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[5] A Merck LiChrospher 100 RP-18(e) column; linear acetonitrile/H_2O gradient from 5/95 to 50/50 at 25 min.

[6] The pure *trans* isomer isolated by HPLC was partially (about 10%) converted into the *cis* isomer by ambient light.

[7] In the determination of the T_m value of the *cis* isomer, UV light was irradiated in the middle of the measurement to minimize the effect of the thermal isomerization to the *trans* form. By this treatment, the fraction of the *cis* isomer was kept almost constant at 70% throughout the measurement, as confirmed by HPLC and UV/Vis spectroscopy.

[8] For the duplex between 5′-GGGXGGGG-3′ and 5′-CCCCCCCC-3′, the *trans*→*cis* isomerization of the incorporated azobenzene moiety resulted in a decrase in T_m from 32.2 to 23.0 °C ([oligonucleotide]$_0$ = 10 μmol L^{-1} at pH 7.1 (without NaCl)). Here the modified oligonucleotide was used as a mixture of the two diastereomers since they could not be separated by HPLC.

[9] The argument is substantiated by the fact that the *trans*-azobenzene moiety of **1a** exhibits a bathochromic shift upon formation of the **1a**–**2** duplex. In aqueous solutions, the absorption maximum of the azobenzene appears at 353 nm. When **2** is added to the solutions (at a temperature below the T_m of the duplex), however, the absorption band shifts towards longer wavelength (e.g., the absorption maximum is located at 359 nm under the conditions presented in the text). As expected, the absorption spectrum is hardly affected by **2** when the temperature is higher than the T_m.

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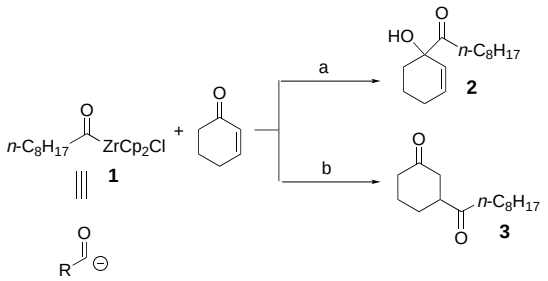
Acylzirconocene Chloride as an "Unmasked" Acyl Anion: Enantioselective 1,2-Addition to α,β-Unsaturated Ketone Derivatives**

Yuji Hanzawa,* Nobuhito Tabuchi, Kosuke Saito, Satoshi Noguchi, and Takeo Taguchi*

Recently, we reported palladium-catalyzed regioselective acylation reactions[1] of α,β-unsaturated ketone derivatives with acylzirconocene chloride.[2] The acyl group of acylzirconocene chloride reacted as a formal "unmasked" acyl anion.[3] In particular, the regioselectivity of the reaction can be controlled by modifying the palladium catalyst system. For example, in the reaction of nonanoylzirconocene chloride (**1**) with cyclohexenone (Scheme 1), the use of [$PdCl_2(PPh_3)_2$] (5 mol%) as catalyst in toluene gave the 1,2-addition product **2**, whereas the use of 10 mol% [$Pd(OAc)_2$]/$BF_3 \cdot OEt_2$ in THF/diethyl ether gave the 1,4-addition product **3** (Scheme 1).[4] A 5 mol% $Pd(OAc)_2$/PPh_3 (Pd/P = 1/2) system was also found to be an effective catalyst for regioselective formation of the 1,2-acylation product **2**. Bidentate diphosphane ligands such as 1,2-bis(diphenylphosphanyl)ethane (dppe) and 1,3-bis(diphenylphosphanyl)propane (dppp) gave lower regioselectivities.



Scheme 1. Regioselective acylation of cyclohexenone with nonanoylzirconocene chloride (**1**): a) 1,2-acylation, 5 mol% [$PdCl_2(PPh_3)_2$] or 5 mol% $Pd(OAc)_2$/PPh_3 (Pd/P = 1/2); b) 1,4-acylation, 10 mol% $Pd(OAc)_2$/$BF_3 \cdot OEt_2$.

