Brønsted Acid Catalyzed Asymmetric Reduction of 2- and 2,9-Substituted 1,10-Phenanthrolines

Costa Metallinos,* Fred B. Barrett, Shufen Xu

Department of Chemistry, Brock University, 500 Glenridge Ave., St. Catharines, ON L2S 3A1, Canada
Fax +1(905)6829020; E-mail: cmetallinos@brocku.ca

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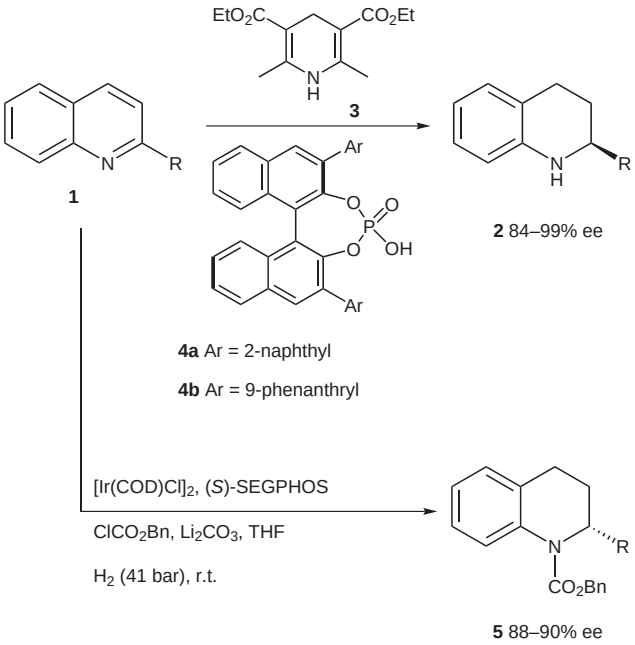
Abstract: Several 2- and 2,9-substituted 1,10-phenanthrolines are reduced asymmetrically for the first time using a Hantzsch dihydropyridine in the presence of BINOL-derived phosphoric acid catalysts. The best results are obtained with phenanthrolines bearing unbranched or nitrogen-containing alkyl groups in the 2- or 2,9-positions, which afford chiral octahydrophenanthrolines in a range of yields (40−88%) and good to excellent levels of enantiomeric purity (78−99% ee).

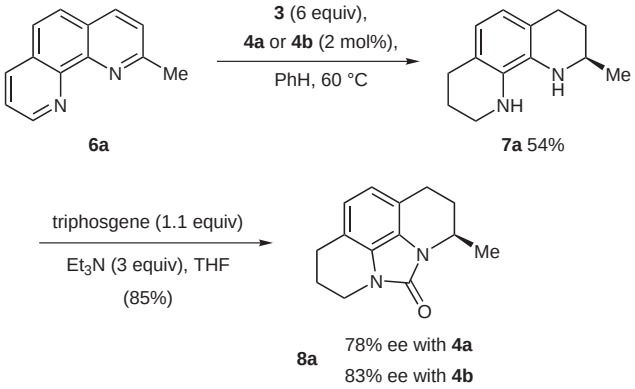
Key words: reduction, phenanthroline, Brønsted acid, enantioselective, organocatalysis

Pioneering work by Akiyama[1], Terada,[2] and others[3,4] has demonstrated the power of BINOL derivatives of phosphoric acid in Brønsted acid catalyzed asymmetric synthesis. Among the growing applications of this methodology is a report by Rueping[5] that 2-substituted quinolines can be reduced to tetrahydroquinolines (**1** → **2**, Scheme 1) in high enantiomeric purity with Hantzsch dihydropyridine **3** in the presence of catalysts **4a** or **4b**.[6] Although several other excellent methods have been developed for the asymmetric reduction of quinolines[7] and pyridines,[8] they involve less convenient high-pressure conditions (e.g. **1** → **5**, Scheme 1), or they are not amenable to the reduction of substituted 1,10-phenanthrolines that are of interest to our group.[9,10]

