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# Enantio- and Diastereoselective Nucleophilic Addition of *N-tert*-Butylhydrazones to Isoquinolinium Ions through Anion-Binding Catalysis

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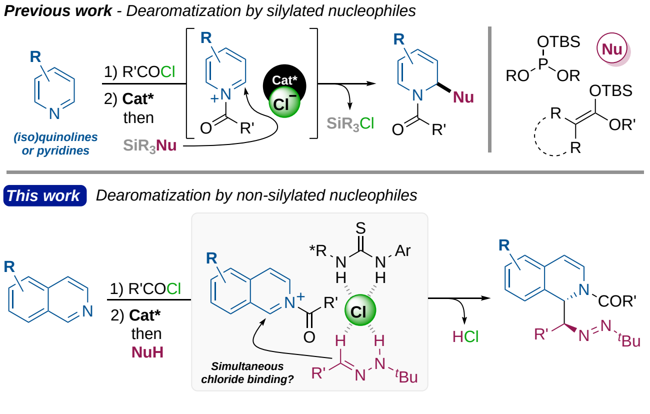
Dedication ((optional))

**Abstract:** A highly enantio- and diastereoselective thiourea-catalyzed dearomatization of isoquinolines employing N-*tert*-butylhydrazones as neutral α-azo carbanion and masked acyl anion equivalents has been developed. Experimental and computational data supports the generation of highly ordered complexes wherein the chloride behaves as a template for the catalyst, the hydrazone reagent and the isoquinolinium cation, providing an excellent stereocontrol in the formation of two contiguous stereogenic centers. Ensuing selective and high-yielding transformations provide appealing dihydroisoquinoline derivatives.

Asymmetric anion-binding catalysis has emerged as a powerful tool in Organic Synthesis.[1] In this type of ion-pairing catalysis, bi- and multidentate H-bond donors play a fundamental role by binding the anionic counterions of the reactive cationic electrophiles.[2] Notably, strategically positioned scaffolds in the catalysts might facilitate additional cooperative noncovalent interactions with at least one of the reacting partners, thereby maximizing the stereochemical control of the process. For example, extended aromatic systems which enable positioning of electrophiles by π-π and cation-π interactions have played this role in a handful of highly enantioselective transformations.[3] This strategy proved to be suitable for asymmetric dearomatizations of azaarenes via *N*-acyl pyridinium and (iso)quinolinium intermediates,[4] making use of different types of chiral X–H bond donor catalysts such as thioureas (N–H),[5] silanediols (O–H)[6] and oligotriazoles (C–H)[7] to bind chloride counteranions. In most cases, silylated nucleophiles such as silyl ketene acetals[5a,6,7a,7b] and silyl phosphites[5b,7c] (Scheme 1, top) were used; the silyl group of the nucleophile behaves as a halide scavenger, enabling catalyst turnover by formation of a strong silicon–chlorine bond, which ultimately serves as the driving force of the reaction. Conversely, the use of non-silylated nucleophiles is rather limited in this context.[8] Over years, we have exploited the nucleophilic character of hydrazones (masked acyl anion equivalents) in asymmetric synthesis.[9] In particular, the use of formaldehyde *N*-*tert*-butylhydrazone in combination with bifunctional H-bonding organocatalysts enabled efficient enantioselective functionalizations of neutral electrophiles, mainly carbonyl compounds.[10] In parallel, other groups used axially chiral Brønsted-acids in asymmetric additions of hydrazones to aldimines[11] or 3-hydroxyisoindolin-1-ones,[12] 6π-electrocyclizations with α,β-unsturated aldehydes,[13] and addition of glyoxylate hydrazones to N-acyliminium salts.[14]

On the other hand, monosubstituted hydrazones behave as bidentate H-bond donors, efficiently binding different anions, including halides, in different contexts.[15] On this basis, we envisaged that an additional interaction of the hydrazone with chloride could be beneficial to generate highly ordered intermediates in the dearomatization of heteroarenes (Scheme 1, bottom), thus facilitating a good stereocontrol in the concomitant formation of two contiguous stereogenic centers, a rare event in the above-mentioned dearomatization processes.[16]

Preliminary experiments were conducted employing isoquinoline (**1a**) as a model substrate, 2,2,2-trichloroethyl chloroformate (TrocCl) as acylating reagent and 2,4-difluoro benzaldehyde *N*-*tert*-butylhydrazone **2A** as a nucleophile with reduced reactivity. A significant background reaction was observed in methyl *tert*-butyl ether (MTBE, 0.1 M), even at low



