Organocatalytic asymmetric synthesis of chiral fluorinated quaternary carbon containing β-ketoesters†

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Organocatalytic enantioselective conjugate addition of α-fluoroketoesters to nitroolefins efficiently catalyzed by a cinchona alkaloid-derivative affords versatile non-enolizable ketoesters by forming two consecutive fluorinated quaternary and tertiary chiral carbon centers with excellent enantioselectivity.

The importance of fluorine-containing compounds has been underlined by their broad applications in the areas of agricultural, medicinal, and material chemistry.[1] Statistic studies reveal that "as many as 30–40% of agrochemical and 20% of pharmaceuticals on market are estimated to contain fluorine."[2] It has been demonstrated that in many cases, the substitution of hydrogen atom(s) with fluorine(s) in a biologically active molecule can improve its properties such as potency and bioavailability significantly as results of its distinctive characteristics of the most electronegative element, highly strong C–F bond and similar size to H atom. Nowadays, it has become a general practice in drug design to incorporate fluorine atom(s) into bioactive molecules to modulate their biological properties. Accordingly, the selective fluorination of organic compounds has been a fascinating topic in the recent past.[2,3]

Construction of chiral quaternary carbons is a formidable challenge in organic synthesis.[4] However, the creation of chiral fluorinated quaternary carbon centers is even more challenging and only a handful of examples that mainly rely on metal catalysis can be identified.[3d,5] Moreover, the use of organocatalytic strategies for the preparation of fluorinated quaternary carbon centers are more scarce. Based on the α-fluorination of aldehydes using an electrophilic fluorinating agent,[3e,6] Jørgensen and co-workers extended the strategy for an asymmetric α-fluorination of α-branched aldehydes to produce fluorinated quaternary centers.[7] Shibata and coworkers disclosed a cinchona alkaloid catalyzed enantioselective fluorination of allyl silanes, silyl enol ethers and oxindoles with NSFI.[8] Kim *et al.* have developed asymmetric fluorination reactions using a phase-transfer catalyst as a promoter.[9]

It is established that ketoesters are effective nucleophiles for organocatalyzed conjugate addition reactions.[10] We envisioned that the use of commercially available α-fluoroketoesters as a nucleophile could produce compounds with a fluorinated quaternary carbon center. However, to our knowledge, the reaction has not been disclosed. It is expected that the reactivity profile of the α-fluoroketoesters is different to that of classic ketoesters. Moreover, the products resulting from a conjugate addition reaction would generate fluorinated quaternary carbon containing non-enolizable β-ketone esters, which can be conveniently elaborated in organic synthesis and could be potentially useful in drug discovery.[11] Toward this end, we disclose an unprecedented conjugate addition reaction between a nucleophilic α-fluoroketoester and nitroolefins. The process is efficiently promoted by a simple cinchona alkaloid derivative with a remarkably low catalyst loading (1 mol%). Significantly, the reaction affords the products with a fluorine containing quaternary carbon center and an adjacent chiral carbon center in high yields and with excellent enantioselectivity.

In our initial investigation, cinchona alkaloid quinine derivatives are explored for the conjugate addition of α-fluoroketoester **1** to *trans*-β-nitrostyrene **2a** in $CHCl_3$ with 1 mol% catalyst loading (Fig. 1 and Table 1).[12] Gratifyingly, the process proceeds smoothly to give the desired adduct **3a** in high yields and with moderate diastereoselectivity (Table 1). The results indicate that α-fluoroketoesters are more active nucleophiles than classic ketoesters. The enantioselectivity of the reaction depends on the catalysts used (entries 1, 2, 9 and 10). Among these catalysts screened, catalyst **II** is superior to others in terms of the observed selectivity of the reactions (Table 1, entry 2). In this case, a high level of enantioselectivity (97% and 97% for both diastereomers) is achieved. Accordingly, we selected catalyst **II** for further optimization of reactions conditions. Favorable aprotic and nonpolar solvents were probed for the H-bonding mediated catalysis. The reactions carried out in $CHCl_3$ and $Cl(CH_2)_2Cl$ afford higher ee

