A facile stereoselective synthesis of (*E*)-2,3-disubstituted allylic alcohols via hydromagnesiation of alkylarylacetylenes

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Hydromagnesiation of alkylarylacetylenes **1** in diethyl ether gave (*E*)-α-arylvinyl Grignard reagents **2**, which reacted with aldehydes or ketones **3** to afford stereoselectively (*E*)-2,3-disubstituted allylic alcohols **4** in good yields.

Keywords: hydromagnesiation, alkylarylacetylene, vinyl Grignard reagent, (*E*)-allylic alcohol, stereoselective synthesis

Allylic alcohols are among the most versatile intermediates in organic synthesis and are pervasive in natural products and commercially important pharmaceuticals.[1] Thus, the stereocontrolled synthesis of allylic alcohols is of considerable interest in organic chemistry.[2] Although substantial progress has been made in the synthesis of (*E*)-di- and (*E*)-trisubstituted allylic alcohols,[3-7] the direct synthesis of (*E*)-2,3-disubstituted allylic alcohols remains a formidable challenge.[8] Hydromagnesiation has emerged as a unique hydrometallation with some attractive features such as the high regioselectivity and stereoselectivity observed with alkylarylacetylenes[9] and alkynylsilanes.[10] We recently have reported the stereoselective syntheses of (*Z*)-2-trimethylsilyl-substituted allylic alcohols,[11] (*E*)-α-selenenylvinylsilanes,[12] 1,3- dienylsilanes[13] and (*E*)-α-aryltellurenylvinylsilanes[14] by the hydromagnesiation of alkynylsilanes. Here we report that (*E*)-2,3-disubstituted allylic alcohols can be conveniently synthesised via the hydromagnesiation of alkylarylacetylenes, followed by the reaction with aldehydes or ketones.

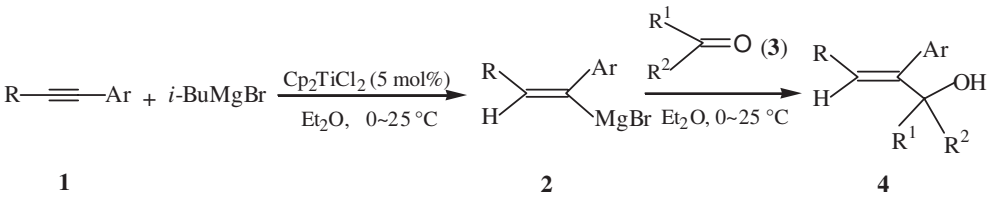
Alkylarylacetylenes **1** were prepared according to the literature procedure.[15] Hydromagnesiation of alkylarylacetylenes is known to proceed with high regioselectivity and stereoselectivity to generate (*E*)-α-arylvinyl Grignard reagents (Scheme 1).[9] We observed that the hydromagnesiation of alkylarylacetylenes **1** at 25 °C in diethyl ether for 1h gave (*E*)-α-arylvinylmagnesium bromides **2**, which reacted with aldehydes or ketones **3** to afford stereoselectively (*E*)-2,3-disubstituted allylic alcohols **4** in good yields (Scheme 1). The typical results are summarised in Table 1.

Investigations of the crude products **4** by ^{1}H NMR spectroscopy (400 MHz) showed their isomeric purities of more than 97%. One olefinic proton signal of compounds **4a–n** splits characteristically into a triplet at δ = 5.67–5.93 with coupling constant J = 7.2 or 7.6 Hz, which indicates that the hydromagnesiation to the alkylarylacetylenes had taken place with strong preference for the addition of the magnesium atom at the carbon adjacent to the aryl group.

In conclusion, a novel convenient synthetic method for (*E*)-2,3-disubstituted allylic alcohols has been developed by the hydromagnesiation of alkylarylacetylenes, followed by the reaction with aldehydes or ketones. Compared with other methods reported, the present method has the advantages of readily available starting materials, straightforward and simple procedures, mild reaction conditions and good yields.

Experimental

Diethyl ether was distilled from sodium immediately prior to use. IR spectra were obtained on a Perkin-Elmer 683 instrument as neat films. ^{1}H NMR spectra were recorded on a Bruker AC-400



