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ARTICLE

Synthesis of α-Heterosubstituted Ketones through Sulfur Mediated Difunctionalization of Internal Alkynes

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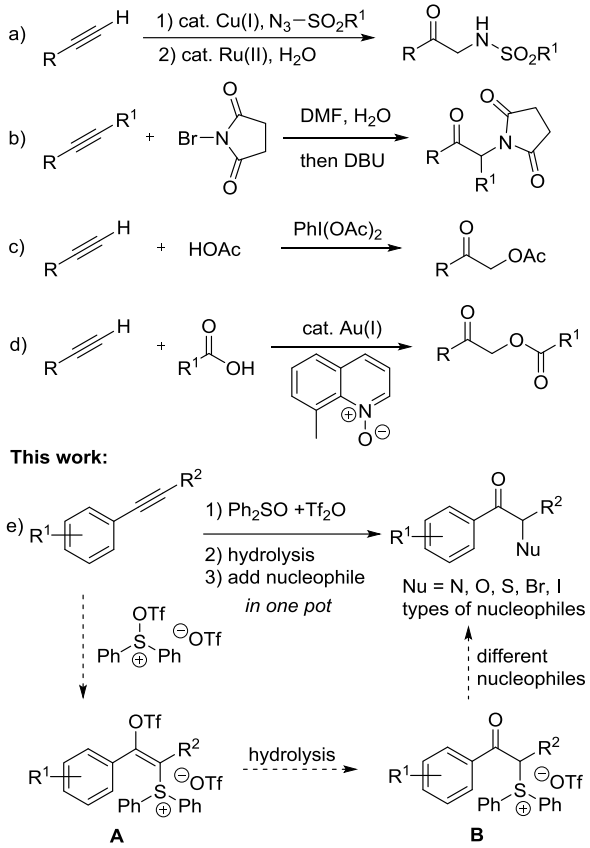
Synthesis of α-heterosubstituted ketones was achieved through sulfur mediated difunctionalization of internal alkynes in one-pot. The reaction design involves: phenyl substituted internal alkyne attacking the triflic anhydride activated diphenyl sulfoxide to give a sulfonium vinyl triflate intermediate, hydrolysis to give the α-sulfonium ketone, and then substitution with various nucleophiles. This method provides a unified route to access α-amino ketones, α-acyloxy ketones, α-thio ketones, α-halo ketones, α-hydroxy ketones, and related heterocyclic structures, in a rapid fashion.

Introduction

Ketones bearing α-heteroatom substituents constitute a class of compounds with significant synthetic interest.[1] Besides being important building blocks for more complex target structures, many drugs and biologically active molecules contain α-amino or α-hydroxy ketone moities. For example, they are key substructures of bupropion[2] and brephedron,[3] which are used in the clinical treatment of psychological disorders.

The most widely used method for synthesizing these compounds include: electrophilic α-halogenation/α-oxidation/α-amination of ketones or corresponding enolates,[4] as well as nucleophilic substitution of α-bromo ketones with oxygen, chalcogen, or nitrogen nucleophiles.[5] Oxidative difunctionalization of alkenes is another attractive route to give α-heterosubstituted ketones.[6] Recently, difunctionalization of alkynes also emerged as an alternative route to access such structure motifs.[7] Murakami's group[8] developed a copper/rhodium catalyzed two-step reaction sequence for converting terminal alkynes to α-amino ketones via triazole intermediates (Scheme 1a). Liang's group[9] reported the synthesis of α-succinimide/phthalimide substituted ketones though bromohydration of alkynes and subsequent substitution (Scheme 1b). Hou et al. reported the conversion of terminal alkynes to α-acetoxy ketones by using $PhI(OAc)_2$ as oxidant (Scheme 1c).[10] Zhang et al. developed a gold catalyzed reaction for converting terminal alkynes to α-acyloxy ketones (Scheme 1d).[11]

On the other hand, to the best of our knowledge, a general one-pot method for converting alkynes to different types of α-heterosubstituted ketone products has not been reported.[12] It should be noted that nitroso aldol reaction of ketones or aldehydes did provide a way to introduce either nitrogen or oxygen atom at the α-position of carbonyls under complementary organocatalyzed or acid catalyzed conditions.[4a, 13] But extra steps were usually required to cleave the resulting N-O bond of such nitroso aldol products. MacMillan's group[14] also developed an efficient $CuBr_2$ catalyzed coupling of α- carbonyls with dialkyl amines. However, extension of such catalytic system to other nucleophiles has not be reported. Recently, Hartwig's group reported a general solution for enantioselective



Scheme 1. Synthesis of α-heterosubstituted ketones through difunctionalization of alkynes.

