# Bifunctional Squaramide Organocatalysts for the Asymmetric Addition of Formaldehyde *tert*-Butyl Hydrazone to Simple Aldehydes

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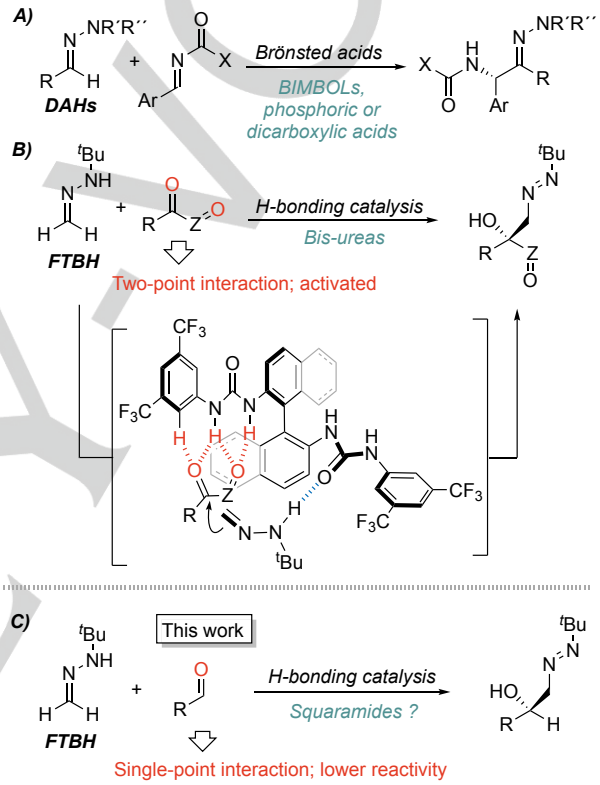
**Abstract:** The nucleophilic addition of formaldehyde *tert*-butyl hydrazone to simple aldehydes (a formal hetero-carbonyl-ene reaction) can be performed with good reactivities and excellent enantioselectivities by virtue of the dual *H*-bonding activation exerted by amide-squaramide organocatalysts. The resulting hydroxydiazenes (azo alcohols) were isolated in high yields as enantiomerically enriched azoxy compounds after a regioselective azo-to-azoxy transformation. Subsequent derivatizations provide an entry to relevant amino alcohols, oxazolidinones and derivatives thereof.

## Introduction

Hydrazones have been frequently exploited as versatile reagents in organic synthesis; primarily for the generation of molecular complexity from simple starting materials and, additionally, enabling distinctive functional group interconversions.[1] Acting as mild carbon π-nucleophiles, their additions to C=X (X = C, N, O) bonds are useful C–C bond forming reactions for the synthesis of enantiomerically pure compounds, including highly functionalized amines and alcohols.[2] The development of asymmetric catalytic versions of these reactions was initially hindered for the sensitivity of these reagents toward most Lewis acidic metal complexes,[3] but the milder nature of organocatalytic activation strategies appeared to solve these compatibility issues.[4] Thus, LUMO-lowering activation of imines by axially chiral BINOL, phosphoric or dicarboxylic acid derivatives allowed 1,2-addition of *N*,*N*-dialkylhydrazones (***DAHs***) to yield enantiomerically enriched α-aminohydrazones (Scheme 1, *A*).[5] Dual *H*-bonding activation by thioureas was also identified as a proper strategy for the conjugate addition of ***DAHs*** to β,γ-unsaturated α-ketoesters.[6] However, none of these catalysts provided satisfactory results




**Scheme 1.** Organocatalytic asymmetric 1,2-additions of hydrazones to imines and carbonyl compounds.

for 1,2-addition of ***DAHs*** to carbonyl compounds. Alternatively, we have exploited the distinct properties of formaldehyde *tert*-butyl hydrazone (***FTBH***) in reactions with activated carbonyl compounds (α-keto esters,[7] α-keto phosphonates[8] and isatins[9]) to afford highly functionalized β-hydroxy diazenes (Scheme 1, *B*).Dual activation by axially chiral BINAM *bis*-ureas, behaving as bifunctional organocatalysts, proved to be key to achieve good catalytic activities and stereocontrol. Accordingly, ***FTBH*** would be activated by one of the urea's carbonyl groups *via* NH–O hydrogen bond, and guided to the reachable carbonyl face of the dicarbonyl substrate which, employing two interaction points, would be activated by the second urea moiety acting this time (as usually) as a double *H*-bond donor. Aimed to expand the scope of this strategy, we next investigated enantioselective reactions with single carbonyl compounds (simple aldehydes and ketones). These are *a priori* more challenging substrates for two main reasons: First, the lower electrophilicity of the carbonyl

