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Highly Enantioselective Addition of Primary Alkyl *Grignard* Reagents to Carbocyclic and Heterocyclic Arylketones in the Presence of Magnesium TADDOLate Preparative and Mechanistic Aspects[1]

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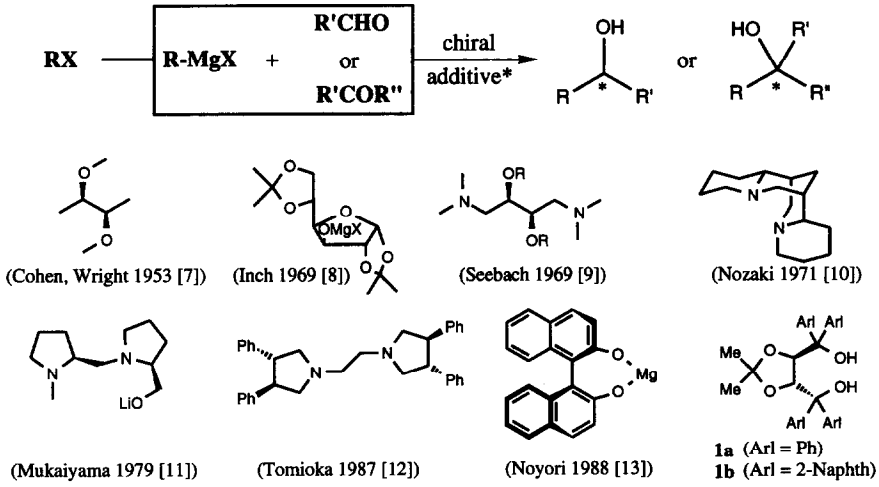
Abstract: In the presence of equimolar amounts of the Mg alkoxide from α,α,α',α'-tetraphenyl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol (a TADDOL) primary *Grignard* reagents (Et, Pr, Bu, Oct, 3-butenyl) add to carbo- and heteroaromatic methyl ketones in THF at -100°C to give *tertiary* alcohols of enantiomeric excesses reaching values above 98%. The scope and limitation of the method are investigated. The reaction, which occurs in a vigorously stirred heterogeneous mixture, gives best results in the absence of steric hindrance of the reacting centers; *Grignard* reagents made from alkyl bromides are superior to those obtained from chlorides; there is a perfect linear relationship between the ee of the TADDOL and of the product 2-phenyl-2-decanol; those *tertiary* alcohols of which the absolute configuration is known, are formed by nucleophilic attack from the *Re* face of the keto carbonyl groups. Three tentative mechanistic models for the stereochemical course of the reaction are discussed.

INTRODUCTION

Hitherto, the most successful enantioselective reactions[3] for organic synthesis involve a chiral catalyst and are functionalizing a given carbon skeleton; essentially none of the enantioselective, C,C-bond forming (connective) transformations gives excellent results when a quaternary stereogenic centre is formed[4,5]. It will remain to be a dream for quite some time that we prepare a *Grignard* reagent in the usual way, add a spatula of some substance, and then an achiral aldehyde or a ketone of C_s symmetry, to isolate an enantiopure or highly -enriched alcohol. There have of course been numerous attempts to do just that[6]: a selection of chiral auxiliaries used for additions of organomagnesium compounds to aldehydes and ketones is presented in Scheme 1[7-13]. It was exactly forty years ago, when Cohen and Wright[7] first used dimethoxy-butane as a chiral solvent to render *Grignard* additions enantioselective. In the last 25 years, many other organometallic compounds have been tested for this purpose, and numerous useful procedures have been elaborated for obtaining enantiopure *secondary* alcohols by nucleophilic additions to aldehydes - the champions being zinc[14] and titanium derivatives[15] in the presence of catalytic amounts of chiral aminoalcohols[14,16] or titanates[15, 17-20]. Unfortunately, none of these methods shows good enantioselectivities (≥95% ee) with ketones as substrates.

Scheme 1. Some Chiral Auxiliaries Which Have Been Used for Enantioselective Additions of *Grignard* Reagents to Aldehydes or Ketones and the TADDOLs **1a** and **1b** Used in this Work.

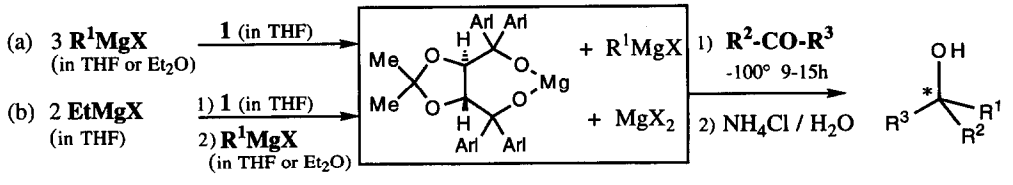


In the course of our ongoing investigations on the use of TADDOLs **1** [α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanols, readily available in two steps from (*R,R*)- or (*S,S*)-tartrate and aryl magnesium bromides[4b,15a,20,21]] as chiral ligands in organometallic reactions, we discovered[1] that primary alkyl *Grignard* reagents, in the presence of Mg-TADDOLate, add to methyl ketones, particularly to aryl methyl ketones with excellent enantioselectivities. It is the purpose of the present paper to describe this new asymmetric synthesis of *tertiary* alcohols in detail, including experimental procedures, applications, and mechanistic considerations.

