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Chiral Ytterbium Complex-Catalyzed Direct Asymmetric Aldol-Tishchenko Reaction: Synthesis of *anti*-1,3-Diols

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Abstract: The asymmetric aldol-Tishchenko reaction of aromatic aldehydes with aliphatic and aromatic ketones has been developed as an efficient strategy for the synthesis of *anti*-1,3-diols in good yield with high diastereocontrol and good levels of enantioselectivity. This domino-type reaction is catalyzed by a chiral ytterbium complex that promotes both the aldol reaction through enolization of the carbonyl compound and the Evans–Tishchenko reduction of the aldol intermediate. The stereochemistry of the resulting diols is also investigated and finally proved by using CD techniques.

Keywords: diols · aldol reaction · aldol-Tishchenko reaction · asymmetric catalysis

Introduction

The development of catalytic asymmetric methodologies for the construction of chiral, nonracemic molecules bearing sequences of stereocenters is currently a challenging research area of interest.[1] The development of a catalytic asymmetric aldol reaction is one of the recent landmarks in this field.[2]

The impressive achievements with regards to the asymmetric aldol reaction made to date rely on the conversion of the donor substrate into more reactive species, such as enol silyl ethers or ketene silyl acetals (Mukaiyama-type aldol reaction),[3] by using no less than stoichiometric amounts of reagents in separate steps. However, the most elegant and most economically attractive way to introduce chirality into a molecule is by using only a catalytic amount of a chiral controller without tedious preactivation of the nucleophile.[4] Only recently has tremendous effort been devoted to the development of catalytic asymmetric methodologies which combine high chemo- and enantioselectivity with the powerful atom economy[5] of the aldol reaction.[6]

Since the first artificial metal complex was documented to be capable of promoting the direct asymmetric aldol reaction,[7] some other metal-based[8] and purely organic molecules[9] were reported to activate unmodified donors under *direct* catalytic conditions.

The direct asymmetric aldol reaction between aldehydes and methylene ketones should provide a powerful tool for the formation of new carbon–carbon bonds and the construction of two continuous chiral centers. In contrast to well-documented transformations of methyl ketones[10] their methylene analogues remain, however, a formidable synthetic challenge.[11] Only some α-substituted methyl ketones, particularly α-hydroxy ketones, work nicely in direct reactions promoted by known polymetalic catalysts.[12] Diastereo- and enantioselective synthesis of aldols, starting from methylene ketones (for example, 3-pentanone) by means of the direct catalytic asymmetric aldol reaction is still immature.[13]

Low reactivity of methylene ketones in the direct aldol reaction could be explained by the strong tendency towards fast retroaldol reaction of formed aldols. This unwelcome tendency can be surpassed by coupling of an irreversible Evans–Tishchenko reduction to a reversible aldol reaction in one tandem-type process.[14] In this regard, Shibasaki[15] and ourselves[16] have attempted the direct catalytic asymmetric aldol-Tishchenko reaction as one of the useful methods for overcoming the problem of the unreactivity of higher ketones. In the one-step process, aldehydes reacted

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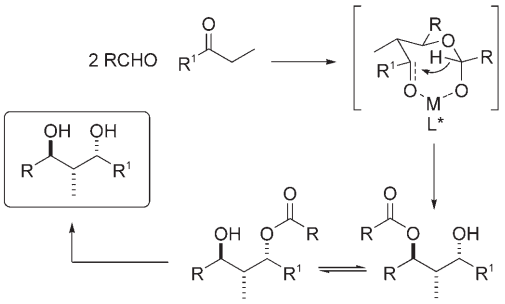
with methylene ketones to give 1,3-diol monoesters, which were formed as a result of the bond reorganization in the cyclic Evans-type intermediate[17] (Scheme 1).



Scheme 1. Condensation of ethyl ketones with aldehydes by means of the aldol-Tishchenko reaction.

The aldol Tishchenko methodology, initially restricted to homocoupling of three identical aldehydes,[14a,b] was later developed by application of lithium ketone enolates[14c,d] furnishing cross aldol-Tishchenko products with an exceptional level of stereoselectivity. Furthermore, the same reaction was performed by using silyl,[14e,f] zinc,[14g] and samarium enolates.[14h]

Simpura[14i,j] and Schneider[14k,l] independently established catalytic cross aldol-Tishchenko reactions of ketone aldols as enol equivalents.

The first examples of direct catalytic aldol-Tishchenko reactions of unmodified ketones and aldehydes to yield 1,3-diol monoesters were presented by Mahrwald[14m] and Morken[14n] using titanium complexes and metal alkoxides, respectively.

Our development of the direct asymmetric aldol reaction of ethyl ketones by the tandem aldol-Tishchenko reaction provided a new venue for our continued interest in asymmetric aldol methodologies.[18]

In contrast to previously presented examples of the stereoselective Tishchenko reactions of two different aldehydes[19] and ketone aldols,[20] three adjacent stereogenic centers are created by the use of a ketone as the substrate in the process, which makes this methodology very effective in terms of chiral economy.

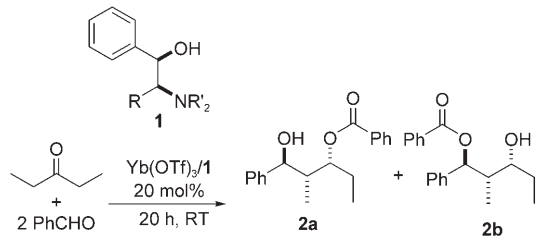
Despite the enormous potential of the aldol-Tishchenko reaction of unmodified ketones with aldehydes leading directly to protected 1,3-diols, its enantioselective variant presents unexplored problems, only preliminarily unraveled. While the stereoselectivity problem was overcome for activated aromatic donors,[15a] there was still paucity for aliphatic substrates for which state-of-the-art methods provide condensation products in moderate *ee* values only.[16]

Herein, we report an efficient application of a chiral aminoalcohol-based catalyst to the enantioselective aldol-Tishchenko reaction between aldehydes and aliphatic ketones. This process provides good product yields and good *ee* values leading to *anti*-1,3-diols in one single operation without tedious preactivation of the donors. This reaction of unmodified ketones is of particular interest not only because of its synthetic potential but also because of its unexplored mechanism with respect to the origin of enantioselectivity.

Results and Discussion

Catalyst development for the direct asymmetric aldol-Tishchenko reaction: Our discovery that ytterbium-triflate complexes with chiral diols[16] and aminoesters[18a] effectively catalyzed the aldol-Tishchenko reaction between diethyl ketone and aromatic aldehydes prompted us to test the catalytic activity of a range of chiral ligands for this process. Based on our previous observations, we expected that ligands containing both a hydroxy group and an amino function should be useful and active for the reaction. To test this hypothesis, the condensation of benzaldehyde and 3-pentanone to afford **2a/b** was performed by using ytterbium triflate and a representative group of chiral aminoalcohols (Table 1). Our initial aim was to identify the best suited chiral ligand in terms of both reaction conversion and enantioselection. An initial study[21] revealed that ephedrine-type aminoalcohols **1** are the most promising candidates for fur-

Table 1. Solvent and ligand studies: reaction of 3-pentanone with benzaldehyde promoted by various ephedrine-type chiral ligands **1**.



