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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

A set of bis-TADDOLs, in which two TADDOL moieties are connected by different linkers, have been prepared. A great dependence of the catalytic activities of the bis-TADDOLs on the distance between the TADDOL moieties was found by the addition of trifluoromethyltrimethylsilane to benzaldehyde and ring-opening of cyclohexene oxide with or without alkali metal salts added.

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Tetrahedron

1. Introduction

Asymmetric organocatalysis with chiral organic Brønsted acids and bases is an important field of investigation in modern asymmetric synthesis.^{1–3} This approach is very attractive due to its conceptual and experimental simplicity, the absence of hazardous heavy metal salts in reaction mixtures and the extremely high efficiency of the catalysis.⁴ The use of chiral Brønsted acids as catalysts for asymmetric C-C bond-forming reactions has recently become a particularly popular and productive field of research.^{5a-h} This class of catalysts includes, amongst other chiral polyfunctional Brønsted acids, $\alpha, \alpha, \alpha', \alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanols [(*R*,*R*)-TADDOLs],^{6a–d} in which the acidity of one hydroxy group increases due to the presence of the other hydroxy group as a result of intramolecular hydrogen bonding, as shown for dioxolane **1** in Figure 1. This type of catalyst activated by Brønsted acids is called Brønsted acid-assisted Brønsted acid catalysts.⁷ Asymmetric Diels-Alder reactions,⁸ Mukaiyama aldol reactions^{6c} and the TADDOL-promoted condensations of nitroso compounds with enamines⁹ provide examples of this class of catalysis.

Evidently, an increase in the acidity of one hydroxy group leads to an increase in the basicity of the other hydroxy group, for which the hydrogen atom is involved in hydrogen bonding.^{6c,7} Hence, TADDOLs would be expected to act as chiral bifunctional catalysts by activating both the electrophilic and nucleophilic components of the reaction, as shown by the hypothetical transition state (Fig. 1).¹⁰

Presumably, the presence of two (R,R)-TADDOL fragments in a single molecule can increase the efficiency of such catalysts due to the spatially favourable arrangement of several acidic groups capable of activating substrates. The use of cyclohexanedionebased bis-TADDOLs^{11,12} in photochemical reactions has been documented.¹³ However, these compounds were used in equimolar amounts with respect to the substrates.



Figure 1. Effect of intramolecular hydrogen bonding on the reactivity of TADDOLs.

Recently, we reported the synthesis of a set of bis-(R,R)-TADD-OLs based on phthalaldehyde, differing in the distances between their pairs of hydroxy groups.¹⁴ The catalytic activities of the bis-(R,R)-TADDOLs were studied by the addition of TMSCN to benzaldehyde and ring-opening of cyclohexene oxide by TMSCN, leading to the formation of hydroxynitriles. The catalytic activities of the chiral tetraols were found to depend crucially on the distances between the TADDOL moieties of the catalysts. Only a few examples of organic catalysts for the addition of TMSCN to benzaldehyde are known, and these involve the use of bases or carbenes.¹⁵

Herein we report some novel applications of the catalytic system for the ring-opening of cyclohexene oxide. Further modification of the catalytic system with alkali metal salts resulted in very efficient catalysts for epoxide ring-opening by *p*-toluidine,



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producing hydroxyamines and highly effective catalysts for trifluoromethylation of aldehydes.

2. Results and discussion

Mono-(*R*,*R*)-TADDOL **1** and bis-(*R*,*R*)-TADDOLs **2–5** (see Fig. 2) were synthesised as described previously.¹⁴



Figure 2. Mono-(R,R)-TADDOL 1 and bis-(R,R)-TADDOLs. 2-5.

2.1. Epoxide ring-opening with *p*-toluidine

Epoxide ring-opening with p-toluidine would be expected to be promoted by the set of (R,R)-TADDOLs acting as Brønsted acids.



Scheme 1. TADDOL/MBPh₄ catalysed ring-opening of cyclohexene oxide with toluidine.

Asymmetric epoxide ring-opening catalysed by chiral Lewis acids^{16,17} has been studied in detail. However, to our knowledge, there are no examples of the asymmetric catalysis of epoxide ring-opening promoted by chiral Brønsted acids activated by weak Lewis acids.

Activation of TADDOLs by the introduction of tetraphenylborate salts of alkali metal ions (Li⁺, Na⁺ and K⁺) into the reaction mixture (Scheme 1) resulted in an increase of TADDOL activity associated with the Lewis acid-assisted Brønsted acid catalysis principle.⁷ To suppress the spontaneous reaction catalysed by the salts themselves (Table 1, entry 1), a fivefold excess of bis-TADDOLs and 10-fold excess of mono-TADDOL relative to the amount of alkali metal salt were used in the experiments to secure almost complete complex formation.