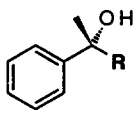
PREPARATIVE RESULTS

The procedure for preparing the actual reagent mixture is most crucial, see variants (a) and (b) in Scheme 2: a THF solution of the TADDOL **1** at low temperature is either mixed with 3 equiv. of alkyl-MgBr, or initially with only 2 equiv. of alkyl-MgBr (for OH deprotonation), followed after 1 min. by an additional equivalent of the same or of a different alkyl-MgBr derivative, and then allowed to warm to room temperature. After cooling the stirred solution to *ca.* -100°C, which leads to a heterogeneous mixture, the *chiral Grignard reagent* is ready to be used: a ketone (neat or THF solution, if solid) is added, and workup after stirring overnight leads to the isolation of the *tert.* alcohol. The procedure for preparing the reagent using 3 equiv. of the

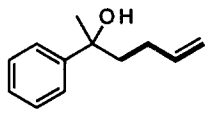
Scheme 2. Preparation of a Mg TADDOLate • RMgX Complex and Addition to Ketones. (The structure of the Mg-TADDOLate is drawn without proof, see discussion of the mechanism).



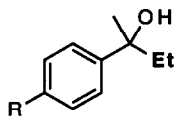
Scheme 3. Tertiary Alcohols obtained in Enantiomerically Enriched Form Using the Procedures Outlined in Scheme 2. *The signs (+) and (-) indicate the sense of optical rotation as measured in MeOH[22]. In those cases where the sense of rotation is missing, the compounds had very small optical rotations, or not enough material was available for a measurement. The groups printed in bold face are those introduced with the* Grignard *reagents by addition to the corresponding ketones. (* 10 mmol scale; equation (a). ** 10 mmol scale; equation (b). All other products obtained in 0.5 mmol scale. # Using* **1b** *as chiral auxiliary.).*



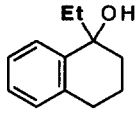
No.	R	% y	% ee
2	Et	62*	98 (*R*)-(+)
3	Pr	84	>98 (*R*)-(+)
4	Bu	75	>98 (*R*)-(+)
5	Oct	58	>98 (+)
6	CH_2Ph	14	70 (*R*)-(+)



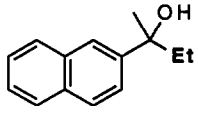
7 60% y, >98% ee (-)



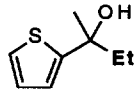
No.	R	% y	% ee
8	Br	60**	98 (+)
9	OMe	76	92 (+)



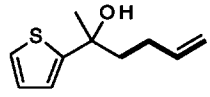
10 28% y, 89% ee (+)
12% y#, 94% ee (+)



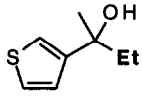
11 75% y, 98% ee (+)



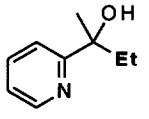
12 43% y, 96% ee (+)



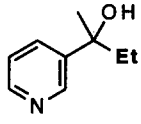
13 30% y**, 97% ee



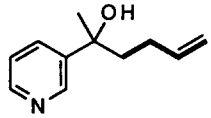
14 24% y, 90% ee



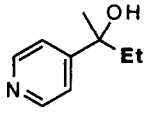
15 41% y, 34%ee



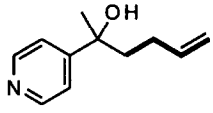
16 51% y, 96% ee (+)



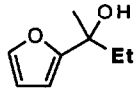
17 58% y**, 86% ee



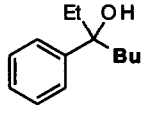
18 96% y, >99% ee (+)



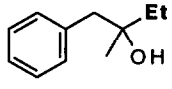
19 51% y**, 98% ee (+)



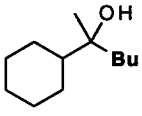
20 53% y, 66% ee



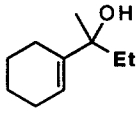
21 7% y, 90% ee (-)



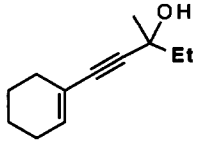
22 22% y, 49% ee



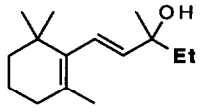
23 trace, 25% ee



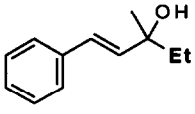
24 55% y, 71% ee



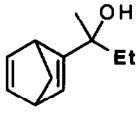
25 88% y, 75% ee
60% y#, 43% ee



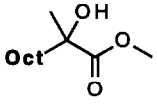
26 64% y, 83% ee (-)
25% y#, 77% ee (-)



