Addition of Crotyltitanocenes to Aldehydes: Influence of Cyclopentadienyl Substituents on the Diastereoselective Formation of Homoallylic Alcohols

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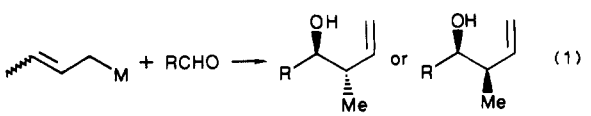
The addition of (η^3-crotyl)titanocenes (**2**, R = H, Me, *i*-Pr) to primary, secondary, and tertiary aldehydes has been investigated. The products of this reaction, homoallylic alcohols, are formed with good to excellent selectivity favoring the anti diastereomer in all cases. The degree of diastereoselectivity correlates with the size of the substituent on the cyclopentadienyl ring and that on the aldehyde. For aliphatic and aromatic aldehydes an increase in diastereoselectivity with increasing steric hindrance at the metal center was observed. The results are consistent with a chairlike transition state for product formation involving slippage of the η^3-allyl ligand of the allyltitanocene to η^1 with retention of allyl geometry.

Introduction

The addition of crotylmetal species to aldehydes provides a versatile route to synthons for 1,3-dioxygenated compounds with defined stereochemistry. The products of this reaction (eq 1) are homoallylic alcohols which can be further transformed into a variety of compounds important in the synthesis of polypropionate-based natural products.[1]



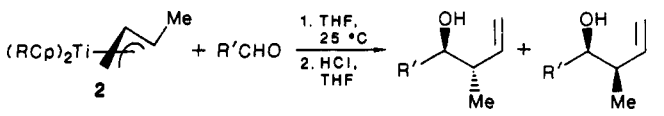
(1)

In 1981, Sato and co-workers discovered that (η^3-allyl)titanocenes (**2**, R = H), prepared from titanocene dichloride (**1**) added efficiently to aldehydes under mild conditions to furnish anti homoallylic alcohols **3** with high regio- and diastereoselectivity (eq 2).[2] Subsequent studies with heteroatom-substituted or cyclic allyltitanocenes of unknown structure suggested that the origin of the diastereoselectivity observed in these condensations resulted from concerted bond formation through a cyclic transition state.[3] As part of a program directed toward the use of these and related reagents for asymmetric synthesis, we have examined the effect of increasing the size of the substituents on the cyclopentadienyl (Cp) rings on the yield and diastereoselectivity of these addition reactions.

Results and Discussion

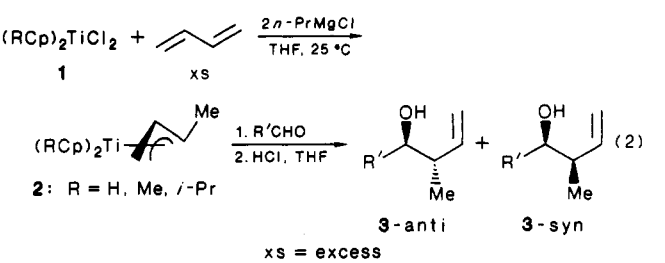
The precursor titanocene dichlorides (**1**, R = Me, *i*-Pr) were prepared by using standard methods from the corresponding lithium cyclopentadienides and $TiCl_4 \cdot 2THF$ in THF solution.[4] The method employed for the preparation of compounds **2** involved using 2 equiv of *n*-PrMgCl and excess 1,3-butadiene at room temperature (eq 2).[5a] An alternative method[5b] employing 2 equiv of crotylmagnesium chloride was also successful for the preparation of compounds **2**, but the diastereoselectivities observed were variable,[6] and as a result, this latter method was not used.

Table I. Addition of Crotyltitanocenes to Aldehydes



			R		
entry	R'	product[a]	H ratio[b] (yield)[c]	Me ratio (yield)	*i*-Pr ratio (yield)
1	$PhCH_2$	**3a**	9:1[d] (86)	16:1[d] (89)	20:1[d] (84)
2	*c*-C_6H_{11}	**3b**	13:1 (92)	18:1 (95)	26:1 (93)
3	*t*-Bu	**3c**	24:1 (94,[e] 83)	37:1 (90[e])	50:1 (92[e])
4	Ph	**3d**	27:1 (90)	42:1 (87)	52:1 (89)
5	mesityl	**3e**	6:1 (85)	10:1 (83)	12:1 (86)

[a] Number refers to the major anti diastereomer—see Experimental Section. [b] Ratios of anti:syn determined by ^1H NMR integration of the mixture after flash chromatography unless otherwise noted. [c] Isolated combined yields of both diastereomers (otherwise homogeneous by TLC) unless otherwise noted. [d] Ratios determined by HPLC (C_{18}, 5 μm, 70:30 MeOH/H_2O). [e] GC yield using *n*-decane as an internal standard.



(2)

(1) For discussions of this reaction and the role of the metal see: (a) Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. b) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. c) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. d) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, *292*, 311. (e) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *Ibid.* **1985**, *285*, 31.

