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Molecular Oxygen-Mediated Radical Alkylation of C(sp^3)−H Bonds with Boronic Acids

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ABSTRACT: A direct and site-specific alkylation of (sp^3)C−H bond with aliphatic boronic acid was achieved. By simply heating glycinates and amines together with alkylboronic acids under an oxygen atmosphere, a variety of unnatural α-amino acids and peptides could be obtained in good yields.

Organoboranes are proven to be valuable radical precursors which have been widely used in synthetic organic chemistry.[1] More interestingly, free-radical-promoted direct C−H arylation and alkylation with organoboranes have also been achieved in the past two decades,[2] among which the radical C(sp)−H and C(sp^2)−H bond alkylation via aliphatic boranes was extensively explored. However, the direct alkylation of the C(sp^3)−H bond using alkylborane as the radical precursor has remained undeveloped.

Previous studies showed that the C(sp^3)−H bond adjacent to an N-atom could couple with an alkyl radical.[3] Also, several methods have been achieved to prepare unnatural amino acids and their derivatives. For instance, Xu and co-workers developed a visible-light-driven decarboxylative alkylation of glycine and peptide in 2018.[4] Peroxide-mediated double C(sp^3)−H bond functionalization was also accomplished by Yu[5] and Correa.[6] Very recently, Wang et al. achieved C(sp^3)−H bond alkylation utilizing peroxide as the alkyl radical source.[7] However, these systems suffered from prefabrication of the radical precursor, a potentially explosive peroxide, and relatively hash conditions. Hence, development of more efficient and greener access to artificial amino acids and peptides is highly desirable.

Inspired by our original strategy for molecular oxygen-mediated alkylation of heteroarene and its derivatives with alkylboronic acid,[8] we began to envision whether this method could meet the challenge of C(sp^3)−H bond alkylation with boronic acid. Fortunately, we found an effective alkylation of a C(sp^3)−H bond with alkylboronic acid by using 1 atm O_2 (Scheme 1).

Initially, we carried out the reaction of ethyl(4-methoxyphenyl)glycinate with isopropyl boronic acid as a model reaction to optimize the conditions (Table 1). As seen from Table 1, factors such as acidic additives, solvent, and temperature seriously affect the efficiency of the reaction. By changing the solvent and its volume, we can get a desired yield

Scheme 1. Radical C−H Alkylation Using Alkylboronic Acid as Precursor

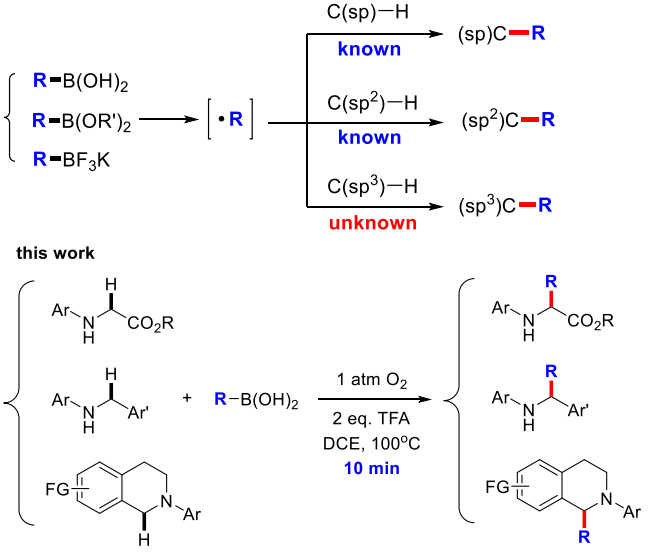

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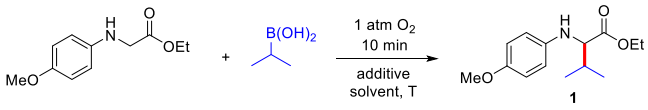
Table 1. Optimization of the Reaction Conditions[a]



