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Site-Selective α-Alkoxyl Alkynation of Alkyl Esters Mediated by Boryl Radicals

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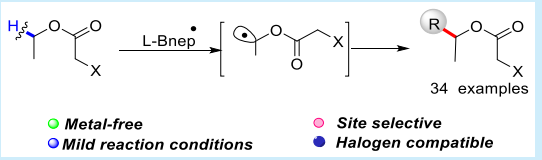
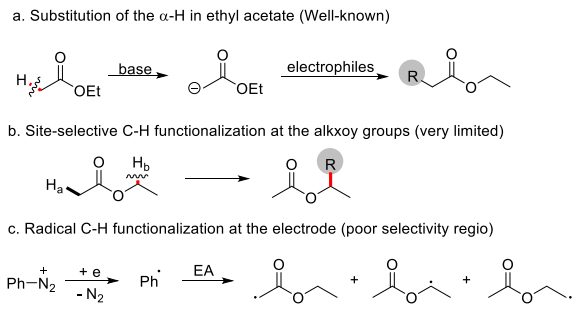
Supporting Information

ABSTRACT: A novel method for site-selective C−H functionalization of ethyl acetate mediated by pyridine−boryl radicals is presented, delivering a variety of 4-phenylbut-3-yn-2-yl acetate derivatives under mild conditions. A distinguishing feature of this reaction is that the pyridine-ligated boryl radicals can abstract the inactive α-hydrogen of the alkoxyl group instead of the α-hydrogen of carbonyl groups described in a previous report using amine-ligated boryl radicals. Significantly, substrates with halogen atoms are compatible under the reaction conditions.



Ethyl acetate (EA) is widely used as an organic solvent and additive in food chemistry due to its good solubility, pleasant aroma, and low toxicity.[1] On the other hand, it is also a cheap and basic chemical feedstock in organic synthesis. In general, the α-hydrogen of the ester has an increased reactivity because of the electron-withdrawing property of the carbonyl group. As a result, two classical synthetic methods, the Claisen ester condensations[2] and enolate alkylations,[3] are well established, affording fundamental processes for carbon−carbon bond formation in the presence of a stoichiometric base (Scheme 1, a). Although these groundbreaking efforts have made significant progress, investigations to access the less active α-sites of alkoxyl groups are highly limited (Scheme 1, b). Indeed, the intrinsic inert properties of these hydrogens make them notably resistant to participating in an ionic reaction. A radical approach may be a good choice.[4] However, the site-selective hydrogen abstraction can be problematic because the bond dissociation energies (BDEs) of these two α-C−H bonds (Scheme 1, b, H_a and H_b) are too close.[5] For example, it was reported that the electrochemical C−H functionalization of EA would occur at all three types of hydrogens (Scheme 1, c).[4a] Patel et al. also reported an interesting functionalization at the α position of the ethoxyl group to afford unsymmetrical *gem*-diacylates. However, only that carbon−oxygen bond was constructed.[4b] Given the significance of radical sp^3 C−H functionalization,[6] the development of a site-selective carbon−carbon bond construction at the α-alkoxyl group is of great importance and should have broad applications in organic synthesis, not only because of the synthetic challenge but also because acetyl-group-protected alcohols could be synthesized in one step.

Scheme 1. Synthetic Application of Ethyl Acetates



In the past decade, the development of ligated-boryl radicals has received great attention from the synthetic community.[7,8] In particular, NHC−boryl radicals, pioneered by Fensterbank et al., have shown versatile reactivities in a range of useful transformations, including in the reduction of a variety of C−X (X = xanthates, halides, CN) bonds to C−H bonds[9] (Scheme 2, a) and other related reactions.[10] Moreover, the challenging addition of NHC−boryl radicals to unsaturated C−C triple bonds was achieved by Curran et al.,[11] providing a facile synthesis of boron-containing alkenes. Very recently, an exciting inverse hydroboration of imines using NHC−boryl radicals was reported by Xie et al.[12] Besides NHC−boryl radicals, the groups of Li and Zhu and Aggarwal independently reported that the homolysis of the B−B bond in pyridine-[13] or amide[14]-coordinated diboranes leads to a variety of reductions and borylations.

