Preparation and Characterization of New C_2- and C_1-Symmetric Nitrogen, Oxygen, Phosphorous, and Sulfur Derivatives and Analogs of TADDOL

Part III

Some New Chiral *Brønsted* Acids for Organocatalysis and pK_a Values in MeO–$(CH_2)_2$–OH/H_2O – A Survey

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A brief overview is presented of the field of organocatalysis using chiral H-bond donors, chiral *Brønsted* acids, and chiral counter-anions (*Fig. 1*). The role of TADDOLs (=α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols) as H-bond donors and the importance of an intramolecular H-bond for acidity enhancement are discussed. Crystal structures of TADDOLs and of their N-, S-, and P-analogs (*Figs. 2* and *3*) point the way to proposals of mechanistic models for the action of TADDOLs as organocatalysts (*Scheme 1*). Simple experimental two-step procedures for the preparation of the hitherto strongest known TADDOL-derived acids, the bicyclic phosphoric acids (**2** in *Scheme 2*) and of a phosphoric-trifluorosulfonic imide (**9** in *Scheme 4*), are disclosed. The mechanism of sulfinamide formation in reactions of TADDAMIN with trifluoro-sulfonylating reagents is discussed (*Scheme 3*). pK_a Measurements of TADDOLs and analogs in DMSO (reported in the literature; *Fig. 5*) and in MeO$(CH_2)_2$OH/H_2O (described herein; *Fig. 6*) provide information about further possible applications of this type of compounds as strong chiral *Brønsted* acids in organocatalysis.

1. Introduction. – *Asymmetric Counterion Catalysis.* As part of the ongoing 'gold rush' [1] for applications of organocatalytic reactions, there is great interest in chiral *Brønsted* acids. The borderlines between H-bond donors (sometimes called 'neutral' *Brønsted* acids), weakly acidic, 'stronger', and 'highly acidic' *Brønsted* acids (*Fig. 1,a*) are difficult to define, especially when we remember that there are no solvent-separated ion pairs in an organic medium (*cf.* toluene), where the ions will be in contact, for instance, by forming H-bonds with each other (*Fig. 1,b*). This was masterfully demonstrated by an NMR investigation of the system $(PhO)_2PO_2H$/*N*-phenylimines of PhCHO and acetophenone [2]. Apart from these delicate mechanistic details, the exciting fact for the synthetic organic chemist is that many typical *Lewis* or *Brønsted* acid-catalyzed textbook reactions can be carried out with chiral *Brønsted* acids to become enantioselective. Formally, intermediate achiral cations with enantio-

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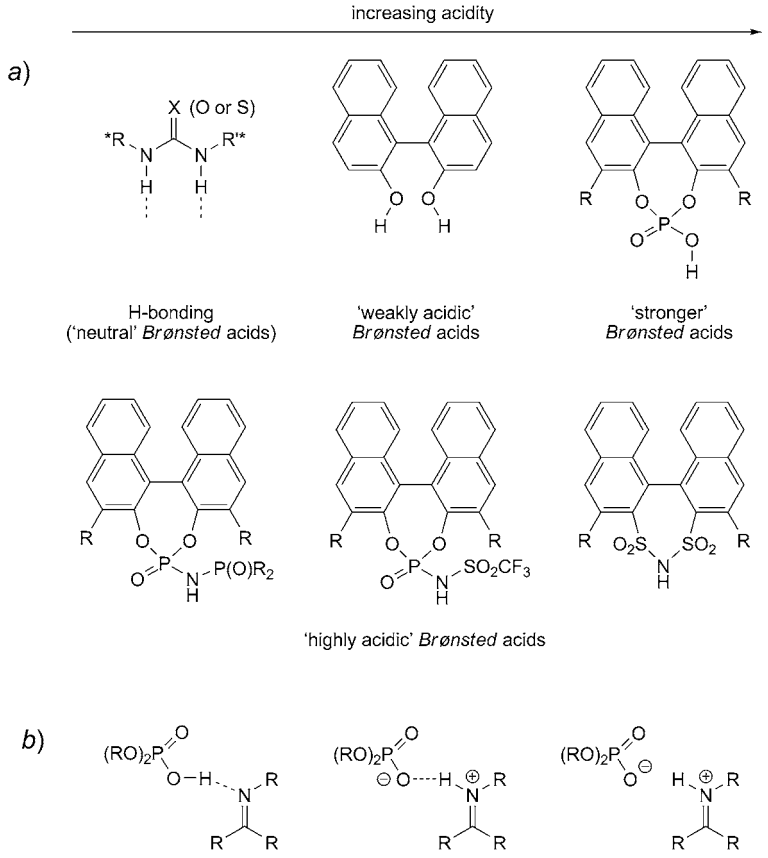

Fig. 1. a) *Selection of chiral H-bonding and* Brønsted *acidic compounds, and* b) *interactions with an imine/iminium derivative*

topic faces[4]) react with nucleophiles preferentially from one of the enantiotopic faces, because the chiral counterion is blocking the other one, to put it in simple terms. In the complex with the chiral counter-*anion* (or H-bond donor), the enantiotopic faces of the electrophile become diastereotopic. This has been realized in recent years for a large variety of systems, some of which are indicated in *Fig. 2*, *a*. So far, the focus has been on iminium (including acyliminium and protonated nitrone) [4] and enoyl-iminium [5] systems (including protonated pyridines [6] and quinolines [7]), conjugated and non-conjugated carbonyl derivatives [8], and conjugatively stabilized carbocations [9][5]).

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[4]) Some use the term 'prochiral' reactants. It is, however, inappropriate to call whole molecules prochiral; see textbooks of stereochemistry (*e.g.*, [3]).

[5]) It is impossible to do justice to all the contributors to this field in this Introduction. The 'major players' in the area of chiral-counter-anion catalysis are (in alphabetical order): *T. Akiyama*, *J. C. Antilla*, *J. N. Johnston, B. List*, *M. Rueping*, *M. Terada*, and *H. Yamamoto*. For a review article entitled '*Modulating the Acidity: Highly Acidic* Brønsted *Acids in Asymmetric Catalysis*', see [9c].

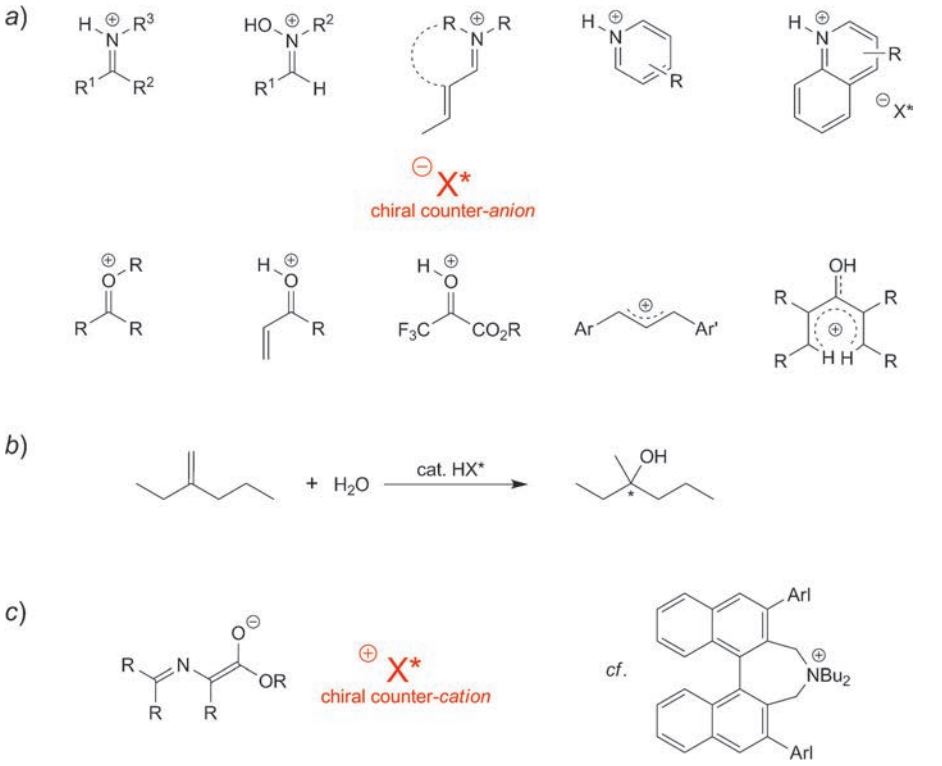

Fig. 2. *Achiral cations with enantiotopic trigonal centers formally involved in chiral counter*-anion *catalysis* (*a*), *in the ultimate challenge* (*b*), *and counter*-cation-*induced enantioselective phase-transfer catalysis* (*c*)

The ultimate challenge will be the enantioselective acid-catalyzed hydration of a simple olefinic C=C bond (*Fig. 2*, *b*). In this context, phase-transfer catalysis (PTC) [10] with chiral counter-*cations* [11], a kind of *umpolung* of the above process, must be mentioned (see the example in *Fig. 2*, *c* [12]).

2. Enantioselective H-Bonding Catalysis with TADDOLs. – The now classical type of enantioselective H-bonding donor catalysis with chiral urea, and especially thiourea derivatives was introduced by *Jacobsen* and has enjoyed numerous applications, especially since the review article appeared in 2006 [13]. As in the counter-ion catalysis [2], the mechanistic details may be more complicated than suggested by the simple picture presented in *Fig. 1*, *a* [14]. Besides the ureas, small synthetic peptides have also been successfully applied as H-bond-donor organocatalysts [15].

As indicated in *Fig. 3*, *b* and *c*, the TADDOLs (= $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanols) are more acidic (better H-bond donors) than simple benzhydrylic alcohols due to an intramolecular H-bond (*cf.* the benzoic acid derivatives in *Fig. 3*, *a*). Intramolecular H-bonds in the crystal structures of TADDOLs, and their derivatives

