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COMMUNICATION

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

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Dedication ((optional))

Abstract: A novel enantioselective anion-binding organocatalytic approach with versatile *N*,*N*-dialkylhydrazones (DAHs) as umpolung nucleophiles is presented. For the application of this concept, a highly ordered hydrogen bond network between a carefully selected CF_3-substituted triazole-based multidentate HB-donor catalyst, the ionic substrate and the hydrazone in the supramolecular chiral ion pair complex was herein envisioned. This was further supported by both experimental and computational studies, showing the crucial role of the anion as template unit. The asymmetric Reissert-type reaction of quinolines has been selected as model test reaction, delivering chemoselectively high enantiomerically enriched hydrazones (up 95:5 e.r.) that can easily 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.[2] However, the implied non-covalent interactions for the anion recognition are less directional and more difficult to control than those implying covalent bonds.[5] 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 dearomatization 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 via H-bonding with the anions of the contact ion-pair complex.

Inspired by the anion-binding properties of ammonium salts via 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 compounds as umpoled nucleophilic reagents, until now only two different activation modes in organocatalysis, *H-bonding*[4] and *chiral counteranion catalysis*[14] (Figure 1b), have been efficiently employed.[15] In fact, the use of hydrazones as nucleophiles through an anion-binding activation approach has only been recently envisioned.[16] Hence, we herein report on the first use of DAHs as suitable umpoled nucleophiles for anion-binding catalysis by embracing an anion-bridging strategy to allow for the facile and direct access to enantiomerically enriched adducts (Figure 1c).

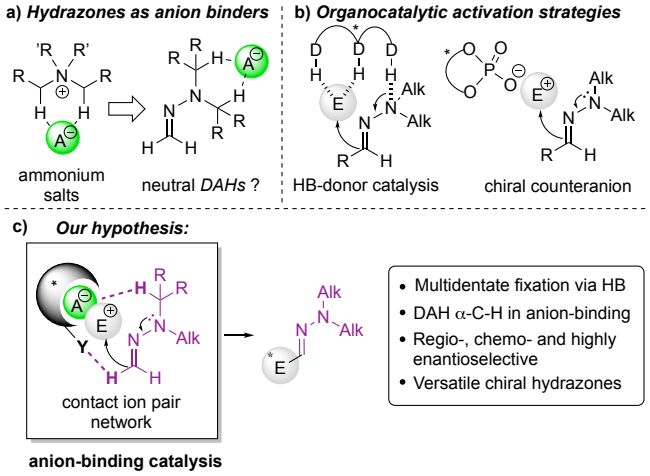

Figure 1. Postulated anion-binding properties and asymmetric organocatalytic approaches with umpoled *N,N*-dialkylhydrazones (DAHs).

In order to evaluate our hypotheses, the enantioselective Reissert-type dearomatization of quinolines was selected as model test reaction (Table 1).[8],[17] We start our study by

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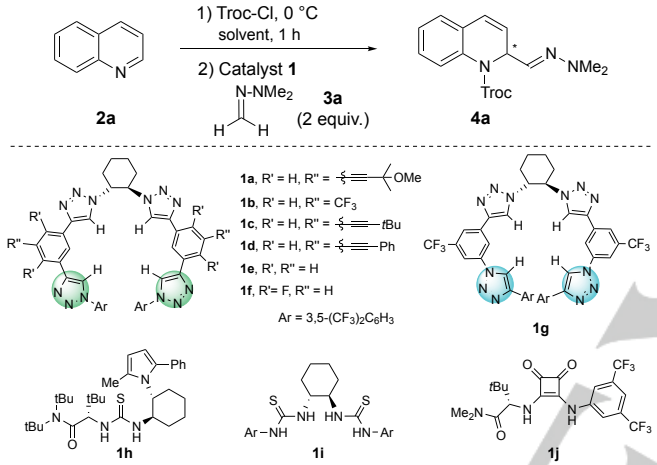
investigating the reaction of quinoline (**2a**), 2,2,2-trichloroethoxycarbonyl chloride (TrocCl) as acylating agent and the commercially available formaldehyde dimethylhydrazone **3a** as nucleophile,[18] in the presence of our most versatile triazole catalyst **1a**[8-10] (10 mol%) in toluene at -78 ºC (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 stereocontrol 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 CF_3 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).

