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Organocatalysis

Chiral Triazoles in Anion-Binding Catalysis: New Entry to Enantioselective Reissert-Type Reactions

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Abstract: Easily accessible and tunable chiral triazoles have been introduced as a novel class of C–H bond-based H-donors for anion-binding organocatalysis. They have proven to be effective catalysts for the dearomatization reaction of different N-heteroarenes. Although this dearomatization approach represents a powerful strategy to build chiral heterocycles, to date only a few catalytic methods to this end exist. In this work, the organocatalyzed enantioselective Reissert-type dearomatization of isoquinoline derivatives employing a number of structurally diverse chiral triazoles as anion-binding catalysts was realized. The here presented method was employed to synthesize a number of chiral 1,2-dihydroisoquinoline substrates with an enantioselectivity up to 86:14 e.r. Moreover, a thorough study of the determining parameters affecting the activity of this type of anion-binding catalysts was carried out.

Introduction

In the last few years, asymmetric hydrogen-bonding organocatalysis has emerged as a powerful synthetic tool.[1] Hydrogen-bond donor catalysts, predominantly (thio)urea[2] or squaramide[3] structures, can act as weak Lewis acids, activating the basic sites of a neutral substrate such as carbonyl or imine moieties by establishing intermolecular hydrogen bonds.[4] Lately, this H-bonding activation approach has evolved into a new class of process, the so-called anion-binding catalysis, which allows the activation of electrophilic ionic substrates by coordination to their counter anions.[5] Among the possible target applications for developing enantioselective anion-binding catalysis, the dearomatization of N-heteroarenes constitutes an interesting synthetic strategy.[6] Thus, chiral nitrogen-containing heterocycles, widely present in pharmaceuticals and biological natural products, can be built in one synthetic step from abundant, economic and commercially available heteroarenes. To date, there are only a few catalytic asymmetric methods for this purpose.[7] A very useful and common strategy is based on the Reissert reaction. It consists of the activation of the N-heteroarene employing an acylating (such as acyl chloride or chloroformate, RCOCl) or alkylating agent to generate the corresponding N-acyl or N-alkyl iminium species **A**. This ionic intermediate is then susceptible to react with a nucleophile, generating a new stereocenter with consequent loss of the aromaticity (Scheme 1).[8] In early reports, the enantioselectivity was achieved through the use of a chiral auxiliary.[9] The first enantioselective catalytic Reissert reaction was reported in 2000 by Shibasaki et al.[10] A chiral aluminum Lewis acid was employed as catalyst for the addition of cyanide to an N-acyl quinolinium or isoquinolinium derivative (Scheme 1, [Eq. (1)]).[10] More recently, the first enantioselective organocatalytic N-acyl Mannich reaction of isoquinolines ("Reissert-type reaction") was reported by the group of Jacobsen, employing thioureas as anion-binding organocatalysts (Scheme 1, [Eq. (2)]).[11]

After this pioneering work in anion-binding catalysis with thioureas, other types of compounds such as thiophosphoramides (also based on N–H bonds),[12] silanediols (based on O–H bonds),[13] or the 1,2,3-triazole-based structures (based on C–H bonds) recently developed in our research group[14,15] have been introduced as alternative potent anion-binding organocatalysts.

We focused our attention on the use of triazoles for the development of a new type of anion-binding catalysts due to their unique structural features: i) 1,2,3-triazoles are easily accessible via click chemistry by the Cu^{I}-catalyzed azide–alkyne cycloaddition (CuAAC) reaction,[16] and ii) the triazole unit presents a highly polarized C–H bond that allows the binding of anions by hydrogen bonding.[17] The large dipole moment ($\mu = 4.3$–4.6 D), almost aligned with the C5–H bond,[18] in combination with the relatively high acidity of this position ($pK_{a(DMSO)} = 27$–28, for the 1*H*-tautomer)[19] makes 1,2,3-triazoles

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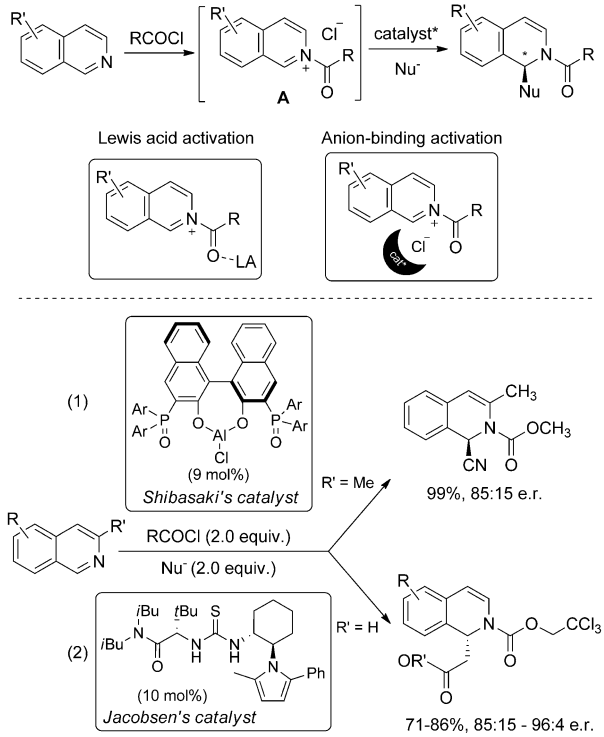


Scheme 1. The Reissert-type approach for the catalytic asymmetric dearomatization of isoquinolines as model N-heteroarenes and early reports.

