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Silver/NBS-Catalyzed Synthesis of α-Alkylated Aryl Ketones from Internal Alkynes and Benzyl Alcohols via Ether Intermediates

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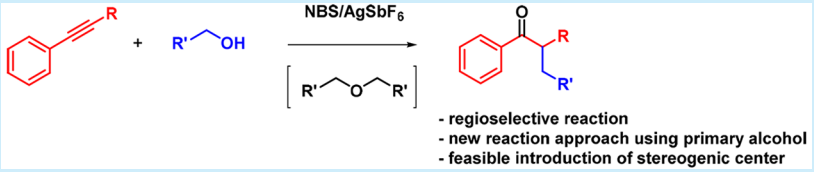
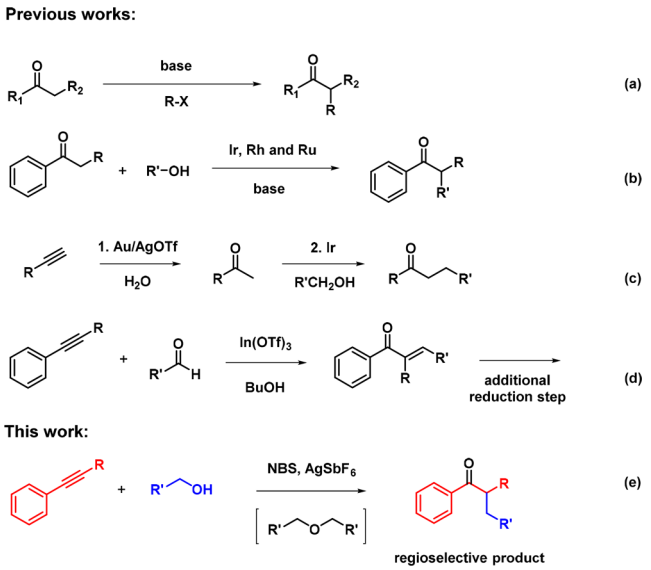
Supporting Information



ABSTRACT: The silver hexafluoroantimonate/*N*-bromosuccinimide (NBS)-catalyzed synthesis of α-alkylated aryl ketones with a tertiary carbon center from internal alkynes and benzyl alcohols is reported. This reaction proceeds via the etherification of benzyl alcohols with an in situ generated benzyl bromide, formed by the reaction of benzyl alcohol with a catalytic amount of NBS and $AgSbF_6$. Ag-catalyzed C−O cleavage of the ether leads to a tolyl radical, which undergoes addition to the alkyne, ultimately leading to the α-alkylated aryl ketone products.

α-Alkylated aryl ketones are a very important class of compounds that have a wide range of pharmacological and physiological activities.[1] Their activities have attracted much research interest in the synthesis of α-alkylated aryl ketones in many groups. Although many methodologies have been developed, there is still interest in exploring new reaction systems.[2] α-Alkylated aryl ketones are synthesized via α-alkylation of nucleophilic enolates derived from ketones with electrophilic alkylating agents in the presence of at least a stoichiometric amount of a strong base (Scheme 1a).[3] However, these procedures suffer from toxicity of the alkylating agents and the generation of a large amount of harmful waste salts. Thus, the α-alkylation of ketones with alcohols (Scheme 1b) has attracted much attention[4] because alcohols can be used as an alkylating agent in the reaction with α-functionalized carbonyl compounds via a hydrogen-borrowing process[5] in the presence of transition-metal catalysts.[6] Recently, the α-alkylation of methylene ketones with alcohol electrophiles has been also studied to prepare α-alkylated aryl ketones.[7] Several years ago, a strategy for the synthesis of α-alkylated ketones via a catalytic hydration of terminal alkynes and α-alkylation with primary alcohols was reported (Scheme 1c).[8] However, no reaction occurred with internal alkynes such as 5-decyne or diphenylacetylene.[9] The use of in situ generated α-substituted ketones from internal alkynes to form α-branched alkylation products is less developed. Aryl ketones may be synthesized by alkyne hydration;[10] however, reactions of internal alkynes often lead to a mixture of ketone regioisomers.[11] Thus, the regioselective functionalization of unsymmetrically substituted alkynes is of fundamental importance in organic synthesis.[12] The coupling of internal alkynes with aldehydes to afford α,β-unsaturated ketones has been studied (Scheme 1d).[13] However, in order to obtain α-alkylated aryl ketones, they must be hydrogenated. Therefore, a new synthetic strategy with a conceptually different reaction pathway is required. We envisioned that the α-alkylation of internal alkynes with alcohols could be a highly desirable strategy for the synthesis of α-alkylated aryl ketones (Scheme 1e) if an alkylating agent could be catalytically generated from primary alcohols and were regioselectively added to internal alkynes.

