Coupling Reaction of Alkenes with α-Bromo Carboxylic Acid Derivatives Using Nickel Boride and Borohydride Exchange Resin in Methanol[†]
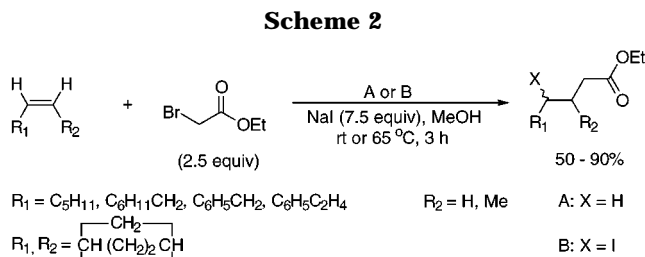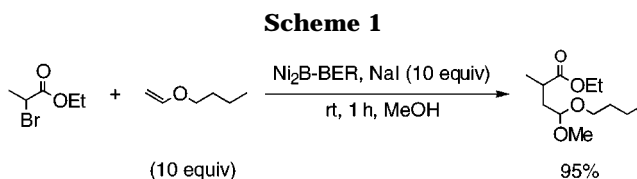
Meyoung Ju Joung, Jin Hee Ahn, Dong Won Lee, and Nung Min Yoon*

Department of Chemistry, Sogang University, Seoul 121-742, Korea

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Introduction

Carbon−carbon bond formation via radical addition or radical cyclization of alkyl halides with alkenes is an important tool for the construction of organic molecules[1] and has been successfully carried out by using tributyltin hydride.[1,2] α-Halo acid derivatives are also reported to be coupled with alkenes, through halogen atom transfer addition or cyclization reactions.[3] Recently we have reported the coupling reaction of α-bromo acid derivatives with vinyl ethers using nickel boride (Ni$_2$B) and borohydride exchange resin (BER). γ-Dialkoxy acid derivatives are produced in very good yields using 10 equiv of vinyl ether in the presence of excess sodium iodide through the methanolysis of the intermediate α-halo ethers which were produced by halogen atom transfer addition[4] (Scheme 1). However in the absence of sodium iodide, both coupling reactions of α-bromo esters and α-iodo esters with vinyl ethers resulted in poor yields (30−55%). In the course of determining the role of sodium iodide, we happened to find out that a moderate yield (55%) of coupling product can be obtained from the reaction of ethyl α-bromopropionate with only 1 equiv of butyl vinyl ether (instead of 10 equiv).[5] This suggests that the radical coupling reaction of α-bromo esters with vinyl ethers is much faster than the reduction of vinyl ethers.[6] Indeed, the reaction of butyl vinyl ether with excess ethyl bromoacetate (2.5 equiv) provided ethyl 4-butoxy-4-methoxybutyrate (**1**) in an improved 73% yield. Encouraged by these results, we extended our study to the reaction of general alkenes with α-bromo esters. We wish

Scheme 1

Scheme 2

R$_1$ = C$_5$H$_{11}$, C$_6$H$_{11}$CH$_2$, C$_6$H$_5$CH$_2$, C$_6$H$_5$C$_2$H$_4$ R$_2$ = H, Me   A: X = H

R$_1$, R$_2$ = CH(CH$_2$)$_2$CH with CH$_2$ bridge   B: X = I

A : Ni(OAc)$_2$ (0.15 equiv) - BER (5 equiv).
B : Ni(OAc)$_2$ (0.075 equiv) - BER (2.5 equiv).

to report here the coupling reaction of representative alkenes with α-bromo acid derivatives in the presence of excess sodium iodide using Ni$_2$B−BER in methanol (Scheme 2).

Results and Discussion

The reaction of 1-heptene with ethyl bromoacetate resulted in a moderate (60%) yield of ethyl nonanoate (**3**), using 5 equiv of BER and 0.15 equiv of Ni(OAc)$_2$ (standard conditions). The reactions of 3-cyclohexylpropene, 3-phenylpropene, and 4-phenyl-1-butene also resulted in moderate yields (50%, 53%, and 54%) of the corresponding coupling products (**5**, **7**, and **8**), whereas the reaction of styrene gave only a trace of the expected product (**6**) at standard conditions.[6] However, when the reaction of 1-heptene was carried out using a limited amount of BER (2.5 equiv) and Ni(OAc)$_2$ (0.075 equiv), the product was ethyl 4-iodononanoate (**4**, 52%) instead of ethyl nonanoate. And similarly, when the reaction of 4-phenyl-1-butene was interrupted after 1 h, a mixture of ethyl 6-phenyl-4-iodohexanoate and ethyl 6-phenyl-hexanoate (∼1:1) was observed at standard conditions.[7] These results clearly suggest that the reaction proceeded via halogen atom transfer reaction, followed by the reduction of iodide. The formation of γ-iodo esters should be important synthetically since the iodo functional group can be readily transformed to many other functional groups. A similar reaction was reported that the addition of excess ethyl bromoacetate (5 equiv) to 1-octene provided 4-bromodecanoate in a 57% yield using a radical initiator at 90 °C.[3c] Reactions of 2-octene and cyclohexene with ethyl bromoacetate proceeded only sluggishly at room temperature and gave the coupling products (**16a**, **16b**, and **17**) in poor yields (15−20%) at 65 °C; however, reaction of cyclooctene resulted in a moderate yield of ethyl cyclooctyl acetate (**18**, 52%). In contrast, the reaction of norbornene proceeded readily at room