Entry	R	R′	Yb(OTf)$_3$/**1**	Solv.	Yield **2a+b** [%][a]	*ee* **2a+b** [%][b]
1	Me	H (**1a**)	1:2	THF	0	–
2	Me	H,Me (**1b**)	1:2	THF	0	–
3	Me	Me (**1c**)	1:2	THF	69	10
4	Me	Me (**1c**)	1:4	THF	70	14
5	Me	Me (**1c**)	1:4	DME	55	20
6	Me	Et (**1d**)	1:4	DME	46	55
7	Me	Pr (**1e**)	1:4	DME	17	50
8	Me	Bu (**1f**)	1:4	DME	46	53
9	Me	$(CH_2)_4$ (**1g**)	1:2	THF	88	42
10	Me	$(CH_2)_4$ (**1g**)	1:4	THF	86	61
11	Me	$(CH_2)_4$ (**1g**)	1:4	DME	80	74
12	Ph	$(CH_2)_4$ (**1h**)	1:4	DME	50	65
13	Me	$(CH_2)_5$ (**1i**)	1:4	DME	55	52
14	Me	$(CH_2)_4$ (**1g**)[c]	1:4	DME	75	−70[d]

[a] Overall isolated yield. [b] The *ee* values of esters and diols were determined by HPLC (Chiralpak AD-H column). [c] (1*S*,2*R*)-**1g** was used. [d] The use of +/− is only a convention to designate opposite enantiomers.

ther optimization of the aldol-Tishchenko condensation. While ligands containing an unprotected amino function, that is, norephedrine (**1a**) and ephedrine (**1b**) were simply unpromising. Application of ligands with protected amino groups led to desired products **2**. Thus, condensation of the substrates in the presence of 20 mol% of the catalyst composed of $Yb(OTf)_3$ and (1*R*,2*S*)-*N*-methylephedrine (**1c**) in a 1:2 ratio in THF at room temperature led smoothly to desired mixtures of esters **2** with excellent diastereoselectivity but low enantiocontrol (Table 1, entry 3). Observed enantioselectivity was improved further when the reaction was carried out in DME (DME = 1,2-dimethoxyetane) in the presence of the catalyst composed of a 1:4 ratio of metal/ligand (entry 5).

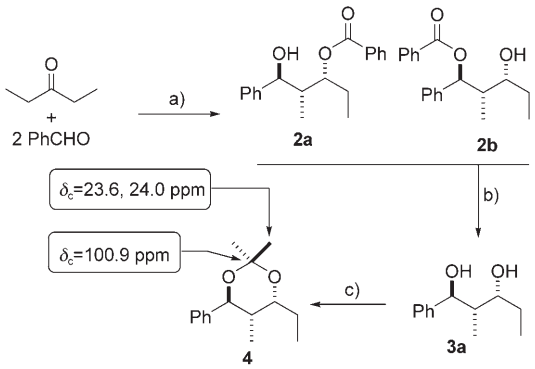
A *syn* orientation of the hydroxy and amino substituents in the ligand turned out to be essential for both the reactivity and selectivity of the catalyst composed of the ephedrine ligand and ytterbium triflate.[21] Thus, (1*S*,2*S*)-*N*-methylpseudoephedrine was not suitable as a ligand, due to the inconvenient orientation of the substituents. Only trace of amounts of product could be isolated from the reaction.

To improve the enantioselectivity in the reaction and provide a better understanding of the requirements for good asymmetric induction, we sought a ligand design that would met both reactivity and selectivity criteria.

As the phenyl substituent at C1 was expected to be indispensable for catalyst reactivity, we decided to modify the C2 positions of the ligands and the type of protection used on the amino group. In the first step, we decided to test the influence of the bulkiness of the amino function protecting group on the catalytic efficiency of the ligand. To realize this concept, we prepared a series of *N*,*N*-protected norephedrine derivatives starting from commercial, optically pure (1*R*,2*S*)-1-phenylo-2-amino-1-propanol ((1*R*,2*S*)-(−)-norephedrine). The synthetic route to approach **1d–g** was reported previously by reaction of amine with alkyl iodides.[22]

As shown in Table 1, the nature of the protection used for the amino group strongly affects the enantioselectivity of the reaction. The enantioselectivity tends to increase as the substituents vary from methyl to more bulky substituents (Table 1 entry 5 versus 6–8). The best result with respect to yield, diastereoselectivity, and enantioselectivity was, however, observed with a catalyst composed of ligand **1g**. Combination of ytterbium triflate and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidynyl)-1-propanol (**1g**) in a 1:4 ratio gave rise to **2a/b** with 80% isolated yield and 74% *ee* (entry 11). Optimal reaction yield and selectivity were observed in DME at room temperature.

To attain higher selectivity in the $Yb(OTf)_3$-catalyzed aldol-Tishchenko condensation, we synthesized novel ligands **1h** and **1i**, which varied from **1b** by a phenyl group and six-membered ring, respectively. Modification of the catalyst structure at C2 (entry 12) and expanding of the nitrogen-containing ring (entry 13) was unfortunately not progressive. It was found that an enantiomer of **1g** with a (1*S*,2*R*) configuration favored formation of the products **2a/b** with a reverse configuration (entry 14). In all cases both regioisomeric esters **2a** and **2b** were detected in the reaction mixture. An enantiomeric excess was determined independently for both esters and diol **3a**. The reaction provides the two esters **2a/b** in similar enantiopurity, suggesting a nonselective intramolecular acyl migration after formation of the aldol-Tishchenko product (Scheme 2).

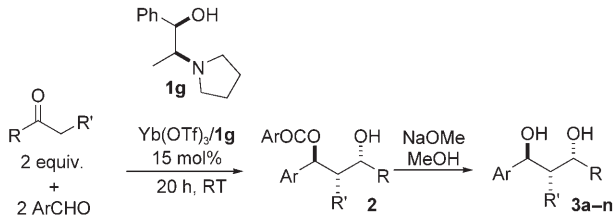


Scheme 2. Aldol-Tishchenko condensation of 3-pentanone with benzaldehyde: a) $Yb(OTf)_3$/**1g**, THF, RT, 20 h; b) NaOMe, MeOH; c) DMP, acetone, RT, 2 h. DMP = 2,2-Dimethoxypropane.

The structural assignment of the esters obtained was corroborated by high-resolution NMR spectroscopic experiments, and is in full agreement with previously published data.[14h,m] The assigned 1,2-*anti*-1,3-*anti* stereochemistry of **2a/b** was supported in both cases by the NMR spectroscopic analysis of separately derived diols **3a** and rigid *O*-isopropylidene derivative **4**. Characteristic signals of the isopropylidene ring in the ^{13}C NMR ($\delta = 23.6$, 24.8, and 100.9 ppm) are in full agreement with the rules presented by Rychnowski for 1,3-diols.[23] Such 1,3-*anti*-acetonides are expected to adopt twist boat conformations in which both methyl groups at the acetyl moiety are in nearly identical environments, which results in similar chemical shifts of approximately 24 ppm.

Preparation of *anti*-1,3-diols: According to the optimized reaction conditions discussed above, various methylene ketones were treated with the aldehydes giving rise to a broad range of 1,3-*anti*-diol monoesters **2** and after hydrolysis by using NaOMe in MeOH, the corresponding diols **3**. Experiments to probe the scope of the methodology are summarized in Table 2. Reactions were performed at room temperature, demonstrating the practical utility of the elaborated catalytic system. Generally good yields were obtained ranging between 60–85% for the two separated steps in which 15 mol% of the catalyst was used. To obtain optimal yields and *ee* values 1.5–2.0 equivalents of the ketone were used. It is noteworthy that this excess of the ketone donor in the reaction mixture did not favor formation of aldols. In all cases, aldol-Tishchenko esters were produced almost exclusively. All tested donors, that is, diethyl- and dipropylketone, pro-

Table 2. Substrate studies: condensation of ethyl and propyl ketones with various aldehydes promoted by $Yb(OTf)_3$ and (1*R*,2*S*)-**1g** (1:4).



