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Stereoselective α-alkylation of carbonyl compounds using tricarbonylchromium-complexed benzyl acetates *

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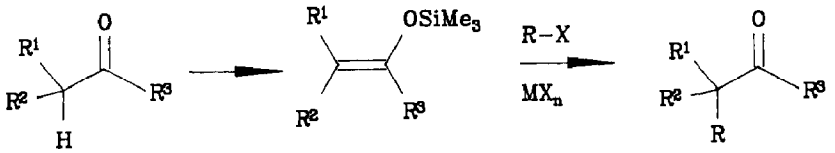
Abstract

Secondary benzyl acetates complexed by $Cr(CO)_3$ react 100% stereoselectively with enolsilanes in the presence of $ZnCl_2$ in a process which amounts to α-alkylation of carbonyl compounds.

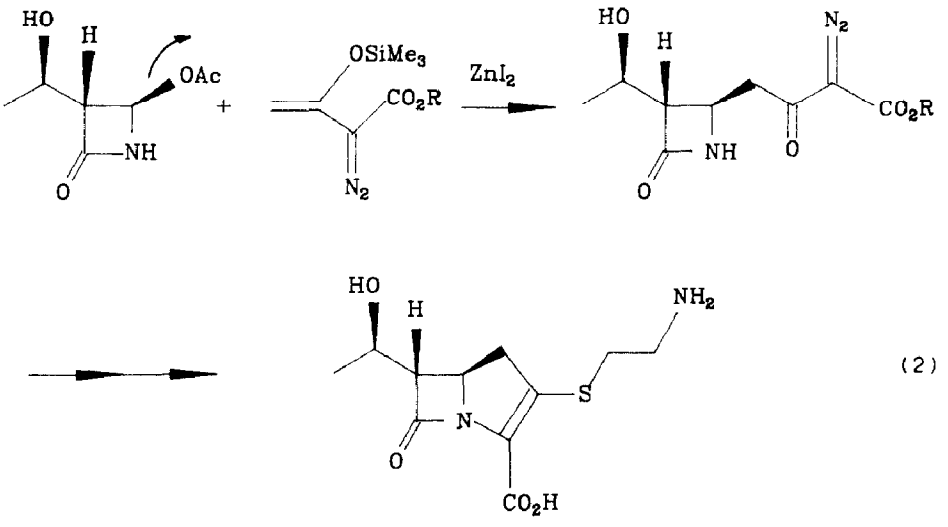
One of the important C–C bond forming reactions in organic chemistry is the α-alkylation of carbonyl compounds. Classically, this is performed by the conversion of the carbonyl compounds into the corresponding lithium enolates followed by alkylation using S_N2-active alkyl halides [1]. This methodology has limitations, since tertiary and a number of secondary alkyl halides fail to undergo S_N2-reactions, olefin-forming HX-elimination being the main reaction path. We have previously solved this long-standing problem by a simple two step sequence [2]: Formation of the enolsilane according to standard methods [3**] followed by the reaction of S_N1-active alkyl halides RX in the presence of Lewis acids MX_n [2]. The mechanism involves the Lewis acid induced formation of intermediate carbocations $R^+ {}^-MX_{n+1}$ which are then trapped by the electron rich (but not basic) enolsilanes (eq. 1).



(1)

An important advancement within this type of chemistry is the discovery that many of the alkyl halides RX can be replaced by the corresponding acetates ROAc,

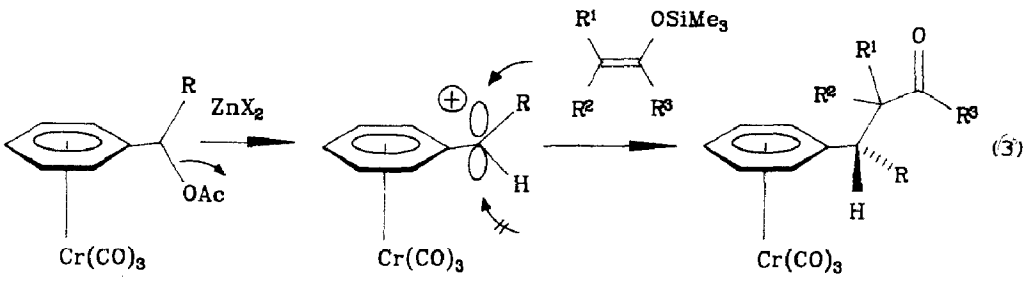
* Dedicated to Prof. Dr. Günther Wilke on the occasion of his 65th birthday.
** Reference number with asterisk indicates a note in the list of references.