**Scheme 1.** Dearomatization of azaarenes.

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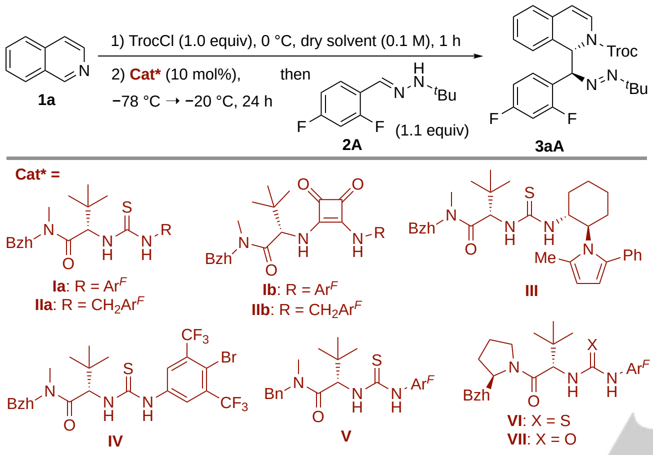
temperatures: using an optimized gradient [−78 °C (20 hours) to −20 °C (over 4 hours)], (*rac*)-dihydroisoquinoline **3aA** was obtained in 57% NMR-yield and 2.7/1 diastereomeric ratio (Table 1, entry 1). In the presence of 10 mol% of several *H*-bond donors (see the Supporting Information for details), the model reaction was efficiently accelerated, reaching regularly higher yields and dr's. From the initial screening, *tert*-Leucine derived thiourea **Ia** was identified as the most promising catalyst, affording the desired product **3aA** in 76% yield, a good 85% ee and excellent dr (>20:1, entry 2). A marked decrease of enantioinduction was observed for derivatives **Ib** and **IIb** featuring squaramide units (entries 3 and 5), as well as for less acidic catalyst **IIa** (entry 4).[17] The ee's also dropped to 60% and 79% with alternative catalysts such as **III**, featuring an additional (1*R*,2*R*)-(−)-1,2-diaminocyclohexane moiety, or *p*-brominated derivative **IV**,[18] respectively (entries 6 and 7). Finally, we evaluated the influence of the terminal dialkylamino fragment. *N*-Benzyl-*N*-methyl derivative **V** (lacking one phenyl ring with respect to **Ia**) provided a poor 48% ee (entry 8), suggesting that a *π*−type interaction with the *N*-acyl quinolinium electrophile might be involved.[3] Finally, catalyst **VI**,[19],[20] containing a more rigid (*R*)-2-(diphenylmethyl)pyrrolidine group, afforded an excellent 98% ee, while maintaining excellent dr (>20:1) and good reactivity (72% NMR yield, entry 9). The urea analogue **VII** was also used, showing a poorer catalytic activity and slightly lower, but still excellent ee (entry 10). Further optimization of the reaction with catalyst **VI** (entries 11-14) led to the use of a slight excess (1.2 equiv) of hydrazone **2A** in $Et_2O$ (0.1 M) as the optimal solvent to obtain (*S*,*S*)-**3aA** in 75% isolated yield as a single diastereoisomer (dr > 20:1) with excellent 99% ee (entry 14). Moreover, the catalyst loading could be reduced to 5 mol% without compromising yield or stereoselectivity (entry 15).