Table 1. Optimization screening for the model reaction with **2a**[a]

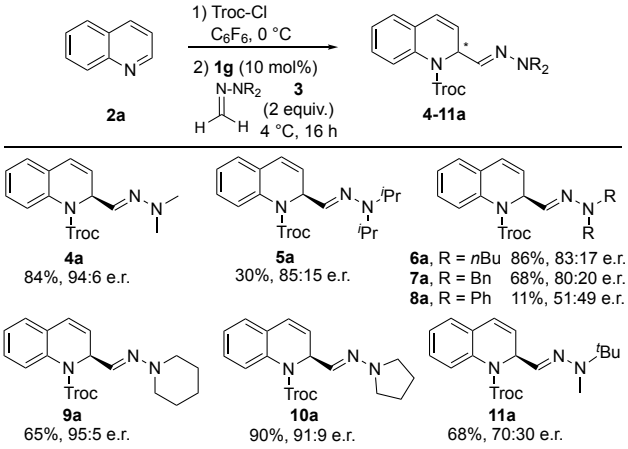


Ent.	**1** (mol%)	Solvent	T (°C)	Yield (%)[b]	e.r.[c]
1	**1a** (10)	Toluene	-78	74	65:35
2	**1b** (10)	Toluene	-78	87	79:21
3	**1b** (10)	Tol/C_6F_6 (3:1)	0	79	81:19
4	**1c** (10)	Tol/C_6F_6 (3:1)	0	76	63:37
5	**1d** (10)	Tol/C_6F_6 (3:1)	0	88	72:28
6	**1e** (10)	Tol/C_6F_6 (3:1)	0	87	74:26
7	**1f** (10)	Tol/C_6F_6 (3:1)	0	69	51:49
8	**1h** (10)	Tol/C_6F_6 (3:1)	0	79	50:50
9	**1i** (10)	Tol/C_6F_6 (3:1)	0	79	52:48
10	**1j** (10)	Tol/C_6F_6 (3:1)	0	92	51:49
11	**1g** (10)	Tol/C_6F_6 (3:1)	0	90	88:12
12	**1g** (10)	C_6F_6	rt	75	92:8[d]
13	**1g** (10)	C_6F_6	4	84	94:6[d]
14	**1g** (5)	C_6F_6	4	72	87:13[d]
15	**1g** (10)	C_6F_6	4	80	92:8[d,e]

[a] Conditions: **2a** (1 equiv.) and TrocCl (1 equiv.) were stirred in the corresponding solvent (0.1 M) at 0 °C for 1 h; then the catalyst **1** and **3a** (2 equiv.) were added at the appropriate temperature and reacted overnight. [b] Isolated yields. [c] e.r. determined by chiral SFC. [d] Reaction using dried C_6F_6 over 4Å MS and freshly distilled **2a** and **3a**. [e] Reaction performed in 0.05 M.

At this point, based on the work of MacMillan *et al.*,[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 (C_6F_6) and toluene was employed, the enantiomeric ratio was slightly enhanced to 81:19 e.r., allowing to perform the reaction at 0 ºC (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 CF_3 substitution at this position. In other to further improve the enantioselectivity, other types of catalysts such as thioureas **1h-i** and squaramide **1j** were tested (entries 8-10). However, disappointing results were obtained with these stronger HB-donors (<10% e.e.), which should bind more tightly the chloride anion to form a chiral contact ion pair. Finally, the regioisomeric CF_3-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 C_6F_6 was used as r.t. (entry 12). Finally, the use of freshly distilled C_6F_6 at 4 ºC gave rise to the best enantiomeric ratio of 94:6 (entry 13).

With the optimized conditions in hand (see S.I. for a complete optimization study), catalyst **1g** (10 mol%) in C_6F_6 at 4 °C, the substrate scope on the hydrazone **3** was explored (Scheme 1). Symmetrically and non-symmetrically substituted *N,N*-dialkyl-hydrazones 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 linear alkyl chains (**6a**) or benzyl (**7a**), and bulky groups such as *i*-Pr (**5a**) or *t*-Bu (**11a**) led to lower enantioselectivities (70:30 – 85:15 vs. 94:6 e.r.*)*.



