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

Katharina Gratzer, 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
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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 4–12 and 5 to synthesize a variety of structurally diverse novel chiral Lewis base catalysts10–12 and chiral phase-transfer catalysts11 (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

Pyrrrolidine 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. With respect to the syntheses of the pyrroldidine-containing catalysts the ‘standard’ TADDOL 2aa (R1 = R2 = Me, Ar = Ph) was first converted into the known azabicyclo[3.3.0]octane 4aa according to the published procedure. 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. In addition, they also reported a surprisingly high instability of the normally rather stable acetonide moiety is also in line with recent results in our group obtained with an analogous trans-azabicyclo[3.3.0]octane derivatized with the formamide Lewis base 13a. Also treatment with several alkyl halides like 1,4-dibromobutane, 1,4-dibromocyclohexane, or 1,4-dibromobenzene resulting in partial acetonide cleavage again. Accordingly, the use of the long-known secondary amine 4aa to prepare novel chiral Lewis bases 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.

Azepane 5-Based Phase-Transfer Catalysts

We have recently succeeded in developing a four-step route to build a small library of azepane-based C2-symmetric acetonide-containing N-spiro catalysts 3a (based on the classical acetonide moiety with R1 = R2 = Me) starting from known TADDOLs 2a (Scheme 3). 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 C2-symmetric acetonide-containing azepane-based PTCs 3a. Reagents and conditions: a) SOCl2, Et3N, CH2Cl2, 25 °C; b) TMSCN, SnCl4, 25 °C, 47–63% (over two steps); c) LiAlH4, mesitylene, reflux, 49–69%; d) Br–Y–Br, K2CO3, MeCN, reflux, 49–69%.

Initial route development was carried out using the parent TADDOL 2aa (R1 = R2 = Me, Ar = Ph). Surprisingly, elongation of the carbon chain of TADDOLs has so far not been systematically investigated. Reacting dichloro compound 13aa with TMSCN (>2.5 equiv) in the presence of catalytic amounts of SnCl4 (25%) 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 decompostion). 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 NaBH4 (also in combination with different additives), Red-Al, LiBH4, or LiAlH4 at room temperature in different ethereal solvents did not affect the cyano groups either. Interestingly, we discovered that refluxing heterogeneous mixtures of 15aa and excess LiAlH4 (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.\(^1\)\(^6\) However, having established a reliable route for the syntheses of the chiral secondary amine 5\(\text{aa}\), 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 5\(\text{a}\) (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 13\(\text{a}\) under a variety of different chlorination conditions, but instead different elimination and also Friedel–Crafts products were formed.\(^1\)\(^7\) On the other hand, strong electron-withdrawing substituents like trifluoromethyl groups did not give the dichlorides either, but instead the stable cyclic sulfites 16\(\text{a}\) were formed\(^1\)\(^8\) (Scheme 4). Unfortunately, neither changing the reaction conditions, nor using other chlorination agents like PCl\(_5\) or oxalyl chloride gave the targeted dichlorides 13\(\text{a}\). Attempts to employ this sulfite further failed due to the high stability of this compound.

Direct dicyanation of TADDOLs 2\(\text{a}\) with TMSCN in the presence of a Lewis acid worked with modest yields in the case of electron-neutral aromatic residues (e.g., 2\(\text{aa}\) was directly converted into 15\(\text{aa}\) 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 15\(\text{af}\) and 15\(\text{ag}\) could be obtained in high yields.\(^1\)\(^9\) All the obtained acetonide-based dicyanides 15\(\text{a}\) could be converted into the secondary amines 5\(\text{a}\) in moderate yields (see Table 1).

The final quaternization step was first investigated targeting N-spiro ammonium salts 3\(\text{aa}\). In contrast to amine 4\(\text{aa}\), the azabicyclo[5.3.0]decane 5\(\text{aa}\) (Ar = Ph) was found to be nucleophilic enough in the reaction with 1,4-dibromobutane, giving the targeted ammonium bromide 3\(\text{aa}\) (see Scheme 3; R\(_1\) = R\(_2\) = Me, Ar = Ph, Y = group a) in 60% isolated yield upon refluxing 5\(\text{aa}\) with 4 equivalents dibromobutane (MeCN, K\(_2\)CO\(_3\)). Noteworthy, whereas only traces of the intermediate tertiary amine were observed, significant amounts of unreacted starting material 5\(\text{aa}\) could be reisolated. Similar results were obtained in the successful syntheses of catalysts 3\(\text{aab}\) (Ar = Ph, Y = group b) and 3\(\text{aac}\) (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.\(^2\)\(^0\) 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 3\(\text{aa}\) and the targeted piperidinium-based catalyst 3\(\text{aad}\) (Figure 1). A careful analysis revealed no striking differences between the parent skeletons of these two ammoni-

