]/% |
|---|---|---|---|---|---|
| 1 | **1aa** | Ts | TsOH (5) | DCE | trace |
| 2 | **1aa** | Ts | $H_2SO_4$ (5) | DCE | 10 |
| 3 | **1aa** | Ts | TfOH (5) | DCE | 43 |
| 4 | **1aa** | Ts | $(Tf)_2NH$ (5) | DCE | 54 |
| 5 | **1aa** | Ts | $Sc(OTf)_3$ (5) | DCE | 27 |
| 6 | **1aa** | Ts | $Fe(OTf)_3$ (5) | DCE | 45 |
| 7 | **1aa** | Ts | $Bi(OTf)_3$ (5) | DCE | 52 |
| 8 | **1aa** | Ts | $(Tf)_2NH$ (10) | DCE | 70 |
| 9 | **1aa** | Ts | $(Tf)_2NH/Bi(OTf)_3$ (1∶1, 5) | DCE | 85 |
| 10 | **1aa** | Ts | $(Tf)_2NH/Bi(OTf)_3$ (1∶1, 5) | $MeNO_2$ | 48 |
| 11 | **1aa** | Ts | $(Tf)_2NH/Bi(OTf)_3$ (1∶1, 5) | dioxane | 39 |
| 12 | **1aa** | Ts | $(Tf)_2NH/Bi(OTf)_3$ (1∶1, 5) | DMF | trace |
| 13 | **1ab** | Ms | $(Tf)_2NH/Bi(OTf)_3$ (1∶1, 5) | DCE | 72 |
| 14 | **1ac** | $POPh_2$ | $(Tf)_2NH/Bi(OTf)_3$ (1∶1, 5) | DCE | trace |
| 15 | **1ad** | POPh | $(Tf)_2NH/Bi(OTf)_3$ (1∶1, 5) | DCE | 25 |
| 16 | **1ae** | Cbz | $(Tf)_2NH/Bi(OTf)_3$ (1∶1, 5) | DCE | trace |

[a] Reaction conditions: benzhydrylamine derivative **1a** (0.20 mmol), alkyne **2a** (0.30 mmol), catalyst, solvent (2.0 mL), 90 ℃ (oil bath), 24 h. [b] Isolated yield.

*p*-toluenesulfonyl-activated primary benzylic amines. In the presence of 5 mol% of $(Tf)_2NH/Bi(OTf)_3$ (1∶1), a range of *N*-diarylmethyl sulfonamides smoothly coupled with terminal alkyne **2a** to afford structurally diverse internal alkynes in good yields (Table 2, **3a**—**3f**). This cross-coupling reaction allowed the synthesis of skipped enynes and diynes from the corresponding *N*-arylvinylmethyl and *N*-alkynylarylmethyl sulfonamides, respectively, and no rearrangement was observed for the carbon-carbon multiple bonds in the reaction (Table 2, **3g** and **3h**). Moreover, the $C(sp^3)$—N bonds of *N*-monobenzylic sulfonamides were also able to be cleaved under the same reaction conditions and underwent cross-coupling reaction with terminal alkyne **2a** to afford the desired alkyne products in moderate yields (Table 2, **3i**—**3m**). This cross-coupling reaction was not applicable to less reactive *N*-benzylic sulfonamides such as *N*-benzyl-*p*-toluenesulfonamide.[13]

**Table 2** Cross-coupling of *N*-benzylic sulfonamides with alkyne **2a**[a,b]




[a] Reaction conditions: sulfonamide **1** (0.20 mmol), alkyne **2a** (0.30 mmol), $(Tf)_2NH/Bi(OTf)_3$ (1∶1, 5 mol%), 1,2-dichloroethane (2.0 mL), 90 ℃ (oil bath), 1 d. [b] Isolated yields are shown.

The cross-coupling reaction was found to occur smoothly between terminal alkyne **2a** and a *p*-toluenesulfonyl-activated secondary benzylic amine. For ex-

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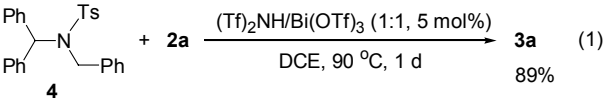
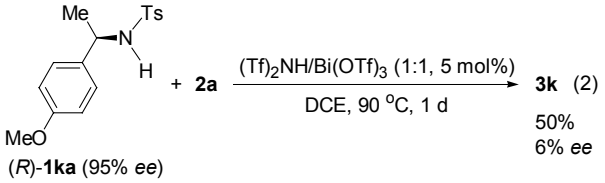
ample, internal alkyne **3a** was obtained in 89% yield from the reaction of sulfonamide **4** with terminal alkyne **2a** in the presence of 5 mol% of $(Tf)_2NH/Bi(OTf)_3$ (1∶1) (Equation 1). It is noteworthy that the monobenzylic $C(sp^3)$—N bond of sulfonamide **4** was not cleaved at all, which is consistent with our aforementioned observation with the reaction of *N*-benzyl-*p*-toluenesulfonamide under the same conditions.