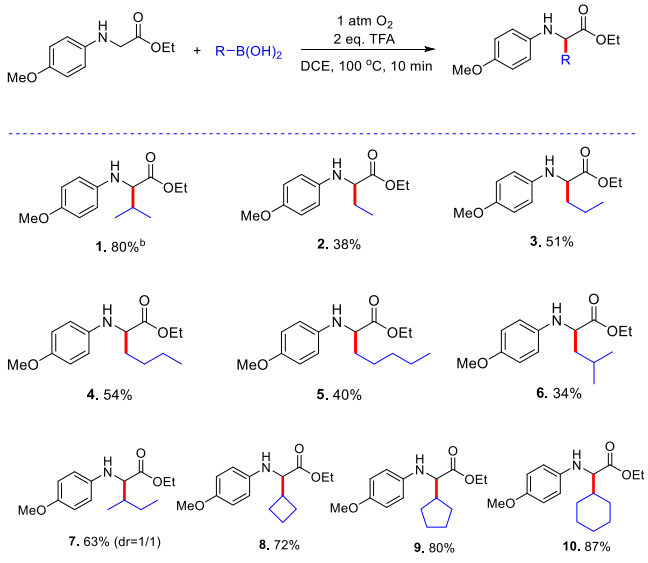
entry	additive (equiv)	solvent (mL)	T (°C)	yield (%)[b]
1	TFA (2)	DCE (2)	100	70
2	TFA (2)	DCE (0.5)	100	80
3	TFA (2)	CH_3CN (0.5)	100	35
4	TFA (2)	HOAc/DCE (0.25/0.25)	100	73
5	TFA (2)	EtOH/DCE (0.25/0.25)	100	70
6	TFA (2)	DCE (0.5)	90	64
7	TFA (1)	DCE (0.5)	100	60
8[c]	TFA (2)	DCE (0.5)	100	57

[a]Reaction conditions: ethyl(4-methoxyphenyl)glycinate (0.2 mmol, 1 equiv), i-PrB(OH)$_2$ (1 mmol, 5 equiv), 1 atm O_2 (oxygen bag), 10 min, unless otherwise noted. [b]Isolated yields. [c]3 equiv of i-PrB(OH)$_2$ used.

(80%) while using 0.5 mL of DCE (entries 1−5). When the temperature was adjusted to 90 °C, the desired product was obtained in 64% (entry 6). In addition, a 60% yield of product was afforded when 1 equiv of TFA was added (entry 7). Finally, a decreased yield of 1 was isolated by utilizing 3 equiv of boronic acids (entry 8). It is worth noting that all these reactions were completed within 10 min.

Next, we evaluated the scope of substrates under the typical conditions (Scheme 2). Also, we found that both linear and

Scheme 2. Molecular Oxygen-Mediated Alkylation of Ethyl(4-methoxyphenyl)glycinate with Boronic Acids[a]

