Additions of Chiral Allyltitanocenes to Aldehydes: Diastereoselective Synthesis of Homoallylic Alcohols with a Recyclable Chiral Transition Metal Reagent

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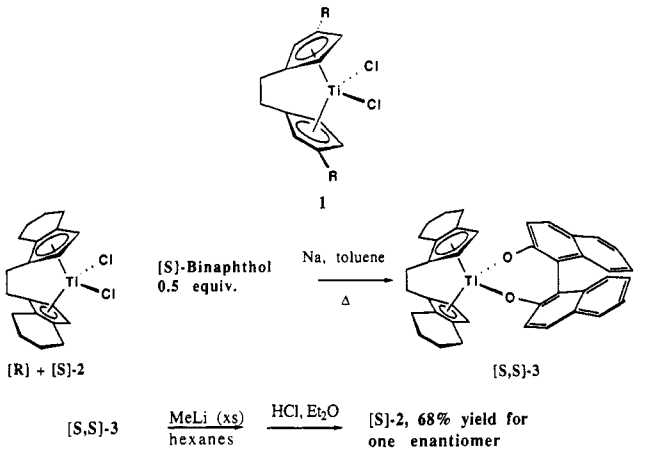
Homochiral allyl- and crotyltitanocenes **4a** (R = H) and **4b** (R = Me) prepared from *ansa*-titanocene dichloride **2** react with aldehydes to provide on workup homoallylic alcohols **5** in excellent yield and with moderate to excellent anti diastereoselectivity in the case of compound **4b**. The enantioselectivity of this process is modest and appears to arise from product formation via competing formation of chair- and boatlike transition states. Titanocene dichloride **2** is recovered in excellent yield on workup without detectable racemization and can be recycled.

Introduction

There is much current interest in the development of enantioselective reagents and/or catalysts for the preparation of homoallylic alcohols. In particular, homochiral tartrate-derived allyl and crotylboronic ester reagents[1] or allyl- and crotylboranes[2] have been developed that provide these compounds with good to excellent levels of stereocontrol. A limitation to this methodology is that these compounds are prepared from simple olefins (i.e. (*E*)-2-butene or (*Z*)-2-butene) by using the Schlosser protocol for metalation of these systems. Application of this procedure to unsymmetrical and/or homochiral olefins containing additional functionality is likely to be complicated by problems of regioselectivity during metalation and/or competing metalation at remote sites. Thus, as presently described, these methods provide an excellent strategy for the *linear* synthesis of natural products of propionate origin.

We have been interested in developing shelf-stable reagents that have comparable levels of stereocontrol for this process that might be employed in convergent synthetic approaches to natural products. Allylic titanium(III) and titanium(IV) or zirconium(IV) reagents derived from metallocene dichlorides by a variety of methods (e.g. from dienes, allylic grignard, and lithium reagents or allylic halides) seemed appropriate for this purpose. The metallocene dichloride precursors are air-stable crystalline solids and anti or syn homoallylic alcohols are available with moderate to excellent diastereoselectivity using allyl reagents derived from them.[3]

Scheme I



In addition, we have recently demonstrated that substituted, η^3-crotyltitanocene reagents [$(\eta^5\text{-}C_5H_4R)_2Ti(\eta^3\text{-}C_4H_7)$; R = H, Me, *i*-Pr], derived from titanocene dichlorides [$(\eta^5\text{-}C_5H_4R)_2TiCl_2$], undergo condensation reactions with aldehydes to provide anti-homoallylic alcohols with no apparent loss in yield and furthermore, that modest increases in steric hindrance at the metal center in these compounds leads invariably to improvements in the kinetic diastereoselection of these reactions.[4] Although literature precedent concerning the level of enantioselection using homochiral titanocene-based allylmetal reagents was not promising,[5] we elected to initiate studies employing a class of titanocene dichlorides exemplified by structure **1** (Scheme I) and, in particular, the tetrahydroindenyl derivative **2** which was prepared several years ago by Brintzinger and co-workers.[6] We report here the results of a study of the additions of allyl- and crotyltitanocenes derived from compound **2** to aldehydes.