(2)

especially if ZnX_2 is used as a mild Lewis acid [4]. Generally, the acetates are more readily accessible and more stable than the halides. This kind of modification has been applied by the Merck group in their synthesis of the antibiotic thienamycin [5]. The key step is the intermediate formation of a carbocation having a neighboring chiral center; addition of the enolsilane occurs stereoselectively anti to the hydroxyl-containing side chain of the β-lactam ring (eq. 2).

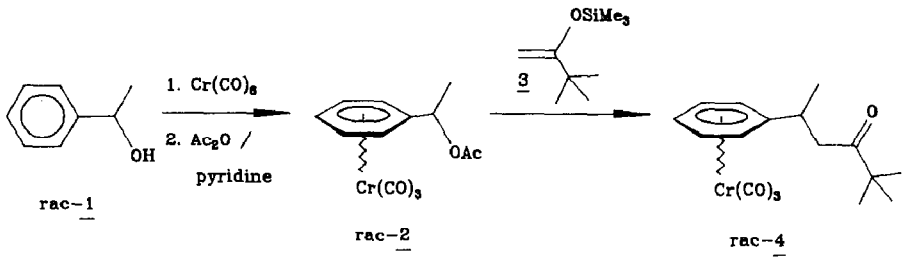
In other cases, e.g., chiral secondary benzyl acetates [1,6], the intermediate prochiral carbocations are attacked at both enantiotopic faces, leading to racemates. In order to solve this problem, we decided to complex the benzyl acetates by a transition metal, specifically by the chromium tricarbonyl moiety. This introduces planar chirality, which means that the intermediate carbocations are chiral. These are likely to be attacked stereoselectively *anti* to the metal centers. It was already known that the S_N1-solvolysis of $Cr(CO)_3$-complexed benzyl halides, alcohols and acetates in the presence of H_2O, ROH or RCN (Ritter reaction) occurs with 72–100% anti-stereoselectivity [7*]. The present paper shows that stereoselective C–C bond formation is indeed possible, the nucleophile being an enolsilane [8]. By working in the optically active series, optically active carbonyl compounds of predictable absolute configuration are therefore accessible following decomplexation.



(3)

Results and discussion

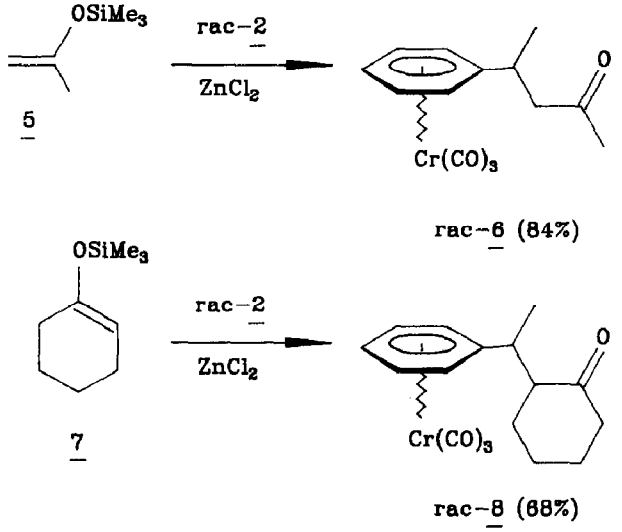
In order to learn whether the above mentioned alkylations are at all possible, model reactions using racemic **2** and the enolsilane **3** derived from pinacolone were performed (eq. 4).