(2) (a) Sato, F.; Iijima, S.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 243. b) Sato, F.; Suzuki, Y.; Sato, M. *Ibid.* **1982**, *23*, 4589. See also: (c) Klei, B.; Teuben, J. H.; De Liefde Meijer, H. J. *J. Chem. Soc., Chem. Commun.* **1981**, 342. (d) Klei, E.; Teuben, J. H.; De Liefde Meijer, H. J.; Kwak, E. J.; Bruins, A. P. *J. Organomet. Chem.* **1982**, *224*, 327.

(3) (a) Sato, F.; Uchiyama, H.; Iida, K.; Kobayshi, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1983**, 921. (b) Kobayshi, Y.; Umeyama, K.; Sato, F. *Ibid.* **1984**, 621.

(4) Sullivan, N. F.; Little, W. F. *J. Organomet. Chem.* **1967**, *8*, 277.

(5) (a) Martin, H. A.; Jellinek, F. *J. Organomet. Chem.* **1967**, *8*, 115. (b) Martin, H. A.; Jellinek, F. *Ibid.* **1966**, *6*, 293.

(6) This is likely due to incomplete consumption of crotylmagnesium chloride prior to addition of the aldehyde. This reagent adds with moderate syn selectivity to some of the aldehydes studied.

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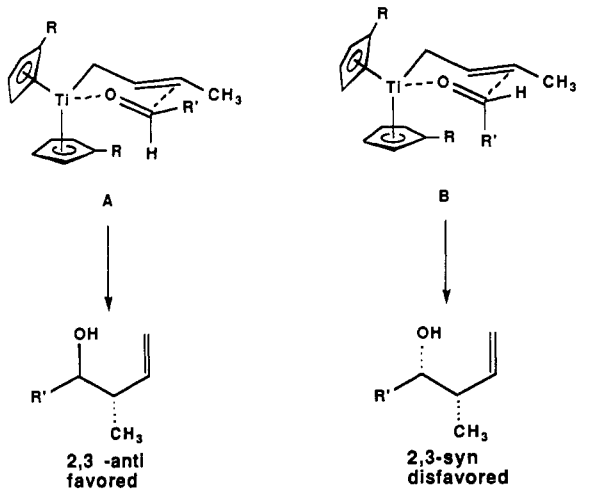
Scheme I



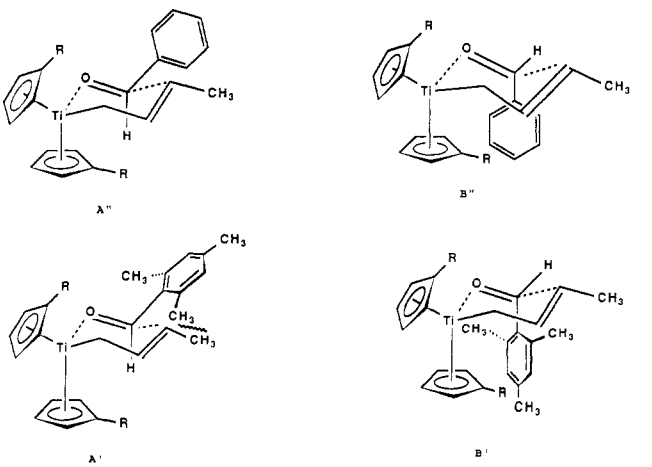
The yields and diastereomeric ratios of a series of homoallylic alcohols obtained from the reactions of compounds **2** with a series of aliphatic and aromatic aldehydes are summarized in Table I. Ratios of the two diastereomers were determined from the ^{1}H NMR spectrum (250 MHz, see Experimental Section) of the purified homoallylic alcohols—initially they were determined by using the crude product mixture but were found not to differ significantly after passage through a short silica gel column. In each case the titanocene dichloride that is regenerated during workup (HCl(aq), THF) can be recovered in excellent yield (80–90%) by precipitation from hexane–THF.

One feature is immediately evident—the yield of the homoallylic alcohols is unaffected by increasing the size of the substituent on the Cp ring. Although a 20% excess of the titanocene dichloride was employed for the experiments summarized in Table I, additional experiments using equimolar amounts established that rate of reaction of the crotyltitanocene with a given aldehyde, as qualitatively determined by quenching aliquots at various times and GC analysis using an internal standard, was not significantly affected by increased steric hindrance at the metal center.[7] This is in sharp contrast to a related condensations involving $(RCp)_2Ti^{IV}$ or $(RCp)_2Zr^{IV}$ enolates[8] where a substantial decrease in yields was observed.[9]

Several other trends are also evident. With all the aldehydes examined, increasing the size of the substituent on the Cp rings led to increased selectivity for the formation of the anti diastereomer. With aliphatic aldehydes increasing steric hindrance at the α-carbon (entries 1–3) led also to increased anti stereoselectivity. Somewhat surprisingly, mesitylenecarboxaldehyde (entry 5) reacted less selectively than did benzaldehyde and indeed gave lower ratios than the least sterically encumbered aldehyde studied.

