Organocatalysis

N,N-Dialkylhydrazones as Versatile Umpolung Reagents in Enantioselective Anion-Binding Catalysis

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Abstract: An enantioselective anion-binding organocatalytic approach with versatile N,N-dialkylhydrazones (DAHs) as polarity-reversed (umpolung) nucleophiles is presented. For the application of this concept, a highly ordered hydrogen-bond (HB) network between a carefully selected CF₃-substituted triazole-based multidentate HB-donor catalyst, the ionic substrate and the hydrazone in a supramolecular chiral ion-pair complex was envisioned. The formation of such a network was further supported by both experimental and computational studies, which showed the crucial role of the anion as a template unit. The asymmetric Reissert-type reaction of quinolines as a model test reaction chemoselectively delivered highly enantioselectively enriched hydrazones (up 95:5 e.r.) that could be further derivatized to value-added compounds with up to three stereocenters.

The ability to efficiently synthesize enantioselective complex molecules employing simple modes of activation has long been considered an essential goal for asymmetric organocatalysis.[1] Among different approaches, enantioselective anion-binding catalysis,[2] which is based on the activation of an ionic substrate towards nucleophilic attack upon binding the anion by a catalyst and formation of a chiral contact ion pair, has recently emerged as a powerful synthetic tool. Since the pioneering work by Jacobsen et al.[3] using chiral thioureas as hydrogen bond (HB) donor catalysts,[4] many applications have been reported in this field.[5] However, the implied noncovalent interactions for the anion recognition are less directional and more difficult to control than those implying covalent bonds.[6] For this reason, over the last few years there have been tremendous efforts for the design of new and original chiral catalysts[6] with the ability for multiple interactions to effectively spatially locate the reaction partners and, hence, achieve high stereochemical control with challenging reagents.[7] In this context, we have developed a novel family of chiral triazole-based organocatalysts,[8] which present multicoordination sites, great modulating capacity and the flexible structure leading to a more effective fixation of the ionic substrates. In consequence, a highly chirality transfer has been achieved in a number of enantioselective reactions such as nucleophilic deamination of N- and O-heteroarenes.[8,9] In fact, computational studies on the action of these catalysts have recently revealed an interesting role of the anion as bridging motif between the catalyst and polarized nucleophiles to achieve an effective orientation of the reactants.[10] This finding opens new possibilities by the careful choice of appropriate nucleophiles able to interact through H-bonding with the anions of the contact ion-pair complex.

Inspired by the anion-binding properties of ammonium salts through H-bonding with the C–H bonds alpha to the N atom and its reliable use in asymmetric catalysis,[11] we reasoned that N,N-dialkylhydrazones (DAHs) could similarly interact with anions (Figure 1a), providing a more rigid HB network and an efficient stereocontrol with such reagents. Moreover, hydrazones are considered an important building block in organic synthesis since they allow the introduction of a broad variety of functionalities in complex molecules.[12] Particularly, DAHs have acquired increasing interest in the past years due to their amphiphilic behavior at the azomethine carbon.[13] However, despite the versatility of these

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Figure 1. Postulated anion-binding properties and asymmetric organocatalytic umpolung approaches with N,N-dialkylhydrazones (DAHs).
compounds exhibiting umpolung reactivity as nucleophilic reagents, until now only two different activation modes in organocatalysis, H-bonding[14] and chiral counteranion catalysis[14] (Figure 1b), have been efficiently employed.[15] In fact, the use of hydrazones as nucleophiles through an anion-binding strategy to allow for the facile and direct access to enantiomerically enriched adducts (Figure 1c).

In order to evaluate our hypotheses, the enantioselective Reissert-type dearomatization of quinolines was selected as model test reaction (Table 1).[8–10] We started our study by investigating the reaction of quinoline (2a), 2,2,2-trichloroethoxy carbonyl chloride (TrocCl) as acylating agent and the commercially available formaldehyde dimethylhydrazone 3a as nucleophile,[16] in the presence of our most versatile triazole catalyst 1a[18] (10 mol%) in toluene at −78°C (entry 1).

Although it proceeded with a complete regioselectivity to the desired 1,2-addition product 4a, an unexpected low enantioselectivity was observed. Bearing in mind the challenging stereo control with this type of hydrazones, we further envisaged the need of an additional fixation point of the nucleophile to the chiral catalyst. Thus, we replaced the alkyne substitution in 1a for a CF3 group in 1b, aiming at enhancing the catalyst polarization and anion-binding affinity, as well as allowing a new F–H bond between this group at the catalyst and the carbonylic H atom of the formaldehyde hydrazone 3a. As predicted, the enantioselectivity could be increased to 79:21 e.r. (entry 2).