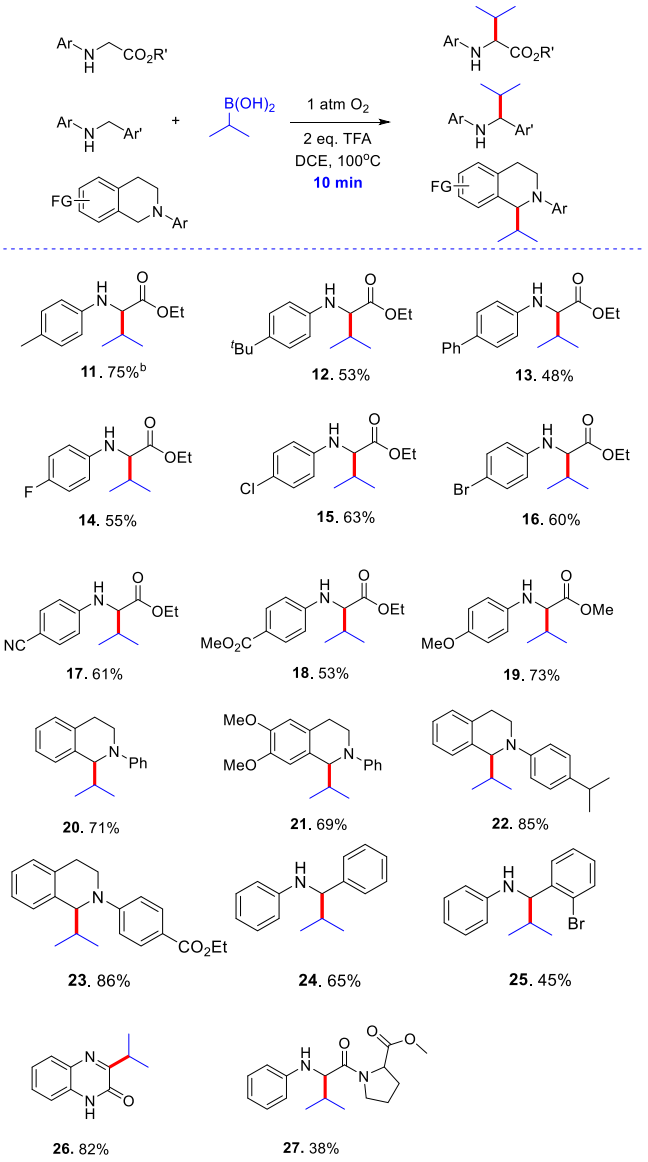


[a]Reaction conditions: ethyl(4-methoxyphenyl)glycinate (1 equiv, 0.2 mmol), alkyl boronic acid (5 equiv, 1 mmol), TFA (2 equiv, 0.4 mmol), DCE (0.5 mL), 1 atm O_2 (oxygen bag), 100 °C, 10 min. [b]Isolated yields.

cyclic aliphatic boronic acids are compatible with this reaction. In addition, the yields were closely related to the stability of the alkyl radical derived from the corresponding boronic acid. It is obvious that 2° boronic acids afforded higher yields than 1° (**1**−**7**). Furthermore, high yields of the alkylated glycinates were obtained with cyclic boronic acids (**8**−**10**).

Moreover, we examined a series of molecules involving the C(sp^3)−H bond adjacent to an N-atom (Scheme 3). First, a

Scheme 3. Molecular Oxygen-Promoted Alkylation of C(sp^3)−H Bonds with Boronic Acids[a]



[a]Typical reaction conditions. [b]Isolated yields.

broad range of *N*-aryl glycinates were effective substrates (**11**−**19**). Both electron-rich and electron-deficient aryl substituents on the N-atom of glycinates gave the corresponding products in moderate to good yields (**11**−**18**). In addition, halogen can be tolerated (**14**−**16**). The products can be easily converted into the corresponding α-amino acids. Then, we discovered that various *N*-aryl tetrahydroisoquinolines were also amenable to this system (**20**−**23**). Also, the alkylation happened specifically on the C1-position. Additionally, *N*-benzylanilines afforded the desired products smoothly (**24** and **25**). In addition, quinoxalin-2(1*H*)-one gave the corresponding alkylated product in high yields (**26**). It is noteworthy that peptides could also be modified by this method (**27**). These data indicate that the present method could be potentially

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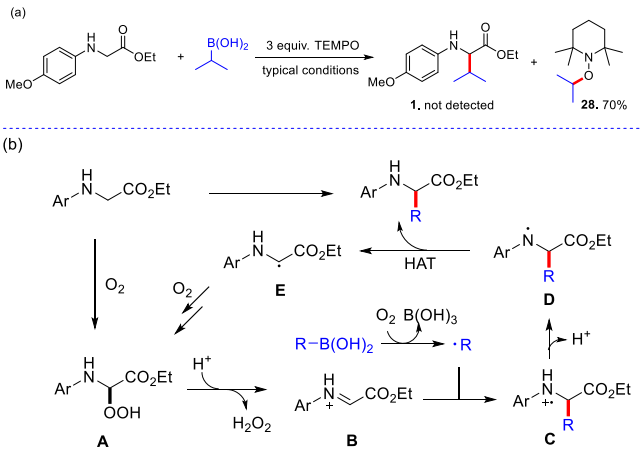
applied in the synthesis of unnatural amino acids, pharmaceuticals, and peptides.

Ultimately, we designed some experiments to get insight into the mechanistic details (Scheme 4). As demonstrated in

Scheme 4. Control Experiments and Suggested Mechanism



Scheme 4a, we did not observe the desired product **1** by addition of 3 equiv of TEMPO. Also, a radical adduct **28** was isolated as expected in 70% yield. According to the previous reports[1,3,8,9] and the data we got on this system, a possible mechanism was proposed in Scheme 4b. Autoxidation of glycinate with O_2 would afford peroxide **A**, and then, it eliminated H_2O_2 followed by protonation leading to **B**. Next, the alkyl radical that was generated from autoxidation of organoboronic acid was added to **B**, and the corresponding radical cation **C** would be formed. Deprotonation of **C** gave an N-centered radical **D**, which abstracted an H-atom from glycinate to produce the product and glycinate radical **E**. This radical intermediate should be relatively stable due to the captodative effect.[10] Finally, radical **E** combined with molecular oxygen, regenerating peroxide **A**.

In summary, we discovered a free-radical alkylation of the (sp^3)C−H bond with organoboronic acid by using 1 atm of oxygen only. This method provides green and efficient access to a wide range of valuable molecules such as unnatural α-amino acids, peptides, and drugs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00948.

Experimental procedures, mechanistic studies, and characterization and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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