In this communication we report our findings regarding the ability of Rueping's conditions to effect the asymmetric reduction of 2- and 2,9-substituted phenanthrolines, which have not been previously investigated as substrates in this process. To begin our study, catalysts **4a**, **4b**[11] and variously 2- and 2,9-substituted 1,10-phenanthrolines[10,12] were prepared according to established procedures. Subjection of 2-methyl-1,10-phenanthroline (**6a**, Scheme 2) to asymmetric reduction under Rueping's conditions[5] [**4a** or **4b** (2 mol%), **3** (6 equiv), 60 °C, PhH) gave octahydrophenanthroline **7a** in 54% yield, regardless which catalyst was used. The enantiomeric purity of **7a** was determined by chiral HPLC analysis of the corresponding urea adduct **8a** to be 78% and 83% ee for catalysts **4a** and **4b**, respectively.[13] This result was encouraging considering that previous achiral reduction of **6a** ($NaBH_3CN$, AcOH−MeOH) afforded **7a** in similar yield (57%),[10] and that the substrate posed a greater challenge to the catalysts over similar quinolines owing to the generation of a basic tetrahydrophenanthroline intermediate.[10]



Scheme 1 Brønsted acid and iridium-catalyzed asymmetric reduction of quinolines.



Scheme 2 Brønsted acid catalyzed asymmetric reduction of 2-methyl-1,10-phenanthroline.

The absolute stereochemistry of product **7a** was determined by comparing the optical rotations of the urea derivatives **8a** with the known rotation of the *S*-enantiomer of **8a** {$[\alpha]_D^{20}$ +21.0 at 68% ee}.[14] In both cases, the measured optical rotations were negative {$[\alpha]_D^{20}$ −23.6 and $[\alpha]_D^{20}$ −26.9 for the products of catalysts **4a** and **4b**, re-

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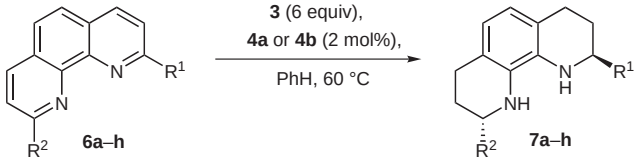
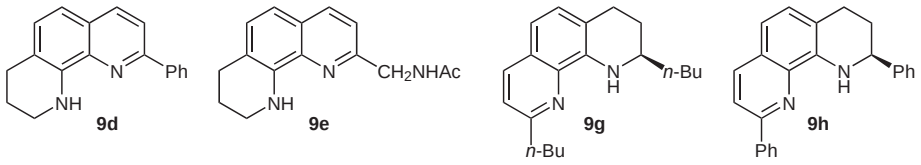
Table 1 Brønsted Acid Catalyzed Asymmetric Reduction of 2- and 2,9-Substituted 1,10-Phenanthrolines



Entry	Substrate	R^1	R^2	Catalyst	Yield of **7** (%)[a]	ee of **7** (%)[b]
1	**6a**	Me	H	**4a**	54	78
2	**6a**	Me	H	**4b**	54	83
3	**6b**	*n*-Bu	H	**4a**	52	56
4	**6b**	*n*-Bu	H	**4b**	54	78
5	**6c**	*i*-Pr	H	**4a**	40	32
6	**6c**	*i*-Pr	H	**4b**	28	40
7	**6d**	Ph	H	**4a**[c]	21	82
8	**6d**	Ph	H	**4b**[c]	11	95
9	**6e**	CH_2NHAc	H	**4b**	40[d]	84
10	**6f**	Me	Me	**4b**[e]	72 (3:2 *ent*/*meso*)	99
11	**6g**	*n*-Bu	*n*-Bu	**4b**[e]	88[f] (3:2 *ent*/*meso*)	99
12	**6h**	Ph	Ph	**4b**[e]	81[g]	25[g]

