

Investigations Concerning the Syntheses of TADDOL-Derived Secondary Amines and Their Use To Access Novel Chiral Organocatalysts

Katharina Gratzner, Mario Waser*

Institute of Organic Chemistry, Johannes Kepler University Linz, Altenbergerstraße 69, 4040 Linz, Austria
Fax +43(732)24688747; E-mail: Mario.waser@jku.at

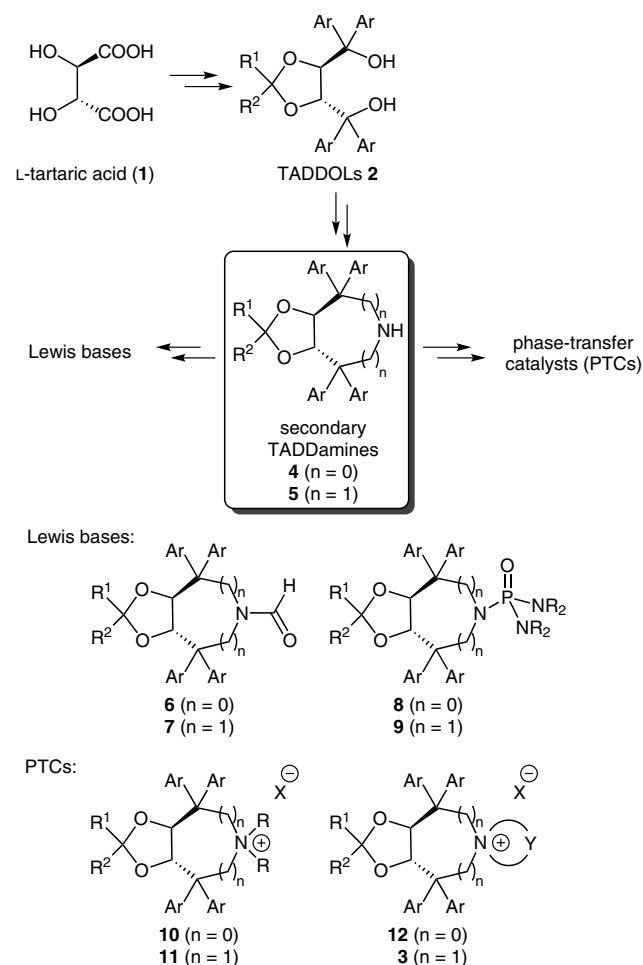
Received: 06.09.2012; Accepted after revision: 24.09.2012

Abstract: A structurally carefully diversified library of novel TADDOL-derived chiral secondary amines was synthesized and investigated for their applicability to obtain new organocatalysts like chiral Lewis bases and chiral phase-transfer catalysts. The scope and limitations of the developed syntheses routes to access these catalysts as well their catalytic performance in different benchmark reactions were systematically investigated. The most powerful of the catalysts prepared was found to be highly useful for the phase-transfer catalyzed α -alkylation of glycine Schiff base (high yields and up to 93% ee).

Key words: chiral pool, tartaric acid, asymmetric phase-transfer catalysis, Lewis base catalysis, asymmetric alkylation

The use of chiral small molecule organocatalysts to facilitate demanding stereoselective applications has attracted considerable interest over the last decade.¹ One of the main prerequisites to develop this methodology further towards new, more generally applicable transformations with a broader reaction scope is the availability of powerful, easily obtainable and easily modified (fine-tuned) catalysts. We have recently started a project targeting the use of tartaric acid (**1**) or easily derived TADDOLs **2** to synthesize novel organocatalysts. Although TADDOLs are omnipresent as ligands in (transition) metal catalysis² and tartaric acid is a versatile starting material for preparing important chiral compounds,³ the use of these easily available natural chiral pool-based starting materials to obtain asymmetric organocatalysts has so far been limited to a few (but often impressive) examples only.^{4–6} Whilst our initial investigations on the syntheses of TADDOL-derived sulfonimides failed,⁷ we recently created a small library of novel TADDOL-derived N-spiro quaternary ammonium salts **3**, which were found to be powerful phase-transfer catalysts (PTCs) for the stereoselective α -alkylation of glycine Schiff bases.⁸ Encouraged by these promising initial results we have now undertaken systematic investigations concerning the syntheses and applicability of TADDOL-derived secondary amines **4**^{2,9} and **5** to synthesize a variety of structurally diverse novel chiral Lewis base catalysts¹⁰ **6–9** and chiral phase-transfer catalysts¹¹ **3**, **10–12** (Scheme 1). The main focus in this work was therefore on the development of reliable and flexible synthetic strategies to achieve the key intermediates and a diverse library of catalysts and to elucidate the

scope and limitations of these synthetic routes. In addition, the catalytic potential and the structure-activity relationship of the newly acquired catalysts in important benchmark reactions were investigated.

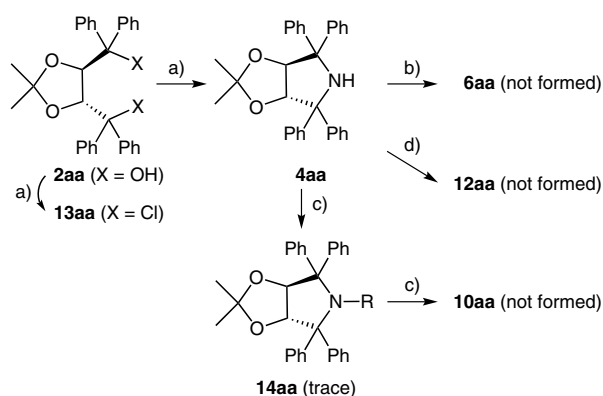


Scheme 1 Targeted key intermediate secondary amines **4** and **5** and envisaged asymmetric Lewis base and phase-transfer catalysts

Pyrrolidine 4-Based Catalysts

The syntheses of TADDOL derivatives have been carefully investigated and described in the past, especially by Seebach's group.^{2,9} Whereas different acetal/ketal groups and aryl substituents have to be introduced early in the synthesis of TADDOLs from tartaric acid (**1**), functionalizations of the hydroxyl groups are most commonly

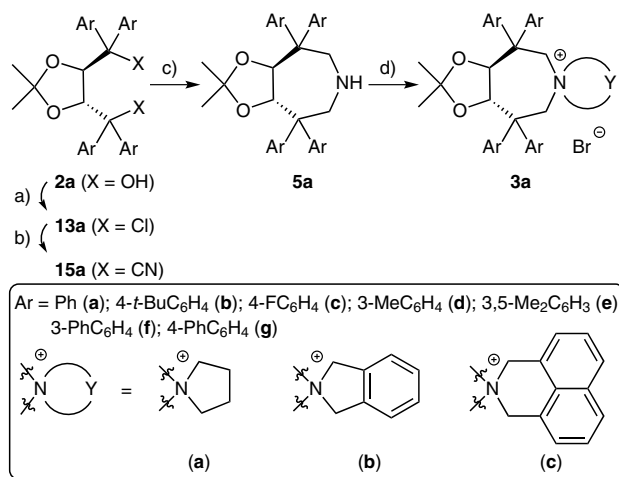
achieved via conversion of TADDOLs **2** into dichloro compounds **13**, which can then be reacted with different nucleophiles.^{7,9} With respect to the syntheses of the pyrrolidine-containing catalysts the ‘standard’ TADDOL **2aa** ($R^1 = R^2 = \text{Me}$, $\text{Ar} = \text{Ph}$)^{2,9} was first converted into the known azabicyclo[3.3.0]octane **4aa** according to the published procedure.^{9b} With this easily available compound in hand we first investigated the formation of the chiral formamide Lewis base **6aa**. However, we were not able to obtain this compound as the secondary amine **4aa** was found to be rather unreactive, even upon treatment with highly reactive acetic formic anhydride. During the course of our investigations we also became aware that the Seebach group experienced similar problems in modifying this compound and has also not been able to obtain **6aa**.¹² In addition, they also reported a surprisingly high instability of the ketal group of this compound under slightly acidic conditions, which fully corresponds to our experience with this highly strained *trans*-azabicyclo[3.3.0]octane. This enhanced instability of the normally rather stable acetonide moiety is also in line with recent results in our group obtained with an analogous *trans*-thiabicyclo[3.3.0]octane based TADDOL-derivative.⁷ Also treatment with several alkyl halides like 1,4-dibromobutane or bromobutane or methyl iodide under a variety of conditions never gave any quaternary ammonium salts **10aa** or **12aa** at all. The only transformation we observed was a very slow formation of traces of intermediate tertiary amines **14aa**, but absolutely no quaternization could be achieved (Scheme 2). Moreover, the bicyclo[3.3.0] skeleton was also found to be unstable under harsher basic reaction conditions resulting in partial acetonide cleavage again. Accordingly, the use of the long-known secondary amine **4aa** to prepare novel chiral Lewis bases¹³ or PTCs is not only limited because of the reduced reactivity of the nitrogen, but also because of an increased instability of this compound. These observations also rationalize why this (on a first glance promising) compound has never really been used in any demanding applications.



