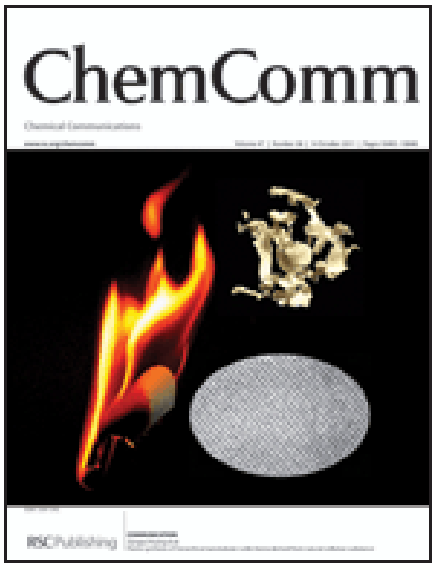

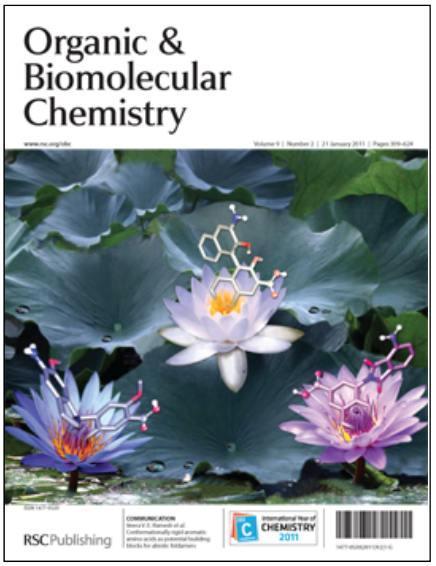

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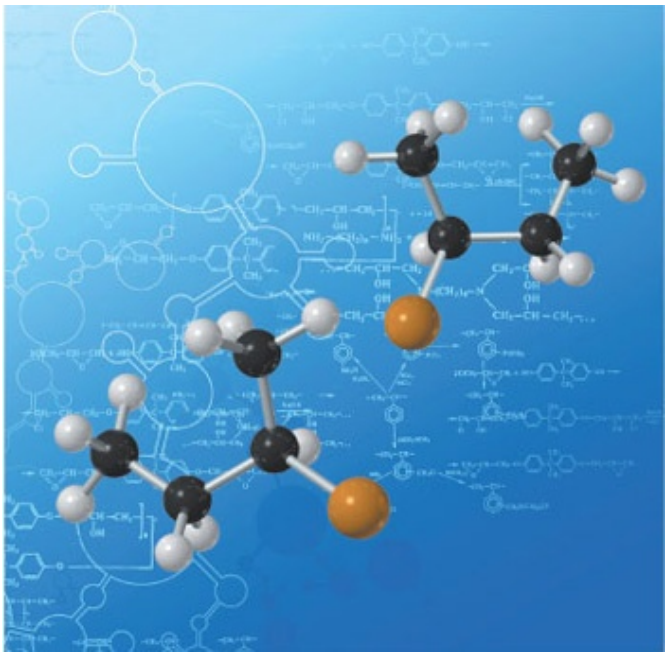

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Organocatalytic asymmetric synthesis of 3-difluoroalkyl 3-hydroxyoxindoles†‡

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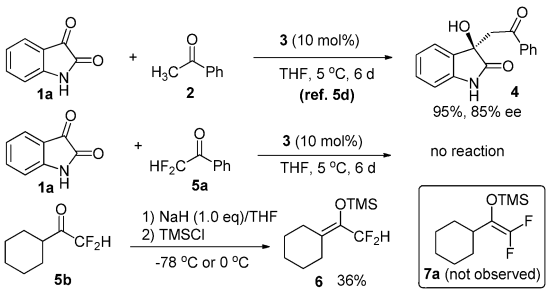
We report the first example of highly enantioselective organocatalytic synthesis of 3-difluoroalkyl substituted 3-hydroxyoxindoles. The total synthesis of the difluoro analogue of convolutamydine E was achieved by this method.