27 40% y, 70% ee



28 13% y (2 : 3 mixture)
33% ee and 29% ee

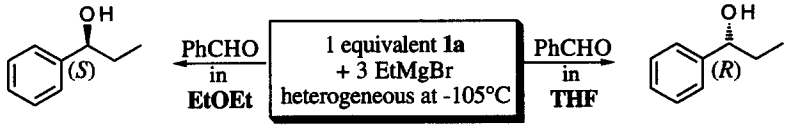


29 9% y, 66% ee

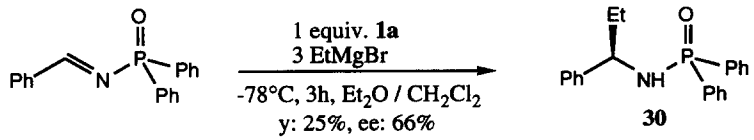
same alkyl-MgBr [(a) in Scheme 2] is less critical: "normal", ethereal *Grignard* reagents may be employed, they must be added in one shot to the well stirred, -70°C cold TADDOL solution, whereupon the temperature may rise to -20°C. In the procedure (b) of Scheme 2, which is of importance for the addition of valuable alkyl-MgBr derivatives, the temperature has to be kept below -50°C, and no ethereal *Grignard* reagent may be employed during the deprotonation step, otherwise the enantioselectivities drop drastically!

The *formulae* of the *tert.* alcohols **2** - **29** obtained under the conditions specified in Scheme 2 are collected in Scheme 3, together with the particular procedures and batch sizes used, the yields, the enantiomeric excesses, and the senses of optical rotation (+/-) and, where known[22,23], of chirality (*R/S*). It is clear, from these data that the enantioselectivities are excellent with aryl and heteroaryl methyl ketones. Thus, the standard substrate, acetophenone, gives essentially complete selectivities with primary alkyl *Grignard* reagents from ethyl to octyl (see products **2** - **5**, **7**; the second isomer is hardly detectable by GC analysis on a chiral column!). In those cases, in which the (*R*) or (*S*) configuration of the product could be assigned (**2** - **4**, **6**), the addition of the nucleophilic reagent has occurred from the *Re*-face of the trigonal centre; we assume that this will be the rule with (*R,R*)-TADDOL at least for the carbocyclic aromatic ketones. Comparison of the data given for the products **22** - **27** reveals that saturated aliphatic methyl ketones give poor (<50% ee), and α,β-unsaturated and acetylenic ones acceptable (≥70% ee) selectivities[24]. The 1,2-adduct **27** to benzal acetone is formed together with an equal amount of the corresponding 1,4-adduct (40% ee). It is also evident by inspection of Scheme 3 that the reaction is highly sensitive to steric hindrance of the carbonyl group in the ketone used (see the yields of **21**, **23**, **28**)[25]. Furthermore, we noticed, that *ortho*-substituents on the aromatic ring of the aryl methyl ketone cause the yields to drop. The sensitivity of the reaction to steric hindrance can also be seen from the fact that isopropyl and *tert*-butyl *Grignard* reagents added to acetophenone to give only traces of products (70% and 0% ee, respectively). Finally, aryl-, vinyl-, and alkinyl magnesium compounds also failed to yield more than traces of the expected products.

Scheme 4. Reaction of Benzaldehyde with EtMgBr in THF and in Diethyl Ether in the Presence of the TADDOLate from **1a** [conditions (a) in Scheme 2].



Scheme 5. Addition of EtMgBr to P,P-Diphenyl-N-(phenylmethylene)phosphinic Amide (→ **30**) in the Presence of 1 equiv. **1a.**



Substrates other than ketones do not react as selectively with our chiral *Grignard* reagent. Thus, benzaldehyde and EtMgBr are probably too reactive a pair to give high enantioselectivities even at -105°C

(Scheme 4): in ether 70% and in THF 58% ee - intriguingly with *Si* attack of the nucleophile in the former and with *Re* attack in the latter solvent! With the phosphinamide derivative shown in Scheme 5, and recommended by *Soai* et al.[26,27] for enantioselective dialkyl zinc additions to imines, only a 66% ee and an even poorer yield of product **30** formed with EtMgBr was observed (preferred *Re* addition in ether, **no** selectivity at all in THF).

MECHANISTIC INVESTIGATIONS AND CONCLUSIONS

Since we are dealing with a slow reaction (9-14 h) in a heterogeneous mixture at -100°C, it will be very difficult to do serious mechanistic investigations and derive a detailed mechanism of the enantioselective *Grignard* additions to ketones in the presence of Mg-TADDOLate! Thus, we present here just some additional practical information about the reaction, as well as a working hypothesis about the mechanism.

a) In contrast to the dialkyl zinc additions to aldehydes[18-20], the *Grignard* reactions with ketones do not give better results when we switch from the tetraphenyl (**1a**) to the tetranaphthyl *substituted TADDOL* (**1b**); also, the α-naphthyl analogue of **1b** and the TADDOLs with Ph/Ph, Ph/H, and H/H instead of two methyl groups in the 2-position of the dioxolan ring gave lower yields and / or selectivities in the reactions leading to the tetralin and to the β-ionone adducts **10** and **26**.

b) As mentioned before, the reaction is extremely *solvent dependent*, THF being the medium of choice. In pure diethyl ether, the addition of EtMgBr to acetophenone (→**2**) is non-selective, in a 5:3 THF/1,4-dioxane mixture the yield is lower (30%) than usual but the selectivity remains high (96% ee). In the case of the addition of 3-buten-1-yl-MgBr to 2-acetylthiophen (product **13**) we have systematically varied the ether content of the reaction mixture, see Fig. 1, under the conditions specified as (a) in Scheme 2 above: the more ether there was in the TADDOL solution before deprotonation with two equiv. *Grignard* reagent in the same solvent, the lower the ee in **13**. On the other hand, if an ethereal *Grignard* solution was employed such that the total ether content of the reaction mixture was 7%, the ee of **13** was 98% *versus* 96% in pure THF.

