Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 4195−4199

pubs.acs.org/OrgLett

Asymmetric Robinson Annulation of 3-Indolinone-2-carboxylates with Cyclohexenone: Access to Chiral Bridged Tricyclic Hydrocarbazoles

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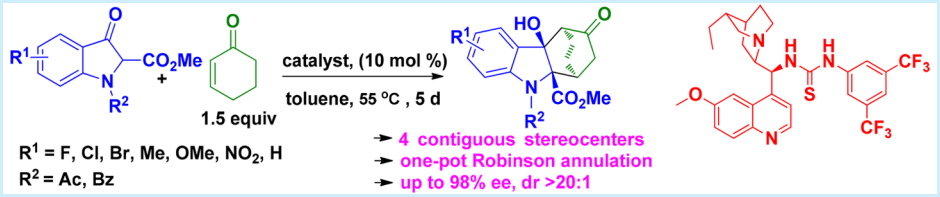
Supporting Information



ABSTRACT: A chiral bifuntional thiourea catalyzed diastereo- and enantioselective Michael addition followed by an intramolecular Aldol reaction of 3-indolinone-2-carboxylates with cyclohexenone has been accomplished using a chiral thiourea catalyst. It is a novel strategy for the construction of chiral bridged tricyclic hydrocarbazole derivatives bearing four contiguous stereocenters with excellent diastereo- and enantioselectivity.

The chiral hydrocarbazole skeleton is often found in many natural products such as strychnine, aspidophytine minovincine, vindoline, minfiensine, etc. (Figure 1).[1] This

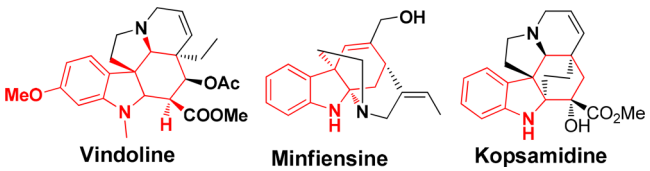


Figure 1. Examples of chiral hydrocarbazole alkaloids.

hydrocarbazole unit is also found in ondansetron and ramatroban. The ramatroban is an athromboxane receptor antagonist, which is used for the treatment of asthama and coronary artery disease.[1q−v] The ondansetron is used for the treatment of nausea and vomiting associated with chemotherapy.[1w−y] In particular, a chiral bridged hydrocarbazole is a core structure of many natural products such as kopsamidine and kopsinine.[1k,l] The construction of chiral bridged compounds is a challenging task in asymmetric synthesis.[2] Furthermore, the creation of *vicinal*-chiral quaternary stereocenters is quite challenging to synthetic chemists.[2] Inspired by their inherent biological activities and fascinating structural features, we attempted the synthesis of chiral bridged hydrocarbazoles using readily available and environmentally friendly organocatalysts.

To date, different methods have been employed for the construction of a chiral tetrahydrocarbazole framework using various catalytic methods.[3] Some were effectively used for the synthesis of natural products.[3i−l] Asymmetric annulations are the most important for the construction of multisubstituted chiral tricyclic hydrocarbazoles using indole derivatives, arynes, and Nazarov reagents with different chiral catalysts.[3c,d]

Indolin-3-one derivatives are privileged substrates for developing various catalytic asymmetric reactions to produce chiral 2,2-disubstituted indolin-3-ones.These chiral compounds are important structural units of various natural products and pharmaceutical drug candidates. In recent years, elegant methods have been developed for the enantioselective conjugate addition of 3-indolinone-2-carboxylates using different Michael acceptors.[4] The asymmetric organocatalytic cascade reactions using indolin-3-one derivatives is a significant strategy for the construction of important core structures with several chiral centers. Very few enantioselective catalytic methods[5] have been explored to date by using indolin-3-one derivatives. On the other hand, cyclohex-2-enones are important building blocks in asymmetric synthesis such as aza-Diels−Alder, annulation, and Michael−Michael cascade reactions[6] for the construction of six-membered chiral frameworks.

The enantioselective Robinson annulation is one of the most effective transformations to produce several natural product intermediates such as cyclic steroids, terpenes, and alkaloid skeletons. Significant developments in organocatalytic asymmetric Michael−aldol cascade reactions have been made in the past several years for the construction of chiral annulation products.[7] In 2009, Akiyama and co-workers reported a sequential Robinson type annulation reaction (Figure 2). A BINOL phosphoric acid catalyzed enantioselective Michael addition followed by an aldol reaction using cyclic β-keto esters

Received: May 18, 2018
Published: July 5, 2018

DOI: 10.1021/acs.orglett.8b01575
Org. Lett. 2018, 20, 4195−4199

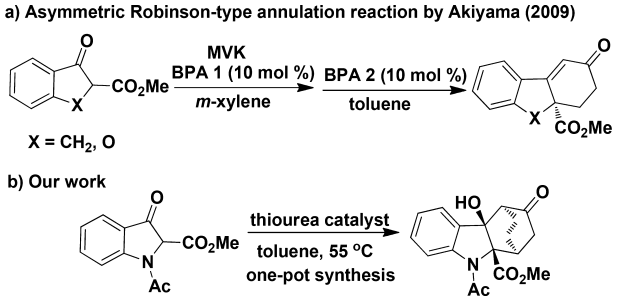


Figure 2. Previous reports.