[a] Unoptimized yields of column-purified material.
[b] Measured by HPLC analysis of the corresponding ureas (**8a**–**g**) on Chiralcel OD-H or Chiralpak AS-H columns.
[c] Catalyst loading was 10 mol%; 9-phenyl-1,2,3,4-tetrahydro-1,10-phenanthroline (**9d**) was also isolated (22% and 30% for catalysts **4a** and **4b**, respectively).
[d] 9-(*N*-Acetyl)methyl-1,2,3,4-tetrahydro-1,10-phenanthroline (**9e**) was also isolated (40%).
[e] Catalyst loading was 5 mol%.
[f] 2,9-Dibutyl-1,2,3,4-tetrahydro-1,10-phenanthroline (**9g**) was also isolated (8%).
[g] Only 2,9-diphenyl-1,2,3,4-tetrahydro-1,10-phenanthroline (**9h**) was isolated; ee measured for the unprotected amine.



spectively) indicating that the *R*-enantiomer of **7a** was formed preferentially during reduction. Notably, the relative stereochemistry of (*R*)-**7a** is identical to that reported by Rueping and coworkers for 2-substituted tetrahydroquinolines[5] (**2**, Scheme 1). Based on these results, it is expected that other octahydrophenanthrolines prepared by this route will have the same relative stereochemistry as (*R*)-**7a**.

The results from reduction of phenanthrolines **6a**–**h** with catalysts **4a** or **4b** are summarized in Table 1. Reduction of 2-*n*-butyl-1,10-phenanthroline (**6b**) provided octahydrophenanthroline **7b** in similar yield as **7a**, but in comparable enantiomeric purity only when the 9-phenanthryl catalyst **4b** (78% ee, entry 4) was employed. The less sterically encumbered 2-naphthyl catalyst **4a** gave **7b** in lower 56% ee (entry 3). A pronounced drop in both yield and enantioselectivity was observed with 2-isopropyl-1,10-phenanthroline (**6c**). In this case, the corresponding octahydrophenanthroline **7c** was obtained in 40% yield and 32% ee using catalyst **4a** (entry 5), versus 28% yield and 40% ee with catalyst **4b** (entry 6). Enantioselectivity was much higher for reduction of 2-phenyl-1,10-phenanthroline (**6d**) which furnished **7d** in 82% ee and 95% ee with **4a** and **4b**, respectively (entries 7 and 8), albeit at the expense of low yields (21% and 11%). It is worth noting that significant quantities of 9-phenyl-1,2,3,4-tetrahydro-1,10-phenanthroline (**9d**) were isolated in each of these experiments (22% and 30%, respectively) indicating a limitation of catalysts **4a** and **4b** in facilitating reduction of the prochiral phenyl-substituted ring of **9d**. Increasing the catalyst loading (20 mol% of **4b**) and temperature (100 °C, PhMe) did not improve the yield of **7d**. Given that only small amounts of tetrahydrophenanthrolines (<5%) were isolated after reduction of **6a**–**c**, it is difficult to identify a general trend of structure versus yield and

enantioselectivity for substrates **6a−d**. While it is clear that the bulkier starting materials **6c**,**d** gave substantially reduced yields of octahydrophenanthrolines, only the alkylated compounds **6a−c** showed a discernible trend of decreasing ee versus increasing steric bulk.

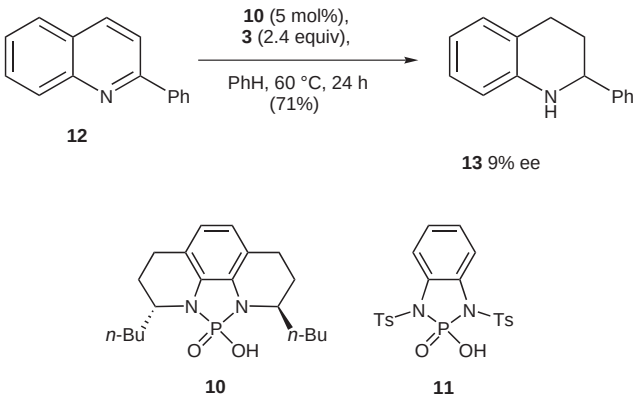
To gain more insight into the effect that substituents have on asymmetric reduction of phenanthrolines, four additional substrates were evaluated. The first of these, 2-(*N*-acetyl)methyl-1,10-phenanthroline (**6e**) was prepared by acetylation of 2-aminomethyl-1,10-phenanthroline.[15] To a first approximation, it was expected that **6e** would be reduced with comparable enantioselectivity as **6a** or **6b** if steric effects were primarily responsible for the trend observed in reduction of **6a−c**. Indeed, **4b**-catalyzed reduction of **6e** provided **7e** in 40% yield and 84% ee (entry 9), in addition to the tetrahydro byproduct **9e** (40% yield). Thus, **6e** fits into the general trend observed for the 2-alkyl derivatives **6a−c**.