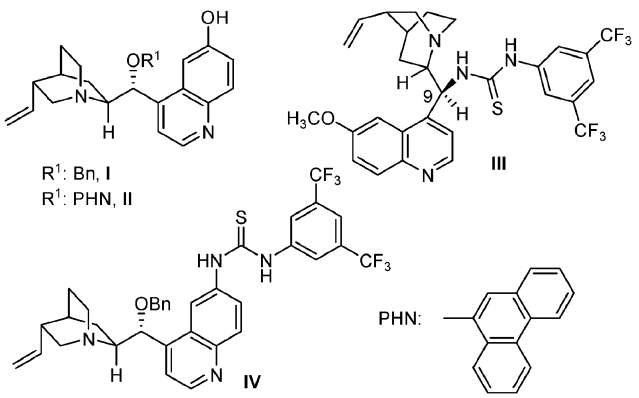

Fig. 1 Screened organocatalysts.

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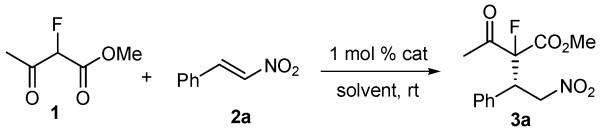
Table 1 Organocatalytic enantioselective Michael reaction of methyl α-fluoromethyl ketoester (**1**) with *trans*-β-ntirostyrene (**2a**)[a]



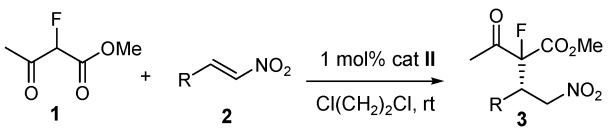
Entry	Cat.	Solvent	*t*/h	Yield[b] (%)	ee[c] (%) A/B	dr A : B[d]
1	**I**	$CHCl_3$	24	94	93/95	1.6 : 1
2	**II**	$CHCl_3$	24	95	97/97	2 : 1
3	**II**	CH_2Cl_2	24	97	96/94	3 : 1
4	**II**	$Cl(CH_2)_2Cl$	24	97	97/96	3 : 1
5	**II**	Toluene	48	92	92/91	1.8 : 1
6	**II**	Xylenes	48	92	90/91	2 : 1
7	**II**	Et_2O	24	96	87/88	3 : 1
8	**II**	THF	24	92	90/88	2 : 1
9	**III**	$CHCl_3$	24	92	88/82	2 : 1
10	**IV**	$CHCl_3$	24	94	70/81	2 : 1

[a] *Reaction conditions*: A mixture of **1a** (0.10 mmol), **2** (0.105 mmol), and a catalyst (0.001 mmol) in a solvent (0.5 mL) was stirred at rt for a specified period of time. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H); A corresponds to the major diastereoisomer. [d] Determined by ^{1}H NMR.

values (entries 2 and 4), while a relatively better dr is obtained in $Cl(CH_2)_2Cl$.

With the optimized reaction conditions in hand, we turned our attention to probing the generality of the conjugate addition processes. As revealed in Table 2, the organocatalytic enantioselective reactions served as an efficient and general route for the preparation of the adducts with excellent levels of enantioselectivity (94–99% ee) and in high yields (75–98%) despite moderate drs (1.7–4 : 1). Importantly, two new stereogenic centers are created with forming a fluorine containing quaternary carbon center and an adjacent chiral carbon center. Significant structural variation of nitroolefins **2** can be tolerated. Both aromatic (entries 1–12) and aliphatic (entry 13) systems can effectively participate in the process. The electronic substitution nature on the aromatic rings of nitroolefins **2** has apparently limited influence on the stereochemical outcome. Electron-neutral (entry 1), withdrawing (entries 2–5), donating (entries 6–10), and hetereoaromatic (entries 11–12) systems undergo reactions smoothly. Probing the steric effect on the enantioselectivity of the conjugate addition processes reveals that such influence is also minimal in terms of yield and enantioselectivity (entry 9). Moreover, 2-fluoromalonate ester can also serve as an effective nucleophile for the conjugate addition process to give rise to a