Results

Racemic ethylenebis(tetrahydroindenyl)titanium dichloride **2** was prepared from indene in 30–40% overall yields by a modification to the original literature procedure.[7] In our hands the resolution of this compound using

(1) For leading references to efficient chiral allylboronate reagents see: (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Roush, W. R.; Halterman, R. L. *Ibid.* **1986**, *108*, 294. (c) Roush, W. R.; Palkowitz, A. D. *Ibid.* **1987**, *109*, 953. (d) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316. (e) Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

(2) For leading references to efficient chiral allylborane reagents, see: (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (b) Brown, H. C.; Bhat, K. S. *Ibid.* **1986**, *108*, 5919. (c) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432. (d) Brown, H. C.; Bhat, K. S.; Randad, R. S. *Ibid.* **1987**, *52*, 3701. (e) Garcia, J.; Kim, B. M.; Masamune, S. *Ibid.* **1987**, *52*, 4831.

(3) (a) Sato, F.; Iijima, S.; Sato, M. *Tetrahedron Lett.* **1981**, 243. (b) Sato, F.; Iida, K.; Iijima, S.; Moriya, H.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1981**, 1140. (c) Klei, B.; Teuben, J. H.; De Liefde Meijer, H. J. *Ibid.* **1981**, 342. (d) Sato, F.; Suzuki, Y.; Sato, M. *Tetrahedron Lett.* **1982**, *23*, 4589. (e) Klei, E.; Teuben, J. H.; De Liefde Meijer, H. J.; Kwak, E. J.; Bruins, A. P. *J. Organomet. Chem.* **1982**, *224*, 327. (f) Sato, F.; Uchiyama, H.; Iida, K.; Kobayashi, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1983**, 921. (g) Kobayashi, Y.; Umeyama, K.; Sato, F. *Ibid.* **1984**, 621. (h) Reetz, M. T.; Sauerwald, M. *J. Org. Chem.* **1984**, *49*, 2292. For a lead reference to allylzirconocene additions, see: Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985**, *285*, 31.

(4) Collins, S.; Dean, W. P.; Ward, D. G. *Organometallics* **1988**, *7*, 2289.

(5) (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.

(6) Wild, F. W. R. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233.

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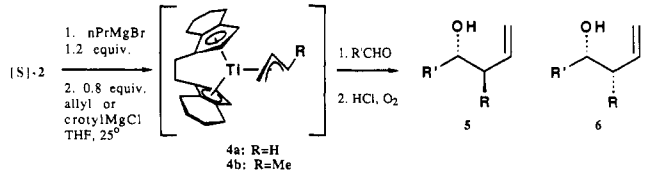
Table I



R′	R	product	yield,[a] %	5:6[b]	R:S[c]
$PhCH_2$	Me	**5a (6a)**	80	2.5:1 (2.2:1)[d]	1:1.2 (2.2:1)[e]
c-C_6H_{11}	Me	**5b**	85	8.0:1	2.0:1
t-Bu	Me	**5c**	83[f]	36:1 (38:1)[d]	3.5:1
Ph	Me	**5d**	90	40:1	1.6:1
$PhCH_2$	H	**5e**	88[f]		2.5:1[g]
c-C_6H_{11}	H	**5f**	85		1.5:1
t-Bu	H	**5g**	92[f]		1:1.1
Ph	H	**5h**	90		1:1.1

[a] Isolated yields based on crotyl- or allylmagnesium chloride unless otherwise noted. [b] Ratios of diastereomers determined from ^1H NMR spectrum of the mixture or by HPLC.[4] [c] Ratios of enantiomers are corrected for the optical purity of compound **2** (93% ee) and were determined by HPLC analysis (Table II, see Experimental Section) unless otherwise noted. Designation of *R* or *S* configuration at the carbinol carbon is as described in the text. [d] Value in parentheses is the ratio observed using isolated compound **4b**. [e] Value in parentheses is the ratio for the syn diastereomer **6a** as determined by HPLC. [f] GC yield using *n*-decane as an internal standard. [g] The absolute configuration of the major enantiomer was determined by HPLC, however, the peaks were insufficiently resolved for accurate integration–the ratio quoted was obtained by integration of appropriate signals in the ^1H NMR spectrum of a mixture of the Mosher's esters in benzene-d_6 (Table III).

(*S*)-2,2′-binaphthol was less efficient than reported,[6] particularly with respect to the optical purity of the unreacted *R* enantiomer of compound **2** (Scheme I).[8,9] Now that 2,2′-binaphthol is available on a large scale in optically pure form by enzymatic resolution[10] gram amounts of optically pure **2** can be prepared in a short period of time without undue expense. The optical purity of compound **2** can be conveniently determined by conversion of this material to the diastereomeric bis((*R*)-*O*-acetylmandelate) derivatives[9] and integration of the appropriate NMR signals in the spectrum of the mixture.

