Catalytic asymmetric umpolung reactions of imines

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The carbon–nitrogen double bonds in imines are fundamentally important functional groups in organic chemistry. This is largely due to the fact that imines act as electrophiles towards carbon nucleophiles in reactions that form carbon–carbon bonds, thereby serving as one of the most widely used precursors for the formation of amines in both synthetic and biosynthetic settings1–5. If the carbon atom of the imine could be rendered electron-rich, the imine could react as a nucleophile instead of as an electrophile. Such a reversal in the electronic characteristics of the imine functionality would facilitate the development of new chemical transformations that convert imines into amines via carbon–carbon bond-forming reactions with carbon electrophiles, thereby creating new opportunities for the efficient synthesis of amines. The development of asymmetric umpolung reactions of imines (in which the imines act as nucleophiles) remains uncharted territory, in spite of the far-reaching impact such reactions would have in organic synthesis. Here we report the discovery and development of new chiral phase-transfer catalysts that promote the highly efficient asymmetric umpolung reactions of imines with the carbon electrophile enals. These catalysts mediate the deprotonation of imines and direct the 2-azaallyl anions thus formed to react with enals in a highly chemoselective, regioselective, diastereoselective and enantioselective fashion. The reaction tolerates a broad range of imines and enals, and can be carried out in high yield with as little as 0.01 mole per cent catalyst with a moisture- and air-tolerant operational protocol. These umpolung reactions provide a conceptually new and practical approach to chiral amino compounds.

Umpolung reactions create new activities by reversing the inherent polarity of common organic functionalities such as carbonyls and consequently allow the development of new reactions of distinct bond connections6. The successful development of numerous C–C bond-forming umpolung reactions with carbonyls as acyl anion equivalents has greatly expanded the repertoire of organic synthesis7–9. The power of carbonyl umpolung reactions has been tapped for asymmetric syntheses10. In contrast, C–C bond-forming umpolung reactions of imines are rarely reported11–14. Aiming at the realization of highly efficient catalytic asymmetric umpolung reactions of imines, we embarked on a search for catalysts to both promote the formation of carbonanions from imines and direct the carbonanions thus formed to react with carbon electrophiles to generate chiral amines in an asymmetric fashion.

We recently reported that modified cinchona alkaloids such as the quinine-derived (Q) catalyst Q-2 could promote highly enantioselective isomerization of trifluoromethyl imines such as 1 (Fig. 1)15,16. This reaction presumably proceeds through the initial formation of the 2-azaallyl anion 3, and then a highly enantioselective protonation of 3. This discovery prompted us to postulate that, if the 2-azaallyl anion 3 could be made to react with carbon electrophiles in a stereoselective manner, novel C–C bond-forming asymmetric reactions transforming imines 1 into enantioenriched amines could be realized (Fig. 1). Although numerous catalytic asymmetric C–C bond-forming reactions with enolates derived from glyoxylateimines17 and glycine imines18 have been documented for the synthesis of amino acids, only two catalytic asymmetric C–C bond-forming reactions with 2-azaallyl anions have been reported19,20. The palladium-catalysed cross-coupling of 2-azaallyl anions with aryl halides and triflates remains the sole example of highly enantioselective C–C bond-forming reactions with 2-azaallyl anions18.

Guided by these considerations, we investigated quinine- and quinidine-derived (QD) organocatalysts Q-2, QD-11 and QD-12 for the reaction of imine 1A and crotonaldehyde (8a) (Table 1). None of them was active towards the desired C–C bond-forming reaction; only the isomerized imine 4A was detected. These catalysts promoted the deprotonation of trifluoromethyl imine 1A to form the 2-azaallyl anion 3, but were unable to direct the conjugate addition of 3 to crotonaldehyde. Presumably, the protonated cinchona alkaloids formed on deprotonation of 1A rapidly protonate 3 to form 4A. As the 2-azaallyl anion 3 was shown to engage in protonation in the presence of a proton donor, we surmise that a novel class of catalysts must be developed to afford the required chemoselectivity in favour of the C–C bond formation over the protonation.