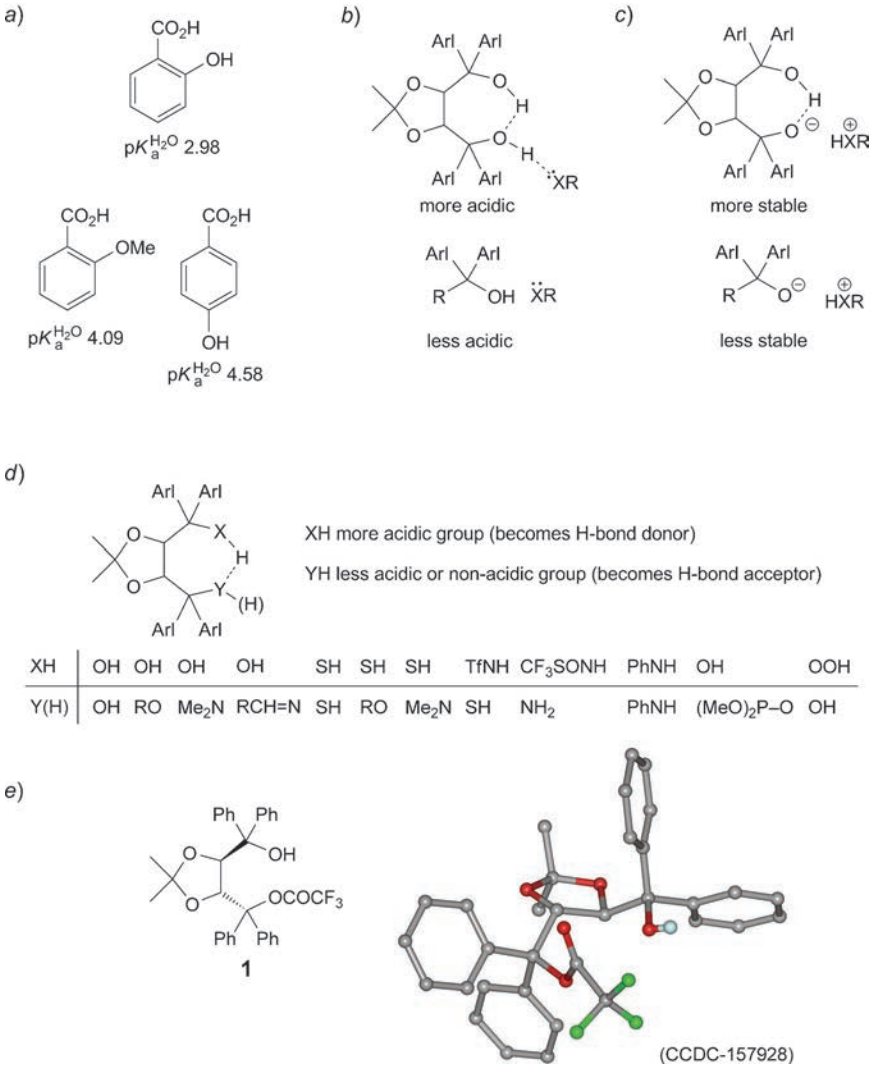

Fig. 3. *Increased acidity by H-bonding* (*a* – *c*) *and intramolecular H-bonding as found in X-ray crystal structures of TADDOL derivatives and analogs* (*d*). For the structures, see [16a,b] and references cited therein. Interestingly, there is no H-bond between the OH and the ester group of the mono-trifluoroacetate ester **1** of TADDOL (*e*); this carbonyl O-atom is a poor H-bond acceptor, and/or the nine-membered H-bonded ring is unfavorable.

and analogs are collected in *Fig. 3*,*d*. An exception is the mono-trifluoroacetate **1** in *Fig. 3*,*e*. TADDOLs are known to be able to form H-bond donor–acceptor complexes with essentially every type of small molecules containing an amino, imino, aziridino, oxaziridino N-atom, or a hydroxy, epoxy, ether, acetal, carbonyl, nitroso, or sulfoxide

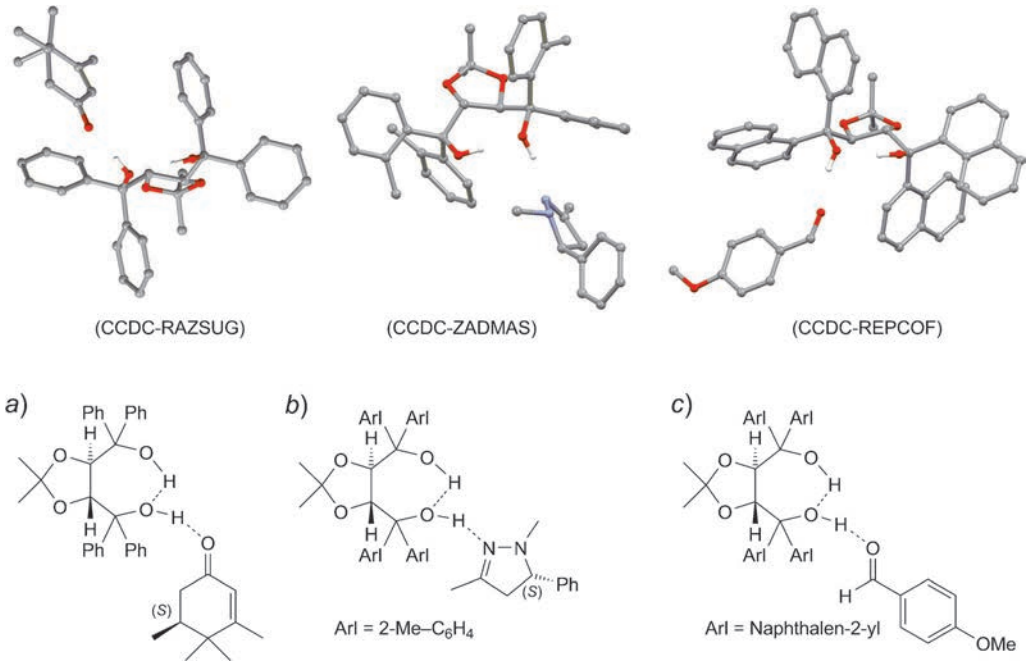

Fig. 4. *Host–guest crystal structures of three TADDOLs* (H-bond donors) *with a ketone* [17], *a 1,2-pyrazoline* [18], *and anisaldehyde* [19] *as H-bond acceptors with the corresponding CCDC* (*Cambridge Crystallographic Data Centre*) *codes*

O-atom, both in the solid (crystalline) state[6]) and in solution: when TADDOLs are crystallized in the presence of racemic mixtures of H-bond acceptors, one enantiomer can become a host in the lattice of the TADDOL crystal; for three examples, see *Fig. 4*. There is a large number of crystal structures of this type, mainly determined by *F. Toda*'s group[6]) (a search in the *Cambridge Crystallographic Data Base* as of February 2012 retrieved 142 examples). The 'clathration' of single enantiomers in TADDOL crystals has been used for resolutions[6]), for dynamic resolutions ('deracemizations') [21], and for performing enantioselective photoreactions within cystals. The H-bond donor–acceptor couples are also present in solution, as evident from the fact that TADDOLs can be used as NMR shift reagents for determining enantiomer ratios [22][7]).

In 2002, *Rawal* and co-workers described the first application of TADDOL (with Arl = naphthalen-1-yl) as an enantioselective H-bonding catalyst [19][23] for activation of aldehyde groups. Some representative examples are collected in *Scheme 1*[8]).

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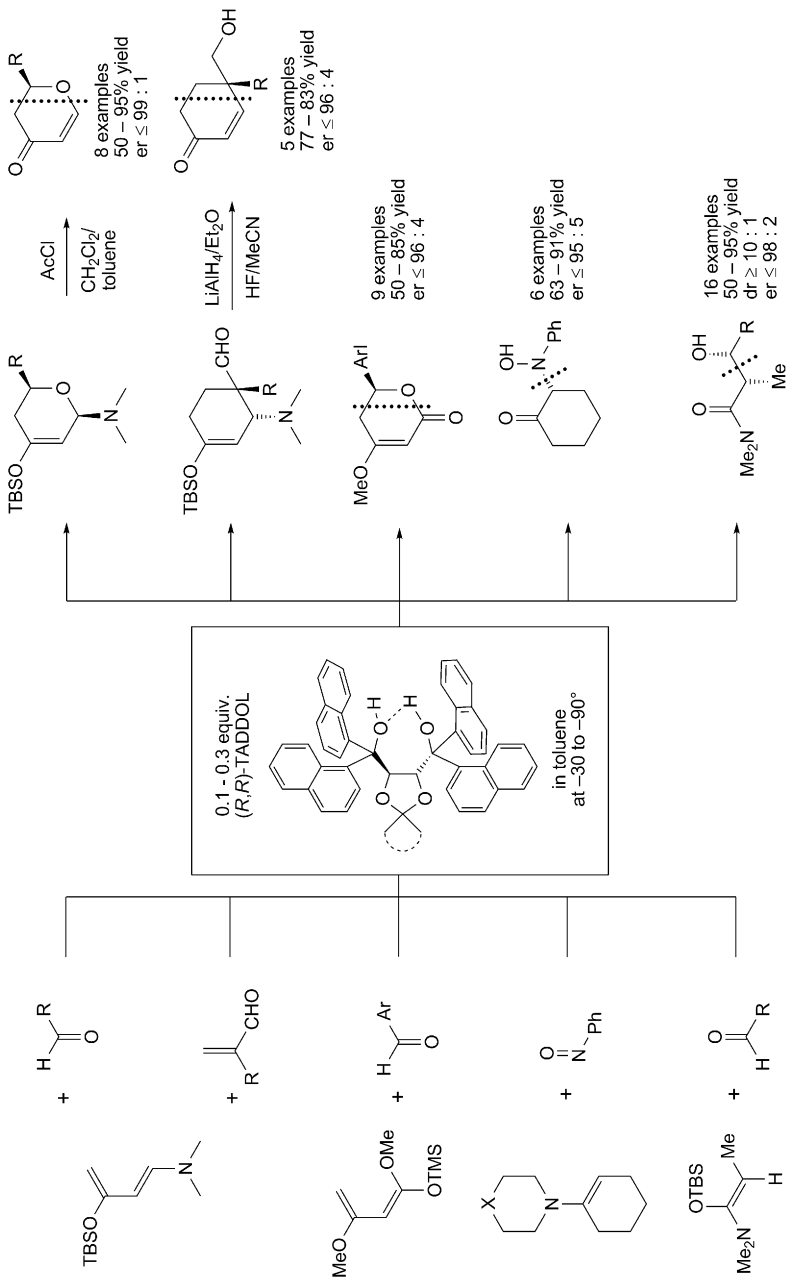
[6]) For selected examples of guest–host X-ray crystal structures of TADDOLs, see Scheme 6 in [20]. See also review articles by the *Toda* group cited in [16a] as ref. 26. Even CCl_4 has been found to form a clathrate with TADDOL; see reference 4 in [16b].

[7]) See also Scheme 5 in [20].

[8]) For quantum-mechanical investigations [25] of this type of catalysis, see especially Section 4.2.1 in the *Chem. Rev.* article [25c].



Scheme 1. *Low-Temperature Enantioselective H-Bond Activation of Aldehydes, Enals, and Nitrosobenzene by a TADDOL for Reactions with Electron-Rich Olefins and Dienes Containing Enamine, Enol Ether, Ketene Acetal and Ketene N,O-Acetal Moieties* [19][23][24]. Note that all additions to aldehyde groups occur from the enantiotopic *Si*-face!

The observed addition from the *Si*-face[9]) of the aldehyde groups is compatible with the crystal structure of the TADDOL (Arl = naphthalen-2-yl)/anisaldehyde complex [19], shown in *Fig. 4*, *c*) and with computational results[8]), according to which the OH ··· O=C H-bond is located next to a *quasi*-equatorial naphthalen-1-yl group in such a way that the enantiotopic *Re*-face is sterically shielded from nucleophilic attack. It looks as if this is a case, in which we have a chance to *predict* the stereochemical outcome of enantioselective reactions by determining the crystal structures of the clathrates formed by the organocatalyst and the electrophilic reactant, the H-bond acceptor.

