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Desymmetrization of *meso*-Dicarbonatecyclohexene with *β*-Hydrazino Carboxylic Esters via a Pd-Catalyzed Allylic Substitution Cascade

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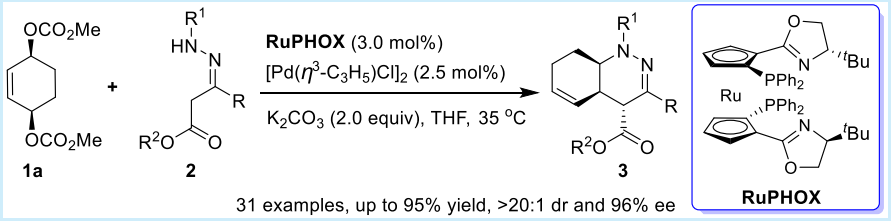

ABSTRACT: The desymmetrization of *meso*-dicarbonatecyclohexene with *β*-hydrazino carboxylic esters has been achieved via a RuPHOX/Pd-catalyzed allylic substitution cascade for the construction of chiral hexahydrocinnoline derivatives with high performance. Mechanistic studies reveal that the reaction exploits a pathway different from that of our previous work and that the first nitrogen nucleophilic process is the rate-determining step. The protocol could be conducted on a gram scale without any loss of catalytic behavior, and the corresponding chiral hexahydrocinnolines can undergo diverse transformations.

Chiral cinnolines and hydrocinnolines are significant structural motifs found in numerous medicinally important compounds, such as cinoxacin, cinnopentazone, analgesics, etc. (Figure 1).[1] For this reason, much effort has been devoted to their preparation, and a series of useful methodologies have been developed and applied generally in the organic and medicinal chemistry fields.[2] Compared with cinnolines, hydrocinnolines remain relatively unfamiliar in modern-day organic chemistry, and their construction has been considerably less exploited. Furthermore, most of the existing synthetic methods are racemic.[1,3] Therefore, the development of synthetic approaches for the efficient construction of novel chiral hydrocinnoline derivatives is greatly important.

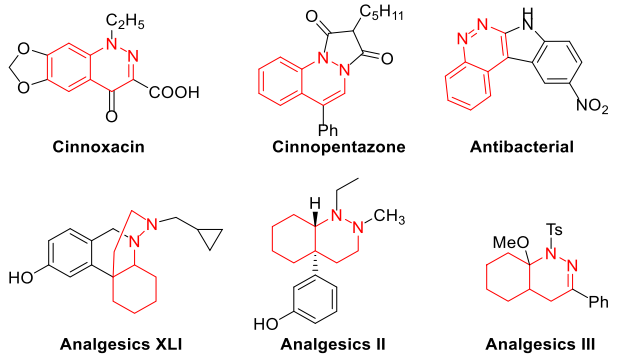

Figure 1. Chiral cinnolines and hydrocinnolines.

The Pd-catalyzed asymmetric allylic substitution cascade reaction is a powerful method for the synthesis of chiral heterocycles, owing to the ability to form successive multiple bonds.[4] Our laboratory has had a long-standing interest in the exploration of novel Pd-catalyzed asymmetric allylic substitutions.[5] Recently, we have focused on the catalytic enantioselective desymmetrization of *meso*-allyl substrates and established several straightforward protocols for accessing chiral oxygen- and nitrogen-containing [4,3,0] fused heterocycles.[6] The efficient catalytic system prompted us to explore the construction of chiral hydrocinnolines, six-membered [4,4,0] fused azabicycles, which has not been reported so far.