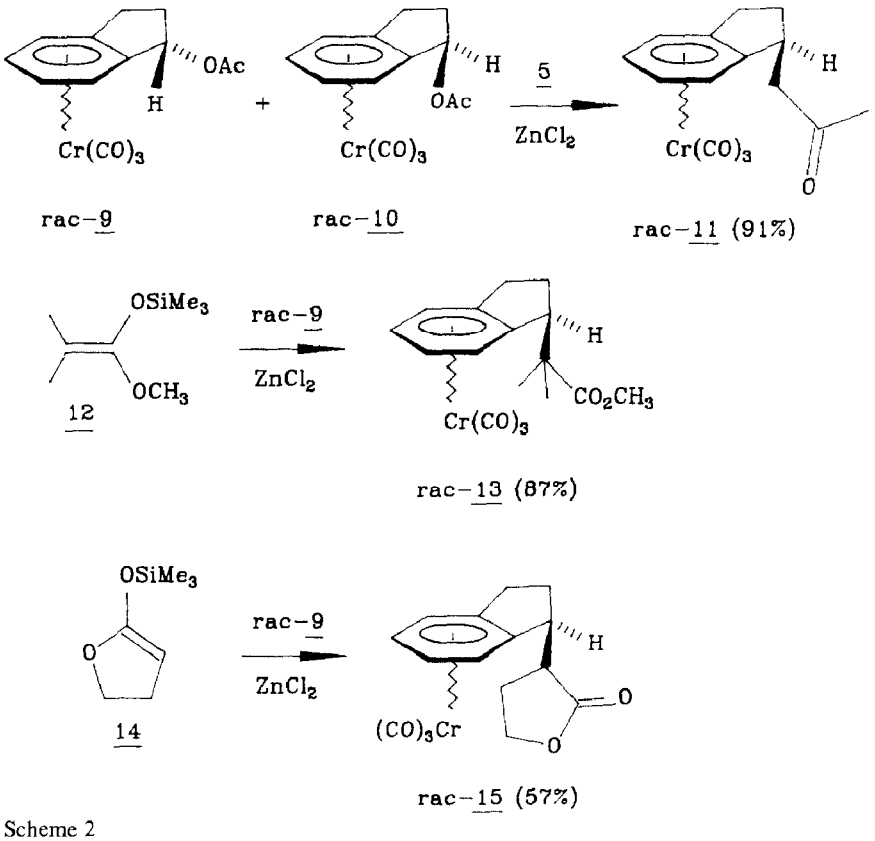
(4)

It turned out that upon employing $ZnCl_2$ as the Lewis acid at room temperature in CH_2Cl_2, an excellent yield (95% conversion; 82% isolated) of the *C*-alkylated product **4** was obtained. ZnI_2 is also active, but part of the product is devoid of the $Cr(CO)_3$ moiety. Apparently, some iodine is formed which induces oxidative decomplexation [9]. Thus, $ZnCl_2$ is the Lewis acid of choice. The reaction is general, as shown by the examples in Scheme 1.

The results show that the desired alkylation occurs very smoothly at room temperature, conversion being essentially complete. This also applies to the very sensitive enolsilane **5** which often causes problems in other Lewis acid mediated α-alkylations [10]. The yields refer to analytically pure isolated products. Secondary benzyl halides and acetates themselves are S_N1-active [2]. The presence of the $Cr(CO)_3$ group enhances S_N1-activity further [7*,8] and contributes to the effi-



Scheme 1

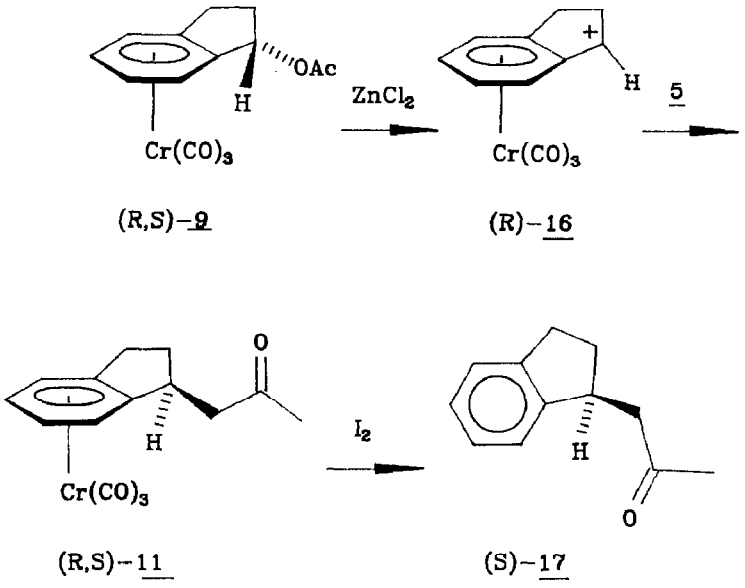


Scheme 2

ciency of alkylation. Compounds **4** and **6** are formed as single diastereomers, as shown by the ^{13}C NMR spectra (single set of lines). In the case of the prochiral enolsilane **7** derived from cyclohexanone, a mixture of racemic diastereomers **8** is obtained, in line with the reaction of non-complexed benzylic alkylating agents [1,4].