Scheme 2 Attempted syntheses of pyrrolidine **4aa** based organocatalysts: *Reagents and conditions*: a) ref. 9b; b) acetic formic anhydride; c) different RX, different conditions; d) 1,4-dibromobutane, different conditions.

Azepane 5-Based Phase-Transfer Catalysts

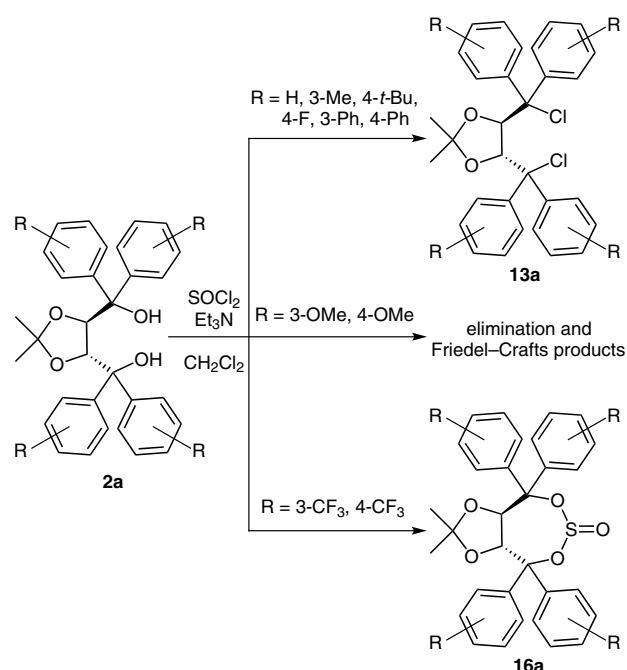
We have recently succeeded in developing a four-step route to build a small library of azepane-based C_2 -symmetric acetonide-containing N-spiro catalysts **3a** (based on the classical acetonide moiety with $R^1 = R^2 = \text{Me}$) starting from known TADDOLs **2a** (Scheme 3).⁸ Based on this initial success we have now undertaken systematic investigations concerning the scope and limitations of this route to synthesize new PTCs and also to employ the key intermediate **5** to realize novel chiral Lewis bases.



Scheme 3 Successful syntheses of a first library of C_2 -symmetric acetonide-containing azepane-based PTCs **3a**.⁸ *Reagents and conditions*: a) SOCl_2 , Et_3N , CH_2Cl_2 , 25 °C; b) TMSCN , SnCl_4 , 25 °C, 47–63% (over two steps); c) LiAlH_4 , mesitylene, reflux, 30–43%; d) Br-Y-Br , K_2CO_3 , MeCN , reflux, 49–69%.

Initial route development was carried out using the parent TADDOL **2aa** ($R^1 = R^2 = \text{Me}$, $\text{Ar} = \text{Ph}$). Surprisingly, elongation of the carbon chain of TADDOLs has so far not been systematically investigated.¹⁴ Reacting dichloro compound **13aa** with TMSCN (>2.5 equiv) in the presence of catalytic amounts of SnCl_4 (25%)¹⁵ was rewarded with the formation of dinitrile **15aa** in excellent yield on a multigram scale. Conversion into the secondary amine **5aa** was found to be rather tricky as dinitrile **15aa** turned out to be unreactive under a variety of different conditions. Attempted saponification failed even under very strong basic conditions (e.g., refluxing with 20% NaOH resulted in the recovery of starting material accompanied with a partial decomposition). Attempted conversion into the corresponding dialdehyde upon treatment with DIBAL-H failed as **15aa** was found to be unreactive under standard DIBAL-H reduction conditions or decomposed under more forcing conditions. Also other hydride donors like NaBH_4 (also in combination with different additives), Red-Al , LiBH_4 , or LiAlH_4 at room temperature in different etheral solvents did not affect the cyano groups either. Interestingly, we discovered that refluxing heterogeneous mixtures of **15aa** and excess LiAlH_4 (20 equiv) in high boiling aromatic solvents (mesitylene was found best) for 30–45 minutes gave access to amine **5aa** in around 30–40% isolated yield. HRMS studies of this re-

action revealed the presence of amidine intermediates besides other unidentified by-products. These by-products were found to be nonpolar, highly fluorescent condensed aromatic compounds, containing no heterofunctionalities like the acetonide or cyano groups anymore. Attempts to increase the yields by using other solvents or different additives did not improve the outcome. Attempted heterogeneous hydrogenation was also not successful so far.¹⁶ However, having established a reliable route for the syntheses of the chiral secondary amine **5aa**, the introduction of different aryl groups to modify the steric and electronic properties of this skeleton was focused next. As depicted in Scheme 3, a variety of different electron-neutral aryl substituents were introduced successfully during our initial investigations. Besides aryl groups with electronic properties similar to a phenyl group in amines **5a** (and the corresponding catalysts), other aromatic residues bearing either electron-rich or electron-deficient groups also aroused our interest. Interestingly, a very strong difference in the reactivity of these compounds was observed. The presence of strong electron-donating groups like methoxy groups did not allow us to obtain the corresponding dichlorides **13a** under a variety of different chlorination conditions, but instead different elimination and also Friedel–Crafts products were formed.¹⁷ On the other hand, strong electron-withdrawing substituents like trifluoromethyl groups did not give the dichlorides either, but instead the stable cyclic sulfites **16a** were formed¹⁸ (Scheme 4). Unfortunately, neither changing the reaction conditions, nor using other chlorination agents like PCl_5 or oxalyl chloride gave the targeted dichlorides **13a**. Attempts to employ this sulfite further failed due to the high stability of this compound.



Scheme 4 Representative overview on the influence of the nature of different aryl groups on the chlorination reaction

Direct dicyanation of TADDOLs **2a** with TMSCN in the presence of a Lewis acid worked with modest yields in the case of electron-neutral aromatic residues (e.g., **2aa** was directly converted into **15aa** in around 30% unoptimized yield) but again no conversion was observed in the case of electron poor aryl group containing TADDOLs. Accordingly, transformations of the benzylic position of the TADDOL-skeleton are highly dependent on the electronic properties of the aromatic substituents. Interestingly, whereas the corresponding naphth-2-yl-substituted dichloride was accessible, dicyanide formation was not possible in this case and just decomposition products were obtained. In contrast, the sterically demanding biphenyl-containing dicyanides **15af** and **15ag** could be obtained in high yields.¹⁹ All the obtained acetonide-based dicyanides **15a** could be converted into the secondary amines **5a** in moderate yields (see Table 1).