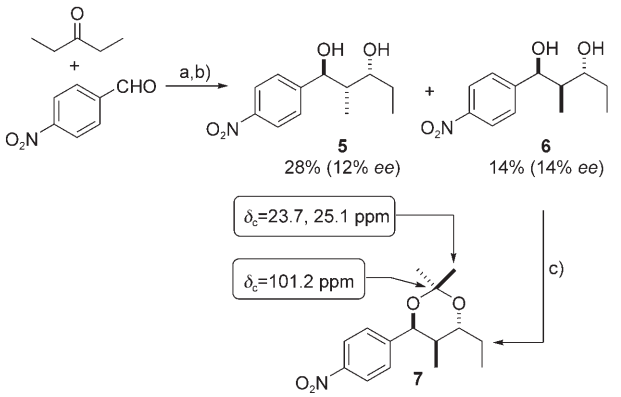
Entry	Ar	R	R′	Product	Yield of **3** [%][a]	*ee* of **3** [%][b]
1	Ph	Et	Me	**3a**	77	75
2	4-MeO-C_6H_4	Et	Me	**3b**	60	86
3	4-Me-C_6H_4	Et	Me	**3c**	76	80
4	4-Cl-C_6H_4	Et	Me	**3d**	76	53
5	4-Br-C_6H_4	Et	Me	**3e**	75	55
6	2-naphthyl	Et	Me	**3f**	67	70
7	Ph	Pr	Et	**3g**	77	65
8	4-MeO-C_6H_4	Pr	Et	**3h**	25	80
9	Ph	Ph	Me	**3i**	85	73
10	4-MeO-C_6H_4	Ph	Me	**3j**	45	75
11	4-Cl-C_6H_4	Ph	Me	**3k**	70	60
12	2-naphthyl	Ph	Me	**3l**	72	70
13	Ph	4-Cl-C_6H_4	Me	**3m**	89	72
14	4-MeO-C_6H_4	4-Cl-C_6H_4	Me	**3n**	92	78

[a] Isolated yield. [b] The *ee* values of esters and diols were determined by HPLC (Chiralpak AD-H and AS-H columns).

piophenone, and 4-chloropropiophenone can be used without loss of reaction efficiency. For dipropylketone a lower yield was observed, probably because of steric hindrance (entries 7 and 8). Activated aromatic ketones were more reactive, but still selective substrates (entries 9–14). All tested aromatic aldehydes gave useful product yields. Besides benzaldehyde (entry 1) other aromatic substrates reacted effectively to give diols in good yields with high *anti* selectivities beyond 94%. Less electrophilic anisaldehyde delivered diols in a slightly lower yield but with higher enantiocontrol (~86%, entry 2). The degree of enantioselectivity for the reaction strongly depends on the electronic nature of the substituents at the *para* position on the aromatic ring. The reactions with 4-methoxy- and 4-methylbenzaldehyde proceeded to give enantioselectivities in the range of 86 and 80%, respectively (entries 2 and 3). On the contrary, low enantioselectivity was observed in the reaction of benzaldehyde (75%) and 4-chloro- (53%) and 4-bromobenzaldehyde (55%). The last two aldehydes underwent condensation with slightly worse diastereoisomeric control (about 91–93%). To gather more information about the influence of the electron nature of the aldehyde on reaction enantioselectivity, we decided to check the reactivity of the 4-nitrobenzaldehyde, expecting isolation of 1,3-diol with low enantioselectivity. Indeed, aldol-Tishchenko condensation of 3-pentanone with this substrate resulted in the formation of the expected 1,2-*anti*-1,3-*anti*-diol **5** in 28% yield and with a low level of *ee* (Scheme 3).

Interestingly, the main product was accompanied by its 1,2-*syn*-1,3-*anti* isomer **6**, isolated

with a similar level of enantioselectivity (14%). Observed loss of diastereoselectivity for substrates with strong electron-donating substituents at the *para* position suggested nonselective formation of the six-membered ring in the postulated active site (Schemes 1 and 3).



Scheme 3. Aldol-Tishchenko condensation of 3-pentanone with *p*-nitrobenzaldehyde: a) $Yb(OTf)_3$/**1g**, DME, RT, 20 h; b) NaOMe, MeOH; c) DMP, acetone, RT, 2 h.

Reaction mechanism: To gather more information about the origin of the enantioselectivity, we examined the correlation between the Hammett aromatic substituent constants (σ_p) and the observed *ee*.

A linear Hammett plot with a negative rho value was observed as shown in Figure 1. This data suggests that the reaction proceeds by coordination of the aldehyde substrate to chiral ytterbium complex. This also indicates that the coordination step should be involved in at least the enantiodeterminating step.

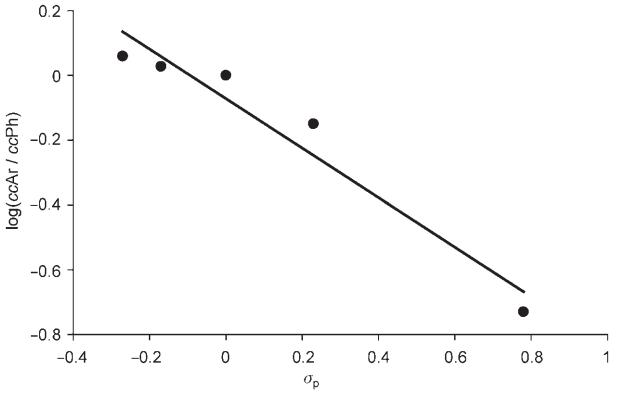
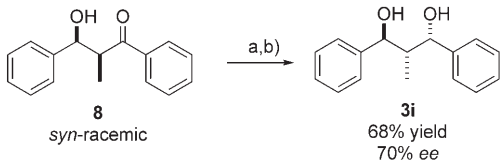


Figure 1. Hammett plot for the enantioselective aldol-Tishchenko reaction of substituted benzaldehydes ($y=-0.7652x-0.0714$; $r^2=0.942$).

To ascertain whether this reaction operates under similar Curtin–Hammett conditions as postulated in Scheme 1 (including initial formation of the aldol from an aldehyde and ethyl ketone), we designed an experiment to illustrate the relation between the aldol product and the Tishchenko product, as well as their stereocorrelation (Scheme 4). Independently prepared racemic hydroxyketone **8** was subjected

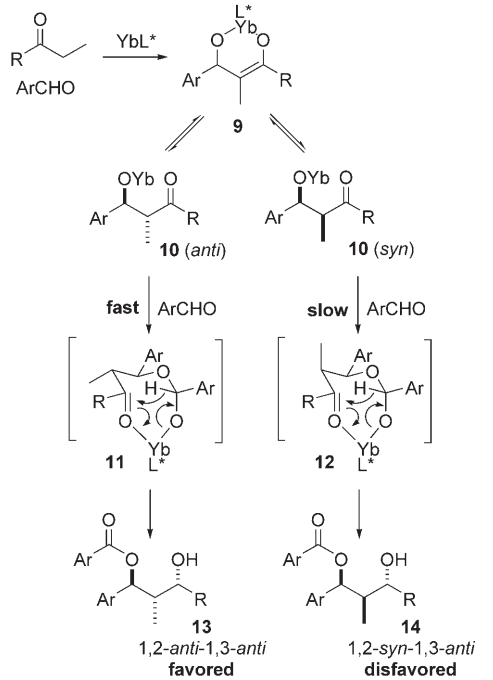


Scheme 4. Evans–Tishchenko reduction of aldol **8** with benzaldehyde: a) PhCHO, $Yb(OTf)_3$/**1g** (20 mol%), DME, RT, 3 h; b) NaOMe, MeOH.

to the Evans–Tishchenko catalytic reduction under conditions elaborated previously. With ligand **1g**, corresponding diol **3i** was obtained in 68% yield and with 70% *ee*. These results strongly indicate that, with the catalyst composed of ytterbium triflate and ligand **1g**, the Tishchenko reduction step is slower than the retroaldol reaction and it is the stereo-determining step. It is noteworthy that starting from *syn*-aldol **8**, the 1,2-*anti*-1,3-*anti*-Tishchenko product was formed exclusively. This observation confirms, as postulated previously, the essential role of the Tishchenko reaction step in controlling the stereoselectivity of the whole domino process.[15a]

Based on our own and previous[14h,15a] observations, a plausible mechanism for the aldol-Tishchenko reaction can be described (Scheme 5).

The first step of the reaction most likely produces a mixture of *syn* and *anti*-aldolates **10** as a result of a reversible reaction of the metal enolate with aldehyde. Isomerization



Scheme 5. Proposed mechanism for the aldol-Tishchenko reaction.

between both aldols (or corresponding metal aldolates) may proceed by means of an enolization–protonation mechanism via aldol enolate **9** under the control of a Lewis acid catalyst. Metal aldolate **9** can form a hemiacetal metal alkoxide with a second equivalent of aldehyde. High stereoselectivity in the Tishchenko step arises from favored formation of the transition structure **11** in which the ytterbium atom is chelated by the alkoxide and carbonyl oxygen atoms. All bulky substituents in the postulated transition state occupy energetically favorable equatorial positions.[17] The reaction is completed by intramolecular hydride delivery towards a proaxially oriented carbonyl group. A *syn*-aldolate **10** can undergo a similar reaction with a slower rate through transition state **12** with the alkyl group in an axial position. The energetically unfavorable structure of the transition state can explain the minor formation of the 1,2-*syn*-1,3-*anti*-diols **14**. Thus, after fast isomerisation of a *syn*-aldol into *anti*-aldol, the subsequent Tishchenko step proceeds via the more favorable transition state to afford the observed 1,2-*anti*-1,3-*anti* products **13**.

