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ORGANIC SYNTHESIS USING HALOBORATION REACTION XVIII. A STEREOSELECTIVE SYNTHESIS OF β-MONO- AND β,β-DISUBSTITUTED α,β-UNSATURATED ESTERS

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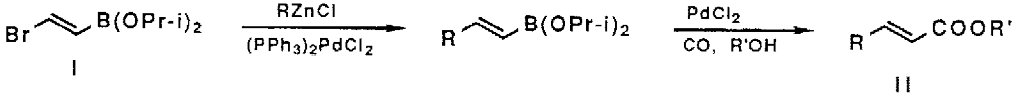
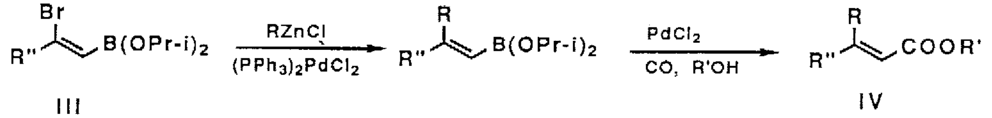
Abstract: β-Mono- and β,β-disubstituted α,β-unsaturated esters can be prepared in good yields stereoselectively by the stepwise alkylation and alkoxycarbonylation of 2-bromo-1-alkenylboronates.

Recently, we have demonstrated that the stepwise cross-coupling reactions of 2-bromo-1-alkenylboranes, readily obtained by the bromoboration reaction of 1-alkynes, are effectively catalyzed by palladium complex, which provide convenient and selective methods for the syntheses of (E)-disubstituted alkenes[1], trisubstituted alkenes[2], and α,β-unsaturated ketones.[3] As an extension of that work, we wish to report here a new method for the stereoselective synthesis of β-mono- and β,β-disubstituted α,β-unsaturated esters by the stepwise cross-coupling alkylation and alkoxycarbonylation of 2-bromo-1-alkenylboranes (eqs. 1 and 2).



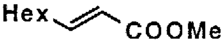
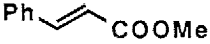
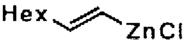
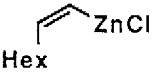
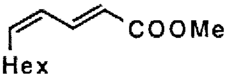
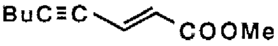
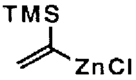
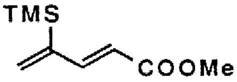
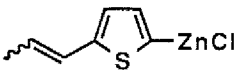
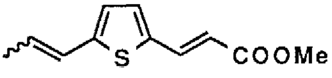
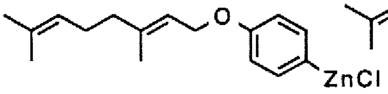
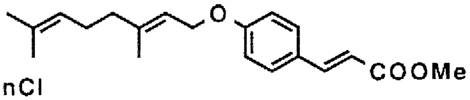
(1)



(2)

In the previous work,[1,2,3] the two cross-coupling reactions were catalyzed by the same palladium-phosphine complex and only an addition of the catalyst was enough to cause both the reactions. However, in this work, the alkoxycarbonylation reaction of 1-alkenylboron derivatives is known to be catalyzed by palladium chloride free from phosphine ligands[4] and the different catalyst is required in each step. Initially, we added the second palladium chloride catalyst and re-oxidant for the second reaction just after the first coss-coupling, and the alkoxycarbonylation was carried out in methanol under the atmosphere of carbon monoxide. However, the expected ester was not obtained almost at all. The reactants used in the first step seemed to disturb the second step.[5] This difficulty was fortunately overcome by removal of the first reactants. Thus, after the first step, the solid part of the reaction mixture was removed by filtration and the filtrate was washed with water. Then, the alkoxycarbonylation step proceeded to give the desired α,β-unsaturated esters in good yields. From (E)-(2-bromoethenyl)diisopropoxyborane (I)[1,3], β-monosubstituted α,β-unsaturated esters (II) were obtained stereoselctively as

Table 1. Stereoselective Synthesis of β–Monosubstituted α,β-Unsaturated Esters[a]

Entry	RZnCl	Product	Yield, %[b]	Stereoselec-tivity, %[c]
1	HexZnCl		76	>98
2	HexZnCl		80	>99
3	PhZnCl		78	>98
4			73[e]	96
5			72[e]	>99
6	BuC≡CZnCl		58[e]	>99
7			63	98
8			50[e]	98
9			74[e]	_[f]

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a. Unless otherwise mentioned, RZnCl (1.5 eq.) and 1 mol% of $(PPh_3)_2PdCl_2$ to 1 were used in the alkylation step, and AcONa (1.5 eq.), LiCl (10 eq.), p-benzoquinone (1.5 eq.), and 3 mol% of $PdCl_2$ were used in the second step.

b. Isolated yield based on 1.

c. Determined by capillary GLPC analysis.