Scheme 1. Various Synthesis Strategies for α-Alkylated Aryl Ketone



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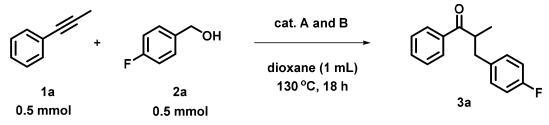
Very recently, $AgSbF_6$/NBS was found to be an excellent catalytic system for the synthesis of α-alkylated aryl ketones bearing a tertiary carbon center from internal alkynes and benzyl alcohols. The reaction is regioselective and applicable to a variety of internal alkynes and benzyl alcohols. A dibenzyl ether was generated in situ as a key intermediate, and a radical pathway, quite different from those proposed by previous studies,[8,13] was proposed. The present protocol provides a green, concise, and benign method to access α-alkylated aryl ketones. We communicate our preliminary results herein.

Organic halogenation compounds such as *N*-bromosuccinimide (NBS, 50%, entry 1), *N*-chlorosuccinimide (NCS, 46%, entry 2), and *N*-iodosuccinimide (NIS, 50%, entry 3) were screened as the catalyst (Table 1). As expected, without NBS

Table 1. Optimization of the Reaction Conditions for Synthesis of α-Alkylated Aryl Ketone



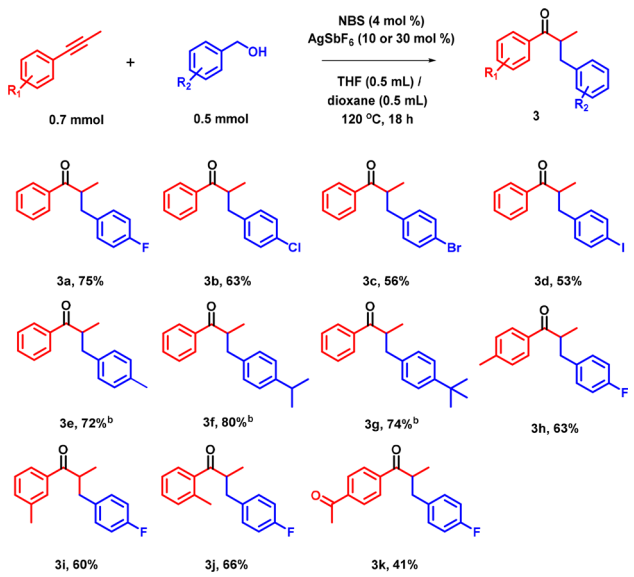
entry	cat. A (mol %)	cat. B (mol %)	solvent (1 mL)	yield[a] (%)
1	NBS (20)	$AgSbF_6$ (20)	dioxane	50
2	NIS (20)	$AgSbF_6$ (20)	dioxane	46
3	NCS (20)	$AgSbF_6$ (20)	dioxane	50
4		$AgSbF_6$ (20)	dioxane	NR
5	NBS (20)		dioxane	NR
6	NBS (20)	$AgNTf_2$(20)	dioxane	36
7[b]	NBS (20)	$AgSbF_6$ (30)	dioxane	57
8[b]	NBS (4)	$AgSbF_6$ (30)	dioxane	67
9[b]	NBS (4)	$AgSbF_6$ (30)	THF	60
10[b]	NBS (4)	$AgSbF_6$ (30)	dioxane/THF (0.3:0.7)	72
11[b]	NBS (4)	$AgSbF_6$ (30)	dioxane/THF (0.5:0.5)	75

[a]Isolated yields. [b]**1a** (0.7 mmol), 120 °C.

