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(*R*)-BINOL-6,6'-bistriflone: Shortened synthesis, characterization, and enantioselective catalytic applications

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Abstract: The title compound, characterized by X-ray crystallography, was accessed in 4 steps with 92% e.e. and 25% yield from an *O*-protected (*R*)-BINOL precursor. This revised synthetic route relied on a chlorosulfonylation reaction, as a shortcut to a previously developed sequence requiring the use of toxic SO₂ gas and bromine. The strongly electron-impooverished (*R*)-6,6'-Tf₂-BINOL proved an effective ligand in metal-catalyzed enantioselective transformations such as a Zr-based Mannich-type reaction. The catalytic species was characterized by X-ray crystallography as a unique tetrameric metal cluster. The 6,6'-bistriflone groups also allowed to exalt the H-bond donor capacity of the BINOL moiety, as illustrated in an organocatalyzed Morita-Baylis-Hillman transformation. Theoretical study indicated that the 6,6'-bistriflone groups induce a drop of the phenol acidity of 5 pKa units in DMSO. Overall, this work simplified the access, completed the characterization and confirmed the potential of (*R*)-6,6'-Tf₂-BINOL as a promising platform to further elaborate activated chiral metal ligands or organocatalysts.

Introduction

1,1'-Bi-2-naphthol (BINOL) is one of the most emblematic axially chiral C₂-symmetrical molecules in organic chemistry, combining a stable absolute configuration, a flexible conformation, and a versatile structure.^{1,2} Various methods have been developed to modify selectively different positions of binaphthol scaffold allowing investigation of BINOL derivatives in a wide scope of applications, ranging from asymmetric transition-metal catalysis³ to organocatalysis.⁴ Such structural modifications are responsible for either a pure steric effect (3,3'-substitution with alkyl groups for

example) or an electronic effect (6,6'-substitution with electron-withdrawing groups) or both (3,3'-substitution with electron-withdrawing groups). The observed catalytic activity and asymmetric induction of BINOL-derived reagents are the result of the subtle balance between these two factors.

Thanks to its conformational flexibility, BINOL can easily chelate different metal centers, forming organometallic catalysts for enantioselective transformations. In this case, substitution of BINOL does not only address the steric environment around the metal center, but also the electronic properties of the coordinating oxygen atoms. The choice of substituents increasing the Lewis acidity of the metal is crucial. Many reports evidenced that electron-withdrawing groups (such as Cl, Br or I) at 6,6'-positions of BINOL strongly improve the chirality transfer.⁵⁻⁷

BINOL also found successful applications in organocatalysis.⁸⁻¹⁰ Another impact of binaphthol scaffold electron-impooverishment in this case is the phenolic protons acidity enhancement, giving rise to potential chiral BINOL-derived Brønsted acidic catalysts. To expand the use of organocatalysis to various substrates and make it competitive with catalysis by chiral metal complexes, the development of Brønsted acid catalysts with enhanced acidity is still to date a relevant challenge. Toward this end, the crucial influence of an electron-withdrawing substituent, namely a NO₂ group, in the 6,6'-positions of the BINOL scaffold was also demonstrated.¹¹ More generally, the introduction of a triflyl group proved determining for increasing catalytic activity.¹²⁻¹³

In this context, our interest was directed toward the trifluoromethanesulfonyl (SO₂CF₃, triflyl, Tf) group, reported as one of the strongest neutral electron-withdrawing groups with high lipophilicity. Due to its remarkable electronegativity (SO₂CF₃, $\sigma_m = 0.83$, $\sigma_p = 0.96$; CF₃, $\sigma_m = 0.43$, $\sigma_p = 0.54$),¹⁴ the SO₂CF₃ has

been used in several fields of chemistry. Several studies have focused on the clarification of the electronic mode of action of this unique substituent.¹⁵

Noteworthy, reports of BINOL triflone derivatives remain scarce. The BINOL-3,3'-bistriflone was obtained by a thia-Fries rearrangement of BINOL triflates. This transformation was observed as a competing process to aryne synthesis by elimination.¹⁶ We previously reported the first synthesis of BINOL-6,6'-bistriflone (6,6'-Tf₂-BINOL),¹⁷ introducing a high electron-withdrawing effect in the 6,6'-positions while leaving free the binaphthol 3,3'-positions available for further substitution. Many 3,3'-disubstituted-BINOL derivatives have been reported, illustrating the toolbox of synthetic transformations available for the functionalization of these positions.¹⁸ 6,6'-Tf₂-BINOL thus represents a potentially versatile platform to access a range of BINOL derivatives combining electronic and steric effects for applications as chiral ligands, organocatalysts, fluorophores, among others.