At this point, based on the work of MacMillan and co-workers,[19] we predicted that the use of perfluoroarenes as solvents should disfavor the possible cation π-interactions between the corresponding quinolinium generated in the media and the solvent and, in consequence, an improvement in the enantioselectivity of the process should be observed. In fact, when a mixture of hexafluorobenzene (C6F6) and toluene was employed, the enantiomeric ratio was slightly enhanced to 81:19 e.r., allowing to perform the reaction at 0°C (entry 3). Next, tetrakistriazole catalysts 1c–f bearing different substituents at the aryl moiety were tested, providing good yields but lower enantioselectivities (entries 4–7), which supports the favorable effect of the CF3 substitution at this position. In order to further improve the enantioselectivity, other types of catalysts such as thioureas 1i and squaramide 1j were tested (entries 8–10). However, disappointing results were obtained with these stronger HB donors (<10% ee), which should bind more tightly the chloride anion to form a chiral contact ion pair. Finally, the regioisomeric CF3-tetrakistriazole 1g was investigated since some reports on triazole anion receptors showed higher anion affinities with this type of isomers.[20] This structural change was translated to a further improvement on the enantioinduction, providing 4a in 88:12 e.r. (entry 11), and 92:8 e.r. when only C6F6 was used at room temperature (entry 12). Finally, the use of freshly distilled C6F6 at 4°C gave rise to the best enantiomeric ratio of 94:6 (entry 13).

With the optimized conditions in hand (see SI. for a complete optimization study), catalyst 1g (10 mol%) in C6F6 at 4°C, the substrate scope on the hydrazone 3 was explored (Scheme 1). Symmetrically and nonsymmetrically...
substituted N,N-dialkylhydrazones provided good yields and moderate to good enantioselectivities (4–7,9–11a), while a substantial drop in the yield and a loss of enantioinduction was observed with an aromatic substitution (8a). N-Monoalkyl and C1-substituted hydrazones led to no reactivity or undesired products such as N-Troc- and 1,4-addition adducts, respectively (see S.I.). Moreover, as is shown in the Scheme 1, the substitution on the N atom of the hydrazone affected significantly to the enantioselectivity, which is in line with our hypothesized participation of the N-alkyl groups in the formation of the key chiral contact ion pair. Thus, the replacement of the methyl group for longer alkyl chains (6a) or benzyl (7a), and bulky groups such as iPr (5a) or tBu (11a) led to lower enantioselectivities (70:30–85:15 vs. 94:6 e.r.).

Conversely, the employment of the freshly prepared 1-piperidine and 1-pyrrolidine hydrazones, gave rise the products 9a and 10a with good to excellent enantioselectivities (up to 95:5 e.r.). However, for practical reasons the subsequent investigations were mostly performed with the commercially available dimethyl hydrazone 3a. Thus, the scope on the quinoline substrate 2 was carried out (Scheme 2). First of all, it is worthy to mention that the reaction could be conducted in an up to 2 mmol scale with no significant erosion in the activity or selectivity of the process (4a: 79%, 93:7 e.r.). The substitution at different positions of the quinoline was well tolerated, except for the C3 (4d) and C8 positions (4e) that led to significant lower enantioselectivity or no reaction, respectively. Moreover, the method showed a good functional group compatibility, allowing many groups such as halogens, methoxy, alkyl, alkenyl, alkynyl, nitro, amides or esters to give the products 4f–s and 9b–g, I, n, k, l, m, n (R2′ = (CH2)5) in good to high enantioselectivities (up to 94:6 e.r.). Furthermore, the absolute configuration of the new stereocenter could be determined as (S) upon X-ray structure analysis of the crystalline product 4s.[8] It is especially remarkable the excellent chemoselectivity observed with quinolines substituted with an additional electrophilic species such as an aldehyde or a nitro-Michael acceptor (4t, 9t and 4u). In these cases, the reaction gave exclusively the 1,2-addition product at the quinoline moiety within good enantioselectivities (up to 92:8 e.r.). Remarkably, the reaction also proceeded in the presence of a boronic ester, leading to the product 4v with an 80:20 e.r. Lastly, phenanthridine, a diazarene and less reactive, more challenging pyridines could also be enrolled, leading to the hydrazone products 12–14 in up to 90:10 e.r.