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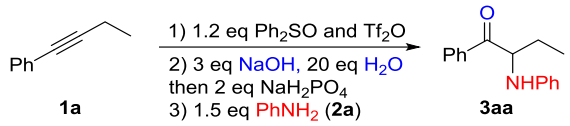
Table 1 Optimization of reaction conditions[a]



entry	deviation from standard conditions	yield/%[b]
1	none	72
2	use 5 eq of NaOH, 4 eq of NaH_2PO_4 in step 2	50
3	use 1.5 eq of NaH_2PO_4 in step 2	62
4	use 2.5 eq of NaH_2PO_4 in step 2	71
5	use 3 eq of $Me_4NOH•5H_2O$ instead of NaOH and H_2O in step 2	49
6	use TfOH instead of NaH_2PO_4 in step 2	63
7	use PTSA instead of NaH_2PO_4 in step 2	63

[a] Standard conditions A: a solution of **1a** (0.4 mmol) and Ph_2SO (0.48 mmol) in 2 mL of CH_2Cl_2 was treated with Tf_2O (0.48 mmol) at - 78 °C, warmed up to 0 °C, added NaOH (1.2 mmol) and H_2O (8 mmol), and stirred at 40 °C for 12 h. Then, NaH_2PO_4 (0.8 mmol) and **2a** (0.6 mmol) was added to the reaction mixture and stirred at 40 °C for 12 h before work-up and purification. [b] Isolated yield after column chromatography.

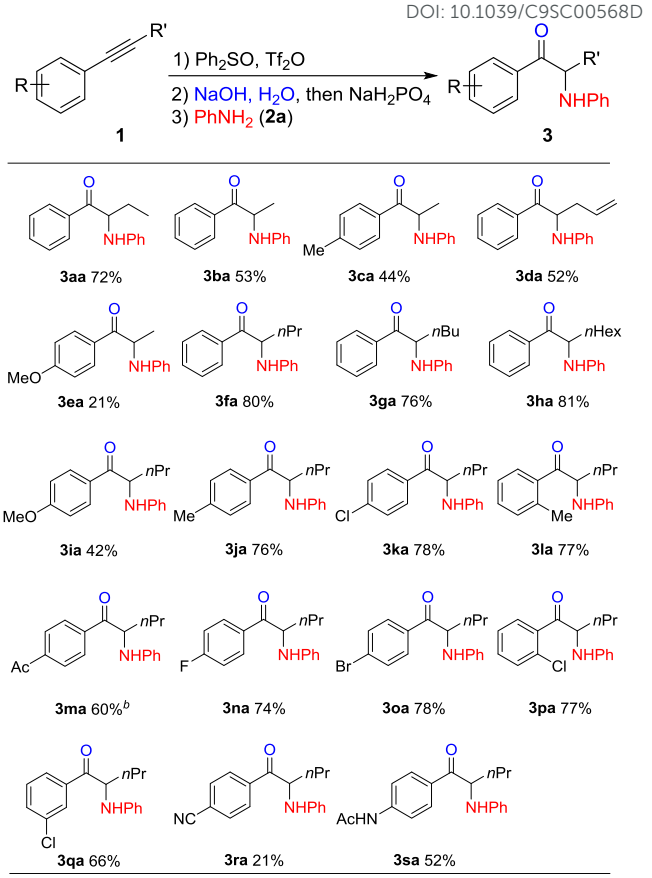
α-functionalizations of ketones via iridium catalyzed reaction of allylic carbonates containing silyl enol ethers as masked ketones.[15] Herein, we describe a one-pot, transition-metal-free method for the synthesis of α-heterosubstituted ketones through sulfur mediated difunctionalization of internal alkynes (Scheme 1e).