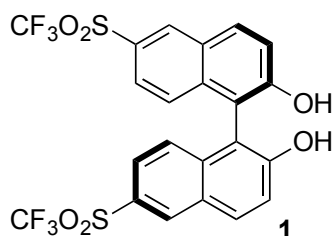
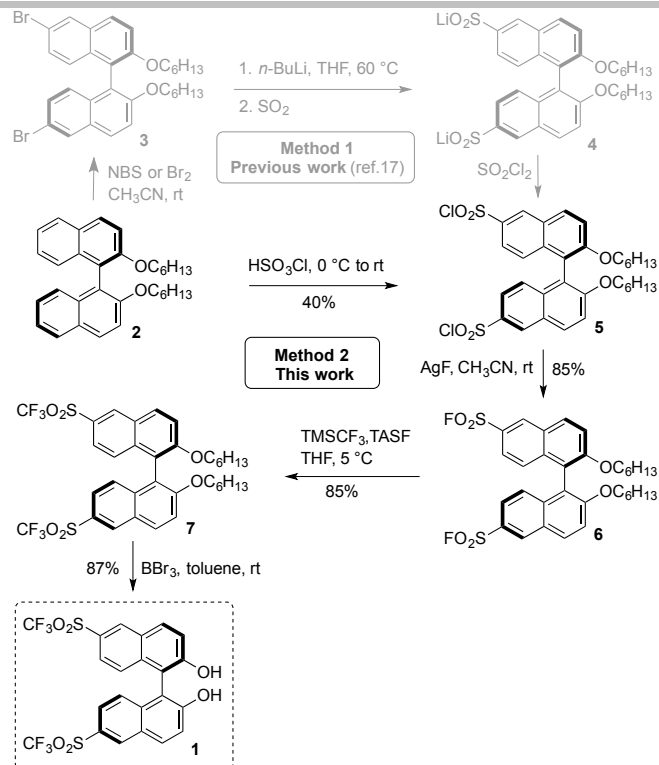


Figure 1. Structure of (*R*)-6,6'-Tf₂-BINOL.

Herein, we report the X-ray structure of the (*R*)-6,6'-Tf₂-BINOL **1** (Figure 1) described during our previous work as well as the determination of the unique nature of the catalyst involved in the enantioselective Mannich reaction studied.¹⁷ Revised synthesis of the (*R*)-6,6'-Tf₂-BINOL **1** is also proposed, avoiding bromine and SO₂ handling and reducing the number of steps required in the previously described synthetic route.¹⁷ We also demonstrate synthetic usefulness of (*R*)-6,6'-Tf₂-BINOL **1** in different metal- or organo-catalyzed reactions.

Results and Discussion

1. Synthesis of (*R*)-6,6'-Tf₂-BINOL. Significant synthetic efforts have been devoted to the development of new CF₃SO₂-containing compounds.¹⁹ Particular attention has been paid to the aryl trifluoromethanesulfones (aryltriflones) which are frequently used as structural units in biologically active molecules,^{20–23} chiral catalysts,^{16,17,24,25} and functional materials.^{26–28} Common methods¹⁹ for preparing aryl triflones include oxidation of the corresponding aryl sulfides, trifluoromethylation of aryl sulfonyl fluorides or aryl sulfonates, direct trifluoromethanesulfonylation of aromatic compounds, and thia-Fries rearrangement of aryl trifluoromethanesulfonates. Yet, the direct introduction of triflyl group onto aromatic rings is still a challenge.^{19,29–33} Several of these methods have been tested in our group for the synthesis of (*R*)-6,6'-Tf₂-BINOL **1** with a variable degree of success. Our methodological efforts resulted in the synthetic pathways presented in Scheme 1.



Scheme 1. Previous (Method 1)¹⁷ and new (Method 2) synthetic sequence to access (*R*)-6,6'-Tf₂-BINOL **1**. NBS: *N*-bromosuccinimide, TASF: tris(dimethylamino)sulfonium difluorotrimethylsilicate.

The selected approach was based on the use of a bis-chlorosulfonyl intermediate **5** that could be readily transformed into the corresponding bis-triflone (Scheme 1). Access to **5** from *O*-protected (*R*)-BINOL **2** was previously realized through a quite cumbersome 4-step sequence including bromination, lithiation, sulfonylation, and chlorination (Method 1). An alternative access to Ar-SO₂F from Ar-Br was recently reported.³⁴ As a shortcut, we found that the (*R*)-6,6'-chlorosulfonyl BINOL **5** could be directly and selectively produced by the action of chlorosulfonic acid on the protected (*R*)-BINOL **2**.^{35,36} A halogen exchange reaction followed by trifluoromethylation with the Ruppert reagent resulted in the targeted (*R*)-6,6'-Tf₂-BINOL **1**, after smooth Lewis acid treatment of the protected intermediate **7**. Overall, the synthetic sequence was thus shortened from 7 to 4 steps and compound **1** was isolated by column chromatography on silica gel (90:10 CH₂Cl₂/EA) as an off-white powder in 25% overall yield. Chiral supercritical fluid chromatography (Chiralpak IC column, CH₃OH/CO₂, UV and MS detection), indicated a 92% ee for this material. It was characterized by NMR, IR and mass spectroscopy. The ¹⁹F NMR spectrum showed in particular the expected signal for the CF₃ group at δ -78.14 ppm.

Crystals suitable for X-ray diffraction analysis of (*R*)-6,6'-Tf₂-BINOL **1** were obtained from toluene allowing its unambiguous characterization (Figure 2). The most important feature of this crystal structure is the torsion angle C2-C1-C1A-C2A of 76.3°, which is in the same range as observed for non-substituted BINOL (78°). The intramolecular distance between the two hydroxyl oxygen atoms O1-O1A is 3.45 Å, reflecting the absence of an intramolecular hydrogen bond. Furthermore, an

intermolecular hydrogen bond between O1 and O2 of another molecule could be observed (O-O distance 2.72 Å).

