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Bianthryl-Based Organocatalyst for Asymmetric Henry Reaction of Fluoroketones†

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We have developed a catalytic system based on bianthrylbis(thiourea) for the asymmetric Henry reaction of fluoroketones and nitroalkanes that resulted from the screening of a library containing 31 chiral non-racemic organocatalysts. The corresponding adducts were isolated in up to 6 times shorter reaction time in comparison with the previously published organocatalysts. High levels of stereocontrol have been generally observed, with measured product enantiomeric excesses up to 97% and diastereomeric ratio 3:2 (*anti*/*syn*) The above catalyst has been successfully applied to the total asymmetric synthesis of CF_3-tethered (*S*)-halostachine, which has proved that this method constitutes an easy entry to the similar enantiopure compounds.

Chiral non-racemic tertiary alcohols containing α-CF_3 or α-CHF_2 group represent interesting and promising compounds for medicinal chemistry and agrochemistry (**Fig. 1**).[1]

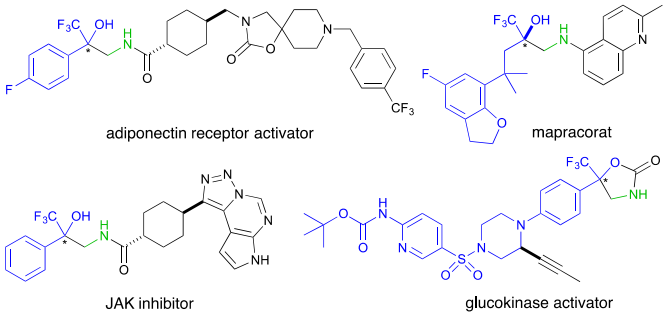

Figure 1. Selected biologically active compounds with depicted units that can be derived from the nitroaldol reaction.[2]

These molecules can be effectively prepared by the nitroaldol (Henry) reaction that belongs to the group of important carbon–carbon bond-forming processes.[3] For many applications, in which the newly formed stereocentres are significant, a control of their configuration is crucial during the nitroaldol process. Therefore considerable efforts have been made towards the development of the asymmetric version of this reaction.[4–5] Nevertheless, in comparison with the asymmetric organocatalyzed Henry reaction between aldehydes and nitroalkanes, the above reaction of fluoroketones and nitroalkanes has still remained considerably underexplored.

In 2001 Matsumoto et al. investigated for the first time the asymmetric organocatalyzed Henry reaction involving trifluoroketones.[6] Although the research provided helpful insights into this type of transformation, the use of quinidine as a catalyst resulted only in the moderate yield (81%) and modest enantioselectivity (21% ee). Narrow substrate scope, a relatively high catalyst loading (20 mol%), the necessity of the very low reaction temperature (–78 °C), and low stereoselective outcome left enough room for further improvements.

In 2008 Bandini and Umani-Ronchi commenced with a novel catalytically active C-9-benzoyl-cupreine derivative.[7] This bifunctional cinchona-alkaloid catalyst provided the corresponding nitroaldol adducts in very good to excellent enantioselectivities (76–99% ee), reasonable reaction time (48 h), and temperature (–25 °C) even at a relatively low catalyst loading (5 mol%).

Subsequently, in 2010, Connon and Palacio presented the quinine-based catalyst with the aryl urea unit incorporated at C-5' position and C-9 position decorated with aryl carbamate.[8] Under the optimized reaction conditions in terms of the reaction temperature (–20 or –30 °C), reaction time (72 h), and catalyst load (10 mol%), the catalyst exhibited similar yields and stereoselectivities for the aryl substrates to those reported by Bandini and Umani-Ronchi (82–96% ee). On the other hand, Connon's catalyst provided nitroaldols of the corresponding alkyl substrates in quite a better level of enantiocontrol.

