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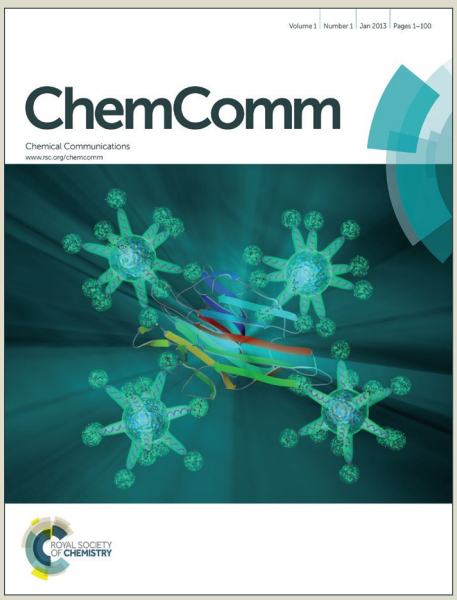

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ARTICLE TYPE

The Asymmetric Synthesis of CF_3 - containing Spiro[pyrrolidin-3,2'-oxindole] through the Organocatalytic 1, 3-dipolar Cycloaddition Reaction

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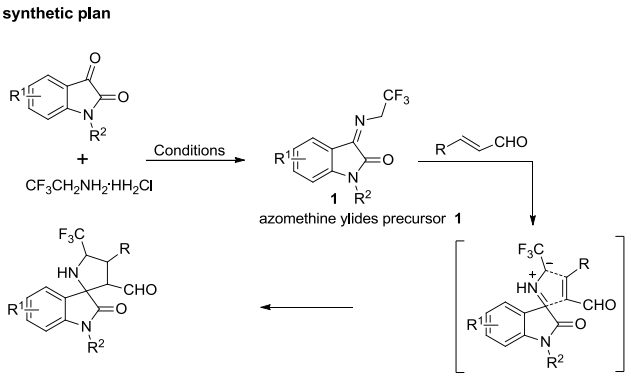
A new strategy for the construction of optically active 5'-CF_3 spiro[pyrrolidin-3, 2'-oxindole] was described. A series of unprecedented 1, 3-dipoles were obtained by condensation of $CF_3CH_2NH_2$ with isatins. The 1, 3-dipolar cycloaddition reactions of these ketimines with enals gave the products bearing four contiguous stereogenic centers in excellent yields, diastereoselectivities and enantioselectivities.

Spiro[pyrrolidin-3, 2'-oxindole], one member of spirooxindoles,[1] has been recognized as a core in many natural products and biologically active molecules[2] and a lot of effort have been invested in the asymmetric construction of this useful structure by synthetic and medicinal chemists. Various groups[3] have been introduced into this motif to execute lead optimization such as ester group, [3(a, c, d, i)] aromatic group, [3(b, e, g, h)] benzoyl, [3(c)] indolone, [3(c, d)] amide group, [3(e)] cyano group [3(f)] and nitro group[3(h)]. It is well known that the incorporation of CF_3 units into a biologically active compound often profoundly affects properties of the parent compound.[4] However, to the best of our knowledge, the introduction of CF_3 units into spiro[pyrrolidin-3, 2'-oxindole] remains a blank field.

Considering the great changes in the basicity and other properties brought by substitution of the hydrogens with fluorine atoms at the β-position of nitrogen, it is beneficial for the introduction of CF_3 units into the 5'-position of spiro[pyrrolidin-3, 2'-oxindole]. Synthetically, [3+2] annulation strategy is a simple and effective method to access the above mentioned compounds.[5] To achieve this annulation strategy, oxindole-derived azomethine ylides precursor [6] **1** containing CF_3 units was synthesised based on our ongoing interest in the synthesis of 3-aminooxindoles with isatins as the starting materials.[7]