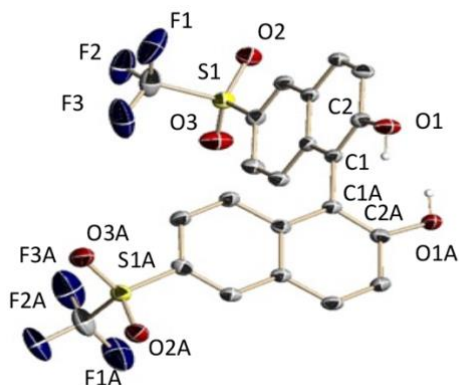
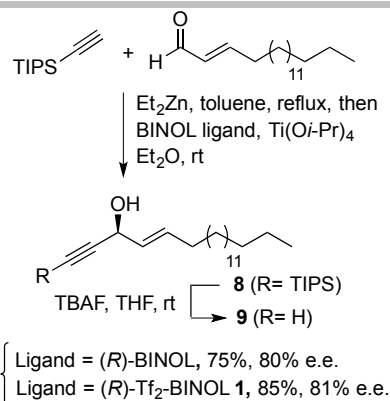


Figure 2. Crystal structure of (*R*)-6,6'-Tf₂-BINOL **1** in the solid state. H-atoms and a non-coordinating toluene molecule have been omitted for clarity. Selected bond distances [Å] and angles [°]: C1-C1A 1.500(4), C2-O1 1.351(3), S1-O2 1.424(2), S1-O3 1.422(2), C2-C1-C1A 120.26(17), C1-C2-O1 124.67(19).

2. (*R*)-6,6'-Tf₂-BINOL **1 in metal catalysis.** Despite the lightning growth popularity of organocatalysis in organic synthesis, chiral metal-based Lewis acid catalysts continue to have a uniquely important role in asymmetric transformations.³⁷⁻⁴⁰ The Lewis acidity of the BINOLate complexes can be easily tuned by variation of the electronic properties of the BINOL. The introduction of bromine, trifluoromethyl or pentafluoroethyl groups in the 6,6'-positions of the binaphthol ring proved efficient to increase the Lewis acidity as well as the chirality transfer of metal-based catalysts.⁴¹⁻⁴² To illustrate the potential of (*R*)-6,6'-Tf₂-BINOL **1** as a chiral ligand for asymmetric metal catalysis, we selected two representative reactions, an asymmetric alkylation reaction with a titanium complex⁴³ and a Mannich-type reaction with a zirconium complex.¹⁷

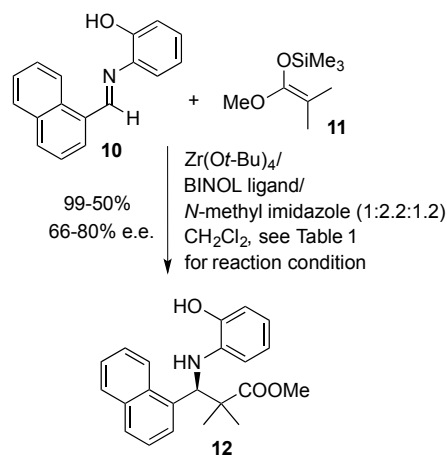
2.1. Titanium-mediated Pu asymmetric alkylation. We have previously reported the first chemistry-driven systematic structure-activity study of the chiral functional alkynylcarbinol fragment as a cytotoxic pharmacophore.⁴³ Our work revealed the remarkable influence of the absolute configuration of the carbinol center on the antitumor activity, emphasizing the importance of the efficient preparation of enantiopure samples. We used the electron-impoverished (*R*)-6,6'-Tf₂-BINOL **1** as a chiral ligand in the Ti-mediated Pu asymmetric alkylation reaction of (*E*)-octadec-2-enal with TIPS-acetylene (Scheme 2) for the synthesis of the natural product 3-(*S*)-eicos-4(*E*)-en-1-yn-3-ol (**9**).⁴⁴ The transformation led to the expected (*S*)-carbinol **8** with 81% ee, a value comparable to the 80% ee obtained with (*R*)-BINOL.⁴³ Of note, compound **8** was isolated in 85% yield, versus 75% using the plain BINOL, opening prospects for further optimization of the Pu asymmetric alkylation methodology.⁴⁵⁻⁴⁷



Scheme 2. Comparative use of (*R*)-6,6'-Tf₂-BINOL **1** and (*R*)-BINOL in Ti-mediated Pu enantioselective alkylation.^{43,44}

2.2. Zirconium-catalyzed Mannich-type reaction. The asymmetric Mannich-type reaction is one of the most attractive way to provide β-aminocarbonyl compounds, which are versatile chiral building blocks for the synthesis of many nitrogen-containing biologically relevant molecules.⁴⁸ Over the past two decades, much efforts have been devoted to developing this synthetic transformation using metal catalysis or organocatalysis.⁴⁹⁻⁵¹ As a general trend in the use of BINOL derivatives as ligands, the presence of electron-withdrawing groups had a positive impact on the yield and on the enantioselectivity of the reaction.

We described a Mannich-type reaction catalyzed by a BINOL-derived zirconium complex.¹⁷ Herein, we focused on determining the structure of the zirconium catalyst. The later was prepared *in situ* from 1 equivalent of Zr(Ot-Bu)₄, 2 equivalents of (*R*)-6,6'-Tf₂-BINOL, and 1.2 equivalents of *N*-methylimidazole (NMI) in CH₂Cl₂. In the presence of this *in situ*-generated catalyst, aldimine **10**, obtained from 1-naphthaldehyde and 2-aminophenol, was treated with the model ketene silyl acetal **11** in CH₂Cl₂ at low temperature (Scheme 3). The reaction proceeded to afford the corresponding adduct **12** in 50 to 99% yield and with up to 80% enantiomeric excess (Table 1).