The final quaternization step was first investigated targeting N-spiro ammonium salts **3aa**. In contrast to amine **4aa**, the azabicyclo[5.3.0]decane **5aa** (Ar = Ph) was found to be nucleophilic enough in the reaction with 1,4-dibromobutane, giving the targeted ammonium bromide **3aaa** (see Scheme 3; $\text{R}^1 = \text{R}^2 = \text{Me}$, Ar = Ph, Y = group a) in 60% isolated yield upon refluxing **5aa** with 4 equivalents dibromobutane (MeCN, K_2CO_3). Noteworthy, whereas only traces of the intermediate tertiary amine were observed, significant amounts of unreacted starting material **5aa** could be reisolated. Similar results were obtained in the successful syntheses of catalysts **3aab** (Ar = Ph, Y = group b) and **3aac** (Ar = Ph, Y = group c). On the other hand, quaternization with 1,2-dibromoethane resulted in the formation of a very unstable aziridinium-based ammonium salt that could not be employed further.

Attempting the quaternization with BuBr or MeI to prepare nonspiro ammonium salts **11**, only the corresponding monoalkylated tertiary amines, but no quaternary ammonium compounds **11** could be obtained under a variety of different conditions.²⁰ Accordingly, it seems that once the tertiary amine is formed, the final quaternization step only takes place intramolecularly. This might be rationalized by the fact that the lone pair of the tertiary nitrogen seems to be shielded towards an external electrophile by the bulky aryl substituents, making an intermolecular alkylation much more difficult than an intramolecular one. This explanation is also supported by additional molecular modeling studies.

Surprisingly, when attempts were made to carry out the quaternization with 1,5-dibromopentane or bis(2-bromoethyl) ether, only formation of the corresponding tertiary amines, and not even traces of the corresponding piperidine- or morpholine-based ammonium bromides could be observed. To elucidate this striking difference in the quaternization step additional calculations were carried out using different force fields and DFT methods to obtain the optimized structures for the pyrrolidinium-based catalyst **3aaa** and the targeted piperidinium-based catalyst **3aad** (Figure 1). A careful analysis revealed no striking differences between the parent skeletons of these two ammoni-

um salts. Interestingly, in both cases two of the bulky phenyl groups are in an unfavored *syn*-pentane interaction (1,3-diaxial strain) with the newly introduced CH₂ group adjacent to the spiro ammonium group. Having a closer look on the calculated tertiary amine intermediate it becomes obvious that the electrophile has to approach the nitrogen lone pair via a rather close channel between the phenyl groups. The calculated distances between the nearest carbon atoms of the phenyl rings is around 4.5 Å and for the nearest protons around 3.7 Å. As the S_N2-type 6-ring formation is supposed to proceed via a sterically more demanding chair-type transition state with additional destabilizing 1,3-diaxial-type interactions between the large N-substituents and the axial β-hydrogens, and whereas the 5-ring formation should proceed via a more planar transition state with a significantly lower transition state strain energy (resulting in a much faster cyclization reaction),²¹ it seems reasonable that our rather tight and crowded structure disfavors 6-ring formation significantly. Steric hindrance in the transition state was also accounted to be the main reason for the unsuccessful cyclization of substituted 1,4-dibromobutanes like (*R,R*)- or (*S,S*)-1,4-dibromo-2,3-dimethoxybutane where again absolutely no formation of quaternary ammonium salts could be observed.

Thus, and in contrast to analogous high-yielding transformations in the syntheses of the powerful Maruoka catalysts,²² the quaternization of amines **5** is a rather difficult

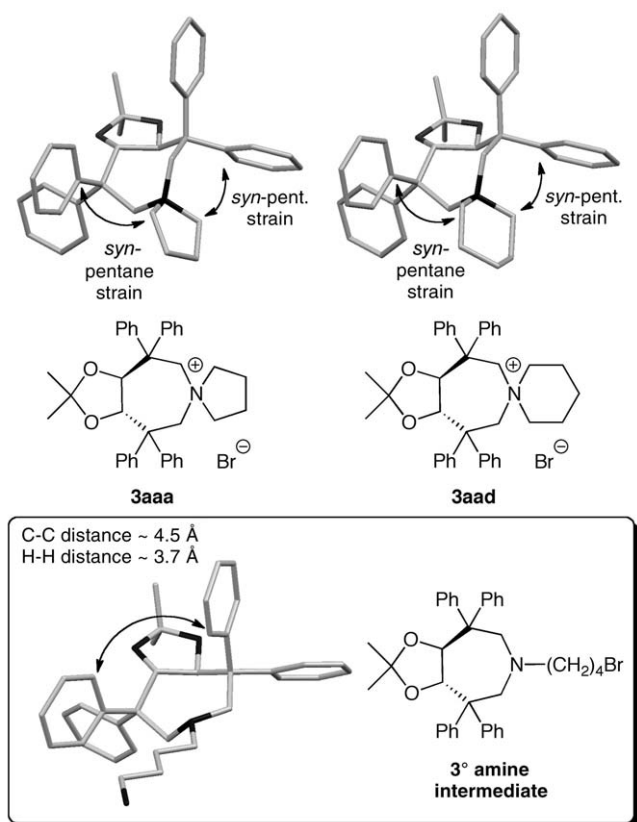
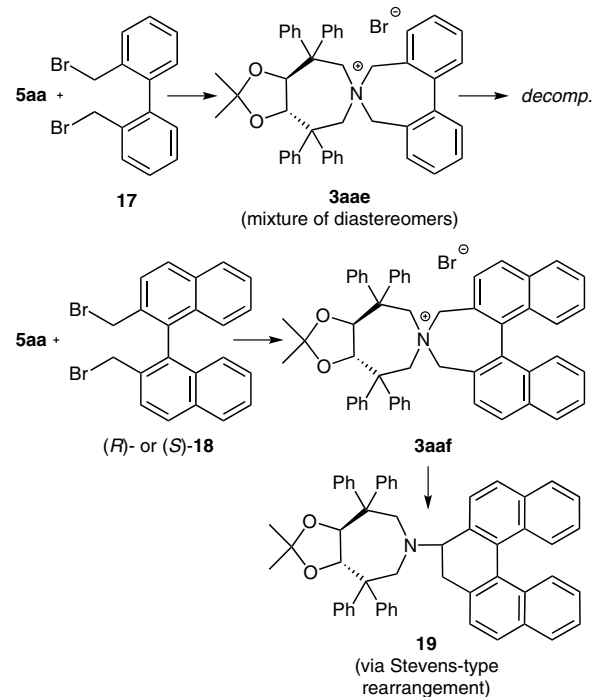


Figure 1 Comparison of the optimized structures of pyrrolidinium and piperidinium-based chiral ammonium salts and the tertiary intermediate in their syntheses

transformation and we found that just small structural changes of the electrophile can be crucial whether ammonium salt formation is possible or not.

As already depicted above, the use of more rigid dihalo-electrophiles (e.g., xylene- or naphthyl-based ones) made quaternization possible (Scheme 3). We therefore attempted to introduce an axially chiral group by either reacting amines **5aa** with dibromobiphenyl **17** or with both enantiomers of binaphthyl **18** (Scheme 5). In both cases the reaction proceeded quickly under the standard reaction conditions. The isolated ammonium salt **3aae** was found to be a mixture of diastereomers containing additional impurities that could hardly be separated. In addition it was found that the amount of these impurities increased upon standing in solution and when the catalyst was exposed to basic conditions. Formation of both diastereomers of the binaphthyl-based salt **3aaf** proceeded easily with full consumption of starting materials within a few hours. Crude NMR, TLC, and HRMS analyses confirmed the formation of the targeted product accompanied by significant amounts of by-products. Column chromatography allowed us to isolate the most polar spot (with *R_f* values similar to those of other PTCs) solely. However, although ESI-HRMS proved the formation of the product, it was not possible to record a clean NMR spectrum of this compound as within minutes the formation of a much less polar product was observed (detected by TLC). Isolation of this compound (accompanied with other unidentified by-products) and analysis indicated the formation of the tertiary amine **19**,²³ most presumably via a Stevens type rearrangement, which is a well-known reaction for binaphthyl and biphenyl-based ammonium salts.²⁴ Accordingly these highly crowded compounds turned out to be



Scheme 5 Attempted syntheses of the centro-chiral-axially-chiral hybrid catalysts **3aae** and **3aaf**

far too unstable to be used as chiral phase-transfer catalysts in asymmetric reactions (this behavior was even more pronounced in the case of amines bearing bulkier aryl groups).