We also examined the reaction of terminal alkyne **2a** with an optically active *N*-benzylic sulfonamide. As demonstrated by Equation 2, the reaction of sulfonamide (*R*)-**1ka** (95% *ee*) with terminal alkyne **2a** proceeded smoothly in the presence of 5 mol% of $(Tf)_2NH/Bi(OTf)_3$ (1∶1) to afford internal alkyne **3k** in nearly racemic form (6% *ee*). This result substantially supports our proposed reaction pathway depicted in Scheme 2, wherein a benzyl cation is involved at an early stage of the reaction.



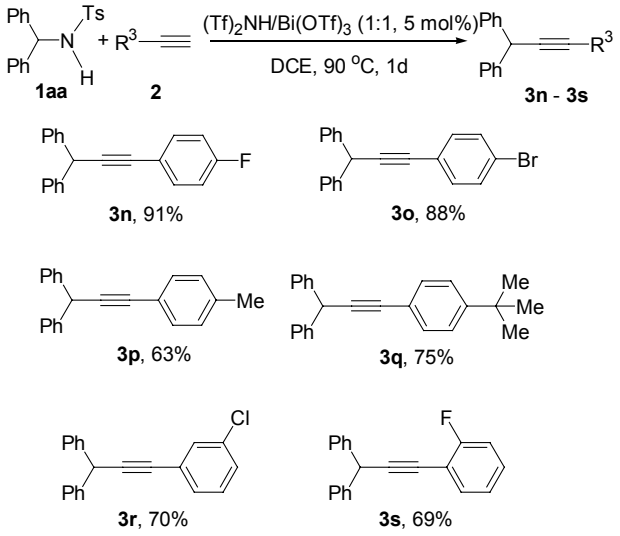

Finally, a range of arylacetylenes were found to be able to couple with sulfonamide **1aa** in the presence of 5 mol% of $(Tf)_2NH/Bi(OTf)_3$ (1∶1) to afford the corresponding internal alkynes in good to excellent yields (Table 3). By contrast, no reactivity was observed with alkylacetylenes such as 1-hexyne. As demonstrated by the results summarized in Tables 2 and 3, a variety of heteroatoms and alkyl groups were successfully introduced into the internal alkynes by employing functionalized *N*-benzylic sulfonamides and terminal alkynes.

## Experimental

### General information

$^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC-300 FT spectrometer (300 and 75 MHz, respectively) or a Bruker AC-400 FT spectrometer (400 and 100 MHz, respectively) using tetramethylsilane as an internal reference. High pressure liquid chromatography (HPLC) analyses were performed on a Hewlett-Packard 1200 Series instrument equipped with an isostatic pump and a Daicel Chiralpak AS column (250 mm×4.6 mm), and the UV detection was monitored at 254 nm. Melting points were uncorrected. *N*-Benzylic sulfonamides and other benzhydrylamine derivatives were prepared according to literature procedures.[14] The rest of chemicals were purchased from the Sinopharm Chemical Reagent Co., Meryer, Acros, Alfa Aesar, and AstaTech Pharmaceutical Co., and used as received. All the solvents were freshly distilled over $CaH_2$ before use.

**Table 3** Cross-coupling of sulfonamide **1aa** with terminal alkynes[a,b]




[a] Reaction conditions: sulfonamide **1aa** (0.20 mmol), alkyne **2** (0.30 mmol), $(Tf)_2NH/Bi(OTf)_3$ (1∶1, 5 mol%), 1,2-dichloroethane (2.0 mL), 90 ℃ (oil bath), 1 d. [b] Isolated yields are shown.

### General procedure for the cross-coupling of *N*-benzylic sulfonamides with terminal alkynes (Tables 2 and 3)

To a solution of *N*-benzylic sulfonamide **1** (0.20 mmol) in dry 1,2-dichloroethane (2.0 mL) under nitrogen were successively added terminal alkyne **2** (0.30 mmol), $Bi(OTf)_3$ (13.1 mg, 0.020 mmol), and $(Tf)_2NH$ (5.6 mg, 0.020 mmol, dissolved in 0.20 mL of DMF). The mixture was heated at 90 ℃ (oil bath) for 24 h, cooled to room temperature, and purified by column chromatography on silica gel, eluting with petroleum ether, to give product **3** (Tables 2 and 3).

## Conclusions

In summary, we have developed a new cross-coupling reaction of *N*-benzylic sulfonamides with terminal alkynes for the synthesis of internal alkynes through the cleavage of $C(sp^3)$—N bonds and C(sp)—H bonds under acidic conditions. In the presence of 5 mol% of $(Tf)_2NH/Bi(OTf)_3$ (1∶1), a broad range of *N*-benzylic sulfonamides react smoothly with arylacetylenes to afford structurally diverse internal alkynes in moderate to excellent yields. Current efforts are directed toward further synthetic applications of activated benzylic amines as carbon electrophiles.

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[13] In addition, no cross-coupling product was obtained from the reaction of terminal alkyne **2a** with *N*-allyl-*p*-toluenesulfonamide, *N*-cyclohexyl-*p*-toluenesulfonamide, or *N*-(1-adamantyl)-*p*-toluenesulfonamide. The lack of reactivity could be attributable to the relatively low stability of the corresponding carbocations generated through $C(sp^3)$—N bond cleavage.

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