Scheme 3. Use of (*R*)-6,6'-Tf₂-BINOL **1** in asymmetric Zr-catalyzed Mannich-type reaction (see Table 1 for reaction conditions and outcomes).¹⁷

Table 1. Mannich-type reaction in presence of Zr(Ot-Bu)₄ and different BINOL derivatives (Scheme 3).^a

Entry	[Zr] (mol%)	BINOL ligand	T (°C)	Time (h)	Yield (%)	ee (%)
1	2	(<i>R</i>)-BINOL	-78	2	6	nd
2	2	(<i>R</i>)-6,6'-Br ₂ BINOL	-78	2	65	68
3	2	1	-78	2	99	66
4	2	1	-95	4	95	72
5	0.5	1	-95	4	50	80

[a] Reagents and conditions: Catalyst Zr(Ot-Bu)₄/BINOL ligand/N-methylimidazole (1:2.2:1.2), CH₂Cl₂, see Table for reaction temperature and reaction time.

We carried out the reaction with the different ligands cited in Table 1.¹⁷ Our results show that the introduction of the trifluoromethanesulfonyl group is beneficial for catalyst turnover, since, in our conditions, **1** gave superior results to (*R*)-BINOL and (*R*)-6,6'-dibromo-BINOL (Table 1, entries 1, 2, and 3). Even at very low temperatures and low concentration (0.5 mol %), the catalyst remains active with improved stereoselectivity (entries 4 and 5).

2.3. Structure of the catalyst 13. To elucidate the nature of the catalyst, the chiral zirconium complex was prepared and characterized. The metal species spontaneously crystallized in the C₆D₆ NMR tube solution. The crystals formed by reacting Zr(Ot-Bu)₄ and (*R*)-6,6'-Tf₂-BINOL **1** in presence of NMI correspond to the original structure **13** (Figure 3) of formula Zr₄(μ-Tf₂BINOLate)₆(μ³-OH)₄ without NMI.

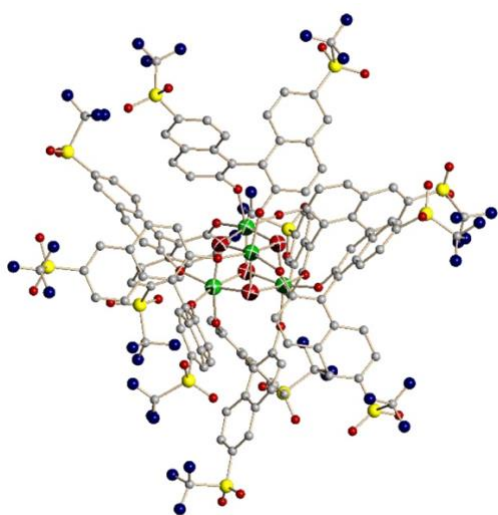


Figure 3. Crystal structure of **13** in the solid state. H-atoms and disordered positions of ligands have been omitted for clarity. Selected bond distances [Å] and angles [°]: Zr1-O3 2.060(6), Zr1-O4 2.037(6), Zr1-O5 2.041(6), Zr2-O6 2.054(6), C1-O3 1.341(11), C11-O4 1.290(11), C21-O5 1.342(11), C31-O6 1.359(11), C1-O3-Zr1 139.6(6), C11-O4-Zr1 148.0(6), C21-O5-Zr1 139.7(6), C31-O6-Zr2 141.1(6).

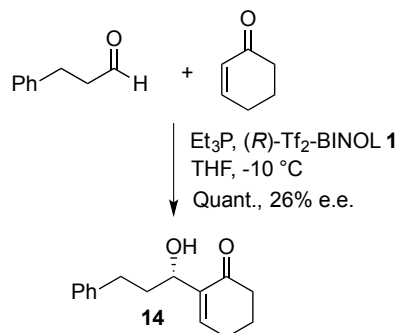
In the inorganic center of this complex, four zirconium cations and four μ³-OH groups form a distorted cube. The coordination sphere of the zirconium is completed by three oxygen atoms coming from three different ligands giving a distorted octahedral geometry around the zirconium center. In the organic outer-sphere of the complex, each BINOLate ligand is bridging two zirconium centers. The zirconium oxygen distances of the Zr₄O₄ cube (2.149 - 2.204 Å) are about 20 pm longer than the distances between the zirconium cations and the BINOLate ligands (1.995 - 2.012 Å). The torsion angles (75.7 - 77.4°) are very similar to the corresponding angle found for **1**.

To compare the catalytic activities of isolated **13** with the in situ-formed catalyst, we run the same Mannich-type reaction using 2 mol% of **13** for 16 hours at -45 °C. Higher selectivity was observed in the case of **13** with a quantitative conversion to the desired product isolated with 76% ee versus 51% using the in situ-formed complex. This complex was also found to be air-stable and highly active catalyst.

3. (*R*)-6,6'-Tf₂-BINOL **1 in organocatalysis.** During the last two decades, organocatalysis has become a powerful bio-inspired synthetic paradigm to overcome the metal required in traditional catalysis.^{8,52,53} There again, BINOL has become a privileged scaffold on which to build up small organic molecules-based organocatalysts, such as chiral hydrogen bond donor or Brønsted acid catalyst.^{8-10,54,55}

(*R*)-6,6'-Tf₂-BINOL **1** itself was evaluated as an organocatalyst in the Morita-Baylis-Hillman (MBH) reaction. One of the major drawbacks of the MBH reaction is the low reaction rate which requires long reaction times. Significant effort has focused on improving the transformation efficiency. The first example of a highly enantioselective asymmetric MBH reaction using a chiral Brønsted acid was reported by Schaus.^{56,57}