In connection with our recent interest in sulfur mediated C-H functionalization of alkenes[16] and alkynes,[17] we are interested in the reactivity of sulfonium vinyl triflate intermediate **A** generated through alkyne attack of triflic anhydride activated diphenyl sulfoxide (see Scheme 1e).[17a, 18] We reasoned that if hydrolysis of **A** could give α-sulfonium ketone **B**, subsequent substitution with various nucleophiles in one-pot would then afford different types of α-heterosubstituted ketones in a rapid and unified fashion.

Results and discussion

We chose 1-phenyl-1-butyne (**1a**) and aniline (**2a**) as our model substrates to find the optimal reaction conditions for the synthesis of α-amino ketone **3aa** (Table 1). For the first step, i.e. alkyne (**1a**) attack of triflic anhydride activated diphenyl sulfoxide, similar conditions were adopted from our previous studies on sulfur mediated propargylic C-H alkylation reaction of alkynes.[17a] We soon realized that the key to success for this one-pot reaction design was the optimal aqueous hydrolysis and buffer conditions for the conversion of sulfonium vinyl triflate intermediate **A** to α-sulfonium ketone **B**. Hydrolysis of **A** seems to proceed best with basic aqueous sodium hydroxide, presumably through an addition/elimination pathway. However, with excessive amount of sodium hydroxide, α-sulfonium ketone **B** would be converted to the corresponding carbonyl stabilized sulfur ylide **C**, which could not be used as the electrophile in our subsequent nucleophilic substitution reaction with aniline (**2a**). And

Table 2 Scope of alkynes **1**[a]



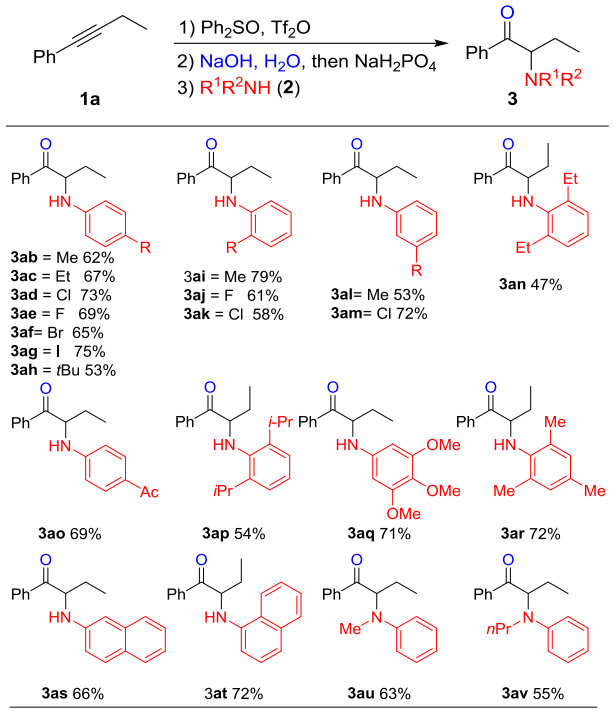
Standard conditions A: 1) **1** (0.4 mmol), Ph_2SO (0.48 mmol), Tf_2O (0.48 mmol); 2) NaOH (1.2 mmol), H_2O (8 mmol), NaH_2PO_4 (0.8 mmol); 3) **2a** (0.6 mmol). [a] Isolated yield. [b] 2 eq of Ph_2SO and Tf_2O was added in step 1.

thus, we have to acidify the reaction mixture appropriately to suppress the deprotonation of **B**, but not to acidify it too much as to protonate our nucleophilic amine base **2a**. Eventually, we found that the use of 3 equivalents sodium hydroxide and 20 equivalents water, followed by addition of 2 equivalents sodium dihydrogen phosphate and 1.5 eq **2a**, gave 72% yield of product **3aa** (Table 1, entry 1). Results for deviation from the optimized reaction conditions were shown in Table 1 (entries 2-7).[19] First, the amounts of sodium hydroxide and sodium dihydrogen phosphate were varied (entries 2-4). Then, tetramethylammonium hydroxide pentahydrate was used as the base (entry 5), and triflic acid (TfOH) or *p*-toluenesulfonic acid (PTSA) was used as the acid in step 2 (entries 6-7). None of these deviations afforded better yields than our standard conditions.