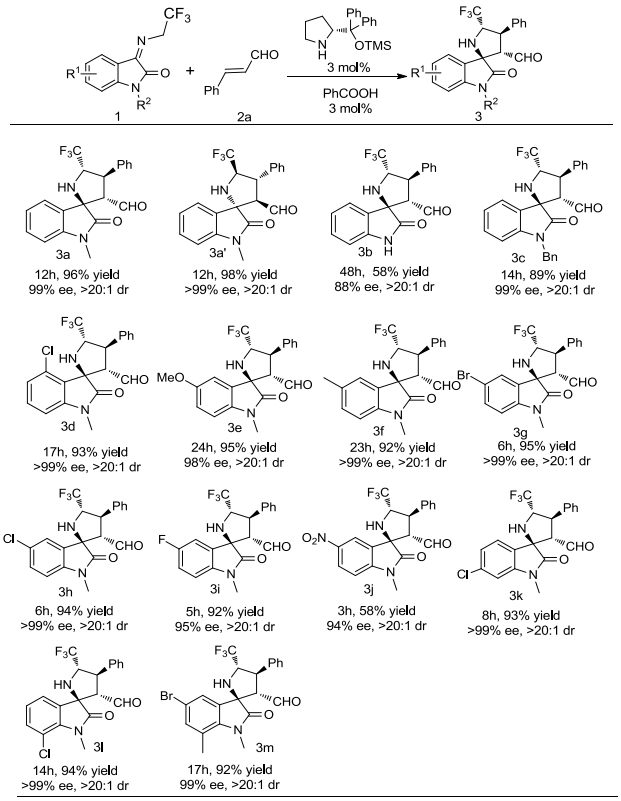
Although significant progress has been made in the use of $CF_3CH_2NH_2$ as CF_3 building block,[8] the direct use in the asymmetric construction of functionalized α-trifluoromethyl amines compounds has been relatively unexplored. We began our studies with the synthesis of azomethine ylides precursor **1**. Through heating a mixture of isatin and trifluoroethylamine hydrochloride in toluene with 5 mol% paratoluenesulfonic acid (see: ESI), the synthesis of precursor **1** was achieved directly. Then, the test of the annulation strategy was carried out. The results of the reaction exceeded our expectations by using (R)-2-(diphenyl((trimethylsilyl)oxy)-methyl)-pyrrolidine as the catalyst, 10 mol% benzoic acid as the additive and cinnamaldehyde as the dipolarophile. The reaction proceeded in accordance with the mode of cycloaddition reaction and gave the spiro-fused product in 93% yield, up to 20:1 dr and 94% ee. After obtaining these



Scheme 1. Strategy for the Synthesis of 5'-CF_3- spiro [pyrrolidin-3, 2'-oxindoles].

entrancing results, we assessed the influence of solvents, temperatures and additives in the reaction of ketimine **1a** with cinnamaldehyde. As shown in the ESI, the best result was obtained in CH_3CN at r.t. and in the presence of 3 mol% (R)-2-(diphenyl ((trimethylsilyl)oxy) methyl)-pyrrolidine and 3 mol% benzoic acid.

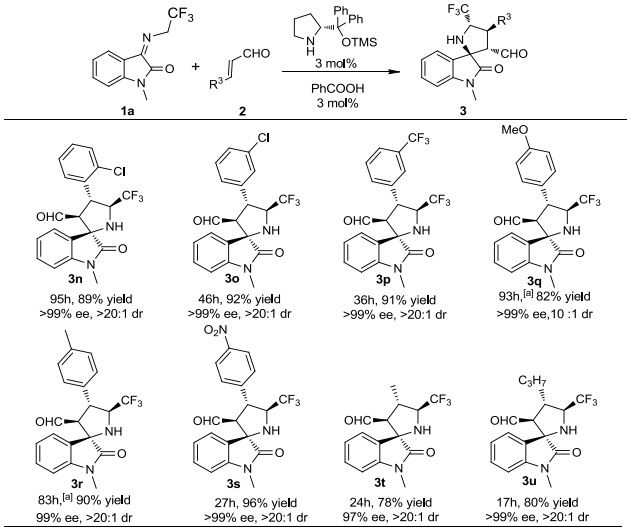
After establishing the optimal reaction conditions, the new method for the synthesis of chiral 5'-trifluoromethyl spiro [pyrrolidin-3, 2'- oxindole] was explored with a variety of substituted *N*-2, 2, 2 trifluoroethyl isatin ketimines and cinnamaldehydes. The results revealed that the substituting groups at the 1-position of ketimine had a significant effect on both diastereoselectivity and reactivity. With methyl and benzyl as the substituting groups, the reaction gave the products in good to excellent yields, excellent enantioselectivities and diastereoselectivities (**3a**, **3a'**, **3c**, Scheme 2).



Scheme 2. The reaction time required for each substrate is given. The reported yields are of the isolated products. The ee values were determined by HPLC analysis and dr were determined by ^{1}H NMR integration of reaction products.

Meanwhile, without substituting group at the 1-position of ketimine, the low yield and moderate ee value were observed (**3b,** Scheme 2). Following exploration showed that various substituted *N*-2, 2, 2 trifluoroethyl isatin ketimines including those bearing electron-withdrawing and electron-donating substituents at different positions of the aromatic ring could be well tolerated, and gave the corresponding compounds (**3d** - **3i**, **3k** - **3l**, Scheme 2) in excellent yields (92% - 95%), diastereoselectivities (>20:1 dr), and high to excellent enantioselectivities (95% - >99% ee). The general conclusion drawn from the results above was that the electronic effect on reactivity and stereoselectivity was more pronounced than the steric effect. For example, the reactions of ketimines containing -Cl at the 4, 5, 6, 7 - position gave the products in similar enantioselectivities (see **3d**, **3h**, **3k** and **3l**, Scheme 2). In the presence of strongly electron-withdrawing groups at 5-position, relatively lower enantioselectivities were observed (**3i** and **3j**, Scheme 2). In addition, it turned out that the disubstitued ketimine also followed the same reaction pattern, which afforded the addition product in 92% yield, 99% ee and >20:1 dr (see **3m**, Scheme 2). Furthermore, the enantiomer **3a'** could also be obtained under the optimal reaction conditions using (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)- pyrrolidine as the catalyst, and has a similar results with **3a**.