Interestingly, Roberts discovered that amine−boryl radicals could be used in polarity-reversal catalysis. In the presence of

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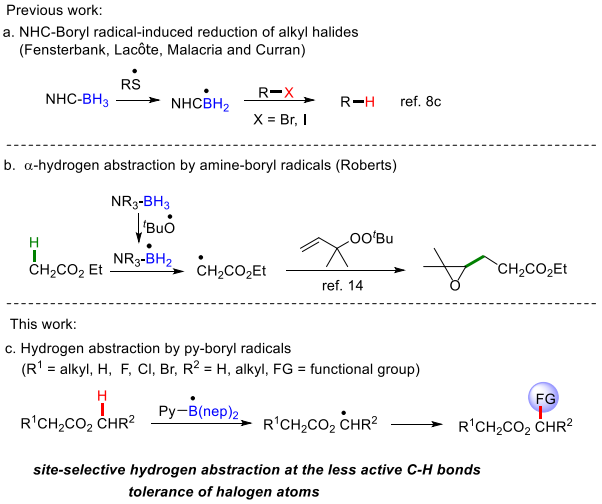
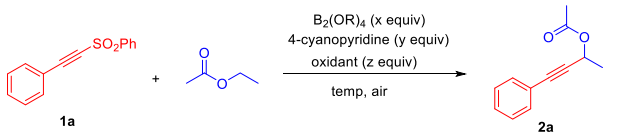
Scheme 2. Previous Studies on Boryl Radicals and Our New Method



an alkoxyl radical (*t*BuO·), amine−boryl radicals can selectively abstract the α-H of ethyl acetate, followed by a radical addition of olefin to yield methyl 3-(3,3-dimethyloxiran-2-yl)propanoates (Scheme 2, b).[15] Likewise, pyridine−boryl radicals can also abstract a hydrogen to generate alkyl radicals with the assistance of an oxidant. Previously, we reported the first pyridine−boryl-radical-mediated α-C−H functionalizations of ethers, DMF (*N*,*N*-dimethylformamide), and amines with 4-cyanopyridine 1-oxide as the oxidant.[16] To continue our research, it was of interest to explore the unique reactivities of such boryl radicals, and we envisioned that α-hydrogen abstraction could occur in ethyl acetate. In fact, the reaction took place at the α-position of the alkoxyl group. In this study, we report an unprecedented boryl radical-initiated C−H functionalization of ethyl acetate with ((arylethynyl)-sulfonyl)benzenes, affording diverse 4-arylbut-3-yn-2-yl acetate derivatives under mild conditions (Scheme 2, c). Notably, the transformation can be extended to other aliphatic acetates, and halogens are compatible with the reaction conditions.

We set out on our research by stirring alkyne sulfones with ethyl acetate in the presence of boryl radical (BPin·) formed *in situ*. First, pyridine 1-oxide (**I**), 4-nitro-pyridine 1-oxide (**II**), 4-cyanopyridine 1-oxide (**III**), pyridine 1-oxide (**IV**), 2,6-dimethylpyridine 1-oxide (**V**), and 2,6-dichloropyridine 1-oxide (**VI**) were employed as the oxidants, and 4-cyanopyridine 1-oxide was the best to furnish the desired product **2a** in 48% yield in 1 h (Table 1, entries 1−6). Next, several borates were tested, and it was found that $\mathbf{B_2}$ [bis(neopentyl glycolato)diboron, $B_2(nep)_2$] exhibited beneficial effects, and the yield of **2a** increased to 59% (Table 1, entries 7−9). When changing the amount of $B_2(nep)_2$ to 3 equiv or 1 equiv, the yields of **2a** decreased in both cases (Table 1, entries 10 and 11). If the amount of 4-cyanopyridine 1-oxide decreased to 2 equiv, interestingly, the yield of **2a** increased slightly to 60% (Table 1, entry 12). However, further reducing the amount of oxidant to 1 equiv only gave the desired product in 11% yield (Table 1, entry 13). The temperature effect was also evaluated, and it was found that 30 °C was more suitable for this transformation (Table 1, entries 15−17). Notably, reaction time was also very important, as performing the reaction in 30 and 10 min, the starting material **1a** was completely consumed, producing the product **2a** in