Scheme 1

Table 1 Synthesis of (*E*)-2,3-disubstituted allylic alcohols **4a–n**

Entry	R	Ar	R^1	R^2	Product	Yield[a]/%
1	n-C_4H_9	Ph	CH_3	CH_3	**4a**	77
2	n-C_4H_9	4-ClC_6H_4	H	3,4-$CH_2O_2C_6H_3$	**4b**	69
3	n-C_4H_9	4-$CH_3C_6H_4$	CH_3	CH_3	**4c**	73
4	n-C_4H_9	4-ClC_6H_4	CH_3	Ph	**4d**	66
5	n-C_4H_9	4-$CH_3C_6H_4$	–$CH_2CH_2CH_2CH_2$–		**4e**	63
6	n-C_4H_9	4-$CH_3C_6H_4$	H	3,4-$CH_2O_2C_6H_3$	**4f**	65
7	n-C_4H_9	4-ClC_6H_4	H	n-C_6H_{13}	**4g**	69
8	n-C_4H_9	Ph	CH_3	Ph	**4h**	59
9	n-C_4H_9	4-$CH_3C_6H_4$	H	Ph	**4l**	68
10	n-C_4H_9	Ph	H	Ph	**4j**	75
11	n-C_6H_{13}	Ph	H	Ph	**4k**	72
12	n-C_6H_{13}	Ph	H	n-C_6H_{13}	**4l**	66
13	n-C_6H_{13}	Ph	CH_3	CH_3	**4m**	79
14	n-C_6H_{13}	Ph	–$CH_2CH_2CH_2CH_2$–		**4n**	58

[a] Isolated yield based on the alkylarylacetylene **1** used.

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(400 MHz) spectrometer using $CDCl_3$ as solvent. Microanalyses were measured using a Yanaco MT-3 CHN microelemental analyser.

General procedure for the synthesis of (E)-2,3-disubstituted allylic alcohols **4a-n**: To a solution of isobutylmagnesium bromide (2.5 mmol) in diethyl ether (4 ml) was added Cp_2TiCl_2 (25 mg, 0.1 mmol) at 0 °C under Ar, and the mixture was stirred for 30 min at that temperature. To this solution was added alkylarylacetylene **1** (2.0 mmol), and the mixture was stirred for 1 h at 25 °C. After being cooled to 0 °C, aldehyde or ketone **3** (2.1 mmol) was added and the mixture was stirred for 4 h at 25 °C, quenched with sat. aq NH_4Cl (15 ml) and extracted with Et_2O (2 × 30 ml). The organic layer was washed with sat. aq NH_4Cl (20 ml) and water (3 × 20 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil, which was purified by column chromatography on silica gel (eluent: light petroleum–AcOEt, 9:1).

Compound **4a:** IR(film): ν(cm^{-1}) 3406, 3056, 3021, 2958, 2855, 1636, 1600, 1573, 1492, 1465, 1378, 1359, 1173, 1125, 769, 706; ^1H NMR: δ_H 7.35–7.08 (m, 5H), 5.81 (t, *J* = 7.2 Hz, 1H), 2.28 (s, 1H), 1.72–1.66 (m, 2H), 1.34 (s, 6H), 1.31–1.17 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{15}H_{22}O$: C, 82.6; H, 10.1. Found: C, 82.3; H, 9.9.

Compound **4b:** IR(film): ν(cm^{-1}) 3403, 3071, 2957, 2924, 1608, 1594, 1503, 1488, 1443, 1091, 1041, 834, 812; ^1H NMR: δ_H 7.20 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.78–6.68 (m, 3H), 5.93 (s, 2H), 5.89 (t, *J* = 7.2 Hz, 1H), 5.29 (s, 1H), 1.93–1.88 (m, 3H), 1.30–1.19 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{20}H_{21}O_3Cl$: C, 69.6; H, 6.1. Found: C, 69.4; H, 5.89.

Compound **4c:** IR(film): ν(cm^{-1}) 3418, 3022, 2959, 2929, 1611, 1567, 1511, 1464, 1360, 1124, 813; ^1H NMR: δ_H 7.14 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.79 (t, *J* = 7.2 Hz, 1H), 2.36 (s, 3H), 2.28 (s, 1H), 1.73–1.67 (m, 2H), 1.33 (s, 6H), 1.31–1.19 (m, 4H), 0.80 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{16}H_{24}O$: C, 82.8; H, 10.3. Found: C, 82.5; H, 10.2.

Compound **4d:** IR(film): ν(cm^{-1}) 3469, 3059, 3028, 2957, 2930, 2871, 1599, 1489, 1447, 1359, 1090, 831, 762, 701; ^1H NMR: δ_H 7.47–7.20 (m, 5H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 8.4 Hz, 2H), 5.93 (t, *J* = 7.2 Hz, 1H), 1.88 (s, 1H), 1.79–1.73 (m, 2H), 1.67 (s, 3H), 1.33–1.19 (m, 4H), 0.81 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{20}H_{23}OCl$: C, 76.2; H, 7.3. Found: C, 76.3; H, 7.3.

Compound **4e:** IR(film): ν(cm^{-1}) 3405, 3057, 3021, 2928, 2876, 1598, 1493, 1464, 1374, 1124, 815; ^1H NMR: δ_H 7.13 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 5.81 (t, *J* = 7.6 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 1H), 1.96–1.82 (m, 2H), 1.78–1.15 (m, 12H), 0.81 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{18}H_{26}O$: C, 83.7; H, 10.1. Found: C, 83.5; H, 10.2.