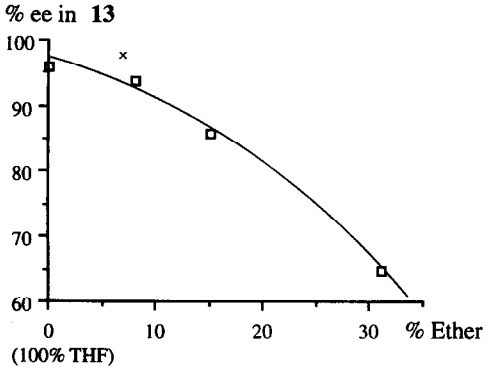


Fig. 1. Solvent Dependence of the Addition of 3-Buten-1-yl Magnesium Bromide to 2-Acetylthiophene (→ **13**) under the Conditions specified as (a) in Scheme 2. - *The ether was present when the Mg-TADDOLate was generated from the diol* ***1a*** *and the* Grignard *reagent (prepared in THF). The cross at* ca. *7% ether content corresponds to an experiment in which an ethereal* Grignard *solution has been added to* ***1a*** *in THF.*

c) The *influence of the counterion X* in alkyl-MgX was studied with the nucleophilic additions of ethyl and butyl groups to acetophenone (products **2** and **4**), see Table 1. It looks like bromide gives the best results and chloride the worst. We noticed that with EtMgCl the reaction mixture remained a clear solution throughout the entire procedure, whereas all the other reaction mixtures were suspensions at -100°C. Addition

of excess $MgBr_2$ etherate did hardly change the result, while the use of Et_2Mg, i. e. the absence of Mg halide from the reaction mixture altogether, still gave product with high ee, but the reaction became very, very slow.

Tab. 1. Influence of the Halide Counter Ion on the Selectivity of Addition of Ethyl and Butyl *Grignard* Reagent to Acetophenone (→ **2**, **4**). *The reactions were carried out under the conditions specified as (a) in Scheme 2. For comparison, an experiment with Et_2Mg (1.5 equiv. / **1a**), i.e. under "salt-free" conditions, is also included (entry 1). In the experiment of entry 3, three extra equiv. of $MgBr_2$ etherate were added.*

Entry	*Grignard* Reagent		Product		
	R^1	X	No.	Yield [%]	ee [%] (Config.)
1	Et	Et	**2**	9	93 (*R*)
2	Et	Br	**2**	62	98 (*R*)
3	Et	Br + 3 $MgBr_2$	**2**	58	97 (*R*)
4	Bu	Cl	**4**	40	87 (*R*)
5	Bu	Br	**4**	75	>98 (*R*)
6	Bu	I	**4**	40	98 (*R*)

d) We have also checked whether one or more than one TADDOLate molecule is involved in the rate determining step of our enantioselective *Grignard* addition by using various mixtures of **1a** and *ent*-**1a** in the reaction leading to 2-phenyl-2-decanol (**5**), see Fig. 2. A clean *linear relationship* was observed between the enantiomeric purity of the TADDOL and of the *tert.* alcohol **5** produced. Thus, unlike many other enantioselective reactions[14,28], and like the Ti-TADDOLate catalyzed dialkyl zinc additions to aldehydes[18-20], there is no hint for the involvement of more than one chiral ligand in the product forming step of this Mg-TADDOLate mediated *Grignard* reaction.

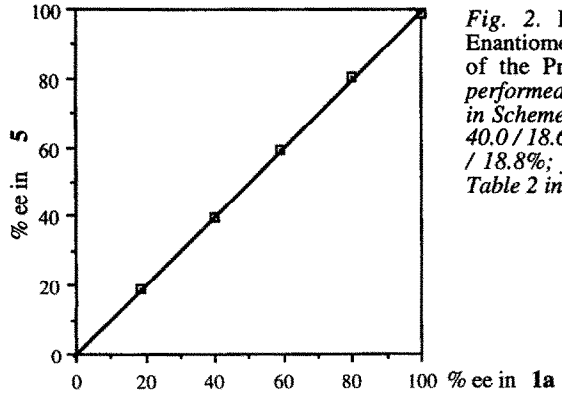


Fig. 2. Linear Correlation Between the Enantiomeric Purities of the TADDOL **1a** used and of the Product **5** obtained. *The reaction was performed in THF under conditions (a) as specified in Scheme 2. With ee in **1a** of >99.9 / 80.0 / 59.1 / 40.0 / 18.6% the ee in **5** was >99 / 80.4 / 59.3 / 39.7 / 18.8%; for the method of ee determination see Table 2 in the experimental section.*

e) An *excess* of the Mg-TADDOLate over the amounts of *Grignard* reagent and ketone does not lower the enantioselectivity of the addition. On the other hand, it is not possible to use the TADDOLate in *substoichiometric amounts:* when TADDOLate, acetophenone, and EtMgBr are mixed in a ratio of 0.25 / 1.0 / 1.0 under the standard conditions a slower than usual reaction ensues, with product alcohol **2** of higher

enantiomeric excess being generated at the beginning and of lower at the end of the reaction period. This would indicate, that the Mg-TADDOLate accelerates the reaction but is deactivated by the product formed.

f) It is remarkable that the reaction mixture containing excess Mg-alkoxide from the very beginning does *not* lead to more extensive *deprotonations* of the methyl ketones, and that even benzyl methyl ketone gives 22% product (**22**; see Scheme 3)[29].