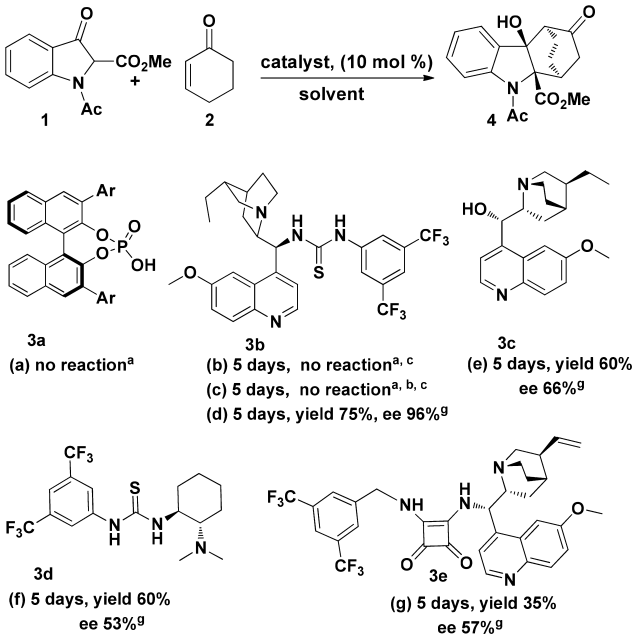
and methyl vinyl ketone afforded the desired products with excellent enantioselectivity.[7d] Nevertheless, to the best of our knowledge, the direct organocatalytic asymmetric one-pot Robinson annulation reaction of 3-indolinone-2-carboxylates using cyclohexene has not been reported.

Following our interest in the area of organocatalysis, we herein report an enantioselective Robinson annulation of 3-indolinone-2-carboxylates with cyclohexenone using a thiourea catalyst derived from hydroquinidine. Initially, we performed the reaction between 3-indolinone-2-carboxylateand cyclohexenone using 10 mol % of binolphosphoric acid (BPA) **3a**[8a−g] and 5 Å molecular sieves in toluene at room temperature. No desired product was obtained under these reaction conditions.

The reaction was further performed using a bifunctional thiourea catalyst **3b**[8h−j] under the above reaction conditions. Only the Michael adduct was obtained after 5 days at room temperature (Table 1, entry b). No annulated product was observed, even after adding 10 mol % of acetic acid (Table 1, entry c). By increasing the reaction temperature from rt to 55 °C, the desired Robinson annulated product was obtained with excellent enantio- (96% ee) and diastereoselectivity (dr >20:1) in 75% yield. The reaction was complete after 5 days with 10 mol % catalyst **3b** (Table 1, entry d). To reduce the reaction time, we repeated the reaction at 100 °C in toluene under similar catalytic conditions. However, the desired product was obtained in low yield with poor enantioselectivity. To improve the enantioselectivity, the reaction was further performed using 10 mol % of the catalyst **3c**[8k−o] in toluene at 55 °C; the desired product was obtained in moderate yield with good enantiomeric excess (Table 1, entry e). No significant improvement in terms of ee or yield was observed by using 10 mol % Takemoto catalyst **3d**[8p−r] or bifunctional squaramide thiourea catalyst **3e**[8s−u] under similar reaction conditions (Table 1, entries f, g). Furthermore, we screened different solvents such as benzene, *o*-xylene, and dichloroethane under similar reaction conditions. None of these solvents produced better results than toluene with respect to yields and enantioselectivity (Table 1, entries h, i, j). Therefore, the use of 10 mol % catalyst **3b** and 5 Å molecular sieves in toluene at 55 °C for 5 days was found to be the best reaction conditions for the asymmetric tandem Michael−aldol reaction.

