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Spirocycles

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Access to All-Carbon Spirocycles through a Carbene and Thiourea Cocatalytic Desymmetrization Cascade Reaction

Shitian Zhuo, Tingshun Zhu, Leijin Zhou, Chengli Mou, Huifang Chai, Yunpeng Lu, Lutai Pan,* Zhichao Jin, and Yonggui Robin Chi*

Abstract: A new catalytic approach for asymmetric quick access to spirocycles is disclosed. The reaction involves a carbene and thiourea co-catalyzed desymmetrization process with simultaneous installation of a spirocyclic core. The use of a thiourea co-catalyst is critical to turn on this reaction, as no product was formed without the presence of the thioureas. Our study constitutes the first success in carbene-catalyzed enantioselective synthesis of all-carbon spirocycles. Products from our reactions can be readily transformed to sophisticated multi-cyclic molecules and chiral ligands.

Spirocylic skeletons enable special spatial arrangements of functional groups that pose specific properties for organic molecules.[1] For example, spiro[4.4]nonane constitutes a privileged scaffold in chiral ligands for highly efficient and stereo-selective metal catalysis (Figure 1a).[2] This scaffold is also found as a core component in complex natural products[3] such as Vannusals A and B,[4] secondary metabolites isolated from the marine ciliate Euplotes Vannus. To date, it remains challenging to prepare such all-carbon spirocylic structures, especially in enantiomerically enriched forms.[5] Most of the available methods require multiple steps to first prepare the molecules in racemic forms, followed by the use of chiral resolution techniques to obtain the desired products in optically pure forms.[6]

Here we disclose a single-step asymmetric catalytic method for quick access to such all-carbon spirocycles bearing up to two spirocyclic centers (Figure 1b). The reaction cascade involves an intermolecular Stetter reaction[7] catalyzed by NHC catalysts,[8] followed by an intramolecular aldol reaction. The Stetter reaction is also a desymmetrization process,[9] with which a remote chiral carbon center is controlled by the chiral catalyst. The subsequent aldol reaction step sets up a newly formed spirocyclic carbon center with high enantioselectivity. It is worth to note that both an *N*-heterocyclic carbene (abbreviated as NHC or carbene) catalyst and a thiourea co-catalyst are essential in this catalytic reaction: no product is formed without the presence of the thiourea co-catalyst. The spirocycles prepared through this approach bear multiple functional groups that are amenable for further transformations. We expect our method to provide shortcut routes to sophisticated chiral functional molecules with spirocyclic structures.

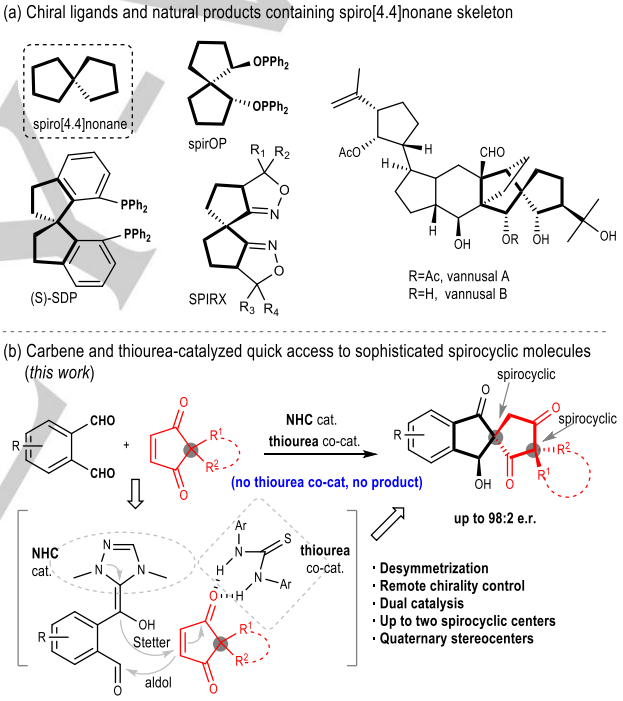

Figure 1. Chiral Spiro[4.4]nonanes and Our Synthetic Design.