Table 1

Cyclohexene oxide ring-opening with toluidine catalysed by a series of bis-TADDOL/ $\rm MBPh_4$ systems in $\rm CH_2Cl_2{}^a$

Entry	TADDOL	Yield (ee ^b),	Yield (ee ^b), % with co-catalyst	
		NaBPh ₄	LiBPh ₄	
1	_	37	80	
2	1	80	80	
3	2	70	90	
4	3	88	90	
5	4a	98	97 (25 ^b)	
6	4b	99	$99(40^{b})$	
7	5	100	100	

^a Reaction conditions: room temperature, CH₂Cl₂ 0.5 mL, cyclohexene oxide 0.5 mmol, *p*-toluidine 0.5 mmol, dry MBPh₄ 0.5 mol %, TADDOLs (5 mol % in case of bis-TADDOLs **2–5** and 10 mol % in case of mono-TADDOL **1**), 72 h under Ar.

^b Enantiomeric analysis by HPLC on a Chiralcel OD-H column, the configuration is (*S*,*S*) in both cases.

The cyclohexene oxide ring-opening with toluidine (Scheme 1) was not catalysed by the mono and bis-TADDOLs and/or KBPh₄. However, the reaction was catalysed by NaBPh₄ and LiBPh₄ alone and their 1:10 mixtures with TADDOLs (Table 1, entries 1–7). Thus, the usual Lewis acidity order Li > Na > K was followed by the catalysts. The observation of some asymmetric induction in the case of LiBPh₄/**4a** (entries 5 and 6) indicated that most (if not all) of the Li cations were involved in complexation with TADDOLs. The very similar activities of **1** and other bis-TADDOLs (entries 2 and 3–7) reflect a monofunctional character of the catalysis with Lewis acid-assisted Brønsted acid activation of cyclohexene oxide, being its predominant function.

2.2. Addition of trifluoromethyltrimethylsilane to aldehydes

Another reaction involving trimethylsilyl nucleophiles is the addition of trifluoromethyltrimethylsilane (Prakash-Ruppert reagent) to aldehydes (see Scheme 2).¹⁸ The reaction is more difficult to promote and usually, either strong base catalysis¹⁹ or a strong Lewis acid/basic ligand combination²⁰ is required for the trifluoromethylation of aldehydes.



R= Ph, 2-Naphthyl, 1-Naphthyl, 4-NO₂-C₆H₄,

Scheme 2. TADDOL/KF or potassium TADDOLate catalysed trifluoromethylation of aldehydes.

It was therefore tempting to apply the bis-TADDOL/metal fluoride (MF) system as a potential bifunctional catalyst. The complexation of the metal fluoride by the hydroxyl groups might lead to MF ion separation and activation of the salt, with the free fluoride ion functioning as a base. Another TADDOL moiety with its OH group manifold would act as a Brønsted acid activating the aldehyde.

No reaction of Me_3SiCF_3 with benzaldehyde was observed in MeCN at room temperature in the presence of KF without any TAD-DOL added. A 1:1 mixture of **4a** and KF was catalytically inert in THF, toluene and CH_2Cl_2 . Mixtures of LiF or NaF with **4a** were also inactive. However, the mixture of KF and **4** was a good catalytic system in MeCN (Scheme 2, Table 2). Even at a 1000:1 ratio of benzaldehyde/**4a**, a small amount (2%) of the product was detected in the reaction mixture after 1 h. A two and a half fold increase of the amount of the catalyst led to 8% of the product after 5 min. A further twofold increase in the amount of the catalyst led to an increase of the yield to 67% (Table 2, run 1). Evidently, the associated nature of the catalytic activity.

Table 2

TADDOL/MF catalysed trifluoromethylation of aldehydes^a

Entry	Time	Catalyst (mol %)	Aldehyde (R in RCHO)	Yield (ee ^b), %
1	5 min	4a /KF (0.5%)	Ph	67/86 ^c
2	1 h	4a /KF (2.5%)	Ph	73 (17)
3	1 h	4a /KF (5%)	Ph	100 (40)
4	24 h	1/KF (10%/5%)	Ph	28
5	24 h	2/KF (5%)	Ph	83 (3)
6	24 h	3/KF (5%)	Ph	80
7	24 h	5/KF (5%)	Ph	12 (52)
8	24 h	4a /KF (5%)	2-Naphthyl	100
9	24 h	4a /KF (5%)	1-Naphthyl	100
10	24 h	4a /KF (5%)	$4 - NO_2 - C_6H_4 -$	100

^a Reaction conditions: room temperature, MeCN 0.5 mL, aldehyde (0.47 mmol), TMSCF₃ (0.92 mmol), catalyst was bis-TADDOLs/dry MF (1:1 ratio) and mono-TADDOL 1/MF (2:1 ratio), vigorous stirring under Ar at 20 °C.

^b Mostly racemic products were obtained, ee of the exceptions indicated in parentheses after chemical yields values. The ee and (*S*)-configuration of product were determined by HPLC (Chiralpak OJ-H).

^c The experiment was run at +40 °C.