In contrast, **4b**-catalyzed reduction of the 2,9-diphenyl-1,10-phenanthroline (**6h**, entry 12) provided only the tetrahydro reduction product **9h** in 81% yield, mirroring the sluggish reactivity observed for **6d**. Unlike **7d**, which was formed in high 95% ee, **9h** was produced in surprisingly low 25% ee. These results imply that steric bulk may explain the recalcitrance to reduction of the second prochiral pyridyl rings of **9d** and **9h**, but a secondary interaction such as π-stacking may be responsible for the high enantiomeric purity observed for **7d**. A similar interaction may be absent during reduction of **6h** as a result of excessive steric demand of the substrate.

Significantly better results were obtained with 2,9-dialkyl-1,10-phenanthrolines. Asymmetric reduction of **6f** ($R^1 = R^2 = Me$, entry 10) with **4b** gave octahydrophenanthroline **7f** in 72% yield as a 3:2 mixture of *ent* and *meso* stereoisomers. Chiral HPLC analysis of the corresponding urea adducts returned a value of 99% ee for *ent*-**7f**. Similarly, reduction of 2,9-di-*n*-butyl-1,10-phenanthroline (**6g**, entry 11) gave **7g**, again as a 3:2 mixture of *ent* and *meso* isomers.[16] The isomeric diamines were easily separated by column chromatography as urea adducts, and chiral HPLC analysis returned a value of 99% ee for (−)-(*R*,*R*)-**8g**.[16] The higher enantioselectivities observed with **7f**,**g** over **7a**,**b** may be a consequence of the formation of *meso* stereoisomers that consume the minor enantiomer during reduction of the second pyridyl ring.

The ease of chromatographic separation of (*R*,*R*)-**8g** from *meso*-**8g** allowed us to explore the utility of *ent*-**7g** as a catalyst precursor. Hydrolysis of (*R*,*R*)-**8g** to (*R*,*R*)-**7g** followed by cyclization with phosphorus oxychloride and aqueous workup provided the enantiomerically pure C_2-symmetric phosphorodiamidic acid **10** (Scheme 3). Previous studies by Terada[17] have shown that the achiral bis-N-tosylated phosphorodiamidic acid **11** was capable of catalyzing the direct Mannich reaction *N*-acyl imines with 1,3-dicarbonyl compounds. Catalyst **10** thus serves to test the importance of an electron-withdrawing group in enhancing the acidity, and hence activity, of such catalysts.

A preliminary experiment has shown that **10** catalyzes the reduction of 2-phenylquinoline[5] **12** [**10** (5 mol%), **3** (2.4 equiv), PhH, 60 °C, 24 h] to the tetrahydroquinoline **13** in good yield (71%), but low enantioselectivity (9% ee). Although the selectivity is low, this result obviates the need for the installation of electron-withdrawing groups to ensure activity of phosphorodiamidic acid catalysts with a phenylenediamine core, and may simplify the preparation of bulkier chiral catalysts in this series.



Scheme 3 Reduction of 2-phenylquinoline catalyzed by phosphorodiamidic acid **10**.