Key results of the condition optimization are summarized in Table 1. Substrate **1a** was slowly added to the reaction mixture to react with cyclic enone **2a** at room temperature with spiro bicyclic **3a** afforded as the final product (Table 1). After extensive optimizations, an acceptable result could be obtained by using triazolium salt **A**[10a] as the NHC precatalyst, thiourea **E** as the co-catalyst, DIPEA as the base, and a mixture of $CHCl_3$/^{t}BuOH (2:1, v/v) as the solvent (entry 1). The product **3a** could not be afforded without either the NHC catalyst (entry 2) or the thiourea co-catalyst (entry 3). Replacement of the *N*-mesity substituent on the NHC pre-catalyst **A** with an *N*-pentaflurophenyl (**B**)[7d] or *N*-phenyl (**C**)[10b] substituent led to no formation of the desired product (entry 4). Switching the NHC pre-catalyst **A** to **D** with a NO_2 group installed on the benezene ring of the indane motif[10c-

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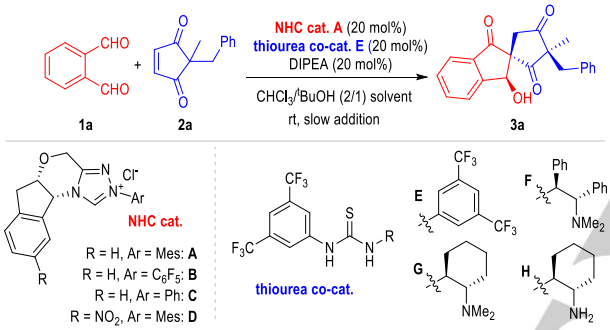
[d] led to drops on both the enantio- and diastereoselectivities in this transformation (entry 5). The thiourea co-catalyst likely activates the 1,3-cyclopentenedione substrate (**2a**) via hydrogen bonding.[11] Additional screening of chiral thiourea co-catalysts (**F-H**, entries 6-8) did not lead to obvious improvements on the rection outcomes (see Supporting Information for more details). The screening of either the bases or the solvents used in this catalytic system resulted in no improvements of the product yields, although the stereoselectivities were not affected (entries 9-12; see Supporting Information for details). The significant distinctions between the reaction yields with various solvents indicated that hydrogen bonding had played important roles in this transformation.[11d] As a technical note, slow addition of the dialdehyde substrate **1a** can attenuate the side reaction of the homocoupling of the aldehydes[12] and favor the formation of the desired product. In contrast, lower yield was observed with **1a** added in one-portion (29%, entry 13).

Table 1. Condition Optimization[a]