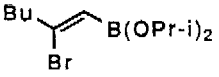
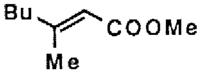
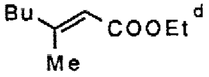
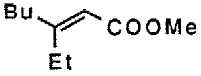
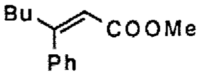
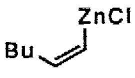
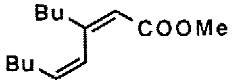
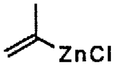
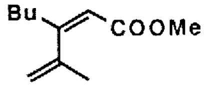
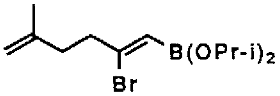
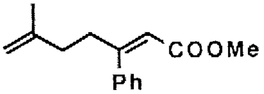
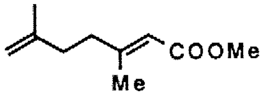
d. Ethanol was used in stead of methanol in the carbonylation step.

e. Two eq. of RZnCl to 1 was used.

f. Decomposed on GLPC.

shown in Table 1. Even dienyl esters can be prepared stereoselectively from simple monoene-units (entries 4, 5, and 7 in Table 1). Furthermore, this method is applicable for the synthesis of the natural compounds such as methyl 5-(1-propenyl)-2-thiopheneacrylate, a constituent of *Anthemis austriaca*[6] and methyl p-geranyloxycinnamate, a constituent of *Acronychia baueri*[7] (entries 8 and 9).

Table 2. Stereoselective Synthesis of β,β-Disubstituted α,β-Unsaturated Esters[a]

Borane	RZnCl	Product	Yield, %[b]	Stereoselectivity, %[c]
	MeZnCl		73	97
	MeZnCl	 [d]	79	96
	EtZnCl		61	>99
	PhZnCl		79	>99
			74	>98
			51	>99
	PhZnCl		70	94
	MeZnCl		57	>98

a. In the alkylation step, RZnCl (2 eq.) and 5 mol% of $(PPh_3)_2PdCl_2$ to alkenylborane were used, and AcONa (1.5 eq.), LiCl (10 eq.), p-benzoquinone (1.5 eq.), and 3 mol% of $PdCl_2$ to borane were used in the second step.

b. Isolated yield based on alkenylborane used.

c. Determined by capillary GLPC analysis.

d. Ethanol was used instead of methanol.

In a similar manner, β,β–disubstituted α,β-unsaturated esters can be synthesized from (E)-(2-bromo-1-alkenyl)diisopropoxyboranes prepared by the bromoboration of 1-alkynes.[8] The representative results for the synthesis of such disubstituted α,β-unsaturated esters are shown in Table 2.

The following procedure for the synthesis of methyl (E)-2-nonenate is representative. To 3 ml of a THF solution of (E)-(2-bromoethenyl)diisopropoxyborane (0.235 g, 1 mmol) and dichlorobis(triphenylphosphine)palladium[9] (0.007 g, 0.01 mmol) was added at 0 °C, hexylzinc chloride (1.5 mmol) in THF prepared from the corresponding Grignard reagent and a THF solution of zinc chloride. After stirring for 3 h at room temperature, the solid part was removed from the reaction mixture by filtration through celite and was washed with ether. The filtrate was washed with water and dried over magnesium sulfate. To the concentrate, palladium chloride (0.004g, 0.03 mmol), sodium acetate (0.123 g, 1.5 mmol), lithium chloride (0.424 g, 10 mmol), p-benzoquinone (0.162 g, 1.5 mmol) and 5 ml of methanol were added, and then a balloon filled with carbon monoxide was attached to the reaction flask. The mixture was stirred at 50 °C for 4 h and the purification by preparative tlc (silica gel/ hexane : ether = 95 : 5) gave methyl (E)-2-nonenate in 76 % yield.

References and Notes

1. (a)S. Hyuga, Y. Chiba, N. Yamashina, S. Hara, and A. Suzuki, Chem. Lett., **1987**, 1757.
   (b)S. Hyuga, N. Yamashina, S. Hara, and A. Suzuki, ibid., **1988**, 809.
2. Y. Satoh, H. Serizawa, N. Miyaura, S. Hara, and A. Suzuki, Tetrahedron Lett., 29, 1811 (1988).
3. M. Ogima, S. Hyuga, S. Hara, and A. Suzuki, Chem. Lett., under submitted.
4. N. Miyaura and A. Suzuki, Chem. Lett., **1981**, 1879.
5. Actually, in the methoxycarbonylation reaction of alkenylboranes, the addition of $Pd(PPh_3)_4$ or magnesium salt was found to cause the serious decrease of the yield.
6. F. Bohlmann, C. Zdero, and H. Schwartz, Ber., 107, 1074 (1974).
7. R. H. Prager and H. M. Thredgold, Aust. J. Chem., 19, 451 (1966).
8. The preparation of (Z)-(2-bromo-1-hexenyl)diisopropoxyborane was carried out as follows; To 30 ml of a dichloromethane solution of tribromoborane (7.5 g, 30 mmol) was added at -78 °C, a dichloromethane solution of 1-hexyne (2.46 g, 30 mmol) dropwise and the mixture was stirred at - 78 °C for 1h. After the addition of diisopropyl ether (7.14 g, 70 mmol), the reaction mixture was stirred at room temperature over night. The volatile part was removed under reduced pressure and then distillation of the residue gave (Z)-(2-bromo-1-hexenyl)diisopropoxyborane in 73 % yield (b. p. 68 °C / 0.07 mmHg). see: ref. 2.
9. Tetrakis(triphenylphosphine)palladium is also effective as the catalyst in the first cross-coupling step.

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