We decided to explore chiral phase-transfer catalysts21. Under phase-transfer catalysis conditions, stronger bases could be explored.

Figure 1 | Design of a catalytic C–C bond-forming umpolung reaction of imines. See text for details.
for the deprotonation of imine 1 to form 2-azaallyl anion 3. Furthermore, in the absence of a protonated cationic species, 3 should be less prone to protonation and therefore more likely to engage in the addition to 8a. A cinchonine-derived (C) phase-transfer catalyst C-13 was first investigated to promote the reaction of 1A and 8a in toluene and aqueous KOH at room temperature. The desired amine 9Aa was formed, albeit in minuscule amounts (entry 1, Table 2). Importantly, the chemoselectivity for the C–C bond formation could be improved, albeit in minuscule amounts (entry 1, Table 2). Importantly, the chemoselectivity for the C–C bond formation could be improved, although both the reaction conversion and the chemoselectivity remained poor (entry 2, Table 2). Subsequently, we found that a reaction at lower temperature afforded significantly improved conversion and chemoselectivity. The absence of 10Aa, which would be formed by conjugate addition from the other end of the 2-azaallyl anion, is noteworthy. However, amine 9Aa was formed with moderate diastereoselectivity and poor enantioselectivity.

Introducing an additional interaction between a conformationally well-defined phase-transfer catalyst and the anionic nucleophile has proven to be a useful strategy to enhance catalytic selectivity21. We hypothesized that a cinchonine-derived phase-transfer catalyst bearing a properly located aromatic group with suitable electronic properties might interact with 2-azaallyl anion 3A via both ionic and π–π interactions22–24, thereby mediating the model umpolung reaction in a highly chemo-, regio-, diastereo- and enantioselective fashion. Analogues C-15 and C-16 bearing electron-withdrawing and electron-donating N-benzyl substituents, respectively, were examined. We found that C-16 afforded only improved conversion whereas C-15 was worse than C-14 (entries 4 and 5, Table 2). Interestingly,

### Table 1 | Experiments with chiral base catalysts

| Entry | T (°C) | Catalyst | Conversion (%) | 9:4 | 9:4 |
|-------|--------|----------|----------------|-----|-----|
| 1     | RT     | Q-2      | 84             | 0:100 | - |
| 2     | RT     | QD-11    | 32             | 0:100 | - |
| 3     | RT     | QD-12    | 9              | 0:100 | - |

Conditions: room temperature (RT), 10 mol%, catalyst, 16 h.

### Table 2 | Screening and optimization of chiral phase-transfer catalysts

| Entry | T (°C) | Catalyst | Conversion (%) | 9:4 | 9:10 | d.r. of 9 | e.e. of 9 (%) |
|-------|--------|----------|----------------|-----|------|-----------|--------------|
| 1     | RT     | C-13     | 41             | 2:98 | ND   | ND        | ND           |
| 2     | RT     | C-14     | 18             | 11:89 | ND   | ND        | ND           |
| 3     | RT     | C-15     | 58             | 37:63; >95/5 | 82:18 | 39        | -           |
| 4     | RT     | C-16     | 54             | 36:64; >95/5 | 67:33 | 18        | -           |
| 5     | 20     | C-17     | 84             | 34:66; >95/5 | 76:24 | 40        | -           |
| 6     | 20     | C-18     | 41             | 32:68; >95/5 | 74:26 | 39        | -           |
| 7     | 20     | C-19     | 14             | 67:33; >95/5 | 87:13 | 68        | -           |
| 8     | 20     | C-20     | 14             | 74:26; >95/5 | 86:14 | 77        | -           |
| 9     | 20     | C-21a    | 39             | 45:55; >95/5 | 96:4 | 55        | -           |
| 10    | 20     | C-21b    | 66             | 68:32; >95/5 | 91:9 | 85        | -           |
| 11    | 20     | C-21a    | 88             | 94:6; >95/5 | 91:9 | 91        | -           |
| 12    | 20     | C-21b    | 99             | 99:1; >95/5 | 93:7 | 96        | -           |
| 13    | 20     | C-21a    | 97             | 99:1; >95/5 | 93:7 | 95        | -           |
| 14    | 20     | C-21b    | 31             | 4:96; ND   | ND   | ND        | -           |