3. TADDOL-Derived *Brønsted* Acids. – To the best of our knowledge, only one type of strong *Brønsted* acids has been prepared from TADDOLs and used as catalysts[10]): *Akiyama et al.* converted a series of seven TADDOLs to cyclic phosphoric acid diesters (*Scheme 2*) and showed that a *Mannich*-type reaction was catalyzed by these acids with enantioselectivities of up to 96 : 4, if the imine substrate was derived from an aromatic aldehyde and 2-amino-5-methylphenol [28][11]). The TADDOP-acids **2** used as catalysts for this transformation were prepared by reaction of TADDOL with PCl_3, hydrolysis, and oxidation with I_2. *Voituiez* and *Charette* have prepared another series of TADDOP-acids [29] by a more elaborate sequence of steps. We describe herein a two-step preparation of the parent acid **2a** by chlorophosphorylation of TADDOL (see previous paper [16b] in this series) and hydrolysis (*Scheme 2*).

It would be desirable to have additional H-bond donors and *Brønsted* acids of the TADDOL skeleton, with acidities in between the parent TADDOL **A** ($R^1 = R^2 = Me$, $R^3 = Ph$) and the phosphoric acids **2**, or even more acidic derivatives[12]) than **2**. There are two ways of increasing the TADDOL acidity, as indicated in formula **A**: stronger electronegative aryl (*cf.* C_6F_5) or non-aromatic groups (*cf.* CF_3) could be introduced, as shown by *Berkessel* and co-workers [33] (*vide infra*), or, heteroatoms XH with more acidic H-atoms (*cf.* SH, NHCOR, $NHSO_2R$) could be introduced by replacement of the TADDOL OH groups. Replacement reactions of this type have been described by us (see the first two parts of this series of publications [16a,b] and earlier papers cited therein). In X-ray crystal structures, which are alluded to in *Fig. 3*, *d*, higher acidities of sulfanyl and triflamido (= trifluoromethanesulfonamido) groups are indicated by the intramolecular H-bonding patterns detected in the solid state. In the late 1990s[1–3]), we had prepared these more acidic derivatives not because we were ahead of our time, foreseeing 'asymmetrical catalysis by chiral H-bond donors' [13] or 'asymmetric counter-anion-directed catalysis' (ACDC [5a – d]), but because we wanted to be able to protonate less basic 'carbanionoid' species than lithium enolates, after we had found

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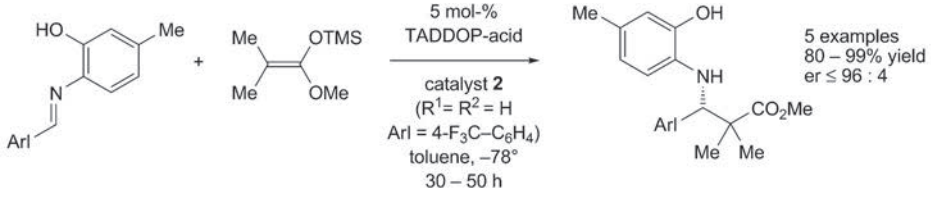
[9]) For the *Re*/*Si*-nomenclature for describing stereochemical courses of reactions, see [3a][3b][3c][3d] and [26].

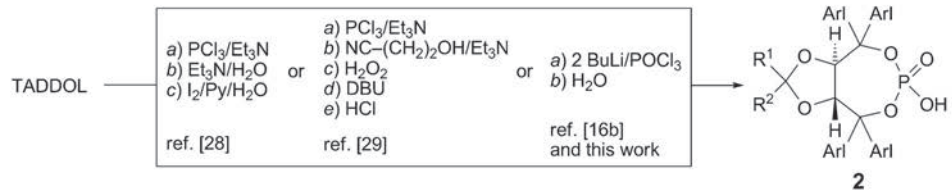
[10]) We are also aware of only one case, in which TADDOL was used in enantioselective PTC: an alanine imino-ester enolate of the type shown in *Fig. 2*, *c* (generated with NaOH or NaH in toluene in the presence of TADDOL), was alkylated enantioselectively [27].

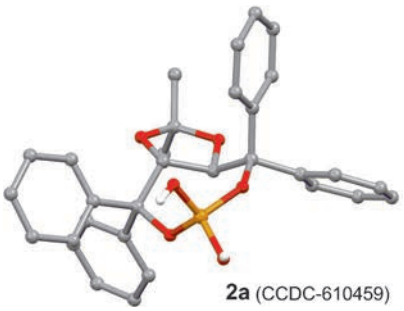
[11]) Formaldehyde-derived TADDOLs (such as the catalyst precursor in *Scheme 2* with $R^1 = R^2 = H$) were first prepared to lend higher acid stability to the system and to allow for better recovery – under acidic conditions – of the TADDOL after catalytic usage [31].

[12]) An attempt to prepare a bis[sulfonic acid] from the dithiol analog of TADDOL was unsuccessful [32].

Scheme 2. *An Enantioselective* Brønsted *Acid-Catalyzed* Mannich *Reaction, Producing a Special Type of β-Amino Acid Derivatives* [28], *with a TADDOP-Acid Catalyst; Preparation* [16b][28][29] *of TADDOP-Acids and a Crystal Structure of* **2a** (not showing H_2O and THF molecules in the unit cell) [29]. For a comparison with a *Lewis* acid-catalyzed variant of this *Michael* addition, see [30]. The acids described in [29] were prepared to be used as precursors of enantioselective *Simmon–Smith*-like cyclopropanating reagents.







ref. [28]

Arl	R^1	R^2
Ph	H	H
4-Ph–C_6H_4	H	H
4-F–C_6H_4	H	H
4-CF_3–C_6H_4	H	H
4-CF_3–C_6H_4	H	H
4-CF_3–C_6H_4	H	Ph
4-CF_3–C_6H_4	H	Naphthalen-1-yl
4-CF_3–C_6H_4	Me	Me

ref. [29]

	Arl	R^1	R^2
2a	Ph	Me	Me
	3,5-Me_2–C_6H_4	Me	Me
	3-Ph–C_6H_4	Me	Me
	4-Ph–C_6H_4	Me	Me
	Naphthalen-2-yl	Me	Me
	Ph	Me	Ph

out that stoichiomeric amounts of the parent TADDOL protonate the achiral Li-enolate of β-methyl-α-tetralone with an enantioselectivity of 98:2 [34][13][14][15]. The progress made in the field of enantioselective protonations between 1995 and 2009 is demonstrated by a comparison of two review articles on this subject [40][41].

Before turning to the acidities of the TADDOL-derived stronger acids, we should like to present some interesting observations made when trying to prepare the

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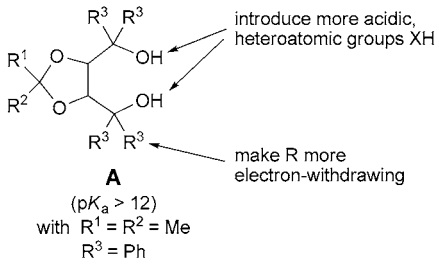
[13]) For an enantioselective enolate protonation (er 90:10), mediated by catalytic amounts of TADDOLs and analogs, see [35].

[14]) For an industrial application of enantioselective enol/ketone tautomerization, see [36]. As far as we know, the first catalytic enantioselective protonation of an enol intermediate was described by *Pracejus* in 1960 (addition of MeOH to a ketene $R^1R^2C{=}C{=}O$ with catalytic amounts of a chiral amine [37]; see also a dendritic effect of this reaction [38]).

[15]) For the enantioselective protonation of a silyl enol ether by phenol in the presence of a typical strong chiral *Brønsted* acid, $(R^*O)_2P(S)NHTf$ (5 mol-%), see [39]; *cf.* also [7].



bis[triflamide] of TADDAMIN **3** (*Scheme 3*). When treated with excess trifluoromethanesulfonic anhydride (Tf_2O)/Et_3N, the diamine **3** gave the mono-triflamide **4** in good yields, no bis[triflamide] was formed[16]). After reaction with excess TfCl/*Hünig* base (EtN^iPr_2; DIPEA), neither the mono- nor the bis[triflamide] was found. Rather, complex mixtures of the products **5**–**7**, plus unidentified compounds, were detected in the crude product mixtures. With DBU (=1,8-diazabicyclo[5.4.0]undec-7-ene) instead of DIPEA as base, the major product was the sulfinamide **6** (see *Table 2* in the *Exper. Part*). The surprising formation of sulfinamides **6** and **7**, the structures of which were established by single-crystal X-ray analyses, can be rationalized by a mechnism analogous to that proposed by *Netscher* and *Bohrer* for the formation of triflinates (=trifluoromethanesulfinates) from reactions of alcohols or phenols with Tf_2O/Et_3N [42]; see *Reaction a* in *Scheme 3:* a mixed anhydride of sulfonic and sulfinic acid is formed, which acts as a sulfinylating agent. As far as we can see, the formaldehyde aminal group in **7** may arise from an impurity or from the solvent CH_2Cl_2. We carefully checked the purity of the TfCl for Me-containing impurities, in vain; a methylamino derivative, such as $^iPr_2NMe$, could be the source of the CH_2 group in **7**, as indicated in *Reaction b* of *Scheme 3*, but we have no evidence for such an impurity in the *Hünig* base (DIPEA) used. A reaction with CH_2Cl_2 is not expected to occur under our reaction conditions (2–4 equiv. of TfCl, $-40°$ to room temperature)[17]). Similarly surprising to us was the formation of the bicyclic sulfuric diamide (=sulfamide) **5**, formally a substitution of F_3C^-, under the reaction conditions (for details, see *Table 2* in the *Exper. Part*)[18]).

As *Brønsted* acids, which are expected [7][8a][39] to be more acidic than the TADDOP-acids **2** (*Schemes 2* and *4*), we have also tried to prepare imides (*cf.* **9b**) from the TADDOP-acid chlorides **8**. These acid chlorides turned out to be surprisingly inert to nucleophilic replacement of chloride: *i*) they readily survived chromatography on silica gel; *ii*) hydrolysis of the acid chloride **8b** to the acid **2a** (THF/H_2O 1:1) required heating at reflux for 24 h; *iii*) conversion of **8b** to the amide **10** (THF/aq. NH_4OH 1:1) takes 60 h at room temparature; *iv*) the Cl/$NHSO_2CF_3$ substitution with acid chloride **8a** (104 mg/$TfNH_2$ (60 mg)/$^iPr_2EtN$ (155 mg)/$CDCl_3$ (0.3 ml)) was carried out by

