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(Z)-α-Selanyl Alkenyl Grignard Reagents as Convenient Precursors for Stereoselective Synthesis of Trisubstituted Alkenes

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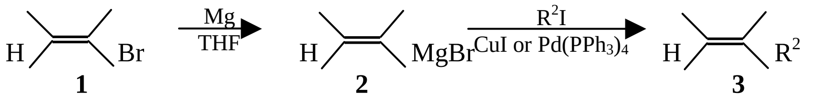
Abstract: (Z)-α-Selanyl alkenyl Grignard reagents **2** were prepared conveniently by treatment of α-bromovinylselenides **1** with magnesium filings in THF. Intermediates **2** were reacted with alkyl iodides in the presence of CuI or $Pd(PPh_3)_4$ to afford (Z)-1,2-disubstituted vinylselenides **3**, which were cross-coupled with Grignard reagents in the presence of $(PPh_3)_2NiCl_2$ to give trisubstituted alkenes **4** stereoselectively in good yields.

Keywords: α-Bromovinylselenides, (Z)-α-selanyl alkenyl Grignard reagents, stereoselective synthesis, trisubstituted alkene.

Many biologically active compounds occurring in nature possess the structural skeleton of trisubstituted alkenes[1-3]. Difunctional group reagents, which have two different functional groups linked to the olefinic carbon atoms, for example, Se-Zr, Se-B, Se-Sn play important roles in organic synthesis, especially in developing a lot of convenient methods for stereoselective synthesis of substituted alkenes[4]. Recently, Tingoli *et al.*[5] reported that (Z)-α-selanylvinyl *p*-toluenesulfonates can undergo sequential transition metal catalyzed cross-coupling reaction with nucleophiles, providing a convenient method for the stereoselective synthesis of trisubstituted alkenes. Huang *et al.*[6] described that (E)-α-selanylvinylstannanes prepared from alkynylselenides by hydrostannation can easily transform to trisubstituted alkenes stereoselectively. Now we wish to report another way to synthesize trisubstituted alkenes *via* the reaction of α-bromovinylselenides with magnesium filings in THF giving the (Z)-α-selanyl alkenyl Grignard reagents, which are then reacted with alkyl iodides in the presence of CuI or $Pd(PPh_3)_4$. Thus obtained 1,2-disubstituted vinylselenides retained (Z)-configuration (**Scheme 1**).

Scheme 1



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The required starting α-bromovinylselenides **1** were easily prepared in good yields with high stereoselectivity according to the literature procedure[7]. The reaction of α-bromovinylselenides with magnesium filings in THF gave (Z)-α-selanyl alkenyl Grignard reagents **2**, which were reacted with methyl iodide at 0°C to give (Z)-1,2-disubstituted vinylselenides **3** in good yields. The intermediates **2** was found to present lower reactivity with alkyl halides other than methyl iodide, however, it was readily alkylated by butyl iodide in the presence of a catalytic amount of CuI. In the presence of $Pd(PPh_3)_4$ catalyst, intermediates **2** could also undergo cross-coupling reaction with iodobenzene at room temperature to give (Z)-1,2-disubstituted vinyl selenides **3** in good yields. The experimental results are summarized in **Table 1.**

Table 1 Synthesis of (Z)- 1,2-disubstituted vinylselenides

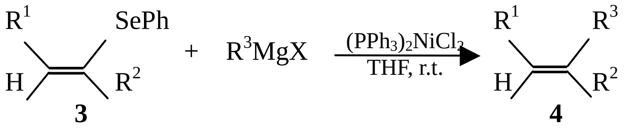
Entry	R[1]	R[2]	Catalyst	Product[a]	Yield[b](%)
1	n-C_4H_9	CH_3		**3a**	66
2	n-C_4H_9	n-C_4H_9	CuI	**3b**	62
3	n-C_4H_9	Ph	$Pd(PPh_3)_4$	**3c**	58
4	Ph	CH_3		**3d**	70
5	Ph	n-C_4H_9	CuI	**3e**	65
6	Ph	Ph	$Pd(PPh_3)_4$	**3f**	60
7	n-C_6H_{13}	CH_3		**3g**	64
8	n-C_6H_{13}	n-C_4H_9	CuI	**3h**	61
9	n-C_6H_{13}	Ph	$Pd(PPh_3)_4$	**3i**	59

[a] All products were characterized by IR、 ^1H NMR and elemental analyses.