**Table 1.** Screening of organocatalysts and optimization of the reaction.[a]



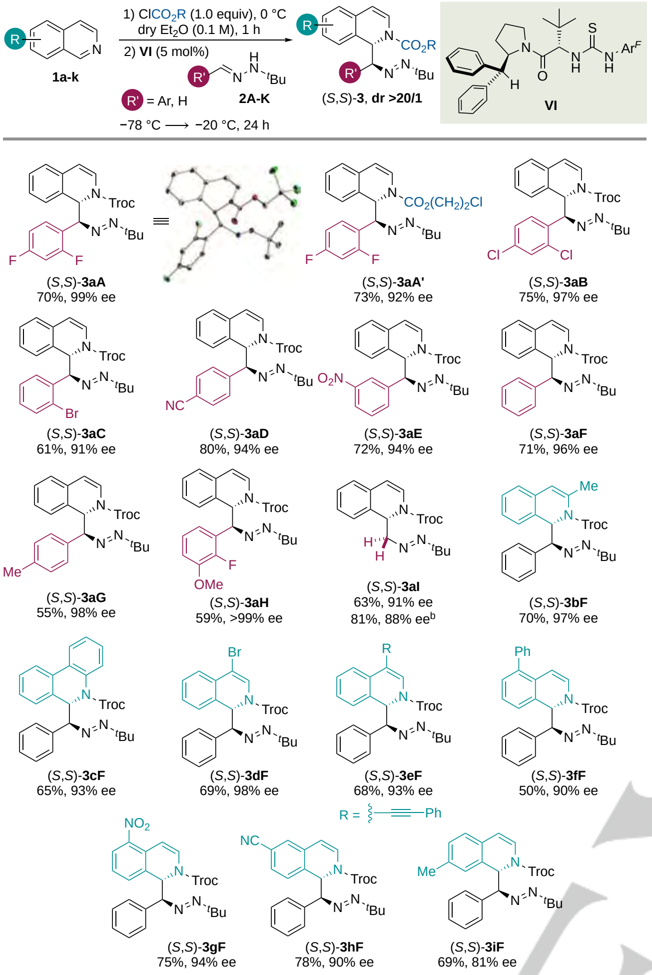
Bzh = Benzhydryl, $Ar^F$ = 3,5-bis(trifluoromethyl)phenyl

| Entry | Cat* [mol %] | Solvent | Yield [%][b] | *ee* [%][c] | d.r.[c] |
|---|---|---|---|---|---|
| 1 | - | MTBE | 57 | - | 2.7:1 |
| 2 | **Ia** (10) | MTBE | 76 | 85 | >20:1 |
| 3 | **Ib** (10) | MTBE | 73 | 40 | >20:1 |
| 4 | **IIa** (10) | MTBE | 75 | 38 | >20:1 |
| 5 | **IIb** (10) | MTBE | 65 | 31 | 13:1 |
| 6 | **III** (10) | MTBE | 64 | 60 | 19:1 |
| 7 | **IV** (10) | MTBE | 70 | 79 | >20:1 |
| 8 | **V** (10) | MTBE | 79 | 48 | >20:1 |
| 9 | **VI** (10) | MTBE | 72 | 98 | >20:1 |
| 10 | **VII** (10) | MTBE | 45 | 95 | >20:1 |
| 11 | **VI** (10) | $Et_2O$ | 85 | 99 | >20:1 |
| 12 | **VI** (10) | THF | 70 | 89 | >20:1 |
| 13 | **VI** (10) | toluene | 83 | 94 | >20:1 |
| 14[d] | **VI** (10) | $Et_2O$ | 88 (75)[e] | 99 | >20:1 |
| 15[d] | **VI** (5) | $Et_2O$ | 84 (70)[e] | 99 | >20:1 |

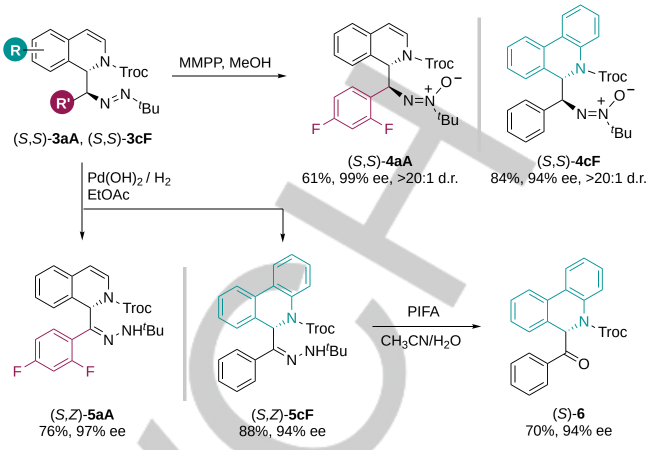
[a] Reactions at 0.1 mmol scale. [b] Estimated by $^1H$ NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Determined by HPLC. [d] Reaction with 1.2 equiv of hydrazone. [e] In parenthesis, yield of isolated product.