Several methods were investigated for the preparation of crotyltitanocene **4b** (see Table I for structure).[3,4,11] Formation of **4b** was inefficient, employing 1 equiv of compound **2**, 2 equiv of *n*-PrMgBr, and excess 1,3-butadiene in THF; reaction of the mixture with benzaldehyde afforded <50% yields of the expected homoallylic alcohol. A titanium(III) hydride has been postulated as an intermediate in this reaction.[11b] In view of the reluctance of a related, achiral, *ansa*-titanocene compound to form a titanium(III) hydride species[12] the low conversion of **2** to the crotyl derivative **4b** under these conditions was, in retrospect, not surprising.

Better results were obtained using 2.0 equiv of crotylmagnesium chloride;[3,4,11a] although high yields of the expected adduct were obtained with a variety of aldehydes the diastereoselectivity observed using this procedure was disappointingly low. We believe this is due to the presence of unconsumed crotylmagnesium chloride in the reaction mixture. Reaction of this compound with aldehydes affords mainly the α-adduct but with variable and modest diastereoselectivity.[13] Isolation of crotyltitanocene **4b** confirmed these suspicions—a general improvement in diastereoselectivity was observed. However, routine isolation of this air- and moisture-sensitive compound was tedious.

We have since discovered that compounds **4a** or **4b** can be generated cleanly and efficiently in situ using the following protocol: (1) Treatment of compound **2** with 1.1–1.2 equiv of *n*-PrMgBr at room temperature followed by heating for 1–2 min at 40–50 °C to effect reduction of the metal center[11] and (2) addition of 0.8–0.9 equiv of allyl or crotylmagnesium chloride at 25 °C and reaction for 30 min at this temperature. Under these conditions, the yields of the homoallylic alcohols (based on allyl- or crotylmagnesium chloride) are high and the level of diastereoselectivity comparable to that using isolated compound **4b** (Table I).

Table I summarizes the results of experiments employing homochiral compounds **4a** and **4b** for homoallylic alcohol synthesis. The designation of the *R* configuration in Table I to the major enantiomer **5** (Table I) is based on the assumption that the R′ group of the aldehyde always has higher priority than that of the crotyl or allyl group to facilitate comparison between entries. In actual fact for entries 1 and 2 the R′ group has lower priority and as such the absolute stereochemistries should be reversed. It is clear (entries 1–3) that there is a gradual improvement in kinetic diastereoselection with increasing size of the alkyl group on the aldehyde. This is consistent with earlier observations.[4] However, very high levels of diastereoselectivity are currently restricted to pivaldehyde and benzaldehyde using reagent **4b**.

The relative stereochemistry of the homoallylic alcohols derived from reagent **4b** was confirmed by correlation with the known β-hydroxy carboxylic acids or esters. Although, the adducts prepared are all known compounds, there appears to be a paucity of ^1H NMR spectral data for some of them in the literature. This data and the conversion sequence has been reported elsewhere.[4]

Enantioselectivity generally increases in the same manner as diastereoselectivity with reagent **4b**, although the levels of selectivity are modest at best. The glaring exception to this trend is observed for benzaldehyde, which

(7) Collins, S.; Kuntz, B. A.; Taylor, N. J.; Ward, D. G. *J. Organomet. Chem.* **1988**, *342*, 21. The precursor to compound **2** is the corresponding η^5-indenyl compound which is prepared from the dianion of bis(indenyl)ethane and $TiCl_4$. Since this work was completed we have noted that this latter reaction is somewhat capricious—trace impurities in the bis(indenyl)ethane, source of the butyllithium employed for and method of deprotonation, and addition time can have profound influences on the yields obtained. On several occasions we have obtained nearly 80% yields while on others as little as 30% has been observed. In view of the importance of compound **2** and the analogous zirconium and hafnium compounds as polymerization catalysts,[21] we will communicate optimal procedures in the near future.