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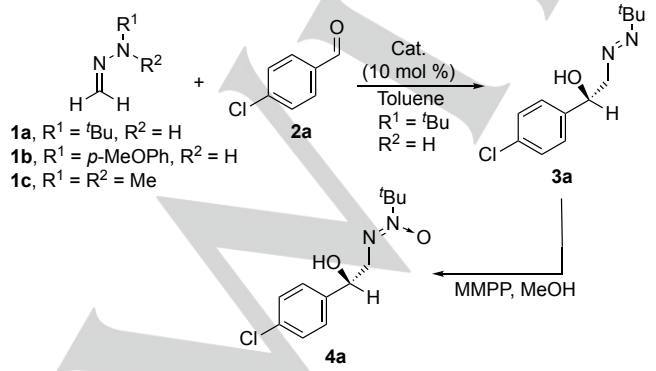
group in these substrates will presumably make necessary to use more active (acidic) catalysts, but the compatibility with the hydrazone reagent could be compromised. Second, the geometry of the catalyst-substrate complex should be fixed using a single interaction site, in contrast with the above-mentioned precedents. In fact, intensive efforts performed with BINOL/BINAM derived *H*-bonding catalysts or common bifunctional thiourea organocatalysts revealed either low-to-moderate catalytic activity or led to products with negligible levels of enantioselectivity, highlighting the importance of auxiliary interacting groups (Z=O) to facilitate the desired stereocontrol (see Supporting information for details). To overcome these difficulties, we envisioned that more acidic *H*-bonding squaramides[10] might provide a better activation of single carbonyl compounds and additionally, the distinctive more canted NH groups might also help fixing the geometry of the complex, thereby enabling a better enantiocontrol. In this paper, we disclose the asymmetric addition of ***FTBH*** to simple aldehydes employing bifunctional amide-squaramides (Scheme 1, *C*).

## Results and Discussion

*p*-Chlorobenzaldehyde **2a**, a relatively reactive aromatic aldehyde, was chosen as a model substrate for preliminary experiments. For comparative purposes, the reactivity of simple formaldehyde hydrazones **1a-c** with **2a** was analyzed (Scheme 2). Not surprisingly, the *N*-anisyl-derivative **1b** and *N,N*-dimethyl hydrazone **1c** showed no reactivity, neither under thermal nor catalytic conditions.[11] In sharp contrast, t*ert*-butyl hydrazone **1a** smoothly added to **2a** in toluene at room temperature (full conversion to **3a** in ca. 60 hours). The thermal reaction proved to be reversible and, hence, diazene **3a** did not resist chromatographic purification. Fortunately, *in situ* oxidation of crude diazene **3a** with magnesium monoperoxyphthalate (MMPP) afforded a stable azoxy compound **4a** with complete regioselectivity (oxidation exclusively at the more hindered N) and 90% isolated yield after two steps (entry 1, Table 1). Cooling to 5 °C slowed down the uncatalyzed reaction (55% conversion to 3a after 60 hours, entry 2) and, therefore, these conditions were used in further studies for the evaluation of different organocatalysts (see the Supporting Information). After




**Scheme 2.** Model reaction of hydrazones **1** with **2a**.

**Table 1.** Optimization of the reaction of **1a** with **2a**.[a]

| Entry | Catalyst | Solvent | T (°C) | Conv. (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | -- | Toluene | rt | 95 (90) | - |
| 2 | -- | Toluene | 5 | 55 | - |
| 3 | **I** | Toluene | 5 | 95 | 39 |
| 4 | **II** | Toluene | 5 | 80 | 50[d] |
| 5 | **II** | TBME | 5 | 55 | 70 |
| 6 | **II** | $CH_3CN$ | 5 | 48 | 52 |
| 7 | **II** | $CH_2Cl_2$ | 5 | 78 | 72 |
| 8 | **II** | $CF_3$-Ph | 5 | 95 | 76 |
| 9 | **III** | $CF_3$-Ph | 5 | >99 | 41 |
| 10 | **IV** | $CF_3$-Ph | 5 | 95 | 72 |
| 11 | **V** | $CF_3$-Ph | 5 | 92 | 66 |
| 12 | **VI** | $CF_3$-Ph | 5 | 96 | 36 |
| 13 | **VII** | $CF_3$-Ph | 5 | 94 | 55 |
| 14 | **VIII** | $CF_3$-Ph | 5 | 88 | 23 |
| 15 | **II** | $CF_3$-Ph | –10 | 92 | 90 |
| 16[e] | **II** | $CF_3$-Ph | –10 | 94 (90) | 90 |

[a] Unless otherwise stated, all reactions were performed at 0.1 mmol scale using 10 mol% catalyst loading at 0.3M (reaction time of the addition step = 60 hours). [b] Conversion to **3a** estimated by $^1$H-NMR (in parenthesis, isolated yield of **4a** after column chromatography). [c] Determined by HPLC. [d] Non-reproducible result. [e] Reaction was performed at 0.5M.