The results obtained in this study are, for the most part, consistent with the transition-state model proposed for these reactions (Scheme I). In particular, a pseudo-1,3-diaxial interaction between the substituent R′ on the aldehyde and one of the Cp rings is expected to destabilize transition state B, leading to the formation of syn homoallylic alcohol, relative to A where such interactions involve the aldehyde proton and the Cp ring. As the size of the substituent on the aldehyde is increased, this interaction in transition state B will become more severe. The same argument would apply to reaction of a given aldehyde with a series of crotyltitanocenes where the effective size of the Cp substituent is increased.[10] Purely steric arguments cannot, however, account for the fact that benzaldehyde apparently reacts as selectively as the more hindered pivaldehyde (entries 3 and 4) and that mesitaldehyde (entry 5) reacts with the lowest selectivity but is the most sterically hindered aromatic substrate.

Scheme II

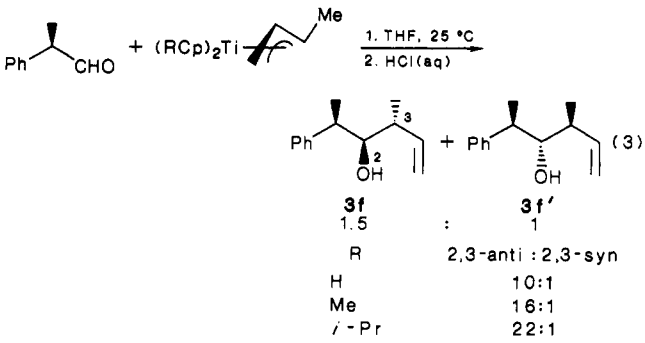


One explanation for the dramatic difference in selectivity observed between benzaldehyde and mesitaldehyde is based on the difference between their ground-state conformations.[11] If the transition state for this reaction is reactant-like, which seems reasonable for a process that is likely to be exothermic, then one can expect that the conformational preferences of the isolated aldehydes will be little perturbed in the transition state. If this is the case, then in the transition states corresponding to A and B involving mesitaldehyde, (Scheme II, A′ and B′), the phenyl ring will be twisted out of conjugation with the carbonyl group whereas in the case of benzaldehyde (A″ and B″) the phenyl group will be coplanar with the keto moiety. With mesitaldehyde, a significant 1,2-diequatorial interaction between the ortho methyl and the methyl group of the η^1-crotyl ligand exists in transition state A′ (and to a lesser extent in B′) and the 1,3-diaxial interaction in state B′ involves the face of the aromatic ring and the Cp ligand. This situation is reversed in the case of benzaldehyde—the 1,2-diequatorial interaction involves the face of the aromatic ring and the crotyl methyl in A″ and the 1,3-diaxial interaction in B″ occurs between the edge of the aromatic ring and the Cp ligand. Since the π-system is more polarizable than the σ-framework of the aromatic ring, one would expect that steric interactions involving the latter would be more severe at a given distance than those of the former. Thus A′ and B′ are probably more comparable in energy than are A″ and B″, and the diastereoselection drops accordingly. Perhaps the most surprising feature is that mesitaldehyde reacts so regioselectively with the crotyltitanocene reagents. For example, reaction of mesitaldehyde with crotylmagnesium chloride provides only traces of the γ-regioisomer, the major product of a complex mixture being the α-adduct.[9]

(7) Ward, D. G.; Collins, S., unpublished results.
(8) a) Murphy, P. J.; Procter, G.; Russell, A. T. *Tetrahedron Lett.* **1987**, *28*, 2037. (b) Evans, D. A.; McGee, L. R. *Ibid.* **1981**, *21*, 3975.
(9) Collins, S. unpublished results.
(10) Obviously, other conformations of the cyclopentadienyl ring are possible where the substituent is not directed toward the region of space where bond formation occurs. However, on a conformationally averaged basis one would expect that the Cp ring is effectively increased in size by the introduction of an alkyl substituent.
(11) The barrier to rotation about the C(aryl)–CHO bond in mesitaldehyde has been estimated at less than 20 kJ·mol^{-1}—Andersson, S.; Carter, R. E.; Drakenburg, T. *Acta Chem. Scand., Ser. B* **1984**, *B38*, 579.

We are currently investigating whether allyltitanocenes and related reagents are useful for the functionalization of other sterically hindered systems.