Since racemic **2** was employed, no conclusion regarding the stereochemistry of these unusual C–C-bond forming reactions was possible. Initial information became available upon treating a 40/60 diastereomeric mixture of racemic **9** and **10** [11] with the enolsilane **5** (Scheme 2). The reaction produced a single (racemic) product **11**. Thus, C–C-bond formation is stereoconvergent, and very likely proceeds via the corresponding metal-stabilized (racemic) carbocations which are attacked in an *anti* manner similar to solvolyses [7*]. The same applies to the alkylation of **12** and **14** by rac-**9**/$ZnCl_2$. In the case of **14**, the racemic lactone **15** is a 40/60 mixture of diastereomers.

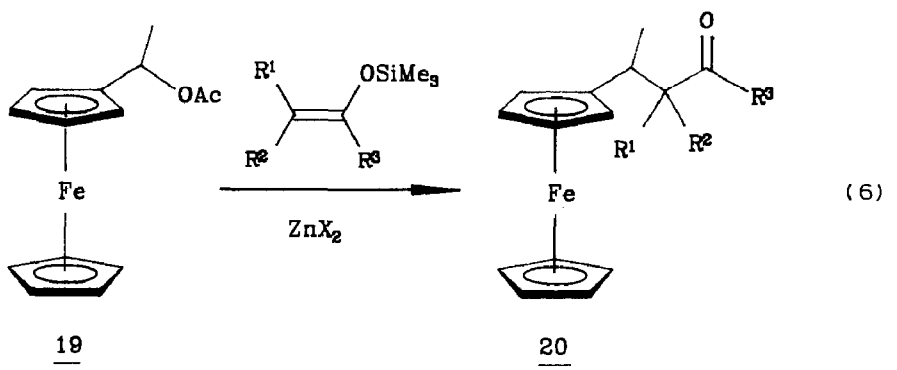
These observations led to the conclusion that optically active **9** or **10** should lead to optically active products with predictable absolute configuration. Although **9**/**10** had not been described in the literature in optically active form, the alcohol corresponding to **9** had been separated into antipodes by Jaouen [11]. We therefore used his method of antipode separation and acylated the (*R*,*S*)-stereoisomer [11] to form (*R*,*S*)-**9** ($[\alpha]_D^{22}$ −267°; *c* 1.90, $HCCl_3$; corresponding to 100% optical purity) [9]. The latter was allowed to react with **5**/$ZnCl_2$, leading to 90% of the expected optically active product **11** ($[\alpha]_D^{22}$ 55°, *c* 1.75, $HCCl_3$). The expectation that **11**



corresponds to the (*R*,*S*)-configuration was demonstrated by I_2-induced cleavage [12] to form **17**. This ketone turned out to have the *S*-configuration and to be 100% optically pure ($[\alpha]_D^{22}$ −32°; *c* 2.24, acetone) as shown by a comparison with the reported *R*-enantiomer which has the corresponding positive rotation (eq. 5) [9,13].

It is clear that the above reaction occurs with complete inversion of configuration. However, in view of the previously mentioned stereoconvergence, a classical S_N2-process is not relevant. Rather, optically active carbocations **16** having planar chirality (in this case the *R*-configuration) are involved. Although solvolyses of $Cr(CO)_3$-complexed benzylic systems are not always completely stereoselective [7*], the present "solvolytic" C–C bond formation occurs with 100% stereoselectivity.

In conclusion, we have shown that chiral chromium complexed benzylic acetates serve as vehicles for stereoselective C–C bond formation under mild Lewis acidic conditions. Any Lewis acidic carbon nucleophile is likely to react analogously. Indeed, following our initial communication [8], it was reported that the reactions of



organotitanium reagents [14] such as CH_3TiCl_3 or aluminum compounds AlR_3 occur similarly [15]. The α-alkylation of carbonyl compounds using 1-acetoxy-1-ferrocenylethane **19** is also mechanistically related (eq. 6) [16].