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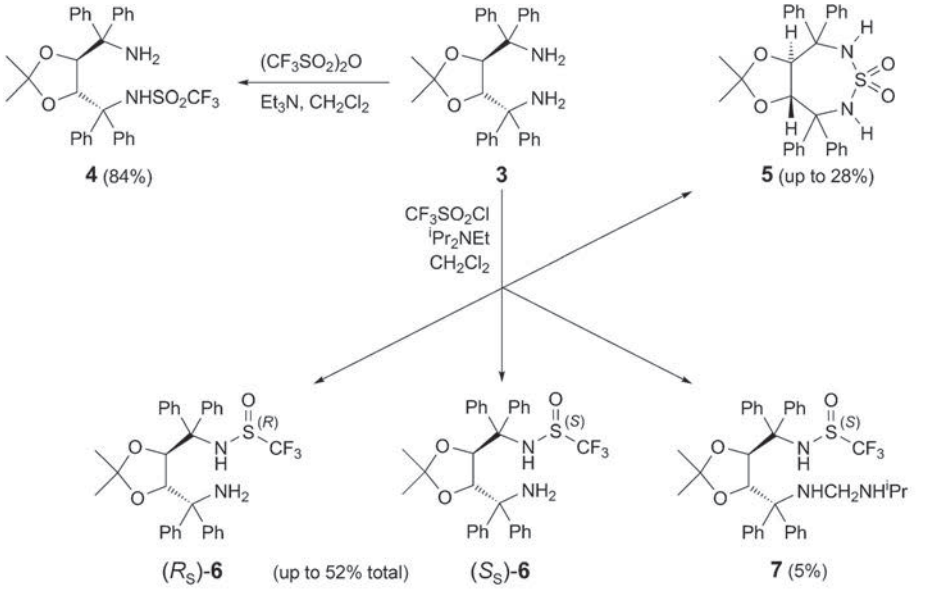
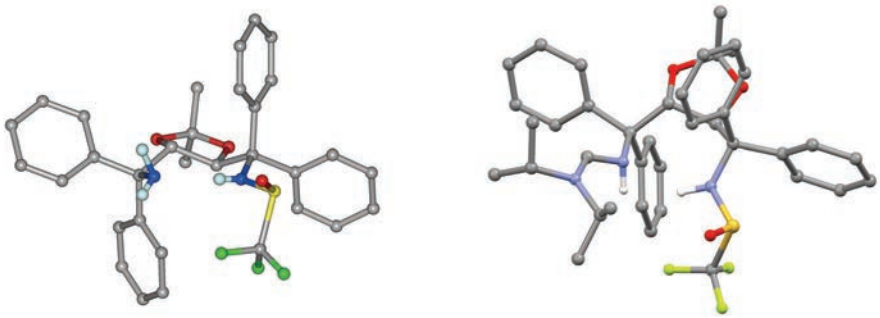
16) Treatment of the mono-triflamide **4** with trifluoromethanesulfonating reagents also failed to produce the bis[triflamide].

17) It is well-known that amines may react, even vigorously, with chlorinated solvents, see, *e.g.*, [43].

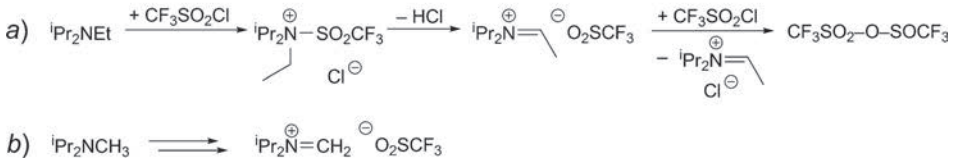
18) Radical reactions, photochemical processes, and Ru-catalyzed transformations can lead to loss of $^•CF_3$ groups from triflic acid derivatives [44].

Scheme 3. *Results of the Reactions of TADDAMIN* **3** *with* Tf_2O *and* $TfCl/Et_3N$ *or* Hünig *Base.* The structures of the sulfinamides **6** and **7** are established by X-ray analysis. In the unit cell of the structure of **7**, there is a molecule of Et_2O (not shown here). Possible mechanisms for the formation of electrophilic sulfinylating and (diisopropylamino)methylating reagents are shown in *a* and *b*, respectively (see also accompanying text).





(*S*$_S$)-**6** (CCDC-157929) **7** (CCDC-867042)



heating at 55° for 14 h, to give the ammonium salt **9a** (for a crystal structure, see *Scheme 4*)[19]). The sluggishness of the TADDOP-acid chlorides **8** in nucleophilic substitution reactions may be discussed simply by considering, in a naive, 'first-order' analysis, a trigonal bipyramidal intermediate **11**, with the nucleophilically introduced substituent Nu and the Cl-atom in apical positions, with an O–P–O bond angle[20]) widened from 110° to *ca.* 120°, and with 1,5-repulsion (*Newman* strain [3e]) between both, the Cl and the Nu group, and the neighboring *quasi*-axial Ph groups (see bottom of *Scheme 4*). If the pentacoordinate intermediate **11** were really a high-energy species in the rate-determining step, it would be responsible for the poor reactivity of the acid chlorides **8**[21]). The ammonium salt **9a**, obtained in two steps from the corresponding TADDOL, can be purified by flash chromatography. In the unit cell of the crystal of this imide, there is also a molecule of toluene (not shown in *Scheme 4*); the *Hünig* base ammonium ion is somewhat disordered, and the $R_3N–H^+$ H-atom forms a H-bond with the P(O) O-atom (not with the N-atom or one of the SO_2 O-atoms)[22]) of the counter-anion. Samples containing the acid **9b** were obtained by preparative TLC; the acid should also be formed by treatment with ion-exchange material.

4. pK_a Determinations in 2-Methoxyethanol/H_2O 4:1 and Comparison with Values in Other Solvents. – The information on acidities of organic and inorganic compounds is of central, paramount importance in chemistry (more than 200 years ago, *G. de Morveau* stated '*Tenir la définition des acides, c'est tenir la clef de la chimie*' [45]). Due to poor solubility of most organic compounds in H_2O, their acidities are determined in non-aqueous media. Since the stability of the involved ions depends strongly on their solvation and on the dielectric constant (*DK*) of the solvent, pK_a values can only be compared when determined in the same solvent (see the representative list of values (relevant for the following discussion) in *Table 1*). For a given compound, the pK_a value in DMSO (*DK* 47) is always higher than that in H_2O (*DK* 78), and the difference can be as large as 15 and as small as 3 units[23]). *Berkessel, O'Donoghue* and co-workers have recently published a thorough investigation of the acidities (in DMSO/2% H_2O) of acids of importance for organocatalysis [33], including the fluoro-activated derivatives of TADDOL and analogs shown in *Fig. 5*.

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[19]) Attempted triflation (Tf_2O, TfCl) of the phosphoric acid amide **10**, with two Me groups on the dioxolane ring (a ketal of acetone), led to mixtures of products lacking the geminal Me groups (NMR analysis). This is why we turned to the dioxolane derived from tartaric acid and formaldehyde, in which this heterocyclic ring is much more stable towards aggressive electrophiles (*cf.* [28]), *Scheme 2*, *Footnote 11*, and discussion of the lability of the TADDOL skeleton in Sect. 4 of [16b]).

[20]) For the crystal structure of **8b**, see compound **23** in Fig. 2 of [16b].

[21]) For a case in which the TADDOL skeleton has a ligand-accelerating effect, see the *ca.* 1000-fold activity of $(^iPrO)_2$Ti-TADDOLate as compared to $(^iPrO)_4$Ti in *Lewis* acid catalysis; for a discussion of this effect, see Chapt. 10 in [20] and references cited therein.

[22]) Thus, in the crystal structure, the P(O) O-atom is the site of highest H-bond acceptor activity (and anionic charge density?) of the phosphoryl-trifluorosulfonyl imide. If this would be the preferred type of interaction also in solution of such imide anions, their achiral partners would be held close to the chirality-inducing centers or axes (*cf. Fig. 1*).

[23]) For a useful compilation of the pK_a values in H_2O and DMSO with references, see [53].

Scheme 4. *Preparation, in Two Steps, of the TADDOP-Acid Derivatives* **2a** *and* **8**–**10** *from TADDOLs, Crystal Structures of* **9a** *and* **10**, *and a Pentacoordinate Intermediate,* **11**, *in Phosphorylations of Nucleophiles by an Acid Chloride,* **8**. The two different conformations in the unit cell of amide **10** are shown.

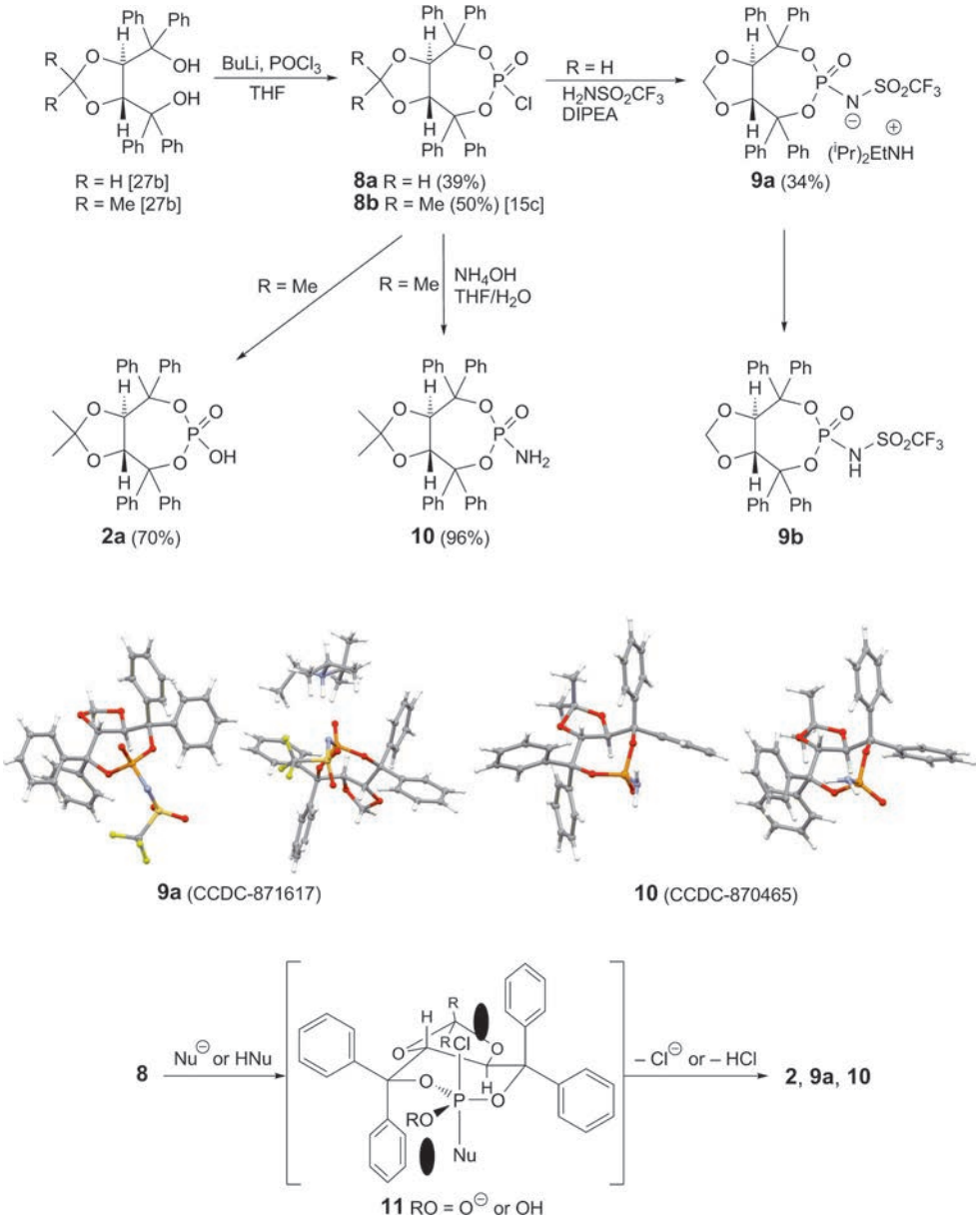


Table 1. *The p*K$_a$ *Values of Compounds with Functional Groups Occurring in the TADDOL Derivatives and Analogs Shown in* Figs. 5 *and* 6. The pK_a values in DMSO (the *Bordwell* scale) are taken from [46], the pK_a values in H_2O are taken from *March*'s textbook [47], and from monographs on amides [48], on sulfonic acid derivatives [49], and on fluoro-compounds [50]. The values for protonated imines $R_2C{=}NHR^+$ and for the phosphoric acid diester $(PhO)_2P(O)OH$ are taken from [51] and [52], respectively.

