Regio- and Stereo-selectivity in CuI-Catalyzed Grignard Reactions with *tert*-Butyl (*Z*)-β-Tosyloxy α,β-Enoates

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Jalander, L., Oksanen, L. and Rosling, A., 1990. Regio- and Stereo-selectivity in CuI-Catalyzed Grignard Reactions with *tert*-Butyl (*Z*)-β-Tosyloxy α,β-Enoates. – Acta Chem. Scand. 44: 842–844.

Alkyl (*Z*)-β-tosyloxy-α,β-enoates (**1a–h**) have been converted into alkyl β-alkyl-α,β-enoates (**2a–h**) by CuI-catalyzed Grignard reactions. The vinylic addition–elimination reactions proceeded almost exclusively with retention of configuration.

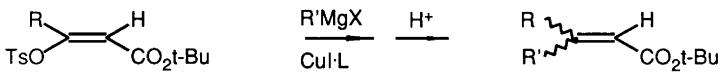
It is well known that the preparation of alkyl β,β-dialkyl substituted enoates in a stereoselective fashion is fraught with difficulties, particularly if the β-substituents are bulky secondary or tertiary alkyl groups. Most of the research done in this area deals with addition–elimination reactions of lithium dialkylcuprates,[1,2] Grignard reactions[3] or CuI- or Ni-catalyzed Grignard reactions[4,5] of alkyl enoates with different leaving groups in the β-position. The kinetics of the nucleophilic vinylic substitution reaction has been exhaustively studied and reviewed by Rappoport[6,7] and Bernasconi.[8] In nucleophilic vinylic substitution reactions, the tosyloxy group is a good nucleofuge.[6,7] In this paper we describe the syntheses of some *tert*-butyl β,β-dialkyl-enoates. We chose the toxyloxy group as the leaving group because we were interested to find out if this group is also a good leaving group in CuI-catalyzed Grignard reactions, although these reactions rarely proceed via the nucleophilic substitution mechanism. The R′ groups in the reagents were either benzyl or secondary or tertiary alkyl groups, because stereochemically pure products of this kind are useful intermediates in further synthesis.

Results and discussion

The results from the reactions according to Scheme 1 are presented in Table 1. The benzyl, secondary and tertiary Grignard reagents reacted with the *tert*-butyl enoates 1a–h, in the presence of a CuI–2,4,4-trimethyloxazoline complex, by replacement of the β-tosyloxy substituent. The reaction proceeded mainly with retention of configuration. The stereoselectivity was moderate to good, taking into account that the alkyl groups of the reagents, with the exception of the benzyl group, are rather bulky secondary and tertiary alkyl groups.

According to this method it is possible to prepare almost pure (*Z*)- and (*E*)-enoates by changing R and R′ in substrate and reagents as is the case with **2f** and **2h** as well as with **2c** and **2g**.

The CuI–2,4,4-trimethyloxazoline complex was either used *in situ* by stirring CuI (1 equiv.) with 2,4,4-trimethyloxazoline (2 equiv.) in diethyl ether together with the substrates, or by using an isolated complex prepared as described in the Experimental part. The structure of this



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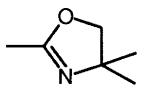
	R	R′
a	Bz	c-Pe
b	Bz	t-Bu
c	Bz	i-Pr
d	Bz	c-Hex
e	i-Pr	t-Bu
f	i-Pr	c-Hex
g	i-Pr	Bz
h	c-Hex	i-Pr

L = 

Scheme 1.

Table 1. Yields of *tert*-butyl enoates (**2a–h**) prepared according to Scheme 1.

2	Yield (%)		Total[b]
	Retention product[a]	Inversion product[a]	
a	97	3	77
b	93	7	71
c	94	6	82
d	95	5	80
e	98	2	78
f	94	6	69
g	89	11	68
h	94	6	75

[a]Relative yield. [b]Refers to isolated products of corresponding acids.

complex was not determined. The only difference seen in the ^{1}H NMR spectra of the CuI complex and neat 2,4,4-trimethyloxazoline in $CDCl_3$ was that the chemical shifts of the methylene and methyl protons of the complex were shifted to lower field by 0.25, 0.31 and 0.42 ppm, respectively.