With the optimized reaction conditions in hand, the internal alkyne substrate scope was examined (Table 2). For phenyl substituted alkynes **1b**, **1f**, **1g**, and **1h**, corresponding α-amino ketone products **3ba**, **3fa**, **3ga**, and **3ha** were obtained in good yields. Olefin containing product **3da** was obtained in 52% yield, showcasing that the reactivity of phenyl substituted internal alkynes toward triflic anhydride activated sulfoxide reagents was higher than the terminal alkene moiety. Phenyl alkyne substrates bearing alkyl or halide (-F, -Cl, -Br) substituents all afforded products (**3ca**, **3la**, **3ja**, **3ka**, **3na**, **3oa**, **3pa** and **3qa**) in good yields. When electron-withdrawing acyl group was attached to the phenyl alkyne, lower yield for product **3ma**

was observed, and we recovered significant amount of alkyne substrate **1m**. The yield of product **3ra** decreased to 21% by using alkyne **1r** bearing a strongly electron-withdrawing cyano group. For methoxy substituted phenyl alkynes **1e** and **1i**, their reactions with triflic anhydride activated sulfoxide reagent could proceed completely, but it seems that the hydrolysis step was slower, which led to the decreased yields for products **3ea** and **3ia**. For the same reason, substrate **1s** gave the product **3sa** in a lower yield of 52%. Using terminal alkynes as substrates could not afford this type of products, but would give alkynyl diphenyl sulfonium salts instead.[18h] When dialkyl or alkyl silyl substituted alkynes were used, propargylic C-H arylation type products were obtained as previously reported by Procter et al. under similar reaction conditions.[18j]

Table 3 Scope of aryl amine nucleophiles **2**[a]

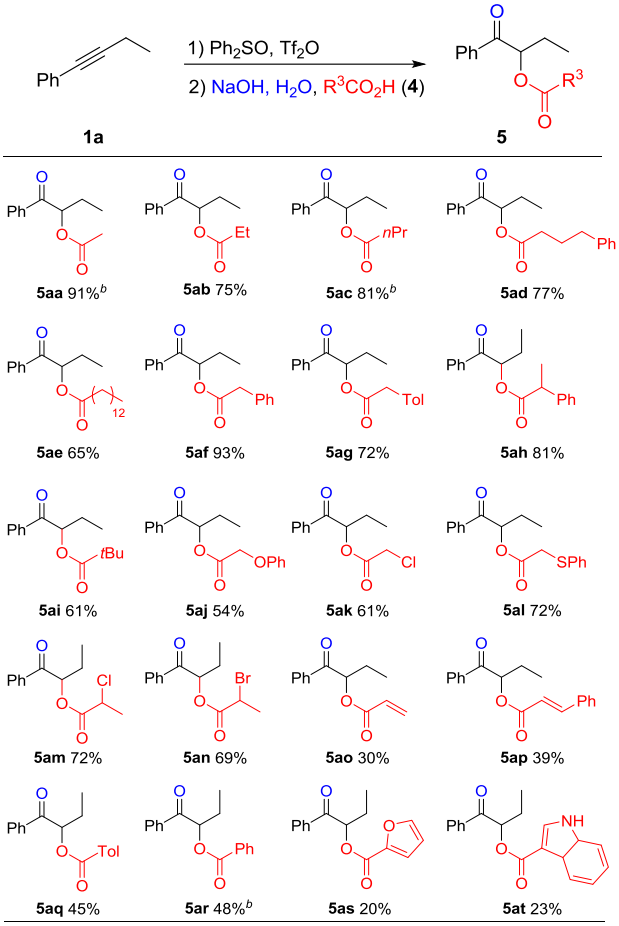


Standard conditions A: 1) **1a** (0.4 mmol), Ph_2SO (0.48 mmol), Tf_2O (0.48 mmol); 2) NaOH (1.2 mmol), H_2O (8 mmol), NaH_2PO_4 (0.8 mmol); 3) **2** (0.6 mmol). [a] Isolated yield.

We then examined the electronic and steric effects for various arylamine nucleophiles for the reaction with alkyne **1a** (Table 3). To our delight, amines having both electron-donating and electron-withdrawing groups, as well as having increased steric hindrance at the *ortho* positions, all reacted smoothly to afford the desired products (from **3ab** to **3av**) in good to moderate yields. Even with sterically very hindered of 2,6-diisopropylphenylamine **2p**, the desired product **3ap** was still obtained in 54% yield. Secondary amines **2u** and **2v** could also afford the corresponding α-amino ketones **3au** and **3av** in 63% and 55% yields, respectively.

