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Letter

4-Aminobenzotriazole (ABTA) as a Removable Directing Group for Palladium-Catalyzed Aerobic Oxidative C−H Olefination

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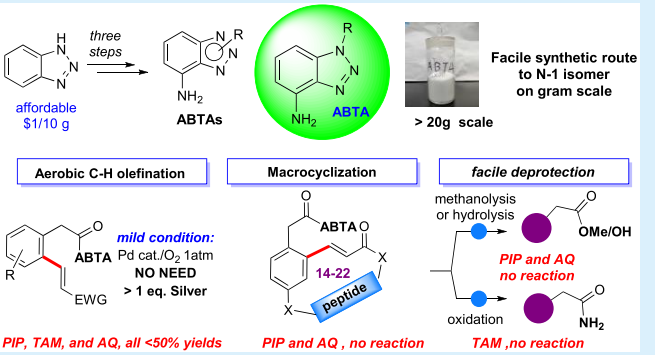
ABSTRACT: 4-Aminobenzotriazole (ABTA) was applied as an effective removable directing group (DG) in Pd-catalyzed C−H activation for the first time. Compared with the widely applied pyridine and quinoline analogs, ABTA showed significantly improved reactivity, achieving aerobic oxidative C−H olefination in excellent yields (up to 95% vs <50% with other reported DGs under identical conditions). Using this new strategy, macrocyclization was achieved to give cyclic peptides in good yields with easy ABTA removal under mild conditions, highlighting the promising potential of this new DG.

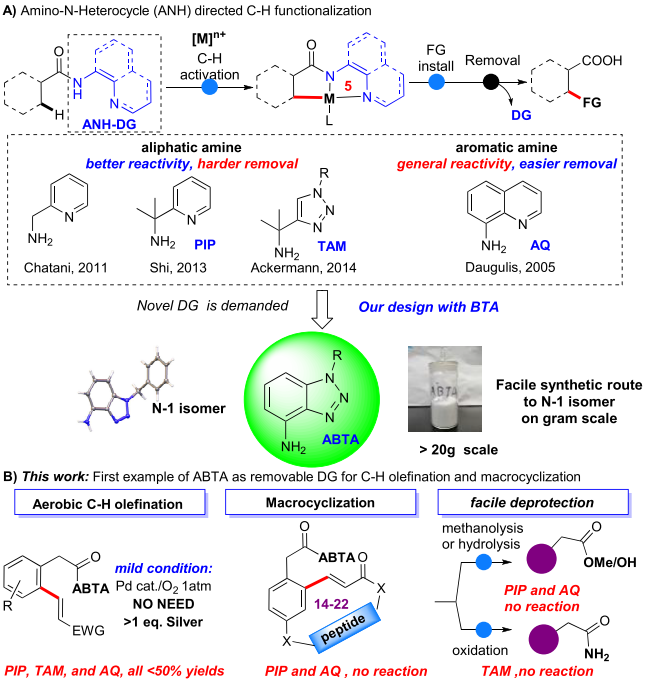


With the ability to achieve late-stage structural modification, metal-catalyzed C−H functionalization has been considered one of the most important developments in chemical synthesis over the past two decades.[1] The incorporation of a removable directing group (DG) has been applied as one general strategy to achieve good selectivity.[2] The benchmarks of good DGs are (1) clear reactivity enhancement and (2) easy removal under mild conditions. Amino *N*-heterocycles (ANHs) are important auxiliary DGs for the substrate containing COOH.[3] The bidentate binding site of the resulting amide could boost the reactivity of the metal center for selected C−H activation (Scheme 1A). The subsequent deprotection of DGs gives C−H functionalization with the initial COOH moiety. According to the literature, both aliphatic amines (pyridine (PIP) and triazole (TAM)) and an aromatic amine (8-amino quinoline (AQ)) were used.[4] Compared with the aliphatic amine, the aromatic amine is much easier to remove, which makes AQ a popular DG with numerous successful applications reported.[5]