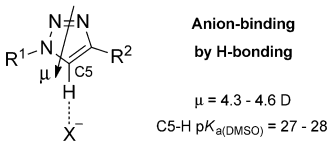
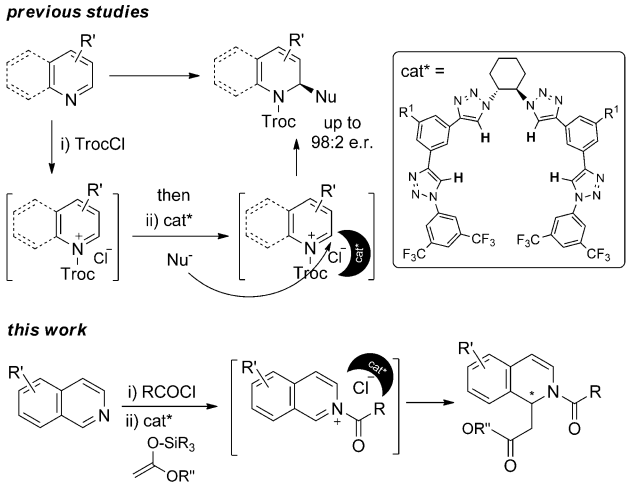


Figure 1. 1,2,3-Triazoles as anion-binding motifs.

extremely good candidates as hydrogen bond donors (Figure 1). Thus, strong hydrogen bonds, as for the inherently more polarized N–H and O–H groups, can be reached by a cooperative use of this type of C–H bonds.[20]

Although the anion-binding ability of triazoles, especially oligo-triazoles, has been well recognized,[21] we have recently employed them for the first time as a new class of anion-binding organocatalysts.[14,15] Thus, highly enantioselective dearomatization of quinolines[15a] and pyridines[15b] has been developed (up to 98:2 e.r., Scheme 2). The triazole-based organocatalysts showed an effective binding to a chloride counter anion, generating a chiral chloride–catalyst complex. This species, a chiral bulky anion, can form a contact ion-pair with the N-acyl iminium substrate, allowing an efficient chiral transfer to the final product. To get a deep insight into the reaction requirements and the action of the organocatalysts, we decided to further explore the activity of our triazole-based organocatalysts in a model dearomatization reaction. Herein, we report the synthesis of novel triazole-based anion-binding catalysts and an extensive study of their catalytic activity in the Reissert-type dearomatization reaction of isoquinolines. (Scheme 2, bottom).

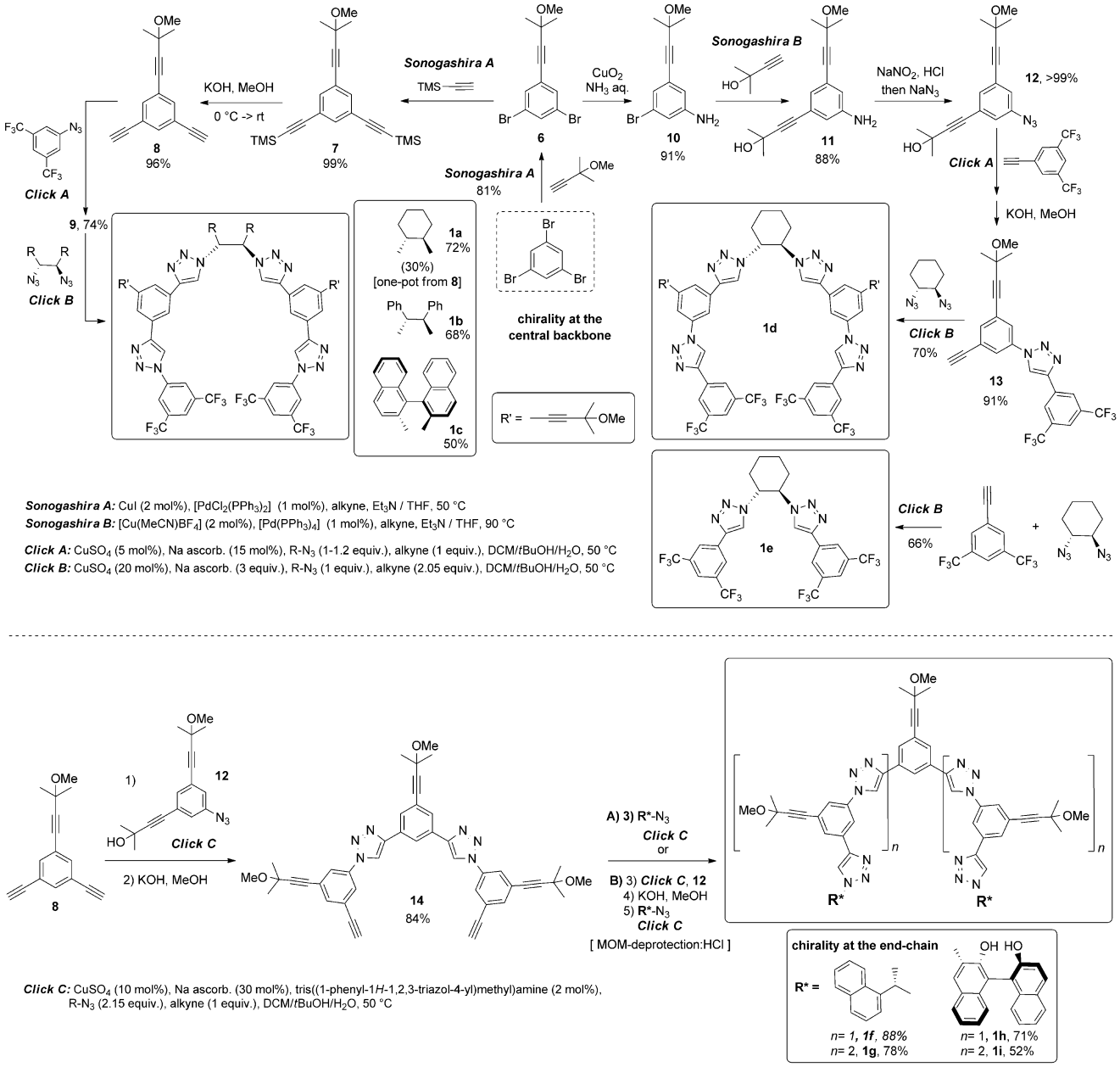


Scheme 2. Reissert-type dearomatization of N-heretoarenes with triazole-based anion-binding catalysts.