We have also investigated the reactions of (η^3-crotyl)-titanccenes with a chiral aldehyde—*rac*-α-phenylpropionaldehyde (eq 3). As shown in the equation, the



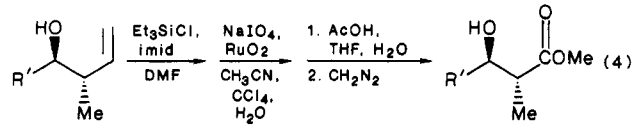
3f	:	3f′
1.5	:	1

R	2,3-anti : 2,3-syn
H	10:1
Me	16:1
i-Pr	22:1

ratio of anti to syn homoallylic alcohols (as determined by GC analyses of mixtures of the corresponding acetates) improves with increasing steric hindrance at the metal center as observed previously. However, for the anti diastereomers **3f** and **3f′** the Cram:anti-Cram selectivity is essentially invariant and only slightly favors the Cram product [Cram (**3f**):anti-Cram (**3f′**) = ca. 1.5:1]. This invariance with steric hindrance at the metal center is not entirely unexpected since in the chairlike transition state that leads to anti product the aldehyde substituent is directed away from the metal center and the interaction of this substituent is chiefly with the methyl group on the crotyl ligand. This interaction should be largely unaffected by increasing steric hindrance at the metal center if the distance between these two substituents is more or less constant. Unfortunately, we were unable to determine whether the ratio of syn-Cram to syn-anti-Cram products was also unaffected by increasing steric hindrance at the metal center—we could not detect the fourth diastereomer (presumed to be syn-anti-Cram) in the reaction mixtures by either ^{1}H NMR of GC.

The Cram:anti-Cram selectivity observed in the additions of crotyltitanocenes to α-phenylpropionaldehyde is unusually low compared with other commonly employed allylmetal reagents.[1e] Of those reagents that are selective for formation of anti homoallylic alcohols, a typical value for the Cram:anti-Cram selectivity is 3:1.[12] The reasons for the diminished selectivity observed in the present case are not obvious.

Proof of Stereochemistry. Although the anti homoallylic alcohols **3a** to **3d**, **3f**, and **3f′** are all known compounds, we were unable to compare spectral data of our samples with data from the literature since in some cases spectral data were not reported. The corresponding β-hydroxycarboxylic acid methyl esters have been previously reported and extensive spectral data or literature precedent was available for comparison and correlation.[13] Compounds **3a–d**, **3f**, and **3f′** were all converted to the corresponding β-hydroxycarboxylic acids methyl esters **4a–d**, **4f**, and **4f′** through the following sequence of operations (eq 4): triethylsilylation (chlorotriethylsilane, 1.2 equiv; imidazole (imid), 2.5 equiv; DMF), oxidative cleavage of the double bond ($NaIO_4$, 4.5 equiv; RuO_2, 0.05 equiv;



3a–d, 3f, 3f′ **4a–d, 4f, 4f′**

$CCl_4/CH_3CN/H_2O$, 2:2:3), desilylation ($AcOH/THF/H_2O$, 8:8:1), and methylation (CH_2N_2, ether) (see Experimental Section). The ^{1}H NMR spectra of these compounds agreed with those reported in the literature. The *anti*-β-hydroxycarboxylic acid ester **4a** derived from **3a** apparently has not been previously characterized; a small amount of the known syn diastereomer was present in the ^{1}H NMR spectrum of compound **4a**, and comparison of vicinal coupling constants between the α-CH and the β-CH allowed assignment of relative stereochemistry (see Experimental Section). The stereochemistry of compound **3e** has been tentatively assigned as anti; the ^{1}H NMR spectral characteristics of both the major and minor diastereomers correspond closely to those of the anti and syn diastereomers of alcohol **3d**.

Conclusions

The results of this preliminary study indicate that the efficiency of the addition of allyltitanocenes to aldehydes is not adversely affected by increasing steric hindrance at the metal center. In most cases, increasing steric hindrance favorable affects the diastereoselectivity of the addition process. The stereochemical trends that are observed are consistent with a cyclic chairlike transition state. Finally, the titanocene dichloride reagents used to prepare the allyltitanocene in situ are readily recovered and can be recycled. It would seem likely based on these results that reusable, effective chiral allyltitanocene reagents might be rationally developed.[14] Indeed, we have completed preliminary studies in this latter area and will report on these results in due course.

Experimental Section

General Data. All solvents and reagents were obtained from commercial sources, purified, and dried as required. Tetrahydrofuran was dried and distilled from potassium benzophenone ketyl. *n*-Propylmagnesium chloride was purchase from Aldrich Chemical Co. and titrated before use. 1,3-Butadiene was purchased from Matheson Gas Ltd., deoxygenated, and dried by passage through (1) a column of MnO[15] and (2) 4-Å molecular sieves (J. T. Baker Ltd.). Titanium tetrachloride bis(tetrahydrofuran) was prepared by a literature method[16] as were the titanocene dichlorides **1** (R = methyl and isopropyl).[4] Bis(cyclopentadienyl)titanium dichloride was purchased from Aldrich Chemical Co. ^{1}H NMR spectra were obtained on a Bruker AM-250 spectrometer, and all spectra were run in $CDCl_3$ solution using tetramethylsilane as an internal reference. IR spectra were recorded on a Perkin-Elmer 983 spectrometer as thin films. Mass spectra were recorded at low resolution on VG-7077F instrument at the University of Guelph. Elemental analyses were obtained by Guelph Chemical Laboratories Ltd. GC analyses were performed by using a 30-m Durabond fused silica capillary column (5% phenylsilicone, J+W Scientific Ltd.) installed on a Varian Vista 6500 gas chromatograph equipped with a Vista 401 electronic integrator. HPLC analyses were performed on a Varian 5000

(12) (a) Tri-*n*-butylcrotylstannane, 10 kbar—2.3:1: see ref 1c. (b) Crotylzirconocenes—2.7:1: Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1981**, 2985. c) Crotylchromium compounds—2.6:1: Buse, C. T.; Heathcock, C. H. *Ibid.* **1978**, 1685.