or $AgSbF_6$, no reaction occurred, even at 130 °C (entries 4 and 5). When Bu_4PF_6, $AgClO_4$, AgO_2CCF_3, $NaSbF_6$, or $[(4\text{-}BrC_6H_4)_3N]SbCl_6$ was used instead of $AgSbF_6$, no reaction was observed. When $AgNTf_2$ was used for the reaction, a certain amount of reaction proceeded (36%, entry 6), but the best activity in terms of efficiency was observed when $AgSbF_6$ was used. The amounts of the alkyne and the alcohol used also had an influence on the yield of the reaction (57%, entry 7). We chose the ratio of alkyne to alcohol to be 0.7:0.5 mmol in 1.0 mL of 1,4-dioxane. The yields of the reaction were dependent upon the amounts of NBS and $AgSbF_6$ used. The amount of NBS could be cut down to 4 mol %, but the amount of $AgSbF_6$ was fixed at 30 mol % (67%, entry 8). The yield of the reaction was also highly sensitive to the reaction medium (entries 9–11). The best yield (75%, entry 11) was observed when the reaction was carried out in a solvent mixture of THF and 1,4-dioxane with a ratio of 1:1. Thus, we established the optimum reaction conditions to obtain an α-alkylated aryl ketone from 1-phenyl-1-propyne and 4-fluorobenzyl alcohol.

With the optimum reaction conditions for the synthesis of α-alkylated aryl ketones at hand, the substrate scope was investigated (Scheme 2). We first tested a reaction between 1-phenyl-1-propyne with 4-substituted benzyl alcohols in the presence of NBS and $AgSbF_6$ (entries **3a**–**g**). The corresponding α-alkylated aryl ketones were isolated in 53–80% yields. In the reaction with 4-halobenzyl alcohols, the yield was

Scheme 2. Synthesis of α-Alkylated Aryl Ketones Using Methyl Aryl Acetylenes with Various Alcohols[a]



[a]30 mol % of $AgSbF_6$ was used unless otherwise noted, and all products were isolated by column chromatography. [b]10 mol % of $AgSbF_6$ was used, and 1 mL of THF was used as solvent.

dependent on the identity of the halogen. The highest yield (**3a**, 75%) was observed with a fluoro group and the lowest (**3d**, 53%) with an iodo group. Interestingly, in the reaction with 4-alkyl benzyl alcohols, the yields were rather insensitive to the identity of the alkyl group (**3e**–**g**, 58–60%). When the same reaction was carried out in THF for 18 h, the yields dramatically improved (**3e**, 59 → 72%; **3f**, 60 → 80%; **3g**, 58 → 74%) even with a sterically bulky substituent. Next, we studied a reaction between prop-1-yn-1-yl-substituted benzenes and 4-fluorobenzyl alcohol in the presence of NBS and $AgSbF_6$ (**3h**–**k**). The yield of the reaction was rather insensitive to the position of a methyl group on the benzene ring (ortho, 66%; meta, 60%; para, 63%). However, a rather lower yield (**3k**, 41%) was observed with an acetyl group on the benzene ring.

Other internal alkynes, including 1-phenyl-1-butyne, 1-phenyl-1-pentyne, 1-phenyl-1-hexyne, and 1,2-diphenylethyne, were also good substrates for reaction with 4-fluorobenzyl alcohol in the presence of NBS and $AgSbF_6$, affording the corresponding α-alkylated aryl ketones in 60–72% yields (**4a**–**g**, Scheme 3). In the reaction of 1,2-diphenylethyne, lengthening the reaction time improved the yield from 45% to 60% (**4d**). Notably, the reaction of benzyl alcohol having an isopropyl substituent with internal alkynes in THF produced relatively higher yields (**4e**,**f**; 68–71%, Scheme 3).

α-Alkylated aryl ketones are particularly useful due to the possibility of a stereogenic center at the α-position to the ketone group. The synthetic utility of our strategy could be enhanced, provided racemic ketones could be transformed into the optically active α-benzyl ketones. Fortunately, several years ago, Tsunoda and co-workers reported[14] the conversion of racemic ketones bearing a stereogenic center α to the carbonyl group into optically active ketones in the presence of TADDOL-type host molecules in H_2O/MeOH in suspension in basic media. Thus, 3-(4-fluorophenyl)-2-methyl-1-phenylpropan-1-one (**3a**) was treated with base in aqueous MeOH in