The recyclability and stability of the catalysts was next explored in the prototypical reaction of 2a, showing no degradation of the enantioselectivity up to three runs (Scheme 3, top). Afterwards, the synthetically valuable of the method and versatile chemistry of the products were illustrated by modifications of 4a (Scheme 3, bottom). Hence, the chiral hydrazone could be easily transformed quantitatively upon acid treatment into the corresponding aldehyde 15, maintaining the enantiomeric purity, which was confirmed

Scheme 2. Substrate scope. [a] Result of both 1 and 2 mmol reactions. [b] Reaction in Et2O at –78 °C for 2 days. Yields are for the isolated product.

Scheme 3. Recycling of the catalyst 1g and synthetic applications.
after reduction and cyclization to the cyclic carbamate 16. Moreover, 4a was also converted into the cyanide 17 by treatment with magnesium monoperoxyphthalate (MMPP·6H₂O). The adduct 17 was then reduced to the tetrahydroquinoline 18, as well as further used as a common precursor for the preparation of the corresponding aziridine 19 and epoxide 20 with complete diastereoselectivity and same high e.r., which were opened in a completely regioselective manner with MeOH in acid media to provide highly decorated chiral tetrahydroquinolines (21 and 22) within three stereocenters. Lastly, the possibility of N-Troc group deprotection was demonstrated by treating 22 with Zn/AcOH, leading to the desired NH-free derivative 23.

Lastly, aiming at gaining insight into the key interactions within the catalyst 1g and the mechanism of the reaction, the standard reaction of 2a and TrocCl with hydrazone 3a was investigated in more detail (Figure 2). The monitoring of the reaction course was performed at room temperature in an NMR tube in C₆F₆/[D₈]toluene (4:1) due to solubility issues (Figure 2a, see S.I.). This revealed a fast transformation, requiring just 1 h to reach 4a in approximately 60% yield (6 h, 76%) and 5 min or less for the final enantioselectivity of 92:8 e.r. Moreover, the chloride anion affinity of the catalyst 1g was determined by NMR titration with tetrabutylammonium chloride (TBACl) as chloride source in a constant [2 mM] of 1g (see S.I. for details). As predicted, the central CF₃ groups boosted the affinity to approximately 3100 M⁻¹ (and ca. 1875 M⁻¹ for its regioisomer 1b vs. ca. 500 M⁻¹ for 1a).¹⁰ Based on that, a plausible mechanism considering the formation of a tight catalyst:substrate contact ion pair complex is shown in Figure 2b. Hence, the real substrate quinolinium salt I is formed in situ by treatment of 2a with TrocCl. This species forms a chiral contact ion pair II with the catalyst 1g. Then, the nucleophilic attack of the hydrazone 3a delivers the intermediate III, which provides the final product upon deprotonation by Cl⁻ or another molecule of 3a, with concomitant formal elimination of HCl and regeneration of the catalyst 1g. Finally, the transition state (TS) of the reaction was computed at DFT-B3LYP/GD3BJ/def2tzvp//AM1 level of theory including the solvent effect (C₆F₆) with COSMOS-RS at BP86/def2tzvp (Figure 2c, see S.I. for more details). The 1g:Cl⁻ complex in I is stabilized by four HBs between Cl⁻ and the C–H bonds of the central triazoles and arenes. Moreover, the approach of the nucleophile 3a is directed by a F–H bond between a CF₃ group of 1g and a carbonyl H of 3a. In the TS, however, only one arms of the catalyst participates in the HB interactions with Cl⁻, while additional stabilization through F–H bonds is suggested.

Figure 2. a) Reaction monitoring and binding constant for 1g:Cl⁻, b) proposed mechanism, and c) computed TS for the model reaction of 2a with 3a in C₆F₆ at room temperature (zoom-in: F–H (red), CH–Cl (black), and Cl–π interactions (blue); new C–C bond (gray)). See the Supporting Information for details.

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with the CF$_3$ group and both the substrate and 3a, as well as a Cl–π interaction between the Troc group and the other arm of the catalyst, takes place. The nucleophilic addition involves a small barrier of 2.7 kcal mol$^{-1}$, leading to the more stable intermediate III (–13.5 kcal mol$^{-1}$) that further evolves to the final product 4a. Moreover, the H-bonding network and preorganization in the TS explained a more favorable Si-face attack and the observed absolute configuration (S) of the product.

In conclusion, an enantioselective umpolung nucleophilic addition of formaldehyde product. The use of the catalyst, takes place. The nucleophilic addition involves a Cl– ion on the hydrazone is also crucial, since it participates in the HB network in the TS to fix the reagent. Further catalytic strategies based on such anion-templated HB assemblies are currently being investigated in our group.

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Conflict of interest

The authors declare no conflict of interest.

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