To summarize, we have reported the first asymmetric reduction of 2- and 2,9-substituted 1,10-phenanthrolines by adapting Rueping's conditions for the reduction of quinolines. The method is useful for reducing phenanthrolines bearing unbranched or nitrogen-containing alkyl groups in the 2- or 2,9-positions (**6a**,**b**,**e**−**g**), providing chiral octahydrophenanthrolines in a range of yields (40−88%) and good to excellent levels of enantiomeric purity (78−84% ee for **7a**,**b**,**e**; 99% ee for **7f**,**g**). The method does not extend easily to substrates with larger substituents (*i*-Pr, Ph), which are plagued by low enantioselectivity (**6c**), low yields (**6d**), or both (**6h**). Nevertheless, it has been demonstrated that catalysts **4a** and **4b** are capable of catalyzing the sequential asymmetric reduction of two pyridyl rings within the same molecule. For this reason, it may be worth investigating the scope of this procedure in additional prochiral bispyridyl systems.

Acknowledgment

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(13) **Reduction of 6a with Catalyst 4b and Enantiomeric Assay**

A flame-dried screw-cap vial with a stir bar was charged with **6a** (50 mg, 0.26 mmol), dihydropyridine **3** (390 mg, 1.54 mmol, 6 equiv), catalyst **4b** (3.6 mg, 0.005 mmol, 2 mol%) and dry benzene (5 mL). The vial was flushed with argon, capped, and the mixture was heated with stirring at 60 °C for 24 h. The reaction mixture was transferred to a round-bottomed flask and the solvent was removed under reduced pressure. Absolute EtOH (5 mL) and KOH (2 pellets, ca. 200 mg) were added, and the mixture was heated to reflux for 45 min. Then, H_2O (5 mL) was added and EtOH was removed under reduced pressure. The remaining aqueous mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extract was dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (silica gel, 83:15:2 hexanes–EtOAc–Et_3N; R_f = 0.28) gave (+)-(*R*)-**7a** (29 mg, 54%).

Compound (+)-(*R*)-**7a**: viscous colorless oil; $[\alpha]_D^{20}$ +53.5 (*c* 1.27, acetone); lit.[14] $[\alpha]_D^{20}$ −41.4 (*c* 1.70, acetone) at 68% ee. ^{1}H NMR (300 MHz, acetone-d_6): δ = 6.23 (ABq, 2 H), 3.62 (b, 2 H), 3.30−3.22 (m, 3 H), 2.79–2.54 (m, 4 H), 1.89–1.74 (m, 3 H), 1.50–1.40 (m, 1 H), 1.20 (d, 3 H, *J* = 6.3 Hz). ^{13}C NMR (75.5 MHz, acetone-d_6): δ = 132.7, 132.1, 119.0, 118.5, 118.2, 117.9, 47.5, 42.2, 30.4, 27.0, 26.7, 22.4, 22.0.

A solution of **7a** (24 mg, 0.12 mmol), triphosgene (39 mg, 0.13 mmol), and Et_3N (33 μL, 0.24 mmol) in dry THF (2 mL) was stirred at r.t. for 16 h. Then, H_2O (4 mL) was added and the THF was removed under reduced pressure. The remaining aqueous mixture was extracted with CH_2Cl_2 (3 × 4 mL), washed with H_2O (5 mL) and brine (5 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (silica gel, 3:1 CH_2Cl_2–Et_2O, R_f = 0.35) gave (−)-(*R*)-**8a** (23 mg, 85%).

Compound (−)-(*R*)-**8a**: colorless solid; $[\alpha]_D^{20}$ −26.9 (*c* 1.08, $CHCl_3$); lit.[14] $[\alpha]_D^{20}$ +21.0 (*c* 4.37, $CHCl_3$) at 68% ee. CSP HPLC analysis [Chiralpak AS-H; eluent: hexanes–*i*-PrOH (80:20), 1.0 mL/min] determined 90.5:9.5 er, 81% ee [t_R(minor) = 10.63 min, t_R(major) = 11.73 min]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76 (s, 2 H), 4.45–4.37 (m, 1 H), 3.89–3.78 (m, 2 H), 2.92–2.72 (m, 4 H), 2.12 (quin, 2 H, *J* = 5.7 Hz), 2.07–1.98 (m, 2 H), 1.40 (d, 3 H, *J* = 6.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.7, 125.2, 124.7, 118.3 (2 C), 116.8, 116.7, 45.3, 38.9, 29.3, 23.4, 22.8, 20.2, 19.2.