Table 1. Optimization of the Reaction Conditions[a]



entry	*x*/*y*/*z*	oxidant	B	temp. (°C)	time (min)	yield (%)[b]
1	2/1/3	**I**	$\mathbf{B_1}$	20	60	9
2	2/1/3	**II**	$\mathbf{B_1}$	20	60	3
3	2/1/3	**III**	$\mathbf{B_1}$	20	60	48
4	2/1/3	**IV**	$\mathbf{B_1}$	20	60	-
5	2/1/3	**V**	$\mathbf{B_1}$	20	60	0
6	2/1/3	**VI**	$\mathbf{B_1}$	20	60	32
7	2/1/3	**III**	$\mathbf{B_2}$	20	60	59
8	2/1/3	**III**	$\mathbf{B_3}$	20	60	-
9	2/1/3	**III**	$\mathbf{B_4}$	20	60	-
10	3/1/3	**III**	$\mathbf{B_2}$	20	60	58
11	1/1/3	**III**	$\mathbf{B_2}$	20	60	11
12	2/1/2	**III**	$\mathbf{B_2}$	20	60	60
13	2/1/1	**III**	$\mathbf{B_2}$	20	60	22
14	2/1/0	-	$\mathbf{B_2}$	20	60	-
15	2/1/2	**III**	$\mathbf{B_2}$	30	60	66
16	2/1/2	**III**	$\mathbf{B_2}$	40	60	62
17	2/1/2	**III**	$\mathbf{B_2}$	50	60	63
18	2/1/2	**III**	$\mathbf{B_2}$	30	30	68
19	2/1/2	**III**	$\mathbf{B_2}$	30	10	74 (71)[c]
20	0/0/2	**III**	$\mathbf{B_2}$	30	10	-

[a]Reaction conditions: 0.3 mmol scale. [b]Yields were determined by gas chromatography using *n*-dodecane as an internal standard. [c]The isolated yield is shown in parentheses. **I**: pyridine 1-oxide; **II**: 4-nitropyridine 1-oxide; **III**: 4-cyanopyridine 1-oxide; **IV**: 4-methylpyridine 1-oxide; **V**: 2,6-dimethylpyridine 1-oxide; **VI**: 2,6-dichloropyridine 1-oxide. $\mathbf{B_1}$: Bis(pinacolato)diboron; $\mathbf{B_2}$: Bis(neopentyl glycolato)-diboron; $\mathbf{B_3}$: 2,2′-Bis-1,3,2-benzodioxaborole; $\mathbf{B_4}$: Bis(hexylene glycolato)diboron.

68% and 74% yields, respectively (Table 1, entries 18 and 19). In the absence of 4-cyanopyridine 1-oxide or without the radical generation system (cyanopyridine and borate), the reaction did not take place (Table 1, entries 14 and 20).

With the best reaction conditions in hand, we next evaluated the substrate scope of the reaction by varying the structure of alkyl sulfones **1** (Scheme 3). For substrates with *para*-substituents, all the reactions proceeded smoothly to furnish the desired products **2b**−**2j** in moderate yields, and the electronic properties of the substituents did not have a significant effect on the reaction outcomes. *Meta*- or *ortho*-substituted substrates were also suitable for this reaction, and the corresponding products **2k**−**2o** were obtained in 60−71% yields. Treatment of a substrate bearing a naphthyl substituent furnished product **2p** in 73% yield. Notably, heteroaromatic rings substituted with sulfones were also tolerated in this reaction and provided corresponding products **2q** and **2r** in 50% and 57% yields, respectively. Furthermore, alkynyls and amides were also compatible with the reaction conditions, and the corresponding products **2s** and **2t** were obtained in 45% and 74% yields, respectively. Notably, the reaction of **1a** could be scaled up to 1 mmol, and **2a** was obtained in 68% yield.