(8) Substantial racemization of compound **2** occurs during silica gel chromatography under the reported conditions[6] if exposure to light is not rigorously avoided. In practice, it proved more practical to photoracemize compound **2** and recycle this material with (*R*)- or (*S*)-binaphthol since the binaphtholate derivative appears to be stable toward photoracemization. We also note that on occasion, unreacted compound **2** from this resolution was virtually racemic and was recovered in low yield prior to any chromatography. Similar difficulties were recently noted by Brintzinger and co-workers.[9]

(9) An alternative procedure for the resolution of compound **2** employing *O*-acetylmandelic acid was reported during the course of our investigations. It appears to be more convenient than the procedure previously reported.[6] Schafer, A.; Karl, E.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1987**, *328*, 87.

(10) Kazlauskas, R. J. *Abstracts of Papers*, 3rd Chemical Congress of North America, Toronto, ON, Canada, 1988, Paper ORGN-229. We thank Prof. Kazlauskas (present address, Department of Chemistry, McGill University, Montreal, PQ) for experimental procedures and a generous donation of (*S*)-2,2′-binaphthol.

(11) (a) Martin, H. A.; Jellinek, F. *J. Organomet. Chem.* **1967**, *8*, 115. (b) Martin, H. A.; Jellinek, F. *Ibid.* **1968**, *12*, 149.

(12) Smith, J. A.; Brintzinger, H. H. *J. Organomet. Chem.* **1981**, *218*, 159.

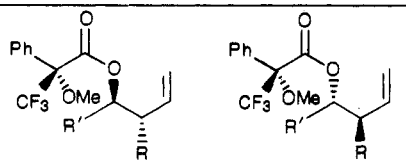
(13) Collins, S.; Ward, D. G. unpublished results.

Table II. HPLC Analyses of (3,5-Dinitrophenyl)carbamate Derivatives of Homoallylic Alcohols

R′	R	solvent ratio[a]	flow rate, mL/min	retention time, min *anti*-(*S*)[b]	retention time, min *anti*-(*R*)
$PhCH_2$	Me	95:5	1.0	25.0 (26.7)[c]	27.7 (29.3)[c]
c-C_6H_{11}	Me	97:3	1.0	21.9	20.5
t-Bu	Me	98:2	1.0	21.1	22.2
Ph	Me	95:5	2.0	16.5	17.6
				(*S*)[b]	(*R*)
$PhCH_2$	H	97:3	2.0	27.9	28.8
c-C_6H_{11}	H	95:5	2.0	11.2	10.1
t-Bu	H	95:5	2.0	8.8	7.9
Ph	H	90:10	2.0	9.9	10.8

[a] In all cases the solvent combination used was hexane–2-propanol in the indicated ratio. Detection at 254 or 280 nm. [b] Configuration at the carbinol carbon designated as explained in text. [c] Times in the parentheses are those for the corresponding syn diastereomers.

Table III. Chemical Shifts and Assignment for Mosher's Ester Derivatives of Homoallylic Alcohols[a]



R′	R	(assignment)	(assignment)
$PhCH_2$	Me	0.65 (d, Me)	0.51 (d, Me)
		2.99 (q, OMe)	3.03 (q, OMe)
c-C_6H_{11}	Me	0.86 (d, Me)	0.94 (d, Me)
		3.15 (q, OMe)	3.22 (q, OMe)
t-Bu	Me	0.84 (s, *t*-Bu)	0.77 (s, *t*-Bu)
		0.95 (d, Me)	1.04 (d, Me)
Ph	Me	3.43 (q, OMe)	3.22 (q, OMe)
$PhCH_2$	H	3.44 (q, OMe)	3.38 (q, OMe)
c-C_6H_{11}	H	3.48 (q, OMe)	3.43 (q, OMe)
t-Bu	H	0.70 (s, *t*-Bu)	0.78 (s, *t*-Bu)
		3.47 (q, OMe)	3.38 (q, OMe)
Ph	H	3.42 (q, OMe)	3.30 (q, OMe)