The selective introduction of fluoroalkyl groups has become a powerful strategy to modulate the pharmacological properties of compounds in drug design.[1] In this context, the incorporation of difluoroalkyl unit is of current interest,[2] since the *gem*-difluoromethylene group can influence the properties of its neighboring groups, and increase the lipophilicity, metabolic stability and bioavailability of the compounds.[3] For example, eflornithine[4a] and gemcitabine[4b] are rationally designed drugs. Given that 3-substituted 3-hydroxyoxindoles are widely present in bioactive natural products and drugs and the C3 substituents greatly influence their biological activities,[5] we are interested in the catalytic synthesis of enantioenriched 3-difluoroalkyl 3-hydroxyoxindoles.[6,7]

Surprisingly, while much progress has been made in the trifluoro- and monofluoromethylation reactions,[1c–e] catalytic asymmetric difluoromethylation remains a challenge.[2a,8] No successful catalytic asymmetric addition of difluoroalkyl-containing nucleophiles to aldehydes or ketones has been reported.[8] The addition of $TMSCF_2SO_2Ph$ or $TMSCF_2SePh$ to carbonyl compounds was independently pioneered by Hu *et al.*[8a] and Shibata *et al.*[1f] (with up to 64% ee). Alternatively, Bandini *et al.*[8b] and Ma *et al.*[8c] tried the addition of CH_3NO_2 or indole to α-CF_2H aryl ketones, with excellent ee for limited examples.

In this context, the challenge was possibly due to the dramatic difluorine effects on the reactivity. For example, we found that a thiourea catalyst could catalyze the Strecker reaction of acetophenone derived ketoimines alone using TMSCN, but could not catalyze that of α-CF_2H ketoimines.[8f] While Zhao *et al.* reported that bifunctional catalyst **3** promoted the aldol reaction of isatin **1a** and acetophenone **2** well (Scheme 1),[5d] we found that it could not catalyze the reaction of isatin **1a** and α-CF_2H ketone **5a**. In addition, we also observed that the deprotonation of ketone **5b** by NaH to react with TMSCl selectively afforded silyl enol ether **6** at −78 or 0 °C, and no difluoroenoxysilane **7a** was detected by NMR analysis. Accordingly, the identification of an effective method to enable easily available difluoroalkyl-containing reagents for reaction design would give an impetus in this field. Here, we report that nitrogen based Lewis bases could effectively activate difluoroenoxysilanes **7**[9] for a highly enantioselective synthesis of 3-difluoroalkyl 3-hydroxyoxindoles.



Scheme 1 Dramatic difluorine effects.

Although difluoroenoxysilane **7** is a versatile synthon for difluoro compounds, its application in asymmetric catalysis was rare.[8d,e] The only successful example was a phosphoric acid catalyzed Mannich reaction of **7** and aryl aldimines developed by Akiyama *et al.*[8e] Since Lewis acid catalyzed reactions of **7** and aldehydes suffered from high catalyst loading or low efficiency,[9a–c] we focused on the use of organocatalysts for reaction development. After optimization (see ESI‡), cinchona alkaloid derived bifunctional (thio)urea catalysts **3**, **9**, **10**[10] turned out to be promising for the reaction of silyl enol ether **7b** and isatin **1b**, using CH_2Cl_2 as the solvent at 0 °C (entries 1–3, Table 1), and quinine derived urea catalyst **10** could afford product **8a** in 91% yield with 80% ee (entry 3). The reaction possibly proceeded *via* the dual activation of both isatin **1b** by urea[11] part of the catalyst and silyl enol ether **7b** by the tertiary amine moiety as a Lewis base for the activation of trimethylsilyl nucleophiles.[12] As is demonstrated, thiourea **11** could not catalyze this reaction (entry 4), but DMAP **12** could catalyze efficiently to give product **8a** in 95% yield (entry 5), and the combination of **11** and **12** could afford product **8a** in 11% ee (entry 6). Further optimization revealed that THF was the optimal solvent (entry 7). Then the evaluation of substrate

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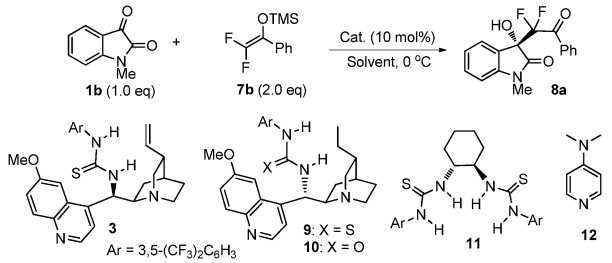
‡ Electronic supplementary information (ESI) available: Experimental details and spectral data. See DOI: 10.1039/c2cc17140f