β-Hydrazino carboxylic esters are useful synthons in a variety of transition-metal-catalyzed reactions.[7] In particular, they show versatile reactivity for the construction of heterocyclic compounds[8] and can also serve as efficient 1,4-bis-nucleophiles for the construction of diazaheterocycles.[9] Recently, Hui and co-workers realized an efficient NHC-catalyzed asymmetric [3+4] annulation of *β*-hydrazino carboxylic esters with 2-bromoenals to synthesize chiral seven-membered diazaheterocycless bearing two consecutive stereocenters in good yields with excellent stereoselectivities

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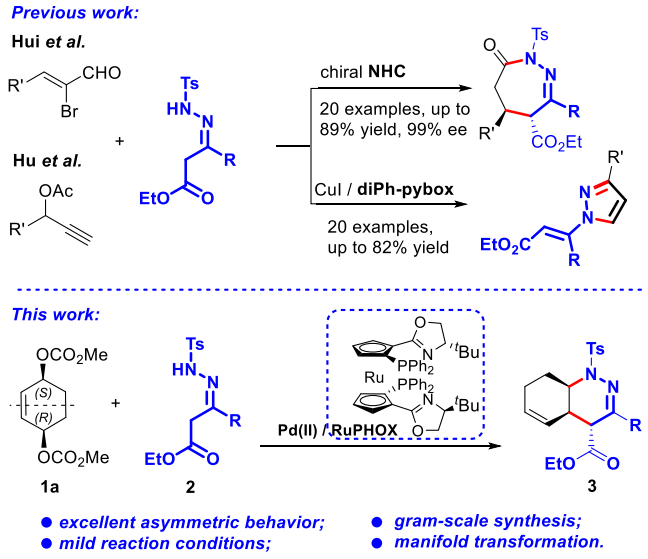
(Scheme 1, top).[9a] By treatment with propargylic acetates via a copper-catalyzed [3+2] cycloaddition, Hu et al. realized the

Scheme 1. Asymmetric Synthesis of Chiral Hexahydrocinnolines

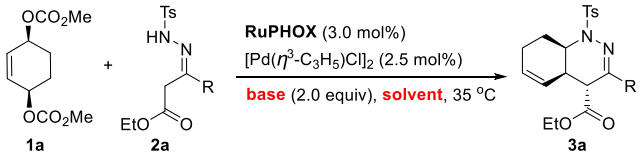


synthesis of nonchiral five-membered diazaheterocycles (Scheme 1, top).[9b] To the best of our knowledge, no example concerning the construction of six-membered skeletons has been reported. Herein, we describe an efficient Pd-catalyzed asymmetric allylic substitution cascade of β-hydrazino carboxylic esters with *meso*-dicarbonatecycloalkene via an enantioselective desymmetrization, providing hexahydrocinnolines bearing three consecutive chiral centers (Scheme 1, bottom).

Initially, we began our investigation by choosing *meso*-dicarbonatecycloalkene (**1a**) and β-hydrazino carboxylic ester (**2a**) as the model substrates in the presence of 2.5 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and DBU (2.0 equiv). The effects of different ligands on the reaction were first examined in THF at 35 °C, and RuPHOX (developed in our lab[10]) was found to be the best choice.[11] Subsequently, several solvents were tested with RuPHOX as the ligand (Table 1, entries 1−8). Excellent diastereomeric ratios (dr) and enantiomeric excesses (ee) were obtained when THF was used (entry 8, 9:1 dr, 90% ee). Further screening of the base revealed that K_2CO_3 gave the best results (entries 9−13, 91% yield, 9:1 dr, 94% ee). The optimized conditions were identified as follows: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), RuPHOX (3.0 mol %), and K_2CO_3 (2.0 equiv) in THF at 35 °C (entry 11).

With the optimized reaction conditions in hand, we then studied the substrate scope of the cascade reaction (Scheme 2). Thus, the reactions of various β-hydrazino carboxylic esters (**2a**−**ae**) with **1a** were carried out. A variety of substituents on the phenyl ring of **2** consisting of either electron-donating or electron-withdrawing groups were well tolerated, affording the desired chiral hexahydrocinnoline products with high performance. Substrates decorated with a methyl group at each position of the phenyl ring were converted to their desired products with good results (**3b**−**d**, 66−90% yields, 4:1−10:1 dr, 90−94% ee). The absolute configuration of (*R*,*R*,*R*)-**3c** was determined by X-ray crystallographic analysis.[12] Substrate **2**, bearing an electron-donating group (4-^{t}Bu or 4-OMe) at the