Acid	$pK_a^{H_2O}$	pK_a^{DMSO}	Acid	$pK_a^{H_2O}$	pK_a^{DMSO}
Alkyl–OH	15–17		MeCONHPh		21.5
Aryl–OH	8–11		$CF_3CONHPh$		17.2
Alkyl–SH	6–8		$PhCONH_2$		23.4
$R_2C{=}NHR^+$ (R = H, Alkyl)	7–8		$H_2N{-}CO{-}NH_2$		26.9
MeOH	15.5	29.0	$MeSO_2NH_2$	10.8	17.5
CF_3CH_2OH	12.8	23.5	$MeSO_2NHMe$	11.8	
$(CF_3)_2CHOH$	9.3	18.2	$MeSO_2NHPh$	9.0	
PhOH	10.0	18.0	$PhSO_2NH_2$	10.0	16.2
PhSH	6.5	10.3	$PhSO_2NHMe$	11.4	
$PhNH_2$		30.6	$PhSO_2NHPh$	8.4	
$Me{-}CO_2H$	4.7	12.3	$CF_3SO_2NH_2$	6.3	9.7
$H{-}CONH_2$		23.5	CF_3SO_2NHMe	7.6	
$Me{-}CONH_2$	15.1	25.5	CF_3SO_2NHPh	4.5	
$Me{-}CSNH_2$		18.5	$(PhO)_2P(O)OH$	1.9	
$CF_3{-}CONH_2$		17.2			

In the 1960s, *Simon* [54] developed an acidity scale in the solvent mixture 2-methoxyethanol ('Methylcellosolve', MCS)/H_2O 4:1 (*DK* 32). The values are determined by titration with Et_4NOH; the upper limit is pK^*_{MCS} *ca.* 11, and the lower limit is pK^*_{MCS} *ca.* 3. The values obtained for H_2O-soluble compounds are between 1 and 2.5 pK_a units higher than those measured in pure H_2O[24]). The pK^*_{MCS} values for some of the TADDOL-derived acids are collected in *Fig. 6*; for comparison, we have also determined the values for BINOL and two bis[triflamides][25]). As might have been expected, the TADDOP-acid **2a** is the most acidic compound of the series (the pK^*_{MCS} 5.5 corresponds to a $pK_a^{H_2O}$ between 3.0 and 4.5; *cf.* AcOH), closely followed by the triflamido-thiol (5.7) and the triflamido-alcohol (5.9). We tried to determine the pK^*_{MCS} value for the imide **9b** by titration of its ammonium salt **9b** with HCl; there was no inversion of the titration curve, which could mean that the pK^*_{MCS} is outside of the lower limit of *ca.* 3. The sulfanyl alcohol and the trifluoroacetamido thiol have remarkably low pK^*_{MCS} values of 8.9 and 7.4 (in the range of thiophenols), respectively. Comparisons of the triflamide with its methylsulfanyl ether (5.7 *vs.* 9.7), and of the sulfanyl alcohol with the sulfanyl ethers (8.9 *vs.* >11) demonstrate the strong influence of intramolecular H-bonding on the acidities of TADDOL derivatives (*cf. Fig. 3*), an effect which is not detected for BINOL, and which is due to the unique conformational lock caused by the two geminal diaryl moieties of the TADDOL scaffold, pushing the

[24]) For extensive tables with more than 1000 pK^*_{MCS} values, see [55].

[25]) The acidimetric titrations were carried out by the Analytical Service Division of the Laboratorium für Organische Chemie, ETH Zürich.

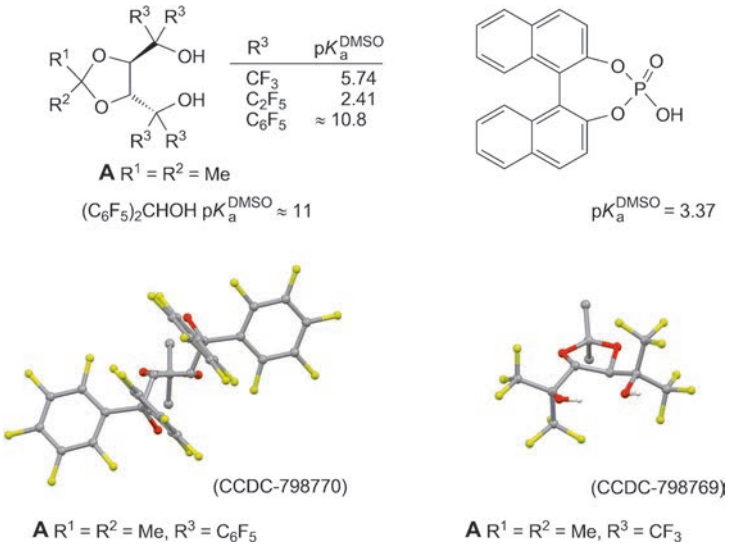


Fig. 5. *Acidities of a TADDOL* (Arl = C_6F_5) *and analogs, and of the BINOL phosphoric acid derivative in DMSO/2% H_2O* [33]. Interestingly, the pK_a value of the TADDOL is essentially the same as that of decafluorobenzhydrol, and the crystal structure of this TADDOL shows that the exocyclic C–C bond has the less frequently observed O–C–C–O *gauche* conformation with the OH groups over the dioxolane ring, *i.e.*, no intramolecular H-bond between the two HO groups, and thus no H-bond-induced increase of acidity [33] (see the discussions in *Sect. 1*, and in [16a] (Sect. 3) and [16b] (Sect. 5). In the CF_3 analog, we see the familiar seven-membered-ring H-bond in the crystal [33]; note that this compound is by 12.5 pK_a^{DMSO} units more acidic than $(CF_3)_2CHOH$ (HFIP, *cf. Table 1*).

OH-groups into close proximity. If we were to make an estimate for the p$K_a^{H_2O}$ of the parent TADDOL (Arl = Ph), we would place it close to 13.

5. Conclusions. – The results presented here show that introduction of various functional groups on the TADDOL backbone can provide *Brønsted* acids with a variety of acidities between pK^*_{MCS} 5.5 and 10.8 (corresponding to p$K_a^{H_2O}$ 3.0–4.5 and 8.3–9.8). Application of the principle of modulating the acidity of compounds of this type by manipulations of the two heteroatomic substituents could provide further strong *Brønsted* acids for applications in enantioselective counter-*cation* organocatalysis.

When considering that we can use TADDAMINs **B** (p$K_a > 30$) for generating chiral Li-amides for deprotonations (lithiations) [56], the statement may be justified that we can cover the entire acid/base range from p$K_a > 30$ all the way down to pK_a 3 by placing suitable functional groups (NH, SH, $NHSO_2CF_3$, P(O)(OH) **C**, **D**, **E**) on the scaffold, which is common to all TADDOLs and their analogs[26]).

We gratefully acknowledge the contributions of the co-workers of the services of the Laboratorium für Organische Chemie: Prof. Dr. *B. Jaun*, *B. Brandenberg*, and *P. Zumbrunnen* (NMR), Dr. *W. Amrein*,

[26]) No configuration is indicated in the formulae **B**–**E** because both enantiomers are equally readily accessible from (*R*,*R*)- or (*S*,*S*)-tartaric acid.

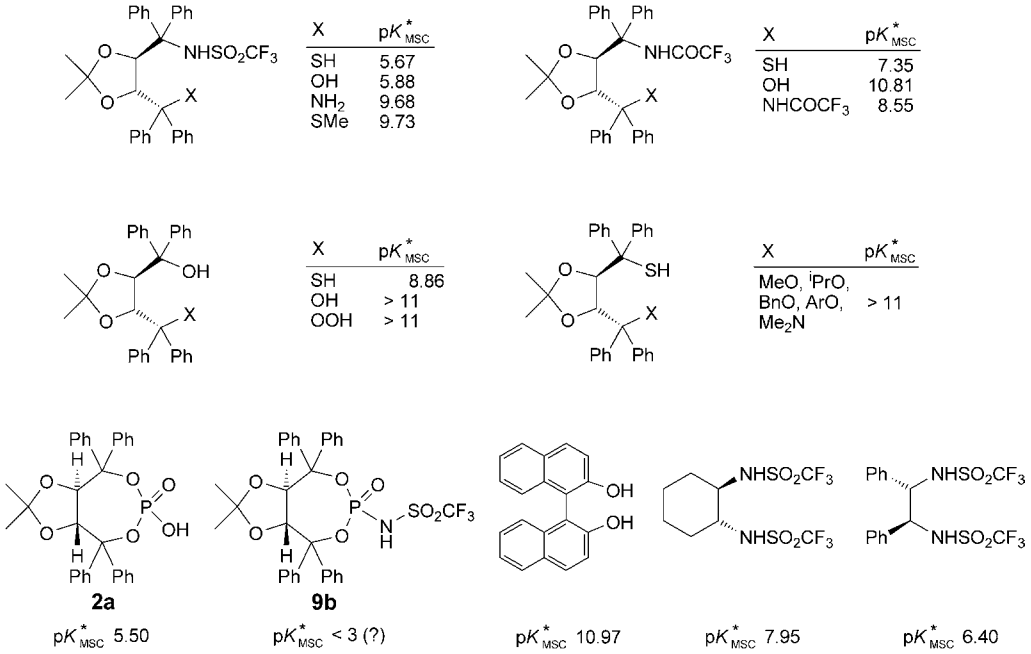
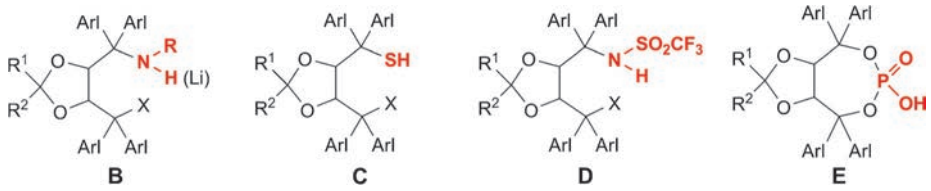


Fig. 6. *The* pK^*_{MCS} *values of* Brønsted *acids derived from TADDOL*. For comparison, the values of BINOL and of two bis[trifluoro-sulfonamides] are also shown. For details of the pK_a titration in ethyleneglycol monomethyl ether/H_2O 4:1, see the accompanying text and [54][55]. The preparation of the compounds shown here is described in the *Exper. Parts* of the present paper, and of Parts I and II of this series of publications [16a,b].



H. U. Hediger, *R. Häfliger*, and *O. Greter* (MS), and *M. Schneider* and *D. Manser* (acidimetric titrations, elementary analyses, molecular weights). We also acknowledge the generous financial support by *ETH Zürich* and *Novartis* AG, Basel.