preliminary screening of diverse bifunctional (thio)ureas with different chiral scaffolds and functionalities, only amino acid derived thioureas afforded a moderate level of asymmetric induction, reaching up to 39% ee (entry 3) by using amide-thiourea **I** (Figure 1). In the seeking of more active and selective catalysts, analogous squaramide **II** was synthesized and analyzed.[12] A better enantioselection was reached (up to 50% ee, entry 4); however, reaction conversions remained lower than expected and could not be regularly reproduced, reaching high values (up to 80%) only in isolated experiments. As the low solubility of II in toluene (<3 mg/mL at rt) was considered as a possible explanation,[13] a survey of different solvents [TBME, $CH_3CN$, $CH_2Cl_2$ (entries 5-7) among others] was performed. $CH_2Cl_2$ performed better, leading to high conversion and a promising 72% ee (entry 7), but again solubility issues (≈3 mg/mL at rt) hampered a further optimization. Finally, α,α,α-trifluorotoluene (TFT)[14] emerged as the best option, leading to better and reproducible results. The higher solubility of **II** (≈15 mg/mL at rt) in this solvent granted homogeneous reactions in which higher conversions (95%) and enantioselectivities (up to 76% ee) were obtained (entry 8). Next, the catalytic performance of several bifunctional amide-squaramides (**II**-**VIII**, Figure 1) was comparatively analyzed. A significant decrease in enantioselectivity was observed by using phenylalanine derivative **III** (41% ee, entry 9) instead of *tert*-leucine-derived **II** (76 % ee, entry 8), highlighting the better conformational control exerted by *tert*-butyl group in the chiral amide fragment. This

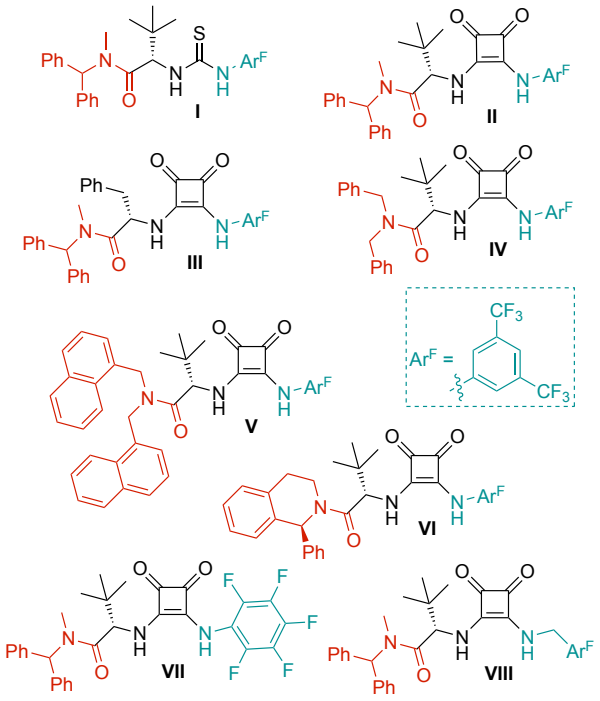


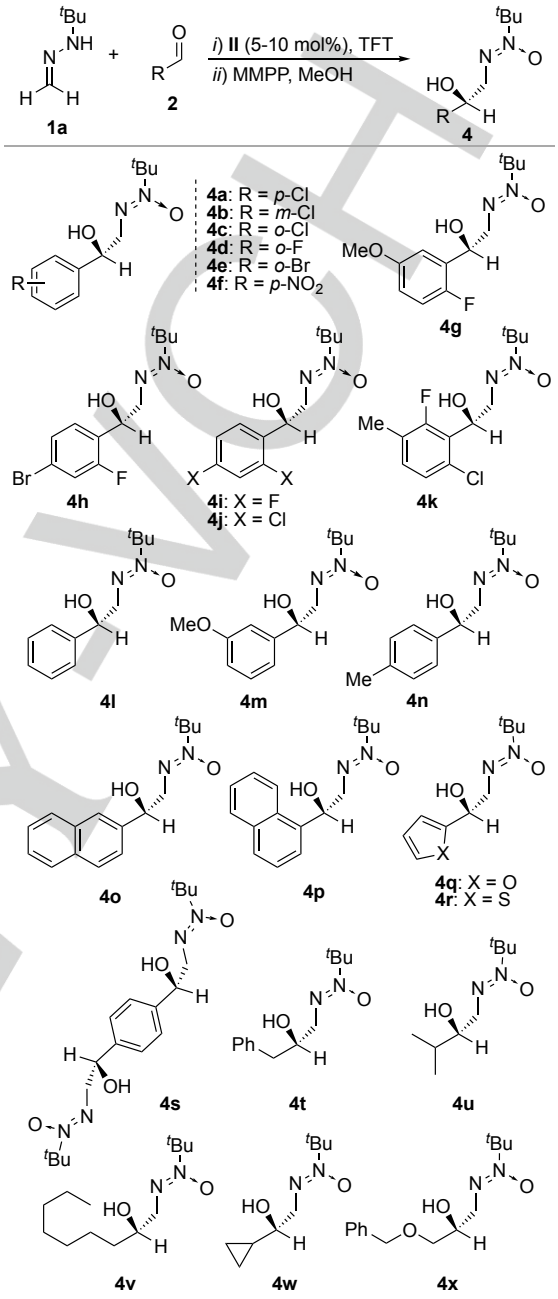

**Figure 1.** Selected amide-thiourea/squaramide organocatalysts tested.

observation is in accordance with $^{1}$H-NMR spectra for both catalysts in DMSO at 303 K, showing (*Z*)/(*E*)-amide rotamers in 4:1 (**III**) and 6:1 (**II**) ratios (see the Supporting Information).