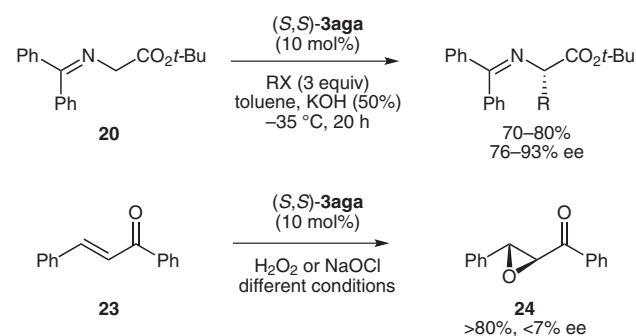
It is worth noting that the quaternary ammonium salts **3** synthesized so far give rather broad ^1H NMR peaks (CDCl_3), especially for the CH_2 groups adjacent to the quaternary ammonium group, thus indicating a certain conformational flexibility of the N-spiro skeleton. Accordingly, it seems that these ammonium salts are structurally less rigid than the axially chiral Maruoka catalysts.

Based on these investigations we were then able to synthesize a carefully investigated and extended library of acetonide containing catalysts **3a** first and to identify the best-suited aryl substituents, quaternary ammonium group, and counter anion by testing these catalysts in the asymmetric α -alkylation of glycine Schiff base **20** using benzyl bromide (**21**) as the electrophile.²⁵ Table 1 gives a detailed overview on the acquired catalysts, the limitations of the developed synthesis route, and the results of the successfully obtained PTCs in the test reaction. After identifying the *p*-biphenyl-containing pyrrolidinium ammonium bromide **3aga** as the most active amongst the tested acetonide-based catalysts (Table 1, entries 1–27) the influence of the ketal group on the catalytic potential of these PTCs was investigated next. Inspired by interesting results reported by the Shibasaki group about the influence of different ketal groups on the catalytic performance of their tartaric acid-derived two-center catalysts,⁶ we targeted a small library of C_1 - and C_2 -symmetric catalysts based on the *p*-biphenyl azepane-*N*-pyrrolidinium skeleton with different ketal moieties (entries 28–35). With respect to the syntheses of these catalysts it was found necessary to start from the corresponding tartrates and bring them through the sequence, as we have so far not been able to carry out a selective transacetalization on one of the later stages. Interestingly, whereas different dialkyl ketals could easily be transferred through the developed sequence, the acetophenone-based catalyst **3fga** was not that easily obtained, as the dicyanation and reduction step were found to give an increased amount of difficult to separate impurities.

Testing the obtained ammonium salts in the asymmetric α -alkylation of **20**, a strong influence of the introduced ketal groups was observed. Amongst the C_2 -symmetric catalysts the parent compound **3aga** was found to be the most active one (Table 1, entry 8 vs. 28, 29). In the case of the C_1 -symmetric ones, the *tert*-butyl containing catalyst **3ega** (entry 31) was found to give by far the lowest selectivity. Interestingly, in contrast to the other catalysts this ammonium salt shows sharp NMR peaks, thus indicating that the *tert*-butyl holding group forces the rest of the skeleton in a more rigid (but less selective) conformation. Use of this catalyst in alternative solvents did not improve the result. Whereas the corresponding isobutyl and benzyl analogues (entries 30 and 33) performed slightly worse than **3aga**, the acetophenone-based catalyst **3fga** gave (*S*)-**22** with the same enantioselectivity (entry 32 vs. 8).²⁶ How-

ever, as this compound was much more difficult to obtain than the others due to low yields and vast amounts of by-products especially in the final steps we did not investigate it further. As most of the introduced substituents reduced the catalytic potential of our PTCs we also attempted to synthesize acetal-based catalysts. However, all attempts to obtain these ammonium salts (e.g., formaldehyde or benzaldehyde as the acetal group, entries 34 and 35) failed because the strong LiAlH_4 -reduction conditions always cleaved off these acetal groups. In addition, we also attempted to replace the dioxolane ring, for example, by a dioxane ring or by two methoxy groups.²⁷ However, in both cases we were not able to prepare the corresponding dichlorides. Instead we observed formation of the corresponding tetrahydrofurans originating from an intramolecular nucleophilic substitution reaction on the monochloro intermediate.

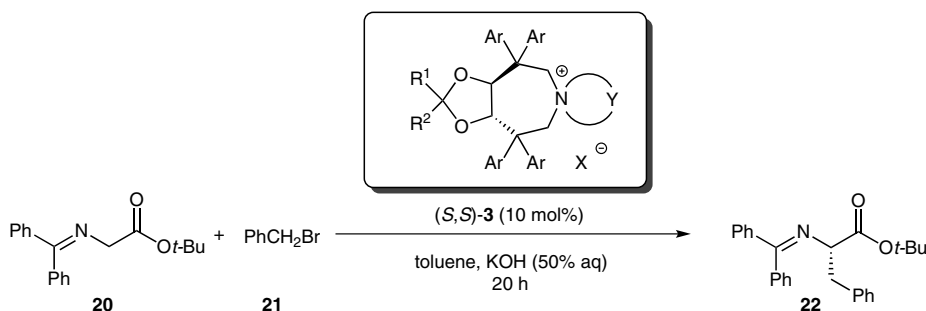
Based on all these studies we finally identified the *p*-biphenyl-containing pyrrolidinium ammonium bromide **3aga** as the most active catalyst for the asymmetric α -alkylation of glycine Schiff base **20** (Table 1, entry 8). As recently disclosed, the use of different electrophiles in this reaction was well tolerated with up to 93% ee and isolated yields of 70–80%,²⁸ (for an overview, see Scheme 6, upper reaction scheme) thus making this compound a versatile catalyst for asymmetric reactions using prochiral nucleophiles. In addition the use of this catalyst was also investigated for the asymmetric epoxidation of chalcone **23**, thus employing an achiral nucleophile and a prochiral electrophile (Scheme 6, lower reaction scheme).²⁹ Unfortunately, despite a thorough screening of different reaction conditions it was not possible to obtain the epoxide **24** in any reasonable enantiomeric excess although the catalyst promoted the reaction well giving the product in high yield.³⁰



Scheme 6 Scope and limitation of TADDOL-derived PTC **3aga** in asymmetric applications

Azepane 5-Based Chiral Lewis Bases

Chiral Lewis bases have proven to be useful catalysts for the activation of Lewis acids like, for example, organosilicon nucleophiles. We reasoned that the chiral secondary amines **5** present versatile starting materials to prepare chiral formamides **7** and chiral phosphoramides **9**. Where-

Table 1 Targeted and Obtained Catalysts and Their Performance in the Asymmetric α -Alkylation of Glycine Schiff Base **20**