(13) For an extensive review see: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Part B, pp 115–118.

(14) For earlier work using chiral titanocene reagents or catalysts see: (a) Sato, F.; Iijima, S.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1981**, 180. (b) Reetz, M. T.; Kyung, S.-H.; Westermann, J. *Organometallics* **1984**, *3*, 1716. (c) Pacquette, L. A.; McKinney, J. A.; McLaughlin, M. L. *Tetrahedron Lett.* **1986**, *27*, 5599.

(15) Jeske, G.; Lauke, H.; Mauermann, H.; Swepston, P. N.; Schumann, H.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 8091 and references therein.

(16) Manzer, L. *Inorg. Synth.* **1982**, *21*, 135.

liquid chromatograph equipped with a 30 cm by 4 mm Varian MicroPak MCH-5 column and UV detector. Relative peak areas were determined by weighing the chromatogram trace after enlarging on a photocopier.

Preparation of Homoallylic Alcohols 3. General Procedure. A suspension of the titanocene dichloride (1.2 mmol) in THF (10 mL) under argon in a dry, two-necked, pear-shaped flask equipped with a stopcock, septum inlet, and a magnetic stir bar was purged with dry, deoxygenated 1,3-butadiene introduced through a syringe needle until the solution was saturated (ca. 15 s). *n*-Propylmagnesium chloride (1.3 mL of 2.0 M solution in Et_2O, 2.6 mmol) was added dropwise to the stirred suspension over 1–2 min. The mixture turned deep purple with vigorous gas evolution and became homogeneous during the addition. The solution was briefly heated with a hot-air gun until gas evolution ceased and then was cooled and allowed to stir at room temperature for 30–60 min. The aldehyde (1.0 mmol) was then added neat, dropwise via syringe. The solution turned green-brown almost immediately but was further stirred at room temperature for 1 h. The solution was treated dropwise with 2.0 mL of a 2 M solution of concentrated HCl in THF. The solution turned deep red and a precipitate separated. Air was passed briefly through the suspension and the mixture poured into ca. 20 mL of hexanes, washing with small portions of Et_2O. Anhydrous $MgSO_4$ was added and the mixture swirled briefly. The mixture was filtered through a frit, washing with Et_2O, and the filtrate concentrated in vacuo to provide the crude homoallylic alcohol that was further purified by flash chromatography on a short, silica gel column eluting with hexanes/ethyl acetate (11:1). The filter cake was washed with dichloromethane until the filtrate was colorless and the filtrate concentrated in vacuo to provide recovered titanocene dichloride, homogeneous by ^1H NMR. Material from several runs was usually accumulated and then crystallized from toluene prior to reuse.

***threo*-3-Methyl-1-phenylpent-4-en-2-ol (3a).**[17] The crude mixture of homoallylic alcohols could be analyzed by HPLC to determine the ratios shown in Table I (mobile phase 70:30 methanol/water, flow rate 0.5 mL/min, t_R = 9.5 min for compound **3a**, t_R = 10.9 min for the syn diastereomer). Compound **3a**: ^1H NMR (250 MHz) δ 7.27–7.12 (m, 5 H), 5.86–5.72 (ddd, J = 16.8, 10.8, 8.0 Hz, 1 H), 5.19–5.02 (m, 2 H), 3.61 (m, 1 H), 2.85–2.75 (dd, J = 13.7, 3.9 Hz, 1 H), 2.60–2.51 (dd, J = 13.7, 9.0 Hz, 1 H), 2.31–2.17 (pseudosextet, 1 H), 1.15 (br s, 1 H, D_2O exchangeable), 1.04 (d, J = 6.9 Hz, 3 H).

***threo*-1-Cyclohexyl-2-methylbut-3-en-1-ol (3b):**[17b,18] ^1H NMR (250 MHz) δ 5.79–5.64 (ddd, J = 16.4, 11.0, 8.3 Hz, 1 H), 5.06–4.99 (m, 2 H), 3.03 (pseudo t, J = 6 Hz, 1 H), 2.31 (pseudosextet, J = 6 Hz, 1 H), 1.77–1.01 (m, 12 H), 0.96 (d, J = 6.8 Hz, 3 H). The ratio of compound **3b** to the minor, syn diastereomer could be determined by integration of the signals at 3.03 (**3a**) and 3.15 (syn diastereomer) ppm.