In the palladium-catalyzed reactions of **1** with α,β-unsaturated ketones, concomitant formation of diketone **4** (< 10%) was observed.[5] This suggests a transmetalation of **1** with Pd^{II} and subsequent reductive elimination of Pd^0 from the resulting bis-acylpalladium complex to give **4** (Scheme 2). Thus, electron transfer from Pd^0 to cyclohexenone, formation of the acylpalladium π-allylic complex **5**, and reductive elimination of Pd^0 would give the 1,2- or 1,4-acylation product (**2** or **3**) (Scheme 2).[6] The role of the triphenylphosphane ligand in the regioselective formation of **2** could be explained by preferred formation of the stereochemically less crowded intermediate complex **5A** rather than **5B** and subsequent reductive elimination of Pd^0 from **5A**.

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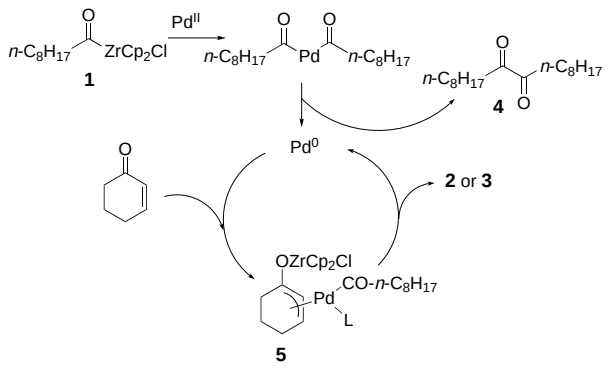
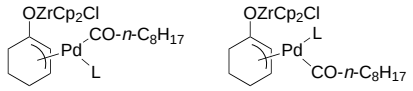


Scheme 2. Generation of Pd^0 and a catalytic cycle for the acylation of cyclohexenone with **1**.



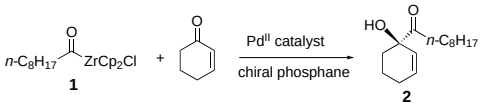
5A > **5B** (L = PPh_3)

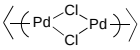
These observations and considerations suggested that enantioselective formation of 1,2-acylation products **2** would be possible by treating cyclohexenone with **1** in the presence of Pd^{II} and a chiral phosphane ligand. To our knowledge, however, there is no precedent for the enantioselective nucleophilic acylation of an "unmasked" acyl anion with carbonyl compounds. The results of Pd^{II}-catalyzed reactions of **1** with cyclohexenone in the presence of chiral phosphane ligands in toluene are listed in Table 1.

All reactions were carried out with 5 mol% palladium catalyst and chiral phosphane ligand (Pd/P = 1/2). The reaction is very slow and not regioselective with the bidentate phosphane ligands (*R*)-BINAP and (*R*,*R*)-CHIRAPHOS (entries 1 and 2).[7, 8] The (*R*)-MOP ligand, which was developed by Hayashi et al.,[9] shows a considerable efficiency of chiral induction into the product (*R*)-**2** (entry 5; $[\alpha]_D^{24} = -42.1$ ($c = 1.04$ in $CHCl_3$), 66% *ee*, 88% yield).[10] There is no significant difference between (*R*)-MOP and its derivatives (BnO-, *i*PrO-, and *t*$BuMe_2SiO$-(*R*)-MOP)[9] in the chiral induction and the reactivity of **1**. The product yield and the reaction rate were significantly increased by using (*R*)-MOP as a ligand instead of triphenylphosphane.