Determination of the absolute configuration of 1,3-diols: To get an insight into the sense of the asymmetric induction of the aldol-Tishchenko reaction resulting from the elaborated procedure we compared the optical rotation and results from HPLC analysis of the obtained diols with published data. The absolute configuration of *anti*-diol **3i** was determined as (1*S*,3*S*) by a comparison of the optical rotation of **3i** ($[\alpha]_D = -13.0$) with those of authentic compounds [(1*S*,3*S*) enantiomer, $[\alpha]_D = -12.1$, 84% *ee*].[15a] The same analysis in the case of *p*-chloro-substituted diol **3k** confirmed the same (1*S*,2*S*,3*S*) orientation of asymmetric carbon atoms ($[\alpha]_D = +1.1$, 70% *ee*; lit.[15a] (1*S*,3*S*) enantiomer, $[\alpha]_D = +1.3$, 95% *ee*). Thus it is important to underline that application of the (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidynyl)-1-propanol (**1g**) as a chiral ligand resulted in the formation of diols **3i** and **3k** with the same (1*S*,3*S*) configuration (Figure 2).

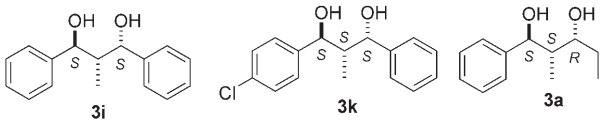


Figure 2. Deduced absolute configuration of compounds **3a**, **3k**, and **3i**.

Determination of the absolute configuration of the diol **3a** was, however, more puzzling. While its relative configuration was proved as 1,2-*anti*-1,3-*anti*, the absolute configurations at C1 (and linked configuration at C2, C3) was still not clear. We expected the same configuration of the asymmetric carbon atoms, that is, (1*S*,2*S*,3*R*) (Figure 2) as observed for compounds **3i** and **3k**. Analysis of the literature data [(1*R*,3*S*)-enantiomer: $[\alpha]_D = -7.6$, 99% *ee*][24] suggested, however, formation of the same isomer (1*R*,3*S*) of compound **3a** ($[\alpha]_D = -36$, 75% *ee*). Such a reverse sense of asymmetric induction was highly improbable, but not impossible in the light of the different nature of aliphatic and aromatic ketones. Although the presence of (1*R*,3*S*)-configured carbon atoms in **3a** would be highly surprising from a synthetic viewpoint, we could not rigorously exclude this possibility, except by additional analysis.

As resolving of this problem requires a really reliable and unambiguous technique we decided to apply circular dichroism spectroscopy (CD). To determine the absolute configuration at C1 and C3 carbon atoms in compound **3a**, the dimolybdenum method appeared to be a very convenient, straightforward, and versatile technique.[25]

The method involves the in situ formation of chiral complexes of optically active 1,3-diols with the achiral dimolybdenum tetraacetate [$Mo_2(OAc)_4$] acting as an auxiliary chromophore. The resulting CD spectra are suitable for the assignment of absolute configuration, as the observed sign of Cotton effects (CE) arising within the d–d absorption bands of the metal cluster depends upon the chirality of the 1,3-diol ligands. An additional advantage of the method is the fact that in the chiral Mo complex an internal conformational mobility of a flexible 1,3-diol molecule becomes substantially restricted due to the steric requirements of the stock complex. As a result, the molecule appears to exist only as a single conformer in which both hydroxy groups adopt a synperiplanar orientation. Consequently, the determination of the absolute configuration becomes possible on the basis of the sector rule correlating the sign of the Cotton effect (CE) occurring around 400 nm with the molecular structure of the 1,3-diol studied. The rule is formulated as follows provided that in the chiral complex the conformation with synperiplanar oriented hydroxy groups is preferred: The sign of the CE occurring around 400 nm in chiral Mo complexes with 1,3-diols is the same as the sign of the sector in which the majority of the molecule is located.[25]

CD data of in situ formed Mo complexes of diol **3a** and, for comparison purposes, of compounds **3l** (analogue of **3i** with two different chromophore groups) and **3k** (the absolute configuration of which is known), are collected in Table 3 and Figure 3. For this purpose diol **3l** was used instead of compound **3i**, which is not suitable for this analysis because of the two identical chromophore groups in the molecule.

Table 3. CD data of in situ formed Mo complexes of compounds **3a**, **3k**, and **3l** recorded in DMSO (ligand-to-metal molar ratio 1:1) in the spectral range 330–550 nm. Values are given as $\Delta\varepsilon'$ [nm].

Diol	Band 1	Band 2
3k	−0.21 (373.0)	+0.08 (432.5)
3l	−0.10 (367.0)	+0.03 (434.0)
3a	−0.12 (369.5)	+0.04 (430.5)

As can be seen, the sign of CE at around 430 nm is positive in all cases studied. Thus, the stereochemistry at C1 and C3 carbon atoms in compounds **3a**, **3k** and **3l** must be the same. According to the sector rule, a positive CE at 430 nm

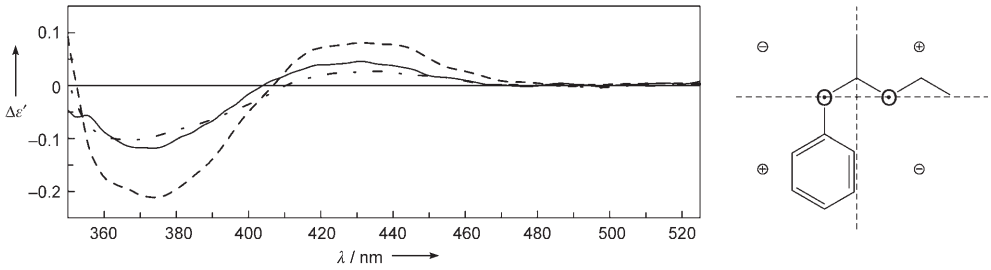


Figure 3. CD spectra of in situ formed Mo complexes of diols **3k** (– – –), **3l** (–•–•) and **3a** (——) recorded in DMSO (left) and projection of the sector rule for diol **3a** (right).

corresponds to a (1*S*,3*R*) absolute configuration in compound **3a**, whilst in the case of compounds **3k** and **3l** it corresponds to a (1*S*,3*S*) absolute configuration (Figure 3, right).[26]

To assure the configurational assignment at C1 in compound **3a** by the independent route we decided to apply the benzene sector rule.[27] According to the rule, the absolute configuration at the stereogenic center contiguous to the benzene ring can be established unambiguously on the basis of the sign of the excitation attributed to the ^1L_b benzene transition occurring around 260 nm. In the case of compound **3a**, the rule predicts a positive sign of the CE at around 260 nm for an (1*S*) isomer, which is in excellent agreement with the experimental data (Figure 4).[27]

It is worth pointing out that the configurational assignment to compound **3a** has been achieved by using two different CD rules for the analysis of the chiroptical properties. Therefore, this assignment can be considered as safe despite its empirical character. Hence, the structure proposed for compound **3a** and its stereochemical assignment presented previously in the literature clearly needs revision.

Conclusion

We have established a new catalyst for the enantioselective aldol reaction between aldehydes and aliphatic ketones to give aldol-Tishchenko products with a dramatic increase in molecular complexity created in a single operation. 1,3-Diol monoesters were formed in good to excellent yields, with high *anti* diastereocontrol, and with up to 85% *ee*. Moreover, this direct catalytic aldol protocol has been demonstrated as a useful method to overcome the retroaldol reaction problem of a direct aldol reaction of ethyl ketones. Aliphatic ketones were demonstrated to be convenient substrates in the direct asymmetric aldol-Tishchenko reaction for the first time. The presented methodology offers a simple yet powerful way to prepare *anti*-1,3-diols in one step from unmodified substrates with high diastereo- and good enantiocontrol.