***threo*-2,2,4-Trimethylhex-5-en-3-ol (3c):**[19] ^1H NMR (250 MHz) δ 5.96–5.81 (ddd, J = 15.1, 11.1, 8.4 Hz, 1 H), 5.00–4.94 (m, 2 H), 3.06 (br d, J = 1.8 Hz, 1 H), 2.55–2.42 (pseudoquintet of d, J = 8.4, 7.1, 1.8 Hz, 1 H), 1.64 (br s, 1 H, D_2O exchangeable), 1.04 (d, J = 7.1 Hz, 3 H), 0.86 (s, 9 H). The ratio of compound **3c** to the minor, syn diastereomer could be determined by integration of the signals at 1.04 (**3c**) and 0.93 (syn diastereomer) ppm.

***threo*-2-Methyl-1-phenylbut-3-en-1-ol (3d):**[20] ^1H NMR (250 MHz) δ 7.37–7.23 (m, 5 H), 5.88–5.74 (ddd, J = 17.2, 10.2, 8.1 Hz, 1 H), 5.23–5.15 (m, 2 H), 4.37–4.33 (dd, J = 7.8, 2.0 Hz, 1 H), 2.52–2.41 (pseudosextet, J = 7 Hz, 1 H), 2.19 (d, J = 2.0 Hz, 1 H, D_2O exchangeable), 0.87 (d, J = 6.8 Hz, 3 H). The ratio of compound **3d** to the minor, syn diastereomer could be determined by integration of the signals at 0.87 (**3d**) and 1.05 (syn diastereomer) ppm.

***threo*-1-(2,4,6-Trimethylphenyl)-2-methylbut-3-en-1-ol (3e):** bp (bulb to bulb) 70 °C (0.1 mmHg); ^1H NMR (250 MHz) δ 6.87 (s, 2 H), 6.01–5.87 (ddd, J = 17.2, 10.1, 8.3 Hz, 1 H), 5.33–5.23 (m, 2 H), 4.84 (d, J = 10.0 Hz, 1 H), 3.01–2.87 (pseudosextet, 1 H), 2.47 (s, 6 H), 2.31 (s, 3 H) 2.13 (br s, 1 H, D_2O exchangeable), 0.86 (d, J = 6.9 Hz, 3 H); IR (cm^{-1}) 3453, 3077, 2967, 1661, 1609, 1456, 1035, 998, 911, 849, 791, 742, 676. MS (EI, 70 eV), m/z 204 (M^+, weak). Anal. Calculated for $C_{14}H_{20}O$: C, 82.30; H, 9.86. Found: C, 82.29; H, 10.02. The ratio of compound **3e** to the minor, syn diastereomer could be determined by integration of the signals at 0.86 (**3e**) and 1.25! (syn diastereomer) ppm.

***rac*-[2*R*,3*R*,4*R*]- and *rac*-[2*R*,3*S*,4*S*]-4-Methyl-2-phenylhex-5-en-3-ol (3f and 3f').**[1c] Following the general procedure outlined above using 358.6 mg (1.20 mmol) of titanocene dichloride **1** (R = H), and 134.2 mg (1.0 mmol) of α-methylphenylacetaldehyde, the crude mixture of homoallylic alcohols was purified by flash chromatography on 20 g of silica gel to give compound **3f'** (71.1 mg, 37%: R_f 0.51; hexanes/ethyl acetate (9:1)) and **3f** (107.5 mg, 56%: R_f 0.40; hexanes/ethyl acetate (9:1)). Compound **3f** was contaminated with a small amount of a third diastereomer assigned to be syn-Cram. Compound **3f**: ^1H NMR (250 MHz) δ 7.27–7.14 (m, 5 H), 5.82–5.69 (ddd, J = 17.2, 10.4, 7.9 Hz, 1 H), 5.06 (dd, J = 10.4, 1.3 Hz, 1 H), 4.97 (dd, J = 17.2, 1.3 Hz, 1 H), 3.46–3.39 (pseudo q, 1 H), 2.84–2.75 (pseudoquintet, 1 H), 2.17–2.09 (pseudosextet, 1 H), 1.44 (d, J = 5.3 Hz, 1 H, D_2O exchangeable), 1.25 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 6.9 Hz, 3 H). Compound **3f'**: ^1H NMR (250 MHz) δ 7.28–7.12 (m, 5 H), 5.87–5.73 (ddd, J = 8.7, 10.4, 17.1 Hz, 1 H), 5.06–4.96 (m, 2 H), 3.46–3.40 (m, 1 H), 2.77–2.71 (pseudoquintet, J = 7 Hz, 1 H), 2.30–2.22 (pseudosextet, 1 H), 1.30 (d, J = 3.3 Hz, 1 H, D_2O exchangeable), 1.20 (d, J = 7.0 Hz, 3 H), 1.05 (d, J = 6.8 Hz, 3 H). In separate experiments the crude mixture of alcohols was directly acetylated (acetic anhydride, 2.0 mmoL; 4-(dimethylamino)pyridine, 2.0 mmoL; dichloromethane, 10 mL; 25 °C; 3 h). The solution was washed with 1.0 N HCl, aqueous Na_2CO_3, water, and then brine and then dried over Na_2CO_3. The mixture of diastereomeric acetates was directly analyzed by capillary GC (70 °C, 2.0 min to 200 °C at 10 °C/min, 10 min at 200 °C) to determine the ratios summarized in eq 4. (acetate of **3f'**, t_R = 12.5 min; acetate of **3f**, t_R = 12.7 min; acetate of syn-Cram diastereomer, t_R = 12.9 min).