In 2014, Ackermann first introduced triazole amine (TAM) in the iron catalyzed C−H functionalization.[4e] Our group later disclosed the TAM-directed Pd-catalyzed C−H alkynylation under silver-free conditions.[6] Compared with pyridine and quinoline, 1,2,3-triazole is a more stable heterocycle under redox conditions, making it a unique DG in promoting C−H activation.[7]

Herein we report the synthesis of 4-amino-benzotriazole (ABTA) derivatives with the confirmation of various N-isomers and application of this new DG in the Pd-catalyzed aerobic C−H olefination and macrocyclization (cyclic peptides, Scheme 1B). Impressively, the ABTA gave a significantly improved reactivity over AQ and PIP with easy

Scheme 1. Direct C−H Functionalization with ANH DGs



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removal under mild conditions, revealing ABTA as a promising new member of auxiliary ANH DGs for metal-catalyzed C−H functionalization

We initiated our investigation with the development of the regioselective synthesis of N-substituted ABTA. As shown in Figure 1A, 4-nitro-benzotriazole **1b** could be prepared from

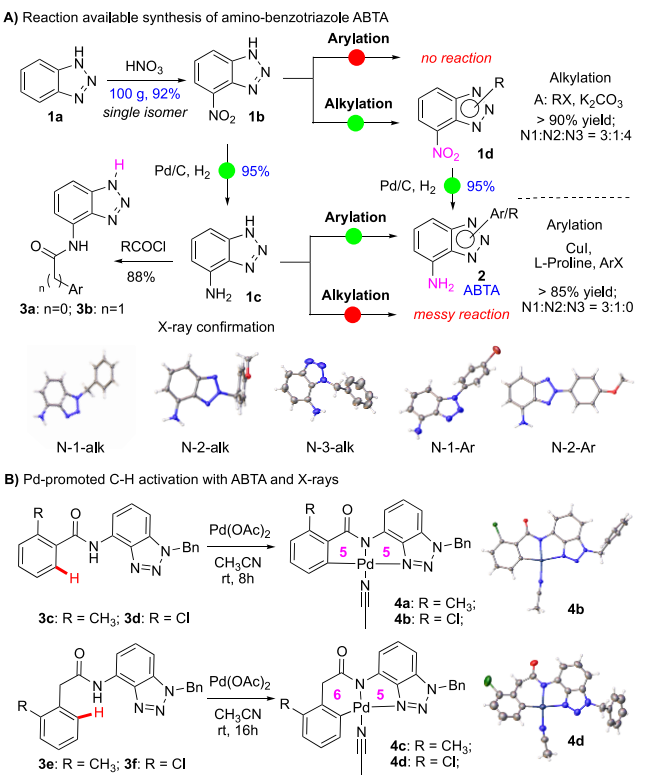


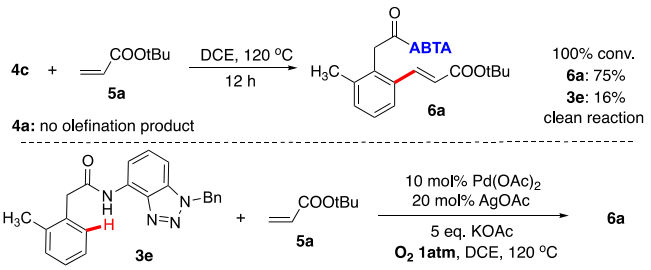
Figure 1. Synthesis of various ABTA isomers and Pd-mediated C−H activation.

benzotriazole (BTA, <$ 0.1/g) in high yield. After testing various reduction conditions, we selected Pd/C-promoted hydrogenation as the practical condition for the NO_2 reduction. The key challenge for N-substituted triazole synthesis is the identification of various N-isomers. Both N-arylation and N-alkylation were explored.[8] (See the details in the SI.) In summary, the reaction of 4-amino-BTA **1c** under copper-catalyzed amination works well to reach *N*-aryl-substituted ABTA, giving N-1 and N-2 isomers in a 3:1 ratio (no N-3). Alternatively, for *N*-alkyl ABTA, the optimal synthetic sequence is 4-nitro-BTA **1d** alkylation (SN_2) followed by NO_2 reduction. All of these isomers have been isolated with structures confirmed by X-ray analysis. Overall, this work offered a systematic investigation of BTA substitution, which set up the foundation to synthesize the ABTA library as a new building block for future applications.[9] (See the details in the SI.) With the substituted ABTA (20−50 g scale) prepared, we investigated its reactivity toward Pd-mediated C−H activation.