All of these reactions are complementary to other transition-metal templates, e.g., synthetically highly useful allylic palladium complexes [17] and cationic tricarbonyl(dienyl)iron reagents [18] which also react stereoselectively with carbon nucleophiles.

Experimental

General

All reactions were performed in dry flasks under nitrogen. The following instruments were used in the analysis of the products. IR: Perkin–Elmer 4657. ^1H NMR: Varian T60 and JEOL JNM-FX 100. ^{13}C NMR: Varian CFT20 and XL100. Elemental analyses were carried out by the Analytical Service of the Fachbereich Chemie Marburg and in the Mikroanalytische Labor Beller (Göttingen). The melting points are uncorrected.

Preparation of the $Cr(CO)_3$-complexed secondary benzyl acetates

The procedure of Jaouen [7*,11] was used to prepare the known acetates. In the case of optically active (*R,S*)-**9**, the known (*R,S*)-alcohol [11] was acylated by a standard procedure: The mixture of 0.66 g (2.4 mmol) of (*R,S*)-*cis*-1-hydroxyindanetricarbonylchromium [11] and 5.2 g (51 mmol) of acetic acid anhydride in 8 ml of dry pyridine is stirred at room temperature for 12 h. It is diluted with 10 ml of ether and washed successively with 5 ml of 2*N* HCl, twice with 5 ml of saturated $NaHCO_3$ and 3 ml of H_2O. After drying over Na_2SO_4, the solvent is removed and the residue is recrystallized from petroleum ether (40–60 °C)/ether (1/1) to afford 0.56 g (73%) of (*R,S*)-**9** having a m.p. of 124–125 °C. $[\alpha]_D^{22}$ −267° (*c* 1.90, $HCCl_3$).

General alkylation procedure

A dry 100 ml flask equipped with a nitrogen inlet is charged with anhydrous $ZnCl_2$ (0.68 g, 5 mmol), 5 mmol of an enolsilane [3] and 20 ml of dry dichloromethane. In the case of the sensitive enolsilane **5**, a 50% excess of the latter is used. A secondary $Cr(CO)_3$-complexed benzyl acetate [7*,11] (5 mmol) is added and the mixture is stirred for 6 h at room temperature. Following filtration from $ZnCl_2$, the solvent is removed and the crude product is either recrystallized or chromatographed over Al_2O_3 (basic, activity IV) using petroleum ether (40–50 °C)/ether (10/1).

*rac-2,2-Dimethyl-5-phenylhexan-3-onetricarbonylchromium (**4**).* 1.4 g (82%) of a solid purified by chromatography, m.p. 65–67 °C. Found: C, 59.80; H, 6.01. $C_{17}H_{20}CrO_4$ calcd.: C, 60.00; H, 5.92%. IR (KBr): 3100, 2970, 1955, 1860, 1695, 1455, 1420, 1380, 1370, 1350, 1305, 1050, 1000 cm^{-1}. ^1H NMR ($DCCl_3$): δ 1.1 (s, 9H), 1.3 (d, *J* 7 Hz, 3H), 2.7 (m, 2H), 3.2 (m, 1H), 5.4 (s, 5H) ppm. ^{13}C NMR ($DCCl_3$): δ 233.0, 213.2, 118.1, 93.8, 92.3, 91.9, 45.2, 44.1, 33.1, 26.0, 20.7 ppm.

*rac-4-Phenylpentan-2-onetricarbonylchromium (**6**).* 1.25 g (84%) of a solid purified by chromatography, m.p. 35–37 °C. Found: C, 56.73; H, 4.75. $C_{14}H_{14}CrO_4$ calcd.: C, 56.38; H, 4.73%. IR (film): 3095, 2970, 2940, 1960, 1870, 1715, 1460, 1420,

1360, 1165, 815 cm^{-1}. ^1H NMR (CCl_4): δ 1.2 (d, J 7 Hz, 3H), 2.0 (s, 3H), 2.5 (m, 2H), 2.9 (m,1H), 5.1 (s,5H) ppm. ^{13}C NMR ($DCCl_3$): δ 232.9, 206.0, 117.8, 93.2, 92.2, 92.1, 51.4, 33.2, 30.4, 20.9 ppm.