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(3) (a) Curran, D. P. *Synthesis* **1988**, 489. (b) Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140. (c) Kharash, M. S.; Skell, P. S.; Fisher, P. *J. Am. Chem. Soc.* **1948**, *70*, 1055. (d) Curran, D. P.; Chang, C. T. *Tetrahedron Lett.* **1986**, *27*, 5893. (e) Degueil-Castaing, M.; De Jeso, B.; Kraus, G. A.; Landgrebe, K.; Maillard, B. *Tetrahedron Lett.* **1986**, *27*, 5927. (f) Curran, D. P.; Chang, C. T. *Tetrahedron Lett.* **1987**, *28*, 2477.

(4) Ahn, J. H.; Lee, D. W.; Joung, M. J.; Lee, K. H.; Yoon, N. M. *Synlett* **1996**, 1224.

(5) Coupling product was obtained in a 95% yield when 10 equiv of butyl vinyl ether was used: ref 4.

(6) Monosubstituted alkenes and norbornene are readily hydrogenated with BER−Ni$_2$B (cat.) in 1 h at 0 °C in methanol, whereas tri- and tetrasubstituted alkenes are not hydrogenated even at 65 °C: Choi, J.; Yoon, N. M. *Synthesis* **1996**, 597.

(7) The compounds were identified by GCMS, and the ratio of the mixture was determined by GC.

(8) The ∼1:1 mixture of ethyl 3-iodo-*exo*-2-norbornyl acetates was isolated in a 90% yield, and the cis and trans ratio was approximately 1:1 by GC. We could not differentiate the cis and trans compounds, but both mass numbers were 308 as identified by GCMS.
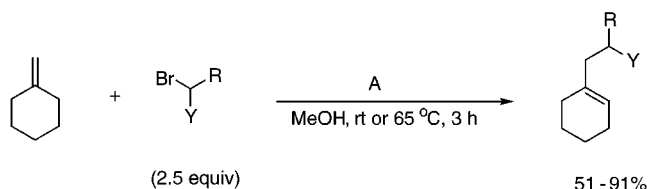
Table 1. Coupling Reaction of Alkenes with α-Bromo Carboxylic Acid Derivatives Using Ni₂B–BER in the Presence of Excess NaI in Methanol at Room Temperature[a]

alkene	α-bromo acid deriv	product (yield %)
butyl vinyl ether	ethyl bromoacetate	ethyl 4-butoxy-4-methoxybutyrate (**1**, 73%)
	ethyl α-bromopropionate	ethyl 4-butoxy-4-methoxy-2-methylbutyrate (**2**, 60%)
1-heptene	ethyl bromoacetate	ethyl nonanoate (**3**, 60%)
		ethyl 4-iodononanoate (**4**, 52%)[b]
3-cyclohexylpropene	ethyl bromoacetate	ethyl 5-cyclohexylpentanoate (**5**, 50%)
styrene	ethyl bromoacetate	ethyl 4-phenylbutanoate (**6**, 5%)[c]
3-phenylpropene	ethyl bromoacetate	ethyl 5-phenylpentanoate (**7**, 53%)
4-phenyl-1-butene	ethyl bromoacetate	ethyl 6-phenylhexanoate (**8**, 54%)
2-methyl-1-pentene	ethyl bromoacetate	ethyl 4-methylheptanoate (**9**, 80%)[d]
methylenecyclopentane	ethyl bromoacetate	ethyl 3-cyclopentylpropionate (**10a**, 70%)[e] and ethyl 3-(1-methoxylcyclopentyl)propionate (**10b**, 18%)
methylenecyclohexane	ethyl bromoacetate	ethyl 3-(1-cyclohexenyl)propionate (**11**, 91%)
	ethyl α-bromopropionate	ethyl 3-(1-cyclohexenyl)-2-methylpropionate (**12**, 51%)
	bromoacetamide	3-(1-cyclohexenyl)propionamide (**13**, 67%)
	N,N-diethylbromoacetamide	N,N-diethyl-3-(1-cyclohexenyl)propionamide (**14**, 85%)
	bromoacetonitrile	3-(1-cyclohexenyl)propionitrile (**15**, 66%)[f]
2-octene	ethyl bromoacetate	ethyl 3-methylnonanoate and ethyl 3-ethyloctanoate (20%)[g] (**16a**:**16b** = 4:3)
cyclohexene	ethyl bromoacetate	ethyl cyclohexyl acetate (**17**, 15%)[g]
cyclooctene	ethyl bromoacetate	ethyl cyclooctyl acetate (**18**, 52%)[g]
norbornene	ethyl bromoacetate	ethyl exo-2-norbornyl acetate (**19**, 88%)
1-methylcyclohexene	ethyl bromoacetate	ethyl (2-methyl-1-cyclohexenyl)acetate and ethyl (2-methyl-2-cyclohexenyl)acetate (40%) (**20a**:**20b** = 5:4)