The use of (*R*)-MOP enabled us to obtain a 1,2-acylation product (67% *ee*, 36% yield)[10, 11] from cyclopentenone, which gave a complex mixture of products with $Pd(OAc)_2$/PPh_3.[1] The present enantioselective reaction is less efficient for acyclic α,β-unsaturated ketones, but high yields and good regioselectivity are obtained (Table 2). The absolute configuration of (*R*)-**2** obtained by using the (*R*)-MOP ligand was confirmed by comparison of the sign of the specific rotation $[\alpha]_D$ with the independently prepared enantiomer (*S*)-**2**. The synthesis of (*S*)-**2** was carried out in seven steps from the readily accessible allylic alcohol **6**[12] (Scheme 3).[10]

Table 1. Pd^{II}-catalyzed reactions of **1** with cyclohexenone in the presence of chiral phosphane ligands.[a]

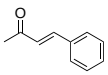
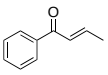


Entry	Pd catalyst[b]	Phosphane[c]	Yield [%][d]	*ee* [%][e]
1	$[PdCl_2\{(R)\text{-BINAP}\}]$	–	19[f]	–
2	$Pd(OAc)_2$	(*R*,*R*)-CHIRAPHOS[g]	14[h]	–
3	$Pd(OAc)_2$	(+)-NMDP[i]	81	–
4	$[PdCl_2(PPh_3)_2]$	(*R*)-MOP[j]	90	12
5	$Pd(OAc)_2$	(*R*)-MOP	88	66
6	$[PdCl_2(PhCN)_2]$	(*R*)-MOP	89	61
7	$[Pd(acac)_2]$	(*R*)-MOP	92	62
8		(*R*)-MOP	48	56
9	$[PdCl_2(CH_3CN)_2]$	(*R*)-MOP	86	64
10	$[Pd_2(dba)_3]\cdot CHCl_3$	(*R*)-MOP	70	64

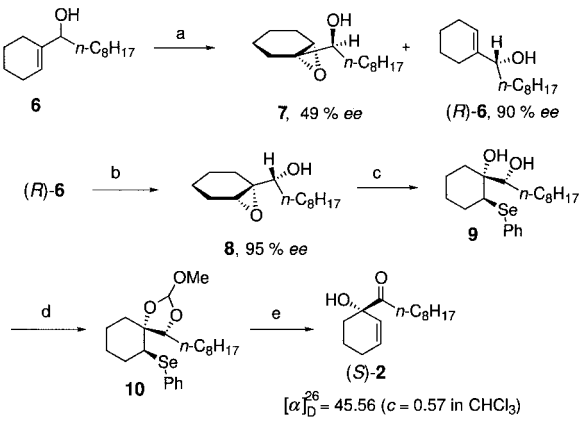
[a] Reactions were carried out at ambient temperature in toluene. [b] 5 mol% catalyst was used; acac = acetylacetonate, dba = dibenzylideneacetonate. [c] Pd/P = 1/2. [d] Yield of isolated product. [e] Determined by HPLC on a chiracel AD column after conversion to the benzoyl ester. [f] Compound **3** was formed in 17% yield. [g] (2*R*,3*R*)-Bis(diphenylphosphanyl)butane. [h] **3** was formed in 11% yield. [i] (+)-Neomenthyldiphenylphosphane. [j] (*R*)-2-(Diphenylphosphanyl)-2′-methoxy-1,1′-binaphthyl.

Table 2. $Pd(OAc)_2$/(*R*)-MOP-catalyzed reactions of **1** with α,β-unsaturated ketones.

1 + α,β-unsaturated ketone $\xrightarrow[10\,\text{mol\% (}R\text{)-MOP}]{5\,\text{mol\% Pd(OAc)}_2}$ 1,2-adduct

ketone	Yield [%]	*ee* [%]
	36	67[a]
	92	38[a]
	91	17
	84	6

[a] See ref. [11].



Scheme 3. Alternative synthesis of (*S*)-**2**: a) *t*BuOOH, $Ti(OiPr)_4$, (+)-DIPT; (R)-**6**: $[\alpha]_D^{23.0} = 6.6$ ($c = 0.50$ in $CHCl_3$), 45%, 90% *ee*; b) *t*BuOOH, $Ti(OiPr)_4$, (−)-DIPT; **8**: $[\alpha]_D^{26.0} = 26.1$ ($c = 1.38$ in $CHCl_3$), 90%, >95% *ee*; c) $(PhSe)_2/NaBH_4$ in EtOH; **9**: $[\alpha]_D^{26.0} = 43.24$ ($c = 0.60$ in $CHCl_3$), 95%, m.p. 91–92.5 °C; d) $HC(OMe)_3$/PPTS in DMF; **10**: quantitative; e) i. $NaIO_4$ in aqueous THF (53%), ii. DIBAL-H in CH_2Cl_2 (78%), iii. Swern oxidation (75%). DIBAL-H = diisobutylaluminum hydride, DIPT = diisopropyl tartrate, PPTS = pyridinium *p*-toluenesulfonate.