Encouraged by this result, we explored the Pd-catalyzed C−H olefination, which is known to undergo Pd(II/0) cycles with the possibility of using O_2 as the oxidant (for Pd^0 oxidation). According to literature, the DG-assisted C−H olefination has been problematic and often requires strong external oxidants (over 1 equiv of Ag salts or 1,4-benzoquinone (BQ)).[10] Thus achieving the reaction under aerobic conditions is of great interest for practical synthesis. Reactions between Pd complexes **4a**/**4c** and alkene **5a** were performed. Whereas the 5,5-bicyclic complex **4a** produces no reaction, even at 120 °C, the 6,5-bicyclic complex **4c** gave the desired olefination product **6a** in 75% yield (16% 3e, C−Pd to C−H). This lack of reactivity of complex **4a** is consistent with literature reports, likely due to the high-energy transition state associated with the 5,5-bicyclic system in the migratory intersection step.[11] Nevertheless, the clean reaction obtained with the 6,5-bicyclic complex **4c** is exciting because it offered a potential new route to achieve C−H olefination using molecular oxygen as the oxidant. It is important to note that other DGs showed significantly reduced reactivity under identical conditions (see details in SI), which highlighted the "boosting effect" of ABTA.

The catalytic conditions were explored by reacting **3e** and **5a** with the Pd catalyst. After screening various conditions, we identified 10% $Pd(OAc)_2$, 20% AgOAc, and 5.0 equiv of KOAc in 1,2-dichloroethane (DCE) at 120 °C for 24 h (sealed tube) with *N*-Bn-modified ABTA as the optimal conditions (see the detailed screening in the SI), giving the desired product **6a** in 92% isolated yield. Alternative N1-substituted ABTAs gave similar results. (See the SI.). The N1-Bn ABTA was selected due to the relatively easy synthesis. Results from representative alternative conditions are summarized in Table 1.

Table 1. Screening Table[a,b]



entry	variation from "standard conditions"	conv. (%)	yield of **6a** (%)
1	none	100	93 (92)
2	no AgOAc	73	67
3	no AgOAc and KOAc	20	15
4	NaOAc instead KOAc	90	81
5	K_2CO_3 instead KOAc	25	19
6	toluene as solvent	81%	73
7	dioxane as solvent	60	53
8	Ar protection	25	17
9	air	34	27
10	100 °C	92	84
11	AQ as directing group	51	43
12	PIP as directing group	<10	trace
13	TAM as directing group	53	47

[a]Conditions: **3e** (0.2 mmol), **5a** (0.8 mmol), base (1.0 mmol), Pd $(OAc)_2$ (0.02 mmol), AgOAc (0.04 mmol), and solvent (2.0 mL) in a 25 mL Schlenk tube under an O_2 atmosphere for 24 h. [b]^{1}H NMR yields using 1,3,5-tribromobenzene as an internal standard (isolated yields).

Although the reaction could occur using O_2 as the only oxidant, the starting material cannot reach complete conversion using only Pd (entry 2). This is likely due to the Pd-ABTA coordination in the product, causing slow catalyst turnover. The addition of a catalytic amount of silver solved this problem. The KOAc base is crucial for good reactivity (entries 4 and 5). Other solvents (toluene and dioxane) gave