As has been pointed out before, it is possible only to speculate about the mechanism and stereochemical course of the reaction, considering the facts that we are dealing with a heterogeneous mixture and that even the detailed mechanism of the addition of simple *Grignard* reagents to aldehydes and ketones is still subject to controversy[30-35].

The reaction does not appear to occur via a one electron transfer since we did not notice pinacol formation as a side reaction, and since there was a dramatic decrease rather than increase of the reaction rate when going from ethyl to isopropyl to *tert*-butyl *Grignard* reagent, as would be expected for an SET mechanism[32,33].

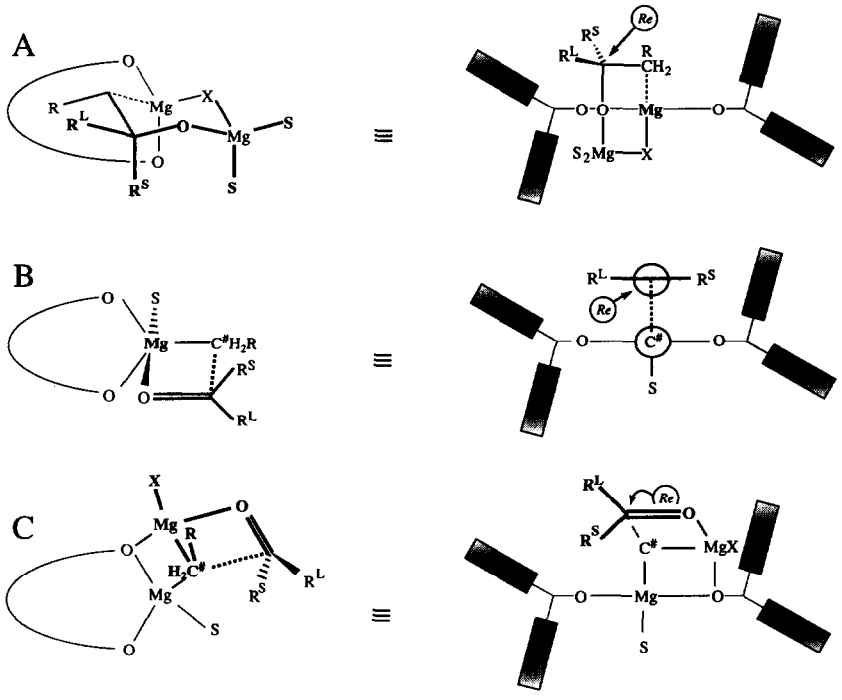


Fig. 3. Three Possible Models for the Nucleophilic Alkyl Transfer of an RCH_2 Group to the *Re* Face of a Ketone in the Ligand Sphere of a Mg-TADDOLate. *R^L and R^S refer to the larger (usually aryl) and smaller substituents on the carbonyl group. S stands for an additional ligand, e.g. a solvent molecule. RCH_2 and $C^\#$ mark the carbon and the group which is actually transferred. The shaded rectangles indicate the axially and equatorially disposed aryl groups of the two $C(Aryl)_2$ moieties in a presumed cyclic Mg-TADDOLate complex*[20]*. The same atomic distances are used for Mg-X, Mg-O, Mg-C, and C-C in these cartoon-type speculative presentations. **A**: Possible product-like arrangement of a 6-ring bimetallic addition mode with two tetracoordinate magnesium centers; the dotted line indicates the Mg-CH_2R bond broken in the process. **B**: Possible educt-like arrangement of a 4-ring addition mode with a pentacoordinate magnesium center; the dotted line indicates the forming C-C bond. **C**: Possible educt-like arrangement of a bimetallic addition mode in which the ketone is attacked by an aggregate of the Mg-TADDOLate with RCH_2MgX.*

Mono-, bi-, and tri-metallic intermediate complexes and transition states have been proposed for the additions of various nucleophilic Li, Mg, and Ti organometallic reagents to aldehydes and ketones[13,15b,20,30-35]. For TADDOL complexes we assume, from the analysis of numerous crystal structures, that reactions occur preferentially in the area of space around the metal where an equatorial rather than an axial aryl substituent of the diaryl methanolate group is located. For bimetallic transition states involving a six-membered ring chair-like arrangement a general model was proposed[20]. Application of this model to the reaction discussed in the present paper leads to the picture **A** in Fig. 3. The outcome of the reaction, i.e. *Re* attack on the trigonal center of the carbonyl group is also described correctly by the planar, four-membered ring arrangement of the reacting components as pictured in **B** of Fig. 3, with a trigonal bipyramidal ligand sphere around the magnesium center. Since it is known that RMgOR' species are dimeric in THF[32], the solvent necessary for resulting high enantioselectivities in our reaction, we also show a model **C** in Fig. 3 in which the interaction of a ketone with such a dimer containing the Mg-TADDOLate is pictured[36]. Other models are conceivable.