Results and Discussion

Synthesis of the triazole-based catalysts

Aiming at the development of a highly enantioselective dearomatization of N-heteroarenes with C–H-based H-donors, a family of chiral triazole-based catalysts was initially developed. We designed the synthesis of the triazole catalysts by iterative Sonogashira couplings, followed by CuAAC reactions to incorporate the triazole moieties to the structure. To explore the effect of the location of the chiral information in the catalyst structure on the later chiral transfer to the products, various catalysts bearing the chirality at the central backbone (**1a–e**)[15] and at the end-chain (**1f–i**) were synthesized (Scheme 3). For the catalysts with chirality at the central backbone (Scheme 3, top), the synthesis started from cheap and commercially available 1,3,5-tribromobenzene, which was mono-alkynylated to form **6**. Alternatively to the previous described synthesis of **1a**,[15] catalysts **1a–c** could also be prepared by a further double Sonogashira reaction with trimethylsilylacetylene, deprotection of the TMS group and desymmetrization via CuAAC reaction with 3,5-ditrifluoromethylphenyl azide. A final CuAAC reaction with the corresponding chiral 1,2-diamine delivered **1a–c** in good yields (50–72%). Interestingly, **1a** could also be obtained from dialkyne **8** in a one-pot process implying two sequential click cycloaddition reactions. However, the overall yield was significant lower (30%/2 steps from **8**; 41 vs. 23% overall yield). On the other hand, the synthesis of the regioisomer **1d** required an initial desymmetrization of **6** to form the amine **10**. Next a Sonogashira coupling, following by a diazotization/substitution with NaN_3 to generate the alkyne–azide **12** was performed. Lastly, a CuAAC reaction, the deprotection of the alkyne group and a final click cycloaddition with (1*R*,2*R*)-diazidocyclohexane provided **1d** in good yield (41% overall yield). The synthesis of the triazoles **1f–i** with chirality at the end-chain was similarly carried out. Consequently, good yields were obtained from the common alkyne **8** and azide **12** precursors as shown in Scheme 3 (bottom). From the same in-



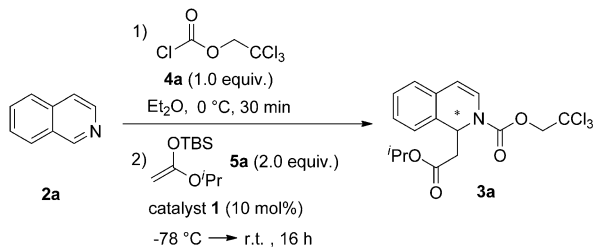
Scheme 3. Synthesis of the triazole organocatalysts bearing the chirality at the central backbone (top) and at the end-chain (bottom).

termediate **14**, the tetrakistriazoles **1f** and **1h** were generated by a CuAAC reaction with the corresponding chiral azide, while the hexakistriazoles **1g** and **1i** required a previous chain extension. Thus, an additional click cycloaddition with **12**, alkyne deprotection and final CuAAC was performed. In the case of the BINOL-containing catalysts, the coupling reactions were made with the MOM-protected derivatives, followed by a final deprotection under acidic conditions.

Enantioselective N-acyl Mannich reaction of isoquinolines

The performance of the triazole catalysts **1** was firstly explored in the asymmetric dearomatization of isoquinoline (**2a**) (Table 1). We started our study by employing the standard screening conditions initially reported by Jacobsen for the same substrate (2,2,2-trichloroethyl chloroformate (TrocCl) as acylating agent, silyl ketene acetal **5a** as nucleophile in Et_2O at $-78\,^{\circ}C$, and slow warming up to room temperature over 16 h). Although in an earlier work a low rate background reaction was reported (12% yield),[13] we surprisingly observed that in the blank reaction under these conditions a relatively strong background process was taking place (44%, entry 1). This shows a remarkable difference between the N-acyl isoquinoline substrates and the previous studies, especially with the N-acyl pyridines. Thus, isoquinolines present a higher intrinsic reactivity towards the attack of a nucleophile at the α-position, making it more challenging to accomplish high enantioselectivities.

Table 1. Screening of the triazole-catalysts.[a]



Entry[a]	Catalyst	Yield [%][b]	e.r.[c]
1	–	44	50:50
2	**1a**	79	68:32
3	**1b**	84	66:34
4	**1c**	68	56:44
5	**1d**	84	69:31
6	**1e**	83	47:53
7	**1f**	69	64:36
8	**1g**	69	49:51
9	**1h**	91	55:45
10	**1i**	68	50:50

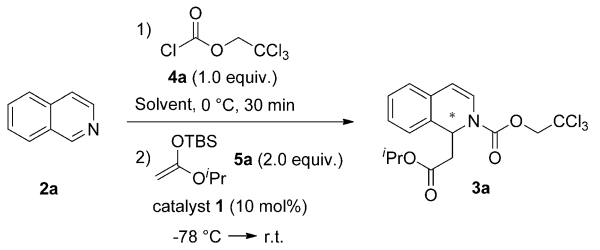
[a] Conditions: i) **2a** (1.0 equiv) and TrocCl **4a** (1.0 equiv) in Et_2O at 0 °C, 30 min; then ii) at −78 °C, catalyst (10 mol%) and **5a** (2.0 equiv) were added and stirred for 16 h, while allowing warming up slowly to room temperature. [b] Isolated yield. [c] Enantiomeric ratios determined by chiral HPLC.