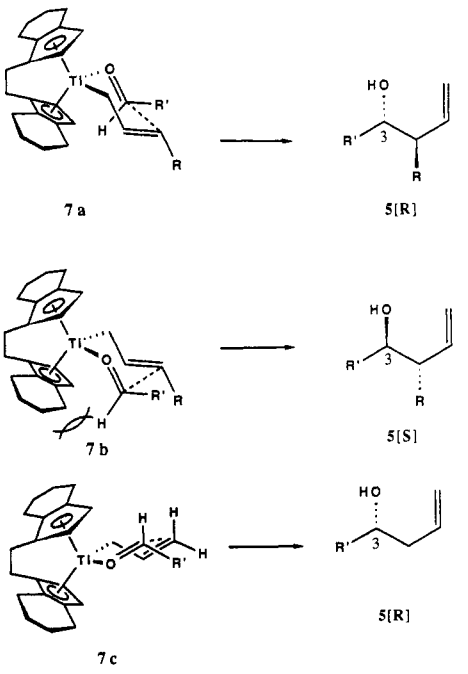
[a] All spectra were recorded at 200 MHz in benzene-d_6 solvent. Chemical shifts are referenced to internal TMS.

undergoes reaction with homochiral **4b** to produce almost exclusively the anti homoallylic alcohol **5d**, but in nearly racemic form. In those cases where significant amounts of the syn diastereomer **6** were produced (e.g. entry 1) the facial selectivity was higher than that observed for the anti diastereomer. Somewhat surprisingly, the reaction of reagent **4a** shows an opposite trend, i.e. the least sterically encumbered aldehydes reacts the most enantioselectivity (entries 5–7). It is interesting to note that the major enantiomer of the homoallylic alcohol **5e** derived from the reaction of **4a** with phenylacetaldehyde (Table I, entry 5) has the same absolute configuration as that of the syn diastereomer **6a** produced from the reaction of compound **4b** with this same aldehyde (Table I, entry 1) and that the level of selectivity is the nearly the same.

The ratio of enantiomers was determined by derivatization of the alcohol mixture with 3,5-dinitrophenyl isocyanate and analysis of the resulting carbamates by HPLC on a Pirkle column (Table II) or by conversion of the crude alcohol mixture to the corresponding Mosher's acid esters and integration of appropriate signals in the ^1H NMR spectra of the ester mixture (Table III).[14,15] In the majority of cases, significant kinetic resolution was observed during esterification with Mosher's acid chloride and in some cases, such as the homoallylic alcohol derived from pivaldehyde, quite forcing conditions were required to consume the major, slow-reacting enantiomer using (*R*)-Mosher's acid chloride. Consequently, the enantioselectivities reported in Table I are those obtained by using the HPLC procedure where adequate resolution of the two peaks for accurate integration was obtained. Authentic samples of these homochiral alcohols were obtained by using Roush's chiral boronic ester methodology.[1,16]

Compound **2** could be recovered in 80–90% yield from these reactions. The optical rotation of this material was not significantly lower than that of the starting material. Thus, significant racemization of the ligand framework does not occur during formation of the allyl or crotyl derivative **4** or on subsequent reaction with an aldehyde. Material from several runs was accumulated and recrystallized from hexanes–toluene prior to reuse. Solutions of compound **2**, particularly in polar solvents (e.g. THF, $CHCl_3$), undergo photoracemization when exposed to visible light. Consequently, all operations were conducted in foil-wrapped vessels in a darkened laboratory.

Scheme II



Discussion

The results of this study are not readily interpreted using the traditional transition state arguments that have been advanced to explain the diastereo- and enantioselectivity observed in the reactions of these and other allylmetal reagents with aldehydes.

We and others have provided indirect evidence that these allyltitanocene additions proceed via six-membered chairlike transition states.[3,4] The diastereoselectivities

(14) (a) Pirkle, W. H.; Pochapsky, T. C.; Mahler, G. S.; Corey, D. E.; Reno, D. S.; Alessi, D. M. *J. Org. Chem.* **1986**, *51*, 4991. (b) Pirkle, W. H.; Mahler, G. S.; Hyun, M. H. *J. Liq. Chromatogr.* **1986**, *9*, 443.

(15) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(16) We experienced considerable difficulty in reproducing the reported preparation of the (−)-diisopropyltartrate derived (*E*)-crotylboronate.[1a,b] Yields were low (typically less than 50% on a 50-mmol scale), and the geometric purity of the reagent was slightly lower than that reported. In contrast, no difficulties were encountered in the preparation and use of the analogous allylboronate derivative. An improved preparation of these crotylboronates has recently been communicated. Roush, W. R.; Ando, K.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. *Tetrahedron Lett.* **1988**, *29*, 5579.

observed in the reactions of compound **4b** with aldehydes appear to conform to these arguments, i.e. the selectivity increases with increasing steric size of the aldehyde R′ group (e.g. Scheme II, structure **7a** where the R′ group is pseudoequatorial). The diastereoselectivity observed in the reactions of primary and secondary aldehydes with reagent **4b** is low by comparison to that observed using achiral, unbridged crotyltitanocenes (typically >15:1 anti:syn).[4] The more rigid ligand framework of compound **4b** may hinder coordination of the aldehyde to the metal centre and the resulting transition state is thus "looser", only aldehydes with large alkyl groups or aromatic aldehydes show significant diastereoselectivity.