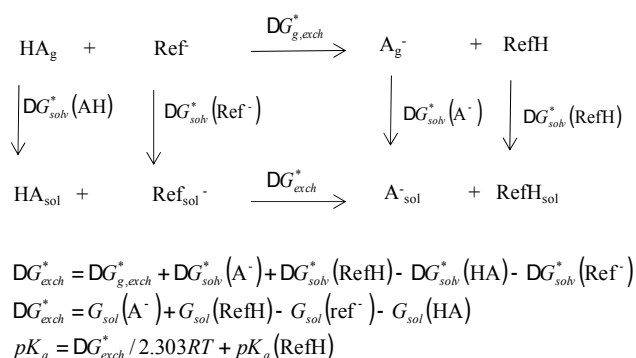
The trialkylphosphine-catalyzed addition of cyclohexenone onto 3-phenyl propanal was selected as a model reaction (Scheme 4). The expected secondary alcohol¹⁷ was produced quantitatively, versus 5% for the control reaction with the plain BINOL.^{56,57} If this outcome illustrates a promising effect of (*R*)-6,6'-Tf₂-BINOL **1** as a hydrogen bond donor catalyst for this transformation, the enantiomeric excess remained < 30%. It is well-known that the introduction of bulky substituents in the 3,3'-positions is crucial for achieving high enantioselectivity.^{56,58} This result thus opens prospect for the development of 3,3'-substituted 6,6'-Tf₂-BINOL as catalysts for enantioselective MBH reaction or other asymmetric nucleophilic addition on aldehydes.



Scheme 4. Use of (*R*)-6,6'-Tf₂-BINOL **1** in organocatalyzed Morita-Baylis-Hillman (MBH) reaction.

4. pKa calculation. The MBH reaction detailed above illustrates the key role of activated BINOL derivatives in hydrogen bond catalysis. In this context, pKa represents a relevant parameter to quantify the impact of the electron-withdrawing groups on catalytic efficiency. More generally, estimation of the pKa of a catalyst is important for mechanistic understanding and selectivity interpretation.

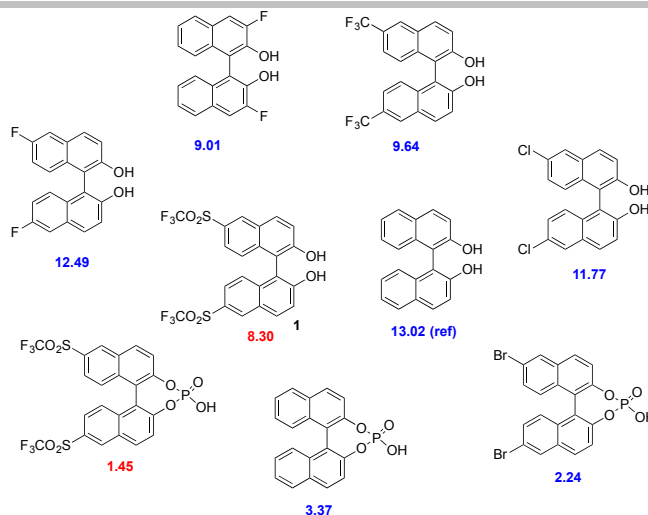
The quantum chemistry method using the DFT functional B3LYP⁵⁹⁻⁶¹ in combination with continuum solvation model SMD (solvation model density) of Truhlar⁶² has been successfully used to evaluate the pKa of different compounds by using an isodesmic reaction (Scheme 5), with a mean absolute deviation of 0.5 to 1 pKa unit following the functional group concerned. The isodesmic reaction could be used with species that undergo large conformational changes between gas phase and solution phase. Indeed, solvation energies errors, especially concerning charged species, are avoided as these values are not required. Reference species and acid species are chosen to present the same electric charge and similar structure. In that case, a good accuracy is expected in the pKa calculation.⁶³ For an accurate determination of pKa, the pKa values of HA and RefH must not differ by more than two units.



Scheme 5. Isodesmic reaction.

BINOL was chosen as reference with an experimental pKa of 13.02 in DMSO determined by X. Ni.⁶⁴ This value is low compared to the pKa of phenol (18) or naphthol (17) in DMSO because of the presence of an intermolecular hydrogen bond between OH and O⁻ in the mono deprotonated form.⁶⁴

A panel of five representative BINOL derivatives substituted by electron-withdrawing groups in the 3,3'- or in the 6,6'-positions was selected (Scheme 6). The different structures were modeled by DFT, using Gaussian 09 at the B3LYP/6-31+G(d,p) level, first in the gas phase then in the DMSO polarizable continuum model (SMD). Frequencies calculations were performed on the optimized geometries at 298K, showing all positive frequencies and allowing evaluation of the Gibbs free energy of the minima. Calculated geometries have also shown the presence of intermolecular hydrogen bond in DMSO for the mono deprotonated form of BINOL derivatives.



Scheme 6. Calculated pKa values / DMSO for a panel of BINOL derivatives.

Compared to the plain BINOL, calculated acidity of the 6,6'-bistrifluoro-BINOL **1** is 5 pKa units lower, suggesting its potential widespread relevance as organocatalyst. Beyond hydrogen bond donor catalysts, BINOL scaffold was widely used in the elaboration of chiral phosphoric acids catalyst.⁶⁵⁻⁶⁷ In view of the strong impact of the 6,6'-trifluoro groups on the calculated phenol pKa, we also attempted computation of the corresponding phosphoric acid pKa. Plain BINOL phosphoric acid was chosen as the reference acid (pKa exp = 3.37).⁶⁸⁻⁶⁹ From our calculation, the 6,6'-trifluoro groups, thanks to their powerful electron-withdrawing effect, should significantly increase the acidity of the corresponding phosphoric acid with a pKa value as low as 1.45, i.e. almost 2 pKa units lower than for the reference compound. These computational results further increase the potential of 6,6'-Tf₂-BINOL in Brønsted acid catalysis and thus strengthen the importance of its synthetic availability.