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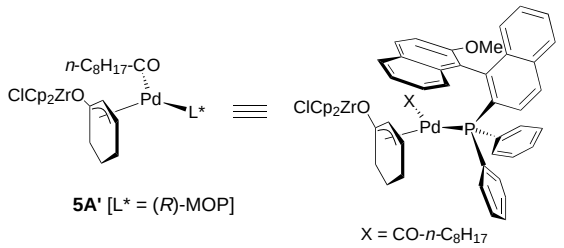
We exploited the Sharpless asymmetric epoxidation[13] and kinetic resolution[14] of **6** to control the absolute configuration. The kinetic resolution of allylic alcohol **6** with (+)-DIPT, $Ti(OiPr)_4$, and *t*BuOOH gave the optically active allylic alcohol (*R*)-**6** (90% *ee*, 45% yield)[15] and epoxy alcohol **7**. The subsequent epoxidation of (*R*)-**6** with $Ti(OiPr)_4$ and *t*BuOOH in the presence of (−)-DIPT gave epoxy alcohol **8** (90%, >95% *ee*).[10, 16] Treatment of **8** with sodium phenylselenide gave *vic*-diol **9**,[10, 17] which was protected as cyclic orthoformate **10**.[10, 18] The oxidation of **10** with sodium periodate at 0 °C, deprotection of the *vic*-diol protecting group (DIBAL-H), and Swern oxidation of the secondary alcohol gave (*S*)-**2** [>95% *ee*, $[\alpha]_D^{26} = 45.5$ ($c = 0.57$ in $CHCl_3$)], which was identical in every respect with the product (*R*)-**2** derived from the enantioselective acylation, except for the sign of specific rotation.[19] Thus, the *R* configuration of the product of the enantioselective palladium-catalyzed reactions of **1** in the presence of (*R*)-MOP was confirmed. On the basis of the hypothetical acylpalladium π-allylic complex **5A** and the X-ray structure of an (*R*)-MOP-ligated π-allylic palladium complex,[8] we assume that the intermediate **5A′** (L* = (*R*)-MOP) is responsible for the chiral induction in the present reactions (Scheme 4). Therefore, the sense of the chiral



Scheme 4. (*R*)-MOP-ligated acylpalladium π-allylic complex **5A′**.

induction under the present reaction conditions indicates the reductive elimination of palladium metal in the (*R*)-MOP ligated acylpalladium π-allylic complex **5A′** (L* = (*R*)-MOP).

In summary, we have demonstrated the first example of enantioselective nucleophilic acylation with an "unmasked" acyl anion. The present nucleophilic acylation of α,β-unsaturated ketone with acylzirconocene chlorides in the presence of the chiral monodentate phosphane ligand (*R*)-MOP opens new possibilities for directly introducing an "unmasked" acyl anion into the carbonyl group of α,β-unsaturated ketones in an enantioselective manner. The stability and easy accessibility of acylzirconocene chlorides favors their use as synthetic reagents over other transition metal acyl complexes.[20]