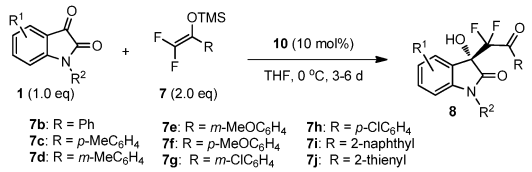
Table 1 Condition optimizations

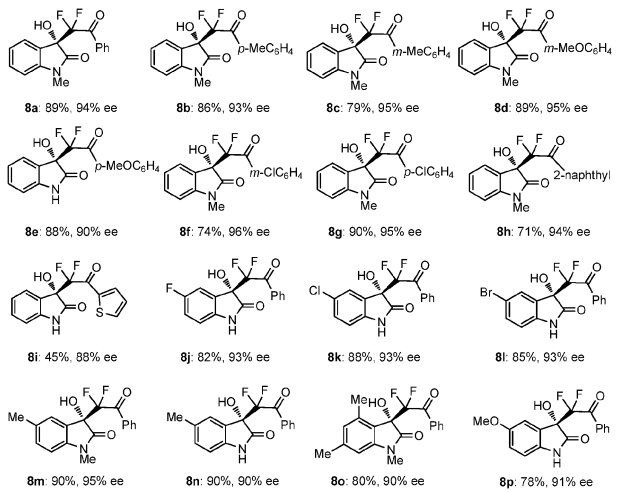


Entry[a]	Cat.	Solvent	Time/d	Yield[b] (%)	ee[c] (%)
1	**3**	CH_2Cl_2	3	85	79[d]
2	**9**	CH_2Cl_2	3	86	73
3	**10**	CH_2Cl_2	3	91	80
4	**11**	CH_2Cl_2	3	—	—
5	**12**	CH_2Cl_2	1	95	—
6	**11** + **12**	CH_2Cl_2	3	94	11
7	**10**	THF	3	93	94

[a] On a 0.10 mmol. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Opposite enantiomer.

Table 2 Substrate scope[a–c]

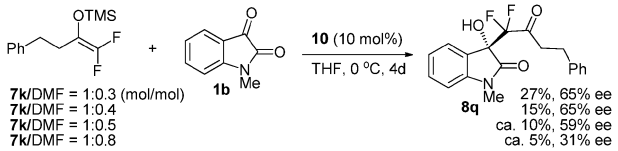




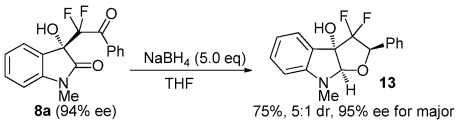
[a] On a 0.25 mmol. [b] Isolated yield. [c] Determined by HPLC analysis.

scope with respect to both difluoroenoxysilanes and electrophiles was carried out by running the reaction in THF at 0 °C, with 10 mol% of catalyst **10** (Table 2).

Different aryl substituted difluoroenoxysilanes **7b–i** gave corresponding products **8a–h** in high yield with excellent ee. Only 2-thienyl substituted enol ether **7j** provided product **8i** in moderate yield with 88% ee. A variety of substituted isatins worked well to give the desired adducts **8j–p** in excellent ee with high yield. Unfortunately, α-aliphatic substituted difluoroenoxysilanes could not be prepared as "pure" compounds[9a] (for details, see ESI‡). For example, difluoroenoxysilane **7k** was isolated as a **7k**/DMF mixture in a ratio of 1 : 0.3. This impure **7k** reacted with isatin **1b** under the standard reaction conditions to afford the desired product **8q** in 65% ee with 27% yield. Unfortunately, DMF was found to have negative effect on both the reactivity and enantioselectivity.