The influence of the acylating reagent on reactivity and selectivity was investigated maintaining **2A** as the model hydrazone. Surprisingly, protecting groups such as Cbz, alloc, benzoyl, acetyl or benzyl completely suppressed the reactivity (See the Supporting Information) but, interestingly enough, a 2-chloropropionyl group was tolerated: the expected product (*S*,*S*)-**3aA'** was obtained in good yield, albeit in slightly lower 92% ee (Scheme 2), suggesting the participation of the Troc or $CO_2(CH_2)_2Cl$ moieties in noncovalent interactions.

We next moved to explore the scope of the reaction (Scheme 2). In general, dearomatization of isoquinoline (**1a**) with differently substituted hydrazones (**2A-K**) afforded diazenes **3** in good-to-high yields, excellent ee's and nearly perfect dr's (>20:1 in all cases). Within the electron-deficient aryl series, dichlorinated analogue **2B** furnished (*S*,*S*)-**3aB** in 75% yield and 97% ee, while **2C** bearing a bulky bromine atom at *ortho* position afforded the expected product (*S*,*S*)-**3aC** in 61% yield and 91% ee. Importantly, hydrazones **2D** and **2E**, containing H-bond acceptor functionalities (*p*-CN and *m*-$NO_2$) were also well tolerated, providing dearomatized products (*S*,*S*)-**3aD** and (*S*,*S*)-**3aE** in high yields and 94% ee in both cases. Benzaldehyde derived hydrazone **2F** and derivatives **2G** and **2H** with diverse electronic character also provided the corresponding products (*S*,*S*)-**3aF-aH** in moderate-to-good yields (55-71%) and excellent ee's. Diazene (*S*)-**3aI**, derived from the simplest formaldehyde *N*-*tert*-butylhydrazone **2I**, was also obtained in good yield and ee. Next, dearomatization of isoquinolines **1b-1k** with representative benzaldehyde derived hydrazone **2F** were performed. 3-Subtituted (3-methylisoquinoline and phenantridine) and 4-substituted [4-bromoisoquinoline and 4-(phenylethynyl)isoquinoline] derivatives proved to be suitable substrates, affording products (*S*,*S*)-**3bF-eF** in good yields and high-to-excellent (93-98%) ee's. Isoquinoline derivative **3f**, which contains a bulky phenyl group at 5-position, afforded diazene (*S*,*S*)-**3fF** in a moderate 50% yield but high 90% ee. Similarly, electron-deficient substrates (5-$NO_2$ and 6-CN derivatives) furnished the dearomatized products (*S*,*S*)-**3gF** and (*S*,*S*)-**3hF** in



**Scheme 2.** Substrate scope. [a] Reactions performed at 0.2 mmol scale. [b] Reaction performed with 2.5 equiv of hydrazone.



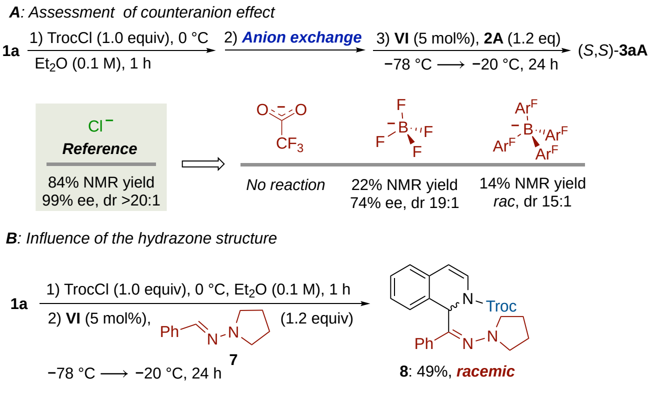
**Scheme 3.** Transformations of adducts (*S*,*S*)-**3**.

high yields and ee's (up to 94%). The introduction of a methyl substituent at C7, however, led to the expected adduct with lower ee [(*S*,*S*)-**3iF**, 81% ee]. Unfortunately, pyridinium salts showed no reactivity under the optimized conditions. Not surprisingly, poor conversion or no reaction were also observed with crowded substrates such as 8-bromoisoquinoline (**1j**) or 1-methylisoquinoline (**1k**), respectively, while aliphatic aldehyde hydrazones afforded products in poor conversions (see the Supporting Information for details). Importantly, the synthesis of (*S*,*S*)-**3aA** (64%, 99% ee, dr >20:1) and (*S*,*S*)-**3cF** (64%, 94% ee, d.r. >20:1) were also efficiently performed at 1.0 mmol scale under slightly different reaction conditions [**VI** (7.5 mol%), 26 h]. Crystals of (*S*,*S*)-**3aA** suitable for X-ray diffraction analysis[20] were used to assign its absolute *S*,*S* configuration.