Experimental Section

(*R*)-**2**: 1-Octene (0.32 mL, 2 mmol) was added to a suspension of [Cp_2ZrHCl] (258 mg, 1 mmol) in CH_2Cl_2 (8 mL) at ambient temperature, and the mixture was stirred for 0.5 h under an argon atmosphere. The argon was replaced by CO (1 atm), and the mixture was stirred for a further 2 h at ambient temperature. Concentration of the solution to dryness in vacuo gave **1** as a pale yellow powder, which was dissolved in toluene (15 mL). To the solution of **1** in toluene were added cyclohexenone (0.05 mL, 0.5 mmol), $Pd(OAc)_2$ (5.5 mg, 0.025 mmol), and (*R*)-MOP (23 mg, 0.05 mmol) with ice cooling, and the mixture was then stirred at ambient temperature for 20 min. After addition of saturated aqueous $NaHCO_3$ solution, the mixture was extracted with diethyl ether. The combined ether extracts were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered. Concentration of the filtrate and purification of the residual oil by silica gel column chromatography (hexanes/ethyl acetate 50/1 to 30/1) gave pure (*R*)-**2** (105 mg, 88% yield). Colorless oil; $[\alpha]_D^{24.0} = -42.1$ ($c = 1.04$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J =$ 6.8 Hz, 3H), 1.26–1.31 (m, 10H), 1.57–1.66 (m, 3H), 1.77–1.88 (m, 3H), 2.03–2.21 (m, 2H), 2.50 (dt, $J = 1.3$, 8.3 Hz, 2H), 4.03 (s, 1H), 5.47 (qd, $J =$ 1.3, 9.9 Hz, 3H), 6.12–6.15 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta =$ 14.1, 18.1, 22.6, 24.0, 24.8, 29.1, 29.2, 29.3, 31.8, 33.3, 36.3, 76.0, 126.1, 133.6, 213.8; IR (neat): $\tilde{\nu} = 3467$, 2927, 1709 cm^{-1}; EI-MS: *m/z*: 238 [M^+]; elemental analysis calcd for $C_{15}H_{26}O_2$: C 75.58, H 10.99; found: C 75.28, H 10.92.

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[4] In these palladium-catalyzed reactions, the α,β-unsaturated ketone framework was an essential factor in facilitating the reaction, since β,γ-unsaturated and saturated ketone derivatives were unreactive toward the acylzirconocene chloride under otherwise identical conditions.
[5] The reaction of **1** with a stoichiometric amount of $Pd(OAc)_2$ without the addition of cyclohexenone also gave **4** in 15% yield.
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[10] Optical purity was determined by HPLC on a chiralcel AD column. All isolated new compounds showed appropriate spectroscopic data (IR, NMR, MS) and correct elemental analyses or high-resolution mass spectra.
[11] 1,2-addition product from cyclopentenone: $[\alpha]_D^{25} = 36.32$ ($c = 1.02$ in $CHCl_3$). 1,2-addition product from cycloheptenone: $[\alpha]_D^{25} = -35.65$ ($c = 0.92$ in $CHCl_3$). The absolute configurations were not determined.

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[12] Alcohol **6** was prepared by the Shapiro reaction of cyclohexanone *p*-toluenesulfonylhydrazone with *n*-nonanal in 48% yield. R. H. Shapiro, *Org. React. (N.Y.)* **1976**, *13*, 405. See also: N. E. Schore, M. J. Knudsen *J. Org. Chem*. **1997**, *52*, 569.
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[15] A similar system to **6** was reported to give the resolved (*R*)-alcohol efficiently by using L-(+)-DIPT under the Sharpless kinetic resolution conditions.[14] The optical purity of (*R*)-**6** was determined by Mosher analysis.
[16] Although the highly diastereoselective epoxidation of (*R*)-**6** is possible without adding chiral tartrate, we added (−)-tartrate, whose chirality matches that of (*R*)-**6**, to improve the optical purity of epoxy alcohol **8**.
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[18] The protection of the diol **9** is required for the subsequent oxidation of the phenylselenide group; otherwise, the selenide **9** was reconverted to the epoxy alcohol **8** under the oxidation conditions.
[19] Starting from epoxy alcohol **7** (49% *ee*), which is obtained by the first kinetic resolution of **6** with (+)-tartrate, gave (*R*)-**2** (43% *ee*) on applying the same synthetic sequence. Therefore, we believe that no epimerization takes place at the quaternary alcohol carbon atom of **9** throughout the reactions.
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Highly Enantio- and Diastereoselective Hetero-Diels–Alder Reactions Catalyzed by New Chiral Tridentate Chromium(III) Catalysts**