Experimental Section

General: Ytterbium(III) triflate prepared from ytterbium(III) oxide (Aldrich) and trifluoromethanesulfonic acid (Fluka) was dried for 24 h at 200 °C under vacuum. All reactions were carried out under argon. Optical rotations were measured with a JASCO Dip-360 Digital Polarimeter at room temperature. ^{1}H NMR spectra were recorded on Varian-400 and Bruker-500 spectrometers in $CDCl_3$ with Me_4Si as the internal standard. HRMS were taken on a Mariner PerSeptive Biosystems mass spectrometer with time-of-flight (TOF) detector. IR spectra were taken with a Perkin–Elmer FTIR-1600 spectrophotometer. Reactions were controlled by using TLC on silica (Merck alu-plates (0.2 mm)). All reagents and solvents were purified and dried according to common methods. All organic solutions were dried over Na_2SO_4. Reaction products were purified by flash chromatography by using Merck's Kieselgel 60 (240–400 mesh). HPLC analyses were performed on a Knauer-HPLC system equipped with Daicel columns with a chiral stationary phase, detection at 254 nm.

CD analysis: UV measurements were made on a Cary 100 spectrophotometer in acetonitrile and DMSO (for UV-spectroscopy, Fluka). CD spectra were measured at room temperature in acetonitrile (for UV-spectroscopy, Fluka) with solutions at concentrations 8×10^{-4} M on a Jasco 715 spectrophotometer by using cells with path length 0.1 to 1 cm (spectral band width 2 nm, sensitivity 5×10^{-6} or 10×10^{-6} [ΔA-unit nm^{-1}], where $\Delta A = A_L - A_R$ is the difference in the absorbance. $\Delta\varepsilon$ is expressed in [L M^{-1} cm^{-1}] units. For CD measurements with $[Mo_2(OAc)_4]$, the solid chiral 1,3-diol (2.0–3.0 mg, approximately 0.0015 M L^{-1}) was dissolved in a

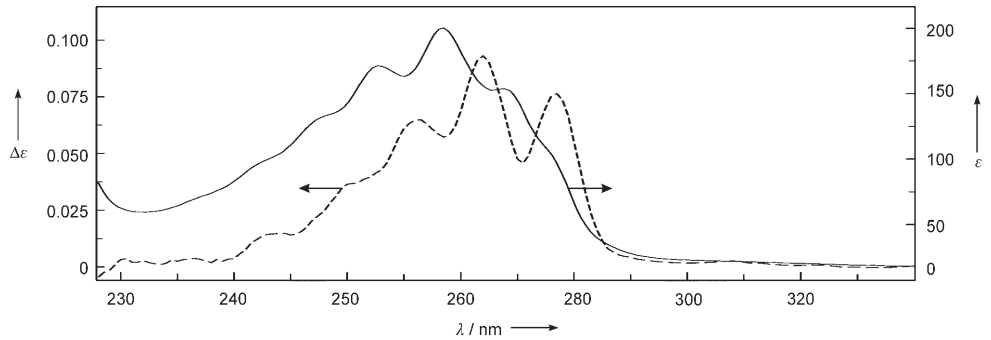


Figure 4. CD (– – –) and UV (——) spectra of diol **3a** recorded in acetonitrile in the range of 230–300 nm.

stock solution of the dimolybdenum tetraacetate (4.4–4.7 mg, approximately 0.0015 M L^{-1}) in DMSO so that the molar ratio of the stock complex to ligand was about 1:1, in general. The spectra were measured immediately after mixing of components and repeated after 1, 2, and 3 h, for comparison purposes. Some of the $\Delta\varepsilon'$ values were very small, but nevertheless the signal-to-noise ratio in all cases was better than at least 10:1.

General procedure for the aldol-Tishchenko reaction: Ytterbium(III) triflate (125 mg 0.20 mmol) was placed in an oven-dried flask with a magnetic stirring bar and the flask was heated at 200 °C for 10 min in vacuo and then flushed with argon. After the flask had been cooled down to RT, a solution of ligand **1g** (164 mg, 0.80 mmol) in DME (2 mL) was added. The resulting solution was stirred for 30 min at RT under argon. The catalyst 3-pentanone (100 μL, 0.95 mmol) and benzaldehyde (101 μL, 1.00 mmol) were then added successively to the solution. The resulting mixture was stirred for 20 h at RT and then poured onto a silica-gel column and eluted with hexane/ethyl acetate 9:1 to afford separated esters **2a**/**b** as an oil. The first fraction contained ester **2a** and the second ester **2b**. Esters **2a**/**b** so obtained were dissolved in MeOH (2 mL) and treated with NaOMe (5–10 mol %) overnight. The resulting mixture was purified by column chromatography on silica gel (hexane/ethyl acetate 3:2) to afford the diol **3a**. Based on this general procedure all other diols were isolated.

(1*S*,2*R*,3*R*)-1-Hydroxy-2-methyl-1-phenylpent-3-yl benzoate (2a) and (1*S*,2*S*,3*R*)-3-hydroxy-2-methyl-1-phenylpentyl benzoate (2b):[14h,m] Ester **2a**: Yield: 42 %; oil; $[\alpha]_D = +3.3$ ($c = 1.00$ in CH_2Cl_2, 72 % *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.75$ (d, $^3J(H,H) = 6.9$ Hz, 3H), 0.99 (t, $^3J(H,H) = J$ 7.4 Hz, 3H), 1.55–1.76 (m, 1H), 1.81–2.12 (m, 2H), 3.71 (d, $^3J(H,H) = J = 3.8$ Hz, 1H; OH), 4.19 (dd, $^3J(H,H) = 3.6$, 9.8 Hz, 1H), 5.62 (ddd, $^3J(H,H) = 1.5$, 5.6, 8.7 Hz, 1H), 7.20–7.64 (m, 8H; Ar), 8.10 ppm (m, 2H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 9.9$, 10.5, 25.7, 44.3, 75.7, 75.8, 127.0, 127.6, 128.3, 128.4, 129.7, 130.2, 133.2, 142.8, 167.6 ppm; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 12.3$ min, $t_2 = 21.6$ min (major). Ester **2b**: Yield: 39 %; $[\alpha]_D = -8.5$ ($c = 0.75$ in CH_2Cl_2, 73 % *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.75$ (d, $^3J(H,H) = 6.9$ Hz, 3H), 0.94 (t, $^3J(H,H) = 7.3$ Hz, 3H), 1.36–1.48 (m, 1H), 1.56–1.67 (m, 1H), 2.02–2.20 (m, 1H), 2.52 (brs, 1H; OH), 3.75 (ddd, $^3J(H,H) = 1.8$, 5.1, 7.0 Hz, 1H), 5.95 (d, $^3J(H,H) = 9.8$ Hz, 1H), 7.20–7.68 (m, 8H; Ar), 8.10 ppm (m, 2H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.9$, 10.8, 27.3, 43.0, 71.2, 78.8, 127.4, 128.1, 128.3, 128.4, 129.7, 129.9, 133.1, 139.4, 166.5 ppm; HPLC (Chiralpak AD-H, hexane/*i*PrOH 97:3, flow rate 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 23.2$ min (major), $t_2 = 24.3$ min; (Chiralpak OD-H, hexane/*i*PrOH 97:3, flow rate = 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 8.1$ min, $t_2 = 8.7$ min (major).

(1*S*,2*S*,3*R*)-2-Methyl-1-phenylpentane-1,3-diol (3a):[14h,m,28] $[\alpha]_D = -36.2$ ($c = 0.60$ in CH_2Cl_2, 75 % *ee*); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.87$ (d, $^3J(H,H) = 7.1$ Hz, 3H), 0.91 (t, $^3J(H,H) = 7.4$ Hz, 3H), 1.39–1.48 (m, 1H), 1.51–1.60 (m, 1H), 1.94 (dq, $^3J(H,H) = 2.1$, 7.0 Hz, 1H), 2.46 (d, $^3J(H,H) = 4.9$ Hz, 1H; OH), 3.09 (d, $^3J(H,H) = 4.1$ Hz, 1H; OH), 3.70–3.75 (m, 1H), 4.72 (dd, $^3J(H,H) = 4.1$, 6.6 Hz, 1H), 7.25–7.30 (m, 1H; Ar), 7.35 ppm (d, 4H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 10.6$, 11.3, 26.7, 43.4, 74.0, 78.3, 126.3, 127.4, 128.4, 143.9 ppm; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 7.8$ min, $t_2 = 10.1$ min (major).