The dialkylamino group had a significant influence in the stereochemical outcome of the reaction. Squaramide **IV**, bearing a relatively flexible dibenzylamino group, afforded similar results (entry 10) to **II**, while introduction of a bulkier bis(naphthalen-1-ylmethyl)amino group in squaramide **V** slightly diminished its catalytic activity and enantioinduction ability (entry 11). Squaramide VI, containing a rigid cyclic amino group derived from (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, exhibited a good catalytic activity but low enantioselectivity (entry 12).

Having established the best amide unit, we analyzed the influence of the *H*-bonding donor group by comparing squaramide **II** [bearing a bis(trifluoromethyl)phenyl substituent] with **VII** (pentafluorophenyl derivative) and **VIII** [bis(trifluoromethyl)benzyl derivative]. As predicted, the results allow to establish a direct correlation between the *H*-bond donor capability of the catalysts [**II** > **VII** > **VIII** (inferred from chemical shift of NH protons in $^{1}$H-NMR, see the Supporting Information)] and the observed enantioselectivity, which drops to 55% (entry 13) and 23% ee (entry 14) for less acidic **VII** and **VIII**, respectively. Using the best catalyst **II**, further optimization of temperature and concentration was carried out (entries 15 and 16). Thus, performing the addition reaction at –10 °C (0.5M) followed by *in situ* oxidation yielded 4a in 90% yield and 90% ee.[15]

The scope of the reaction was then explored with representative aromatic, heteroaromatic and aliphatic aldehydes (Scheme 3). The collected data summarized in Table 2 show




**Scheme 3.** Scope of the addition of **1a** to aldehydes **2**.

that aryl-substituted azoxy compounds 4a-p can be obtained in good to excellent yields and high enantioselectivities (81-96% ee) in most cases. A correlation between the reaction rate and the electronic properties of the aryl group was observed: electron-poor aldehydes **2a**-**k** reacted at −10/−20 °C for 60–72 hours (entries 1-11), while benzaldehyde (**2l**) and more electron-rich substrates (**2m**-**p**) required longer reaction times for completion (entries 12-16). Remarkably, an excellent enantiocontrol was observed for *ortho*/*para*- and *ortho*/*ortho*-di halogenated benzaldehydes (**2h**-**k**), leading to highly enantioenriched derivatives 4h-k (94-96% ee). 2-Furyl and 2-

**Table 2.** Scope of the addition of **1a** to aldehydes **2**.[a]

| Entry | 4 | T (°C) | t (h)[b] | yield (%)[c],[d] | ee (%)[d],[e] |
|---|---|---|---|---|---|
| 1 | **4a**[f] | −10 | 72 | 96 (95) | 91 (90) |
| 2 | **4b** | −10 | 72 | 94 (94) | 87 (86) |
| 3 | **4c** | −10 | 60 | 96 (96) | 91 (86) |
| 4 | **4d** | −10 | 60 | 99 (97) | 92 (88) |
| 5 | **4e** | −10 | 72 | 99 (94) | 90 (87) |
| 6 | **4f** | −10 | 60 | 94 (93) | 92 (92) |
| 7 | **4g** | −10 | 60 | 90 | 88 |
| 8 | **4h** | −20 | 60 | 99 (98) | 94 (92) |
| 9 | **4i** | −20 | 60 | 99 (98) | 96 (94) |
| 10 | **4j** | −20 | 60 | 93 (90) | 94 (92) |
| 11 | **4k** | −20 | 60 | 99 (97) | 95 (93) |
| 12 | **4l** | −10 | 80 | 95 | 88 |
| 13 | **4m** | −10 | 92 | 77 | 81 |
| 14 | **4n** | −10 | 80 | 85 | 90 |
| 15 | **4o** | −10 | 80 | 92 | 84 |
| 16 | **4p** | −10 | 92 | 52 | 82 |
| 17 | **4q** | −10 | 60 | 76 | 94 |
| 18 | **4r** | −10 | 92 | 77 | 92 |
| 19 | **4s**[g] | −10 | 96 | 90 | >99 |
| 20 | **4t** | −20 | 96 | 84 | 75 |
| 21 | **4u** | −20 | 96 | 75 | 84 |
| 22 | **4v** | −20 | 96 | 79 | 81 |
| 23[h] | **4w** | −10 | 168 | 55 | 90 |
| 24 | **4x** | −10 | 60 | 76 | 94 |