With the exception of benzaldehyde, the enantioselectivity also increases in the same manner as diastereoselectivity using reagent **4b**, and one might conclude from the configuration of the major enantiomer produced in those cases where moderate selectivity is observed that the preferred chair structure is **7a** in which a pseudo-1,3-diaxial interaction between the aldehyde proton and the tetrahydroindenyl ligand is minimized. At the same time, interactions of the aldehyde R′ group with the tetrahydroindenyl ring occur in **7a** but not in **7b**. In the case of benzaldehyde, CPK molecular models indicate that this interaction is comparable to the 1,3-diaxial interaction mentioned earlier and this might account for the drop in selectivity observed. It is not obvious why this does not also apply to the reactions of compound **4b** with hindered aliphatic aldehydes.

While this explanation serves to partially rationalize the results observed in the case of reagent **4b**, the results obtained with reagent **4a** are not consistent with these arguments. Molecular models reveal that a twist boatlike structure **7c** (Scheme II) places both the R′ group and the aldehyde proton away from the tetrahydroindenyl ligand. This arrangement appears to be more sterically favourable than either **7a** or **7b** for unhindered aldehydes where interactions of the R′ group of the aldehyde and the allyl ligand are modest. This is one possible explanation why the syn homoallylic alcohol **6a** produced from **4b** and phenylacetaldehyde (entry 1, Table I) and that produced from reagent **4a** and this aldehyde (entry 5, **5e**) are produced with the same absolute configuration and with the same level of selectivity. For the more sterically hindered aldehydes, structure **7c** may not be energetically accessible. This explanation is not very satisfying, however, in that both the preferred chairlike structure **7a** (in the case of reagent **4b** or **4a**) and the twist boat structure **7c** gives rise to a product with the same absolute configuration. The drop in selectivity observed in the reactions of reagent **4a** and sterically hindered aldehydes seems inconsistent with either of these interpretations.

In the absence of more compelling results (i.e. higher diastereo- and enantioselectives) it is questionable whether these arguments can be defended with confidence, and further study is warranted.

Conclusions

Although useful levels of diastereoselectivity are not uniformly observed with reagent **4b** and enantioselectivities are modest, there is some promise to reagents of this class in that they are configurationally stable and easily reusable. In our opinion, what is required to rationally study both the origins and the level of diastereoselectivity and enantioselectivity in this and related reactions is general and efficient synthetic routes to compounds exemplified by structure **1**, where the size or electronic characteristics of the R group can be modified. We have recently accomplished this and will report on the preparation and synthetic utility of this class of compounds in due course.

Experimental Section

All solvents were reagent grade that were obtained from commercial sources and purified as required by distillation. Tetrahydrofuran, diethyl ether, toluene, and hexane were refluxed and distilled from sodium benzophenone ketyl under nitrogen. Allylmagnesium chloride was purchased from Aldrich Chemical Co. and titrated for total base and active Grignard (by reaction with excess benzaldehyde and analysis of the product mixture by ^{1}H NMR) prior to use. Crotylmagnesium chloride or propylmagnesium bromide were prepared from crotyl chloride or propyl bromide and Mg metal and analyzed in the same way. 2,2′-Binaphthol was resolved by the method of Cram et al.[17] or Kazlauskas.[10] 3,5-Dinitrobenzoyl azide was prepared using the method of Pirkle et al.[14b] (*R*)-Mosher's acid was purchased from Aldrich Chemical Co. and was converted to the acid chloride according to the method of Sharpless et al.[18] All reactions were conducted under an atmosphere of dry, deoxygenated argon gas. All operations involving the resolution or use of compound **4** were conducted in a darkened laboratory and/or in foil-wrapped flasks. NMR spectra were recorded on a Bruker AC-200 spectrometer. Optical rotations were determined using a JASCO DIP-360 automatic polarimeter at room temperature. HPLC analyses were performed on a Waters 600E instrument equipped with a Waters 484 UV–visible detector and Waters 745 recording integrator. GC separations were performed on a Varian Vista 6000 chromatograph equipped with a 30-m capillary column (J + W Scientific, Durabond DBN-5) and interfaced to a Vista 401 recording integrator.