(1*S*,2*S*,3*R*)-1-(4-Methoxyphenyl)-2-methylpentane-1,3-diol (3b): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) $\delta = 0.83$ (d, $^3J(H,H) = 7.1$ Hz, 3H), 0.93 (t, $^3J(H,H) = 7.2$ Hz, 3H), 1.40–1.50 (m, 1H), 1.52–1.60 (m, 1H), 1.92 (m, 1H), 2.30 (brs, 2H; 2 × OH), 3.72–3.76 (m, 1H), 3.81 (s, 3H), 4.66 (d, $^3J(H,H) = 7.1$ Hz, 1H), 6.87–6.90 (m, 2H; Ar), 7.25–7.28 ppm (m, 2H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 10.7$, 11.5, 26.5, 43.5, 55.2, 74.2, 77.7, 113.7, 127.4, 135.9, 158.9 ppm; IR (film): $\tilde{\nu} = 3361$, 2964, 2936, 1612, 1513, 1248, 1175 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{20}O_3$: 247.1305 $[M+Na]^+$; found: 247.1319; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 11.3$ min, $t_2 = 12.7$ min (major).

(1*S*,2*S*,3*R*)-2-Methyl-1-(4-methylphenyl)pentane-1,3-diol (3c): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) $\delta = 0.85$ (d, $^3J(H,H) = 7.1$ Hz, 3H), 0.92 (t, $^3J(H,H) = 7.4$ Hz, 3H), 1.38–48 (m, 1H), 1.49–1.61 (m, 1H), 1.92 (m, 1H), 2.34 (s, 3H), 2.44 (s, 2H; 2 × OH), 3.72 (ddd, $^3J(H,H) = 2.2$, 4.6, 8.9 Hz, 1H), 4.67 (d, $^3J(H,H) = 6.8$ Hz, 1H), 7.16 (d, $^3J(H,H) = 7.7$ Hz, 2H; Ar), 7.20–7.26 ppm (m, 2H; Ar); ^{13}C NMR (100 MHz, CDCl3, 25 °C, TMS): $\delta = 10.6$, 11.4, 21.0, 26.6, 43.3, 74.0, 78.1, 126.1, 129.0, 137.0, 140.7 ppm; IR (film): $\tilde{\nu} = 3351$, 2966, 2936, 1514, 1458, 1379, 1103 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{20}O_2$: 231.1356 $[M+Na]^+$; found: 231.1354; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 8.4$ min, $t_2 = 9.1$ min (major).

(1*S*,2*S*,3*R*)-1-(4-Chlorophenyl)-2-methylpentane-1,3-diol (3d): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.88$ (d, $^3J(H,H) = 7.1$ Hz, 3H), 0.90 (t, $^3J(H,H) = 7.4$ Hz, 3H), 1.39–1.49 (m, 1H), 1.50–1.58 (m, 1H), 1.85–1.92 (m, 1H), 2.60 (s, 2H; 2 × OH), 3.68 (ddd, $^3J(H,H) = 2.1$, 4.7, 8.8 Hz, 1H), 4.69 (d, $^3J(H,H) = 6.4$ Hz, 1H), 7.26–7.33 ppm (m, 4H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 10.5$, 11.3, 26.7, 43.1, 74.0, 77.6, 127.5, 128.4, 132.9, 142.4 ppm; IR (film): $\tilde{\nu} = 3339$, 2967, 2937, 1597, 1491, 1380, 1090 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{17}ClO_2$: 251.0809 $[M^+ + Na]$; found: 251.0818; HPLC (Chiralpak AS-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 7.1$ min, $t_2 = 10.4$ min (major).

(1*S*,2*S*,3*R*)-1-(4-Bromophenyl)-2-methylpentane-1,3-diol (3e): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) $\delta = 0.89$ (d, $^3J(H,H) = 7.1$ Hz, 3H), 0.90 (t, $^3J(H,H) = 7.4$ Hz, 3H), 1.37–1.47 (m, 1H), 1.48–1.59 (m, 1H), 1.84–1.91 (m, 1H), 2.46 (brs, 1H; OH), 3.51 (brs, 1H; OH), 3.65 (ddd, $^3J(H,H) = 2.2$, 4.8, 8.8 Hz, 1H), 4.67 (d, $^3J(H,H) = 6.4$ Hz, 1H), 7.20–7.27 (m, 2H; Ar), 7.44–7.49 ppm (m, 2H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 10.5$, 11.3, 26.7, 43.1, 74.0, 77.6, 121.0, 127.9, 131.3, 142.9 ppm; IR (film): $\tilde{\nu} = 3339$, 2966, 2936, 1592, 1487, 1380, 1098 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{17}BrO_2$: 295.0304 $[M+Na]^+$; found: 295.0307; HPLC (Chiralpak AS-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 6.9$ min, $t_2 = 10.1$ min (major).

(1*S*,2*S*,3*R*)-2-Methyl-1-(2-naphthyl)-pentane-1,3-diol (3f): ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.87$ (t, $^3J(H,H) = 7.4$ Hz, 3H), 0.90 (d, $^3J(H,H) = 7.1$ Hz, 3H), 1.31–1.66 (m, 2H), 1.96–2.10 (m, 1H), 2.69 (brs, 1H, OH), 3.51 (brs, 1H, OH), 3.71 (m, 1H), 4.86 (d, $^3J(H,H) = 6.3$ Hz, 1H), 7.40–7.49 (m, 3H; Ar), 7.78–7.86 ppm (m, 4H; Ar); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 10.6$, 11.5, 26.7, 43.0, 74.0, 78.3, 124.2, 125.0, 125.7, 126.0, 127.6, 127.9, 128.1, 132.8, 133.1, 141.2 ppm; IR (film): $\tilde{\nu} = 3339$, 2966, 2936, 1602, 1459, 1247, 1123 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{20}O_2$: 267.1355 $[M+Na]^+$; found: 267.1368; HPLC (Chiralpak AS-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 8.7$ min, $t_2 = 11.7$ min (major).

(1*S*,2*S*,3*R*)-2-Ethyl-1-phenylhexane-1,3-diol (3g): ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.84$ (t, $^3J(H,H) = 6.9$ Hz, 3H), 0.93 (t, $^3J(H,H) = 7.4$ Hz, 3H), 1.15–1.70 (m, 7H), 2.88 (d, $^3J(H,H) = 4.9$, 1H; OH), 3.47 (d, $^3J(H,H) = 4.6$ Hz, 1H; OH), 3.62–3.85 (m, 1H), 4.89 (t, $^3J(H,H) = 5.0$ Hz, 1H), 7.20–7.45 ppm (m, 5H; Ar); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 12.5$, 13.9, 18.4, 19.4, 35.6, 50.3, 71.7, 75.7, 126, 127.1, 128.2, 143.9 ppm; IR (film): $\tilde{\nu} = 3307$, 2960, 2874, 1455, 1198, 1117, 1013, 701 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{22}O_2$: 204.1514 $[M-H_2O]^+$; found: 204.1508; HPLC (Chiralpak AS-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 5.1$ min, $t_2 = 5.7$ min (major).

(1*S*,2*S*,3*R*)-2-Ethyl-1-(4-methoxyphenyl)-hexane-1,3-diol (3h): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.87$ (t, $^3J(H,H) = 7.1$ Hz, 3H), 0.89 (t, $^3J(H,H) = 7.4$ Hz, 3H), 1.19–1.66 (m, 7H), 2.99 (brs, 1H; OH), 3.30 (brs, 1H; OH), 3.75 (m, 1H), 3.80 (s, 3H), 4.82 (d, $^3J(H,H) = 6.0$ Hz, 1H), 6.88 (d, $^3J(H,H) = 8.8$ Hz, 2H; Ar), 7.25 ppm (d, $^3J(H,H) = 8.4$ Hz, 2H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 12.5$, 14.0, 18.7, 19.5, 35.3, 50.5, 55.2, 71.9, 75.6, 113.6, 127.3, 136.0, 158.7 ppm; IR (film): $\tilde{\nu} = 3325$, 2959, 2933, 1612, 1513, 1248, 1174 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{24}O_3$: 275.1620 $[M+Na]^+$; found: 275.1621; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, $\lambda = 254$ nm): $t_1 = 8.1$ min (major), $t_2 = 9.4$ min.