With the optimized reaction conditions in hand, the scope of this reaction was studied and the results are summarized in Table 2. Initially, the effect of halide on the aromatic ring of 3-indolinone-2-carboxylate was examined. The indolin-3-one bearing substituents such as fluoro, chloro at the C-6 position on the aromatic ring afforded the desired products in good yields with excellent enantioselectivity (Scheme 1, **4b**, 91% ee and 72% yield; **4c**, 92% ee and 70% yield). Similarly, the presence of bromide and chloride at the C-5 position also gave the products **4d** and **4e** with excellent enantioselectivity (Scheme 1, **4d**, 92%

Table 1. Optimization of Catalyst and Reaction Condition[d]



entry	catalyst	solvent	*t* (°C)	time (h)	yield[e](%)	ee[f,g]
h	**3b**	benzene	55	120	60	76
i	**3b**	*o*-xylene	55	120	50	64
j	**3b**	DCE	55	120	60	40

[a]Reaction was performed at rt. [b]Reaction at rt after adding 10 mol % AcOH. [c]Only Michael addition product observed. [d]Unless otherwise specified, all reactions were performed with 1 equiv of **1**, 1.5 equiv of **2**, 10 mol % of **3b**, and 5 Å MS (100 mg) in 4 mL of toluene at 55 °C. [e]Isolated yields after column chromatography. [f]Enantiomeric excess was determined by chiral HPLC analysis. [g]Diastereomeric excess >20:1.

ee and 70% yield; **4e**, 94% ee and 71% yield). Furthermore, the substrate bearing a methyl group at either the C-4 or C-5 position furnished the desired products **4f** and **4g** in good yields and enantioselectivity (Scheme 1, **4f**, 94% ee, 60% yield; **4g**, 98% ee, 70% yield), whereas the presence of methyl substituent at the C-7 position afforded the desired product **4h** in 60% yield, with low enantiomeric excess (Scheme 1, **4h**, 74% ee, 60% yield). However, the substrate bearing an electron-withdrawing group such as NO_2 at the C-5 position on the aromatic ring afforded the product with slightly lower ee (Scheme 1, **4i**, 84% ee, 65% yield). Furthermore, a slight decrease in the enantioselectivity was observed in the case of ethyl ester (Scheme 1, **4j**, 89% ee, 72% yield). The reaction was also performed with *N*-benzoyl 3-oxoindoline. To our delight, the annulated product was obtained with excellent enantiomeric excess (Scheme 1, **4k**, 97% ee, 78% yield).

The scope of the asymmetric Robinson annulation was extended to other Michael acceptors. However, the use of cyclopentenone as a Michael acceptor gave the Michael adducts exclusively (Scheme 1, **4l**, 64% ee, 91% yield) without further aldolization. Similarly, a heteroaromatic substrate also afforded the Michael adduct **4m** with 90% ee and 63% yield without further aldol reaction. However, a sterically hindered naphthyl derivative gave the Robinson annulated product **4n** in 80% yield and 95% ee. This methodology was further studied with acyclic α,β-unsaturated carbonyl compounds (Scheme 2, R = H, Me, Ph). Only Michael adducts were obtained without annulation.

DOI: 10.1021/acs.orglett.8b01575
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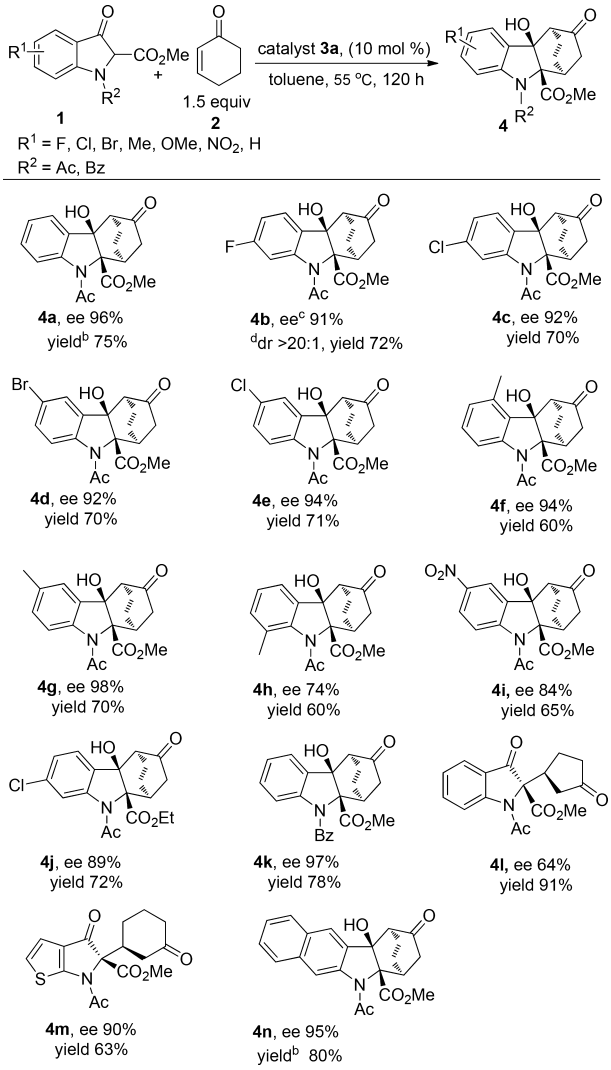
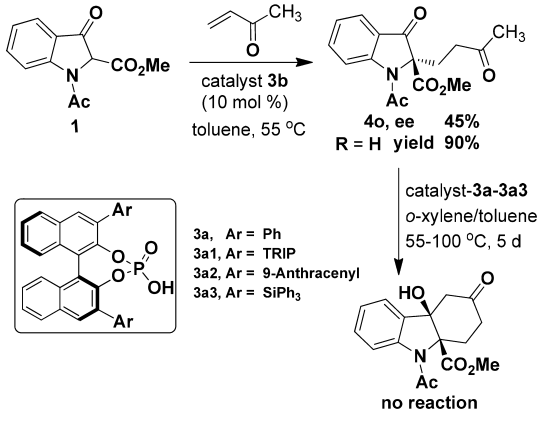
Scheme 1. Substrate Scope[a,d]



