Enantioselective organocatalyzed Henry reaction with fluoromethyl ketones†

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Remarkable generality in scope of new *C*9-benzoylcupreines bearing electron-withdrawing substituents for the nitroaldol condensation with fluoromethyl ketones is presented. Both tri- and difluoromethyl ketones provided excellent levels of stereoinduction (ee 76–99%) under mild reaction conditions and low loading of catalyst (1–5 mol%).

Nitroaldol condensation, also known as the Henry reaction,[1] is one of the most important C–C bond forming transformations. The high scientific and commercial value of enantiomerically enriched nitroaldol compounds is testified by their ubiquity as building blocks for pharmaceuticals and agrochemicals.[2] In this scenario, the search for new, eco-friendly and effective catalytic enantioselective versions of nitroaldol condensations is deserving great attention by numerous research teams both in industry and academia.[3] Although aldehydes and aldoimines (aza-Henry)[4] have been subjected to extensive efforts, the use of more challenging simple ketones, as Henry acceptors, has remained relatively unexplored.[5] In fact, only activated α-ketoesters were found to react successfully with nitromethane in the presence of chiral Lewis acids[6a–e] or organocatalysts.[6f]

As a part of our ongoing interests in this field,[7] we became interested in simple aryl and alkyl trifluoromethyl ketones **1**[8] that would lead to synthetically useful trifluoromethyl β-nitroalcohols **2**,[9] bearing quaternary stereocenters.[10] Despite this interest, challenging issues such as: poor stereodiscrimination due to steric similarity of the substituents of the C=O moiety and concomitance of uncatalyzed background reactions, account for the limited exploration of **1** in catalytic enantioselective C–C bond forming reactions (Fig. 1).[11]

These considerations affected also the nitroaldol condensation, where only ethyl trifluoromethyl pyruvate[6c,d] and 3-phenyl-1,1,1-trifluoroacetone[12] were employed, with unacceptable enantioselection. During the preparation of the manuscript, Tur and Saá reported on the use of a chiral lanthanum(III) triflate salt complex for the direct nitroaldol reaction of trifluomethyl ketones with high ees.[13] However, high loading of catalyst (25 mol%), and prolonged reaction times (4–7 days) still represent important issues to be addressed. Here, considering the high reactivity of **1** we speculated that organo-catalysis could provide valuable solutions to these tasks.

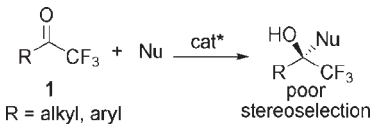
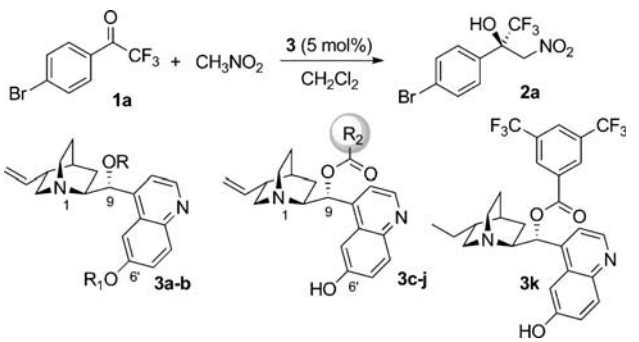


Fig. 1

In the realm of metal-free asymmetric protocols, we were particularly attracted by the recent studies of Deng[6f] and Hiemstra[14] on the use of bifunctional catalysts cupreines and cupreidines[15] in promoting the addition of $MeNO_2$ to α-ketoesters and aldehydes, respectively. Therefore, by considering the 4′-bromo-2,2,2-trifluoroacetophenone (**1a**) as a

Table 1 Optimization of reaction conditions for the enantioselective organocatalyzed condensation of $MeNO_2$ with **1a**[a]