Further investigations of this cycloaddition reaction was carried out to delineate the scope of the α, β-unsaturated aldehydes. As presented in scheme 3, the results showed that the present process was a general and efficient method for the preparation of 3-amino- 5'- trifluoromethyl spirooxindole compounds. In general,



Scheme 3. The reaction time required for each substrate is given. The reported yields are of the isolated products. The ee values were determined by HPLC analysis and dr were determined by ^{1}H NMR integration of reaction products. [a] 10 mol% catalyst was used.

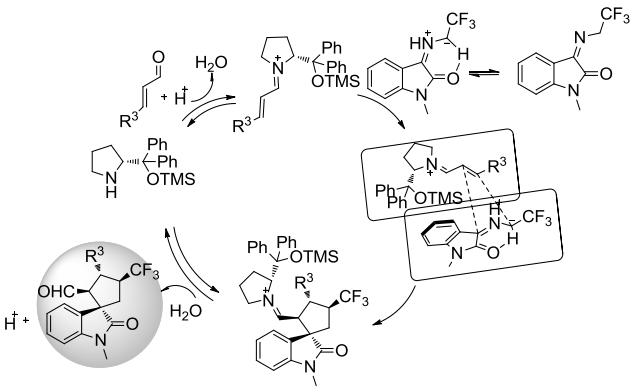
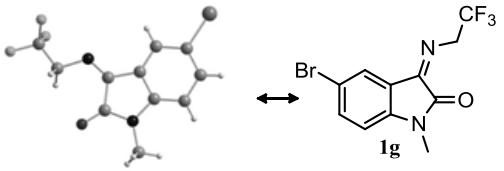


Figure 1. Proposed catalytic cycle for the cycloaddition reaction.

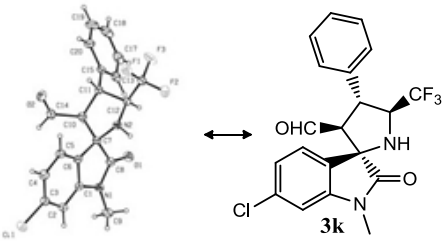
the rate of these cycloaddition reactions was influenced by both steric and electronic effects. With 2-chlorocinnamaldehyde as substrate, lower reaction rate was shown. By contrast, with 3-chlorocinnamaldehyde as substrate, the reaction time was shortened by half (**3n** and **3o**, Scheme 3). As the use of 4-substitued-cinnamaldehyde, the time of reaction was reduced with the change of the electronic properties from electron-donating to electron-withdrawing (**3q**, **3r** and **3s**, Scheme 3). The same tendency appeared with changing from -Cl to -CF_3 at the 3-position of substrate (**3o** and **3p**, Scheme 3). Additionally, as expected, alkyl substituted 2-enals were also tolerated and gave the products in moderate yields, excellent dr and ee values (**3t** and **3u**, Scheme 3).

Based on the X-ray crystal structure of ketimine **1g** (Scheme 4)[9] and product **3k** (Scheme 5)[10], a potential transition state structure has been proposed. As displayed in Figure 1, the reaction of diphenylprolinol silyl ether with the 2-enals gives the intermediate iminium ion. Due to the efficient shielding of the Re-face of the chiral iminium intermediate by the bulky aryl

groups, a diastereoselective Si-facial cycloaddition on the oxindole-derived azomethine ylide gave the cycloadduct iminium ion.[11] Then, hydrolysis releases the product (Figure 1) from the catalytic cycle and the catalyst is regenerated.



Scheme 4. The X-ray structure of ketimine **1g**.



Scheme 5. The X-ray structure of product **3k**.

Conclusions

In summary, the construction of optically active 5'-CF_3 spiro [pyrrolidin-3, 2'-oxindole] was developed. In the presence of 3 mol% diphenylprolinol ether benzoate, the cycloaddition reaction of N-(2, 2, 2-trifluoroethyl) ketimines, which were obtained from the condensation of trifluoroethylamine and isatins, with 2-enals gave the products bearing four contiguous stereogenic centers, and, in general, excellent diastereoselectivies, stereoselectivities and yields were obtained.

Acknowledgements

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Notes and references

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9 CCDC 1046963 contains the supplementary crystallographic data for the compound **1g** reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

10 CCDC 918717 contains the supplementary crystallographic data for the compound **3k** reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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