Scheme 1. Screening of the substitution on the hydrazone **3**.

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

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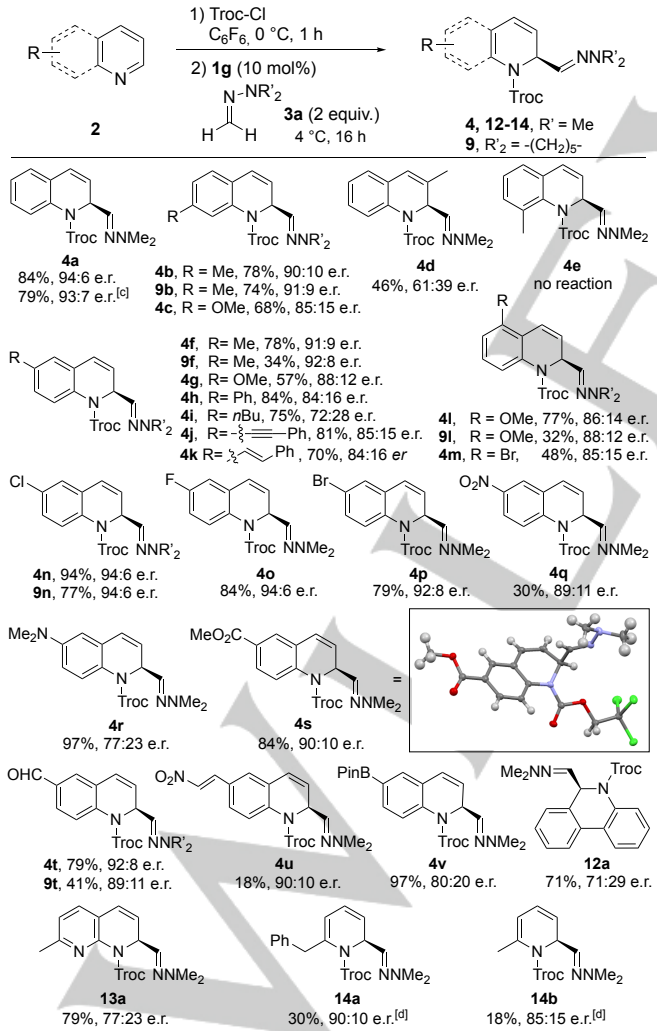
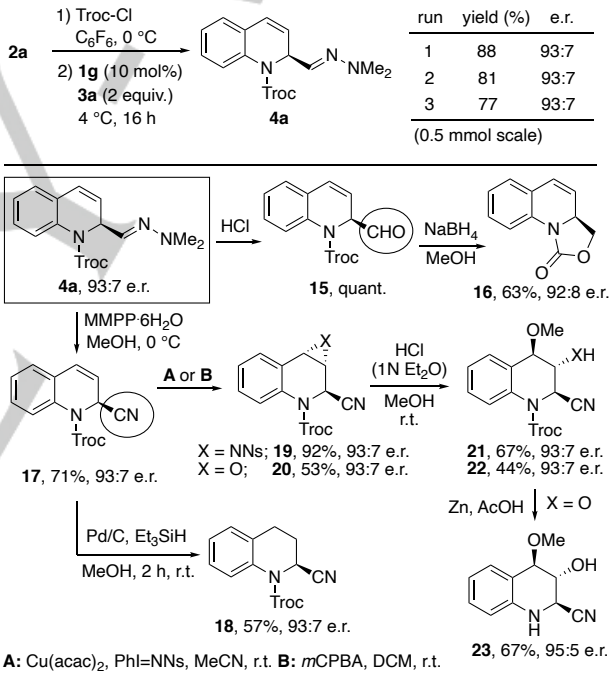
available dimethyl hydrazone **3a**. Thus, the scope on the quinoline substrate **2** was carried out (Scheme 2). First of all, it is worthy to mention that the reaction could be conducted in an up to 2 mmol scale with no significant erosion in the activity or selectivity of the process (**4a**; 79%, 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,l,n** (R'_2= $(CH_2)_5$) 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**.[21] 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.