[a] 2 mmol of alkenes were reacted with 5 mmol of α-bromo acid derivatives using Ni(OAc)₂ (0.3 mmol) and BER (10 mmol) in the presence of 15 mmol of NaI in methanol (6 mL) for 3 h. [b] Ni(OAc)₂ (0.15 mmol) and BER (5 mmol) in the presence of 15 mmol of NaI in methanol (6 mL). [c] GC yield. [d] Four stereoisomers of ethyl 4-methyl heptenoate were initially obtained in a 86% yield and hydrogenated to ethyl 4-methylheptanoate. [e] Product mixture of olefinic ester (14:1) was reduced to ethyl 3-cyclopentylpropionate. [f] The reaction was carried out at 65 °C for 3 h. [g] Reactions were carried out using 10 mmol of ethyl bromoacetate at 65 °C.

temperature to give a mixture of cis and trans isomers, ethyl 3-iodo-*exo*-2-norbornyl acetates,[8] using a limited amount of reagent, and the final product ethyl *exo*-2-norbornyl acetate (**19**, 88%) was isolated at standard conditions. Recently, an *exo*-norbornyl glycine derivative is reported to be produced by xanthate transfer addition of glycine radical to excess norbornene (5 equiv), followed by reduction in a 61% yield.[9]

On the other hand, the reaction of 2-methyl-1-pentene with ethyl bromoacetate gave an excellent yield of the corresponding unsaturated esters, four stereoisomers of ethyl 4-methylheptenoates[10] (cis/trans mixtures of 3- and 4-heptenoates), and ethyl 4-methyl heptanoate (**9**, 80%) was isolated after hydrogenation over Pd/C. However the reaction of methylenecyclopentane resulted in a mixture of olefinic esters (14:1, 75%), presumably ethyl 3-(1-cyclopentenyl)propionate and 3-cyclopentylidenylpropionate, accompanied by ethyl 3-(1-methoxylcyclopentyl)-propionate (**10b**, 18%), and the former mixture was hydrogenated over Pd/C to ethyl 3-cyclopentylpropionate (**10a**, 70%). On the other hand, the reaction of methylenecyclohexane with the bromo ester proceeded cleanly to give an excellent yield of ethyl 3-(1-cyclohexenyl)-propionate (**11**, 91%) without being contaminated with the methoxy derivative (Scheme 3). Reactions of methylenecyclohexane with other α-bromo acid derivatives such as bromoacetamide, N,N-diethylbromoacetamide, and bromoacetonitrile also gave good yields of the corresponding coupling products, 3-(1-cyclohexenyl)propionamide (**13**, 67%), N,N-diethyl-3-(1-cyclohexenyl)propionamide (**14**, 85%), and 3-(1-cyclohexenyl)propionitrile (**15**, 66%). In contrast to ethyl bromoacetate, the addition of ethyl bromopropionate to methylenecyclohexane gave a lower yield of the coupling product, ethyl 3-(1-cyclo-

