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Highly Enantioselective Construction of Strained Spiro[2,3]hexanes via Michael-Ring Expansion-Cyclization Cascade Strategy

Chuan-Gang Zhao, Zhi-Tao Feng, Guo-Qiang Xu*, Ang Gao, Jing-Wei Chen, Zhu-Yin Wang and Peng-Fei Xu*

Abstract: We herein report a general organocatalytic enantioselective strategy for the construction of highly strained spiro[2,3]hexane skeletons from methylenecyclopropanes and a broad selection of *α,β*-unsaturated aldehydes. The reaction proceeds through a Michael addition followed by ring expansion of methylenecyclopropanes and the nucleophilic attack of an enamine to realize the construction of spiro[2,3]hexanes. The key to the success of this approach is the utilization of an electron-deficient difluoro-substituted secondary amine catalyst and the intrinsic reactivities of methylenecyclopropanes.

The synthesis of spirocyclic hydrocarbon frameworks, especially the ones containing cyclobutane or cyclopropane units,[1] has risen in prominence over the last few years due to an increased recognition of their importance as bioactive natural products (Figure 1).[2] Compared with the common cyclic molecules, the advantages of the spiro compounds in some elementary aspects are obvious: a) The compactness of spirocycles causes reduced lipophilicity;[3] b) The spatial diversification of the spirocyclic compounds is further promoted through isomerization;[1a] c) The higher sp^3/sp^2 ratio of spirocyclic compounds facilitate the design of new classes of biologically-active molecules with improved properties.[4] Unexplored scaffolds may be promising bioactive compounds, and those inherent characteristics make the spiro compounds more attractive than common cyclic compounds in drug discovery.[5]

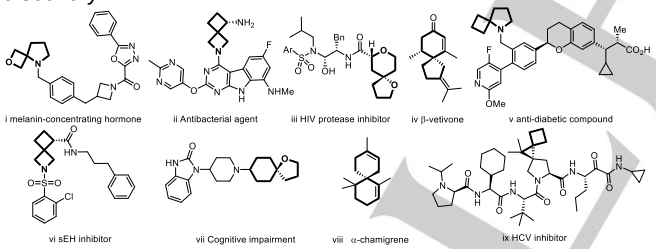
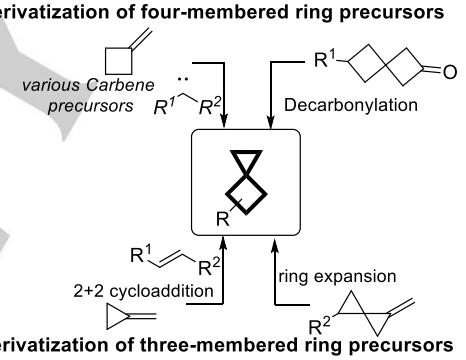


Figure1 Examples of pharmaceutical compounds containing spirocyclic rings.

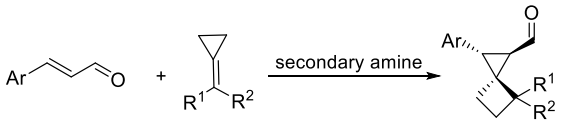
However, the synthesis of spirocyclic hydrocarbon frameworks containing small rings is considered to be more challenging because the common carbon atom which connects the two neighboring rings is a quaternary atom. The construction of quaternary stereocenters itself was considered to be one of the most difficult tasks among synthetic transformations.[6] Considerable efforts have been made in the last few years towards the development of protocols to prepare spirocyclic compounds, particularly the ones containing at least one middle ring. Traditionally, the synthesis of spiro[2,3]hexane was limited to the derivatization of ternary or four-membered ring precursor: a) cyclopropanation of methylenecyclobutane derivatives or decarbonylation of spiro[3.3]heptan-2-one and its derivatives. (Scheme 1, eq a)[8], [9] b) [2 + 2] cycloaddition of methylenecyclopropane derivatives or ring expansion of corresponding spiro precursors (Scheme 1, eq. b).[7], [9] All of these strategies had one of the small rings, present in the starting materials, reserved after the reaction. To the best of our knowledge, asymmetric synthesis of spiro[2,3]hexane derivatives have not been reported. Therefore, developing a mild and efficient method for constructing asymmetric spiro[2,3]hexanes is still highly desired.

a. Derivatization of four-membered ring precursors



b. Derivatization of three-membered ring precursors

c. This work : Michael-ring expansion-cyclization cascade strategy



Scheme 1 Feasible Approach to synthesize spiro[2,3]hexanes.