The hegemony of the cinchona alkaloid-based catalysts has been partially disrupted in 2014 by Feringa et al. who introduced a responsive chiral thiourea catalyst containing

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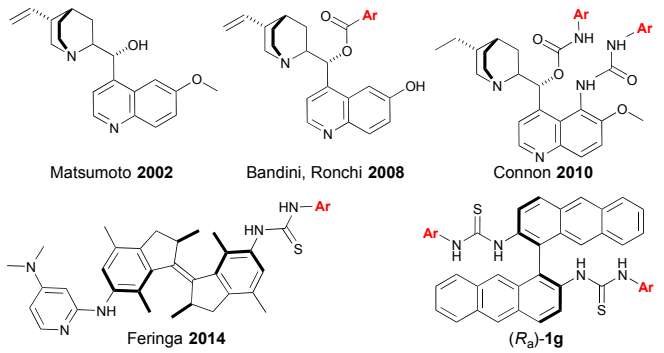
2,2',4,4',7,7'-hexamethyl-2,2',3,3'-tetrahydro-[1,1'-biindenylidene]-6,6'-diamine scaffold.[9] This work gave a proof-of-concept that a single multitasking catalyst with a distance between the two catalytic moieties controlled by a light-driven molecular motor can provide access to both enantiomers on command. Regrettably, the stereodiscrimination, which was not a primary goal of this work, was only low to moderate (14–72% ee).



Note: Ar = 3,5-$(CF_3)_2C_6H_3$.

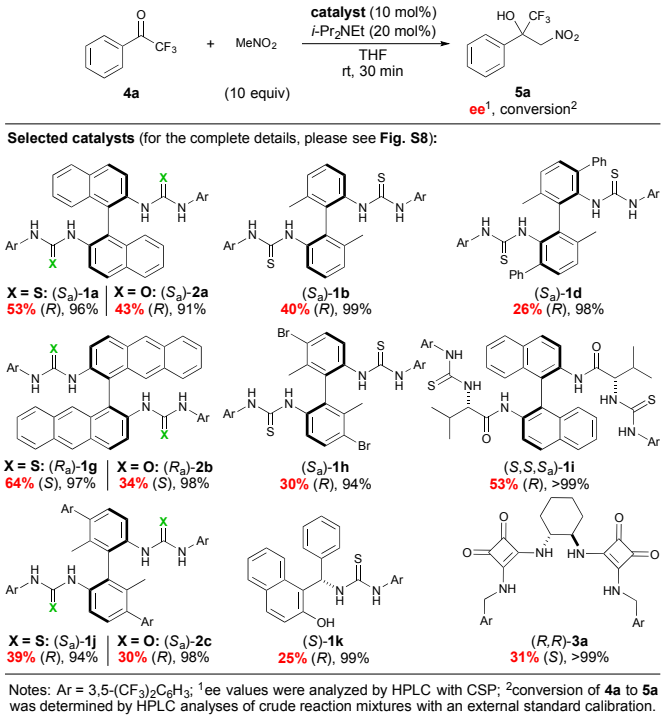
Figure 2. Structures of the available organocatalyst applied to the asymmetric Henry reaction of nitroalkanes and fluoroketones.

To the best of our knowledge, the aforementioned four organocatalysts were the only known asymmetric organocatalysts for this type of transformation at the outset of our study (**Fig. 2**). The fact that only two of them exhibited synthetically useful enantioselectivities and both these organocatalysts are cinchona-based compounds, which rely on the hydrolytically labile ester or carbamate functional group suggests that the development of the more robust catalytic systems with completely different chiral scaffolds is highly justifiable.

Our previous investigations on the asymmetric Henry reaction of aromatic aldehydes indicated that the formation of nitronate species represents at least a partially rate-limiting step of the overall transformation.[4b] While taking this into consideration, we have hypothesized that the catalyst design with an external base, which can be in terms of type and amount adjusted separately, can help to overcome the sluggish reaction rates of the organocatalyzed reactions between fluoroketone and nitroalkane at diminished temperatures without compromising consumption of the precious chiral catalyst.