Entry	Cat ^a	Catalyst structure Ar	R ¹ /R ²	Y	X ⁻	Catalyst synthesis ^b				Alkylation			
						13	15	5	3	21 (equiv)	Temp (°C)	Yield ^c (Conv.) ^d (%)	ee (%) ^e (Conf.) ^f
1	3aaa	Ph	Me/Me	a^g	Br ⁻	+	+	+	+	1.2	-20	55 (~70)	45 (S)
2	3aba	4- <i>t</i> -BuC ₆ H ₄				+	+	+	+			30 (~50)	61 (S)
3	3aca	4-FC ₆ H ₄				+	+	+	+			35 (~50)	34 (S)
4	3ada	3-MeC ₆ H ₄				+	+	+	+			77 (~90)	55 (S)
5	3aea	3,5-Me ₂ C ₆ H ₃				+	+	+	+			47 (~60)	5 (S)
6	3afa	3-PhC ₆ H ₄				+	+	+	+			45 (~60)	7 (S)
7	3aga	4-PhC ₆ H ₄				+	+	+	+			65 (~80)	79 (S)
8	3aga	4-PhC₆H₄	Me/Me	a^g	Br⁻	+	+	+	+	3	-35	81 (quant)	87 (S)
9	3aha	4-(4-MeOC ₆ H ₄)C ₆ H ₄				+	+	+	+			72 (~95)	76 (S)
10	3aia	4-(3-F ₃ CC ₆ H ₄)C ₆ H ₄				+	+	+	+			65 (~80)	80 (S)
11	3aja	4-(2,4,6-Me ₃ C ₆ H ₂)C ₆ H ₄				+	+	+	+			45 (~60)	47 (S)
12	3aka	4-(naphth-2-yl)C ₆ H ₄				-	-	-	-			-	-
13	3ala	4-F ₃ CC ₆ H ₄				-	-	-	-			-	-
14	3ama	3-F ₃ CC ₆ H ₄				-	-	-	-			-	-
15	3ana	3-MeOC ₆ H ₄				-	-	-	-			-	-
16	3aoa	4-MeOC ₆ H ₄				-	-	-	-			-	-
17	3apa	naphth-2-yl				+	-	-	-			-	-
18	3aga	4-PhC ₆ H ₄			BF ₄ ⁻	+	+	+	+	1.2	-20	67 (~80)	77 (S)
19	3aga	4-PhC ₆ H ₄			PF ₆ ⁻	+	+	+	+			61 (~80)	20 (S)
20	3agb	4-PhC ₆ H ₄		b^g	Br ⁻	+	+	+	+			57 (~80)	51 (S)
21	3agc	4-PhC ₆ H ₄		c^g		+	+	+	+			21 (~30)	25 (R)
22	3aad	Ph		d^h		+	+	+	-			-	-
23	3agd	4-PhC ₆ H ₄				+	+	+	-			-	-
24	3aae	Ph		eⁱ		+	+	+	-			-	-
25	3age	4-PhC ₆ H ₄				+	+	+	-			-	-
26	3aaf	Ph		fⁱ		+	+	+	-			-	-
27	3agf	4-PhC ₆ H ₄				+	+	+	-			-	-
28	3bga	4-PhC ₆ H ₄	<i>n</i> -Bu/ <i>n</i> -Bu	a^g		+	+	+	+	3	-35	73 (~95)	78 (S)
29	3cga	4-PhC ₆ H ₄	(CH ₂) ₅			+	+	+	+			69 (~90)	82 (S)
30	3dga	4-PhC ₆ H ₄	Me/ <i>i</i> -Bu			+	+	+	+			72 (~95)	84 (S)
31	3ega	4-PhC ₆ H ₄	Me/ <i>t</i> -Bu			+	+	+	+			75 (quant)	50 (S)
32	3fga	4-PhC ₆ H ₄	Me/Ph			+	+	+	+			70 (~90)	87 (S)
33	3gga	4-PhC ₆ H ₄	Me/Bn			+	+	+	+			79 (quant)	80 (S)
34	3hga	4-PhC ₆ H ₄	H/H			+	+	-	-			-	-
35	3iga	4-PhC ₆ H ₄	H/Ph			+	+	-	-			-	-

^a The first alphabet denotes the ketal group, the second the aryl group, and the third the quaternary ammonium group.

^b The sign + or - indicates whether formation of the respective product was possible or not.

^c Isolated yields.

^d Judged by NMR of the crude product.

^e Determined by HPLC using a chiral stationary phase.

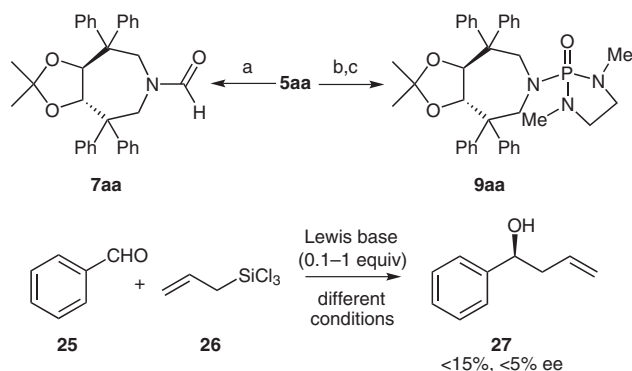
^f Absolute configuration was determined by comparison of the HPLC retention time and optical rotation with literature values.^{22h,31}

^g See Scheme 3.

^h See Figure 1, compound **3aad**.

ⁱ See Scheme 5, compounds **3aae** and **3aaf**.

as synthesis of **7aa** was easily accomplished by the reaction of **5aa** (Ar = Ph, R¹ = R² = Me) with acetic formic anhydride (88% yield), synthesis of **9aa** turned out to be rather difficult. Although reaction of **5aa** with PCl₃ or POCl₃ proceeded smoothly, further reaction with (di)amines was found to be problematic, especially due to the observed good leaving group ability of **5aa**, which often resulted in the hydrolysis or P–N bond cleavage of the intermediates. Direct reaction with POCl(NR₂)₂ was also not possible. However, after some optimization, it was found that a two-step reaction of **5aa** with POCl₃ first and immediate reaction with *N,N*-dimethylethylenediamine was possible to obtain the phosphoramidate **9aa** in 86% yield (Scheme 7). Interestingly, this compound tends to partially hydrolyze upon standing in solution (e.g., 3 days in aqueous MeOH). To test these compounds for their catalytic potential the allylation of benzaldehyde (**25**) with trichloroallylsilane (**26**) was chosen as a benchmark reaction. Unfortunately, the homoallylic alcohol **27** was never obtained in reasonable yield, even when stoichiometric amounts of Lewis base activator were used, only racemic product could be obtained under a variety of different conditions with both activators (Scheme 7).³²



Scheme 7 Syntheses of chiral TADDOL-derived Lewis bases and attempted application: *Reagents and conditions*: a) acetic formic anhydride, Hünig's base, CH₂Cl₂, 0–25 °C, 88%; b) POCl₃, KH, DMAP, 4 Å MS, toluene, 60 °C; c) *N,N*-dimethylethylenediamine, Et₃N, CH₂Cl₂, 0–25 °C, 86% (over two steps).

In conclusion, we have found that the literature known TADDOL-derived amine **4aa** is not suitable as a starting material for the syntheses of novel PTCs or chiral Lewis bases due to a rather low reactivity of the nitrogen and an increased sensitivity of this compound under acidic and basic conditions. In contrast, the novel azepane-based amines **5** could be successfully employed to synthesize both PTCs and Lewis bases. Whereas the Lewis bases **7aa** and **9aa** were found to be catalytically inactive in the chosen test reaction, the N-spiro PTCs **3** were found to be powerful catalysts for the asymmetric α -alkylation of glycine Schiff base **20** (up to 93% ee). Noteworthy, the developed synthesis route proved to be suitable for the synthesis of amines/catalysts containing electron-neutral aromatic residues mainly. Surprisingly, the final quaternization step was found to be possible with a limited num-

ber of dihalo-electrophiles in an intramolecular fashion only, whereas sterically more demanding electrophiles or intermolecular approaches stalled at the tertiary amines. Further applications of the PTCs are currently investigated and will be reported in due course.