Conclusion

A shortened synthetic route to (*R*)-6,6'-Tf₂-BINOL **1**, avoiding the use of toxic SO₂ gas and bromine, was developed. It delivered the expected compound in 4 steps with 92% e.e. and 25% yield from the readily accessible *O*-protected (*R*)-BINOL **2**. The latter was fully characterized including by crystallographic analysis. The efficiency of **1** in both metal-based catalysis and organocatalysis was illustrated. Of note, an enantioselective Zr-based Mannich-type reaction was developed relying on an original tetrameric catalytic species that could be isolated and fully characterized by X-ray crystallography. The potential of **1** as a H-bond donor catalyst was also demonstrated in a phosphine-promoted MBH reaction in which plain BINOL was ineffective. A DFT theoretical study was used to quantify the impact of the 6,6'-bistrifluoro groups on the electronic density of the BINOL core of **1**. Calculated acidity of the 6,6'-Tf₂-BINOL **1** in the DMSO was found to be 5 pKa units lower than the reference BINOL. Conversely, the corresponding phosphoric acid was estimated to have a pKa almost 2 pKa units lower than the plain BINOL-derived reference compound. Overall, this work opens prospects for the catalytic use of **1** as an electron-impooverished chiral metal ligand or chiral organocatalyst

precursor, notably through the preparation of sterically hindered 3,3'-substituted derivatives. Work along this line is currently in progress and will be reported in due course.

Experimental Section

General information: Reactions were monitored using Merck silica gel 60 F₂₅₄ precoated plates. Chromatograms were observed under UV light and/or were visualized by heating plates that were dipped in 10% phosphomolybdic acid in ethanol. Column chromatography was carried out with SDS 35–70 μm flash silica gel. NMR spectroscopic data were recorded on a Bruker Avance 300, 400 or 500 MHz spectrometer with solvent peaks as reference. Chemical shifts are quoted in parts per million (ppm) relative to residual solvent peak and coupling constants are in Hertz. The multiplicity of the ¹H NMR signals are expressed as follows: d (doublet), dd (doublet of doublet), dt (doublet of triplet), m (multiplet), p (pentuplet), q (quadruplet), s (singlet), t (triplet), td (triplet of doublet). For convenience, assignments of chemical shifts are described according to the numbering drawn on schemes following the numbering of unsubstituted DNJ. Mass spectrometry (MS) data were obtained on a ThermoQuest TSQ 7000 spectrometer. High-resolution mass spectra (HRMS) were performed on a ThermoFinnigan MAT 95 XL spectrometer. Optical rotations were measured on a Jasco P 2000 polarimeter. $[\alpha]_D$ values are given in 10⁻¹ deg cm² g⁻¹. Infrared spectra were recorded on a Nicolet 6700 ThermoScientific (Diamond ATR) apparatus. (R)-BINOL was purchased from Aldrich. The known (R)-2,2'-dihexyloxy-1,1'-binaphthyl (**2**) was prepared according to a published procedure.⁷⁰ Anhydrous solvents were obtained by drying prior to use according to standard methods (D.D. Perrin, W.L. Amarego, Purification of Laboratory Chemicals, 3rd Ed., Pergamon Press, 1998).

(R)-6,6'-dichlorosulfonyl-2,2'-dihexyloxy-1,1'-binaphthyl (5). Under argon atmosphere, to a solution of (R)-**2** (3 g, 6.6 mmol) in CHCl₃ (10 mL) at 0 °C, was slowly added chlorosulfonic acid (5.27 mL, 79.2 mmol), keeping the temperature at 0 °C. The mixture was stirred overnight at room temperature, then poured on crushed ice and extracted with CHCl₃. The combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. Purification of the crude mixture by flash chromatography on silica gel (gradient 90:10 to 85:15 Petroleum ether/EA) yielded (R)-**5** as a purple wax (1.72 g, 40%). The crude product can be used without purification in the next step to avoid degradation on silica gel. ¹H NMR (300 MHz, CDCl₃): δ 8.66 (d, *J* = 3 Hz, 2H), 8.20 (d, *J* = 9 Hz, 2H), 7.76 (dd, *J* = 9, 3 Hz, 2H), 7.64 (d, *J* = 9 Hz, 2H), 7.25 (d, *J* = 9 Hz, 2H), 4.10-3.98 (m, 4H), 1.5-1.38 (m, 4H), 1.1-.90 (m, 12H), 0.76-0.69 (m, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 158.07, 137.02, 132.03, 131.58, 127.38, 127.15, 126.88, 122.87, 118.87, 116.52, 69.29, 31.26, 30.71, 29.08, 25.39, 22.54, 13.95 ppm. HRMS (DCI/CH₄) *m/z* [M⁺] calcd for C₃₂H₃₆O₆S₂Cl₂ 650.1330; found 650.1313.