Table 1. Optimization of the Reaction Conditions[a]



entry	base	solvent	yield (%)[b]	dr[c]	ee[d]
1	DBU	DCE	47	2:1	80/56
2	DBU	CH_2Cl_2	90	5:1	77/70
3	DBU	MeCN	54	5:1	71/60
4	DBU	toluene	31	1:1	97/88
5	DBU	dioxane	82	2:1	92/90
6	DBU	DME	30	4:1	90/84
7	DBU	MTBE	53	3:1	94/87
8	DBU	THF	32	9:1	90/90
9	DIPEA	THF	43	2:1	96/91
10	Na_2CO_3	THF	78	2:1	96/87
11	K_2CO_3	THF	91	9:1	94/94
12	Cs_2CO_3	THF	80	4:1	93/93
13	−	THF	65	2:1	99/93

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), RuPHOX (3.0 mol %), and base (2.0 equiv) in a solvent (2 mL) at 35 °C for 36 h. [b]Isolated yield related to combined diastereoisomers. [c]Determined by ^{1}H NMR integration. [d]Determined by HPLC analysis using an IE column.

para positions of the phenyl ring, gave the desired products **3e** in 87% yield (4:1 dr, 91% ee) and **3f** in 94% yield (2:1 dr, 96% ee). Substrates with electron-withdrawing groups (F, Cl, Br, CO_2Me, CN, CF_3, and CF_3O) on the phenyl rings of **2** also gave the corresponding **3g**−**r** in good to excellent yields (73−95%) and enantioselectivities (78−94% ee). A substrate with a phenyl group on the β-hydrazino carboxylic ester bearing an *o*-fluorine substituent afforded the corresponding products with better diastereoselectivity than those bearing *m*- and *p*-fluorine groups (**3g**−**i**). Notably, chloride and bromide groups were also tolerated (**3j**−**n**). Substrate **2p** with a cyano substituent showed good catalytic behavior, albeit with somewhat low diastereoselectivity (2:1 dr). Compound **2** bearing an electron-withdrawing substituent (CF_3) at the *para* position led to a decrease in enantioselectivity and only moderate yield and diastereoselectivity (**3q**). Substrates with disubstituted phenyl rings gave their corresponding products with excellent yields and good to excellent enantioselectivities (**3s**−**u**). To our delight, 2-naphthyl-, 2-furyl-, and 3-thienyl-derived β-hydrazino carboxylic esters **2v**−**x** also proved to be suitable substrates for this reaction (**3v**−**x**, 65−84% yields, 3:1−5:1 dr, 90−95% ee). Reaction of a β-hydrazino carboxylic ester with a linear alkyl group (*n*-Pr) group gave the corresponding chiral hexahydrocinnoline product in comparatively lower yield (**3y**). A substrate bearing a benzyl group in place of the *n*-Pr group afforded its corresponding product in moderate yield and ee (**3z**). Finally, substrates **2aa**−**ae** with different N-protecting groups and esters were examined, with the desired products **3aa**−**ae** being obtained in good yields and excellent enantioselectivities.

To confirm the scalability of this method, a gram-scale synthesis of (*R*,*R*,*R*)-**3a** was carried out under the standard reaction conditions. The asymmetric desymmetrization of **1a** (2.5 mmol) with **2a** (3.8 mmol) proceeded smoothly to afford **3a** in 87% yield, 9:1 dr, and 94% ee (Scheme 3, top).