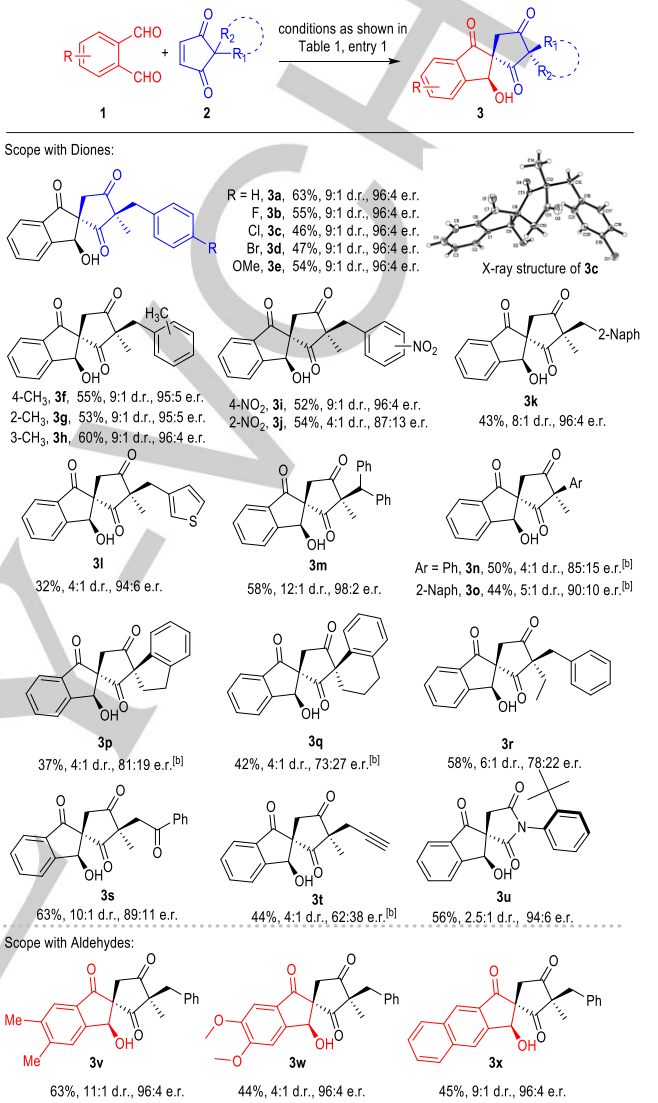


entry	variation from standard condition	yield [%]	d.r.	e.r.
1	standard condition[a]	63	9:1	96:4
2	no NHC	0	-	-
3	no thiourea	0	-	-
4	NHC: **B** or **C**	<5	-	-
5	NHC: **D**	60	3:1	94:6
6	thiourea: **F**	44	10:1	96:4
7	thiourea: **G**	53	9:1	96:4
8	thiourea: **H**	50	9:1	96:4
9	other bases (Cs_2CO_3, K_3PO_4, ^{t}BuOK, DBU)	0~20	9:1	95:5~96:4
10	other solvents (THF, acetone, Et_2O, DMF)	0~9	9:1	96:4
11	^{t}BuOH as solvent	32	9:1	96:4
12	$CHCl_3$ as solvent	45	9:1	96:4
13	without slow addition of **1a**	29	9:1	96:4

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.1 mmol), NHC **A** (0.02 mmol), base (0.02 mmol), thiourea **E** (0.02 mmol), solvent (1 mL), rt, 12 h. Yields are isolated yields based on **2a**; d.r. was determined by ^{1}H NMR; e.r. was determined via chiral phase HPLC analysis.

With an acceptable reaction condition in hand, the generality of the reaction was then evaluated (Scheme 1). Phthalaldehyde **1a** was selected as a model substrate to study the scope of the 1,3-cyclopentenedione substrates **2**. When R^1 was fixed with a methyl group, R^2 could be benzyl groups with various substitution patterns (**3a-j**). The benzene rings of the benzyl group could also be replaced with either a naphthene or a thiophene group, with little erosion of the product diastereoselectivities (**3k-l**). Increasing the steric hindrance of the benzyl group with a benzhydryl group resulted in a slight enhancement of the product enantioselectivity (**3m**). Switching the benzyl group on substrate **2a** to either a phenyl or a

Scheme 1. Substrate Scope[a]



[a] Reaction conditions as in Table 1, entry 1, unless otherwise noted. The absolute configuration of the major enantiomer was assigned based on the X-ray structure of **3c**. [b] Used **D** instead of **A**.

naphthene group led to drops on both the enantio- and diastereoselectivities of the final products (**3n-o**). Spirocyclic 1,3-cyclopentenedione substrates could also give the desired products bearing two all-carbon spirocycles in moderate yields and enantioselectivities (**3p-q**). The benzene ring on substrate **2a** could also be replaced with a benzaceto group or an alkyne group, with corresponding products afforded in moderate yields and stereoselectivities (**3s-t**). The R^1 group could also be switched to an ethyl group (**3r**), although both of the dr and er values of the product were decreased. It is worth noting that 2,5-pyrroledione bearing a prochiral axial could also be used in this transformation, with the axial chiral product afforded in excellent diastereo- and enantioselectivities (**3u**). Replacing the methyl group on the dione substrate **2** with either a F or Cl group led to no product formation,

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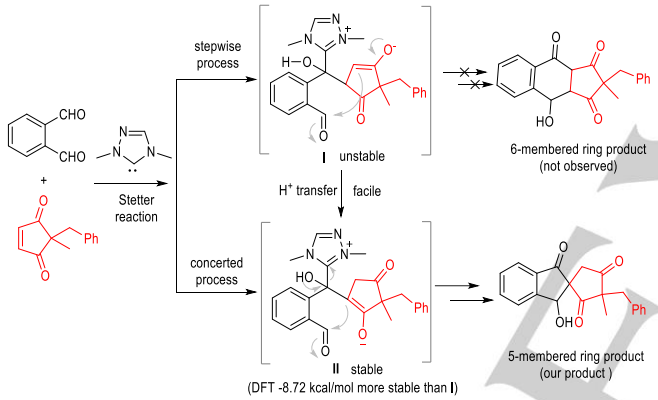
since these substrates decomposed under the current catalytic reaction condition (see Supporting Information for details). The aromatic 1,2-dialdehydes **1** bearing various substitution patterns also worked well in this desymmetrization process, with the spirocyclic products afforded in moderate yields with good to excellent stereoselectitities (**3v-x**).