[b] Isolated yield based on the α-bromovinylselenide used.

Vinylselenides are important synthetic intermediates owing to the versatile reactivity of the selanyl group and the carbon-carbon double bond[8]. (Z)-1,2-disubstituted vinylselenides **3** are also effective precursors for stereoselective synthesis of trisubstituted alkenes. Therefore, we carried out the cross-coupling reaction of **3** with Grignard reagents in the presence of $(PPh_3)_2NiCl_2$ at room temperature in THF for 48 h to give the selenium free trisubstituted alkenes **4** in good yields with retention of configuration (**Scheme 2**).

Scheme 2



4a: R^1=Bu, R^2=Ph, R^3=Me, 64%
4b: R^1=n-C_6H_{13}, R^2=Ph, R^3=Me, 58%
4c: R^1=Ph, R^2=Bu, R^3=Ph, 68%

In conclusion, we have developed a novel approach to the stereoselective synthesis of trisubstituted alkenes by using (Z)- α-selanyl alkenyl Grignard reagents as the precursors. Comparing to the reported methods[5,6], the present method for the synthesis of stereodefined trisubstituted alkenes has the advantages of readily available starting materials, straightforward and simple procedures, mild reaction conditions and good yields.

Experimental

^{1}H NMR spectra were recorded on a EM-360(90MHz) spectrometer with TMS as an internal standard (δ in ppm). IR spectra were obtained on a Perkin-Elmer 683 instrument as neat films. Microanalysis were measured using a Yanaco MT-3 CHN microelemental analyzer. THF was distilled from sodium-benzophenone ketyl before use. $Pd(PPh_3)_4$ and $(PPh_3)_2NiCl_2$ were prepared according to literature procedure[9,10].

General procedure for the synthesis of ***3a, 3d, 3g***

A drop of ethylene dibromide was added to magnesium filings (2 mmol) in THF (2.5 mL) to start the reaction and α-bromovinylselenide (2 mmol) was then added. The mixture was stirred under nitrogen at 60℃ for 4 h. After being cooled to 0℃, methyl iodide (2.5 mmol) in THF (1 mL) was added and the mixture was stirred at 0℃ for 10 min and then at room temperature for 2 h. The mixture was treated with sat. aq NH_4Cl(5 mL) and extracted with ether (2×30 mL). The ethereal solution was washed with water (3×20 mL) and dried ($MgSO_4$). Removal of solvent under reduced pressure gave an oil which was purified by column chromatography on silica gel using light petroleum as eluent.

General procedure for the synthesis of ***3b, 3e, 3h***

Butyl iodide (2.2 mmol) in THF (2 mL) and CuI (0.2 mmol) were added into the Grignard reagent **2** prepared as above and the mixture was stirred at 0℃ for 1 h and then at room temperature for 2 h. After the usual workup (see above) the residue was chromatographed through a silica gel column using light petroleum as eluent.

General procedure for the synthesis of ***3c, 3f, 3i***

Iodobenzene (2.2 mmol) in THF(2 mL) and $Pd(PPh_3)_4$ (0.1 mmol) were added into the Grignard reagent **2** prepared as above and the mixture was stirred at room temperature for 6 h. After the usual workup (see above) the residue was chromatographed on a silica gel column using petroleum as eluent.

General procedure for the synthesis of trisubstituted alkenes ***4***

To a stirred suspension of $(PPh_3)_2NiCl_2$ (0.05 mmol) and (Z)-1,2-disubstituted vinylselenide **3** (1 mmol) in THF (5 mL) was added a solution of R^3MgX(4 mmol) in THF (6 mL) at room temperature and the mixture was stirred for 48 h. After the usual workup (see above) the residue was chromatographed on a silica gel column using petroleum as eluent.

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