(9) Udding, J. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1994**, *59*, 3721.
(10) All four isomers have the same mass number (170) as identified by GCMS, and the mixture was isolated in 86% yield.
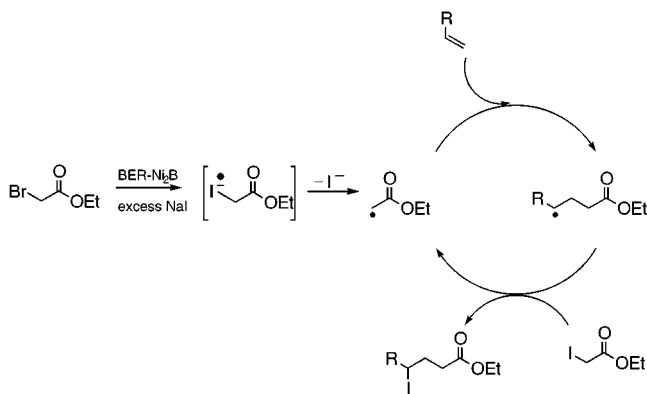
Scheme 3

(2.5 equiv) 51 - 91%

R = H, Me   Y = CO₂Et, CONH₂, CONEt₂, CN
A : Ni(OAc)₂ (0.15 equiv) - BER (5 equiv), NaI (7.5 equiv).

hexenyl)-2-methylpropionate (**12,** 51%). These olefinic acid derivatives are believed to be formed by the rapid dehydrohalogenation of the corresponding tertiary iodides produced by halogen atom transfer reaction. Reaction of trisubstituted alkenes such as 1-methylcyclohexene gave the corresponding olefinic esters, a 5:4 mixture of ethyl (2-methyl-1-cyclohexenyl)acetate (**20a**) and ethyl (2-methyl-2-cyclohexenyl)acetate (**20b**) in lower yield (40%). The much lower yield, compared with methylenecyclohexene (91%), is presumably due to the steric hindrance of the secondary olefinic carbon of 1-methylcyclohexene. The coupling reaction of 1,1-disubstituted and trisubstituted alkenes with α-bromo acid derivatives should be a unique method for the synthesis of olefinic acid derivatives in one step.

The coupling reaction of alkenes with ethyl bromoacetate is believed to proceed through the formation of an α-ester radical from bromoacetate by Ni₂B–BER, and the addition of the radical to alkenes. The α-ester radical produced from the bromoacetate seems to be stabilized in the form of an iodoacetate radical anion (Figure 1). In the absence of sodium iodide, the reactions of methylenecyclohexane with ethyl bromoacetate and ethyl iodoacetate give the coupling products in poor (3% and 35%) yields, respectively, whereas both reactions proceeded excellently in the presence of excess sodium iodide (7.5 equiv).

Figure 1.

Conclusion

In conclusion, the coupling reaction of alkenes with α-bromo acid derivatives in the presence of excess NaI can be carried out using Ni_2B-BER in methanol. The reactions of monosubstituted alkenes and norbornene give the corresponding γ-iodo carboxylates with a limited amount of reagents, but the corresponding deiodinated products at standard conditions, whereas 1,1-disubstituted and trisubstituted alkenes give the corresponding coupling products, unsaturated carboxylates. The Ni_2B- BER-methanol system tolerates many functional groups such as acetals, esters, amides, nitriles, and epoxides and has another advantage of a simple workup and mild conditions.

Experimental Section

General Procedure. BER (5 equiv, 10 mmol) was added to the methanol solution (4 mL) of $Ni(OAc)_2 \cdot 4H_2O$ (0.15 equiv, 0.3 mmol) and NaI (7.5 equiv, 15 mmol) with gentle stirring at room temperature. Immediately a black coating of Ni_2B on BER and slow hydrogen evolution were observed. After 1 min, the reaction was started by the addition of a methanol solution (2 mL) of methylenecyclohexane (0.192 g, 2 mmol) and ethyl bromoacetate (0.835 g, 2.5 equiv, 5 mmol) at room temperature (standard conditions). After 3 h, the Ni_2B-BER was filtered, and the filtrate was evaporated under reduced pressure. The crude product was chromatographed on a silica gel column (eluent; hexane/EtOAc 49:1) to give 0.331 g (91%) of ethyl 3-(1-cyclohexenyl)propionate.

Ethyl 4-Iodononanoate (4): ¹H NMR (200 MHz, CDCl₃): δ 0.90 (t, 3 H, J = 7.2 Hz), 1.24−1.33 (m, 9 H), 1.82−1.94 (m, 2 H), 2.07 (q, 2 H, J = 7.5 Hz), 2.50 (t, 2 H, J = 7.5 Hz), 4.07− 4.21 (m, 1 H), 4.14 (q, 2 H, J = 7.2 Hz); IR (neat) 1736, 1181; MS *m/z* (relative intensity) (EI, 70 eV) 267 (5), 185 (57), 139 (55), 121 (50), 97 (85), 81 (26), 69 (100), 55 (97). Anal. Calcd for $C_{11}H_{21}O_2I$: C, 42.318; H, 6.781. Found: C, 42.243; H, 6.868.