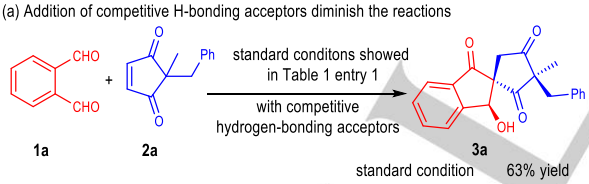
The postulated reaction pathway is illustrated in Scheme 2. The reaction starts with an NHC-catalyzed Stetter reaction of one aldehyde moitey with the electron-deficient alkene. A related study from Glorius[7u] on the related reaction between aldehydes and alkenes suggested that this Stetter-type process might be a concerted process and the intermediate **II** could be formed directly or through a fast protonation step from intermediate **I**. This suggests that the 5-membered ring product observed in our reation shall be favored, which is consistent with our experimental resutls that the possible 6-membered ring adduct is not observed. DFT caculation (see Supporting Information for details) also suggests that intermedate **I**, the key precursor of the possible 6-membered ring adduct, is much less stable than intermediate **II** that leads to our 5-membered ring product.

Scheme 2. Postulated Reaction Pathway



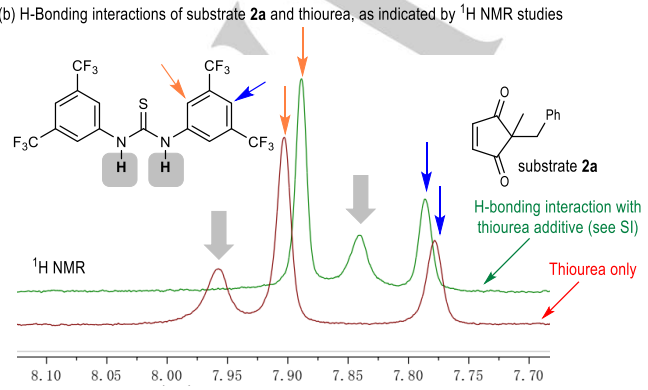
Scheme 3. Mechanistic Studies

(a) Addition of competitive H-bonding acceptors diminish the reactions



standard condition	63% yield
with 10 equiv. DMSO	23% yield
with 20 equiv. DMSO	0% yield
with 10 equiv. HMPA	0% yield

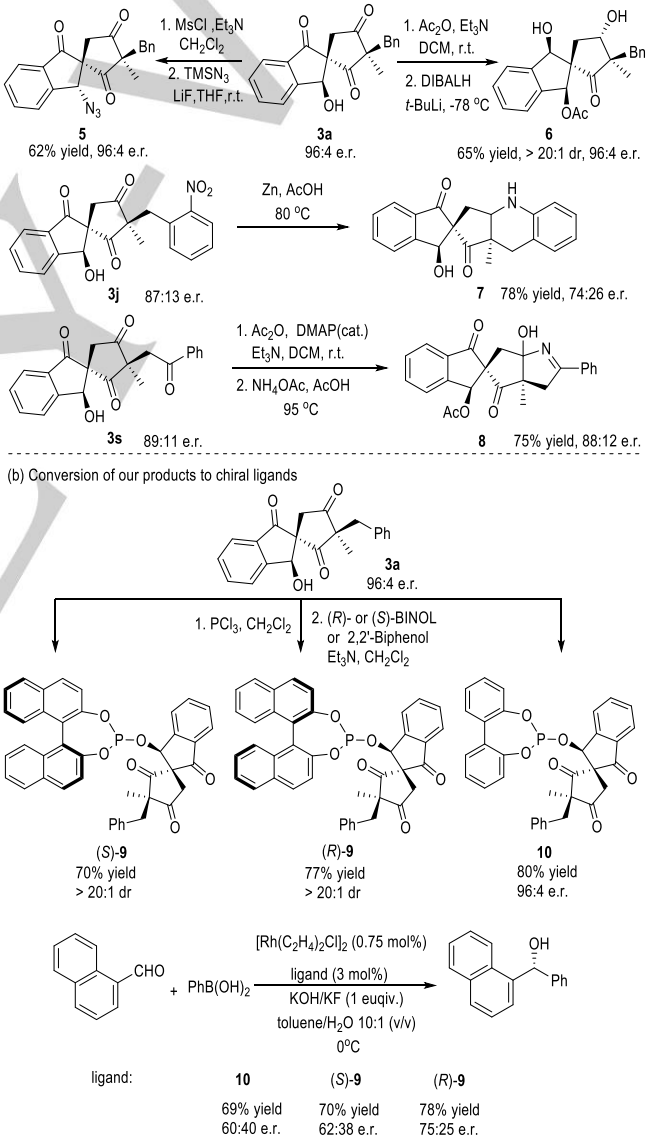
(b) H-Bonding interactions of substrate **2a** and thiourea, as indicated by ^{1}H NMR studies