The presented results are another demonstration of the frighteningly wide gap between the spectacular practical achievements of stereoselective organic synthesis and the humiliating state of our knowledge of mechanistic details and understanding[37].

EXPERIMENTAL PART

General. Abbreviations: THF (tetrahydrofuran), Et (ethyl), Pr (propyl), Bu (butyl), Oct (octyl). Solvents and reagents: Ether was distilled over Na/K alloy, THF was distilled over K, dichloromethane was dried over molecular sieves 4Å. The solvents used for workup and purification were distilled at normal pressure, the liquid ketones were filtered through basic aluminum oxide, benzaldehyde was distilled under reduced pressure (12 Torr). Basic aluminum oxide (*Alumina Woelm B*), neutral aluminum oxide (*Alumina Woelm N*). The *Grignard* reagents were prepared in the usual way[38] from Mg turnings and the appropriate halides in either THF or ether, and were titrated with *sec*-BuOH[39]. Flash chromatography: performed at 0.2 bar, silica gel (230-400 mesh, *Merck*). Mp: *Büchi* 510, uncorrected. Optical rotations: *Perkin-Elmer* 241 polarimeter, in 10 cm cells. ^{1}H- and ^{13}C-NMR spectra: *Varian Gemini* 200 (200 or 50 MHz, respectively), δ in ppm downfield of TMS ($\delta = 0$), *J* in Hz. GC: *Carlo Erba Instrumentazione* Fractovap 4160 with FID detector and DP 700 integrator; columns: WCOT fused silica 50 m x 0.25 mm, S1: *Chrompack* CP Cyclodextrin β-2,3,6,-m-19 (Heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin), S2: *Machery-Nagel* FS-Lipodex E (Octakis(3-O-butanoyl-2,6-dipentyl)-γ-cyclodextrin). Elemental analyses were performed by the Microanalytical Service Laboratory of ETH-Zürich.

Addition of Grignard *Reagents According to the Conditions Specified (a) in Scheme 2 - Procedure A*

In a 250 ml *Schlenk* tube equipped with magnetic stirring bar and PT100 thermometer 10 mmol (4.66 g) TADDOL **1a** was dissolved in 40 ml of THF under argon atmosphere and cooled to -70°C. To the colorless solution was added 31 mmol (8.9 ml 3.5 M in ether) EtMgBr, the cooling bath was removed, another 70 ml THF was added and the reaction mixture warmed to room temperature by immersing the flask into a 20°C water bath. The colorless solution was then cooled to -105°C, resulting in the formation of a colorless precipitate. With vigorous stirring, 9.4 mmol ketone (neat if liquid or dissolved in 10 ml THF) was added. Stirring was continued for 9 to 14 h at -105°C to -100°C[40]. Afterwards the reaction mixture was quenched with 40 ml of a saturated NH_4Cl solution, ether was added, and the organic layer was separated, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the product was freed from TADDOL by distillation in a kugelrohr apparatus.

Procedure A (small scale)

Same conditions as in Procedure A on a 0.5 mmol scale. The products were isolated by kugelrohr distillation and analysed without further purification. Yields were calculated from the amount of isolated

product and its purity by GC. The enantioselectivities were determined by GC analysis on chiral columns as specified in Table 2.

Addition of Grignard *Reagents According to the Conditions Specified (b) in Scheme 2 - Procedure B (described for 3-Buten-1-yl Magnesium Bromide).*

In a 250 ml *Schlenk* tube equipped with magnetic stirring bar, PT100 thermometer and rubber-septum, 10 mmol (4.66 g) TADDOL **1a** was dissolved in 120 ml of THF and cooled to -90°C. To the colorless solution was added 19 mmol (27 ml 0.68 M in THF) EtMgBr via syringe as fast as possible. The cooling bath was removed immediately and the temperature rose within 1 min to -50°C. Then 13 mmol (10 ml 1.3 M in ether) homoallyl magnesium bromide was added, and the reaction mixture warmed to room temperature by immersing the flask into a 20°C water bath, while warming up, first a grey suspension was formed, which turned to a solution at about 0°C. This chiral *Grignard* reagent was cooled to -105°C whereupon a colorless precipitate was formed. Under vigorous stirring 9.3 mmol ketone was added via syringe. Stirring was continued for 9 to 14 h at -105°C to -100°C. Afterwards the reaction mixture was quenched with 50 ml of saturated NH_4Cl solution, and ether was added. The organic layer was separated, washed three times with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the product was freed from the TADDOL by distillation in a kugelrohr apparatus (150°C, 0.1 Torr). Crude alcohol was obtained, which was further purified by means of flash chromatography and distillation.

Preparation of rac-2 - rac-29 (Procedure C)

Of all products we first prepared *rac* samples to learn about their properties and about the best analysis of the enantiomeric ratios (cf. Table 2).