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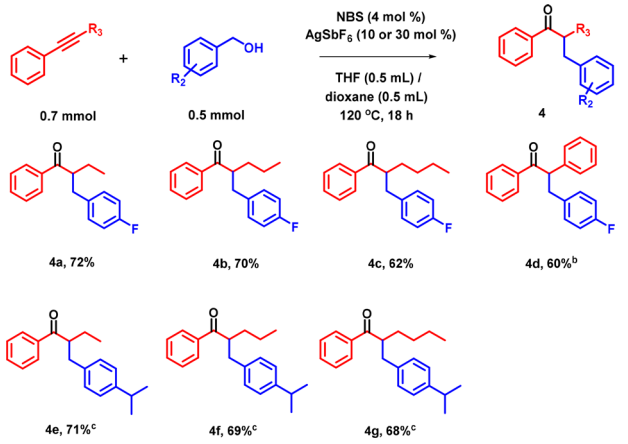
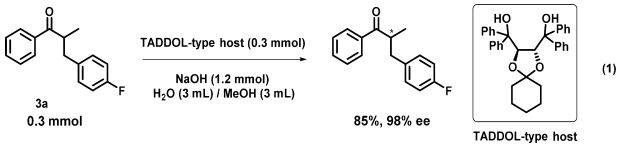
Scheme 3. Variation of the Acetylene Alkyl Group in the Synthesis of α-Alkylated Aryl Ketones[a]



[a]30 mol % of $AgSbF_6$ was used unless otherwise noted, and all products were isolated by column chromatography. [b]24 h. [c]10 mol % of $AgSbF_6$ was used, and 1 mL of THF was used as solvent.

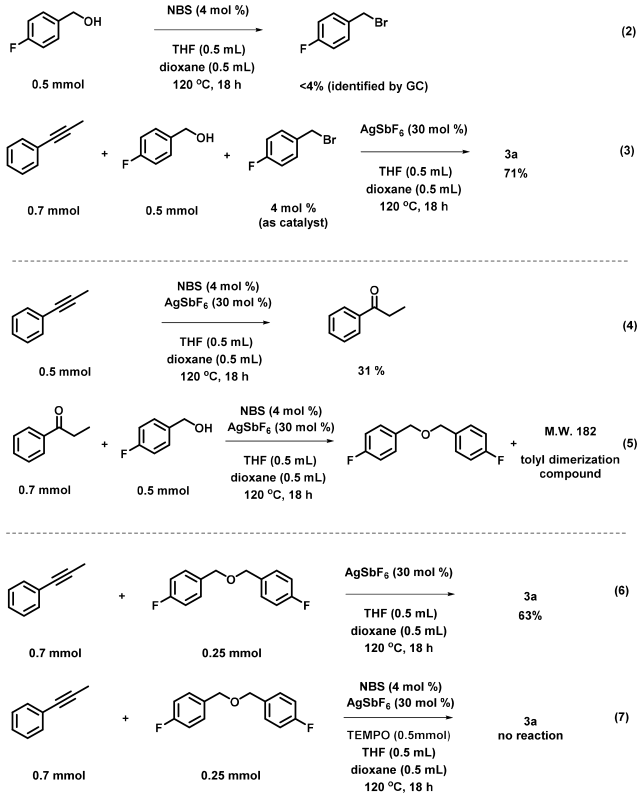
the presence of (−)-(2*R*,3*R*)-*trans*-2,3-bis-(hydroxyldiphenylmethyl)-1,4-dioxaspiro[5.4]decane (eq 1). After workup, a highly optically pure ketone was isolated in 85% yield with 98% ee.



While we were studying the $AgSbF_6$/NBS-mediated synthesis of **3a** from the reaction of 1-phenyl-1-propyne with 4-fluorobenzyl alcohol, the formation of a symmetric ether, 1,1′-[oxybis(methylene)]bis[4-fluorobenzene], was always observed. Furthermore, formation of toluene was observed by ^{1}H NMR. $AgSbF_6$/NBS was also found to be a catalyst in the etherification of benzyl alcohol (see the Supporting Information (SI)). It seems that alcohols can be activated via halogenation reactions to give more reactive organohalides, and further serve as the alkylating reagents to afford symmetric ethers.