[a] Standard conditions. [b] Isolated yields. [c] Result of both 1 and 2 mmol scale reactions. [d] Reaction in Et_2O at -78 °C for 2 days.

Scheme 2. Substrate scope.[a,b]

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 value 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 after reduction and cyclization to the cyclic carbamate **16**. Moreover, **4a** was also converted into the cyanide **17** by treatment with magnesium monoperoxyphthalate (MMPP•$6H_2O$). The adduct **17** was then reduced to the tetrahydoquinoline **18**, as well as further used as 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 tetrahydoquinolines (**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**.



Scheme 3. Recycling of the catalyst **1g** and synthetic applications.

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 C_6F_6/toluene-d_8 (4:1) due to solubility issues (Figure 2a, see S.I.). This revealed a fast transformation, requiring just 1 h to reach **4a** in ~60% yield (6 h, 76%) and ≤5 min 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 CF_3 groups boosted the affinity to ~3100 M^{-1} (and ~1875 M^{-1} for its regioisomer **1b** vs. ~500 M^{-1} for **1a**).[10] Based on that, a plausible mechanism considering the formation of a tight catalyst:substrate contact ion

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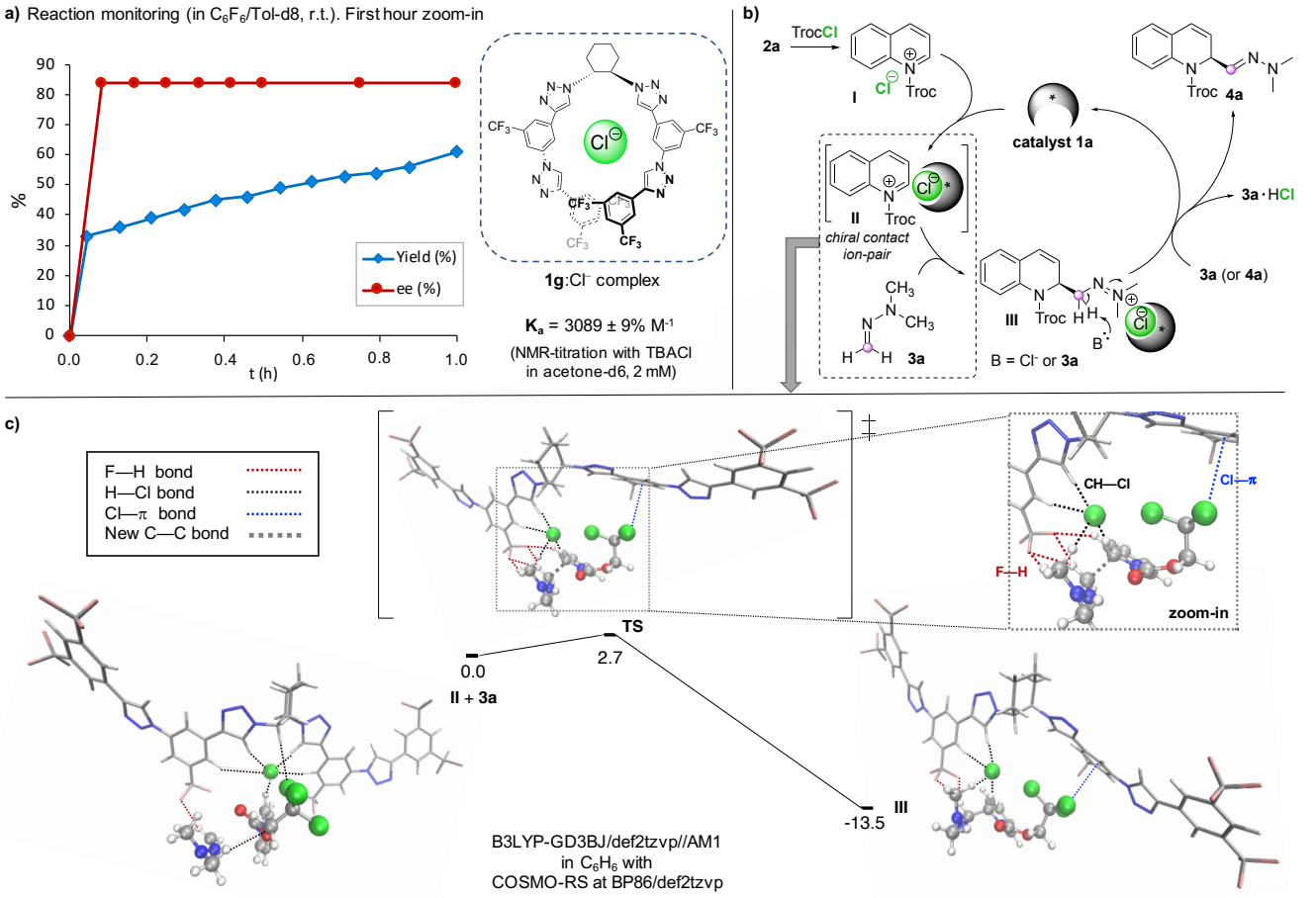