[a] Unless otherwise indicated, all reactions were performed at 0.2 mmol scale using **II** (10 mol%) as the catalyst. [b] Reaction time of the addition step. [c] Isolated overall yield after column chromatography. [d] In parenthesis, data for reactions performed with 5 mol% catalyst. [e] Determined by HPLC. [f] This result is slightly better than for the reaction performed at 0.1 mmol scale (compare with Table 1, entry 16). [g] 9:1 dr. [h] 2 eq. of **1a** were sequentially added after 96 and 120 hours, respectively.

thienyl heteroaromatic derivatives afforded also the expected products **4q**,**r** with high enantioselectivities (94 and 92% ee, respectively: entries 17 and 18). Double addition of **1a** to terephthalaldehyde **2s** generated two stereogenic centers to yield bis-azoxy compound **4s** with good diastereoselectively (9:1 dr) and excellent enantioselectivity (entry 19). Aldehydes bearing representative alkyl chains [R = Bn (**2t**), R = *i*-Pr (**2u**) and R = heptyl (**2v**), (entries 20-22)] were also well tolerated; reactions with **1a** at −20 °C for 96 hours gave products **4t**-**v** in good yields and moderate to good enantioselectivities (75-84% ee). Cyclopropyl-substituted aldehyde **2w** was the less reactive substrate within this series, giving **4w** with a modest 55% yield but in higher 90% ee (entry 23). Finally, **2x**, bearing a benzyloxy group that might act as an auxiliary *H*-bond acceptor, afforded **4x** with 76% yield and an excellent 94% ee (entry 24). Remarkably, it was possible to reduce the catalyst loading to 5 mol% without compromising the either the chemical yield or the reaction time, and with a minor impact in the enantioselectivity, as shown for representative examples (entries 1-6 and 8-11). To further explore the efficiency of the catalytic system, the synthesis of **4a** (94%, 90% ee), **4i** (98%, 94% ee), **4l** (95%, 86% ee) and **4t** (80%, 75% ee) were performed on a 1 mmol scale. The catalyst **II** survived the oxidative reaction conditions and could be recovered (85-90% after chromatographic purification) and reused.

Product **4a** was crystallized and its structure elucidated by X-ray diffraction analysis (Figure 2),[16] unequivocally confirming the absolute (*S*) configuration of the newly created stereogenic center and the assigned regioselectivity of the *N*-oxidation. The absolute configuration of other adducts **4** were assigned by analogy assuming a uniform reaction pathway (See stereochemical model, *vide infra*). Azoxy alcohols **4** are valuable derivatives considering the growing interest in bioactive azoxy compounds,[17] which contrast with the lack of methodologies for their stereo and regioselective synthesis. Additionally, some useful transformations of adducts **4** are presented in Scheme 4. For example, under $S_N2$ Mitsunobu reaction conditions, the hydroxyl group was efficiently substituted by a protected amino group, as exemplified for the synthesis of 5. Additionally, the direct conversion of the azoxy

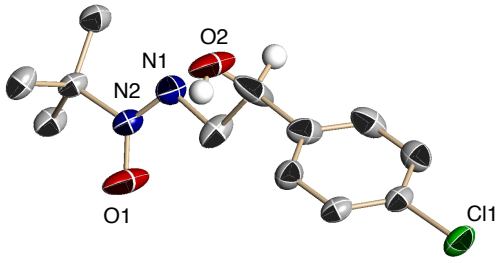
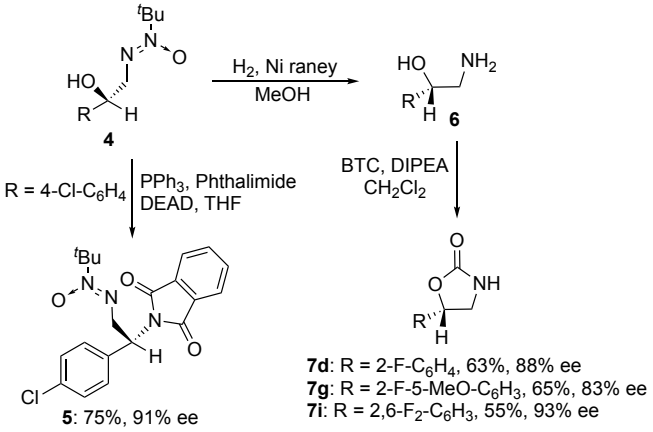



**Figure 2.** X-Ray structure of (*S*)-**4a**. H atoms (except H1 and H7) are omitted for clarity. Thermal ellipsoids drawn at 50% probability.