Experimental Part

1. *General. Abbreviations*: DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; FC, flash chromatography; h.v., high vacuum, 0.01–0.1 Torr; Tf_2O, trifluoromethanesulfonic anhydride; TfCl, trifluoromethanesulfonyl chloride; THF was freshly distilled over K before use. Et_3N was distilled over CaH_2. CH_2Cl_2 was used in *puriss.* quality. Solvents for workup and chromatography: pentane and hexane were distilled over P_4O_{10} or *Sikkon* (anh. $CaSO_4$; *Fluka*), AcOEt over *Sikkon*, Et_2O over KOH/$FeSO_4$, and CH_2Cl_2 over P_4O_{10}. PCl_3 was distilled before use. All other reagents were used as received from *Fluka* or *Aldrich*. All indicated reaction temp. were monitored with an internal thermometer (*Ebro-TTX-690* digital

thermometer). TLC: *Macherey-Nagel Alugram SIL G/UV$_{254}$* or *Merck 60 F$_{254}$* silica gel plates; detection by UV light (λ 254 nm) or I_2, or by dipping in/spraying with phosphomolybdic acid soln. (phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot 4\,H_2O$ (10 g), H_2SO_4 (60 ml), H_2O (940 ml)), followed by heating. FC: *Fluka* silica gel 60 (0.040–0.063 mm), at *ca.* 0.3 bar. M.p.: *Büchi-510* apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter (10-cm, 1 ml cell), at r.t. IR Spectra: *Perkin-Elmer-1620-FT-IR* spectrometer, in cm^{-1}. NMR Spectra: *Bruker AMX-500* (^{1}H: 500 and ^{13}C: 125 MHz), *AMX-400* (^{1}H: 400 and ^{13}C: 100 MHz), *Varian Gemini-300* (^{1}H: 300, ^{13}C: 75, and ^{19}F: 282 MHz), *Mercury-300* (^{1}H: 300, ^{13}C: 75, and ^{19}F: 282 MHz) or *Gemini-200* (^{1}H: 200 and ^{13}C: 50 MHz); chemical shifts (δ) in ppm downfield from TMS (δ 0.0) as internal standard; *J* values in Hz. MS: *VG Tribrid* (EI; 70 eV), *VG ZAB-2 SEQ* (FAB; 3-nitrobenzyl alcohol matrix), *IonSpec Ultima* (FT-ICR-MALDI; 4.7 T; 2,5-dihydroxybenzoic acid matrix), *Bruker REFLEX* (TOF-MALDI; N_2 Laser), or *Finnigan MAT TSQ 7000* (ESI) spectrometer; in *m/z* (% of basic peak). HR-MS: *IonSpec Ultima* (FT-ICR-MALDI; 4.7 T; 2,5-dihydroxybenzoic acid matrix). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH Zürich.

2. *Preparation of the Compounds* **1** *and* **4**–**7**. *{(4*R*,5*R*)-5-[(Hydroxy)(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}(diphenyl)methyl 2,2,2-Trifluoroacetate* (**1**). To a soln. of the parent TADDOL **A** ($R^1 = R^2 = Me$, $R^3 = Ph$; 1.50 g, 3.21 mmol) in THF (15 ml) was added BuLi (4.70 ml, 7.07 mmol; 1.5M soln. in hexane) at $-75°$. The mixture was allowed to warm to r.t. (*ca.* 2 h), whereupon a colorless precipitate was formed. After cooling to $-30°$, $(CF_3CO)_2O$ (1.34 ml, 2.02 g) was added dropwise over 10 min. The mixture was allowed to warm to r.t., and stirred for further 2 h. The yellow soln. was washed with sat. aq. $NaHCO_3$ soln. (20 ml) and sat. aq. NaCl soln. (20 ml), and the aq. phase was extracted with Et_2O (2 × 30 ml). The combined org. phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was recrystallized (acetone, $-20°$) to afford **1** (1.16 g). After partially removing the solvent from the mother liquor, further **1** (0.42 g) was obtained. Total yield: 1.58 g (87%). Colorless crystals. M.p. $>102°$ (dec.). $[\alpha]_D^{r.t.} = -146.6$ ($c = 1.04$, $CHCl_3$). IR ($CHCl_3$): 3597*w*, 3063*w*, 3008*w*, 2936*w*, 1788*s*, 1710*w*, 1496*m*, 1448*m*, 1382*w*, 1371*m*, 1169*s*, 1148*s*, 1083*m*, 1050*m*, 1032*w*, 884*m*, 636*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.78 (*s*, Me); 0.86 (*s*, Me); 2.42 (br. *s*, OH); 5.08 (*d*, *J* = 7.3, CH); 5.69 (*d*, *J* = 7.3, CH); 7.29–7.59 (*m*, 20 arom. H); 9.85 (br. *s*, NH). ^{13}C-NMR (50 MHz, $CDCl_3$): 27.10, 27.36, 76.56, 79.00, 80.56, 89.63, 111.15, 127.12, 127.18, 127.50, 127.95, 128.17, 128.55, 129.60, 129.79, 139.53, 141.79, 142.13, 147.69. Anal. calc. for $C_{33}H_{29}F_3O_5$ (562.59): C 70.45, H 5.20; found: C 70.32, H 5.49.

N-*[{(4*S*,5*S*)-5-[(Amino)(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}(diphenyl)methyl]-1,1,1-trifluoromethanesulfonamide* (**4**). A soln. of **3** (2.32 g, 5.0 mmol) in CH_2Cl_2 (450 ml) at $-70°$ was added dropwise over 25 min to a soln. of Tf_2O (2.0 ml, 12.0 mmol) in CH_2Cl_2 (30 ml). Then, a soln. of Et_3N (1.75 ml, 12.66 mmol) in CH_2Cl_2 (120 ml) was added during 3.5 h. After warming slowly to r.t. and stirring overnight, the mixture was washed with H_2O (2 × 50 ml) and sat. aq. NaCl soln. (2 × 50 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by FC (SiO_2 (100 g); pentane/Et_2O 2:1 → Et_2O) to yield **4** (2.50 g, 84%). Recrystallization from ^{i}PrOH/H_2O afforded **4** (1.60 g, 54%). Colorless solid. M.p. 235–237°. R_f (pentane/Et_2O 1:1) 0.43. $[\alpha]_D^{r.t.} = -70.1$ ($c = 0.8$, $CHCl_3$). IR ($CHCl_3$): 3361*w*, 3298*w*, 3062*w*, 3039*w*, 2991*w*, 2936*w*, 2532*w*, 1955*w*, 1890*w*, 1810*w*, 1582*w*, 1496*m*, 1447*m*, 1371*s*, 1178*m*, 1144*m*, 1087*m*, 1065*m*, 1037*m*, 958*m*, 878*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.86 (*s*, Me); 1.09 (*s*, Me); 3.94 (*d*, *J* = 8.0, CH); 4.54 (*d*, *J* = 8.0, CH); 7.06–7.10 (*m*, 2 arom. H); 7.19–7.29 (*m*, 8 arom. H); 7.38–7.45 (*m*, 8 arom. H); 7.63–7.68 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 26.67, 26.96 (Me); 62.13, 68.68 (C); 79.31, 81.34 (CH); 108.56, 119.23 (*q*, ^1J(C,F) = 323, CF_3) (C); 126.95, 126.97, 127.29, 127.50, 127.63, 128.07, 128.12, 128.58, 129.29, 129.72, 130.76 (CH); 138.44, 139.13, 140.16, 148.86 (C). ^{19}F-NMR (282 MHz, $CHCl_3$): −77.23. EI-MS: 597 (0.1, $[M+1]^+$), 209 (4.7), 208 (30.0), 207 (11.7), 196 (10.3), 183 (18.7), 182 (100), 180 (15.6), 179 (11.8), 178 (8.1), 167 (5.1), 165 (5.0). Anal. calc. for $C_{32}H_{31}F_3N_2O_4S$ (596.67): C 64.42, H 5.24, N 4.69, S 5.37; found: C 64.37, H 5.47, N 4.71, S 5.51.

Preparation of **5**–**7** *by Treatment of TADDAMIN* **3** *with TfCl. General Procedure* (*GP*). To a soln. of **3** (1 equiv.) in CH_2Cl_2 (0.35M) was added the indicated base (4.5 equiv.), and the mixture was cooled to $-40°$. TfCl (4 equiv.) was added dropwise, and the mixture was allowed to warm to r.t. (*ca.* 4 h). After stirring at r.t. for 0.5–98 h, the reaction was quenched with 1N HCl soln., the org. layer was separated, and the aq. phase was extracted with Et_2O (3 ×). The combined org. layers were washed with sat. aq. NaCl

Table 2. *Reactions of the TADDAMIN* **3** *with* CF_3SO_2Cl (Tf-Cl)/*DIPEA* (*Entries 1–6*) *or DBU* (*Entry 7*) *in* CH_2Cl_2 *According to the* GP. The reactions were followed by TLC analysis of withdrawn samples. In most cases, the starting material **3** had disappeared, when room temperature was reached (exceptions, see *Entries 1* and *4*). The crude product mixtures were subjected to (sometimes multiple) FC. The yields given herein are those of the products obtained from the various FC fractions.

Entry	Equiv. CF_3SO_2Cl	Warm-up time/Time at r.t. [h]	Isolated products (Yield [%])
1	2	1/0.5	**3** (60), (R_S)-**6** (4), (S_S)-**6** (4), n.i.p.[a]) (15)
2	4	4/16	**5** (24), (R_S)-**6** (12), (S_S)-**6** (14)
3	4	4/4	**5** (26), (R_S)-**6** + (S_S)-**6** (52), n.i.p. (10)
4	2.2	4/–	**3** (29), **5** (12), n.i.p. (5)
5	4	4/98	**5** (19), (S_S)-**6** (11), n.i.p. (35)
6	4	4/6	**5** (28), (R_S)-**6** (15), (S_S)-**6** (13), **7** (5), n.i.p. (22)
7[b])	4	4/15	**5** (5), (R_S)-**6** (39), (S_S)-**6** (27), n.i.p. (7)

[a]) Not identified products. b) DBU instead of DIPEA.

soln., dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by FC.

For a compilation of the experiments performed, see *Table 2*. The experiment of *Entry 6* is detailed in the following procedure for the isolation of **5**, **6**, and **7**.

*(3a*S*,8a*S*)-Hexahydro-2,2-dimethyl-4,4,8,8-tetraphenyl-1,3-dioxolo[4,5-*d*][1,2,7]thiadiazepine 6,6-Dioxide* (**5**) *and* (S_S)-N-*[[(4*S*,5*S*)-5-[([Bis(1-methylethyl)amino]methyl}amino)(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}(diphenyl)methyl]-1,1,1-trifluoromethanesulfinamide* (**7**; *Table 2*, *Entry 6*). TADDAMIN **3** (4.65 g, 10.0 mmol) in CH_2Cl_2 (27 ml) was treated with EtN^iPr_2 (7.50 ml, 45.0 mmol) and TfCl (4.24 ml, 40.0 mmol) according to the *GP* (stirring at r.t. for 6 h). The residue (7.23 g), a mixture of at least six products (R_f (pentane/Et_2O 1:1) 0.80, 0.73, 0.66, 0.52, 0.36, 0.10), was purified by FC (SiO_2 (40 cm × 50 mm); pentane/Et_2O 1:1 → 1:2). The *Fractions* (40 ml each) *2–20* yielded a mixture of six products (3.25 g), and *Frs. 21–50* afforded **5** (1.46 g, 28%). A second FC (SiO_2 (35 cm × 50 mm); pentane/Et_2O 1:1) of the product mixture yielded, in *Frs.* (each 40 ml) *15–22*, **7** (0.35 g, 5%).