(R)-6,6'-difluorosulfonyl-2,2'-dihexyloxy-1,1'-binaphthyl (6). Under argon atmosphere, (R)-**5** (2 g, 3 mmol) was dissolved in anhydrous ACN (35 mL). AgF (0.93 g, 7.35 mmol) was added. The reaction was stirred for 2 h at room temperature then filtered over celite and washed with CH₂Cl₂. The organic phase was concentrated under reduced pressure. (R)-**6** was isolated by flash chromatography purification on silica gel (gradient 100:0 to 90:10 Petroleum ether/EA) as an orange wax (1.6 g, 85%). $[\alpha]_D^{20} + 56.7$ (c 2.4, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 8.63 (d, *J* = 3 Hz, 2H), 8.16 (d, *J* = 9 Hz, 2H), 7.64 (dd, *J* = 9, 3 Hz, 2H), 7.61 (d, *J* = 9 Hz, 2H), 7.25 (d, *J* = 9 Hz, 2H), 4.10-3.97 (m, 4H), 1.52-1.37 (m, 4H), 1.10-.88 (m, 12H), 0.76-.67 (m, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 158.18, 138.84, 136.79, 132.35, 129.64, 127.00, 126.90, 122.04, 118.86, 116.57, 69.31, 31.26, 29.06, 27.05, 25.37, 22.54, 13.98 ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ 66.62 ppm; IR (ATR) ν 3079, 2954, 2936, 2871, 2857, 1611, 1590, 1501, 1461, 1406, 1347, 1338, 1278, 1252, 1218, 1196, 1147, 1104, 1086, 1067, 1042, 906, 850, 826, 809, 775, 761, 672, 607, 578, 461 cm⁻¹; HRMS (ESI) *m/z* [M+H⁺] calcd for C₃₂H₃₇F₂O₆S₂ 619.200; found 619.1977.

(R)-6,6'-bis(trifluoromethanesulfonyl)-2,2'-dihexyloxy-1,1'-binaphthyl (7). Under argon and at 5 °C, TASF (138 mg, 0.5 mmol) and TMSCF₃ (1.5 mL, 10 mmol) were added to the compound (R)-**6** (1.5 g, 2.42 mmol) dissolved in anhydrous THF (3 mL). The mixture was stirred for 24h at 5 °C. Water was then added and the aqueous phase was extracted with CH₂Cl₂. The combined organic layers were washed with brine and dried over MgSO₄. Solvents were removed by evaporation under reduced pressure yielding the protected (R)-Tf₂-BINOL **7** (1.49 g, 85%) as an orange wax. The crude product was used without purification in the next step. $[\alpha]_D^{20} + 12.3$ (c 1.5, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 8.59 (d, *J* = 3 Hz, 2H), 8.12 (d, *J* = 9 Hz, 2H), 7.58 (dd, *J* = 9, 3 Hz, 2H), 7.53 (d, *J* = 9 Hz, 2H), 7.23 (d, *J* = 9 Hz, 4H), 4.04-3.90 (m, 4H), 1.41-1.29 (m, 4H), 1.01-.78 (m, 12H), 0.65-0.56 (m, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 158.52, 137.58, 134.63, 132.43, 127.43, 126.93, 125.20, 124.31, 120.10 (q, *J* = 323 Hz) 118.72, 116.52, 69.29, 31.17, 28.97, 25.28, 22.41, 13.85 ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ -78.31 ppm; IR (ATR) ν 3066, 2955, 2928, 2876, 2857, 1663, 1612, 1590, 1499, 1460, 1407, 1348, 1278, 1252, 1216, 1196, 1146, 1102, 1045, 948, 907, 847, 810, 771, 723, 692, 671, 609, 575, 518, 461 cm⁻¹; HRMS (ESI) *m/z* [M+H⁺] calcd for C₃₄H₃₇F₆O₆S₂ 719.1936; found 719.1940.

(R)-6,6'-bis(trifluoromethanesulfonyl)-2,2'-dihydroxy-1,1'-binaphthyl (1). Under argon atmosphere, the protected (R)-Tf₂-BINOL **7** (1.4 g, 1.94 mmol) was dissolved in distilled toluene (40 mL). BBr₃ (2.43 g, 9.7 mmol) was added dropwise and the solution was stirred overnight at room temperature. Following water addition, saturated NaHCO₃ was added, and the aqueous phase was extracted with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. (R)-**1** was isolated by flash chromatography purification on silica gel (90:10 DCM/EA) as a white solid (0.92 g, 87 %). $[\alpha]_D^{20} - 90.3$ (c 0.85, CH₂Cl₂); mp 147 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.68 (d, *J* = 3 Hz, 2H), 8.20 (d, *J* = 9 Hz, 2H), 7.76 (dd, *J* = 9, 3 Hz, 2H), 7.61 (d, *J* = 9 Hz, 2H), 7.30 (d, *J* = 9 Hz, 2H), 6.19 (bs, OH) ppm; ¹³C NMR (75 MHz, CD₃OD): δ 157.17, 137.65, 134.49, 134.01, 128.26, 126.06, 126.01, 125.81, 120.89, 119.9 (q, *J* = 326 Hz), 111.24 ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ -78.14 ppm; HRMS, IR (KBr) ν 3474, 1611, 1498, 1465, 1356, 1281, 1216, 1131, 1084, 1069, 898, 848, 666, 631 cm⁻¹ (ESI) *m/z* [M+H⁺] calcd for C₂₂H₁₃F₆O₆S₂ 551.0058; found 551.0078. Analytical SFC (Chiralpak IC 3 μm , 4.6x100 mm column, CH₃OH/CO₂, 1 mL/min, UV detection, λ 254 nm), 92% e.e.

Preparation of Zr₄(μ -Tf₂BINOLate)₆(μ^3 -OH)₄ **13. The tetranuclear organometallic complex of Zr has crystallized in an NMR tube while attempting to determine the structure of the catalyst formed in situ during Mannich-type reaction.**

A solution of Zr(*o*-t-Bu)₄ (23.37 μL , 0.06 mmol, 0.5 eq.) in C₆D₆ (0.25 mL) was added to a solution of (R)-6,6'-Tf₂BINOL **1** (66 mg, 0.12 mmol, 1 eq.) and *N*-methyl imidazole (9.56 μL , 0.12 mmol, 1 eq.) in C₆D₆ (0.25 mL). The mixture was then left under magnetic stirring for 1 h at room temperature. Afterwards, the reaction was immersed in an oil bath at 50 °C for 3 h under vacuum. A few days later, crystals were formed in the NMR tube. The X-ray diffraction study of the crystals showed structure **13** with a formula of Zr₄(μ -Tf₂BINOLate)₆(μ^3 -OH)₄.