With the rapid development of organocatalysis, chiral secondary amine catalysis has become one of the most powerful tools in the realm of chiral molecule synthesis.[10], [11] With our ongoing interest in the synthesis of small ring compounds, we tried to challenge the asymmetric synthesis of small ring spiro compounds.[12] We envisioned that the iminium ion generated by difluoro-substituted secondary amine catalysts may provide further opportunities for developing new reactions. Electron-rich olefins, one of the most common weak nucleophiles, have been widely explored as building blocks in the presence of transition metal catalysts. In contrast, they are rarely applied in organic catalysis. We questioned whether olefins can enable conjugate additions to the *β*-carbon atom of iminium ion intermediates. This strategy, if successful, would complement the nucleophile library of traditional iminium ion catalysis. On the other hand, a method for enantioselective

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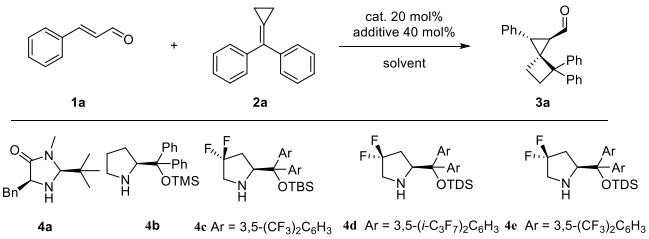
synthesis of strained spiro[2,3]hexanes, a compound with synthetic potential and biological activity, in mild conditions would be constructed.

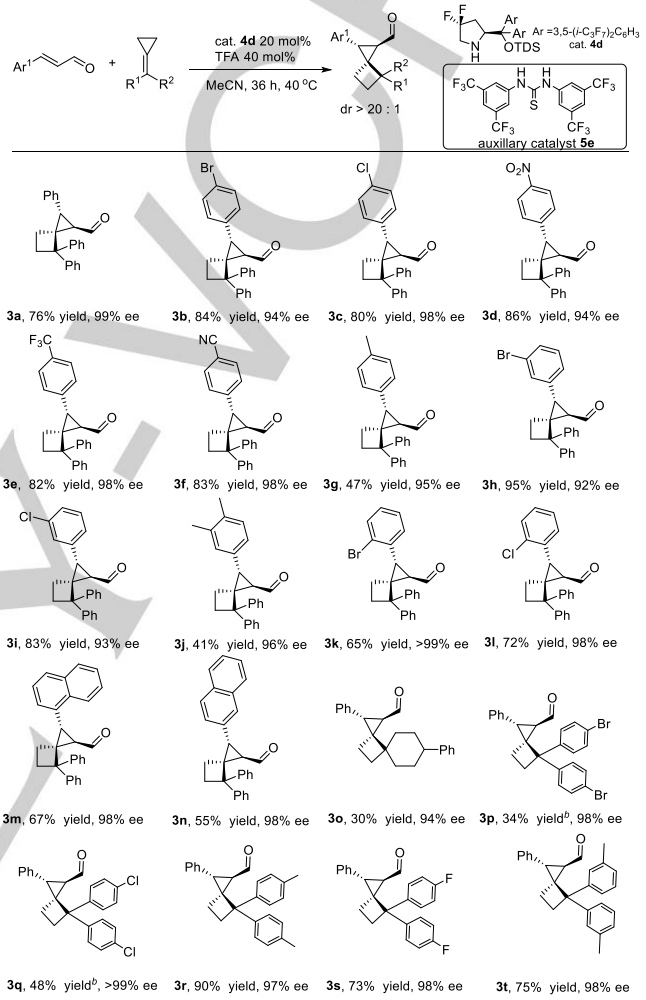
Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Additive	Yield[e] (%)	dr.[f]	ee[g] (%)
1	**4a**	TFA	nr.	-	-
2	**4b**	TFA	nr.	-	-
3	**4c**	TFA	45	>20:1	79
4	**4d**	TFA	69	>20:1	99
5	**4e**	TFA	50	>20:1	99
6	-	TFA	nr.	-	-
7	**4d**	TsOH	60%	>20:1	92
8	**4d**	TfMsA	32%	>20:1	82
9	**4d**	TCA	trace	nd.	nd.
10	**4d**	BA	nr.	-	-
11	**4d**	AcOH	nr.	-	-
12[b]	**4d**	TFA	38	>20:1	99
13[c]	**4d**	TFA	76	>20:1	99
14[d]	**4d**	TFA	68	>20:1	99