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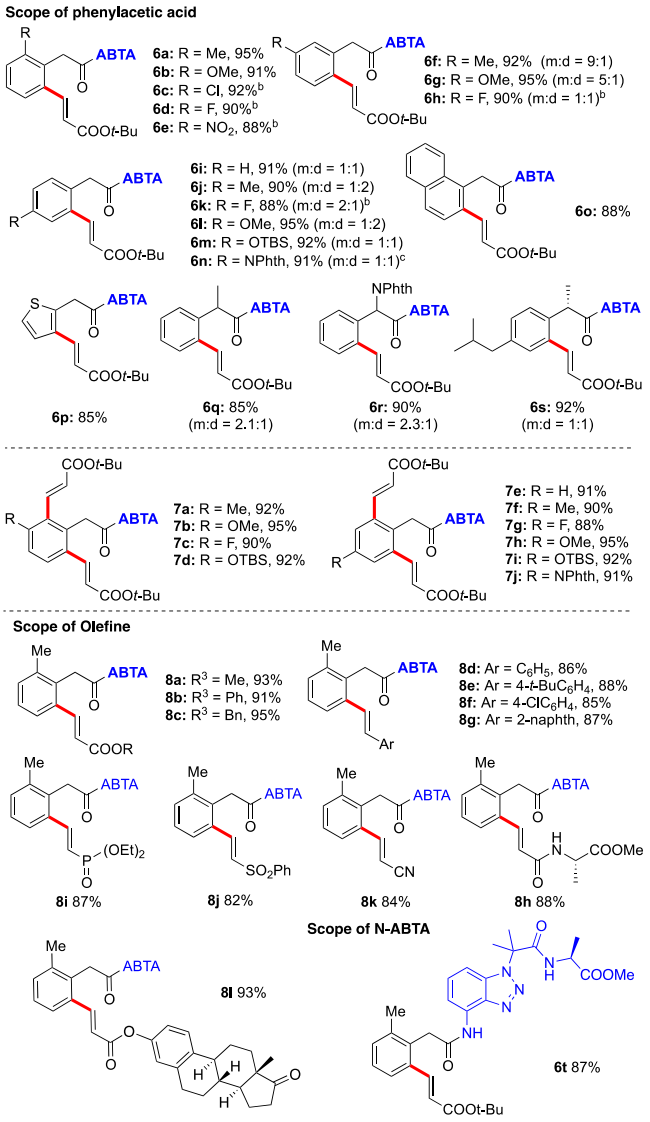
lower yields than DCE (entries 6 and 7). Significantly reduced conversion was observed if the reaction was conducted under Ar, confirming the important role of O_2 as the oxidant (entries 8 and 9). Lowering the reaction temperature to 100 °C led to slightly lower conversion (entry 10). It is important to note that other DGs (AQ, PIP, TAM) all gave much poorer results under identical conditions (entries 11−13), highlighting the boosting effect of this new ABTA DG. With the optimal reaction conditions developed, we explored the substrate scope, as summarized in Table 2.

Table 2. ABTA Substrate Scope[a,d,e]



[a]Reaction conditions: **3** (0.2 mmol), alkene (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol), AgOAc (0.04 mmol), and KOAc (1.0 mmol) in DCE (2.0 mL) under an O_2 atmosphere for 24 h. Isolated yield. [b]36 h. [c]48 h. [d]Alkene (2.4 mmol), 48 h for diolefination. [e]Ratio of mono and di substitution was determined by ^{1}HNMR.

The electron-donating group (EDG)-modified arenes (**6a**, **6b**) ran smoothly, giving the desired products in excellent yields (>90%). Substrates with electron-withdrawing group (EWG)-modified arenes (**6c**−**6e**) required longer reaction time (36 h) to reach completion. For the meta-substituted benzenes, substitution occurred at the less hindered ortho position (**6f**−**6h**). The selectivity of mono- and diolefination was less ideal with substrates containing both of the two accessible *ortho*-C−H bonds (**6i**−**6n**). The application of excess alkene (12 equiv) gave the diolefination product in excellent yields (**7a**−**7j**). The OTBS and NPhth groups were compatible with this transformation, offering new synthetic handles (**6m**, **6n**, **6r**). Some valuable carboxylic derivatives, such as 2-thenoic acid (**6p**), 2-phenylpropionic acid(**6q**), and (*S*)-ibuprofen (**6s**), all worked well and gave the desired products in good yields.