*rac-2-(1-Phenylethyl)cyclohexanonetricarbonylchromium (**8**).* 1.15 g (68%) of a 45/55 diastereomeric mixture of a solid purified by recrystallization (petroleum ether 40–60 °C/ether 1/2), m.p. 94–97 °C. Found: C, 60.20; H, 5.32. $C_{17}H_{18}CrO_4$ calcd.: C, 60.35; H, 5.36%. IR (KBr): 3060, 2940, 2860, 1960, 1870, 1700, 1525, 1450, 1430, 1420, 1370, 1295, 1255, 1210, 1125, 1025 cm^{-1}. ^1H NMR (CCl_4): δ 1.2 (d, J 6 Hz), 1.3 (d, J 6 Hz), 1.5–2.6 (m), 5.2 (s) ppm. ^{13}C NMR ($DCCl_3$): δ 233.1, 210.9, 210.3, 116.0, 96.4, 95.1, 92.6, 92.2, 91.9, 91.6, 57.4, 57.1, 42.3, 36.6, 36.0, 31.0, 28.3, 27.5, 27.3, 24.9, 17.5, 16.6 ppm.

*rac-trans-[1(1-Indanyl)propan-2-one]tricarbonylchromium (**11**).* 1.25 (81%) of a solid isolated by chromatography, m.p. 81–83 °C. Found: C, 58.24; H, 4.56. $C_{15}H_{14}CrO_4$ calcd.: C, 58.07; H, 4.55%. IR (KBr): 3080, 2960, 2930, 1960, 1870, 1710, 1450, 1435,1400, 1360, 1270, 1180, 1160, 1150 cm^{-1}. ^1H NMR ($DCCl_3$): δ 1.6–3.0 (m, 6H), 2.1 (s, 3H), 3.4 (m, 1H), 5.0–5.6 (m, 4H) ppm. ^{13}C NMR ($DCCl_3$): δ 233.2, 206.3, 116.4, 113.8, 92.3, 91.3, 90.8, 90.0, 48.8, 39.0, 30.3, 29.8, 29.7 ppm.

*(R,S)-trans-[1-(1-Indanyl)propan-2-one]tricarbonylchromium (**11**).* Using optically active (*R*,*S*)-**9**, obtained by acylation of the corresponding optically active alcohol [11], a 90% yield of optically active (*R*,*S*)-**11** is obtained. $[\alpha]_D^{22}$ −55°, $c = 1.75$, $HCCl_3$.

*rac-trans-[2-(1-Indanyl)-2-methylpropionic acid methyl ester]tricarbonylchromium (**13**).* 1.54 g (87%) of a solid purified by chromatography, m.p. 88–90 °C. Found: C, 57.70; H, 5.10. $C_{17}H_{18}CrO_4$ calcd.: C, 57.63; H, 5.12%. IR (KBr): 3080, 2980, 1950, 1860, 1720, 1470, 1450, 1430, 1385, 1250, 1190, 1140, 1120 cm^{-1}. ^1H NMR ($DCCl_3$): δ 1.1 (s, 6H), 1.6–2.9 (m, 4H), 3.3 (m, 1H), 3.7 (s, 3H), 4.9–5.4 (m, 4H) ppm. ^{13}C NMR ($DCCl_3$): δ 233.1, 177.0, 115.3, 113.9, 93.2, 91.1, 90.6, 89.6, 52.0, 51.3, 47.5, 31.6, 26.3, 22.7, 22.1 ppm.

*rac-trans-[3-(1-Indanyl)dihydrofuran-2-one]tricarbonylchromium (**15**).* 0.97 g (57%) of a 40/60 diastereomeric mixture of a solid purified by recrystallization from petroleum ether (40–60 °C)/ether (1/3) at −20 °C, m.p. 120–135 °C. Found: C, 56.43; H, 4.25. $C_{16}H_{14}CrO_5$ calcd.: C, 56.81; H, 4.17%. IR (KBr): 3080, 2960, 2900, 1950, 1870, 1760, 1450, 1430, 1375, 1215, 1160, 1135, 1020, 1005 cm^{-1}. ^1H NMR ($DCCl_3$): δ 1.5–3.1(m), 3.4(m), 4.1(m), 5.0–5.7(m) ppm. ^{13}C NMR ($DCCl_3$): δ 232.9, 177.0, 114.6, 114.1, 113.5, 112.9, 92.9, 91.6, 91.3, 90.9, 90.7, 89.6, 66.2, 44.5, 44.1, 43.6, 43.0, 30.6, 28.2, 27.7, 26.6, 25.4 ppm.