Ethyl 4-Methylheptanoate (9): ¹H NMR (200 MHz, CDCl₃): δ 0.86−1.69 (m, 16 H), 2.25−2.34 (m, 2 H), 4.13 (q, 2

H, J = 7.2 Hz); IR (neat) 1739, 1174; MS *m/z* (relative intensity) (EI, 70 eV) 172 (M⁺, 1), 143 (5), 129 (12), 127 (26), 101 (100), **88** (90), 73 (38). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.720; H, 11.703. Found: C, 69.836; H, 11.862.

Ethyl 3-(1-Cyclohexenyl)propionate (11): ¹H NMR (200 MHz, CDCl₃): δ 1.25 (t, 3 H, J = 7.1 Hz), 1.43−1.68 (m, 4 H), 1.92−1.95 (m, 4 H), 2.24 (t, 2 H, J = 7.1 Hz), 2.40 (t, 2 H, J = 7.1 Hz), 4.13 (q, 2 H, J = 7.1 Hz), 5.41 (s, 1 H); IR (neat) 1737, 1176; MS *m/z* (relative intensity) (EI, 70 eV) 182 (M⁺, 23), 153 (1), 137 (26), 109 (12), 95 (100), 81 (29). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.487; H, 9.955. Found: C, 72.253; H, 10.171.

Ethyl *exo*-2-Norbornyl Acetate (19). The *exo* orientation of the ethyl acetate group was confirmed by ¹³C DEPT, HET-COR, and NOESY experiments. ¹H NMR (300 MHz, CDCl₃): δ 1.00−1.13 (m, 3 H), 1.17−1.29 (m, 2 H), 1.26 (t, 3 H, J = 7.1 Hz), 1.44−1.51 (m, 3 H), 1.84−1.88 (m, 1 H), 1.95−1.96 (m, 1 H), 2.05−2.12 (m, 1 H), 2.18−2.28 (m, 2 H), 4.09 (q, 2 H, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 13.96, 28.29, 29.52, 34.96, 36.50, 37.50, 38.24, 40.92, 41.12, 59.91, 173.45; IR (neat) 1737, 1178; MS *m/z* (relative intensity) (EI, 70 eV) 182 (M⁺, 3), 153 (17), 137 (34), 113 (100), 109 (26), 95 (76), 67 (92). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.487; H, 9.955. Found: C, 72.226; H, 10.295.

Ethyl (2-Methyl-1-cyclohexenyl)acetate (20a) and Ethyl (2-Methyl-2-cyclohexenyl)acetate (20b). The assignment of the two structural isomers was derived from hydrogenation of the isomers using BER−Ni_2B (cat.) and Pd/C. The isomers were not hydrogenated with BER−Ni_2B (cat.) at 65 °C in methanol. This result showed that the two isomers should be tri- or tetraolefinic ester.[6] And we observed that only one of the two isomers was readily hydrogenated over Pd/C, whereas, the other was very slowly hydrogenated. It is confidently believed that the isomers are tri- and tetraolefinic esters. The ratio of tetrasubstituted to trisubstituted olefinic ester (**20a:20b**) was 5:4 as determined by a NMR spectrum; ¹H NMR (300 MHz, CDCl₃, characteristic signals): δ 2.99 (s, 1.11 H, α-hydrogens of ester group in **20a**), 5.43 (brs, 0.44 H, olefinic hydrogen in **20b**); IR (neat) 1739, 1163; **20a**: ¹³C NMR (75 MHz, CDCl₃): δ 13.95, 21.65, 22.78, 22.92, 29.94, 31.61, 38.85, 60.14, 129.14, 135.34, 173.67; MS *m/z* (relative intensity) (EI, 70 eV) 182 (M⁺, 55), 153 (2), 137 (4), 109 (55), 108 (100), 95 (21), 93 (60), 67 (39); **20b**: ¹³C NMR (75 MHz, CDCl₃): δ 13.95, 18.82, 19.11, 25.13, 27.88, 35.38, 37.97, 60.10, 123.72, 128.91, 172.47; MS *m/z* (relative intensity) (EI, 70 eV) 182 (M⁺, 8), 153 (1), 137 (5), 108 (29), 95 (56), 94 (100), 79 (34). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.487; H, 9.955. Found: C, 72.330; H, 10.216.

Supporting Information Available: IR, NMR, MS, and elemental analyses of 16 compounds and copies of spectra (¹H NMR, ¹³C NMR, DEPT) of **20a** and **20b** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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