We then turned our attention to the preparation of α-acyloxy ketones. It is reasoned that carboxylic acid substrates could act not only as nucleophiles, but also as acidic additives to replace the use of sodium dihydrogen phosphate to protonate the initially formed sulfur ylide during the hydrolysis step, and give the desired α-sulfonium ketone intermediate. Under further optimized reaction conditions, various carboxylic acids reacted nicely to give α-acyloxy ketone products in good yields (Table 4). In general, saturated carboxylic acids gave higher yields (**5aa-5an**), while alkenyl, aryl and hetero-aryl substituted carboxylic acids gave lower yields (**5ao-5at**).

Table 4 Scope of carboxylic acid nucleophiles **4**[a]



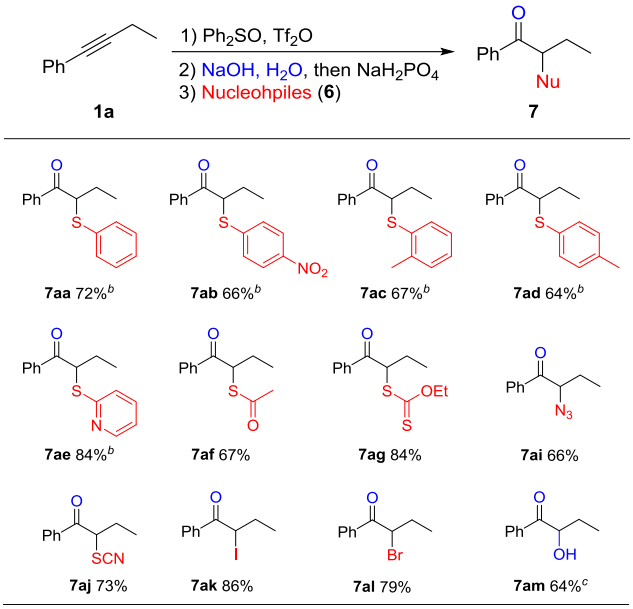
Standard conditions B: 1) **1a** (0.4 mmol), Ph_2SO (0.48 mmol), Tf_2O (0.48 mmol); 2) NaOH (2 mmol), H_2O (6 mmol), **4** (2 mmol). [a] Isolated yield. [b] Using RCO_2M (2 mmol) instead of NaOH and RCO_2H.

This reaction could also be applied with other nucleophiles (Table 5). A number of thiophenols gave good yields (**7aa-7ad**). Other sulfur, nitrogen, or halogen based nucleophiles, such as 2-mercaptopyridine (**6e**), potassium thioacetate (**6f**), potassium *O*-ethyl carbonodithioate (**6g**), sodium azide (**6i**), potassium thiocyanate (**6j**), potassium iodide (**6k**) and potassium bromide (**6l**), all gave the desired products (**7ae-7al**) in good yields. Besides, α-hydroxyl ketone **7am** could also be obtained in 64% yield in the same fashion by using tetrabutylammonium hydroxide (**6m**) as both the base and nucleophile. Compared with the previous results obtained with sodium hydroxide or tetramethylammonium hydroxide (Table 1, entry 5), the better phase-transfer nature for **6m** seems to be the key factor for the successful formation of **7am**.

By using appropriate ambident nucleophiles, a number of interesting heterocyclic structures can be prepared, since the initially formed α-hetero substituted ketones could undergo intramolecular condensation reactions (Table 6).[20] When thiourea **8a** and phenylthiourea **8b** were used as nucleophiles, 2-aminothiazoles **9aa**