Resolution of Compound 2. Sodium metal (2.0 g, 87 mmol) in 350 mL of dry toluene was heated to reflux with vigorous stirring until the sodium metal melted. The resulting suspension was cooled to 80 °C while stirring, and compound **2** (2.70 g, 7.05 mmol) and (*S*)-binaphthol (1.01 g, 3.52 mmol) were added in one portion. The deep red mixture was heated at 80 °C for about 4 h at which time TLC showed no unreacted binaphthol. The mixture was cooled and filtered through Celite while warm to remove Na and NaCl, washing well with dry toluene. The filtrate was concentrated in vacuo and extracted with toluene–petroleum ether 1:5. The extract which contained mainly the desired binaphtholate derivative was passed down a column of silanized silica gel eluting with the same solvent. A dark red band eluted rapidly under these conditions and was collected and concentrated in vacuo to provide the crude binaphtholate derivative **3**, which was crystallized from pentane and a minimum volume of chloroform (1.64g, 78% based on one enantiomer, $[\alpha]_{577} = +4085°$ (l = 10 cm, c = 4.5 mg/100 mL, $CHCl_3$).[19] The column was eluted with dichloromethane to provide a small amount of (*R*)-**2**, which was combined with the material insoluble in toluene–petroleum ether. Crystallization of this material from hexanes–toluene provided spectroscopically pure compound **2** (0.54 g, 40% recovery), which had a rotation, $[\alpha]_{435} = +900°$ (l = 10 cm, c = 2.5 mg/mL, $CHCl_3$). Thus under these conditions there is substantial racemization of (*R*)-**2**.[8] The binaphtholate derivative **3** was dissolved in 200 mL of dry hexanes, and methyllithium (28 mL, 1.1 M in ether, 30 mmol) was added at −78 °C. The solution was warmed to room temperature and stirred overnight at room temperature. The yellow suspension was filtered through dry Celite under argon, washing with dry hexanes. After evaporation of the solvent in vacuo to ca. 50 mL a solution of anhydrous HCl in ether (20 mL, 2.0 M, 40 mmol) was added to the filtrate dropwise by syringe at 0 °C after shielding the flask from fluorescent light. The solvents were removed in vacuo to provide compound **2**, homogeneous by ^{1}H NMR spectroscopy (0.72 g, 68% yield based on **3**), which was crystallized from hexanes–toluene ($[\alpha]_{435} = -3085°$ (10 cm, c = 2.5 mg/100

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(19) The literature value reported[6] for compound **3** is $[\alpha]_{577} = +3100°$ (1 cm, c = 40 mg/100 mL). In view of the similarity in optical rotation obtained for compound **2** and the optical purity of this material as determined by spectroscopic methods we would suggest that the correct value for compound **3** is +4100°.

mL, $CHCl_3$)).[20] The optical purity of (S)-2 (93% ee) was determined by conversion of a portion of this material to the bis-((R)-O-acetylmandelate) derivatives in $CDCl_3$ as described by Brintzinger et al.[9] and integration of the cyclopentadienyl resonances observed in the ^1H NMR spectrum of the mixture.