Considering this key issue and the excellent performance of **1a** with the other N-heteroarenes (quinolines, up to 98:2 e.r.; pyridines, up to 99:1 e.r.), we next studied our triazole catalysts possessing the chirality at the central backbone (**1a**–**e**) (entries 2–6). The tetrakistriazole catalysts derived from 1,2-cyclohexanediamine **1a** and **1d** led to good enantioselectivities, 68:32 e.r. and 69:31 e.r., respectively (entries 2 and 5). Furthermore, the catalyst derived from the 1,2-diphenyldiamine **1b** provided an inferior chiral induction (66:34 e.r., entry 3), whereas the BINAM derivative **1c** led to an almost racemic product (56:44 e.r., entry 4). Moreover, the bistriazole **1e** was also studied (entry 6), leading to a poor inverse enantioselectivity of 47:53 e.r. These results indicate that the central chirality at the backbone is not the only and principal element involved in the chirality transfer, showing that four triazoles are required to have a cooperative effect for the effective chloride anion binding and enantioinduction.

Afterwards, the reaction with the triazole structures presenting the chiral unit at the end-chain derived from (*S*)-methylnaphthyl azide or 2-azido BINOL was conducted. However, these catalysts led to lower enantioselectivities compared to the previous ones. Thus, the tetrakistriazoles (**1f** and **1h**) provided low to moderate enantioselectivities (entries 7 and 9), whereas the hexakistriazoles (**1g**, **1i**) led to no appreciable enantioinduction (entries 8 and 10). Despite the disappointing results, these experiments provided valuable information, confirming that four is the optimal number of triazoles in the catalyst. This could be explained by a less localized and effective binding of the chloride anion by the more flexible hexakistriazoles, which might allocate more anions in a non-specific manner.

Being aware of the strong solvent effect in reactions proceeding through a charged intermediate, we considered investigating different solvent systems with the best two catalyst structures, **1a** and its triazole regioisomer **1d** (Table 2). The use of methyl *tert*-butylether (MTBE) instead of Et_2O was beneficial,

Table 2. Solvent and catalyst loading screening.[a]



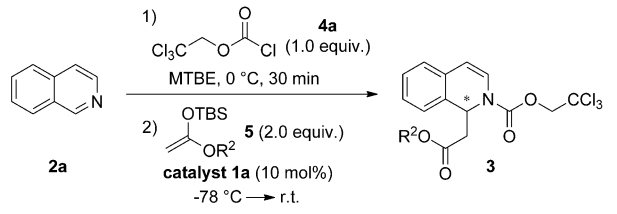
Entry[a]	Catalyst (mol%)	Solvent	Yield [%][b]	e.r.[c]
1	**1a** (10)	MTBE	79	75:25
2	**1a** (10)	MTBE	75	75:25[d]
3	**1a** (5)	MTBE	76	70:30
4	**1d** (10)	MTBE	74	78:22
5	**1d** (5)	MTBE	64	69:31
6	**1d** (10)	THF	38	52:48
7	**1d** (10)	toluene	61	57:43
8	**1d** (10)	DCM	77	54:46

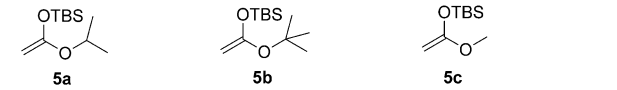
[a] Conditions: i) **2a** (1.0 equiv) and TrocCl (1.0 equiv) in the corresponding solvent at 0 °C, 30 min; then ii) at −78 °C, catalyst and **4** (2 equiv) were added and stirred for 16–17 h, while allowing warming up slowly to room temperature. [b] Isolated yield. [c] Enantiomeric ratios determined by chiral HPLC. [d] Reaction at −78 °C for 24 h.

providing the product **3a** in higher enantiomeric ratios (entries 1 and 4). Additionally, the use of THF, DCM, or toluene as solvents led to a drastic drop of the enantioinduction. It could also be observed that the reaction at −78 °C gave the same enantiomeric excess obtained as when, after the addition of the catalyst and nucleophile, the reaction was allowed to warm up to room temperature (entry 2 vs. 1). Therefore, for practical reasons only the addition of the catalyst and nucleophile was conducted at −78 °C. As expected, a reduction of the catalyst loading from 10 to 5 mol% led to a decrease of the enantioselectivity (entries 3 and 5).

From the previous screenings, catalysts **1a** and **1d** provided **3a** with a similar enantioselectivity (75:25 and 78:22 e.r., entries 1 and 4, respectively). Although **1d** showed a slightly better enantioselectivity in MTBE, **1a** was chosen as the catalyst for the optimization of the nucleophile and acylating agent. Thus, the effect of the nucleophile substitution on the enantioselectivity of the reaction was then studied by varying the initial isopropyl group at the oxygen in the silyl ketene acetals **5** (Table 3). An increase of the steric hindrance with a *tert*-butyl substituent (**5b**) did not improve the initial enantioselectivity, providing a similar result (73:27 vs. 75:25 e.r.). On the other hand, the use of a less demanding methyl group in **5c** led to the corresponding addition product **3c** in a significantly lower enantioinduction (67:33 e.r.).