Considering the growing interest in azoxy compounds as therapeutic agents,[21] the selective oxidation of representative adducts (*S*,*S*)-**3aA** and (*S*,*S*)-**3cF** was targeted as an interesting transformation (Scheme 3). Magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) efficiently afforded azoxy compounds (*S*,*S*)-**4** in good yields, as single regioisomers and without compromising the stereochemical integrity.[22] Additionally, adducts (*S*,*S*)-**3** underwent a fast tautomerization to hydrazones (*S*)-**5** under standard hydrogenation conditions [$Pd(OH)_2$/1 atm $H_2$].[23] The synthetic usefulness of these intermediates was demonstrated by accessing cyclic α-amino ketones. Thus, employing [bis(trifluoroacetoxy)-iodo]benzene (PIFA) as the oxidant, (*S*,*Z*)-**5cF** was transformed into α-amino ketone (*S*)-**6** in 70% isolated yield without racemization.

According to the predicted activation model, the geometry, size and coordination ability of the counteranion should have a marked effect in the reaction outcome. Hence, anion exchanges (Cl→TFA, $BF_4$, BARF) were performed prior to the addition of hydrazone **2A** (Scheme 4A). As expected, poorer reactivities and enantioselectivities were observed in all cases, highlighting the importance of the spherical and small chloride anion to reach optimal results. An additional experiment performed with pyrrolidine-derived hydrazone **7** was designed to indirectly assess the role of the N–H group in hydrazones **2**. Under the previously optimized conditions, the reaction with **1a** yielded adduct **8** in a modest 49% yield and in racemic form (Scheme 4B), confirming the essential role of the chloride binding ability of the hydrazone.

The binding of catalyst **VI** to the chloride anion in the presence of hydrazone **2D** was also analyzed by $^1$H-NMR titration with tetrabutylammonium chloride (TBACl) in 9:1 toluene-$d_8$/$CD_2Cl_2$ under catalytically relevant conditions: [**VI**] = 0.01 M, [**2D**] = 0.12 M).[24] As shown in Figure 1, the thiourea N–H protons and the *ortho* C–H protons of the 3,5-bis-(trifluoro-



**Scheme 4.** Control experiments.

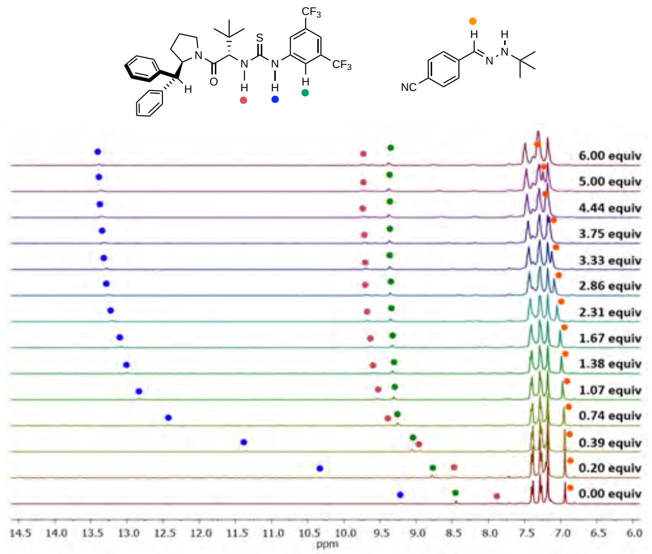
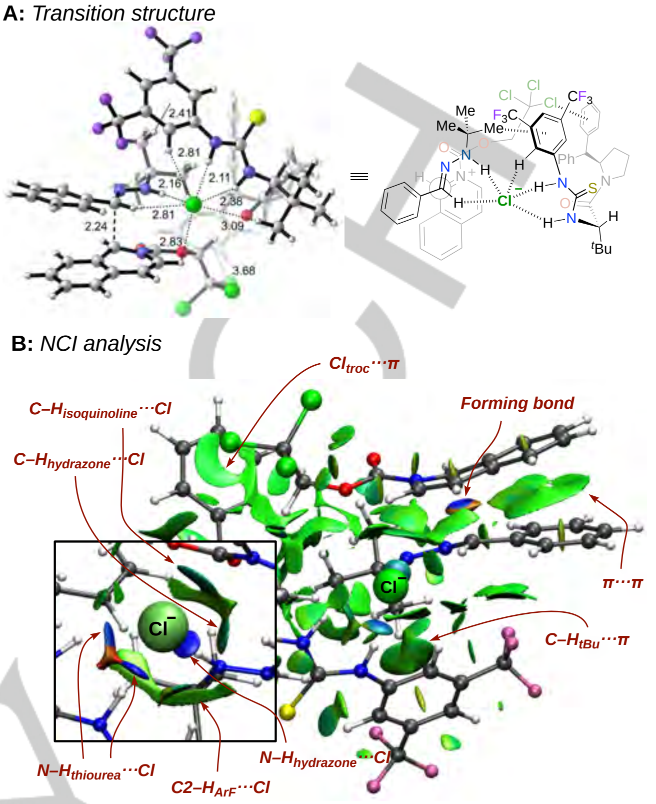