(1*S*,3*S*)-2-Methyl-1,3-diphenylpropane-1,3-diol (3i):[15a,28] $[\alpha]_D = -13.0$ ($c = 0.60$ in CH_2Cl_2, 75 % *ee*) (lit.[15a] $[\alpha]_D = -12.1$ ($c = 1.0$ in CH_2Cl_2, 84 % *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.71$ (d, $^3J(H,H) = 7.1$ Hz, 3H), 2.14 (m, 1H), 3.05 (d, $^3J(H,H) = 3.4$ Hz, 1H; OH), 3.15 (d, $^3J(H,H) = 3.4$ Hz, 1H; OH), 4.64 (dd, $^3J(H,H) = 3.6$, 6.6 Hz, 1H), 4.96 (t, $^3J(H,H) = 3.1$ Hz, 1H), 7.20–7.40 ppm (m, 10H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) $\delta = 11.2$, 45.7, 74.3, 77.7, 125.9, 126.2,

126.9, 127.5, 127.9, 128.3, 142.5, 143.4 ppm; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, λ = 254 nm): t_1 = 11.4 min, t_2 = 14.5 min (major).

(1*S*,2*S*,3*S*)-1-(4-Methoxyphenyl)-2-methyl-3-phenylpropane-1,3-diol (3j):[29,30] ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.66 (d, ^3J(H,H) = 7.1 Hz, 3H), 2.05–2.20 (m, 1H), 3.35 (brs, 1H, OH), 3.57 (brs, 1H; OH), 3.78 (s, 3H), 4.57 (d, ^3J(H,H) = 7.1 Hz, 1H), 4.98 (d, ^3J(H,H) = 2.2 Hz, 1H), 6.84–6.88 (d, ^3J(H,H) = 8.8 Hz, 1H; Ar), 7.18–7.37 ppm (m, 7H; Ar); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ = 11.2, 45.5, 55.0, 74.3, 77.4, 113.5, 125.8, 126.6, 127.2, 127.7, 135.4, 142.3, 158.6 ppm; IR (film): $\tilde{\nu}$ = 3368, 2968, 1611, 1513, 1451, 1248, 1175, 1032, 830 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{20}O_3$: 272.1412 $[M]^+$; found: 272.1404; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, λ = 254 nm): t_1 = 16.2 min, t_2 = 20.8 min (major).

(1*S*,2*S*,3*S*)-1-(4-Chlorophenyl)-2-methyl-3-phenylpropane-1,3-diol (3k):[15a] $[\alpha]_D$ = +1.1 (c = 0.50 in CH_2Cl_2, 70% *ee*) (lit.[15a] $[\alpha]_D$ = +1.3 (c = 1.75 in CH_2Cl_2, 95% *ee*)); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 0.75 (d, ^3J(H,H) = 7.1 Hz, 3H), 2.18 (m, 1H), 3.00 (d, ^3J(H,H) = 3.6 Hz, 1H; OH), 3.30 (d, ^3J(H,H) = 4.1 Hz, 1H; OH), 4.67 (dd, ^3J(H,H) = 4.3, 6.6 Hz, 1H), 5.00 (t, ^3J(H,H) = 2.9 Hz, 1H), 7.12–7.40 ppm (m, 9H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 11.3, 45.5, 74.4, 77.0, 125.9, 127.1, 127.5, 128.0, 128.4, 133.0, 141.9, 142.1 ppm; HPLC (Chiralpak AD-H, hexane/*i*PrOH 95:5, flow rate = 1 mL min^{-1}, λ = 254 nm): t_1 = 22.8 min, t_2 = 28.8 min (major).

(1*S*,2*S*,3*S*)-2-Methyl-1-(2-naphthyl)-3-phenylpropane-1,3-diol (3l): ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.73 (d, ^3J(H,H) = 7.2 Hz, 3H), 2.14–2.34 (m, 1H), 3.48 (d, ^3J(H,H) = 3.9 Hz; 1H, OH), 3.63 (d, ^3J(H,H) = 3.8 Hz, 1H; OH), 4.78 (dd, ^3J(H,H) = 3.3, 6.1 Hz, 1H), 4.96 (brs, 1H), 7.20–7.31 (m, 5H; Ar), 7.38–7.50 (m, 3H; Ar), 7.75–7.83 ppm (m, 4H; Ar); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ = 11.4, 45.4, 74.4, 77.8, 124.1, 125.1, 125.8, 125.9, 126.1, 126.9, 127.6, 127.9, 128.2, 132.8, 133.1, 140.8, 142.4 ppm; IR (film): $\tilde{\nu}$ = 3339, 3027, 2975, 2882, 1451, 756 cm^{-1}; HRMS (ESI): calcd for $C_{20}H_{20}O_2$: 315.1355 $[M+Na]^+$; found: 315.1345; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, λ = 254 nm): t_1 = 16.8 min, t_2 = 21.7 min (major).

(1*S*,2*R*,3*S*)-1-(4-Chlorophenyl)-2-methyl-3-phenylpropane-1,3-diol (3m): ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.67 (d, ^3J(H,H) = 7.2 Hz, 3H), 1.99–2.24 (m, 1H), 3.51 (d, ^3J(H,H) = 3.1, 1H; OH), 3.86 (d, ^3J(H,H) = 3.9 Hz, 1H; OH), 4.59 (dd, ^3J(H,H) = 3.1, 6.5 Hz, 1H), 4.86 (m, 1H), 7.00–7.40 ppm (m, 9H; Ar); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ = 11.2, 45.6, 73.6, 77.7, 74.0, 126.1, 127.3, 127.6, 128.0, 128.4, 132.4, 141.0, 143.1 ppm; IR (KBr): $\tilde{\nu}$ = 3364, 2981, 2927, 1491, 1454, 1091, 1011 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{17}ClO_2$: 258.0811 $[M-H_2O]^+$; found: 258.0807; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, λ = 254 nm): t_1 = 9.9 min, t_2 = 15.0 min (major).

(1*S*,2*R*,3*S*)-1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-2-methylpropane-1,3-diol (3n):[29] ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.67 (d, ^3J(H,H) = 7.2 Hz, 3H), 2.03–2.20 (m, 1H), 3.00 (brs, 1H; OH), 3.50 (brs, 1H; OH), 3.80 (s, 3H), 4.59 (d, ^3J(H,H) = 7.0 Hz, 1H), 4.98 (d, ^3J(H,H) = 2.2 Hz, 1H), 6.86–6.88 (d, ^3J(H,H) = 8.8, 2H; Ar), 7.18–7.32 ppm (m, 6H; Ar); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ = 11.3, 45.8, 55.2, 73.8, 76.9, 113.8, 127.3, 127.4, 128.0, 132.4, 135.3, 141.1, 159.1 ppm; IR (film): $\tilde{\nu}$ = 3368, 2971, 2935, 1611, 1512, 1249, 1175 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{19}ClO_3$: 306.1022 $[M]^+$; found: 306.1016; HPLC (Chiralpak AD-H, hexane/*i*PrOH 4:1, flow rate = 1 mL min^{-1}, λ = 254 nm): t_1 = 8.1 min, t_2 = 10.4 min (major).