**Scheme 4.** Synthetic transformations of azoxy compounds **4**.

compound **4** into free amino alcohols **6** was performed by applying standard hydrogenation conditions [Ni-raney, $H_2$ (25-50 mbar), room temperature]. This unprecedented transformation, which formally involves three consecutive steps [Hydrogenolytic N–O bond cleavage (azoxy-to-azo compound reduction), N=N bond hydrogenation (azo-to-hydrazine reduction) and N–N bond hydrogenolysis (hydrazine-to-amine)] afforded amino alcohols **6**[18] which were subsequently protected by reaction with triphosgene to yield the corresponding oxazolidinones[19] **7** in good overall yields and enantioselectivities (Scheme 4).

## Mechanistic aspects

Squaramide **II** is believed to act in a bifunctional fashion, as previously proposed for BINAM-bis-urea/dicarbonyl compound/**1a** systems.[6a] Consistent with structure/activity and selectivity relationships [see the screening of organocatalysts (Chart 1, Table 1) and the Supporting Information], the experimental data allowed to identify 3,5-bis(trifluoromethyl)phenyl-substituted squaramide and *tert*-leucine-derived amide fragments as key elements for a plausible cooperative catalysis. To assess the organocatalytic activity of **II**, 2,6-difluorobenzaldehyde **2i** was chosen as substrate. The presence of fluorine atoms in *ortho*- and *para*- positions facilitates the monitoring of the reaction mixture by recording, in relatively short reaction times, $^{19}$F NMR spectra of the mixture (Figure 3). Reactions of **1a** with **2i** in α,α,α-trifluorotoluene at −10 °C using catalyst **II**, and resembling monofunctional units **IX** (achiral squaramide) and **X** (achiral amide) were comparatively analyzed (Scheme 5) revealing a much higher catalytic activity of **II** (>90% conv. after 10 hours) in comparison with fragments **IX** (<30% conv.) and **X** (<30% conv.), acting either alone or combined (**IX** + **X**).[20]

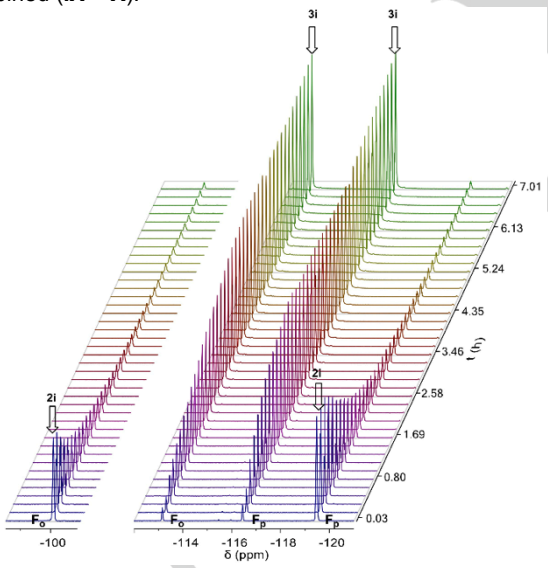
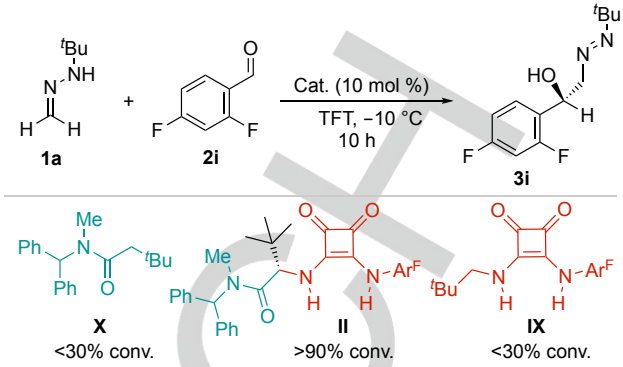



**Figure 3.** $^{19}$F NMR spectra obtained for the reaction **1a** + **2i** → **3i** catalyzed by **II** in α,α,α-trifluorotoluene at −10 °C. Hollow arrows show the decay of the signals corresponding to **2i** and the rise of the signals corresponding to **3i**.