Entry	Catalyst	Yield **2a**[b] (%)	Ee **2a**[c] (%)
1	**3a** R = H, R_1 = H (CPN)	93	23 (*R*)
2	**3b** R = H, R_1 = Me (QN)	55	0
3	**3c** R_2 = Ph (CPN-Bz)	96	62 (*R*)
4	**3d** R_2 = 3,4-$(OMe)_2C_6H_3$	87	53 (*R*)
5	**3e** R_2 = 3,5-$Me_2C_6H_3$	75	55 (*R*)
6	**3f** R_2 = 4-$NO_2C_6H_4$	98	65 (*R*)
7	**3g** R_2 = 3,5-$(CF_3)_2C_6H_3$	98	70 (*R*)
8	**3h** R_2 = 2,3,4,5,6-C_6F_5	97	73 (*R*)
9	**3i** R_2 = 3,5-$(NO_2)_2C_6H_3$	85	82 (*R*)
10	**3j** R_2 = *t*-Bu	84	56 (*R*)
11	**3g**	95	90 (*R*)
12[de]	**3g**	90	85 (*R*)

[a] All the reactions were carried out in open-air vials with reagent grade CH_2Cl_2 (**1a** : $MeNO_2$ = 1 : 10) at 0 °C, unless otherwise specified. [b] Isolated yield after flash chromatography. [c] Determined by HPLC with chiral column. The absolute configuration was determined by comparison of the optical rotation value with known compounds. [d] Reaction temperature −25 °C. [e] 1 mol% of **3g** was employed, 72 h reaction time.

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model substrate, we verified the performances of the cupreine **3a** (CPN, 5 mol%) as the catalyst, obtaining the nitroalcohol **2a** in 93% yield and modest 23% enantiomeric excess (0 °C, entry 1, Table 1).

The cooperating effect of *C*6′-OH and the quinuclidine *N*1 was proved by using quinine as the catalyst (QN, **3b**, *C*6′-OMe) that furnished **2a** in racemic form (entry 2). Analogously to the observation of Deng and co-workers[6f] the increasing stereocontrol obtained with CPN-Bz (Bz: benzoyl) alkaloid **3c** (ee = 62%, entry 3) stressed the role of "rigid" substituents at the *C*9 position in the enantiodiscriminating event.

In an effort to reach synthetically useful enantiocontrol, we reasoned that an electronic fine-tuning of the functionalisation at the *C*9-position could strengthen of the substrate–catalyst interactions, with consequent enhancement of the stereodiscrimination.[16]

To prove such an hypothesis, we synthesized a range of new *C*9-benzoylcupreines (**3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**) bearing electron-withdrawing (EWG) and electron-donating (EDG) groups in the arene rings.

Here, a narrow trend between the electronic properties of the C*9*-Bz group and the enantiodifferentiation was observed. In particular, while electron-rich 3,4-$(OMe)_2C_6H_3$ and 3,5-$Me_2C_6H_3$ groups (**3d**, **3e**) led to a drop in enantioselectivity (ee = 53–55%), the employment of CPN-Bz bearing electron-withdrawing substituents furnished **2a** with highest enantiocontrol up to 82% with *C*9-3,5-$(NO_2)_2$-benzoylcupreine **3i** (entry 9). Proofs of the role of electronic effect in the stereodiscrimination of the reaction came from a control experiment with pivaloyl-based catalyst **3j** that furnished **2a** in 84% yield but with modest ee (56%, entry 10).

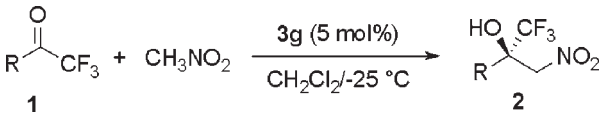
On the other hand, the relatively low stability and solubility of **3i**, under best operational conditions,[17] led to scarce reproducibility in terms of chemical and optical yields. Therefore we addressed our interest in the readily available and more soluble/stable *C*9-3,5-$(CF_3)_2$-benzoyl catalyst **3g** that provided **2a** in 95% yield and 90% ee at −25 °C (CH_2Cl_2, entry 11).[18] Remarkably, under best conditions efficient nitroaldol condensation was observed using as little as 1 mol% of **3g** (entry 12) that furnished **2a** in comparable yield (90%) and 85% ee.