Conditions: 10 mol%, catalyst, 10 mol%, KOH(aq.), 16 h, TBAB, tetra-n-butylammonium bromide. ND, not determined; d.r., diastereomeric ratio; e.e., enantiomeric ratio.

*1.0 mol% catalyst, 10 mol% KOH(aq.), 2 h.
+0.2 mol% of C-21b used, 5 h.
we observed that a decrease in the loading of C-16 did not affect the catalytic selectivities negatively (entry 6 versus 5, Table 2). We therefore decreased the catalyst loading from 10 mol% to 1 mol% in our subsequent catalyst screening and optimization studies. We next turned to C-17, an analogue containing a biphenyl group. C-17 afforded substantially improved chemo-, diastereo- and enantioselectivity, thereby allowing amine 9Aa to be formed as the major product (entry 7 versus 6, Table 2).

Assuming the improved catalysis resulted from a π-π interaction between the biaryl moiety of C-17 and 3A, we designed and synthesized catalyst C-18 (Table 2). We reasoned that the presence of the C2-symmetric terphenyl moiety could render C-18 a more efficient catalyst than C-17. This working hypothesis received support from the superior performance of C-18 in catalytic activity as well as chemo- and enantioselectivity (entry 8 versus 7, Table 2). Further tuning of the catalyst was initially attempted by introducing electron-withdrawing and electron-donating groups on the 3- and 5-phenyl terphenyl moiety. However, C-18 furnished higher stereoselectivity but lower chemoselectivity than those produced by C-18 (entry 10 versus 8, Table 2).

We next examined catalyst C-21a (Table 2) which was designed to create an electron-rich terphenyl moiety with an electron-donating substituent in a position not causing obstructive steric interference between the catalyst and 2-azaallyl anion 3. Gratifyingly, C-21a not only turned out to be much more active, but also afforded 9Aa with synthetically useful chemo-, regio-, diastereo- and enantioselectivity (entry 11, Table 2). Catalyst C-21b with a more electron-donating and bulky tert-butyldimethylsilyl ether (OTBS) group was more active and selective; a loading of only 0.2 mol% produced imine 9Aa rapidly with almost complete chemoselectivity and excellent stereoselectivity (entry 13, Table 2). We attributed the superior performance of C-21b over C-21a to two factors resulting from the substitution of the 4-methoxy group with 4-OTBS group: (1) the terphenyl moiety is more electron rich due to the presence of the more electron-donating 4-OTBS group; (2) the terphenyl moiety has less conformational flexibility due to steric hindrance of the rotation of the 3,5-phenyl rings by the bulky 4-OTBS group. Both factors could reinforce the π-π interaction between 3A and the catalyst C-21b.

Only a trace of 9Aa was formed from 1A and 8a using tetrabutylammonium bromide (TBAB) as the quaternary ammonium salt (entry 14, Table 2), which confirmed that the structural characteristics of C-21b were responsible for both the catalytic activity and the selectivity observed for the umpolung reaction between imine 1A and enal 8a. To ascertain that 2-azaallyl anion 3 originated only from imine 1 rather than also from the isomerized imine 4, we established that no reaction occurred between 4A and 8a under the optimized conditions.