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

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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 Sₓ₂-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), 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, the quaternization of amines 5 is a rather difficult 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 Rf 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, most presumably via a Stevens type rearrangement, which is a well-known reaction for binaphthyl and biphenyl-based ammonium salts. Accordingly these highly crowded compounds turned out to be

![Figure 1](image.png)

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

**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 gave rather broad $^1$H 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 acetone 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 $\alpha$-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 acetone-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 tartratic 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 ketal groups 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 $\alpha$-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 However, 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 $\alpha$-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% (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](image)

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

![Chemical structure](image)

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<th>Catalyst structure</th>
<th>Catalyst synthesis(^b)</th>
<th>Alkylation</th>
<th>Temp (°C)</th>
<th>Yield(^c) (Conv.)(^d)</th>
<th>ee (%)(^e) (Conf.)(^f)</th>
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<td>3bga</td>
<td>4-PhC(_6)H(_4)</td>
<td>+ + + +</td>
<td>70 (–90)</td>
<td>87 (S)</td>
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<tr>
<td>33</td>
<td>3bga</td>
<td>4-PhC(_6)H(_4)</td>
<td>+ + + +</td>
<td>79 (quant)</td>
<td>80 (S)</td>
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<tr>
<td>34</td>
<td>3bga</td>
<td>4-PhC(_6)H(_4)</td>
<td>+ + + +</td>
<td>79 (quant)</td>
<td>80 (S)</td>
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<tr>
<td>35</td>
<td>3bga</td>
<td>4-PhC(_6)H(_4)</td>
<td>+ + + +</td>
<td>79 (quant)</td>
<td>80 (S)</td>
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</tbody>
</table>

\(^a\) 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 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 POCl3[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-dimethylthelylenediamine was possible to obtain the phosphoramide 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 alkylation 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, Hüning’s base, CH2Cl2, 0–25 °C, 88%; b) POCl3, KH, DMAP, 4 Å MS, toluene, 60 °C; c) POCl3, KH, Hünig’s base, 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 number 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 EI 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 (5,5′)-3ag
Dicynide 15ag: SOCl3 (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 biphase reaction mixture was stirred vigorously for 90 min, the layers were separated, the organic phase was dried (Na2SO4), and evaporated to dryness. The crude product was 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 dicynide 15ag in 59% (7.26 g, 9.2 mmol) as a light brown solid; mp >220 °C (dec.); [α]25D = +104.6 (c = 1.6, CHCl3).

IR (film): 3055, 3030, 1485, 1373, 1234, 1159, 1076, 1006, 2983, 1770 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), 13.97 (d, J = 8.4 Hz, 4 H), 7.53 (d, 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).

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

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give 5ag (631 mg, 30.8% mmol) as a white foam; \( [\alpha]_{D}^{20} = 143.4 \) (c 1.14, CHCl₃).

IR (film): 3028, 2983, 1736, 1598, 1487, 1371, 1247, 1213, 1161, 1078, 1006, 837, 765, 740, 696 cm⁻¹.

A mixture of 5ag (134 mg, 0.172 mmol), 1,4-dibromobutane (81 μL, 0.689 mmol), and K₂CO₃ (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 (CH₂Cl₂–MeOH, 10:1) to obtain ammonium salt 3aga as a white solid (108 mg, 57%, 0.118 mmol); mp 163–168 °C; \( [\alpha]_{D}^{20} = –57.4 \) (c 0.74, CHCl₃).

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**Phase-Transfer Catalyzed \( \alpha \)-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 °C. Aq 50% KOH (2 mL/mmol 20) was added and the vigorously stirred mixture (~1200 rpm) cooled to −35 °C. After addition of the electrophile (3 equiv), the biphasic mixture was stirred for 20 h at −35 °C. After extraction with CH₂Cl₂ (2 × 15 mL) and washing the combined extracts with brine (5 mL), the organic phase was concentrated and dried (Na₂SO₄), evaporated to dryness. The product was purified by column chromatography (CH₂Cl₂–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, \( [\alpha]_{D}^{20} = 125.7 \) (c 1.53, CHCl₃).

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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


(3) For a recent report describing the syntheses of tartaric acid derived 1,4-diteriary carbinols, see: Budschagea, T.; Roller, A.; Widhalm, M. Synthesis 2012, 44, 3238.


(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.


(16) BH3·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 dinitriile under the Lewis acidic cyanation conditions.

(18) The 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 SnCl2 to obtain the dicyanides in a reliable and reproducible manner.

(20) Using Mel, trace amounts of the targeted ammonium iodide could be detected by ESI-HRMS of the crude reaction mixture, but no product could be isolated.


(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.

(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.


(28) For detailed scope, see the tables in the Supporting Information and the preliminary results in our recent communication (ref. 8).


(30) No background reaction was observed in the absence of the catalyst.


(32) Also the use of more reactive p-nitrobenzaldehyde did not result in a better conversion.