To better understand the hydrogen-bonding activation effect, several control exeriments were performed. As shown in Scheme 3a, the reactions were diminished on the addition of several competitive hydrogen-bonding acceptors such as DMSO or HMPA (to compete with substrate **2a** for hydrogen bonding interaction with the thiourea co-catalyst). The addition of substrate **2a** to a solution of thiourea led to significant change on the ^{1}H NMR chemical shifts of the thiourea (Scheme 3b). These results indicate that the thiourea co-catalysts likely activate the diketone substrates (e.g. **2a**) via hydrogen-bonding interactions under our conditions.

Scheme 4. Synthetic Transformations

(a) Synthetic derivatization of our products



(b) Conversion of our products to chiral ligands

The reaction products were amenable for further transformations through simple protocols (Scheme 4). For example, the hydroxyl group of **3a** could be transformed to azido

compound **5** through an S_N2 substitution with $TMSN_3$ in 62% yield and 96:4 e.r. value. Product **3a** could also be stereoselectively reduced by DIBAL-H / ^{t}BuLi to afford **6** in moderate yield without erosion of the optical pruity. Product **3j** could be stereoselectively reduced to give tetrahydrospiro cyclopenta[b]quinoline **7** in good yield with little erosion of the optical purity. The spiro cyclopenta[b]pyrrole **8** could be efficiently afforded from chiral product **3s** through simple protocols with retention of the er value. Notably, the chiral spiro heterocyclic molecules afforded here (**5-8**) have great values in various biological and pharmaceutical investigations[3] and had been difficult to be synthesized through traditional methods. Moreover, the product **3** could also transform to chiral ligands with interesting applications in transition metal catalysis. For example, phosphite ligand **9** derived from **3a** and BINOL showed good activity and moderate enantioselectivity in rhodium-catalyzed 1,2-addition of arylboronic acid to aldehyde in our preliminary studies (Scheme 4b). It is worth to note that the configuration of the product was mostly determined by the chiral moiety from **3a** in ligand **9**.

In summary, we have developed a new approach for direct asymmetric access to spirocycles bearing multiple chiral centers. Our method involves a desymmetrization process with reaction stereo-selectivity controlled by a chiral NHC catalyst. Thiourea co-catalyst was essential in this reaction. Our study represents the first success in carbene-catalyzed formation of all-carbon spirocyclic skeletons. Products afforded in this transformation are rich in functionalities and are amenable for further transformations. Sophisticated multi-cyclic molecules and chiral phosphite ligands could be prepared from our products. We expect our cooperative catalytic process to encourage re-evaluations of many possible reactions that do not occur with only carbene catalysts used. Our study shall also provide useful tools in building complex functional molecules bearing spirocyclic cores.

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Keywords: all-carbon quaternary chiral center • remote chirality control • metal-free dual catalysis • desymmetrization • spirocyclic • *N*-heterocyclic carbene

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Layout 2:

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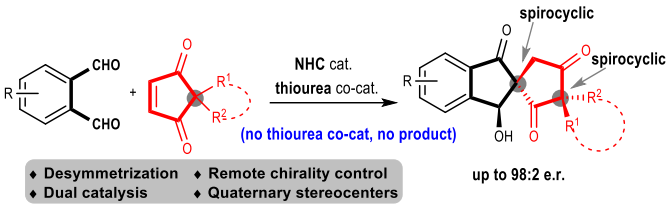

All-carbon spirocycles: A new catalytic approach for asymmetric quick access to spirocycles is disclosed. The reaction involves a carbene and thiourea co-catalyzed desymmetrization process with simultaneous installation of a spirocyclic core. Our study constitutes the first success in carbene-catalyzed enantioselective synthesis of all-carbon spirocycles. Products from our reactions can be readily transformed to sophisticated multi-cyclic molecules and chiral ligands.

Shitian Zhuo, Tingshun Zhu, Leijin Zhou, Chengli Mou, Huifang Chai, Yunpeng Lu, Lutai Pan, Zhichao Jin, and Yonggui Robin Chi

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Access to All-Carbon Spirocycles via Carbene and Thiourea Co-Catalytic Desymmetrization and Cascade Reaction