Compound **4f:** IR(film): ν(cm^{-1}) 3412, 3022, 2957, 2923, 1609, 1502, 1487, 1441, 1041, 932, 818; ^1H NMR: δ_H 7.26–6.71 (m, 7H), 5.93 (s, 2H), 5.81 (t, *J* = 7.2 Hz, 1H), 5.31 (s, 1H), 2.30 (s, 3H), 1.95–1.87 (m, 3H), 1.36–1.25 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.8; H, 7.4. Found: C, 77.5; H, 7.3.

Compound **4g:** IR(film): ν(cm^{-1}) 3376, 3033, 2956, 2929, 2858, 1654, 1594, 1490, 1466, 1378, 1091, 832; ^1H NMR: δ_H 7.31 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.69 (t, *J* = 7.2 Hz, 1H), 4.24 (t, *J* = 6.0 Hz, 1H), 1.91–1.85 (m, 2H), 1.63 (s, 1H), 1.47–1.17 (m, 14H), 0.90–0.81 (m, 6H); Anal. Calcd. for $C_{19}H_{29}OCl$: C, 73.8; H, 9.4. Found: C, 73.5; H, 9.15.

Compound **4h:** IR(film): ν(cm^{-1}) 3475, 3058, 3027, 2957, 2929, 2871, 1599, 1492, 1447, 1072, 761, 701; ^1H NMR: δ_H 7.48–7.17 (m, 10H), 5.89 (t, *J* = 7.2 Hz, 1H), 1.80–1.72 (m, 3H), 1.68 (s, 3H), 1.34–1.19 (m, 4H), 0.80 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{20}H_{24}O$: C, 85.7; H, 8.6. Found: C, 85.5; H, 8.4.

Compound **4i:** IR(film): ν(cm^{-1}) 3411, 3028, 2958, 2858, 1602, 1512, 1492, 1453, 1378, 1085, 822, 731, 700; ^1H NMR: δ_H 7.30–7.21 (m, 5H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 5.81 (t, *J* = 7.2 Hz, 1H), 5.40 (s, 1H), 2.29 (s, 3H), 1.96–1.90 (m, 3H), 1.35–1.20 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{20}H_{24}O$: C, 85.7; H, 8.6. Found: C, 85.45; H, 8.4.

Compound **4j:** IR(film): ν(cm^{-1}) 3419, 3061, 3029, 2957, 2928, 2871, 1600, 1493, 1455, 1057, 757, 700; ^1H NMR: δ_H 7.36–6.91 (m, 10H), 5.85 (t, *J* = 7.2 Hz, 1H), 5.43 (s, 1H), 1.97–1.88 (m, 3H), 1.35–1.21 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.45; H, 8.1.

Compound **4k:** IR(film): ν(cm^{-1}) 3401, 3059, 3029, 2956, 2925, 2855, 1600, 1493, 1454, 1378, 1067, 1010, 758, 700; ^1H NMR: δ_H 7.42–6.90 (m, 10H), 5.84 (t, *J* = 7.2 Hz, 1H), 5.42 (s, 1H), 2.05–1.85 (m, 3H), 1.36–1.19 (m, 8H), 0.84 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{21}H_{26}O$: C, 85.7; H, 8.8. Found: C, 85.5; H, 8.7.

Compound **4l:** IR(film): ν(cm^{-1}) 3400, 3056, 3021, 2926, 2857, 1599, 1493, 1456, 1378, 1072, 768, 702; ^1H NMR: δ_H 7.36–7.13 (m, 5H), 5.67 (t, *J* = 7.2 Hz, 1H), 4.27 (t, *J* = 6.0 Hz, 1H), 1.91–1.86 (m, 2H), 1.62 (s, 1H), 1.46–1.17 (m, 18H), 0.89–0.83 (m, 6H); Anal. Calcd. for $C_{21}H_{34}O$: C, 83.4; H, 11.3. Found: C, 83.2; H, 11.1.

Compound **4m:** IR(film): ν(cm^{-1}) 3399, 3056, 3022, 2926, 2855, 1599, 1493, 1465, 1378, 1359, 1173, 1124, 769, 706; ^1H NMR: δ_H 7.35–7.08 (m, 5H), 5.81 (t, *J* = 7.2 Hz, 1H), 2.25 (s, 1H), 1.71–1.65 (m, 2H), 1.34 (s, 6H), 1.28–1.15 (m, 8H), 0.84 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{17}H_{26}O$: C, 82.9; H, 10.6. Found: C, 82.6; H, 10.4.

Compound **4n:** IR(film): ν(cm^{-1}) 3403, 3058, 3022, 2929, 2875, 1599, 1498, 1463, 1376, 1126, 820; ^1H NMR: δ_H 7.35–7.11 (m, 5H), 5.84 (t, *J* = 7.6 Hz, 1H), 2.28 (s, 1H), 1.98–1.91 (m, 2H), 1.85–1.15 (m, 16H), 0.84 (t, *J* = 7.2 Hz, 3H); Anal. Calcd. for $C_{19}H_{28}O$: C, 83.8; H, 10.3. Found: C, 83.55; H, 10.1.

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