Table 3 | Substrate scope for umpolung reactions of trifluoromethyl imines with enals

| Entry | R1 | Time (h); conversion (%) | 9/4: 9/10 | d.r. of 9 | Yield (%) | e.e. (%) |
|-------|-----|--------------------------|-----------|----------|-----------|----------|
| 1     | H2C- | 5: 99                    | >95/5      | >95/5    | 93/7      | 81       |
| 2     | Cy   | 5: 97                    | >95/5      | >95/5    | 91/9      | 84       |
| 3     | Br-  | 5: 98                    | >95/5      | >95/5    | 91/9      | 83       |
| 4     | CN   | 5: 99                    | >95/5      | >95/5    | 91/9      | 75       |
| 5     | C3    | 7: 94                    | >95/5      | >95/5    | 91/9      | 72       |
| 6     | C4    | 12: 98                   | 91/9       | >95/5    | 93/7      | 54       |

Table 3 | Substrate scope for umpolung reactions of trifluoromethyl imines with enals

| Entry | R2 | Time (h); conversion (%) | 9/4: 9/10 | d.r. of 9 | Yield (%) | e.e. (%) |
|-------|-----|--------------------------|-----------|----------|-----------|----------|
| 7     | CH3  | 5: 99                    | 89/11     | >95/5    | 64        | 22Ab     |
| 8     | CH3(CH2)5 | 12: 93                | 86/14     | >95/5    | 51        | 22Ac     |
| 9     | Ph   | 8: 93                    | >95/5      | 68/32    | 51        | 22Ad     |

Table 3 | Substrate scope for umpolung reactions of trifluoromethyl imines with enals

| Entry | R2 | Time (h); conversion (%) | 9/4: 9/10 | Yield (%) | e.e. (%) |
|-------|-----|--------------------------|-----------|-----------|----------|
| 10    | H2C- | 3: 95                    | >95/5      | 89        |
| 11    | Cy   | 3: 99                    | >95/5      | 82        |
| 12    | Br-  | 3: 97                    | >95/5      | 84        |
| 13    | CN   | 3: 99                    | >95/5      | 90        |
| 14    | Ph   | 3: 99                    | 94/6       | 71        |
| 15    | p-MeOC6H4 | 3: 94                   | 92/8     |
| 16    | p-CF3C6H4 | 3: 99                | 88/12     |
| 17    | Ph   | 1: 99                    | >95/5      | 90        |

Conditions: imine 1 (0.2 mmol), aldehyde 8 (0.4 mmol), C-21b (0.2 mol%), KOH (2.2 ml, 50 wt%), PhMe (2.0 ml). Conversion, regioselectivity (9/10) and d.r. of 9 were determined by 1H NMR analysis of the crude umpolung reaction mixture. Chemoselectivity (9/4) was determined by 19F NMR analysis.

*Overall yield for the transformation of imine 1 to either 22 or 23.
†t.r.s. of 22 or 23, determined by HPLC analysis.
‡Reaction was performed at −10 ºC.
It should be noted that amine 9Aa may also form via a [3 + 2] cycloadDITION between 1A and 8a followed by a retro-Mannich reaction. However, we did not detect the formation of the [3 + 2] adduct when monitoring the reaction by 1H and 19F NMR analyses.

Our investigation of the substrate scope began with the reaction of 1A and 8a with 0.2 mol% of C-21b (entry 1, Table 3). The reaction proceeded to full conversion within 5 h with excellent chemo-, regio-, distereo- and enantioselectivities. The optically active amine 9Aa was then converted to the more stable N-benzyl aminoalcohol 22Aa by reducing first the aldehyde with NaBH4 and then the imine with NaBH4 and acetic acid, which could be readily isolated as a single diastereomer in good yield. Reactions of 8a with a series of trifluoromethylated amines (1B–E, Table 3) bearing simple and functionalized linear alkyl substituents consistently proceeded in high yield and excellent chemoselectivity and stereoselectivity. The reaction tolerated an amine bearing a β-branched alkyl substituent (1F). The reaction accepted larger β-alkyl groups on the enal (entries 7 and 8, Table 3).

Cinnamaldehyde (8d) reacted with 1A to give a 68:32 mixture of the desirable amine 9Ad and the regioisomer 10Ad. Nonetheless, 9Ad was produced with high chemo-, diastereo- and enantioselectivity in synthetically useful yield (entry 9, Table 3).