Melting points were measured on a Kofler melting point microscope (Reichert, Vienna). ¹H and ¹³C NMR spectra were recorded on a Bruker Avance DRX 500 MHz spectrometer, a Bruker Avance III 300 MHz spectrometer, and on a Bruker Avance III 700 MHz spectrometer with TCI cryoprobe. All NMR spectra were recorded at 298 K and referenced on the solvent peak. High-resolution mass spectra were obtained using an Agilent 6520 Q-TOF mass spectrometer with an ESI source and an Agilent G1607A coaxial sprayer. IR spectra were recorded on a Shimadzu IR Affinity-1 FT IR spectrometer. Optical rotations were recorded on a Perkin-Elmer Polarimeter Model 241 MC. HPLC was performed using a Dionex Summit HPLC system with a Chiralcel OD-H (250 × 4.6 mm) chiral stationary phase. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. All reactions were performed under an argon atmosphere. Starting TADDOLs were synthesized according and in analogy to known methods.^{2,9,33} Molecular modeling studies of the ground states were performed using the MMFF94 force field (Pcmodel) and on the B3LYP/6-31G level (Gaussian).

Catalyst (*S,S*)-**3ag**

Dicyanide 15ag: SOCl₂ (5.65 mL, 77.9 mmol) was added to a solution of **2ag** (12.01 g, 15.6 mmol) in CH₂Cl₂ (280 mL) and stirred at r.t. A solution of Et₃N (15.1 mL, 109 mmol) in CH₂Cl₂ (140 mL) was added dropwise over 30 min. The mixture was stirred for 1 h at r.t., cooled to 5 °C and sat. aq NaHCO₃ (400 mL) was added. The biphasic mixture was vigorously stirred for 90 min, the layers were separated, the organic phase was dried (Na₂SO₄), and evaporated to dryness. Crude **13ag** formed was directly dissolved in CH₂Cl₂ (400 mL), cooled to 5 °C and TMSCN (9.73 mL, 77.8 mmol) and SnCl₄ (1.82 mL, 15.6 mmol) were added. The mixture was warmed to r.t. over 1 h and stirred for 12 h. After quenching with sat. aq K₂CO₃ (200 mL), the phases were separated, and the organic phase washed with sat. aq K₂CO₃ (2 × 200 mL) and brine (2 × 200 mL) (**CAUTION! Aqueous phases contain residual cyanide!**). After drying (Na₂SO₄) and evaporation to dryness, the product was purified by column chromatography (heptanes–EtOAc, 5:1) to give dicyanide **15ag** in 59% (7.26 g, 9.2 mmol) as a light brown solid; mp >220 °C (dec.); [α]_D²⁰ +104.6 (*c* 1.6, CHCl₃).

IR (film): 3055, 3030, 1485, 1409, 1373, 1234, 1159, 1076, 1006, 835, 742, 694 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 1.65 (s, 6 H), 5.68 (s, 2 H), 7.24–7.36 (m, 14 H), 7.39 (d, *J* = 8.4 Hz, 4 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.52 (t, *J* = 7.3 Hz, 4 H), 7.65 (d, *J* = 8.8 Hz, 8 H), 7.63 (d, *J* = 7.8 Hz, 4 H).

¹³C NMR (125 MHz, CDCl₃): δ = 28.0 (CH₃), 56.6 (CCN), 81.9 (CH), 111.2 (CO₂), 120.8 (CN), 126.9 (ArC), 127.1 (ArC), 127.2 (ArC), 127.4 (ArC), 127.5 (ArC), 127.6 (ArC), 127.7 (ArC), 128.8 (ArC), 128.9 (ArC), 135.0 (ArC), 138.4 (ArC), 139.5 (ArC), 140.1 (ArC), 140.6 (ArC), 140.7 (ArC).

HRMS (ESI): *m/z* calcd for C₅₇H₄₄N₂O₂: 806.3741 [M + NH₄]⁺; found: 806.3751.

Amine 5ag: A mixture of **15ag** (2.13 g, 2.7 mmol) and LiAlH₄ (2.05 g, 54 mmol) in mesitylene (100 mL) was refluxed for 30–45 min, cooled in an ice bath, and carefully quenched with EtOAc (200 mL) first, followed by the addition of H₂O (150 mL). After phase separation, the aqueous phase was extracted with EtOAc (2 × 150 mL) and the combined organic layers were washed with brine (3 × 150 mL). After drying (Na₂SO₄) and evaporation to dryness, the product was purified by column chromatography (heptanes–EtOAc, 5:1) to

give **5ag** (631 mg, 30%, 0.81 mmol) as a white foam; $[\alpha]_{\text{D}}^{20}$ -143.4 (c 1.14, CHCl_3).

IR (film): 3028, 2983, 1732, 1598, 1485, 1369, 1240, 1215, 1166, 1072, 1006, 831, 763, 742 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 0.86 (s, 6 H), 3.54 (d, J = 14.5 Hz, 2 H), 3.89 (d, J = 14.5 Hz, 2 H), 5.21 (s, 2 H), 7.31–7.34 (m, 4 H), 7.41–7.44 (m, 12 H), 7.51–7.64 (m, 20 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 27.0 (CH_3), 53.7 (Ar_2C), 63.1 (CH_2N), 79.7 (CH), 109.6 (CO_2), 125.7 (ArC), 126.9 (ArC), 127.1 (ArC), 127.2 (ArC), 127.3 (ArC), 127.4 (ArC), 128.8 (ArC), 128.9 (ArC), 131.7 (ArC), 139.0 (ArC), 139.1 (ArC), 140.9 (ArC), 141.0 (ArC), 142.8 (ArC), 147.6 (ArC).

HRMS (ESI): m/z calcd for $\text{C}_{57}\text{H}_{49}\text{NO}_2$: 818.3395 $[\text{M} + \text{K}]^+$; found: 818.3376.

Catalyst 3aga: A mixture of **5ag** (134 mg, 0.172 mmol), 1,4-dibromobutane (81 μL , 0.689 mmol), and K_2CO_3 (95 mg, 0.689 mmol) in MeCN (10 mL) was refluxed for 2 days. The inorganic salts were filtered off, the solvent evaporated, and the residue purified by column chromatography (CH_2Cl_2 –MeOH, 10:1) to obtain ammonium salt **3aga** as a white solid (108 mg, 57%, 0.118 mmol); mp 163–168 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{20}$ -57.4 (c 0.74, CHCl_3).

IR (film): 3028, 2931, 1736, 1487, 1371, 1247, 1213, 1161, 1078, 1006, 837, 765, 740, 696 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 0.89 (s, 6 H), 1.24 (br, 2 H), 1.62 (br, 2 H), 3.57 (br m, 2 H), 3.77 (br m, 2 H), 5.03 (br m, 2 H), 5.44 (br m, 2 H), 5.64 (s, 2 H), 7.31–7.41 (m, 8 H), 7.46 (t, J = 7.2 Hz, 4 H), 7.52–7.62 (m, 12 H), 7.67 (d, J = 7.8 Hz, 4 H), 7.74 (d, J = 7.5 Hz, 4 H), 7.97 (br s, 4 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 20.7 (CH_2), 25.8 (CH_3), 52.6 (Ar_2C), 66.8 (CH_2N^+), 70.6 (CH_2N^+), 79.2 (CH), 110.9 (CO_2), 127.0 ($2 \times \text{ArC}$), 127.1 (ArC), 127.5 (ArC), 127.7 (ArC), 127.8 (ArC), 129.0 ($2 \times \text{ArC}$), 129.1 (ArC), 131.3 (ArC), 138.1 (ArC), 139.9 (ArC), 140.0 (ArC), 140.1 (ArC), 140.3 (ArC), 143.6 (ArC).

HRMS (ESI): m/z calcd for $\text{C}_{61}\text{H}_{56}\text{NO}_2^+$: 834.4306 $[\text{M}]^+$; found: 834.4317.