**Scheme 5**. Model reaction to assess the bifunctional activity of **II**.

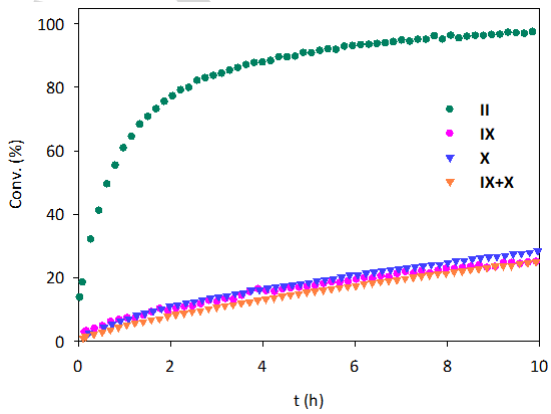
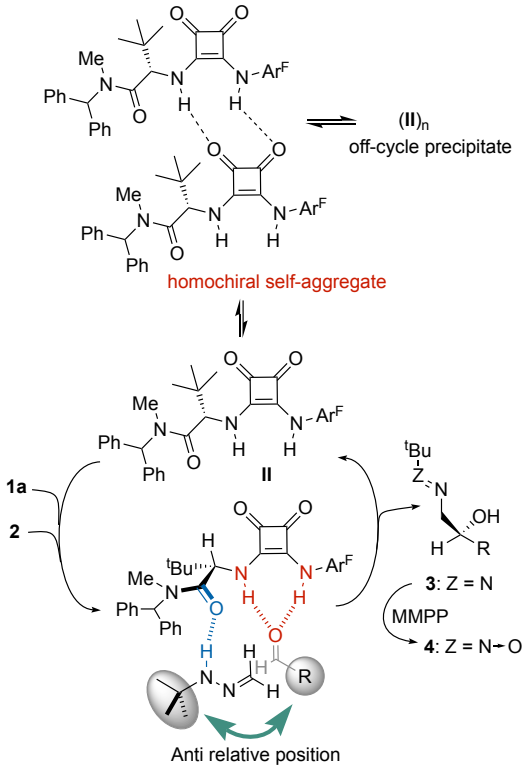



**Figure 4.** Conversion over time for the **1a** + **2i** → **3i** transformation in the presence of bifunctional amide-squaramide **II**, achiral squaramide **IX**, amide **X**, and the mixture **IX** + **X**. All reactions were monitored in TFT at 263 K by $^{19}$F-NMR (500 MHz).

The evolution of these reactions over time (Figure 4) shows also a maximum differentiation at the beginning of the process [>80% conv. after 3 hours (**II**) vs <15% **IX**, **X** or (**IX** + **X**)]. These results highlight the importance of the so-called 'entropic gain' facilitated by bifunctional catalysts in which two or more activating functionalities work in close proximity in the same molecule. Consequently, a model to explain the high selectivity and the observed absolute configuration is proposed (Scheme 6). In this model, the aldehyde is activated by double *H*-bonding by the squaramide moiety, while the amide carbonyl group serves as an *H*-bond acceptor for the hydrazone NH group. Simultaneous activation/positioning of both reagents while minimizing steric repulsions during the C–C bond formation is consistent with an *anti* approach of azomethine carbon to the *Re* face of the aldehyde carbonyl. A slightly negative nonlinear effect (see the Supporting Information) suggests a more complex scenario involving self-aggregates, with different solid-solution phase behavior.[21] Indeed, enantiopure catalyst (*S*)-**II** and racemic catalyst (*rac*)-**II** show very different solubilities (≈15 mg of (*S*)-**II**/mL TFT at rt; ≈28 mg of (*rac*)-**II**/mL TFT at rt).




**Scheme 6.** Proposed catalytic cycle and stereochemical model.

Moreover, all attempts to crystalize racemic catalyst led to precipitate forms not suitable for X-ray diffraction studies while crystals obtained for enantiopure catalyst (*S*)-**II** show a perfect packing based on linear head-to-tail ladder networks (See homochiral self-aggregate in Scheme 6, and X-ray structure).[21] However, the effect observed is relatively low as reactions become completely homogeneous upon mixing of reagents.

To gain some insight into reagents-catalyst interactions, additional NMR experiments were performed. However, non-confident data were collected due to solubility issues.[22] Moreover, we tried to co-crystallize (*S*)-**II** with several aldehydes. Nevertheless, squaramide (*S*)-**II** crystallized instead and its monomeric structure was analyzed by X-ray diffractometry (Figure 5).[23] As usual, the squaramide ring adopts an *anti*/*anti* conformation, with the *bis*-trifluoromethyl-phenyl ring slightly twisted [torsion angle: C(24)-N(3)-C(25)-C(26) = −35.0(7)°] with respect to the cyclobutendione unit. The co-planarity and directionality of the two NH groups [torsion angles: H(2)-N(2)-C(21)-C(24) = 4.7(5)°; H(3)-N(3)-C(24)-C(21) = −5.3(3)°] might ensure their participation in the aldehyde carbonyl group activation with a minimal entropic cost. In the chiral amide fragment, the preferred conformation places the *tert*-butyl group almost perpendicular to the squaramide plane [torsion angle: C(17)-C(16)-N(2)-C(21) = 105.6(5)°]. Importantly, the low dihedral O(1)-C(15)-C(16)-N(2) angle of −41.9(6)° places the amide carbonyl group [C(15)=O(1)] in a convenient orientation to drive the approach of the hydrazone to aldehyde.