The desired reaction products were not formed in an uncatalyzed Grignard reaction. However, the specific role of CuI in these reactions is not known. Some kind of complex between a copper or cuprate reagent and the enoate is possible since the yields of retention and inversion products are almost independent of the bulk of the reagents (Fig. 1).

Experimental

Electron ionisation mass spectra (EIMS) were determined at 70 eV on a VG-7070E spectrometer equipped with a gas chromatograph (fused silica column, DB-1, 15 m×0.5 mm I.D.). The ^{1}H NMR and 2D ^{1}H NOESY spectra were recorded in $CDCl_3$ at 400 MHz on a Jeol GX-400 spectrometer. The signal positions are reported using the δ scale with tetramethylsilane as an internal standard. The quantitative analyses were carried out on a Varian 3300 gas chromatograph equipped with an FID detector, using the same column as for the MS analyses. Grignard reagents were prepared in dry diethyl ether under an argon atmosphere. Synthetic grade magnesium turnings were used. The concentration was determined by standard titrations. The CuI–2,4,4-trimethyloxazoline complex was prepared by stirring CuI (1 equiv.) and 2,4,4-trimethyloxazoline (2 equiv.) in THF for 1 h at 20 °C. The solvent was partly evaporated and the precipitate was filtered and washed with cold diethyl ether. It was necessary to store the complex in the cold in a well sealed container. The enol tosylates were prepared according to a modified method[9] based on that reported by Fleming *et al.*[10] by treatment of the appropriate β-keto esters (1 equiv.) with *p*-toluenesulfonic anhydride (1.1 equiv.) in the presence of potassium *tert*-butoxide (1 equiv.) for 24 h in THF and *tert*-butyl alcohol.

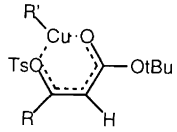


Fig. 1.

CuI–2,4,4-trimethyloxazoline-complex-catalyzed Grignard reactions. The Grignard reagents (16.0 mmol) were added drop by drop to a solution of *tert*-butyl (*Z*)-β-tosyloxy α,β-enoates (4.0 mmol) and the CuI–2,4,4-trimethyloxazoline complex (1.6 mmol) in dry diethyl ether (30 ml) at −10 °C. The reaction mixture was stirred for 4 h at −10 °C and hydrolyzed with a solution of saturated ammonium chloride and diluted ammonia. The water phase was repeatedly extracted with diethyl ether. The combined ether phases were treated with sodium carbonate solution and dried with sodium sulfate. The solvent was evaporated. The relative yields of (*Z*)- and (*E*)-reaction products were determined by GLC. The total yields of the enoates **2a–2h** were determined gravimetrically by weighing the corresponding acids after hydrolysis. The configuration of (*Z*)- and (*E*)-isomers was determined by 2D ^{1}H NOESY experiments.

tert-*Butyl (Z)-3-cyclopentyl-4-phenyl-2-butenoate* (**2a**). EIMS: [IP 70 eV; *m/z* (% rel. int.)]: 230 (96 [*M*−56]), 213 (20), 171 (18), 139 (67), 121 (28), 91 (100), 57 (80), 41 (92). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (9 H, s), 1.55, 1.76 (8 H, m), 3.42 (2 H, s), 4.32 (1 H, m), 5.31 (1 H, s), 7.15–7.30 (5 H, Ph). H-2 displays an NOE on the protons of the benzyl group.

tert-*Butyl (Z)-3-benzyl-4,4-dimethyl-2-pentenoate* (**2b**). EIMS: [IP 70 eV; *m/z* (% rel. int.)]: 218 (50 [*M*−56]), 201 (33), 185 (40), 157 (22), 127 (80), 115 (43), 91 (62), 57 (100), 41 (62). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (9 H, s), 1.49 (9 H, s) 3.46 (2 H, s), 5.29 (1 H, s), 7.20–7.35 (5 H, Ph). H-2 displays an NOE on the protons of the benzyl group.