**Figure 1.** Simultaneous $^{1}$H NMR titration experiment of **VI** and **2D** with TBACl (9:1 toluene-d$_8$/CD$_2$Cl$_2$, [**VI**] = 0.01 M; [**2D**] = 0.12 M).

methyl)phenyl group[25] are strongly shifted downfield upon the stepwise addition of TBACl. Interestingly, the hydrazone azomethine and N–H protons are also perturbated, even at high hydrazone/chloride ratios,[26] suggesting a concurrent chloride binding of both catalyst and hydrazone. Additionally, the absence of a significant non-linear effect suggests that a 2:1 [**VI**]$_2$/Cl$^-$ complex might not be operating in this case.[27] Moreover, the method of continuous variation[28] was used to determine the binding stoichiometry between catalyst **VI** and TBACl and, as expected, the collected data fits with a 1:1 complex (see Supporting Information).

Computational studies for the synthesis of compounds **3aF** and **3aI** were performed to corroborate the presence of a highly ordered supramolecular transition structure involving the chloride ion. In the most favored transition structure the azomethine carbon approaches to the *Si* face of the isoquinolinium C(1)=N bond (Figure 2, top). Differences of 17.3 and 10.5 kcal mol$^{-1}$ (for **3aI** and **3aF**, respectively) were found with respect to the most stable transition structure leading to the (*R*)-enantiomer, accounting for a complete enantioselectivity. The formation of minor amounts of the latter in some cases is attributed to a residual background reaction. Notably, NCI analysis[29] of the lowest energy transition structure showed the presence of stabilizing Cl-π, CH-π and π-π interactions (Figure 2, bottom). Moreover, a recently developed tool for quantitative NCI analysis[30] confirmed that noncovalent interactions of the chloride ion with the NH's of the thiourea moiety and hydrazone as well as with the azomethine hydrogen atom are stronger in the preferred TS (Figure 2, bottom square). These interactions are responsible for fixing the orientation of the reagents in a highly ordered [**VI**]–Cl–hydrazone complex as the key intermediate, from which the preferential approach of the azomethine carbon to the *Si* face of the isoquinolinium C(1)=N bond accounts for the high enantio- and diastereoselectivity reached and the observed (*S*,*S*) absolute configuration.


**A:** *Transition structure*

**B:** *NCI analysis*

**Figure 2.** Lowest-energy transition structure leading to the (*S*,*S*)-enantiomer of **3aF**. Top: Optimized geometry at the wb97xd/def2svp/pcm=diethyl ether level of theory. Bottom: NCI analysis showing main noncovalent interactions. Detailed interactions of the chloride ion are indicated in the square.

In summary, a *tert*-Leucine derived thiourea has been shown to catalyze a three-component dearomatization reaction employing isoquinolines, 2,2,2-trichloroethyl chloroformate (TrocCl) and *N*-*tert*-butyl hydrazones as neutral π-nucleophiles to obtain functionalized dihydroisoquinolines bearing two contiguous stereogenic centers with excellent enantio- and diastereoselectivities. Experimental and computational evidences support the key role of the chloride anion as a template for the formation of highly ordered transition structures stabilized by a set of cooperative noncovalent interactions that explain the exquisite stereocontrol of the reaction. The extension of this multiple anion binding strategy to other substrates and/or reagents is currently object of study in our laboratory.