We next examined the reactions of trifluoromethylated imines 1 with acrolein (8e). We found that at –10 °C the reaction between 1A and 8e proceeded cleanly and in a highly enantioselective fashion to furnish the corresponding amine 9Ae as the only detectable product by NMR analysis of the crude reaction mixture. The reactions of acrolein (8e) with trifluoromethyl imines 1 bearing a variety of alkyl, aryl and alkenyl substituents were equally successful, affording the corresponding trifluoromethylated amines 9 containing a tetrasubstituted stereocentre in high optical purity (entries 11–17, Table 3).

Alkyl trifluoromethylated amines (9Ae–Fe) were converted to N-benzyl aminoalcohols 22 (entries 10–13, Table 3). Aryl and alkenyl amines 9Ge–Je were converted to aminoalcohols 23 by reduction of the aldehyde with NaBH4 and hydrolysis of the imine with aqueous HCl (entries 14–17, Table 3). In all these cases, the aminoalcohols 22 and 23 were obtained in good yields and high optical purity.
A gram-scale reaction of 1A with 8a with 0.01 mol% of C-21b went to completion without deterioration in selectivity (Fig. 2a). This remarkable catalytic efficiency indicates the utility of this new reaction in preparative-scale organic synthesis. To demonstrate the synthetic versatility of this reaction, we converted chiral aminoaldehyde 9Aa to aminoalcohol 23Aa and pyrrolidine 24Aa as shown in Fig. 2a. Similarly, the phenyl substituted product 25Ge was converted to pyrrolidine 24Ge (Fig. 2b). The absolute configurations of 24Aa and 24Ge were determined by X-ray crystallography.

We are interested in extending the scope to simple imines, which would greatly expand the reach of this asymmetric umpolung reaction in organic synthesis. However, 2-azaallyl anions 26 derived from aryl imines 25 (Fig. 3a) are substantially less stable than those derived from the corresponding trifluoromethyl imines 21c. As a consequence, deprotonation of phenyl imine 25A should form 2-azaallyl anion 26A, which is flanked by the phenyl and the 4-nitrophenyl rings (Fig. 3b). Thus, there is an inherent electronic bias for an electrophile to react with 26A by attacking preferentially the more electron-rich C3. Nonetheless, the remarkable catalytic efficiency of C-21b made us hopeful that it could provide powerful catalytic activity and selectivity to overcome this undesirable substrate bias while still affording the required stereoselectivity for an efficient asymmetric imine umpolung reaction.

Accordingly, we investigated the reaction of phenyl imine 25A with acrolein (8e) applying the conditions established with trifluoromethyl imines 1. As expected, 25A was far less reactive than 1A; only a trace amount of the desired product 29Ae was detected. With a substantially increased catalyst loading (entry 1, Fig. 3b), the reaction progressed to high conversion and in excellent enantioselectivity. A new catalyst bearing a 4-0Bu group (C-21c) was found to be more active and afforded better enantioselectivity (entry 2, Fig. 3b); this allowed a clean and complete reaction to occur at 0 °C in excellent enantioselectivity.

### Table 4 | Substrate scope for umpolung reactions of aryl aldimines with acrolein (8e)

| Entry | R          | Time (h) | 29/30     | Yield of 31 (%) | e.e. of 31 (%) |
|-------|------------|----------|-----------|-----------------|---------------|
| 1     | Ph; 25A    | 8        | >95/5     | 55              | 93            |
| 2     | o-CH3C6H4; 25B | 8    | >95/5     | 51              | 94            |
| 3†    | 2-Naphthyl; 25C | 8    | 90/10     | 54              | 94            |
| 4     | 2-Thienyl; 25D | 8    | >95/5     | 53              | 95            |
| 5†    | p-BrC6H4; 25E | 5    | >95/5     | 52              | 99            |
| 6     | p-BrC6H4; 25F | 5    | >95/5     | 56              | 95            |
| 7†    | p-MeOC6H4; 25G | 8    | 83/17     | 53              | 90            |
| 8     | p-MeOC6H4; 25H | 18   | >95/5     | 45              | 95            |

Conditions: reactions were performed with 25 (0.20 mmol), 8e (0.40 mmol), C-21c (2.5 mol%) and KOH (2.2 µl, 50 wt%, aq. 10 mol%) in PhMe (2.0 ml) until full conversion. Regioselectivity (29/30) was determined by 'H analysis of the crude umpolung reaction mixture.