[a]All reactions were performed with 1 equiv of compound **1**, 1.5 equiv of cyclohexenone **2**, 10 mol % catalyst-**3b**, and 5 Å MS (100 mg) in 4 mL of toluene at 55 °C for 5 days. [b]Isolated yields after column chromatography. [c]Enantiomeric excess was determined by chiral HPLC analysis. [d]Diasteromeric excess >20:1 was determined by ^{1}H NMR analysis.

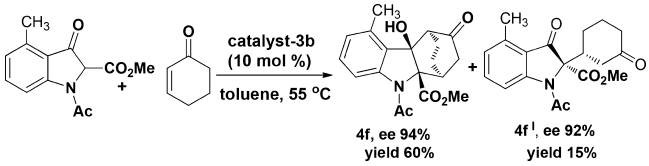
Scheme 2. Asymmetric Robinson Annulation of Acyclic Enones



For example, methyl vinyl ketone gave the Michael adduct exclusively under the present reaction conditions (Scheme 2, **4o**, 45% ee, 90% yield). Furthermore, we attempted the asymmetric Aldol reaction of **4o** using 10 mol % BINOL phosphoric acid catalysts (Scheme 2, catalysts **3a**−**3a3**) at 55 °C in toluene or *o*-xylene. Unfortunately, the desired product was not formed, even at 100 °C.

The kinetic resolution was observed in the reaction of substrate **1** with cyclohexenone (Scheme 3). A less reactive Michael adduct **4f**[l] was isolated as a minor isomer with excellent enantioselectivity (92% ee) along with annulated product **4f** under similar reaction conditions.

Scheme 3. Kinetic Resolution in the Aldol Condensation



The major isomer arises from the *Si*-face attack of enol onto the carbonyl group of the 3-indolinone-2-carboxylate, whereas *Re* face attack of the enol prevents the cyclization.

The structure and relative stereochemistry of **4a** were determined by a single crystal X-ray analysis (CCDC 1837201) (Figure 3).

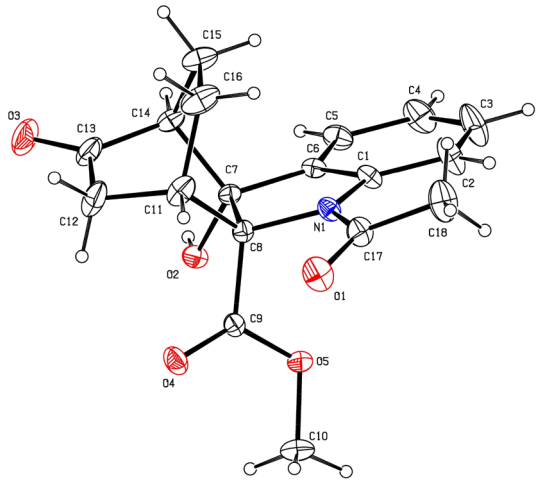


Figure 3. ORTEP diagram of **4a**.

In summary, a chiral bifuntional thiourea catalyzed Robinson annulation of 3-indolinone-2-carboxylates with cyclohexenone has been developed for the first time using a chiral thiourea catalyst. This method provides chiral bridged hydrocarbazole derivatives bearing vicinal quaternary centers with excellent diastereo- and enantioselectivity. The end products are useful building blocks for the construction of hydrocarbazole alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01575.

Copies of ^{1}H, ^{13}C NMR spectra and HPLC data of products, ORTEP diagram (PDF)

DOI: 10.1021/acs.orglett.8b01575
Org. Lett. 2018, 20, 4195−4199

Accession Codes

CCDC 1837201 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

S.Y. thanks UGC, and G.S.S. thanks CSIR, New Delhi for the award of fellowships.

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