Data of **5**. Colorless powder. M.p. 265–267°. R_f (pentane/Et_2O 1:6) 0.38. $[\alpha]_D^{r.t.} = -183.4$ ($c = 0.64$, $CHCl_3$). IR ($CHCl_3$): 3362*w*, 3063*w*, 3007*w*, 2937*w*, 1960 *w*, 1900*w*, 1810*w*, 1600*w*, 1496*m*, 1447*m*, 1423*m*, 1383*m*, 1372*m*, 1330*m*, 1161*s*, 1087*m*, 1064*m*, 1020*m*, 933*m*, 914*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.78 (*s*, 2 Me); 5.40 (*s*, 2 CH); 5.51 (br. *s*, 2 NH); 7.34–7.22 (*m*, 12 arom. H); 7.44–7.38 (*m*, 4 arom. H); 7.59–7.50 (*m*, 4 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 26.44 (Me); 67.10 (C); 80.40 (CH); 110.93 (C); 127.43, 127.56, 127.77, 128.49, 129.92 (CH); 139.98, 145.54 (C). MALDI-TOF-MS: 1075 ($[2M + Na]^+$), 549 ($[M + Na]^+$). EI-MS: 526 (0.01, M^+), 281 (7), 224 (6), 223 (9), 222 (17), 207 (12), 194 (12), 183 (15), 182 (100), 180 (29). Anal. calc. for $C_{31}H_{30}N_2O_4S$ (526.66): C 70.70, H 5.74, N 5.32, S 6.09; found: C 70.53, H 5.81, N 5.25, S 6.03.

Data of **7**. Greenish foam. M.p. 203–206°. R_f (pentane/Et_2O 3:1) 0.55. $[\alpha]_D^{r.t.} = -41.7$ ($c = 0.93$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 10.65 (br. *s*, NH); 6.52 (*s*, 1 H); 4.92 (br. *s*, 1 H); 4.30 (*d*, $J = 8$, CH); 3.98 (*d*, $J = 8$, CH); 3.38 (br. *s*, 1 H); 1.19 (*s*, Me); 1.16 (*s*, Me); 0.88 (*d*, $J = 7$, 4 Me). ^{13}C-NMR (100 MHz): 154.9; 145.9; 143.3; 141.6; 140.1; 130.6; 130.1; 129.7; 127.9; 127.8; 127.7; 127.5; 127.0; 126.9; 126.6; 124.3 (*q*, $J = 333$, CF_3); 107.1; 82.8; 70.7; 69.3; 27.2; 27.1; 22.3; 14.1.

(R_S*)- and (*S_S*)-*N-*[[(4*S*,5*S*)-5-[(Amino)(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl](diphenyl)methyl]-1,1,1-trifluoromethanesulfinamide* ((R_S)-**6** and (S_S)-**6**, resp.; *Table 2*, *Entry 7*). TADDAMIN **3** (0.93 g, 2.00 mmol) in CH_2Cl_2 (6 ml) was treated with DBU (1.35 ml, 9.0 mmol) and TfCl (0.85 ml, 8.00 mmol) according to *GP* (stirring at r.t. for 15 h). The residue was purified by FC (2 × ; 1. SiO_2 (60 g); pentane/Et_2O 1:1; 2. SiO_2 (60 g); pentane/Et_2O 6:1) to afford (R_S)-**6** (0.45 g, 39%) and (S_S)-**6** (0.31 g, 27%).

Data of (R_S)-**6**. White foam. M.p. 194–195°. R_f (pentane/Et_2O 6:1) 0.27. $[\alpha]_D^{r.t.} = -48.8$ ($c = 0.62$, $CHCl_3$). IR ($CHCl_3$): 3363*w*, 3290*w*, 3060*w*, 3007*m*, 2745*w*, 1950*w*, 1890*w*, 1810*w*, 1581*w*, 1495*m*, 1446*m*, 1382*w*, 1372*w*, 1172*s*, 1153*s*, 1082*m*, 1032*w*, 955*w*, 891*w*, 638*w*. ^{1}H-NMR (400 MHz, CD_2Cl_2): 0.85 (*s*, Me); 1.25 (*s*, Me); 2.34 (br. *s*, NH_2); 4.01 (*d*, $J = 8.0$, CH); 4.66 (*d*, $J = 8.0$, CH); 7.09–7.41 (*m*, 16 arom. H); 7.47–7.51 (*m*, 2 arom. H); 7.56–7.60 (*m*, 2 arom. H); 11.34 (br. *s*, NH). ^{13}C-NMR (100 MHz, CD_2Cl_2): 26.76, 27.38 (Me); 62.98, 67.44 (C); 80.72, 82.67 (CH); 108.66, 125.53 (*q*, ^1J(C,F) = 317, CF_3) (C); 127.29, 127.41, 127.77, 128.05, 128.10, 128.15, 128.48, 128.69, 128.92, 129.27, 130.56, 131.31 (CH); 140.12, 140.88, 142.22, 150.58 (C). ^{19}F-NMR (282 MHz, $CHCl_3$): −76.90. MALDI-TOF-MS: 603 ($[M + Na]^+$). Anal. calc. for $C_{32}H_{31}F_3N_2O_3S$ (580.67): C 66.19, H 5.38, N 4.82; found: C 66.27, H 5.28, N 4.86.

Data of (S_S)-**6**. White foam. M.p. 204–206°. R_f (pentane/Et_2O 6:1) 0.11. $[\alpha]_D^{r.t.} = -61.1$ ($c = 1.61$, $CHCl_3$). IR ($CHCl_3$): 3359*w*, 3295*w*, 3061*w*, 3007*m*, 2778*w*, 1950*w*, 1890*w*, 1810*w*, 1599*w*, 1582*w*, 1496*m*, 1447*m*, 1382*m*, 1371*m*, 1170*s*, 1153*s*, 1083*s*, 1032*m*, 956*w*, 890*m*, 867*w*, 634*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (*s*, Me); 1.27 (*s*, Me); 2.23 (br. *s*, NH_2); 3.88 (*d*, $J = 8.2$, CH); 4.41 (*d*, $J = 8.2$, CH); 7.03–7.07 (*m*, 2 arom. H); 7.10–7.30 (*m*, 8 arom. H); 7.33–7.49 (*m*, 8 arom. H); 7.77–7.82 (*m*, 2 arom. H); 10.95 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 26.73, 27.35 (Me); 62.81, 68.94 (C); 80.61, 83.39 (CH); 108.54, 125.12 (*q*, ^1J(C,F) = 334, CF_3) (C); 127.20, 127.29, 127.67, 128.10, 128.17, 128.45, 128.52, 128.73, 129.80, 130.11, 130.22 (CH); 140.31, 141.11, 141.49, 150.33 (C). ^{19}F-NMR (282 MHz, $CHCl_3$): −77.81. MALDI-TOF-MS: 603 ($[M + Na]^+$). Anal. calc. for $C_{32}H_{31}F_3N_2O_3S$ (580.67): C 66.19, H 5.38, N 4.82, S 5.52; found: C 66.43, H 5.52, N 4.90, S 5.52.

3. *Preparation of the P-Containing Compounds* **2a**, **8**, **9**, *and* **10**. *(3a*R,*8a*R*)-Tetrahydro-6-hydroxy-2,2-dimethyl-4,4,8,8-tetraphenyl-1,3-dioxolo[4,5-*e*][1,3,2]dioxaphosphepin 6-Oxide* (**2a**). To a soln. of *(3a*R,*8a*R*)-6-Chlorotetrahydro-2,2-dimethyl-4,4,8,8-tetraphenyl-1,3-dioxolo[4,5-*e*][1,3,2]dioxaphosphepin 6-oxide* (**8b**; 547 mg, 1.00 mmol) [16b] in THF (10 ml) at r.t. was added H_2O (10 ml), and the mixture was heated for 24 h under reflux. The solvents were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (10 ml). Hexane (20 ml) was added at r.t., and the soln. was cooled to −50°, whereby precipitation occurred. The solid was collected by filtration, washed with cold (−50°) CH_2Cl_2/hexane 1:2, and co-evaporated with CH_2Cl_2 (5×). Drying of the residue in h.v. afforded **2a** (372 mg, 70%) as an inclusion compound with THF and hexane (**2a** · 0.05 C_4H_8O · 0.21 C_6H_{14}). Colorless solid. M.p. 155–158°. $[\alpha]_D^{r.t.} = -216.0$ ($c = 1.01$, $CHCl_3$). IR ($CHCl_3$): 2933*w*, 1496*m*, 1448*m*, 1373*w*, 1215*m*, 1166*m*, 997*s*, 940*s*, 900*w*, 741*s*, 725*m*, 694*s*, 640*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.67 (*s*, Me); 4.64 (br. *s*, POH); 5.23 (*s*, CH); 7.21–7.42 (*m*, 16 arom. H); 7.54–7.60 (*m*, 4 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 26.6 (Me); 79.4 (CH); 88.0 (*d*, ^2J(C,P) = 6.4); 113.7 (C); 126.9, 127.2, 127.6, 128.1, 128.2, 128.7, 139.5 (*d*, ^3J(C,P) = 9.0, C); 143.3 (*d*, ^3J(C,P) = 2.2, C). ^{31}P-NMR (162 MHz, $CDCl_3$): −8.08. MALDI-TOF-MS: 551.1606 ($[M - Na]^+$). Anal. calc. for $C_{31}H_{29}O_6P$ · 0.05 C_4H_8O · 0.21 C_6H_{14} (550.24): C 70.86, H 5.92; found: C 70.64, H 6.03. The anal. data are in agreement with those reported in [29].