### Table 5 | Substrate scope for umpolung reactions of alkenyl aldimines with acrolein (8e)

| Entry | Alkenyl | Time (h) | 32/33 | Yield of 34 (%) | e.e. of 34 (%) |
|-------|---------|----------|-------|-----------------|---------------|
| 1     | Ph      | 16       | 86/14 | 51              | 92            |
| 2     | Me      | 16       | 95/5  | 50              | 92            |
| 3†    | Me      | 24       | 82/18 | 46              | 95            |
| 4     | p-BrC6H4 | 12      | 77/23 | 44              | 92            |
| 5†    | p-MeOC6H4 | 24    | 83/17 | 41              | 90            |
| 6†    | Br      | 6        | 95/5  | 37%             | 90            |

Conditions: reactions were performed with 27 (0.20 mmol), 8e (0.40 mmol), C-21c (2.5 mol%) and KOH (2.2 µl, 50 wt%, aq. 10 mol%) in PhMe (2.0 ml) until full conversion. Regioselectivity (32/33) was determined by 'H analysis of the crude umpolung reaction mixture.

*Overall yield for the transformation of imine 27 to 34.
†Determined by HPLC analysis.
‡5.0 mol% C-21c used.
§Overall yield for a four-step transformation of (E)-3-bromobut-2-enal to 34Fe, see Supplementary Information for details.
with 2.5 mol % of C-21c (entry 3, Fig. 3b). Amine 29Ac was converted to the Boc-protected aminoalcohol 31Ac in high optical purity and good yield in three steps (entry 1, Table 4). Subsequently, we established that the umpolung reaction tolerated a broad range of aryl and heteroaryl aldimines of varying steric and electronic properties (entries 2–8, Table 4). Electron-rich aryl imines such as 25H appeared to be less active, but the umpolung reaction with C-21c still went to completion with high chemoselectivity, regioselectivity and enantioselectivity.

Owing to the synthetic versatility of the olefin and amine functionalities, chiral alicyclic amines are highly valuable chiral building blocks29. If we could extend the substrate scope to α,β-unsaturated imines 27 (Fig. 3a), the impact of the imine umpolung reactions would be further enlarged. However, the 2-azaallyl anions 28 derived from α,β-unsaturated imines 27 were expected to be even less stable than those derived from arylaldimines30. Furthermore, the conjugation of an azaallyl anion with an olefin renders 32 a more challenging nucleophile from the viewpoint of achieving catalytic control of regioselectivity (Fig. 3a). Gratifyingly, C-21c provided highly selective catalysis to efficiently promote the umpolung reaction of 27A and 8e (entry 1, Table 5). Importantly, the efficiency of C-21c remained undiminished for reactions involving a variety of α,β-unsaturated imines bearing di- and trisubstituted olefins (entries 2–6, Table 5). As alicyclic amines could be readily hydrogenated to the corresponding aliphatic amines (Table 5), these results established this imine umpolung reaction as a useful method for the asymmetric synthesis of both chiral alicyclic and aliphatic amines.

We have identified a new class of tunable chiral phase-transfer catalysts and demonstrated their unique ability to promote C–C bond-forming reactions with 2-azaallyl anions in a highly chemoselective, regioselective, diastereoselective and enantioselective fashion. This discovery releases the potential of imines as nucleophiles, thereby allowing the realization of catalytic asymmetric umpolung reactions of imines, and providing a fundamentally new approach towards chiral amino compounds. With a simple operational protocol and low catalyst loading, this transformation also provides a practical method for organic synthesis.

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