Table 3. Screening of the nucleophile **5**.[a–c]





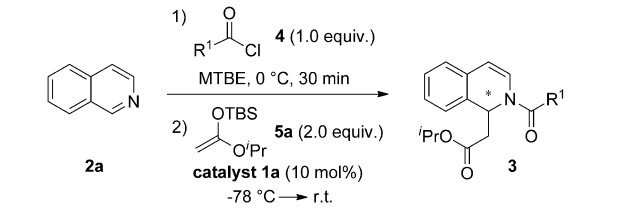
3a, 79%,75:25 e.r. **3b**, 93%, 73:27 e.r. **3c**, 99%, 67:33 e.r.

[a] Conditions: i) **2a** (1.0 equiv) and TrocCl **4a** (1.0 equiv) in MTBE at 0 °C, 30 min; then ii) at −78 °C, **1a** (10 mol%) and **5** (2.0 equiv) were added and stirred for 16 h, while allowing warming up slowly to room temperature. [b] Isolated yields. [c] Enantiomeric ratios determined by chiral HPLC.

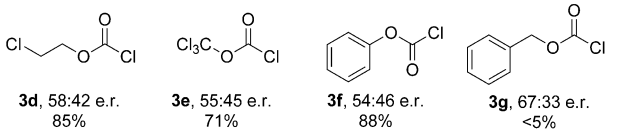
Considering the better performance of the isopropyl silyl ketene acetal **5a**, this nucleophile was employed for the rest of the study. Then, different acylating agents were subsequently tested (Table 4). First, several chloroformates were investigated to determine the importance of the 2,2,2-trichloroethyl group of the Troc moiety. Low enantioselectivities were observed with the related 2-chloroethyl carbonochloridate (**3d**), presenting only one chlorine, or the trichloromethyl carbonochloridate (**3e**), in which the CCl_3 group is directly bonded to the oxygen atom. A similar disappointing result was obtained with benzoyl chloride (**3f**). On the other hand, when the phenyl substituent was placed slightly further away (**3g**), like for the CCl_3 group in the Troc, the enantioselectivity improved. However, the reactivity was almost suppressed (67:33 e.r., <5% yield). A variety of acyl chlorides were also tested, but they gave poor enantioselectivities. All these observations showed the great influence of the acylating agent on both the reactivity and the enantioselectivity of the process. Thus, the use of TrocCl appears to be key for inducing a high enantioselectivity. It seems that a carbamoyl group with a bulky group at the β position is required. Moreover, the unique behavior of the Troc group could also be attributed to possible additional positive weak interactions, such as Cl–π or halogen–halogen,[22] with the isoquinolinium intermediate and the catalyst–chloride complex. This might then assist in the fixation and orientation of the substrate in the chiral contact ion-pair prior attack of the nucleophile.

Having identified the optimal reaction conditions, (use of TrocCl as acylating reagent, **5a** as nucleophile, and 10 mol% of the catalyst in MTBE as solvent at −78 °C to room temperature), a number of isoquinolines with various substitution patterns were explored in the presence of the most efficient catalyst **1d** (Table 5). Different bromo-substituted isoquinolines were initially examined. Good enantioselectivity values were obtained with the 4-bromo (**3l**) and 5-bromo derivatives (**3m**) (81:19 and 82:18 e.r., respectively), whereas a slightly lower se-

Table 4. Screening of the acylating reagent **4**.[a–c]

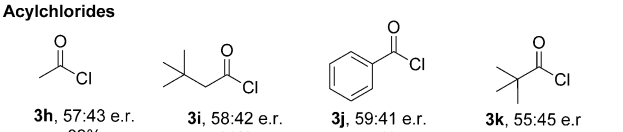


Chloroformates



3d, 58:42 e.r. 85% **3e**, 55:45 e.r. 71% **3f**, 54:46 e.r. 88% **3g**, 67:33 e.r. <5%

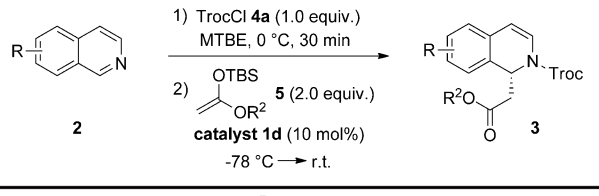
Acylchlorides

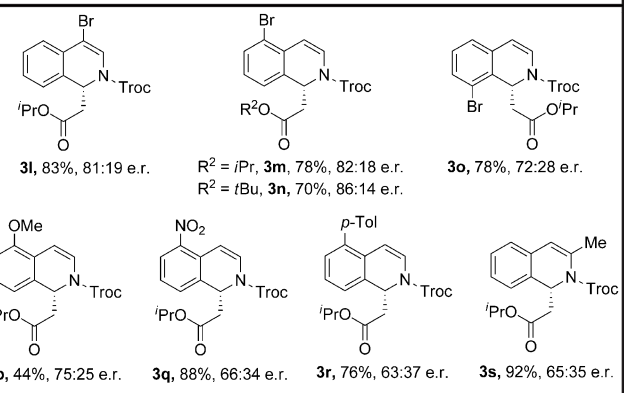


3h, 57:43 e.r. 82% **3i**, 58:42 e.r. 60% **3j**, 59:41 e.r. 86% **3k**, 55:45 e.r <5%

[a] Conditions: i) **2a** (1.0 equiv) and **4** (1.0 equiv) in MTBE at 0 °C, 30 min; then ii) at −78 °C, **1a** (10 mol%) and **5a** (2.0 equiv) were added and stirred for 16 h, while allowing warming up slowly to room temperature. [b] Isolated yields. [c] Enantiomeric ratios determined by chiral HPLC.