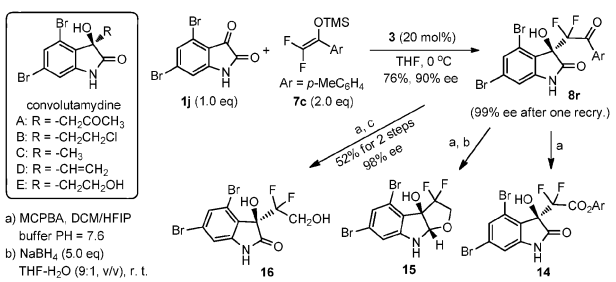
The thus obtained enantioenriched adducts were versatile building blocks for a variety of fluorinated compounds. For example, the reductive cyclization of product **8a** readily afforded the fluorinated 3a-hydroxyfuroindoline **13** in 75% yield and 5 : 1 dr, without loss of enantioselectivity.



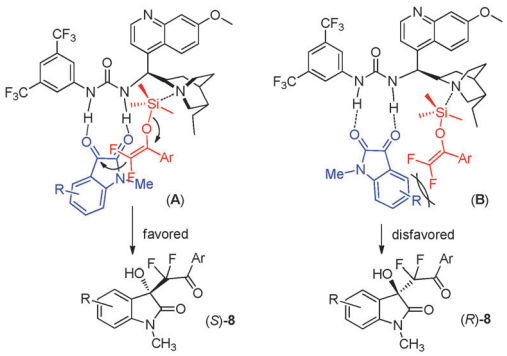
We further tried the synthesis of difluoro analogues of convolutamydines A–E (Scheme 2),[13] whose bioactivity was greatly affected by the C3 side chains. For example, convolutamydine A exhibited potent inhibitory activity on the differentiation of HL-60 human promyelocytic leukaemia cells at 0.1 μg mL^{-1} activity, but convolutamydine B at 12.5 μg mL^{-1}.[13a,b] The synthesis of their difluoro analogues would be interesting to modulate their properties for drug discovery.

Quinidine derived catalyst **3** was used for the reaction of isatin **1j** and **7c** since the configuration of convolutamydines is *R*. Product **8r** was obtained in 76% yield with 90% ee (99% ee after one recrystallization). The Baeyer–Villiger oxidation of **8r** gave **14** in 85% yield without loss of ee. By choosing the correct reduction condition, the 3a-hydroxyfuroindoline **15** could be obtained in 78% yield and 92% ee in two steps from **8r**, and difluoro analogue of convolutamydine E **16** could be readily prepared in 52% yield with 98% ee (2 steps from **8r**). Compounds **13** and **15** can be potentially used for the synthesis of the difluoro analogues of (+)-madindoline.[14]

It should be noted that our result is the first example of organocatalytic asymmetric synthesis of tertiary alcohols *via* the addition of trimethylsilyl enol ethers to ketones.[15] In addition, highly enantioselective Mukaiyama-aldol reaction catalyzed by a bifunctional chiral nitrogen-based uncharged Lewis base is unprecedented.[11] All the known Lewis base catalyzed protocols relied on the use of chiral salts such as



Scheme 2 Synthesis of difluoro analogues of A–E.



Scheme 3 Proposed transition states.

quaternary ammonium salts[11c,d] and carboxylate-ammonium salts,[11e] with counter anions as anionic Lewis base catalysts to activate trimethylsilyl enol ethers.

Based on the absolute configuration of the product **8**, a plausible mechanism was proposed for the observed enantiofacial control of this reaction. As shown in Scheme 3, the activation of difluoroenoxysilane **7** by the tertiary amine in the quinine urea catalyst backbone forms a reactive pentacoordinate silicate[12a,b] to react with isatin **1** which was activated by the urea part of the catalyst **10** through H-bonding interaction. The bifunctional catalysis was supported by the results shown in Table 1 (entries 4–6). Among the two possible orientations, the isatin was organized to avoid the unfavorable interaction between the isatin benzene ring and the enolate, which made the attack of the enolate from the *Re* face of the isatin favorable to afford the *S*-enantiomer as the major product.[5d]

In conclusion, we have developed a highly enantioselective synthesis of 3-difluoroalkyl 3-hydroxyoxindoles. Most importantly, the identification of nitrogen-based Lewis bases as effective catalysts to activate difluoroenoxysilane **7** would offer the premise of a straightforward method for the catalytic asymmetric construction of stereogenic carbon centers featuring a difluoroalkyl group.

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