tert-*Butyl (Z)-3-benzyl-4-methyl-2-pentenoate* (**2c**). EIMS: [IP 70 eV; *m/z* (% rel. int.)]: 204 (100), 187 (32), 171 (34), 145 (33), 113 (35), 91 (100), 57 (55), 41 (52). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (6 H, d, *J* 6.7 Hz), 1.35 (9 H, s), 3.33 (2 H, s), 3.88 (1 H, septet, *J* 6.7 Hz) 5.13 (1 H, s), 7.04–7.26 (5 H, Ph). H-2 displays an NOE on the protons of the benzyl group.

tert-*Butyl (Z)-3-cyclohexyl-4-phenyl-2-butenoate* (**2d**). EIMS: [IP 70 eV; *m/z* (% rel. int.)]: 244 (100 [*M*−56]), 227 (17), 197 (8), 153 (50), 135 (33), 91 (42), 57 (23), 41 (23). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17, 1.64, 1.80 (10 H, br m), 1.36 (9 H, s), 3.32 (2 H, s), 3.51 (1 H, br m), 5.13 (1 H, s), 7.05–7.24 (5 H, Ph). H-2 displays an NOE on the protons of the benzyl group.

tert-*Butyl (Z)-3-isopropyl-4,4-dimethyl-2-pentenoate* (**2e**). EIMS: [IP 70 eV; *m/z* (% rel. int.)]: 183 (2 [*M*−43]), 170 (8 [*M*−56]), 153 (23), 127 (100), 113 (18), 109 (23), 83 (17), 57 (76), 41 (57). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (6 H, d, *J* 6.7 Hz), 1.20 (9 H, s), 1.48 (9 H, s), 2.52 (1 H, septet, *J* 6.7 Hz), 5.54 (1 H, s). H-2 displays an NOE on the methyl protons of the isopropyl group.

tert-*Butyl (Z)-3-cyclohexyl-4-methyl-2-pentenoate* (**2f**). EIMS: [IP 70 eV; *m/z* (% rel. int.)]: 196 (53 [*M*−56]), 179 (15), 153 (100), 135 (20), 114 (15), 113 (13), 81 (10), 69 (12), 67 (15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (6 H, d, *J* 6.7 Hz), 1.21, 1.37, 1.69 (10 H, br m), 1.48 (9 H, s), 2.54 (1 H, septet *J* 6.7 Hz), 3.65 (1 H, br m), 5.54 (1 H, s). H-2 displays an NOE on the methyl protons of the isopropyl group.

tert-*Butyl (E)-3-cyclohexyl-4-methyl-2-pentenoate* (**2g**). EIMS: [IP 70 eV; *m/z* (% rel. int.)]: 196 (100) [*M*−56]), 179 (35), 153 (77), 135 (23), 114 (82), 113 (68), 67 (21). The ^{1}H NMR spectrum was taken from the corresponding acid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (6 H, d, *J* 6.7 Hz), 1.22, 1.25, 1.76 (10 H, br m), 2.15 (1 H, br m), 4.07 (1 H, septet *J* 6.7 Hz), 5.65 (1 H, s), 11.02 (1 H, s). H-2 displays an NOE on the protons of the cyclohexyl group.

tert-*Butyl (E)-3-benzyl-4-methyl-2-pentenoate* (**2h**). EIMS: [IP 70 eV; *m/z* (% rel. int.)]: 204 (100 [*M*−56]), 187 (18), 186 (28), 171 (46), 159 (22), 145 (37), 143 (32), 115 (23), 91 (58), 57 (45), 41 (38). The ^{1}H NMR spectrum was taken from the corresponding acid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (6 H, d, *J* 7.0 Hz), 2.28 (1 H, septet *J* 7.0 Hz), 4.02 (2 H, s), 5.80 (1 H, s), 7.05–7.23 (5 H, Ph), 11.04 (1 H, s). H-2 displays an NOE on the methyl protons of the isopropyl group.

2,4,4-Trimethyloxazoline. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (9 H, s), 1.80 (3 H, s), 3.81 (2 H, s).

2,4,4-Trimethyloxazoline–CuI complex. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (9 H, s), 2.22 (3, H, s), 4.06 (2 H, s).

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Received March 7, 1990.