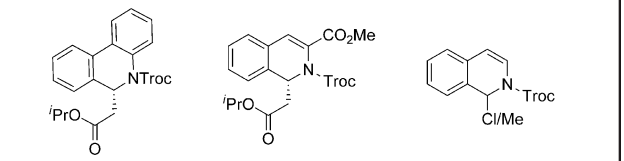
Table 5. Screening of the substrate scope.[a–c]





3l, 83%, 81:19 e.r. R^2 = *i*Pr, **3m**, 78%, 82:18 e.r. R^2 = *t*Bu, **3n,** 70%, 86:14 e.r. **3o,** 78%, 72:28 e.r.

3p, 44%, 75:25 e.r. **3q,** 88%, 66:34 e.r. **3r,** 76%, 63:37 e.r. **3s,** 92%, 65:35 e.r.

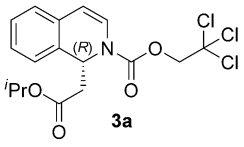


3t, 70%, 84:16 e.r. **3u**, no reaction **3v/3w**, no reaction

[a] Conditions: i) **2a** (1.0 equiv) and TrocCl **4a** (1.0 equiv) in MTBE at 0 °C, 30 min; then ii) at −78 °C, **1d** (10 mol%) and **5** (2 equiv) were added and stirred for 16–17 h, while allowing warming up slowly to room temperature. [b] Isolated yields. [c] Enantiomeric ratios determined by chiral HPLC.

lectivity was observed for the 8-bromo-substituted isoquinoline (**3o**, 72:28 e.r.). The use of the bulkier *tert*-butyl ketene acetal **5b** led to a slight increase of the enantiomeric ratio, giving **3n** with 86:14 e.r. The introduction in the 5-position of an electron-donating group such as methoxy or a bulkier aryl group, as well as a strong electron-withdrawing group such as nitro was well tolerated. However, the more electron-rich derivative (**3p**, 75:25 e.r.) led to a significantly better level of enantioselectivity compared to the more sterically hindered *p*-tolyl-substituted (**3r**) or the electron-poor derivatives (**3q**). Methyl substitution at the 3-position led to a notable decrease of the enantioselectivity, (**3s**, 65:35 e.r.), most probably due to steric reasons. Interestingly, at this position a less sterically demanding fused ring system provided high levels of enantioselectivity (**3t**, 84:16 e.r.), whereas a deactivating ester group led to no conversion (**3u**). Finally, 1-chloro- or 1-methyl-substituted isoquinolines did not participate in this reaction. This also showed an important steric effect on the reactivity, a non-substituted C1-isoquinoline being required to allow the approach of the nucleophile to this position in the contact ion-pair system. In summary, the reaction can be employed in a wide substrate scope, high substitution tolerance of functional groups in almost all positions with exception of the substitution at the C1, and the presence of deactivating groups at the C3.

Lastly, and assuming similar behavior for all the substrates, the absolute configuration of the dihydroisoquinoline products **3** was assigned as (*R*) by comparison of the sign of the observed optical rotation for **3a** with the one reported in the literature (Figure 2).[11]



78:22 e.r. $[\alpha]^{20}_D$ = -128.4 (*c* = 0.21, $CHCl_3$)

Lit. (*R*)-**3a**, 93:7 e.r., $[\alpha]^{23}_D$ = -240 (*c* = 1.1, CH_2Cl_2)

Figure 2. Assignment of the absolute configuration by comparison of the reported $[\alpha]_D$ for **3a**.

Reaction course and anion-binding studies

A comparative study of the course of the reaction with quinoline and isoquinoline as substrates with the silyl ketene acetal **5a** in the presence and absence of catalyst **1a** in MTBE at −78 °C for 22 h was next carried out (Figure 3). The evolution of the enantiomeric excess and yield was monitored by HPLC and GC,[23] respectively. As previously reported,[15a] the reaction with quinoline using catalyst **1a** provided the addition product in a high enantioselectivity of 97:3 e.r. (Figure 3, left). Although a moderate 82:18 e.r. was observed after 15 min, an almost constant high enantiomeric excess was recorded after a reaction time of 4 h. Despite the less efficient background reaction (52% vs. 83%, 22 h), a slight inhibition of the reaction rate could be detected in the presence of the catalyst in the first hours. Similarly, the reaction course with isoquinoline was studied (Figure 3, right). Although there was a considerable background reaction (65%, 22 h), the catalyzed process was more efficient (98%) showing no initial inhibition. However, in this case a significantly lower enantioinduction was reached and the enantiomeric excess remained constant after 30 min (70:30 e.r.).

The reaction profile of the catalyzed reaction with the regioisomeric catalyst **1d** showed unexpected behavior (Figure 4,