*(S)-1-Indanylpropanone (**17**).* A solution of 0.31 g (1 mmol) of the complex (*R*,*S*)-**11** in 10 ml of ether is treated with a solution of 0.9 g (3.5 mmol) of iodine in 20 ml of ether at room temperature. After stirring for 4 h, 100 ml of petroleum (40–60 °C) are added. The solution is washed twice with 10 ml of $Na_2S_2O_3$ and three times with 10 ml of H_2O, dried over $MgSO_4$, shaken with 20 mg of active charcoal and finally filtered. The solvent is stripped off and the crude product is chromatographed over silica gel using petroleum ether (40–60 °C) as the eluant to produce 130 mg (75%) of the desired product 17 [13] having $[\alpha]_D^{22}$ −32°; c 2.24, acetone ($[\alpha]_D^{22}$ +32° of the known *R*-enantiomer [13]). ^{13}C NMR ($DCCl_3$): δ 207.9, 146.0, 143.7, 126.6, 126.2, 124.5, 123.3, 49.3, 40.1, 32.5, 31.2, 30.3 ppm.

Acknowledgement

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References

1 H.O. House, Modern Synthetic Reactions, 2nd edit., W.A. Benjamin, Menlo Park, 1972.
2 Review: M.T. Reetz, Angew. Chem., 94 (1982) 97; Angew. Chem. Int. Ed. Engl., 21 (1982) 96.
3 For a review of the synthesis and reactions of enolsilanes see P. Brownbridge, Synthesis, 1983, 1 and 85.
4 M.T. Reetz, S. Hüttenhain and F. Hübner, Synth. Commun., 11 (1981) 217.
5 P.J. Reider and E.J.J. Grabowski, Tetrahedron Lett., 23 (1982) 2293.
6 M.T. Reetz, S. Hüttenhain, P. Walz und U. Löwe, Tetrahedron Lett., 20 (1979) 4971; I. Paterson, ibid., 20 (1979) 1519.
7 The first $Cr(CO)_3$-complexed arene was reported by Fischer in 1957; E.O. Fischer and K. Öfele, Chem. Ber., 90 (1957) 2532; synthesis and S_N1-solvolyses of $Cr(CO)_3$-complexed benzylic systems: S. Top, G. Jaouen and M.J. McGlinchey, J. Chem. Soc. Chem. Commun., (1980) 1110; G. Jaouen, ibid., (1979) 224; W.R. Jackson and C.H. McMullen, J. Chem. (1965) 1170; S.G. Davies, Organotransition Metal Chemistry, Pergamon Press, Oxford, 1982; stereoselective reactions of $Cr(CO)_3$-complexed aryl-ketones: A. Meyer and O. Hofer, J. Am. Chem. Soc., 102 (1980) 4410.
8 Preliminary communication: M.T. Reetz and M. Sauerwald, Tetrahedron Lett., 24 (1983) 2837.
9 M. Sauerwald, Dissertation, Univ. Marburg, 1983.
10 M.T. Reetz, W.F. Maier, H. Heimbach, A. Giannis and G. Anastassious, Chem. Ber., 113 (1980) 3734.
11 G. Jaouen and A. Meyer, J. Am. Chem. Soc., 97 (1975) 4667.
12 M.F. Semmelhack, H.T. Hall, R. Farina, M. Yoshifuji, G. Clark, T. Barger, K. Hiotsu and J. Clardy, J. Am. Chem. Soc., 101 (1979) 3535.
13 H.E. Smith, B.G. Padilla, J.R. Neergard and F.M. Chen, J. Am. Chem. Soc., 100 (1978) 6035; R.J. Lorentzen, Dissertation, Purdue University, 1971.
14 M.T. Reetz, Organotitanium Reagents in Organic Synthesis, Springer-Verlag, Berlin, 1986.
15 M. Uemura, K. Isobe and Y. Hayashi, Tetrahedron lett., 26 (1985) 767.
16 M.T. Reetz and M. Sauerwald, J. Organomet. Chem., 328 (1987) 155.
17 B.M. Trost, Aldrichimica Acta, 14 (1981) 43; J. Tsuji and I. Minami, Acc. Chem. Res., 20 (1987) 140.
18 A.J. Pearson, Acc. Chem. Res., 13 (1980) 463.