Preparation of Compounds 4a–d and 4f and 4f'. The same general procedure was adopted throughout the exemplified for compound **3f**: compound **3f** (156 mg, 1.0 mmol) and imidazole (360 mg, 2.5 mmol) were dissolved in 2.0 mL of dry DMF under argon. Chlorotriethylsilane (200 μL, 1.2 mmol) was added via syringe. The mixture was stirred for 12 h at 25 °C, diluted with pentane (15 mL), washed quickly with ice-cold water (10 mL) and saturated $NaHCO_3$ (5 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to give the crude silyl ether which was used in the next step without purification. The silyl ether, dissolved in 4 mL of CCl_4/CH_3CN (1:1), was treated sequentially with an aqueous solution of $NaIO_4$ (4.5 mmol dissolved in 3 mL of water) and $RuO_2 \cdot xH_2O$ (10 mg, Ru content 57%) and the resulting mixture vigourously stirred for 3–4 h at room temperature. The mixture was diluted with dichloromethane, washed with brine, and dried over $NaSO_4$. The solvents were removed in vacuo and the residue dissolved in ether. The ether was filtered through Celite and the filtrate concentrated in vacuo to provide the crude β-(triethylsiloxy)carboxylic acid. The acid was dissolved in a minimal volume (ca. 2 mL) of $CH_3COOH/THF/H_2O$ (8:8:1) and stirred for several hours at room temperature. The solution was diluted with ether, washed with brine, and dried over Na_2SO_4 and the solvents removed in vacuo to provide crude β-hydroxycarboxylic acid. The methyl ester **4f** was prepared by using excess diazomethane in ether and was purified by chromatography on silica gel eluting with hexanes/ethyl acetate (4:1).

The ^1H NMR spectra of compounds **4a–d** and **4f** and **4f'** summarized below were all recorded in $CDCl_3$ containing formic acid (ca. 10%) to eliminate coupling of the OH proton to that of the carbinol proton.

Methyl *threo*-3-Hydroxy-2-methyl-4-phenylbutanoate (4a). This compound was obtained as an oil: ^1H NMR (250 MHz) δ 7.36–7.18 (m, 5 H), 3.92 (m, 1 H), 3.72 (s, 3 H), 2.90 (dd, J = 13.8, 4.8 Hz, 1 H), 2.75 (dd, J = 13.8, 8.0 Hz), 2.61 (pseudoquintet, 1 H), 1.27 (d, J = 7.2 Hz, 3 H). Separate signals for the minor syn diastereomer were observed at δ 4.17 (m, 1 H) and 3.70 (s, 3 H). Irradiation at 1.27 ppm caused collapse of the quintet at 2.61 ppm

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to a doublet (J = 6.1 Hz). In addition, a signal at 2.57 ppm was observed for the syn diastereomer (J = 3.9 Hz). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.43; H, 7.82.

Methyl *threo*-3-hydroxy-2-methyl-4-cyclohexylbutanoate (4b):[21] ^{1}H NMR (250 MHz) δ 3.70 (s, 3 H) 3.44 (pseudotriplet, J = 6 Hz, 1 H), 2.72 (pseudoquintet, J = 7 Hz, 1 H), 1.9–1.5 (m, 6 H), 1.5–1.0 (d at 1.21 ppm (J = 7.1 Hz) superimposed on multiplet, total 8 H). Irradiation of the doublet at 1.21 ppm caused collapse of the signal at 2.72 ppm to a doublet (J = 5.9 Hz).

Methyl *threo*-3-hydroxy-2,4,4-trimethylpentanoate (4c):[22] ^{1}H NMR (250 MHz) δ 3.70 (s, 3 H), 3.24 (d, J = 2.0 Hz, 1 H), 2.77 (qd, J = 7.2, 2.0 Hz, 1 H), 1.35 (d, J = 7.2 Hz, 3 H), 0.89 (s, 9 H).

Methyl *threo*-3-hydroxy-2-methyl-3-phenylpropanoate (4d):[23] ^{1}H NMR (250 MHz) δ 7.36–7.26 (m, 5 H), 4.77 (d, J = 8.6 Hz, 1 H), 3.74 (s, 3 H), 2.84 (pseudoquintet, 1 H), 1.02 (d, J = 7.1 Hz, 3 H).

(±)-Methyl [2*R*,3*R*,4*S*]-3-hydroxy-2-methyl-4-phenylpentanoate (4f):[24] ^{1}H NMR (250 MHz) 7.39–7.03 (m, 5 H), 3.65–3.53 (s at 3.60 ppm superimposed on m, total 4 H), 2.78 (pseudoquintet, J = 7.1 Hz, 1 H), 2.38 (qd, J = 7.2, 4.6 Hz, 1 H), 1.24 (d, J = 7.0 Hz, 3 H), 1.12 (d, J = 7.2 Hz, 3 H). Irradiation at 1.24 ppm collapsed the signal at 2.78 ppm (d, J = 7.6 Hz) whereas irradiation at 1.12 ppm collapsed the signal at 2.38 ppm (d, J = 4.6 Hz).