To a stirred solution of 2 mmol ketone in about 5 ml ether was added at -20°C 1.2 equiv. of alkyl magnesium bromide. The reaction mixture was allowed to warm to room temperature. After 1 h saturated NH_4Cl solution was added, the organic layer was separated, washed with brine, dried over Na_2SO_4 and freed from the solvent under reduced pressure. The product was further purified by means of flash chromatography and / or distillation.

The ^{1}H-NMR spectra of all products *rac*-**2** - *rac*-**29** were measured and had the expected signals. The CAS Registry numbers of those *rac* compounds described previously are: **2**: 1565-75-9; **3**: 4383-18-0; **4**: 4396-98-9 **5**: 21078-96-9; **6**: 5342-87-0; **7**: 85924-68-1; **8**: 58977-33-6; **9**: 30068-21-4; **10**: 93927-12-9; **12**: 36888-24-1; **15**: 67674-34-4; **16**: 20928-26-1; **18**: 19731-52-3; **20**: 4229-86-1; **21**: 4436-93-5; **22**: 772-46-3; **25**: 15331-97-2; **26**: 51547-40-1; **27**: 62232-91-1.

(R)-2-Phenylbutan-2-ol ((*R*)-**2**): Following the *Procedure A*, the reaction was performed with 1.13 g acetophenone. After flash chromatography (pentane/ether 10:1) and kugelrohr distillation (150°C, 0.1 Torr) 0.88 g (62%) of a colorless oil was formed. $[\alpha]_D^{RT}$ = +17.3 (neat) [Lit.[23a]: $[\alpha]_D^{27}$ = -17.7 (neat) for the *S* enantiomer]; 98% ee (GC).

(+)-2-(4-Bromophenyl)-2-butanol ((+)-**8**): Following the *Procedure A*, the reaction was performed with 1.9 g 4-bromoacetophenone, yielding 1.3 g (60%) of a colorless oil after flash chromatography with pentane/ether (6:1) and kugelrohr distillation (150°C, 0.1 Torr). $[\alpha]_D^{RT}$ = +15.2 (c = 1, MeOH); 98% ee (GC).

(-)-2-(2-Thienyl)-5-hexen-2-ol ((-)-**13**) was prepared according to *Procedure B*, with 1.16 g 2-acetylthiophene, yielding 0.50 g (30%) of a colorless wax after chromatography through neutral aluminum oxide (activity grade III) with pentane/ether (10:1), and kugelrohr distillation (150°C, 0.1 Torr). Anal. Calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.74. Found: C, 65.96; H, 7.93. $[\alpha]_D^{RT}$ = 0 (c = 1, MeOH); $[\alpha]_{365}^{RT}$ = -9.9 (c = 1, MeOH); 97.2% ee (GC). ^{1}H-NMR: δ = 1.64 (s, 3 H, CH_3); 1.9-2.2 (m, 5 H, CH_2-CH_2-C-OH); 4.9-5.1 (m, 2 H, C(6)H_2); 5.7-5.95 (m, 1 H, C(5)H); 6.86-7.0 (m, 2 H, arom.); 7.18-7.22 (m, 1 H, arom.).

(+)-2-(3-Pyridyl)-5-hexen-2-ol ((+)-**17**) was prepared according to *Procedure B*, with 1.09 g 3-acetylpyridine, yielding 0.93 g (58%) of a colorless oil after flash chromatography with pentane/ether (1:1), and distillation. An analytically pure sample was obtained after flash chromatography with ether/dichloromethane (1:3). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.50; H, 8.38; N, 8.07. Bp.: 109-111°C (0.1 Torr). $[\alpha]_D^{RT}$ = 0 (c = 1, MeOH); $[\alpha]_{365}^{RT}$ = +7.3 (c = 1, MeOH); 86% ee (GC). ^{1}H-NMR: δ = 1.60 (s, 3 H, CH_3); 1.8-2.2 (m, 5 H, CH_2-CH_2-C-OH); 4.88-5.05 (m, 2 H, C(6)H_2); 5.65-5.9 (m, 1 H, C(5)H); 7.27 (dd, 1 H, *J* = 7.9, *J'* = 4.7, C(5')H); 7.78 (ddd, 1 H, *J* = 7.9, *J'* = 1.8, *J''*=1.8, C(6')H); 8.48 (dd, 1 H, *J* = 4.7,

Table 2. GC-Separation of the non-racemic Products **2** - **29** (cf. Scheme 3).