Phase-Transfer Catalyzed α -Alkylation of Glycine Schiff Base **20**; General Procedure

A mixture of **20** (0.2–1 mmol) and catalyst **3aga** (10 mol%) in toluene (6.5 mL/mmol **20**) was cooled to 0 $^\circ\text{C}$. Aq 50% KOH (2 mL/mmol **20**) was added and the vigorously stirred mixture (>1200 rpm) cooled to -35 $^\circ\text{C}$. After addition of the electrophile (3 equiv), the biphasic mixture was stirred for 20 h at -35 $^\circ\text{C}$. After extraction with CH_2Cl_2 (2×15 mL) and washing the combined extracts with H_2O (5 mL) and brine (5 mL), the combined organic phases were dried (Na_2SO_4), evaporated to dryness, and purified by column chromatography. The alkylation products were isolated using heptanes–EtOAc (15:1) as eluent whereas the catalyst could be recovered in >85% by flushing with CH_2Cl_2 –MeOH (10:1). The catalyst could be reused several times without any decrease in yield or enantioselectivity.

Compound (S)-22

Obtained in 81% yield and with 87% ee upon reacting **20** with benzyl bromide (**21**); colorless oil. Analytical data are in full accordance with those reported in the literature,^{22h,31} $[\alpha]_{\text{D}}^{20}$ -125.7 (c 1.53, CHCl_3).

^1H NMR (300 MHz, CDCl_3): δ = 1.43 (s, 9 H), 3.11–3.23 (m, 2 H), 4.10 (dd, J = 9.0, 4.2 Hz, 1 H), 6.59 (d, J = 6.6 Hz, 2 H), 7.03–7.40 (m, 11 H), 7.61 (d, J = 8.2 Hz, 2 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 28.0, 39.6, 68.0, 81.2, 126.2, 127.7, 127.9, 128.0, 128.1, 128.3, 128.8, 129.9, 130.1, 136.4, 138.4, 139.6, 170.3, 170.9.

HRMS (ESI): m/z calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_2$: 386.2115 $[\text{M} + \text{H}]^+$; found: 386.2113.

Formamide 7aa

A solution of **5aa** (123 mg, 0.258 mmol) and Hünig's base (88 μL , 0.516 mmol) in CH_2Cl_2 (6 mL) was cooled to 0 $^\circ\text{C}$ and acetic formic anhydride (38 μL , 0.516 mmol) was added. The mixture was warmed to r.t. over 1 h and stirred for 2 h. After washing with brine (5 mL), the organic layer was dried (Na_2SO_4), and evaporated to dryness. The product was purified by column chromatography (heptanes–EtOAc, 1:1) to give formamide **7aa** as a white foam (115 mg, 88%, 0.228 mmol); $[\alpha]_{\text{D}}^{20}$ -247.5 (c 2.3, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ = 0.51 (s, 3 H), 0.89 (s, 3 H), 3.03 (d, J = 14.8 Hz, 1 H), 4.28 (d, J = 15.0 Hz, 1 H), 4.36 (d, J = 15.0 Hz, 1 H), 4.91 (d, J = 8.6 Hz, 1 H), 5.18 (d, J = 14.8 Hz, 1 H), 5.26 (d, J = 8.6 Hz, 1 H), 7.20–7.35 (m, 18 H), 7.40–7.45 (m, 2 H), 7.54 (s, 1 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 26.1 (CH_3), 27.2 (CH_3), 52.9 (Ar_2C), 54.9 (Ar_2C), 55.4 (CH_2N), 59.1 (CH_2N), 77.9 (CH), 78.5 (CH), 110.6 (CO_2), 126.1 (ArC), 126.4 (ArC), 126.5 (ArC), 126.6 ($2 \times \text{ArC}$), 127.0 (ArC), 127.5 (ArC), 127.8 (ArC), 128.1 ($2 \times \text{ArC}$), 129.9 (ArC), 130.8 (ArC), 141.2 (ArC), 141.7 (ArC), 145.8 (ArC), 146.8 (ArC), 163.9 (NCHO).

HRMS (ESI): m/z calcd for $\text{C}_{34}\text{H}_{33}\text{NO}_3$: 504.2533 $[\text{M} + \text{H}]^+$; found: 504.2543.

Phosphoramidate 9aa

A mixture of **5aa** (52 mg, 0.109 mmol), KH (17 mg, 0.424 mmol), DMAP (13 mg, 0.106 mmol), and activated 4 \AA molecular sieves (50 mg) in anhyd toluene (4 mL) was cooled to 0 $^\circ\text{C}$ and a solution of POCl_3 (40 μL , 0.429 mmol) in anhyd toluene (1 mL) was added dropwise over 30 min. The mixture was warmed to 60 $^\circ\text{C}$ over 1 h and stirred at this temperature for 40 h. After filtration over a pad of Celite, the solvent was evaporated and the residue dissolved in anhyd CH_2Cl_2 (3 mL), followed by the addition of Et_3N (58 μL , 0.418 mmol) and cooling to -10 $^\circ\text{C}$. After dropwise addition of a solution of N,N' -dimethylethylenediamine (23 μL , 0.212 mmol) in anhyd CH_2Cl_2 (1 mL), the mixture was allowed to warm up to r.t. over 2 h, and stirred for 16 h. The resulting mixture was evaporated to dryness and the residue was purified by column chromatography (EtOAc) to give phosphoramidate **9aa** (57 mg, 86%, 0.094 mmol) as an oily residue (the compound tends to be sensitive to hydrolysis upon standing in solution); $[\alpha]_{\text{D}}^{20}$ -141.2 (c 2.85, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ = 0.69 (s, 6 H), 1.74 (d, J = 9.7 Hz, 3 H), 2.49 (m, 1 H), 2.52 (d, J = 9.7 Hz, 3 H), 2.84 (m, 1 H), 3.07 (m, 2 H), 3.60 (dd, J = 14.8, 8.3 Hz, 2 H), 4.58 (dd, J = 14.8, 8.3 Hz, 2 H), 5.10 (s, 2 H), 7.16–7.34 (m, 16 H), 7.52–7.58 (m, 4 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 26.8 (CH_3), 30.2 (d, J = 4 Hz, CH_3), 31.3 (d, J = 5 Hz, CH_3), 46.1 (d, J = 13 Hz, CH_2), 48.2 (d, J = 11 Hz, CH_2), 53.8 (Ar_2C), 53.9 (Ar_2C), 61.5 (CH_2N), 78.5 (CH), 109.9 (CO_2), 126.2 (ArC), 126.6 (ArC), 121.1 (ArC), 128.1 (ArC), 128.9 (ArC), 131.6 (ArC), 142.7 (ArC), 148.0 (ArC).

^{31}P NMR (81 MHz, CDCl_3): δ = 31.6.

HRMS (ESI): m/z calcd for $\text{C}_{37}\text{H}_{42}\text{N}_3\text{O}_3\text{P}$: 608.3037 $[\text{M} + \text{H}]^+$; found: 608.3044.

Acknowledgment

This work was supported by the Austrian Science Funds (FWF): Project No. P22508-N17. We are grateful to Dr. Manuela Haunschmidt and Dr. Markus Himmelsbach for their support with HRMS analysis and to Christian Rückl for his help with the HPLC analysis. We are grateful to Dr. Christoph Etlstorfer for assisting with the molecular modeling studies. The used NMR spectrometers were acquired in collaboration with the University of South Bohemia (CZ) with financial support from the European Union through the EFRE INTERREG IV ETC-AT-CZ program (project M00146, 'RERI-uasb').

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synthesis>. Included are analytical data of catalyst analogues, precursors, alkylation products, and copies of NMR spectra, HPLC chromatograms, and Tables with details of optimization and scope of the PT-catalyzed α -alkylation.