[*a*] Reaction conditions: Reactions performed with **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (20 mol%), additives (40 mol%) in solvent (1 mL) at room temperature for 36 h. For detailed experimental procedures, see the supporting information. [*b*] **1a** (0.3 mmol), **2a** (0.1 mmol). [*c*] Reaction was performed at 40 °C. [*d*] Under 50 °C. [*e*] Isolated yield. [*f*] dr. was determined by ^{1}H NMR analysis of the crude products; nr. = no reaction. [*g*] ee was determined by chiral-phase HPLC analysis; nd. = not determined. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, TDS = thexyl-dimethylsilyl TFA = trifluoroacetic acid, TfOH = triflic acid, TfMsA = trifluoromethanesulfonic acid, TCA = trichloroacetic acid, BA = benzoic acid, AcOH = acetic acid.

To test the feasibility of our design, the reaction was investigated using cinnamaldehyde **1a** and electron-rich methylenecyclopropane **2a** as the model substrates. First, the commonly used secondary amines were screened (Table 1, entries 1−3). Neither the chiral imidazolidinone catalyst **4a** nor diarylprolinol silyl ether catalyst **4b** worked in this system. In order to increase the reactivity of the iminium ion, catalyst **4c**, which contains two electronegative fluorine atoms, was then tested. We were pleased to find that the desired product **3a** was successfully produced in moderate yield with an encouraging level of stereoselectivity (Table 1, entry 3). The chiral amine catalyst **4d**, with high steric hindrance and a perfluoro-isopropyl group on the arene scaffold, gave a dramatic increase in both yield and stereoselectivity (Table 1, entry 4). Moreover, when the reaction was carried out in the absence of the secondary amine catalyst, no product was detected even after 36 h (Table 1, entry 6), which revealed that trifluoroacetic acid was unable to make the reaction proceed smoothly as the only catalyst. To achieve higher yield, we attempted to use some additives which play an important role in the construction of iminium ion (Table 1, entris 7-11). The originally used additive, trifluoroacetic acid, gave the best results. Further study of the reaction temperature indicated that increasing the temperature gave slightly better results (Table 1, entry 13). However, increasing the temperature to 50 °C led to decomposition of some starting materials and therefore caused a slight decrease of the yield (Table 1, entry 14).

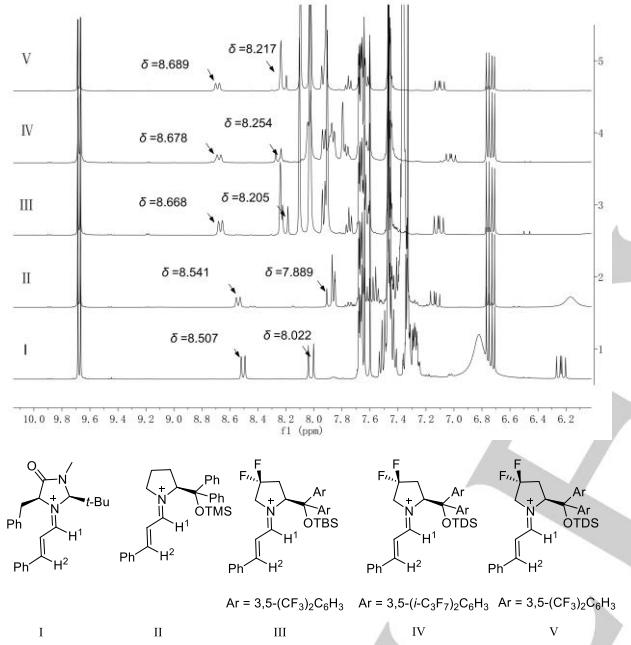


Reaction Conditions: [*a*] Reactions performed with **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (20 mol%) , TFA (40 mol%) in acetonitrile (1 mL) at 40 °C for 36 h. [*b*] with the help of an auxiliary catalyst **5e** (40 mol%) in DCE (1 mL) for 48 h. All of the dr of products were > 20 : 1,determined by ^{1}H NMR analysis of the crude products

Scheme 2 Substrate Scope of the Reaction[a]