In addition to acrylate, styrene and 2-vinylnaphthalene also worked well in this transformation (**8a**−**8g**). Impressively, alternative EWG-activated alkenes, such as acrylamide (**8h**), acrylonitrile (**8i**), vinyl phosphate (**8j**), and vinyl sulfone (**8k**), were all suitable, giving the desired olefins in excellent yields. The coupling with an estrone derivative was successfully achieved, showing the application of this method for the late-stage functionalization of drug-like molecules (**8l**). Notably, the amino-acid-modified ABTA (**6t**) worked well, and the corresponding olefination product was obtained in excellent yield. The feasibility of introducing various functional groups highlighted the advantage of ABTA over other DGs for the preparation of bioactive compounds.

With the confirmation of ABTA as a new DG in C−H olefination, we focused on the more challenging macrocyclization.[12] Recently, Wang reported the first example of amino-acid-directed peptide macrocyclization through C−H olefination.[13] Whereas this seminal work initiated a new strategy for achieving cyclic peptides, the transformation relied on an *α*-*t*-Bu amino acid DG, likely due to the needed conformation control for a better Pd coordination. We compared reactions of ABTA with AQ, PIP, and the L-*t*-Bu-leucine (Wang's strategy) substrates. As expected, no cyclization was observed with either AQ or PIP substrates. (See the SI.) With the ABTA DG, the cyclization product was observed in 77% yield. Notably, under identical conditions, Wang's amino acid DGs gave a much lower overall yield (22%) due to the slow reaction rate (Table 3). In 2010, Yu reported aerobic Pd(II)-catalyzed C−H olefination with free carboxylic acids.[1g] We also carried out the macrocyclization reaction with free carboxylic acid. No reaction was observed, even under its optimal conditions. These results highlighted the importance of using DGs to promote challenging macrocyclization with boosted Pd stability and reactivity. (See the SI.) Encouraged by this result, we prepared various ABTA substrates for this macrocyclization. The results are summarized in Table 3.

Products with different ring sizes (14 to 22) were prepared with good yields (**10a**−**10e**). Impressively, linkers containing Gly, Abu, Ala, Val, and Ile residues worked well (**10f**−**10l**), suggesting the possibility of applying this method for peptide cyclization. In fact, with the use of dimethylformamide (DMF) as the solvent, the cyclic peptides were produced in good yields with ring sizes of 16 (**10m**−**10o**) and 19 (**10p**). Notably, the ring size has a large impact on the E/Z selectivity. Smaller rings (14−16) were favored for the Z conformation to release the ring strain. (See the SI for details.) 13-Membered polyamides gave a messy reaction mixture, which might be due to the higher ring strain. Other DGs could not promote this transformation under either aerobic or silver oxidative conditions, giving significantly reduced yields.

In addition to the enhanced reactivity, the other critical feature of a good DG is the feasibility to remove it under mild conditions.[14] With the electron-deficient benzotriazole, ABTA

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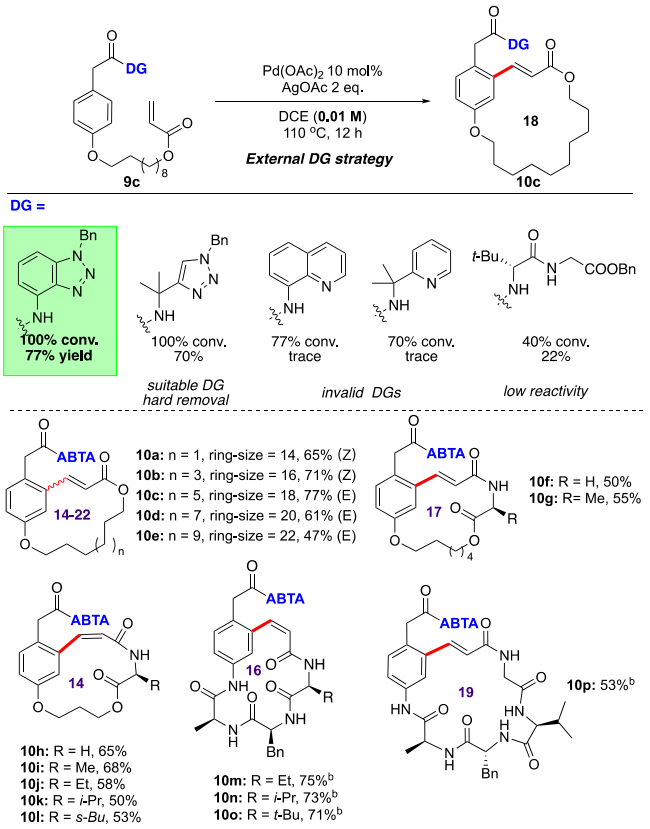
Table 3. ABTA-Promoted Macrocyclization[a]