References

- (1) For comprehensive overviews about organocatalysis, see: (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, **2005**. (b) Dalko, I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, **2007**. (c) Waser, M. In *Progress in the Chemistry of Organic Natural Products*; Vol. 96; Kinghorn, A.-D.; Falk, H.; Kobayashi, J., Eds.; Springer: Berlin, **2012**.
- (2) For reviews on TADDOLs, see: (a) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92. (b) Pellissier, H. *Tetrahedron* **2008**, *64*, 10279.
- (3) For a recent report describing the syntheses of tartaric acid derived 1,4-ditertiary carbinols, see: Budragchaa, T.; Roller, A.; Widhalm, M. *Synthesis* **2012**, *44*, 3238.
- (4) For the application of TADDOLs and derived organocatalysts as chiral H-bonding donors or Brønsted acids, see: (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b) McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 6130. (c) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *347*, 1523. (d) Lauber, M.; Fröhlich, R.; Paradies, J. *Synthesis* **2012**, *44*, 3209. (e) Seebach, D.; Beck, A. K.; Bichsel, H.-U.; Pichota, A.; Sparr, C.; Wünsch, R.; Schweizer, W. B. *Helv. Chim. Acta* **2012**, *95*, 1303.
- (5) For TADDOLs as PTCs, see: (a) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Singh, I.; Parmar, V. S.; Vyskocil, S.; Kagan, H. B. *J. Org. Chem.* **2000**, *65*, 7041. (b) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Parmar, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851.
- (6) For tartaric acid derived PTCs, see: (a) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539. (b) Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206. (c) Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7743. (d) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4564. (e) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem.-Asian. J.* **2007**, *2*, 794.
- (7) Waser, M.; Haunschmidt, M.; Himmelsbach, M. *Monatsh. Chem.* **2010**, *141*, 1347.
- (8) Waser, M.; Gratzner, K.; Herchl, R.; Müller, N. *Org. Biomol. Chem.* **2012**, *10*, 251.
- (9) (a) Seebach, D.; Beck, A. K.; Hayakawa, M.; Jaeschke, G.; Kühnle, F. N. M.; Nageli, I.; Pinkerton, A. B.; Rheiner, P. B.; Duthaler, R. O.; Rothe, P. M.; Weigand, W.; Wünsch, R.; Dick, S.; Nesper, R.; Wörle, M.; Gramlich, V. *Bull. Soc. Chim. Fr.* **1997**, *134*, 315. (b) Seebach, D.; Hayakawa, M.; Sakaki, J.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711. (c) Beck, A. K.; Bastani, B.; Plattner, D. A.; Petter, W.; Seebach, D.; Braunschweiger, H.; Gysi, P.; Lavecchia, L. *Chimia* **1991**, *45*, 238. (d) Pichota, A.; Gramlich, V.; Beck, A. K.; Seebach, D. *Helv. Chim. Acta* **2012**, *95*, 1239.
- (e) Pichota, A.; Gramlich, V.; Bichsel, H.-U.; Styner, T.; Knöpfel, T.; Wünsch, R.; Hintermann, T.; Schweizer, W. B.; Beck, A. K.; Seebach, D. *Helv. Chim. Acta* **2012**, *95*, 1273.
- (10) For reviews on chiral Lewis base catalysis, see: (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560. (b) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432.
- (11) For reviews about asymmetric phase-transfer catalysis, see: (a) Maruoka, K. *Asymmetric Phase Transfer Catalysis*; Wiley-VCH: Weinheim, **2008**. (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (d) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (e) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (f) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.
- (12) Weibel, D. *Ph.D. Dissertation*; ETH: Zürich, **2003**, Nr. 1529.
- (13) Due to the failed syntheses of catalysts **6**, **10**, and **12**, the synthesis of phosphoramides **8** was not exhaustively investigated anymore after the failure of a few initial experiments.
- (14) Seebach et al. coincidentally observed the formation of trityl derivatives upon treatment of dichloro compound **13** with diphenylamine or methylaniline: Seebach, D.; Pichota, A.; Beck, A. K.; Pinkerton, A. B.; Litz, T.; Karjalainen, J.; Gramlich, V. *Org. Lett.* **1999**, *1*, 55.
- (15) Reetz, M. T.; Chatzhosifidis, I.; Künzler, H.; Müller-Starke, H. *Tetrahedron* **1983**, *39*, 961.
- (16) $\text{BH}_3 \cdot \text{DMS}$ in refluxing THF was the only other reducing agent that gave small amounts of **5aa** (?20%).
- (17) *p*-Methoxy-substituted TADDOL gave elimination and Friedel–Crafts products in the chlorination step exclusively, whereas the *m*-methoxy one gave at least small amounts of the dichlorides, which then formed only Friedel–Crafts products, but not dinitrile under the Lewis acidic cyanation conditions.
- (18) Synthesis of the TADDOL **2aa** based sulfite **16aa** was reported by Seebach et al. in ref. 9b.
- (19) In these two cases it was necessary to use 5 equiv of TMSCN and 1 equiv SnCl_4 to obtain the dicyanides in a reliable and reproducible manner.
- (20) Using MeI, trace amounts of the targeted ammonium iodide could be detected by ESI-HRMS of the crude reaction mixture, but no product could be isolated.
- (21) For detailed investigations concerning the kinetics of $\text{S}_{\text{N}}2$ -type cyclization reactions, see: (a) Freundlich, H.; Kroepelin, H. *Z. Physik. Chem.* **1926**, *122*, 39. (b) Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051.
- (22) (a) Shirakawa, S.; Liu, K.; Ito, H.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 1515. (b) Kano, T.; Yamamoto, A.; Song, S.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 4358. (c) Shirakawa, S.; Terao, S. J.; He, R.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 10557. (d) Hashimoto, T.; Sakata, K.; Maruoka, K. *Adv. Synth. Catal.* **2010**, *352*, 1653. (e) Lan, Q.; Wang, X.; Shirakawa, S.; Maruoka, K. *Org. Process Res. Dev.* **2010**, *14*, 684. (f) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (g) Shirakawa, S.; Liu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 916. (h) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.
- (23) This compound was not unambiguously proven by NMR analysis due to the presence of other by-products (maybe also due to the presence of other possible Stevens rearrangement products), but could be clearly identified by HRMS in the positive ion mode.

- (24) Goncalves-Farbos, M.-H.; Vial, L.; Lacour, J. *Chem. Commun.* **2008**, 829.
- (25) For optimization of the reaction conditions and catalyst amount, please see the detailed tables in the Supporting Information and the preliminary results in our recent communication (ref. 8).
- (26) We have also synthesized the corresponding 2-acetylnaphthalene-based derivative, which performed slightly better (88% ee in the benchmark alkylation), but was even harder to obtain as the last steps were significantly lower yielding and vast amounts of difficult to remove impurities were formed.
- (27) For successful applications of acyclic TADDOL-backbone containing ligands in asymmetric catalysis, see: (a) Teller, H.; Flügge, S.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *122*, 1993. (b) Teller, H.; Fürstner, A. *Chem.–Eur. J.* **2011**, *17*, 7764.
- (28) For detailed scope, see the tables in the Supporting Information and the preliminary results in our recent communication (ref. 8).
- (29) For a recent example using cinchona-based PTCs, see: Yoo, M. S.; Kim, D. G.; Ha, M. W.; Jew, S.; Park, H.; Jeong, B. S. *Tetrahedron Lett.* **2010**, *51*, 5601.
- (30) No background reaction was observed in the absence of the catalyst.
- (31) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
- (32) Also the use of more reactive *p*-nitrobenzaldehyde did not result in a better conversion.
- (33) (a) Weber, E.; Dörpinghaus, N.; Wimmer, C.; Stein, Z.; Krupitsky, H.; Goldberg, I. *J. Org. Chem.* **1992**, *57*, 6825. (b) Voituriez, A.; Charette, A. B. *Adv. Synth. Catal.* **2006**, *348*, 2363. (c) Kelly, T. R.; Cai, X.; Elliott, E. L.; Grossmann, G.; Laurent, P. *Org. Lett.* **2004**, *6*, 4953.