Encouraged by the above results, we next attempted to expand this method to other esters instead of ethyl acetate. Upon conducting the reactions of **1** with 2 equiv of $B_2(nep)_2$, 1 equiv of 4-cyanopyridine, and 3 equiv of 4-cyanopyridine 1-oxide in 30 min in several commercially available ester

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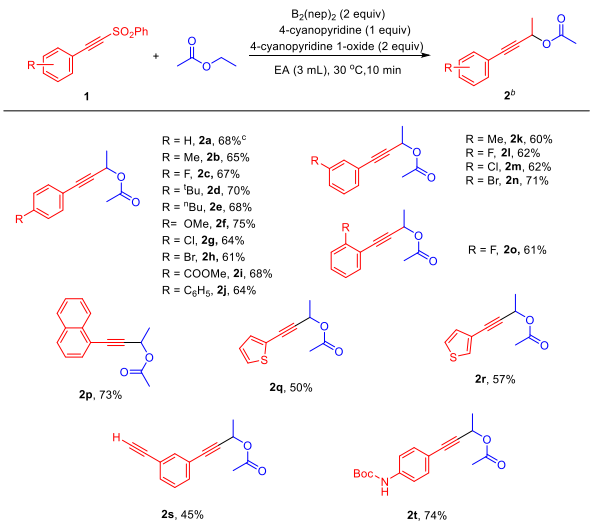
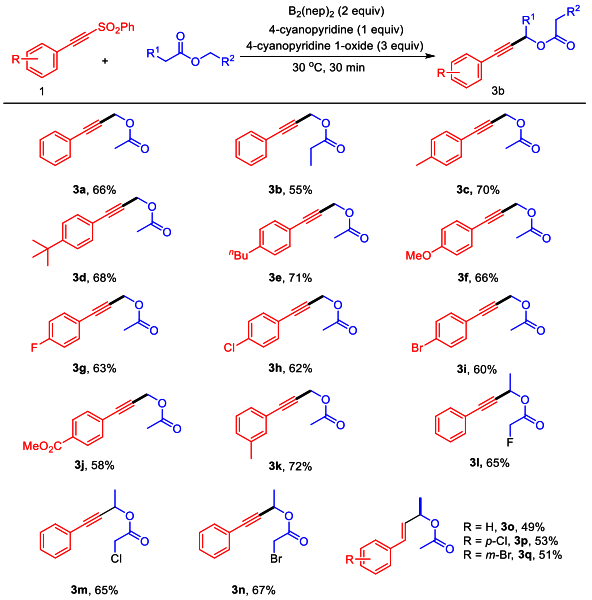
Scheme 3. Reactions of Various Alkyl Sulfones 1 with EA[a]



[a]All reactions were carried out on a 0.3 mmol scale in 3 mL of EA. [b]Isolated yields. [c]1 mmol scale.

solvents, the desired products **3a**−**3n** were obtained in moderate yields with excellent site selectivities (Scheme 4).

Scheme 4. Reactions of 1 with Other Esters[a,b]

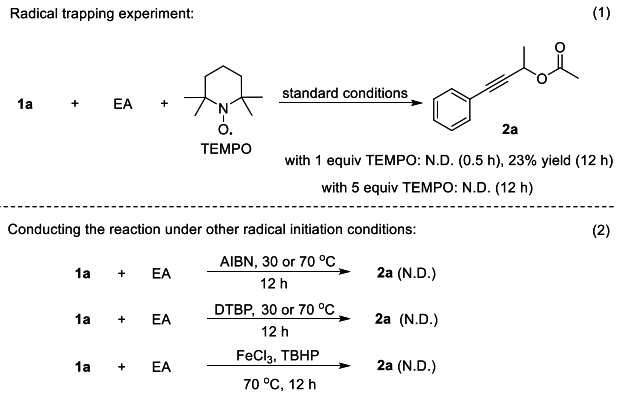


[a]All reactions were carried out on a 0.3 mmol scale. [b]Isolated yields.

It is worth noting that for halogen-containing solvents, such as ethyl chloroacetate, ethyl bromoacetate, and ethyl fluoroacetate, the reactions also took place exclusively at the α-C−H bond of the ethoxy groups. No dehalogenation[9c] was observed in any of the three cases. Further, vinylation was also successful under the standard reaction conditions, and corresponding *trans*-allyl ester derivatives **3o**−**3q** were formed in moderate yields.