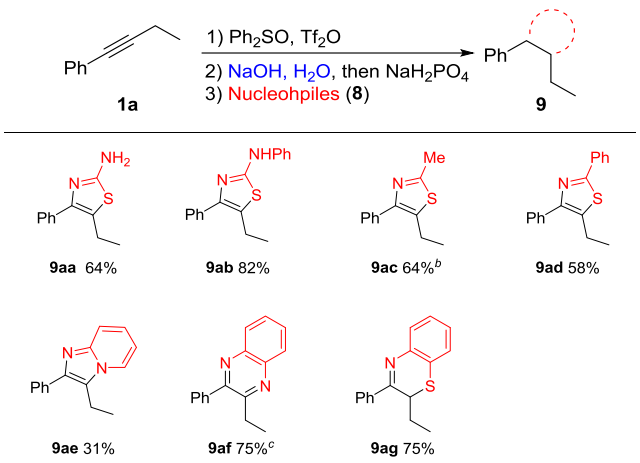
and **9ab** were afforded in 64% and 82% yields, respectively. Similarly, when thioamides **8c** and **8d** were used, thiazole products **9ac** and **9ad** were obtained in 64% and 58% yield, respectively. 2-Aminopyridine **8e** gave 3-ethyl-2-phenylimidazo[1,2-*a*]pyridine **9ae** in 31% yield. When *ortho*-diaminobenzene **8f** was used as the nucleophile, the initially formed product was easily oxidized and hard to purify. So we added 3 equivalents of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in one-pot after step 3 to give quinoxaline **9af** in 75% yield. Similarly, 2-aminothiophenol **8g** gave product **9ag** in 75% yield.

Table 5 Scope of other nucleophiles **6**[a]

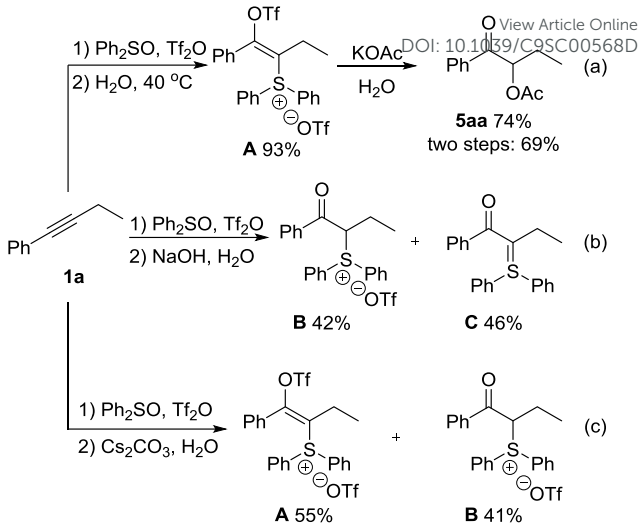


Standard conditions A: 1) **1a** (0.4 mmol), Ph_2SO (0.48 mmol), Tf_2O (0.48 mmol); 2) NaOH (1.2 mmol), H_2O (8 mmol), NaH_2PO_4 (0.8 mmol); 3) **6** (0.6 mmol). [a] Isolated yield. [b] The reaction was performed without adding NaH_2PO_4 in step 2. [c] Skipped step 2 and added aqueous nBu$_4$NOH solution as the nucleophile in step 3.

Table 6 Scope of ambident nucleophiles **8**[a]

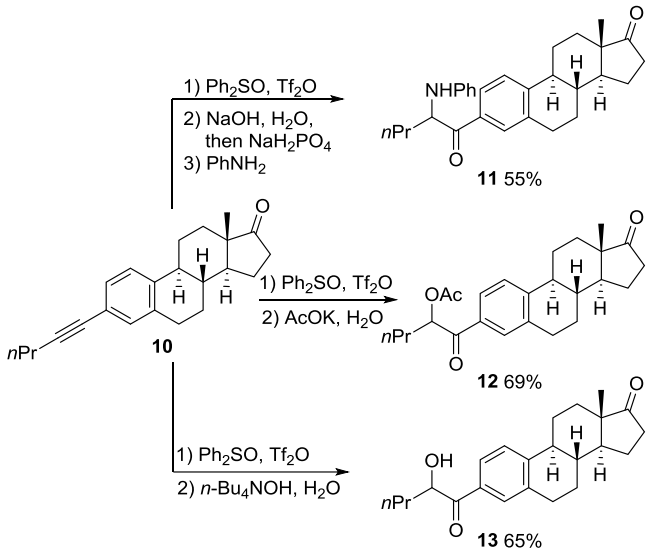


Standard conditions A: 1) **1a** (0.4 mmol), Ph_2SO (0.48 mmol), Tf_2O (0.48 mmol); 2) NaOH (1.2 mmol), H_2O (8 mmol), NaH_2PO_4 (0.8 mmol); 3) **8** (0.6 mmol). [a] Isolated yield. [b] Added extra 2 mL dichloroethane and stirred at 60 °C in step 3. [c] Added 3 eq DDQ after step 3.