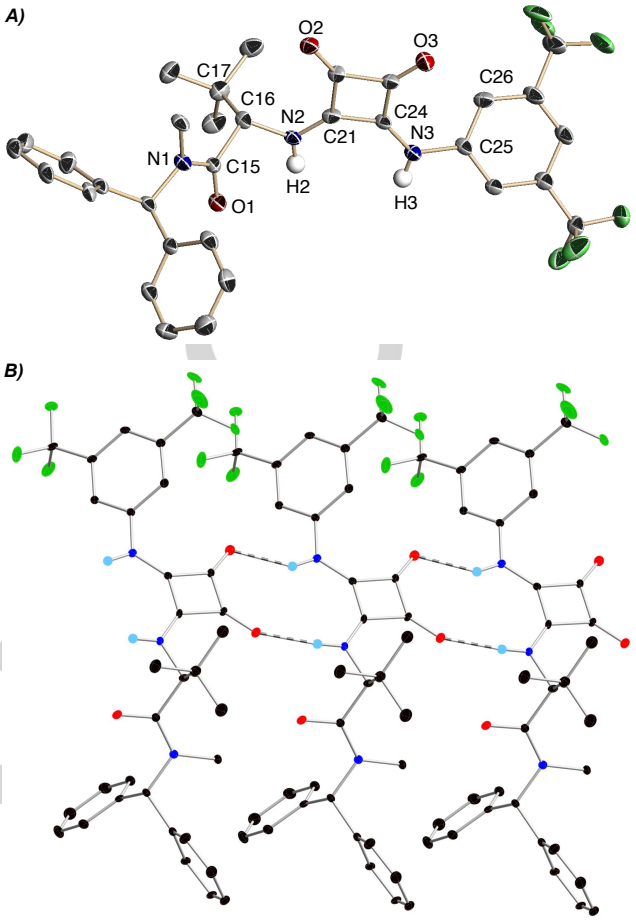



**Figure 5.** *A)* X-Ray structure of **II**. H atoms (except H1 and H7) are omitted for clarity. Thermal ellipsoids drawn at 50% probability. *B)* Head-to-tail *H*-bonding interactions in the solid state (three monomers shown).

## Conclusions

In summary, amide-squaramide catalysts enabled the highly enantioselective addition of formaldehyde *tert*-butyl hydrazone (***FTBH***) to simple aldehydes. The use of α,α,α-trifluorotoluene was essential to ensure homogeneous reaction media which led to good and reproducible results. Experimental data suggest that the ability of the squaramide group to behave as efficient *H*-bond donor and the presence of a *H*-bond acceptor in *tert*-leucine derived amide fragment of catalyst **II** are key for the dual activation of the reactants, leading to enantioenriched products via a highly ordered complex that explains the observed stereochemistry. The presented approach allows for an efficient route to asymmetric functionalization of simple aldehydes affording a broad spectrum of optically active alcohols and derivatives thereof.

## Experimental Section

**General procedure for the catalytic enantioselective reactions of *tert*-butyl hydrazone 1a with aldehydes 2 and subsequent regioselective *N*-oxidation:**

Freshly distilled formaldehyde *tert*-butyl hydrazone **1a** (34 µL, 0.3 mmol) was added to a solution of aldehydes **2** (0.2 mmol) and catalyst **II** (0.02 mmol, 12 mg) in α,α,α-trifluorotoluene (0.4 mL) at the temperature specified for each substrate (see Table 2). The mixture was stirred until consumption of the starting material ($^1$H-NMR monitoring). After this time, MeOH (0.4 mL) and MMPP (360 mg, 0.6 mmol) were subsequently added and the reaction mixture was allowed to warm up to rt for completion (1-2 hours). The mixture was then diluted with $H_2O$ (3 mL) and extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (Cy/$CH_2Cl_2$/AcOEt 1/8/1) to afford azoxy compounds **4**. Enantiomeric excess was determined by HPLC analysis.

## Acknowledgements

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[23] CCDC 1825081 contains the supplementary crystallographic data for (*S*)-**II**.

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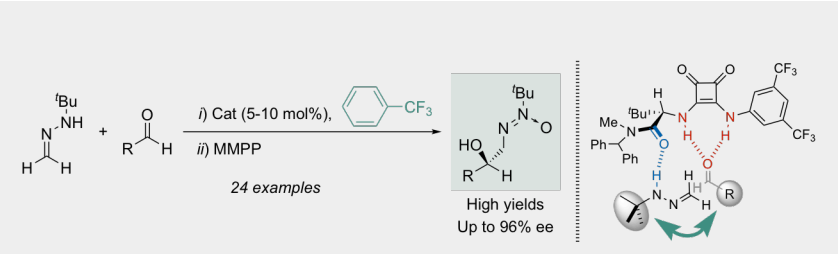


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**Bifunctional Squaramide Organocatalysts for the Asymmetric Addition of Formaldehyde *tert*-Butyl Hydrazone to Simple Aldehydes**

Bifunctional amide-squaramide catalysts enabled the highly enantioselective addition of formaldehyde *tert*-butyl hydrazone to simple aldehydes. The use of α,α,α-trifluorotoluene was essential to afford good and reproducible results. Subsequent derivatizations provide an entry to relevant amino alcohols, oxazolidinones and derivatives thereof.