Figure 2. a) Reaction monitoring and binding constant for **1g**:Cl⁻,[22] b) proposed mechanism, and c) computed **TS** for the model reaction of **2a** with **3a** in C_6F_6 at r.t.. Zoom-in: F–H (red), CH–Cl (black), and Cl–π interactions (blue); new C–C bond (grey). See S.I. for details.

pair complex is shown in Figure 2b. Hence, the real substrate quinolinium salt **I** is formed *in situ* by treatment of **2a** with TroCl. 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**.[18] Finally, the transition state (**TS**) of the reaction was computed at DFT-B3LYP[23]-GD3BJ[24]/def2tzvp[25]//AM1[26] level of theory including the solvent effect (C_6F_6) with COSMOS-RS[27] at BP86[28]/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 CF_3 group of **1g** and a carbonyl H of **3a** (see weakly bounded **II**···**3a**). In the **TS**, however, only one arms of the catalyst participates in the HB-interactions with Cl^-, while additional stabilization via F–H bonds 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 pre-orientation in the **TS** explained a more favorable *Si*-face attack and the observed absolute configuration (*S*) of the product.

In conclusion, an enantioselective nucleophilic addition of umpoled formaldehyde *N,N*-dialkylhydrazones to quinolinium chloride salts embracing a novel catalytic anion-binding approach has been developed. The synthetic versatility of the method was also demonstrated by derivatization of the obtained chiral hydrazones into value-added heterocyclic compounds with up to three stereocenters. The use of a multidentate triazole-based H-donor as catalyst bearing CF_3 groups in the central aromatic units allows for the formation of a supramolecular tight chiral contact ion pair complex by a highly ordered HB-network between the catalyst, ionic substrate and nucleophilic hydrazone to ensure a high enantioselectivity even at room temperature. Based on experimental and computational observations, the chloride anion has an important role as it acts as junction between all components of the reaction. Moreover, the nature of N-alkyl group 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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Keywords: Hydrazones • Umpolung • Anion-binding catalysis • Enantioselective catalysis • Heterocycles

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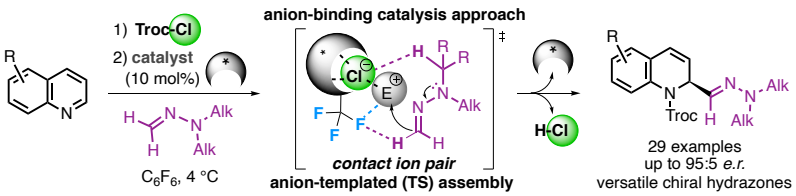

Networking for success! Umpoled *N,N*-dialkylhydrazones have been identify for the first time as versatile nucleophiles with multiple-networking ability for self-assembled chiral contact ion pair complexation in enantioselective anion-binding catalysis, leading to a highly ordered non-covalent interactions network with the anion as central template motif that allows high enantiomeric inductions in a model Reissert-type reaction with quinolines.