Scheme 2 Isolation of reaction intermediates.

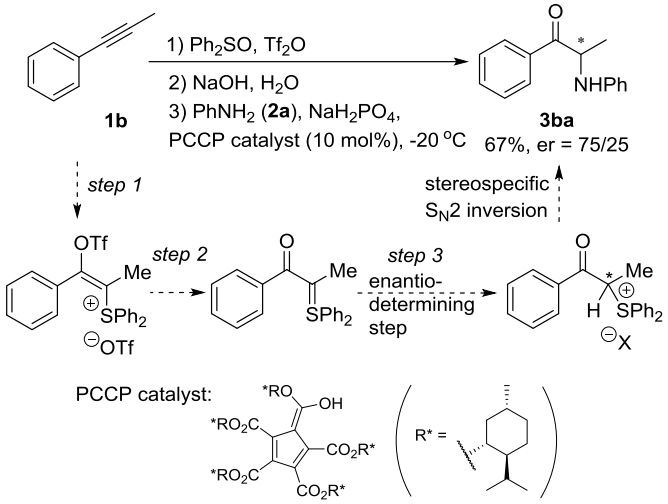
Our proposed reaction pathway is supported by the isolation and reactivity study of potential reaction intermediates (Scheme 2). When alkyne **1a** was treated with triflic anhydride activated diphenyl sulfoxide, we could isolate the sulfonium vinyl triflate intermediate **A** in 93% yield, which could afford the product **5aa** after reacting with potassium acetate and water (Scheme 2a). The attempted hydrolysis of intermediate **A** with water alone did not occur in this case before the addition of basic potassium acetate. While hydrolysis of intermediate **A** did occur with sodium hydroxide and water, sulfonium salt **B** and sulfur ylide **C** were isolated in 42% and 46% yields, respectively (Scheme 2b). With the weaker base cesium carbonate instead of the stronger base sodium hydroxide, α-sulfonium ketone intermediate **B** was obtained in 41% yield in addition to the 55% yield of sulfonium vinyl triflate **A** (Scheme 2c).[21]



Scheme 3. Functionalization of estrone derivative **10.**

To further explore the application of this reaction in the context of natural product derivatization, alkyne **10** was prepared in two steps from estrone (Scheme 3). Our difunctionalization reactions proceeded smoothly, and desired products **11**, **12** and **13** were afforded in 55%,

69% and 65% yields (ca. 1:1 mixture of two epimers with the newly generated stereocenters), respectively.



Scheme 4. Preliminary results for a catalytic asymmetric version.

Our preliminary results for a catalytic asymmetric version of this reaction is shown in Scheme 4. When chiral PCCP catalyst[22] was added in step 3 and the reaction temperature lowered to -20 °C, *α*-amino ketone **3ba** was obtained in 67% yield and 50% ee, which indicate the feasibility to develop a chiral Brønsted acid catalyzed reaction to prepare enantioenriched *α*-amino ketones directly from alkynes.

Conclusions

In conclusion, we have developed a general procedure for the synthesis of α-heterosubstituted ketones through sulfur mediated difunctionalization of internal alkynes. A variety of α-substituted ketones could be prepared by using nitrogen, oxygen, sulfur and halogen nucleophiles. Applications for the synthesis of heterocycles and derivatization of natural product are also realized. We are currently exploring the catalytic asymmetric version of this reaction, and those results will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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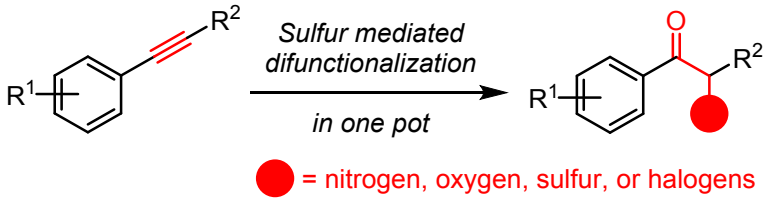
Synthesis of α-heterosubstituted ketones and related heterocyclic structures was achieved through sulfur mediated difunctionalization of internal alkynes in one-pot.



● = nitrogen, oxygen, sulfur, or halogens