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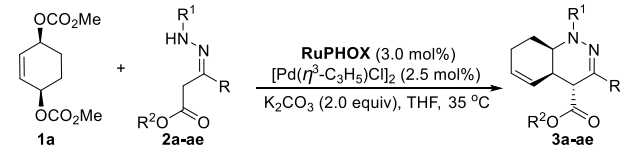
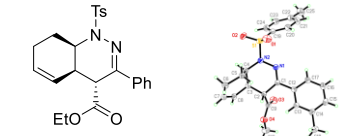
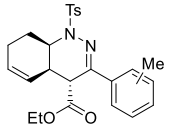
Scheme 2. Substrate Scope[a,b]



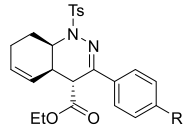


3a: 91%, 9:1 dr, 94% ee

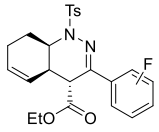
3c



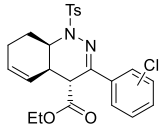
3b (*o*-Me): 66%, 10:1 dr, 90% ee
3c (*m*-Me): 78%, 4:1 dr, 90% ee
3d (*p*-Me): 90%, 4:1 dr, 94% ee



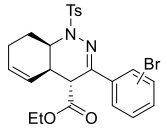
3e (R = ^{t}Bu): 87%, 4:1 dr, 91% ee
3f (R = MeO): 94%, 2:1 dr, 96% ee



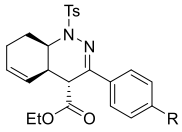
3g (*o*-F): 84%, 11:1 dr, 90% ee
3h (*m*-F): 91%, 5:1 dr, 91% ee
3i (*p*-F): 90%, 6:1 dr, 90% ee



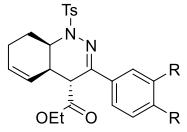
3j (*o*-Cl): 90%, 5:1 dr, 87% ee
3k (*m*-Cl): 95%, 5:1 dr, 90% ee



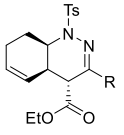
3l (*o*-Br): 77%, 7:1 dr, 92% ee
3m (*m*-Br): 82%, 7:1 dr, 94% ee
3n (*p*-Br): 80%, 8:1 dr, 92% ee



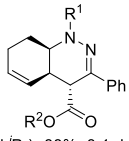
3o (R = CO_2Et): 73%, 5:1 dr, 90% ee
3p (R = CN): 81%, 2:1 dr, 88% ee
3q (R = CF_3): 75%, 6:1 dr, 78% ee
3r (R = CF_3O): 79%, 6:1 dr, 87% ee



3s (R = Me): 82%, 2:1 dr, 94% ee
3t (R = F): 84%, 7:1 dr, 93% ee
3u (R = Cl): 89%, 4:1 dr, 91% ee



3v (R = 2-naphthyl): 72%, 5:1 dr, 93% ee
3w (R = 3-furyl): 65%, 3:1 dr, 90% ee
3x[b] (R = 3-thienyl): 84%, 3:1 dr, 95% ee
3y (R = *n*-Pr): 37%, 4:1 dr, 86% ee
3z (R = Bn): 75%, >20:1 dr, 70% ee

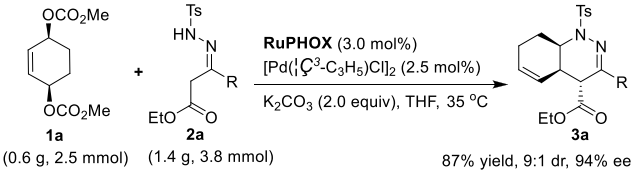


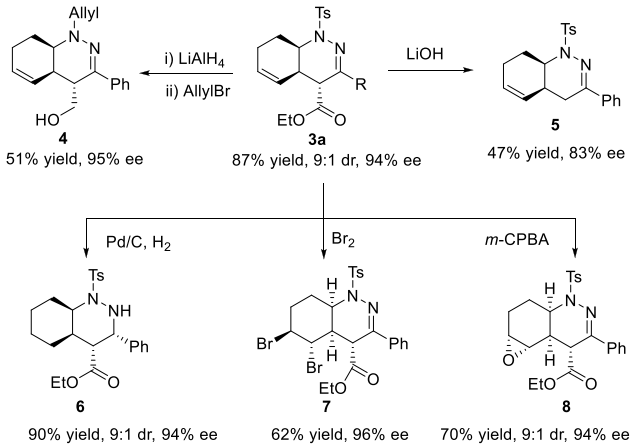
3aa (Ts and ^{i}Pr): 88%, 3:1 dr, 95% ee
3ab (Ts and ^{t}Bu): 70%, 3:1 dr, 92% ee
3ac (Ms and Et): 87%, 8:1 dr, 85% ee
3ad (^{i}PrSO$_2$ and Et): 95%, 5:1 dr, 90% ee
3ae (PhCO and Et): 91%, 5:1 dr, 94% ee