Preparation of Compounds 4a and 4b and Reaction with Aldehydes: General Procedure. Titanocene dichloride 2 (190 mg, 0.5 mmol) was suspended in 2 mL of dry THF under argon. n-Propylmagnesium bromide (275 μL, 2.0 M in ether, 0.55 mmol) was added dropwise by syringe at room temperature to give a homogeneous brown red solution with some gas evolution being observed. The solution was heated with a hot air gun for several minutes until gas evolution ceased. The resulting purple-brown solution was cooled to room temperature. Crotylmagnesium chloride (250 μL, 1.8 M in THF, 0.45 mmol) was added dropwise by syringe to give a deep purple solution. After stirring for 30 min at room temperature, the aldehyde (0.5 mmol) was added neat by syringe. The resulting brown solution was stirred at room temperature for 1 h and 0.7 mL of a solution of concentrated HCl in THF (2.0 M, 1.4 mmol) added dropwise by syringe with vigorous stirring. Dry air was bubbled through the mixture for about a minute to give a red suspension. Anhydrous $MgSO_4$ was added, and the mixture was swirled briefly and filtered, washing with THF. The filtrate was concentrated in vacuo and taken up in hexane–ether, 1:1, and filtered (to remove salts and compound 2), washing with additional hexanes. The filtrate was concentrated in vacuo to give the crude homoallylic alcohols and some additional titanocene dichloride 2. The titanocene dichloride could be precipitated by washing the oily solid with pentane and filtering again, washing with pentane. The pentane was removed in vacuo, and the crude homoallylic alcohols were purified by passage through a short column of silica gel, eluting with hexanes–ethyl acetate, 11:1. Under these conditions no fractionation of diastereomers is observed.[4] The original filter cake that contained compound 2 and magnesium salts was washed with CH_2Cl_2, and the filtrate was combined with additional compound 2 that had been removed by precipitation from pentane. The filtrate was concentrated to dryness in vacuo; recovery was generally 80–90% of spectroscopically pure material. Material was accumulated from run to run and crystallized from hexanes–toluene prior to reuse. No decrease in optical activity was observed if care was exercised to avoid exposure to light.

Preparation and Analysis of (3,5-Dinitrophenyl)carbamates. 3,5-Dinitrobenzoyl azide (62.0 mg, 0.25 mmol) was heated in 1.0 mL of dry toluene at reflux for 15 min. A solution of the homoallylic alcohol (0.2 mmol) in 3 × 1.0 mL of toluene was added dropwise by syringe. The resulting solution was heated at reflux for 4 h and then cooled to room temperature. The solution was diluted with ether (10.0 mL) and washed with cold 2 M HCl, aqueous $NaHCO_3$, and brine. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was passed through a short silica gel column, eluting with hexanes–ethyl acetate, 5:1, to remove a polar yellow impurity. The eluate was concentrated in vacuo, and the carbamate derivatives, homogeneous by ^1H NMR, were dissolved in ~20 mL of 90:10 hexanes–isopropyl alcohol and separated on a Pirkle Covalent [D]-naphthylalanine column (Regis Chemicals Ltd., 5 μm, 25 cm by 4.6 mm i.d.). The separation conditions and retention times are summarized in Table II.

Preparation of Mosher's Acid Esters. The homoallylic alcohol (1.0 mmol) dissolved in 5 mL of dry dichloromethane was added to a solution of (R)-α-methoxy-α-(trifluromethyl)phenylacetyl chloride (287 mg, 1.1 mmol), 4-(dimethylamino)pyridine (120 mg, 1.1 mmol) and triethylamine (480 mg, 4.7 mmol) in 5 mL of dichloromethane. The solution was stirred at room temperature or heated at reflux until the alcohol was consumed as judged by TLC analyses (silica gel, hexanes–ethyl acetate, 10:1). With sterically hindered alcohols (e.g. derived from reagent 4b and pivaldehyde) it was necessary to add additional acid chloride and DMAP to ensure complete reaction. After reaction was complete, the solutions were cooled, diluted with ether, washed with cold, 1 M HCl, saturated $NaHCO_3$, and brine, and the organic phase was dried over $MgSO_4$. Concentration in vacuo provided crude products which were analyzed by ^1H NMR spectroscopy in benzene-d_6 to determine diastereomer ratios. The relevant chemical shifts and assignments of the signals integrated are summarized in Table III.

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(20) At these concentrations photoracemization of compound 2 is extremely rapid and exposure to visible light must be avoided prior to measurement.

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Stereoselectivity of Organometallic Reagents Addition to 7-Oxabicyclo[2.2.1]hept-5-en-2-one[1]

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The reaction between 7-oxabicyclo[2.2.1]hept-5-en-2-one and a variety of organolithium, Grignard, and organocuprate reagents is described. Organolithium and Grignard reagents yield the expected endo alcohols with high selectivity. Alternatively, lithium organocuprates add with high stereoselectivity to the hindered endo face of the carbonyl functionality to afford the corresponding exo alcohols.

The past few years have witnessed an upsurge of interest in the chemistry of derivatives of 7-oxabicyclo[2.2.1]heptane,[2] important starting materials for syntheses of natural products and derivatives of biological interest.[3] Within this context, oxanorbornenic substrates 1 and 2 (Chart I)

Chart I

1 2

are especially versatile starting materials for the preparation of a number of natural products.[4] These synthetic

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