To investigate the substrate scopes of this asymmetric transformation, various *α,β*-unsaturated aldehydes were tested under the optimized conditions (Scheme 2). A series of functional groups, such as halides (**3b**-**3c**), nitro group (**3d**), trifluoromethyl group (**3e**), and cyano group (**3f**), at the para position of the phenyl group were compatible with this transformation. Aldehydes with electron-donating groups on the aryls could also produce the corresponding spirocyclic compounds with excellent diastereo- and enantioselectivities albeit in decreased yields (Scheme 2, **3g, 3j**). This phenomenon proved that the activities of iminium ions were sensitive to the electronic effect of substrates. Substrates with the aryl group

replaced with a naphthyl group also provided the corresponding products **3m-3n**. As exemplified by **3o-3t** (Scheme 2), this protocol was also effective for various substituted methylenecyclopropanes. Considering the insolubility of methylenecyclopropanes bearing a bromine or chlorine atom at the para position in acetonitrile, the solvent was replaced with DCE. Nevertheless, the substrates were not converted into products effectively (conversion rate is less than 10%). To our delight, with the help of an auxiliary catalyst **5**, the reaction could produce the products with good enantioselectivities and increased yields (Scheme 2, **3p, 3q**).[13] To further explore the practicability of this strategy, a large-scale asymmetric synthesis of **3a** was performed. Fortunately, the reaction proceeded smoothly to obtain the spirocyclic compound in good yield with a slight decrease of ee. The absolute configuration of **3b** was determined by X-ray crystallographic analysis (see the Supporting Information), and the rest were assigned by analogy.[14]



Conditions: this is a mixed spectrum. *a*) a mixture solution of cinnamic aldehyde : chiral amine : Trifluoroacetate = (1:1:1.3) in deuterated acetonitrile.

Figure 2 ^{1}H NMR of Various iminium ion intermediates.[a]

To determine the influence of secondary amine catalysts on the reactivities of the intermediates, several ^{1}H NMR experiments were carried out in CD_3CN (Figure 2). It was found that the chemical shifts of iminium ion intermediates in ^{1}H NMR were obviously different from one another, and the chemical shifts of H^1 and H^2 in intermediates III, IV and V were significantly higher. This experiment demonstrated that the difluoro-substituted iminium ion intermediates had higher reactivities.

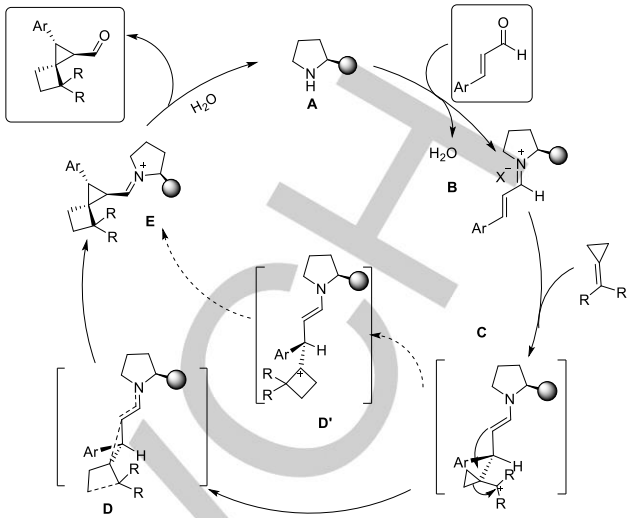


Figure 3 Proposed Reaction Mechanism

Based on our experimental results, the following reaction mechanism was proposed (Figure 3). First, the secondary amine condenses with the *α,β*-unsaturated aldehyde to form the iminium ion (Figure 3 intermediate **B**). Then Michael attack of the electric-rich methylenecyclopropane to the *β* position of the iminium ion occurred. After that, the cyclopropane expands to form a four-membered ring, at the same time a new cyclopropane was constructed. The rearrangement and the electrophilic addition happened in a concerted process, rather than a carbon cation (Figure 3 intermediate **D'**) process. Finally, product **3** was obtained by hydrolysis of intermediate **E**.