Catalytic test of Zr₄(μ -Tf₂BINOLate)₆(μ^3 -OH)₄ **13 in the Mannich-type reaction with the imine derived from 1-naphthalene-carboxaldehyde.** A solution of Zr₄(μ -Tf₂BINOLate)₆(μ^3 -OH)₄ **13** (36 mg, 9.67 μmol , 2%) in anhydrous CH₂Cl₂ (0.75 mL) was cooled to -45 °C before adding a solution of the imine derived from 1-naphthalene-carboxaldehyde **10** (119 mg, 481 μmol , 1 eq.) in anhydrous CH₂Cl₂ (0.5 mL). A solution of the silylated enol ether derived from methyl isobutyrate **11** (0.12 mL, 577 μmol , 1.2 eq.) in anhydrous CH₂Cl₂ (0.5 mL) was then added to the mixture. The reaction was left under magnetic stirring for 16 h at -45 °C, and saturated NaHCO₃ was added to quench the reaction. After a standard work up, the

crude was chromatographed on silica gel (95:5 DCM/EA) to give the expected product **12** in a quantitative yield (167.9 mg). Characterization and spectroscopic data were in agreement with lit. values.⁴⁴ HPLC Chiralcel® OD-H (95:5 hexane/*i*-PrOH, 1 mL/min, UV detection, λ 244 nm) gave an e.e. of 76%.

Asymmetric reaction of MBH of cyclohexenone with 3-phenylpropionaldehyde. (*R*)-6,6'-Tf₂BINOL **1** (27.5 mg, 50 μ mol, 5%) and anhydrous THF (1 mL) were introduced into a Schlenck tube placed under argon atmosphere. The obtained solution was cooled to -78 °C before adding sequentially cyclohexenone (193.6 μ L, 2 mmol, 2 eq.), Et₃P (2 mL of a 1M solution in THF, 2 mmol, 2 eq.), and 3-phenylpropionaldehyde (132.85 μ L, 1 mmol, 1 eq.). The mixture was then left under magnetic stirring at -10 °C for two days. Standard work up and chromatography on silica gel (gradient 80:20 to 50:50 Pentane/EA) gave the expected product **14** in a quantitative yield (229 mg). Characterization and spectroscopic data were in agreement with lit. values.⁷¹ HPLC Chiralcel® OD-H (90:10 hexane/*i*-PrOH, 1 mL/min, UV detection, λ 254 nm) gave an e.e. of 26%.

Crystallographic data for **1 and **13**.** All data were collected at low temperature using oil-coated shock-cooled crystals at 133(2) K (**1**) and 193(2) K (**13**) on a Bruker-AXS APEX II diffractometer with MoK α radiation (λ = 0.71073 Å). The structures were solved by direct methods⁷² and all non-hydrogen atoms were refined anisotropically using the least-squares method on F^2 .⁷³ The absolute structure parameters have been refined using the Flack-method.⁷⁴

Some residual electron densities were difficult to modelize for compound **13** and therefore, the SQUEEZE function of PLATON⁷⁵ was used to eliminate the contribution of the electron density in the solvent region from the intensity data, and the solvent-free model was employed for the final refinement.

Some parts of the structure of **13** were strongly disordered. Three Tf-phenyl groups were disordered over two positions, for which occupancies were refined. Several restraints (SAME, SIMU, DELU, ISOR, FLAT) were also applied to refine these groups and to avoid the collapse of the structure during the least-squares refinement by the large anisotropic displacement parameters.

1: C₂₉H₂₀F₆O₆S₂, Mr = 642.57, crystal size = 0.60 x 0.60 x 0.50 mm³, tetragonal, space group *P*4₃2₁2, *a* = *b* = 9.381(1) Å, *c* = 32.735(2) Å, *V* = 2880.7(2) Å³, *Z* = 4, 16856 reflections collected, 2962 unique reflections (*R*_{int} = 0.0304), *R*₁ = 0.0390, *wR*₂ = 0.0910 [*I* > 2 σ (*I*)], *R*₁ = 0.0425, *wR*₂ = 0.0928 (all data), absolute structure factor *x* = -0.01(10), residual electron density = 0.245 e Å⁻³.

13: C₁₃₂H₆₀F₃₆O₄₀S₁₂Zr₄, Mr = 3719.40, crystal size = 0.38 x 0.26 x 0.24 mm³, hexagonal, space group *P*6₃, *a* = *b* = 23.798(2) Å, *c* = 23.212(2) Å, *V* = 11384.7(14) Å³, *Z* = 2, 238573 reflections collected, 12904 unique reflections (*R*_{int} = 0.0706), *R*₁ = 0.0574, *wR*₂ = 0.1478 [*I* > 2 σ (*I*)], *R*₁ = 0.0873, *wR*₂ = 0.1796 (all data), absolute structure factor *x* = -0.025(8), residual electron density = 0.925 e Å⁻³.

CCDC-2037435 (**1**) and CCDC-2037436 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Computational data. Geometries and energies (*E* and *G* /au) of BINOL derivatives were calculated calculated at B3LYP/6-31+G(d,p) level of theory in the gas phase and in the DMSO polarizable continuum model (SMD).

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