However, at the beginning of our present work, we faced a serious challenge on how to discover a suitable chiral auxiliary for a design of a novel organocatalyst with the predefined properties. Therefore, initially, the extensive screening of a relatively large compound library with a special emphasis on the atropisomeric scaffolds was performed under the model reaction conditions (**Scheme 1**,[10] more in detail **Fig. S8**). This effort resulted in two hits – catalysts **1a** (53% ee) and **1b** (40% ee). Next, we tried to adjust their structures in order to increase the observed stereoselectivity. Unfortunately, none of the catalysts with the modified structures, i.e. **1d** or **1h–j**, was able to outperform the above patterns in terms of enantiocontrol (26–53% ee). This issue was finally solved out after the condensed aromatic system of **1a** was expanded, which was hypothesized that can enhance both the substrate binding and the asymmetric induction (cf. **1a** vs. **1b**). Hence the bis(thiourea) catalyst **1g** derived from 1,1'-bianthryl-2,2'-diamine (BIANAM) was prepared and tested (64% ee).

BIANAM was originally synthesized and resolved into enantiomers by Vyskocil, Kocovsky, and others in 2001.[11] However, the published synthesis relied on a cumbersome copper complex catalyzed oxidative dimerization step, which was substantially improved with the more convenient rhodium-catalyzed dimerization by Shindo et al. in 2014.[12] Although the authors of the former article envisioned the potential use of BIANAM in asymmetric catalysis, it has never been successfully applied until now.



Notes: Ar = 3,5-$(CF_3)_2C_6H_3$; [1]ee values were analyzed by HPLC with CSP; [2]conversion of **4a** to **5a** was determined by HPLC analyses of crude reaction mixtures with an external standard calibration.

Scheme 1. Catalyst screening conditions showing entries with the highest stereoselective outcome for **5a**.

After the expedient chiral scaffold was found, the hydrogen-bond donor properties of the catalyst were optimized. Accordingly, structures **2a**, **2b**, and **2c** were prepared. Regretfully, neither of them was superior to **1g** (30–43% ee). Furthermore, the bis(squaramide) derivatives of the above atropisomeric scaffolds exhibited a critically low solubility in any of the tested solvents, which made the structural characterization and potential synthetic use of this class of compounds practically impossible.

With the proper catalyst **1g** in hands, we have, indeed, proceeded to investigate the remaining reaction parameters. First, the kind of auxiliary base was optimized. We have evaluated six types of external bases including *i*-Pr_2NEt, Et_3N, *n*-Bu_3N, TMEDA, DMAP, and *N*-methylpyrrolidine. It was observed that TMEDA and DMAP, which are approximately one order of magnitude weaker than other bases from the

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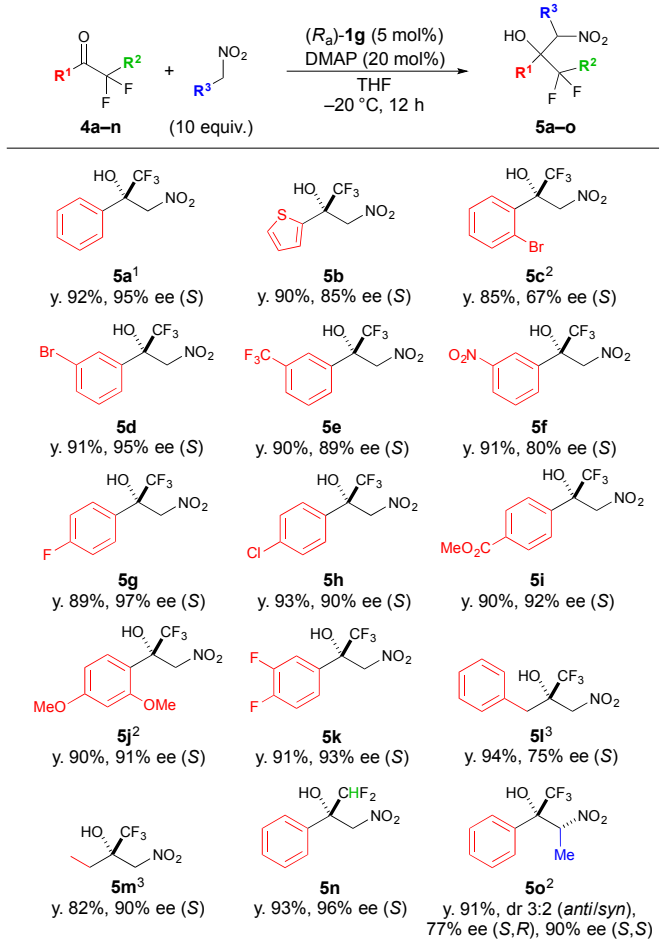
above list, provided the corresponding nitroaldol adduct in much higher enantioselectivity (**Tab. S2**). It can be attributed to the sufficiently suppressed non-enantioselective background reactions in these cases. In accordance with our previous results, the subsequent solvent screening protocol has proved that the ethereal solvents were the most suitable choice for this transformation (**Tab. S2**).[4b,13] The best ee values were achieved with THF, which has the highest Lewis basicity among the tested solvents.[14] The origin of this solvent effect remains unclear, however, it indicates that the energy difference between the transition states leading to opposite enantiomers is enough small to be substantially influenced by the solvent properties. In the next optimization step, the amount of the catalyst was reduced to 5 mol% without any detectable loss of the measured selectivity and performance. The additional attempt to decrease the loading thereof to 2.5 mol% resulted in a slight drop in enantioselectivity (79% ee) and the reaction rate. The same tendency was observed during the lowering of the base load (**Tab. S3**).