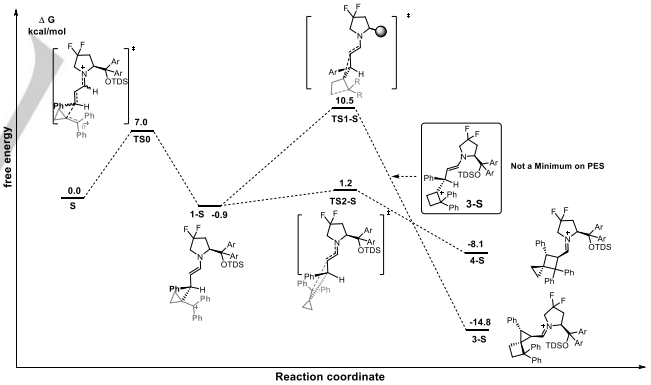
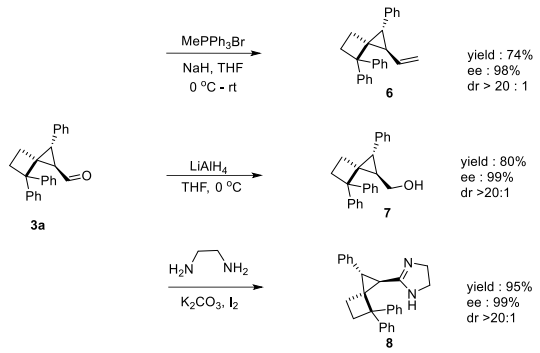


Figure 4 DFT calculation of the energy profiles for the reaction process. Geometries and frequency analysis were performed under B3LYP-D3/6-31G(d) level of theory.

Next, computational studies were carried out to gain mechanistic insight into the reaction process. After the formation of **1-S** (Figure 4), the reaction process can be carried out in two ways. However, only one product **3-S** was observed. Even though the predicted free energy barrier via **TS2-S** is 1.2 kcal mol^{-1} lower than that for **TS1-S**. We speculated that the predicted free energy barrier via **TS2-S** is too close to the intermediate **1-S** so that this process is reversible at room temperature. Whereas, the one through **Ts1-S** could produce product irreversibly. The cyclobutyl cationic structure **3-S** (Figure 4) is not a minimum on the potential energy surface. Thus, the rearrangement and the electrophilic addition happens in a

concerted but highly asynchronous pattern (for detailed IRC of this procedure, see the supporting information).

In order to further demonstrate the synthetic utility of the current methodology, some selected transformations were performed. Product **3a** could be converted to the corresponding alkene **6** by a Wittig reaction in good yield with maintained enantioselectivity. Product **3a** could also be reduced to the corresponding alcohol by lithium aluminum hydride. All of the cyclopropane substituted methanol and ternary cyclic olefin derivatives were useful synthons in organic synthesis.[15] On the other hand, cibenzoline derivative **8** could be obtained without loss of enatioselectivity.



Scheme 3. Transformations of Product 3a

In conclusion, we have developed a highly enantioselective approach for the synthesis of strained spiro[2,3]hexane derivatives by Michael-ring expansion-cycloaddition strategy in a cascade process, and a broad selection of *α,β*-unsaturated aldehydes were smoothly transformed to the corresponding spirocyclic products in moderate to high yields with excellent diastereo- and enantioselectivities. The reaction could be scaled up easily, and the synthetic potentials of the obtained products were illustrated by selective transformations into more complex skeletons. We believe this approach will find more applications since it provides ready access to unexplored spiro[2,3]hexane derivatives.

Acknowledgements

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Keywords: spirocyclic hydrocarbon frameworks • organocatalysis • enantioselective

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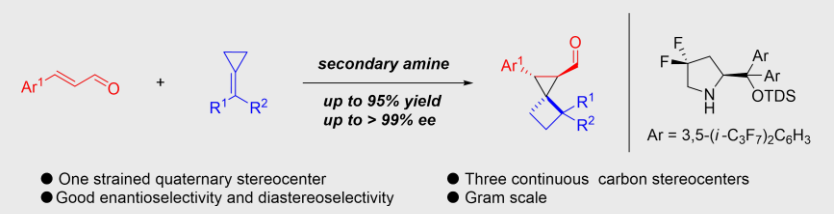

Highly strained spiro[2,3]hexane skeletons are accessed from readily prepared starting materials in a Michael-ring expansion-cycloaddition cascade strategy. The process does not require metals, proceeds by organocatalysis, and can be used to contribute three continuous carbon stereocenters with good enantioselectivity and diastereoselectivity.

C.-G. Zhao, Z.-T. Feng, G.-Q. Xu, A. Gao, j-W. Chen, Pro. Dr. Z.-Y. Wang and Pro. Dr. P.-F. Xu**

Page No. – Page No.

Highly Enantioselective Construction of Strained Spiro[2,3]hexanes via Michael-Ring Expansion-Cyclization Cascade Strategy