To further validate the reaction mechanism, additional experiments were performed (Scheme 4, eqs 2−7). When 4-fluorobenzyl alcohol was treated with 4 mol % of NBS in a solvent mixture of THF (0.5 mL) and 1,4-dioxane (0.5 mL) at 120 °C for 18 h, the formation of 4-fluorobenzyl bromide was identified by GC analysis (eq 2). When 1-phenyl-1-propyne was reacted with 4-fluorobenzyl bromide in the presence of $AgSbF_6$ (30 mol %) in a solvent mixture of THF (0.5 mL) and 1,4-dioxane (0.5 mL) at 120 °C for 18 h, **3a** was isolated in 71% yield (eq 3). When 1-phenyl-1-propyne was reacted under our reaction conditions, ethyl phenyl ketone was isolated in 31% yield (eq 4). However, when ethyl phenyl ketone was treated with 4-fluorobenzyl alcohol in the presence of NBS (4 mol %) and $AgSbF_6$ (30 mol %) in a solvent mixture of THF (0.5 mL) and 1,4-dioxane (0.5 mL) at 120 °C for 18 h, no desired product was observed (eq 5). Instead, formation of 1,1′-[oxybis(methylene)]bis[4-fluorobenzene] and 1,2-diphenylethane (a tolyl dimerized compound) was observed. This observation suggests that a direct transformation of 1-phenyl-1-propyne to ethyl phenyl ketone did not occur during the reaction. When 1-phenyl-1-propyne was reacted with 1,1′-[oxybis(methylene)]bis[4-fluorobenzene] in the presence of $AgSbF_6$ in a solvent mixture of THF (0.5 mL) and 1,4-dioxane (0.5 mL) at 120 °C for 18 h, **3a** was isolated in 63% yield (eq 6), indicating that an ether was probably the reaction intermediate. However, when 0.5 mmol of TEMPO was added to the above solution, no reaction was not observed (eq 7). In the same way, no reaction was observed in the presence of 2,6-di-*tert*-butyl-4-methylphenol. The observation of the formation of toluene and the dimerized tolyl product may provide some evidence that the reaction proceeds via a radical pathway.

Scheme 4. Control Experiments



Based on our findings and previous studies,[15] we propose a possible mechanism as depicted in Figure 1. Two catalytic cycles may operate: one is the generation of ether and oxonium

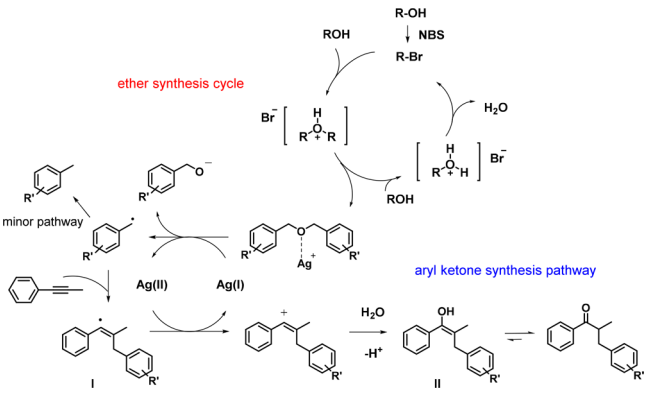


Figure 1. Proposed mechanism for synthesis of α-alkylated aryl ketones using alkynes and alcohols.

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bromide intermediates, and the other is the generation of α-alkylated aryl ketones through a radical process. Thus, benzyl alcohol is transformed into benzyl bromide in the presence of NBS. Benzyl bromide then reacts with another benzyl alcohol in the presence of $AgSbF_6$ to afford dibenzyl ether via oxonium bromide intermediates.[16] The in situ generated benzyl radical from benzyl bromide (see the SI) or dibenzyl ether in the presence of $AgSbF_6$ adds to the triple bond of 1-phenyl-1-propyne regioselectively, providing a vinyl radical intermediate **I**. The generation of the benzyl radical could be indirectly verified by the observation of toluene. The vinyl radical **I** must be oxidized to the vinyl cation by Ag(**II**). Sequential reaction of the vinyl cation with water would produce an enol intermediate **II**, which subsequently undergoes a keto−enol tautomerism to produce the product.

In conclusion, we have developed a silver/NBS-mediated synthesis of α-alkylated aryl ketones with a tertiary carbon center from internal alkynes and benzyl alcohols. Thus, an atom-economic direct functionalization of internal alkynes was achieved by using alcohol as both a hydration and alkylation source. Further efforts on the mechanism of the reaction are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02252.

Experimental procedures and characterization data of products (PDF)

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Notes

The authors declare no competing financial interest.

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