(1*S*,2*S*,3*R*)-1,3-*O*-Isopropylidene-2-methyl-1-phenylpentane-1,3-diol (4): Camphorosulfonic acid (small crystal) was added to a solution of the 1,3-diol **3a** (97 mg, 0.5 mmol) in acetone and 2,2-dimethoxypropane (5 mL, 4:1) at RT. The mixture was stirred at ambient temperature for 1 h, then quenched with one drop of Et_3N, concentrated under reduced pressure, and purified by flash chromatography (hexane/ethyl acetate 95:5) to yield diacetonide **4** as an oil (113 mg, 93%); $[\alpha]_D$ = −40.1 (c = 0.65 in CH_2Cl_2, 43% *ee*); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.88 (d, ^3J(H,H) = 6.8 Hz, 3H), 0.97 (t, ^3J(H,H) = 7.3 Hz, 3H), 1.43, 1.45 (2s, 2×3H; O*i*Pr), 1.39–1.46 (m, 1H), 1.49–1.58 (m, 1H), 2.00–2.07 (m, 1H), 3.73 (ddd, ^3J(H,H) = 2.1, 4.6, 6.8 Hz, 1H), 3.95 (m, 1H), 4.24 (d, ^3J(H,H) = 8.3 Hz, 1H), 7.26–7.42 ppm (m, 5H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.6, 11.3, 23.6, 24.0, 24.8, 41.7, 71.1, 77.6, 100.9, 126.9, 127.6, 128.4, 142.0 ppm; IR (film): $\tilde{\nu}$ = 2984, 2966, 2937, 2878, 1496, 1455, 1378, 1223 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{22}O_2$: 234.1619 $[M]^+$; found: 234.1618; HPLC (Chiralpak AS-H, hexane/*i*PrOH 99:1, flow rate = 1 mL min^{-1}, λ = 254 nm): t_1 = 3.3 min (major), t_2 = 3.6 min.

(1*S*,2*S*,3*R*)-1-(4-Nitrophenyl)-2-methylpentane-1,3-diol (5): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.87 (t, ^3J(H,H) = 7.4 Hz, 3H), 0.97 (d, ^3J(H,H) = 7.1 Hz, 3H), 1.39–1.49 (m, 1H), 1.50–1.60 (m, 1H), 1.89–1.97 (m, 1H), 2.40 (brs, 1H; OH), 3.60–3.64 (m, 1H), 4.07 (brs, 1H; OH), 4.83 (d, ^3J(H,H) = 6.0 Hz, 1H), 7.52–7.54 (m, 2H; Ar), 8.19–8.22 ppm (m, 2H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.6, 11.4, 27.1, 43.1, 74.2, 77.8, 123.7, 127.2, 147.3, 151.8 ppm; IR (KBr): $\tilde{\nu}$ = 3524, 3393, 2919, 1606, 1523, 1457, 1348, 1090 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{17}NO_4$: 262.1049 $[M+Na]^+$; found: 262.1057; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, λ = 254 nm): t_1 = 12.9 min, t_2 = 13.7 min (major).

(1*S*,2*R*,3*R*)-1-(4-Nitrophenyl)-2-methylpentane-1,3-diol (6): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.81 (d, ^3J(H,H) = 7.1 Hz, 3H), 1.02 (t, ^3J(H,H) = 7.4 Hz, 3H), 1.67–1.80 (m, 2H), 1.84–1.92 (m, 1H), 2.27 (brs, 1H; OH), 3.64 (dd, ^3J(H,H) = 5.2, 11.7 Hz, 1H), 3.74 (brs, 1H; OH), 5.28 (s, 1H), 7.51 (d, ^3J(H,H) = 8.4 Hz, 2H; Ar), 8.17–8.22 ppm (m, 2H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.0, 10.8, 28.2, 43.1, 72.9, 77.2, 123.2, 126.7, 146.9, 151.0 ppm; HRMS (ESI): calcd for $C_{12}H_{17}NO_4$: 262.1049 $[M+Na]^+$; found: 262.1050; HPLC (Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 1 mL min^{-1}, λ = 254 nm): t_1 = 11.7 min, t_2 = 13.6 min (major). Based on the procedure described for **4** diol, **6** was transformed into (1*S*,2*R*,3*R*)-1,3-*O*-isopropylidene-2-methyl-1-(4-nitrophenyl)pentane-1,3-diol (**7**).

(1*S*,2*R*,3*R*)-1,3-*O*-Isopropylidene-2-methyl-1-(4-nitrophenyl)pentane-1,3-diol (7): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.49 (d, ^3J(H,H) = 6.9 Hz, 3H), 1.00 (t, ^3J(H,H) = 7.3 Hz, 3H), 1.40, 1.48 (2s, 2×3H; O*i*Pr), 1.55–1.67 (m, 2H), 1.97–2.04 (m, 1H), 3.29 (dt, ^3J(H,H) = 4.0, 7.9 Hz, 1H), 5.14 (d, ^3J(H,H) = 5.2 Hz, 1H), 7.42–7.46 (m, 2H; Ar), 8.17–8.20 ppm (m, 2H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.4, 12.9, 23.7, 25.1, 27.6, 41.4, 70.3, 77.2, 101.2, 123.2, 126.6, 146.7, 148.1 ppm.

Ligand synthesis: general procedure for the synthesis of *N,N*-dialkylnorephedrines:[22] A mixture of (1*S*,2*R*)-(+)- or (1*R*,2*S*)-(−)-norephedrine (10 mmol), alkyl iodide (20 mmol), K_2CO_3 (20 mmol), and CH_3CN (10 mL) was refluxed for 2–24 h. After this time, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc).

(1*S*,2*R*)-2-(Diethylamino)-1-phenylpropan-1-ol (1d):[22] $[\alpha]_D$ = −22.7 (c = 0.30 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.87 (d, ^3J(H,H) = 6.9 Hz, 3H), 1.00 (t, ^3J(H,H) = 7.1 Hz, 6H), 2.46 (q, ^3J(H,H) = 7.1 Hz, 4H), 2.95–3.08 (m, 1H), 4.22 (brs, 1H; OH), 4.67 (d, ^3J(H,H) = 4.7 Hz, 1H), 7.08–7.20 ppm (m, 5H; Ar).

(1*S*,2*R*)-2-(Di-*n*-propylamino)-1-phenylpropan-1-ol (1e):[22] $[\alpha]_D$ = −42.0 (c = 1.00 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.80 (t, ^3J(H,H) = 7.4 Hz, 6H), 0.90 (d, ^3J(H,H) = 7.0 Hz, 3H), 1.12–1.49 (m, 4H), 2.68–2.40 (m, 4H), 2.94–3.07 (m, 1H), 4.13 (brs, 1H; OH), 4.65 (d, ^3J(H,H) = 5.0 Hz, 1H), 7.08–7.20 ppm (m, 5H; Ar).

(1*S*,2*R*)-2-(Di-*n*-butylamino)-1-phenylpropan-1-ol (1f):[22] $[\alpha]_D$ = −20.1 (c = 0.98 in hexane); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.87 (t, ^3J(H,H) = 7.0 Hz, 6H), 0.89 (d, ^3J(H,H) = 7.0 Hz, 4H), 1.34–1.53 (m, 8H), 2.12–2.41 (m, 4H), 2.94–3.07 (m, 1H), 4.16 (brs, 1H; OH), 4.66 (d, ^3J(H,H) = 5.2 Hz, 1H), 7.08–7.18 ppm (m, 5H; Ar).

(1*S*,2*R*)-1,2-Diphenyl-2-(1-pyrrolidinyl)-ethan-1-ol (1h): $[\alpha]_D$ = +90.9 (c = 1.00 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS) δ = 1.70–1.95 (m, 4H), 2.50–2.82 (m, 4H), 3.28 (d, ^3J(H,H) = 3.5 Hz, 1H), 3.65 (brs, 1H; OH), 5.22 (d, ^3J(H,H) = 3.5 Hz, 1H), 6.86–6.99 (m, 4H), 7.02–7.15 ppm (m, 6H); ^{13}C NMR (50 MHz): δ = 23.5, 52.9, 74.0, 76.8, 126.0, 126.6, 127.0, 127.1, 127.4, 129.2, 137.4, 140.6 ppm; IR (film): $\tilde{\nu}$ = 3465, 3034, 2968, 2799, 1453 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{21}NO$: 268.1695 $[M]^+$; found: 268.1693.

(1*S*,2*R*)-2-Piperydynyl-1-phenylpropan-1-ol (1i):[31] $[\alpha]_D = -1.2$ ($c = 0.17$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.82$ (d, $^3J(H,H) = 7.0$ Hz, 3H), 1.35–1.62 (m, 6H), 2.41–2.57 (m, 4H), 2.63–2.75 (m, 1H), 4.10 (br s, 1H; OH), 4.81 (d, $^3J(H,H) = 4.2$ Hz, 1H), 7.17–7.32 ppm (m, 5H; Ar); ^{13}C NMR (50 MHz): $\delta = 10.2$, 24.5, 26.5, 51.7, 64.5, 72.1, 125.9, 126.6, 127.8, 142.2 ppm.

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