Compound	Column[a)]	Initial Temp. [°C]	Heating Rate [°C/min]	Inlet Pressure [bar]	Approximate Retention Time [min]	Ratio of Enantiomers first : second eluted	Sense of Optical Rotation[b)]
2	S1	100	1.0	1.0	22	1:99	(+)
3	S2	80	0.5	1.2	35	>99:1	(+)
4	S1	100[c)]	0.3	1.2	60	>99:1	(+)
5	S1	125	0.2	1.1	107	>99:1	(+)
6[d)]	S1	60	1.0	1.2	40	85:15	(+)
7	S1	100	0.5	1.0	65	>99:1	(-)
8	S1	100	0.5	1.2	62	99:1	(+)
9	S2	90	0.5	1.2	50	96:4	(+)
10	S1	100	1.0	1.2	50	3:97	(+)
11	S2	115	0.2	1.2	90	99:1	(+)
12	S1	75	0.5	1.3	52	2:98	(+)
13	S1	70	1.0	1.2	63	98:2	
14	S1	80	0.9	1.2	40	5:95	
15	S1	70	0.7	1.2	51	67:33	
16	S1	80	0.5	1.0	86	2:96	(+)
17	S1	100	0.4	1.2	91	93:7	
18	S1	100	0.5	1.2	62	>99:1	
19	S1	100	0.3	1.2	110	1:99	
20	S1	70	0.7	1.2	32	17:83	
21	S1	90	0.5	1.2	70	95:5	(-)
22	S1	90	0.5	1.0	50	25:75	
23	S1	80	0.5	1.2	77	62:38	
24	S1	80	1.0	1.1	30	15:85	
25	S1	100	0.5	1.1	105	12:88	
26	S1	100	0.5	1.3	70	16:84	(-)
27	S1	90	0.7	1.1	92	15:85	
28[e)]	S2	60	0.5	1.1	58	64:36	
28[f)]	S1	70	1.0	1.1	45	71:29	
29	S1	100	1.0	1.2	50	17:83	

a) Specification see: Experimental Part - General. b) In MeOH; see Scheme 1. c) Initial time (20 min) was used. d) 50 mg of **6** was oxidized with $RuCl_3/NaIO_4$ [41], *in situ* treatment with diazomethane and workup gave dimethyl citraconate, which could be separated into its enantiomers. e) Minor diastereoisomer is separated. f) Major diastereoisomer is separated.

J'=1.8, C(4')H); 8.68 (d, 1 H, *J* = 1.8, C(2')H). ^{13}C-NMR (assignment according to a DEPT experiment): δ = 28.1 (CH_2); 30.0 (CH_3); 42:8 (CH_2); 73.1 (C); 114.6 (CH_2); 122.8 (CH); 132.6 (CH); 134.0 (CH); 142.9 (C); 146.5 (CH); 147.4 (CH).

(+)-2-(4-Pyridyl)-5-hexen-2-ol ((+)-**19**) was prepared according to *Procedure B*, with 1.09 g 4-acetylpyridine, yielding 0.81 g (51%) of a colorless wax after flash chromatography with toluene/ethyl acetate (1:1), and kugelrohr distillation (150°C, 0.1 Torr). An analytically pure sample was obtained after crystallisation from ether/hexane. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.36; H, 8.25; N, 7.90. Mp.: 74-75°C. $[\alpha]_D^{RT}$ = +0.8 (c = 1, MeOH), $[\alpha]_{365}^{RT}$ = -7.1 (c = 1, MeOH); ≥99% ee (GC). ^{1}H-NMR: δ = 1.54 (s, 3 H, CH_3); 1.8-2.2 (m, 4 H, CH_2-CH_2); 3.0 (s broad, 1 H, OH); 4.86-5.02 (m, 2 H, C(6)H_2); 5.65-5.9 (m, 1 H, C(5)H); 7.34 (d broad, 2 H, *J* = 6.2, C(2')H and C(6')H); 8.52 (d broad, 2 H, *J* = 6.2, C(3')H and C(5')H). ^{13}C-NMR (assignment according to a DEPT experiment): δ = 28.2 (CH_2); 30.1 (CH_3); 42.6 (CH_2); 73.9 (C); 115.0 (CH_2); 120.2 (CH); 138.2 (CH); 149.5 (CH); 157.0 (C).

(R)-P,P-Diphenyl-N-(1-phenylpropyl)phosphinic amide ((*R*)-**30**): In a 250 ml *Schlenk* tube equipped with magnetic stirring bar and PT100 thermometer 0.43 mmol (0.20 g) TADDOL **1a** was dissolved in 3 ml ether under argon atmosphere and cooled to -70°C. To the colorless solution was added 1.35 mmol (0.54 ml 2.45 M in ether) EtMgBr, the cooling bath was removed, another 3 ml ether was added and the reaction mixture warmed to room temperature by immersing the flask into a 20°C water bath. The colorless solution was then cooled to -78°C resulting in the formation of a colorless precipitate. With vigorous stirring a solution of 0.32 mmol (0.10 g) P,P-diphenyl-N-(phenylmethylene)phosphinic amide in 0.5 ml CH_2Cl_2 was added. Stirring was continued for 3 h at -78°C. Afterwards the reaction mixture was quenched with 2.5 ml of a saturated NH_4Cl solution, ether was added, and the organic layer separated, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and 27 mg (25%) of **30** isolated by means of flash chromatography (pentane/ethyl acetate 2:1). Determination[26] of enantiomeric composition on a chiral HPLC column Chiralcel OD: 66% ee: ^{1}H-NMR: δ = 0.79 (t, 3 H, J = 7.3, CH_3); 1.7-2.15 (m, 2 H, CH_2); 3.15-3.3 (m, 1 H, NH); 4.0-4.2 (m, 1 H, CH); 7.1-7.5 (m, 11 H, arom.); 7.7-7.95 (m, 4 H, arom.).

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