*(3a*R,*8a*R*)-6-Chlorotetrahydro-4,4,8,8-tetraphenyl-1,3-dioxolo[4,5-*e*][1,3,2]dioxaphosphepin 6-Oxide* (**8a**). To a soln. of TADDOL **A** ($R^1 = R^2 = H$, $R^3 = Ph$) [31b] (1.10 g, 2.50 mmol) in THF (13 ml) was added BuLi (3.44 ml, 11.0 mmol) at −78°. The mixture was allowed to warm to r.t. and stirred for 1 h, before it was cooled again to −78° and combined with $POCl_3$ (0.30 ml, 3.25 mmol). The mixture was stirred for 3 h at −78°, the reaction was quenched with sat. aq. $NaHCO_3$ soln., and the mixture was diluted with Et_2O. The org. layer was washed with sat. aq. $NaHCO_3$ soln., dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (hexane/AcOEt 1:10) to afford (next to an unidentified side-product) **8a** (507 mg, 39%). Colorless solid. M.p. 135–138°. R_f (hexane/AcOEt 4:1) 0.30. $[\alpha]_D^{r.t.} = -174.8$ ($c = 1.01$, $CHCl_3$). IR ($CHCl_3$): 2871*w*, 1495*m*, 1448*m*, 1297*s*, 1164*w*, 1091*w*, 1055*w*, 995*s*, 907*s*, 863*w*, 726*s*, 695*s*, 657*w*, 639*w*, 625*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.21 (*s*, C*H*H); 4.55 (*s*, CH*H*); 5.15 (*d*, $J = 7.3$, CH); 5.34 (*d*, $J = 7.3$, CH); 7.31–7.42 (*m*, 12 arom. H); 7.45–7.48 (*m*, 4 arom. H); 7.53–7.66 (*m*, 4 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 78.6 (*d*, ^3J(C,P) = 2.2); 80.0, 90.6 (*d*, ^2J(C,P) = 10.5); 91.1 (*d*, ^2J(C,P) = 9.9); 96.6 (C); 126.7, 127.1, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 128.4, 128.5, 128.5, 128.8, 137.5 (*d*, ^3J(C,P) = 7.6, C); 137.8 (*d*, ^3J(C,P) = 8.9, C); 141.4 (*d*, ^3J(C,P) = 2.6, C); 142.0 (*d*, ^3J(C,P) = 4.4, C). ^{31}P-NMR (162 MHz, $CDCl_3$): −10.4. HR-MALDI-MS: 541.0943 ($[M + Na]^+$).

*1,1,1-Trifluoro-*N*-[(3a*R,*8a*R*)-tetrahydro-6-oxido-4,4,8,8-tetraphenyl-1,3-dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-yl]methanesulfonamide* N*-Ethyl-*N*-(1-methylethyl)propan-2-amine Salt* (**9a**) *and the Salt-*

Table 3. *Crystallographic Data for* **1**, *(*S_S*)-*, **7**, **9a**, *and* **10**

	1	(*S*$_S$)-**6**	**7**	**9a**	**10**
Formula	$C_{39}H_{41}F_3O_7$	$C_{32}H_{31}F_3N_2O_3S$	$C_{43}H_{56}F_3N_3O_4S$	$C_{45}H_{52}F_3N_2O_7PS$	$C_{31.80}H_{33.20}NO_6P$
Formula weight [g/mol]	678.72	580.65	767.97	852.92	556.37
T [K]	200(2)	203(2)	293(2)	100(2)	100(2)
Wavelength [Å]	1.54184	1.54184	0.71073	0.71073	1.54178
Source	CuK_α	CuK_α	MoK_α	MoK_α	CuK_α
Crystal dimensions [mm]	$0.4 \times 0.3 \times 0.3$	$0.2 \times 0.2 \times 0.1$	$0.35 \times 0.15 \times 0.15$	$0.12 \times 0.10 \times 0.01$	$0.09 \times 0.09 \times 0.01$
Crystal system	triclinic	monoclinic	orthorhombic	triclinic	monoclinic
Space group	$P1$	$P2_1$	$P2_12_12_1$	$P1$	$P2_1$
θ Range [°]	$4.4 < \theta < 68.9$	$4.2 < \theta < 67.9$	$1.5 < \theta < 25.0$	$2.67 < \theta < 26.52$	$2.78 < \theta < 66.95$
a [Å]	9.339(1)	9.371(1)	11.170(3)	10.2943(13)	9.7089(4)
b [Å]	9.836(1)	14.735(2)	14.163(5)	10.6110(14)	18.4783(9)
c [Å]	10.636(2)	10.513(2)	27.019(14)	11.7055(16)	15.8813(8)
α [°]	70.11(1)	90	90	88.716(4)	90
β [°]	79.46(1)	94.80(1)	90	66.831(4)	91.582(4)
γ [°]	77.07(1)	90	90	69.433(4)	90
V [Å^3]	889.4(2)	1446.6(4)	4274(3)	1090.6(2)	2848.1(2)
Z	1	2	4	1	4
$\rho_{calc.}$ [g cm^{-3}]	1.267	1.333	1.193	1.299	1.298
μ [mm^{-1}]	0.805	1.468	0.131	0.175	1.230
Total reflections measured	3515	2757	4244	12505	13332
Independent reflections	3515	2455	4217	6311	6553
Reflections observed	3502	2286	2709	4036	5680
No. of variables	447	377	454	586	758
Criterion	$I > 3\sigma(I)$	$I > 3\sigma(I)$	$I > 3\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
Final R [%]	3.66	6.26	5.58	5.39	5.98
wR_2 [%]	12.98	20.91	15.51	11.41	15.87
Goodness-of-fit	1.367	1.891	1.398	1.010	1.153
$\Delta\rho$ (max, min) [e Å^{-3}]	0.244, −0.197	0.887, −0.631	0.254, −0.421	0.366, −0.484	0.718, −0.355
CCDC No.	157928	157929	867042	871617	870465

Free Imide **9b**. A mixture of **8a** (104 mg, 0.2 mmol), trifluoromethanesulfonamide (59.6 mg, 0.4 mmol), and EtN^{i}Pr$_2$ (155 mg, 1.2 mmol) in $CDCl_3$ (0.3 ml) was stirred at 55° for 14 h in a sealed vial. The mixture was allowed to cool to r.t. and was then directly purified by FC (hexane/AcOEt 1:1) to afford **9a** (43.4 mg, 34%). Colorless solid. M.p. 234–236°. R_f (hexane/AcOEt 1:2) 0.35. $[\alpha]_D^{r.t.} = -58.0$ ($c = 1.01$, $CHCl_3$). IR ($CHCl_3$): 2996*w*, 1495*m*, 1449*m*, 1396*w*, 1305*s*, 1258*s*, 1203*s*, 1166*s*, 1088*s*, 1055*m*, 1039*m*, 1009*s*, 956*s*, 9001*m*, 888*m*, 789*m*, 736*s*, 698*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.83 (*t*, $J = 7.4$, Me); 0.86–0.95 (*m*, 12 H, Me); 2.40–2.56 (*m*, 2 H, CH_2); 2.83–2.98 (*m*, 2 H, CH); 3.69 (*s*, 1 H, CH_2); 4.63 (*d*, $J = 7.6$, CH); 5.06 (*s*, 1 H, CH_2); 5.82 (*d*, $J = 7.6$, CH); 7.18–7.67 (*m*, 12 arom. H); 7.44–7.59 (*m*, 4 arom. H); 7.68–7.80 (*m*, 4 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 11.0 (Me); 17.6 (4 Me); 40.8 (CH_2); 52.5 (2 CH), 77.9 (*d*, ^3J(C,P) = 1.84, CH); 83.6 (CH); 84.1 (*d*, ^2J(C,P) = 7.3); 84.7 (*d*, ^2J(C,P) = 6.1); 95.6 (CH_2); 120.8 (q, ^1J(C,F) = 322.7); 127.2, 127.3, 127.3, 127.5, 127.7, 127.7, 127.8, 127.9, 128.3, 139.3 (*d*, ^3J(C,P) = 10.6, C); 141.2, 144.3 (*d*, ^3J(C,P) = 12.5, C); 145.6, 171.2. ^{19}F-NMR (376 MHz, $CDCl_3$): −78.9. ^{31}P-NMR (162 MHz, $CDCl_3$): −10.0. HR-MALDI-MS: 630.0967 ($[M-H]^-$).

Data of **9b**. To obtain a sample of the salt-free compound, **9a** was subjected to prep. TLC (CH_2Cl_2/MeOH 10:1). Colorless wax. R_f (CH_2Cl_2/MeOH 15:1) 0.25. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.66 (*s*, 1 H, CH_2); 4.61 (*d*, *J* = 7.6, CH); 5.08 (*s*, 1 H, CH_2), 5.86 (*d*, *J* = 7.6, CH); 7.19–7.62 (*m*, 12 arom. H); 7.45–7.52 (*m*, 2 arom. H); 7.53–7.62 (*m*, 2 arom. H); 7.68–7.74 (*m*, 2 arom. H); 7.76–7.82 (*m*, 2 arom. H). ^{19}F-NMR (376 MHz, $CDCl_3$): −78.9. ^{31}P-NMR (162 MHz, $CDCl_3$): −10.0.

*(3a*R*,8a*R*)-Tetrahydro-2,2-dimethyl-4,4,8,8-tetraphenyl-1,3-dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine 6-Oxide* (**10**). To a soln. of **8b** (54.7 mg, 100 μmol) [16b] in THF (2.0 ml) was added at r.t. aq. NH_3 soln. (2.0 ml, 24 %), and the mixture was stirred at r.t. for 60 h. The solvents were removed under reduced pressure, and the residue was co-evaporated with CH_2Cl_2 (5×). Drying of the residue in h.v. afforded **10** (50.5 mg, 96 %). Colorless solid. M.p. 312° (dec.). $[\alpha]_D^{r.t.} = -200.8$ (*c* = 1.00, $CHCl_3$). IR ($CHCl_3$): 3063*w*, 1559*w*, 1495*m*, 1448*m*, 1383*w*, 1249*m*, 1218*m*, 1165*m*, 1089*m*, 1057*s*, 998*s*, 935*w*, 903*s*, 725*s*, 696*s*, 642*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.65 (*s*, Me); 0.71 (*s*, Me); 2.82 (br. *s*, NH_2); 5.25 (*J* = 8.1, CH); 5.41 (*J* = 8.1, CH); 7.23–7.46 (*m*, 14 arom. H); 7.49–7.53 (*m*, 2 arom. H); 7.59–7.65 (*m*, 4 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 26.4 (Me); 26.7 (Me); 79.0 (*d*, ^3J(C,P) = 1.1); 79.5 (*d*, ^3J(C,P) = 1.4); 86.5 (*d*, ^2J(C,P) = 5.9); 88.4 (*d*, ^2J(C,P) = 8.6); 113.8 (C); 127.0, 127.2, 127.3, 127.6, 127.6, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 129.2, 139.8 (*d*, ^3J(C,P) = 6.3, C); 140.0 (*d*, ^3J(C,P) = 10.6, C); 143.4 (C); 144.2 (*d*, ^3J(C,P) = 3.8, C). ^{31}P-NMR (162 MHz, $CDCl_3$): −0.26. HR-ESI-MS: 528.1955 ($[M + H]^+$).

4. *p*K^*_{MCS} *Measurements*. The measurements were carried out in degassed solvent (2-methoxyethanol ('methylcellosolve', MCS)/H_2O 80:20) at 25° under Ar. Before titration, the electrode was calibrated by a three-point calibration (pH 4, 7, and 9). As reference compounds $PhCO_2H$ (pK^*_{MCS} = 6.63) or 2-I–$C_6H_4CO_2H$ (pK^*_{MCS} = 5.73) were used; a deviation of up to 0.08 p*K* units was considered acceptable. The titration was carried out with Me_4NOH with a continuous addition mode. pK^*_{MCS} Values in the range between 3 and 12 can be determined by the method; for a detailed description of the method, see [54], and for a comprehensive collection of pK^*_{MCS} values determined this way see [55].

5. *X-Ray Data*. See *Table 3*.

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Received March 23, 2012