Table 2 Catalyst **II** promoted enantioselective Michael reaction of methyl α-fluoromethyl ketoester (**1**) with *trans*-nitroolefins (**2**)[a]



Entry	R	**3**	*t*/h	Yield[b] (%)	ee[c] (%) A/B	dr A : B[d]
1	Ph	**3a**	24	97	97/96	3 : 1
2	4-FC_6H_4	**3b**	24	95	98/97	3 : 1
3	4-ClC_6H_4	**3c**	24	98	98/97	3 : 1
4	4-BrC_6H_4	**3d**	24	97	99/94	3.5 : 1
5	3-BrC_6H_4	**3e**	24	94	98/97	3.5 : 1
6	4-MeC_6H_4	**3f**	24	92	99/98	4 : 1
7	4-$MeOC_6H_4$	**3g**	24	95	98/95	3 : 1
8	4-$BnOC_6H_4$	**3h**	24	96	98/97	3 : 1
9	2-$BnOC_6H_4$	**3i**	48	90	97/95	1.7 : 1
10	3,4-$(OCH_2O)C_6H_3$	**3j**	48	95	97/99	3 : 1
11	2-Furanyl	**3k**	48	94	99/99	4 : 1
12	2-Thienyl	**3l**	48	97	99/98	3.5 : 1
13	*n*-C_5H_{11}	**3m**	36	75	98/96	4 : 1
14[e]	2-ClC_6H_4	**3n**	72	98	86	—

[a] *Reaction conditions*: unless specified, see footnote *a* in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H, or Chiralcel OD-H); A corresponds to the major diastereoisomer. [d] Determined by ^{1}H NMR. [e] Methyl 2-fluoromalonate used as nucleophile and 20 mol% catalyst used in $CHCl_3$.

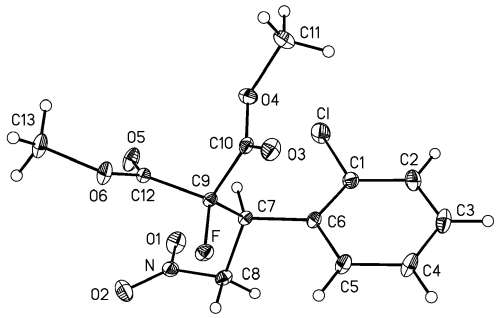
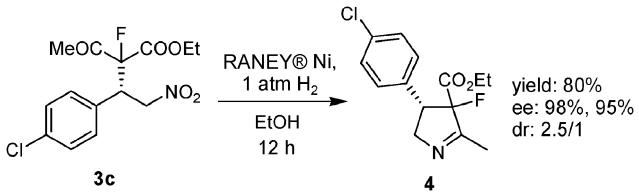


Fig. 2 X-Ray crystallographic structure of **3n**.

product **3n** in 98% yield and 86% ee. The absolute stereoconfiguration of the products was determined by single-crystal X-ray structural analysis based on the product **3n** (Fig. 2).[13]

In an exploratory study, we demonstrated that product **3c** can be conveniently converted to synthetically useful chiral Δ^1-pyrrolidine **4** by RANEY®-Ni mediated hydrogenation with high efficiency (Scheme 1).[14]



Scheme 1 Transformation of **3c** to chiral Δ^1-pyrrolidine **4**.

In conclusion, we have uncovered an unprecedented organocatalytic, enantioselective conjugate addition reaction of α-fluoroketoester and nitroolefins. The process is efficiently catalyzed by a readily available chiral cinchona alkaloid derivative using as low as 1 mol%. Significantly, a fluorine containing quaternary carbon center and an adjacent chiral carbon center are created with an excellent level of enantioselectivity and in high yields in the conjugate addition process. In principle, the strategy we have described can be extended to other fluorinated nucleophilic reagents and Michael receptors. This constitutes our future direction aimed at expanding the scope of powerful organocatalytic processes for the asymmetric synthesis of fluorine containing compounds.

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