(±)-Methyl [2*S*,3*R*,4*R*]-3-hydroxy-2-methyl-4-phenylpentanoate (4f'):[24] mp 57–59 °C (lit.[24] mp 59–60 °C); ^{1}H NMR (250 MHz) δ 7.20–7.10 (m, 5 H), 3.72 (pseudo t, J = 5.5 Hz, 1 H), 3.54 (s, 3 H), 2.81 (pseudoquintet, J = 7 Hz, 1 H), 2.45 (pseudoquintet, J = 7 Hz, 1 H), 1.26 (d, J = 7.2 Hz, 3 H), 1.17 (d, J = 7.2 Hz, 3 H). Irradiation at 1.26 ppm collapsed the signal at 2.81 ppm (d, J = 5.3 Hz) whereas irradiation at 1.17 ppm collapsed the signal at 2.45 ppm (d, J = 5.9 Hz).

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Registry No. 1 (R = H), 1271-19-8; 1 (R = Me), 1282-40-2; 1 (R = *i*-Pr), 12130-65-3; 2 (R = H), 12087-70-6; 2 (R = Me), 116148-77-7; 2 (R = *i*-Pr), 116148-78-8; *anti*-3a, 106651-02-9; *syn*-3a, 116129-24-9; *anti*-3b, 106650-99-1; *syn*-3b, 106651-03-0; *anti*-3c, 81437-87-8; *syn*-3c, 81437-88-9; *anti*-3d, 63553-62-8; *syn*-3d, 63553-63-9; *anti*-3e, 116129-25-0; *syn*-3e, 116129-26-1; 3f (Cram product), 68040-43-7; 3f (*syn*-Cram product), 116183-26-7; 3f (Cram Ac derivative), 116129-27-2; 3f (*syn*-Cram Ac derivative), 116183-28-9; 3f', 68070-07-5; 3f' (Ac derivative), 116183-27-8; *anti*-4a, 116129-28-3; *syn*-4a, 116129-29-4; *anti*-4b, 116183-29-0; *anti*-4c, 116183-30-3; *anti*-4d, 116129-30-7; 4f, 40954-97-0; 4f', 40954-96-9; $PhCH_2CHO$, 122-78-1; c-$C_6H_{11}CHO$, 2043-61-0; *t*-BuCHO, 630-19-3; PhCHO, 100-52-7; 1,3-butadiene, 106-99-0; mesitylaldehyde, 487-68-3; (±)-α-methylphenylacetaldehyde, 34713-70-7.

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Scope and Mechanism of the Phase-Transfer Carbonylation of Organic Halides Catalyzed by Pentacarbonyliron To Give Ketones and Carboxylic Acids

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Various substituted benzyl halides are readily converted into 1,3-diaryl-2-propanones, RCOR, or arylacetic acids, RCO_2H (R = $ArCH_2$), under CO pressure on reaction with a catalytic amount of pentacarbonyliron in a liquid–liquid phase transfer (PT) system (CH_2Cl_2 (or $C_6H_5CH_3$)/H_2O, NaOH, $(Bu_4N^+)_2SO_4^{2-}$). These reactions involve the in situ generation of the acyltetracarbonyliron anion, $RCOFe(CO)_4^-$, which is maintained in the organic phase as the tetrabutylammonium ion pair. Further reaction of benzyl halides with this anion starts the catalytic conversion to give either ketones, RCOR, or acids, RCO_2H. With less reactive halides such as alkyl bromides (for instance, RX = *n*-C_4H_9Br), the reaction stops after the stoichiometric conversion of $Fe(CO)_5$ into the acyl anion, $RCOFe(CO)_4^-$. A detailed examination of the reaction was made by using benzyl bromide (RX = $C_6H_5CH_2Br$) as the organic substrate. Selectivity toward formation of a ketone, RCOR, or an acid, RCO_2H (R = $C_6H_5CH_2$), as the dominant product depends on the aqueous concentration of the hydroxide anion, the stirring speed, the temperature, and the CO pressure. From these results and a kinetic study, it is inferred that two catalytic cycles compete in the PT system, both involving the acyl anion $RCOFe(CO)_4^-$ and the neutral complex $RCOFe(CO)_4R$. Reductive elimination from the latter unstable complex gives rise to the ketone, RCOR, whereas PT base-catalyzed cleavage with hydroxide generates the acid, RCO_2H, and the acyl anion, $RCOFe(CO)_4^-$. Two catalytic cycles are proposed for these reactions.

The use of metal carbonyl derivatives in organic synthesis or catalysis under homogeneous conditions is well established.[1] Recent reviews have shown the great interest of the application of the phase transfer (PT) principle[2] for many of these reactions, particularly in the area of carbonylation; the advantages are (i) mild and simple reaction conditions, (ii) unexpected reactivity due to the unusual

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