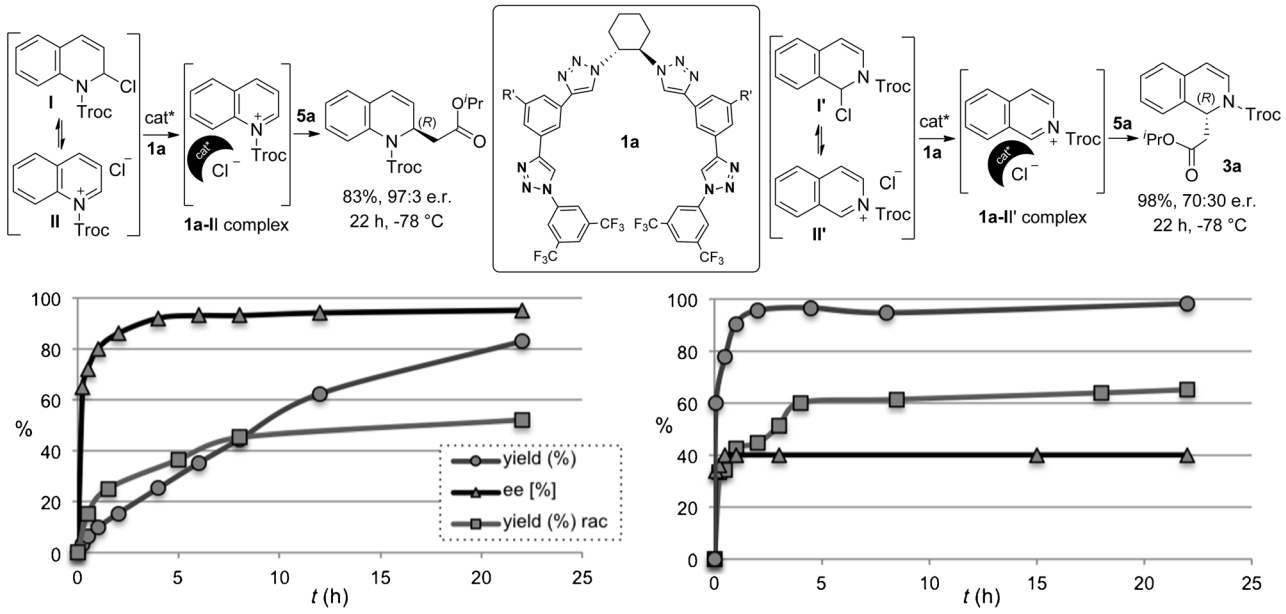


Figure 3. Kinetic study of the dearomatization reaction of quinoline (left) and isoquinoline (right) in the presence and absence of catalyst **1a** in MTBE at −78 °C.

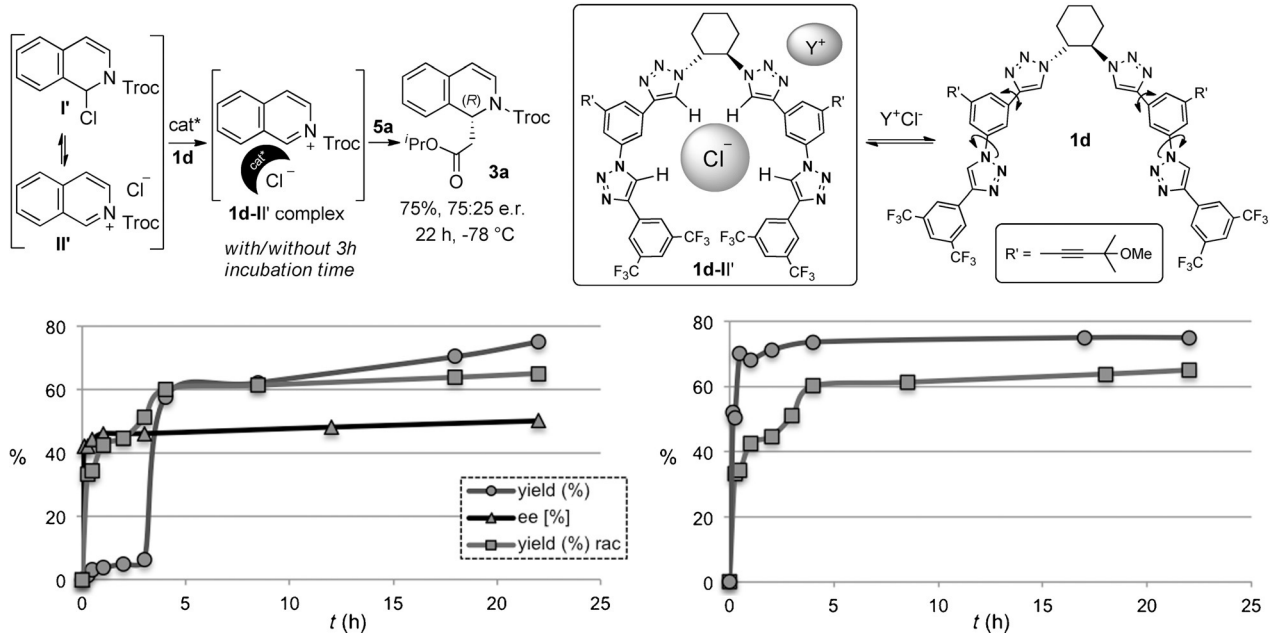
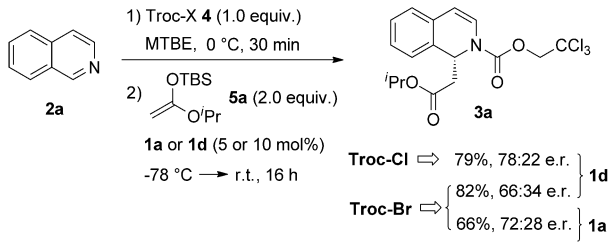


Figure 4. Study of the reaction course for the dearomatization of isoquinoline with catalyst **1 d** in MTBE at −78 °C without (left) and after 3 h incubation of **1 d** with the pre-formed isoquinolium substrate (right).