[a]Reaction conditions: 9 (0.1 mmol), Pd(OAc)2 (0.01 mmol), and AgOAc (0.2 mmol) in DCE (10 mL) for 12 h. Isolated yield. [b]DMF (10 mL).

is expected to be a better leaving group than other DGs. As shown in Figure 2A, ABTA could be removed upon the methanolysis of Boc-protected amide with less nucleophilic MeOH under mild conditions. The Boc-protected **1c** could be recycled in >90% yield. Notably, whereas more stable aliphatic amide TAM, PIP, and amino acid DGs required much harsher conditions for their removal, the aromatic amine AQ DG could not be deprotected under these mild conditions. Through hydrolysis using LiOH, ABTA can be easily removed, giving the corresponding acid derivative **11b** in 90% yield. Similarly, treating cyclic compound **10i** with 3.0 equiv of 2-iodoxybenzoic acid (IBX) in HFIP/H_2O (1:1) at 60 °C gave amide **11c** in 73% yield, whereas the TAM DG failed to be deprotected under identical conditions. This result clearly emphasized the unique reactivity of ABTA in directed C−H functionalization with both boosted reactivity and easier deprotection.

In conclusion, we have unveiled ABTA as a novel effective DG in promoting aerobic C−H oxidative olefination. This study confirmed the clearly improved reactivity of ABTA over other ANH auxiliary DGs in promoting Pd-catalyzed C−H activation with improved reactivity. Furthermore, the success in macrocyclization bearing amino acid chains allowed the facile synthesis of cyclic peptides in excellent yields. Considering that other DGs lead to poor results under identical conditions, it is expected that this new ABTA DG strategy will have a promising potential to achieve more challenging chemical transformations via C−H functionalization, which is currently under investigation in our lab.

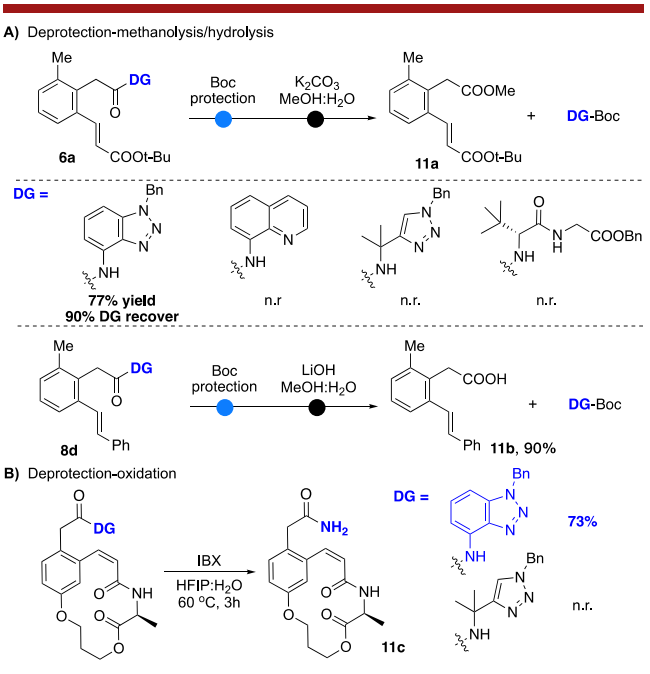


Figure 2. Removal of the directing group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00285.

Experimental details, characterization for all of the products, NMR spectra, and crystal structures (PDF)

Accession Codes

CCDC 2125400−2125403, 2126272, 2126286, 2126355, and 2128332 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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