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**Keywords:** • Asymmetric catalysis • Hydrazones • Dearomatization • Organocatalysis • Acylation

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[20] CCDC 2022437 and 2022436 [**VI**, and **3aA**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[21] Bioactive azoxy compounds: a) L. Ding, B. L. T. Ndejouong, A. Maier, H. H. Fiebigand, C. Hertweck, *J. Nat. Prod.* **2012**, *75*, 1729–1734; b) R. P. Garg, X. L. L. Qian, L. B. Alemany, S. Moran, R. J. Parry, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 6543–6547; c) M. Nakayama, Y. Takahashi, H. Itoh, K. Kamiya, M. Shiratsuchi, G. Otani, *J. Antibiot.* **1989**, *42*, 1535–1540.

[22] For a related oxidation see: a) D. Monge, A. Crespo-Peña, E. Martín-Zamora, E. Álvarez, R. Fernández, J. M. Lassaletta, *Chem. Eur. J.* **2013**, *19*, 842–8425; b) I. Serrano, D. Monge, E. Álvarez, R. Fernández, J. M. Lassaletta, *Chem. Commun.* **2015**, *51*, 4077–4080.

[23] In contrast, Zhu and co-workers described the hydrogenation of diazene into the corresponding hydrazine under similar reaction conditions in analogous linear products. See ref 10b. The isomerization under usual acidic conditions led to partial decomposition of the product.

[24] This solvent mixture, chosen for solubility reasons, was used in the model reaction to afford the product **3aA** in 71 % NMR yield and 92% ee.

[25] The participation of the *ortho* C–H bonds of 3,5-bis(tri-fluoromethyl)phenyl groups as H-bond donors in thiourea organocatalysis is well documented. See, for instance: K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919–5927.

[26] In the simultaneous titration, the **2D**/$Cl^-$ ratio is 12-fold higher than the **VI**/$Cl^-$ ratio. A more pronounced displacement of the hydrazone azomethine and N–H protons is observed in the individual titration. See the Supporting Information for separate titrations of **VI** and **2D**.

[27] In related contexts, however, Jacobsen and co-workers have reported positive non-linear effects due to the formation of 2:1 thiourea–$Cl^-$ complex in the stereodeterming transition state: a) D. D. Ford, D. Lehnherr, C. R. Kennedy, E. N. Jacobsen. *J. Am. Chem. Soc.* **2016**, *138*, 7860–7863; b) D. Lehnherr, D. D. Ford, A. J. Bendelsmith, C. R. Kennedy, E. N. Jacobsen, *Org. Lett.* **2016**, *18*, 3214–3217; c) D. D. Ford, D. Lehnherr, C. R. Kennedy, E. N. Jacobsen *ACS Catal.* **2016**, *6*, 4616–4620; d) C. R.; Kennedy, D. Lehnherr, N. S. Rajapaksa, D. D. Ford, Y. Park, E. N. Jacobsen, *J. Am. Chem. Soc.* **2016**, *138*, 13525–13528.

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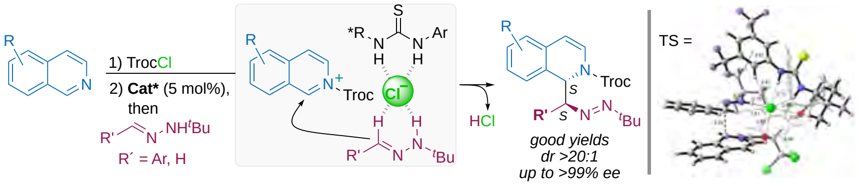
## Entry for the Table of Contents

## COMMUNICATION



**Two is better than one!** The ability of the chloride anion to simultaneously bind a thiourea catalyst and a hydrazone nucleophile results in a highly ordered termolecular transition structure stabilized by a cooperative set on noncovalent interactions, ultimately resulting in an exquisite stereocontrol in the dearomatization of isoquinolines

*Esteban Matador, Javier Iglesias-Sigüenza, David Monge,* Pedro Merino,* Rosario Fernández* and José M. Lassaletta**

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**Enantio- and Diastereoselective Nucleophilic Addition of *N-tert*-Butylhydrazones to Isoquinolinium Ions through Anion-Binding Catalysis**