Increasing the reaction temperature to 40 °C led to an almost quantitative yield of the product after 5 min (Table 2, run 1). The reaction could be carried out at -15 °C but as in the other cases, no asymmetric induction was observed. When the reaction was carried out with 2.5 mol % of catalyst the product was obtained in 73% yield and 17% ee (run 2). Further increase in the amount of the catalyst to 5 mol % gave a quantitative yield of the product with 40% ee (run 3). The data also indicate that several catalytic species may participate in the reaction and their asymmetric induction properties differ.

A 2:1 mixture of **1** and KF was a much less efficient catalyst, giving only 28% of the product after 24 h (entry 4). Other bis-TADDOLs **2**, and **3**, were less active than **4a**, though better catalysts than **1** (entries 4 and 5). bis-TADDOL **5** was the least effective in the series, although the product had the largest ee of 52% (entry 7). Other aromatic aldehydes were also trifluoromethylated smoothly under **4a**/ KF catalysis conditions (entry 8–10).

The superiority of **4a** over mono-TADDOL and other bis-TADD-OLs seems to be a consequence of a cooperative interaction in a dimeric form of **4a** as discussed above. One set of (R,R)-TADDOL moieties of the two molecules forms a KF complex supported by a hydrogen bonded H–F array and O–K interaction, keeping the structure together in solution, and the other two moieties, functioning as catalytic duets, separated the K and F ions, activate both aldehyde (OH–O hydrogen bond) and CF₃SiMe₃ (Si–F supervalent interaction) and bring the two reactants together.

3. Conclusion

In conclusion, a new generation of bifunctional acid/base catalysts derived from (R,R)-bis-TADDOLs and their complexes with al-

kali metal salts has been developed and tested in a set of reactions involving the addition of trimethylsilyl nucleophiles to aldehydes and epoxide ring-opening reactions. The importance of simultaneous acidic and basic activation of both electrophiles and nucleophiles was studied and its dependence on the activity of the electrophiles and nucleophilic reagents was established. Although the control of enantioselection of the reaction is modest, future modifications of the system based on this mechanistic understanding may improve the stereochemical performance of the catalysts.

4. Experimental

4.1. 2-(p-Toluidino)cyclohexanol

A Schlenk flask was evacuated and filled with argon. A catalyst (0.024 g. 0.025 mmol), dichloromethane (0.5 mL), cvclohexene oxide (0.05 mL, 0.5 mmol) and *p*-methylaniline (0.05 g, 0.5 mmol) were placed in the flask. The reaction mixture was stirred at \sim 20 °C for 72 h. To determine the yield of the product, the mixture was evaporated and the residue was dissolved in CDCl₃ and analysed by ¹H NMR spectroscopy (no signals of byproducts were observed). Then the product was purified by silica gel chromatography using a 5:1 hexane/ethyl acetate mixture as the eluent (R_f 0.8). ¹H NMR: 7.03–7.01 (d, 2H, J = 6.1); 6.68–6.66 (d, 2H, J = 6.2); 3.39–3.33 (m, 1H); 3.14–3.08 (m, 1H); 2.26 (s, 3H); 2.15-2.11 (m, 2H); 1.81-1.70 (m, 2H); 1.46-1.29 (m, 3H); 1.10-1.00 (m, 1H). The ee and configuration of the product was determined by HPLC (Chiralpak OD-H, *n*-hexane/iso-propanol = 9:1, 1 mL/min). t_R (major, (*S*,*S*)-according to the lit. data²¹) = 9.82 min and t_R (minor, (*R*,*R*)-according to the lit. data²¹) = 17.48.

4.2. 2,2,2-Trifluoro-1-phenylethanol

To a mixture of benzaldehyde (0.05 mL, 0.47 mmol), catalyst (22.4 mg, 0.0235 mmol) and KF (1.2 mg, 0.0235 mmol) in CH₃CN (0.5 mL) was added Me₃SiCF₃ (0.13 mL, 0.92 mmol) at room temperature. After stirring for 1 h, the reaction was quenched with water and the aqueous layer was extracted with ethyl acetate. The solvent was removed in vacuo. Then HF (500 µL, prepared by dilution of 49% aq HF with CH₃CN) was added and the combined solution was stirred at room temperature until all the TMS protected intermediate was converted to product. Water (15 mL) was added and the aqueous layer was extracted with CH₂Cl₂ $(3 \times 10 \text{ mL})$. The combined organic layers were dried over anhydrous Na₂SO₄. Solvent was removed under vacuum to give the crude product, which was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1). ¹H NMR: 7.54–7.49 (m, 2H), 7.48–7.46 (m, 3H), 5.02 (q, 1H, J = 6.8), 3.4 (c, 1H). The ee and configuration of product was determined by HPLC (Chiralpak OJ-H, *n*-hexane/*iso*-propanol = 95:5, 1 mL/min). t_R (major, (S)-stereoisomer corresponding to the lit. $data^{22}$) = 21.01 min and $t_{\rm R}$ (minor, (*R*)-stereoisomer corresponding to the lit. data²²) = 16.47.

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