left). Although a good yield of 75% was obtained in the presence of the catalyst **1 d** after 22 h, a remarkable retarded reaction was observed in the first few hours. However, from a critical point (around 3 h) the reaction rate suddenly increased, so that the catalyzed reaction became faster than the non-catalyzed process. This fact might indicate an induction time for the formation of a more active catalytic species. In order to shed some light on the observed induction period, a further kinetic study was carried out (Figure 4, right). Prior to its use, the catalyst **1 d** was incubated for 3 h at −78 °C with the pre-formed isoquinolinium chloride salt **II′**, which is in equilibrium with the neutral chloride derivative **I′**.[24] The reaction was then monitored after the addition of the nucleophile **5 a**. There was no positive influence on the final enantioselectivity (73:27 vs. 75:25 e.r.). However, the induction period was not observed on this occasion. This observation reinforces the postulated induction period required for **1 d** to form the active catalytic species. Since for **1 a** a sigmoidal curve was also not observed, the induction time might be extremely fast (< 5 min) or does not occur with this catalyst. Furthermore, the main structural difference between **1 a** and **1 d** is the presence of regioisomeric triazole units at the end-chain. This indicates a pre-orientation requirement of the rotational flexible tetrakis triazole catalysts **1**, which seems to be more critical for **1 d**, to effectively bind the chloride anion and coordinate with the substrate to form the active **1-II′** complex. A plausible pre-orientation with **1 d** is depicted in Figure 4 (top-right).

Additionally, the effect of the counter anion, chloride versus bromide, on the enantioselectivity was investigated (Scheme 4). A notably higher enantioselectivity using TrocCl compared to the result with TrocBr[25] in the presence of catalyst **1 d** was obtained (78:22 e.r. vs. 66:34 e.r., respectively). However, with the Br anion a similar good 72:28 enantiomeric ratio could be achieved when employing the regioisomer catalyst **1 a** (5 mol%). These results showed that a bromide anion can also be accommodated inside the chiral cavity of this type of tetrakistriazole catalysts and efficiently transfer the chirality to the *N*-acyl iminium substrate.



Scheme 4. Comparison between Cl and Br counter anions.

A final comparison between the typical N–H-based hydrogen bond donor organocatalysts thioureas and squaramides, and the tetrakistriazole **1 d** was made (Figure 5). Although the thiourea **1 j** employed in the early work by Jacobsen and co-workers provided **3 a** in a high 90:10 enantiomeric ratio (reported 93:7 e.r.),[11] squaramide **1 k**[26] (67:33 e.r.) proved to be slightly less efficient than **1 d** (78:22 e.r.). This shows the competitive good performance of the tetrakistriazole structures as a new type of H-donor catalysts.

Conclusion

A family of chiral triazoles has been developed as a new type of anion-binding organocatalysts based on C–H bonds as H-donors. We have introduced these structures as effective and competitive catalysts for the Reissert-type dearomatization

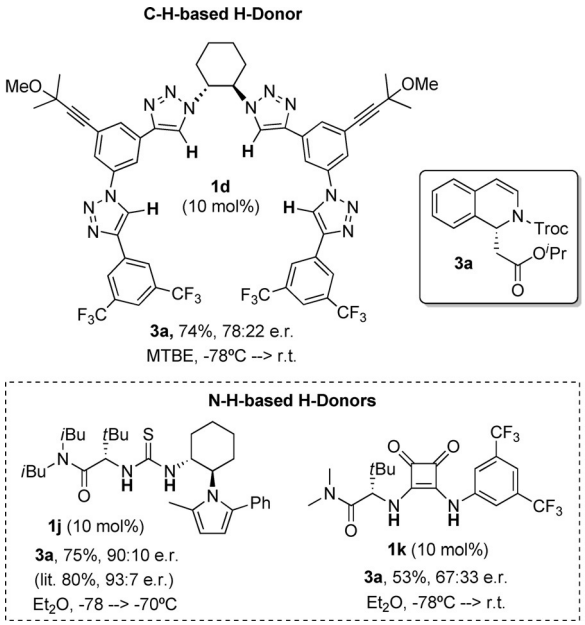


Figure 5. Comparison with other H-donors.

reaction of different N-heteroarenes. Thus, outstanding or good enantioselectivities were obtained with quinolines and pyridines, (up to 99:1 e.r.) or isoquinolines (up to 86:14 e.r.), respectively. Using isoquinolines as model substrates, a thorough study of the parameters affecting the activity of this class of anion-binding catalysts was carried out. Accordingly, it could be observed that the introduction of the chirality in the backbone of the catalyst using chiral *trans*-1,2-diaminocyclohexane was crucial for attaining high enantioselectivities. Moreover, the solvent and acylating agent are also determining factors. The use of TrocCl (or TrocBr) and ethereal solvents was crucial to getting optimal enantioinductions. In addition, kinetic studies suggested a 3 h induction period for the formation of the active catalysts with **1 d**, whereas this induction time was not observed for catalyst **1 a**. To sum up, this work unveils essential issues for the application of the presented triazole-based catalysts in further anion-binding-type catalysis.

Experimental Section

Detailed experimental synthetic procedures and analytical data for the new compounds can be found in the Supporting Information.

General procedure of the organocatalytic reaction

In a dried Schlenk tube, isoquinoline derivative **2** (0.1 mmol) was dissolved in MTBE (1 mL). TrocCl (**4 a**) or TrocBr (**4 b**) (1.0 equiv) was added at 0 °C, and the mixture was stirred for 30 min. The reaction mixture was cooled down to −78 °C (dry ice/acetone bath), and catalyst **1** (10 mol%), silyl ketene acetal **5** (2.0 equiv), and 1 mL MTBE were added. The resulting reaction mixture was stirred for 16–17 h and allowed to warm to ambient temperature during that time. The crude product was adsorbed on silica and purified by flash column chromatography to afford the desired product.

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