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(16) **Reduction of 6g with Catalyst 4b and Enantiomeric Assay**

A flame-dried screw-cap vial with a stir bar was charged with **6g** (58 mg, 0.20 mmol), dihydropyridine **3** (304 mg, 1.20 mmol, 6 equiv), catalyst **4b** (7 mg, 0.01 mmol, 5 mol%) and dry benzene (4 mL). The vial was flushed with argon, capped, and the mixture was heated with stirring at 60 °C for 24 h. The reaction mixture was transferred to a round-bottomed flask and the solvent was removed under reduced pressure. Column chromatography [silica gel, hexanes–EtOAc (97:3)] gave, sequentially, 2,9-dibutyl-1,2,3,4-tetrahydro-1,10-phenanthroline (**9g**, 5 mg, 8%, R_f = 0.39) and octahydrophenanthroline **7g** (53 mg, 88%, R_f = 0.19) as a 3:2 mixture of *ent* and *meso* isomers.

Compound **9g**: pale yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.98 (d, 1 H, *J* = 8.4 Hz), 7.26 (d, 1 H, *J* = 8.4 Hz), 7.06 (d, 1 H, *J* = 8.1 Hz), 6.93 (d, 1 H, *J* = 8.1 Hz), 6.10 (b, 1 H), 3.49–3.39 (m, 1 H), 2.93–2.82 (m, 5 H), 1.82–1.75 (m, 2 H), 1.68–1.43 (m, 9 H), 0.95 (t, 6 H, *J* = 7.5 Hz).

Compound *ent/meso*-**7g**:[10] pale yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ = 6.26 (s, 1 H), 6.25 (s, 1 H), 3.59 (b, 1 H), 3.50 (b, 1 H), 3.20–3.05 (m, 2 H), 2.71–2.60 (m, 4 H), 1.93–1.88 (m, 2 H), 1.56–1.32 (m, 14 H), 0.92 (t, 6 H, *J* = 6.9 Hz). ^{13}C NMR (75.5 MHz, acetone-d_6): δ = 133.2, 133.1, 119.9, 119.8 118.9, 118.7, 52.8, 52.7, 37.1, 37.0, 28.9, 28.8, 28.6, 27.2, 23.5, 14.3.

A solution of *ent/meso*-**7g** (51 mg, 0.17 mmol), triphosgene (55 mg, 0.19 mmol), and Et_3N (47 μL, 0.34 mmoL) in dry THF (4 mL) was stirred at r.t. for 16 h. Then, H_2O (4 mL) was added and the THF was removed under reduced pressure. The remaining aqueous mixture was extracted with CH_2Cl_2 (3 × 4 mL), washed with H_2O (5 mL) and brine (5 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography [silica gel, hexane–EtOAc (90:10)] gave, sequentially, (−)-(*R*,*R*)-**8g** (30 mg, 55%, R_f = 0.16), and *meso*-**8g** (20 mg, 36%, R_f = 0.08).

Compound (−)-(*R*,*R*)-**8g**: clear colorless oil; $[\alpha]_D^{20}$ −102 (*c* 1.50, $CHCl_3$). CSP HPLC analysis [Chiralcel OD-H; eluent: hexanes−*i*-PrOH (98:2), 0.5 mL/min] determined 99.5:0.5

er, 99% ee [t_R(minor) = 11.09 min, t_R(major) = 11.81 min]. IR (KBr, neat): 2954, 2931, 2858, 1703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.72 (s, 2 H), 4.31–4.28 (m, 2 H), 2.83–2.75 (m, 4 H), 2.19–2.13 (m, 2 H), 2.00–1.95 (m, 2 H), 1.83–1.78 (m, 4 H), 1.53–1.32 (m, 10 H), 0.91 (t, 6 H, *J* = 6.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.8, 124.8, 118.0, 116.5, 49.5, 33.0, 28.1, 26.2, 22.6, 20.0, 14.0. MS (EI): *m/z* (%) = 326 (71) [M^+], 269 (100). HRMS (EI): *m/z* calcd for $C_{21}H_{30}N_2O$: 326.2358; found: 326.2356.

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