The scope of the protocol was then investigated by subjecting a range of trifluoromethyl ketones (**1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, **1i**, **1j**) to the nitroaldol condensation. Typical results are listed in Table 2.‡

It is worth noting that very high enantiomeric excesses were recorded with both aromatic and aliphatic substrates (ee up to 99%). Here, high tolerance toward substituents in different positions of the aromatic ring, was observed.

Of particular relevance is the result obtained with ketone **1d** (*m*-CF_3, yield = 86%, ee = 96%, entry 3) that proved to be a challenging substrate under organometallic catalysis (ee = 67%).[13] Again, aliphatic/enolizable ketones **1b**, **1j** reacted smoothly in the present Henry process affording the corresponding nitroalcohols **2**, chemoselectively, with ee = 92 and 93%, respectively (entries 1, 9). As expected, lower reactivity was shown by the electron-rich heteroaromatic ketone **1i** that, under optimal conditions, afforded **2i** in 79% yield and 76% ee.

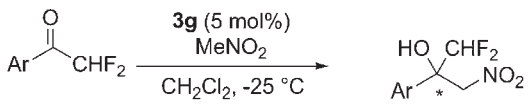
Table 2 Scope of the enantioselective **3g**-catalyzed Henry reaction[a]



Entry	Ketone	Yield **2a**[b] (%)	Ee **2a**[c] (%)
1	**1b** R = Bn	70	92 (*R*)
2	**1c** R = 4-ClC_6H_4	80	92 (*R*)
3	**1d** R = 3-$CF_3C_6H_4$	86	96 (*R*)
4	**1e** R = 4-PhC_6H_4	99	97 (*R*)
5	**1f** R = Ph	85	99 (*R*)
6	**1g** R = 4-FC_6H_4	85	95 (*R*)
7	**1h** R = 4-tolC_6H_4	85	90 (*R*)
8	**1i** R = thienyl	79	76 (*R*)
9	**1j** R = Et	67	93 (*R*)

[a] All the reactions were carried out in open air vials with reagent grade CH_2Cl_2 in the presence of 10 eq. of $MeNO_2$, 48 h reaction time. [b] Isolated yield after flash chromatography. [c] Determined by HPLC with chiral column. The absolute configurations were determined by comparison of the optical rotation value with known compounds or by analogy.

The catalytic performances of **3g** in promoting Henry reaction with fluoro ketones was further underlined by using the difluoro ketones (**1k**, **1l**). Interestingly, the synthetically useful difluoro tertiary alcohols **2k**[19] and **2l** were isolated in 71–77% yield and excellent enantiomeric excesses (ee = 92–99%, eqn (1)).[20]



1k: Ar = Ph
1l: Ar = 2-naphth

2k: yield = 77%, ee = 99%
2l: yield = 71%, ee = 92%

(1)

In conclusion, we have presented an unprecedented mild organocatalyzed nitroaldol condensation of fluoromethyl ketones in the presence of cinchona catalysts. The corresponding fluorurate β-nitroalcohols, bearing quaternary stereocenters, were isolated in high yield and excellent enantiomeric excesses. Mechanistic elucidations and the use of *C*9-benzoylcupreines in different enantioselective carbon–carbon forming processes involving trifluoromethyl ketones are underway.

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Notes and references

‡ A sample vial containing reagent grade CH_2Cl_2 (0.5 mL) was charged with 0.2 mmol of the desired ketone **1**, the reaction mixture was cooled to −78 °C then 108 μL (2 mmol) of $MeNO_2$ and 5.5 mg of **3g** (10 μmol) were added. The reaction temperature was warmed to −25 °C and stirred at the same temperature for 48 h. The volatiles were evaporated and directly purified by flash chromatography (*c*Hex–AcOEt 8 : 2, see ESI†).

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