Notes: reported yields are of isolated products obtained after the full conversion of starting material; ee values were analyzed by HPLC with CSP; dr ratios were determined by ^{1}H and ^{19}F NMR; ^{1}y. 81% at the 1.5 mmol scale; ^{2}reaction performed at –20 °C for 24 h; ^{3}reaction performed at –30 °C for 12 h.

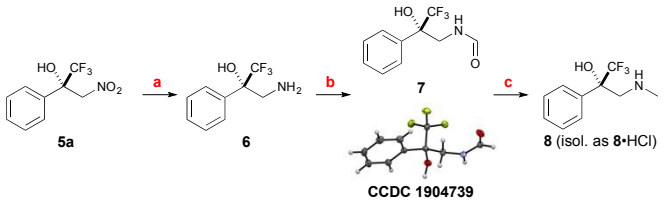
Scheme 2. Substrate scope of the (R_a)-1g catalyzed asymmetric Henry reaction.

Based on the aforementioned optimization efforts, we were pleased to find that the developed asymmetric Henry reaction furnished **5a** in 30 min with a very good stereoselectivity (83% ee) even at ambient temperature. The selectivity of the above process was further improved under 0 °C (91% ee, 6 h) and –20 °C (95% ee, 8–12 h) offering a complete conversion of **4a** to **5a** in a still pretty reasonable reaction time (**Tab. S4**).

Our next task was to analyze the substrate scope of this process. The obtained results are summarized in **Scheme 2**. The best outcome in terms of enantioselectivity was observed for the ring-unsubstituted and *para*-substituted derivatives. It is worth noting that one of the most difficult substrate **4b** and also the regular substrate **4g** were converted to the corresponding aldols **5b** and **5g** in the best enantiomeric excesses reported for the organocatalyzed process thus far. Similarly, products **5a**, **5e**, **5h**, **5m**, and even difluoromethyl-appended derivative **5n** were isolated in ee values comparable to Bandini–Umani-Ronchi's or Connon's catalyst, however in the four to six times shorter reaction time, respectively.[7–8] It is remarkable that more *meta*- or *para*-substituted adducts, i.e. **5d**, **5i**, and also highly electron-rich **5j**, exceeded the 90% level of enantioselectivity.[15] On the other hand, the sterically demanding *ortho*-substituted derivative **5c** was formed in a moderate stereoselectivity only (67% ee) with a penalty of doubled reaction time (24 h). Nevertheless, the *ortho*-substituted substrate **4c** has never been tested yet in the literature and therefore we cannot assess if the obtained ee of this benchmark entry represents success or a failure of our catalytic system.

The enolizable aliphatic ketones **4l** and **4m** required a slightly decreased reaction temperature (–30 °C) to provide good enantiomeric excesses while preserving the same reaction time as other standard substrates (12 h). The resulting adducts **5l** and **5m** were isolated without any self-aldolization by-products.