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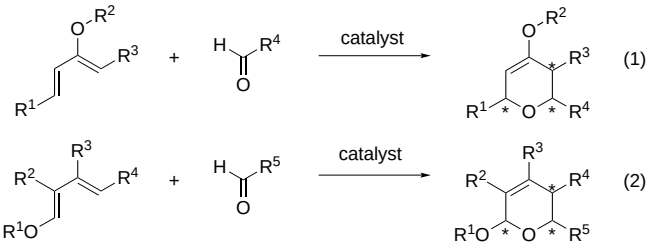
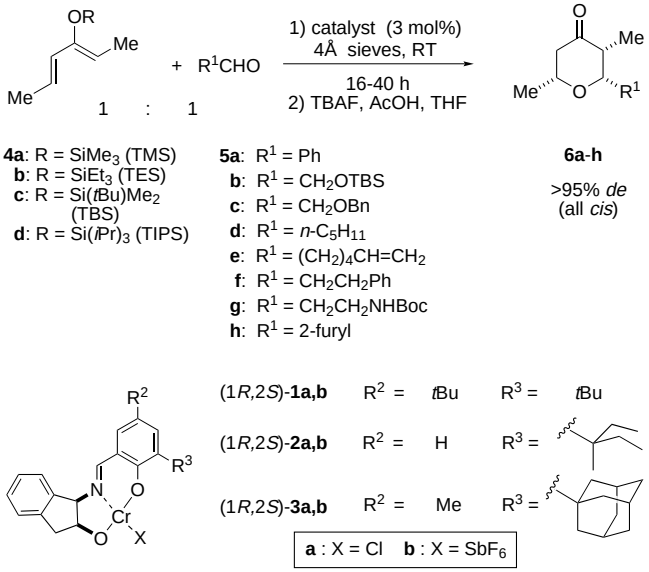
The formal hetero-Diels–Alder reaction (HDA) between dienes and carbonyl compounds[1] has emerged as an important target for asymmetric catalysis. Successes reported in this area have involved the reaction of electron-rich dienes such as 1-methoxy-3-(trimethylsilyloxy)butadiene (Danishefsky's diene) and/or electron-deficient dienophiles such as glyoxylate derivatives.[2–4] As yet, however, there exists no effective method for asymmetric HDA reactions between less nucleophilic dienes bearing fewer than two oxygen substituents and unactivated carbonyl compounds [Eq. (1) and (2)]. This new



class of asymmetric HDA reaction would provide a direct route to enantiomerically enriched dihydropyran derivatives from simple achiral starting materials, setting up to three stereocenters in the cyclization and allowing ultimate access to tetrahydropyran derivatives with five defined stereocenters by elaboration of the resultant double bond. Herein we describe highly effective chiral catalysts for these types of HDA reactions.[5]

Evaluation of tridentate Schiff base chromium(III) complexes of the type **1a** and **1b** revealed catalysis of the HDA reaction between (2*Z*,4*E*)-triethylsilyloxy-2,4-hexadiene (**4b**) and aldehydes **5a** and **5b**, affording tetrahydropyranones **6a** and **6b** after desilylation (Scheme 1). In both cases, nearly



Scheme 1. Hetero-Diels–Alder reaction between substituted hexadienes **4** and aldehydes **5**. Bn = benzyl; Boc = *tert*-butoxycarbonyl; MS = molecular sieve; TBAF = tetrabutylammonium fluoride.

perfect selectivity for the *endo* cyclization product (all-*cis* configuration) was observed, in 80% and 57% *ee*, respectively (Table 1, entries 1 and 2).[6] Chromium(III) complexes **2a** and **2b**, bearing the larger 1-ethyl-1-methylpropyl group, retained the high diastereoselectivity exhibited by **1a** and **1b** and provided an increase in *ee*, particularly in the case of aliphatic aldehydes such as **5b** (85% *ee* with catalyst **2b**; Table 1, entry 3).

As part of this examination of the relationship of catalyst structure to reaction enantioselectivity, adamantyl-substituted chromium(III) complex **3a** was prepared from readily acces-

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