To probe the reaction mechanism, several control experiments were performed. With 1 equiv of TEMPO, the reaction was notably sluggish. Only a small amount of **2a** was obtained after 12 h, while in the presence of 5 equiv of TEMPO, the reaction was totally inhibited. These results indicate that the reaction probably proceeds through a radical pathway (Scheme 5, eq 1). Furthermore, upon the replacement of the radical

Scheme 5. Control Experiments



initiation system by AIBN [2,2′-azobis(2-methylpropionitrile)], DTBP (di-*tert*-butyl peroxide), and TBHP (*tert*-butyl hydroperoxide), no desired product was observed in any of the cases (Scheme 5, eq 2) (see Supporting Information for detailed information).

To further understand the polar effects in this reaction, a calculation was conducted to determine the electron density distribution (Figure 1). The spin density on the B atom is only

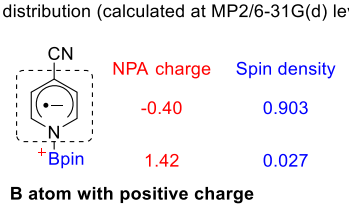
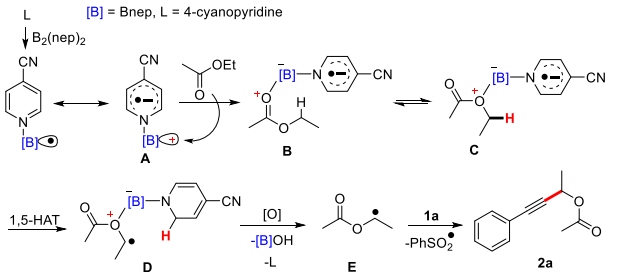


Figure 1. Computational calculation at the MP2/6-31G(d) level.

0.027, indicating that the single electron of the free radical is not localized on the boron atom but is delocalized on the pyridine ring. According to polar effects reported by Ryu[6a] and Macmillan,[6h] the pyridine−boryl radicals should act as electrophilic species to facilitate the most hydridic hydrogen abstraction.

Based on the results of the above experiments and our previous study,[16] a plausible mechanism using **1a** as a model was proposed as shown in Scheme 6. Initially, the pyridine−boryl radical is generated by homolysis of the B−B bond, and the resonance **A** is more stable according to computational calculation. Then, the empty orbital of the boron atom may

Scheme 6. Proposed Mechanism



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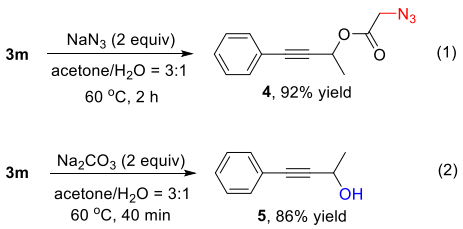
coordinate with EA to generate complex **B**, which exists in equilibrium with intermediate **C**. The following intramolecular 1,5-HAT by the 4-cyanopyridine−boryl radical at the C2 position gives intermediate **D**,[17] which is quickly oxidized to intermediate **E** together with the formation of HOBnep byproduct and ligand. Subsequent addition of intermediate **E** to the alkynyl sulfone **1a** furnishes the final products **2a**.

To demonstrate the synthetic utility of this method further, derivatizations of **3m** were performed. Upon treatment of **3m** with NaN_3, the substitution reaction was completed in 2 h and furnished the corresponding product **4** in 92% yield (Scheme 7, eq 1), In addition, in the presence of a base, Na_2CO_3, **3m** was easily hydrolyzed to give alcohol **5** in 86% yield after 40 min (Scheme 7, eq 2).

Scheme 7. Synthetic Applications of Product 3m



In summary, we have developed a site-selective C−H functionalization of esters through boryl-radical-enabled hydrogen abstraction under mild conditions. The substrate scope is broad, and a variety of functional groups are compatible with the reaction. A distinguishing feature of this reaction is that the boryl radical specifically abstracts the hydrogen of the alkoxyl C−H bond, instead of the α-hydrogen adjacent to the carbonyl group. This discovery will be a good addition to electrophilic boron radical chemistry because there was only one case of the electrophilic ligated boryl radical (NHC−BF_2·) reported by Curran, Lalevée, and Lacôte.[18] Moreover, halogens are tolerated under the reaction conditions. Further investigations into the mechanism and applications of this method in organic synthesis are currently underway in our laboratory and will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00985.

Experimental procedures, characterization data for all new compounds, and selected NMR spectra and IR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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