The promising catalytic performance of (R_a)-**1g** was also demonstrated on the challenging diastereoselective nitroaldol reaction of nitroethane with **4a**. This transformation did not lead to completion even after 89 h with any of the Connon's catalysts.[8] Gratifyingly, in our case, the reaction reached the full conversion of the starting material in 24 h and afforded the respective epimeric mixture **5o** in 3:2 ratio in favor of *anti*-adduct. The above *anti*-adduct was obtained with a good enantioselectivity (77% ee), while the minor *syn*-adduct even in 90% ee.



Reagents and conditions: a) H_2 (15 psi), 10% $Pd(OH)_2$/C, MeOH, rt, 3 h, y. 86%; **b)** AcOCHO, THF, 0 °C to rt, 12 h, y. 63%; **c)** 60% SMEAH in MePh, MePh, rt, 48 h, y. 56%.

Scheme 3. Asymmetric synthesis of CF_3-tethered (*S*)-halostachine analog.

The robustness of the developed catalytic process was further surveyed in the total synthesis of enantiopure CF_3-tethered (*S*)-halostachine carried out at the 1.5 mmol scale (**Scheme 3**).

As such, the corresponding isolated adduct (*S*)-**5a** (y. 81%, 95% ee), $[\alpha]^{25}_D$ +42 (*c* 1.0; MeOH), lit.[16] 96% ee, $[\alpha]^{25}_D$ +42.0 (*c* 1.7; MeOH), was hydrogenated over $Pd(OH)_2/C$ under 15 psi of H_2 to (*S*)-**6** (y. 86%), $[\alpha]^{25}_D$ +40 (*c* 0.2; $CHCl_3$), lit.[16] $[\alpha]^{25}_D$ +40.5 (*c* 0.8; $CHCl_3$), then formylated with acetic formic anhydride to (*S*)-**7** (y. 63%, $[\alpha]^{25}_D$ +64.0 (*c* 0.2; $CHCl_3$),[17] and finally subjected to SMEAH reduction to give (*S*)-**8**, which was isolated as the corresponding HCl salt (y. 56% $[\alpha]^{25}_D$ +25 (*c* 0.6; MeOH) in 25% overall yield.

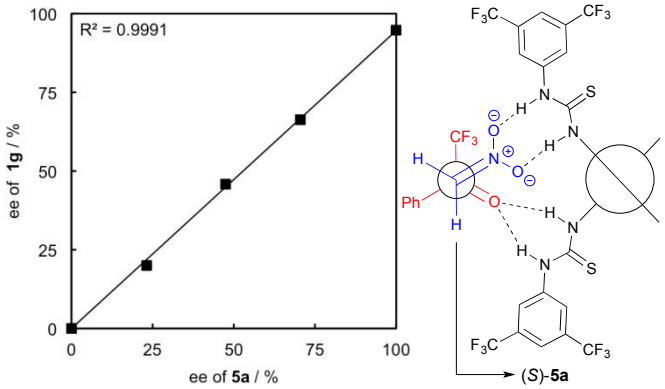


Figure 3. A relationship between catalyst ee (**1g**) and product ee (**5a**) for the asymmetric Henry reaction (left). A possible mode of activation for the (R_a)-**1g** catalyzed asymmetric Henry reaction (right).

To shed some light on the catalyst structure, the investigation of a possible non-linear effect was conducted. Accordingly, a linear dependence between the product ee and the catalyst ee was observed (**Fig. 3**). Hence, it is plausible to assume that the active state of the catalyst is a monomer.[18] Further studies regarding the reaction mechanism are currently underway.

Conclusions

In summary, we have developed a mild and reliable catalytic system for the asymmetric Henry reaction of fluoroketones and nitroalkanes that resulted from the screening of a library containing 31 chiral non-racemic organocatalysts. High levels of stereocontrol have been generally observed, with measured product enantiomeric excesses up to 97% and diastereomeric ratio 3:2 (*anti*/*syn*). The substrate scope including 15 entries suggests the considerable generality of the developed asymmetric transformation without a special preference for the electronic properties of the substrates. The catalyst has been successfully applied to the total asymmetric synthesis of CF_3-tethered (*S*)-halostachine, which has proved that the above method constitutes an easy entry to the similar enantiopure compounds. The additional preliminary mechanistic experiment has revealed that the catalyst does not exhibit a non-linear effect.

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Conflicts of interest

The authors declare no competing financial interest.

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