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Pd(η^3-C_3H_5)Cl]$_2$ (2.5 mol %), RuPHOX (3.0 mol %), and K_2CO_3 (2.0 equiv) in THF (2 mL) at 35 °C for 36 h. Isolated yields related to combined diastereomers and the major diastereomers were isolated via preparative HPLC. Ee values were determined by chiral HPLC analysis of **3** using an IE, OX, or IC-3 column. [b]The absolute configuration of minor diastereomer **3x** was determined by single-crystal analysis and is shown in the Supporting Information.[12].

To test the utility of these methodologies, several transformations of the chiral hexahydrocinnoline product were performed (Scheme 3, bottom). After screening a series of deprotecting methods, we found that $LiAlH_4$ could remove the Ts group efficiently and reduce the ester group to the alcohol. Subsequent protection with an allyl group in situ afforded product **4** in 51% yield and 95% ee. Treatment of **3a** with LiOH in a MeOH/H_2O/THF mixed solvent system at rt resulted in a decarboxylation to give **5** in 47% yield with 83% ee. Hydrogenation of the C=C bond of **3a** with H_2 catalyzed by Pd/C in aqueous MeOH afforded **6** in 90 yield, 9:1 dr, and

Scheme 3. Gram-Scale Synthesis and Transformation of 3a





94% ee. When **3a** was treated with Br_2 in the presence of *i*-Pr_2NEt, dibromination product **7** was formed in 62% yield and 96% ee. The C=C bond could also be oxidized by *m*-CPBA to give the corresponding epoxidation product **8** in 70% yield without any loss of stereoselectivity.[13]

On the basis of the experimental results and our previous studies, we initially proposed a catalytic cycle for the formation of chiral hexahydrocinnolines (Scheme 4, pathway a). First, the RuPHOX/Pd complex coordinates with the C=C bond from the back of the two OCO_2Me groups of *cis*-**1a**. The allyl Pd complex **A** intermediate is formed because of the enantioselective desymmetrization.[14] Next, intermediate **A** reacts with *β*-hydrazino carboxylic ester **2a**, producing **B′** via a carbon nucleophilic substitution. Finally, the terminal chiral hexahydrocinnoline product (**9**) is obtained via a cascade intramolecular nitrogen nucleophilic substitution. However, the position of the C=C bond in the terminal product is not identical to that of desired product **3a**. This means that the sequence of the carbon and nitrogen nucleophilic substitution may proceed through a different pathway compared with our previously reported reaction.[6] That is, after the formation of intermediate **A**, the cascade process involves nitrogen nucleophilic substitution prior to carbon nucleophilic substitution via intermediates **B** and **C** (pathway b). The strong acidity of the NH in **2a**, most likely resulting from a carbonyl functional group, must be responsible for the reversed nucleophilic pathway.

We attempted to obtain the nucleophilic nitrogen intermediate by either decreasing the reaction temperature or shortening the reaction time. However, only desired product **3a** was obtained with starting materials **1a** and **2a** being recycled. This suggests that the second intramolecular carbon nucleophilic substitution is much faster than the first intermolecular nitrogen nucleophilic substitution. That is, the first nitrogen nucleophilic process is the rate-determining step in the cascade reaction process. In addition, the asymmetric catalytic reaction of **1a** and **2a** was also quenched at different

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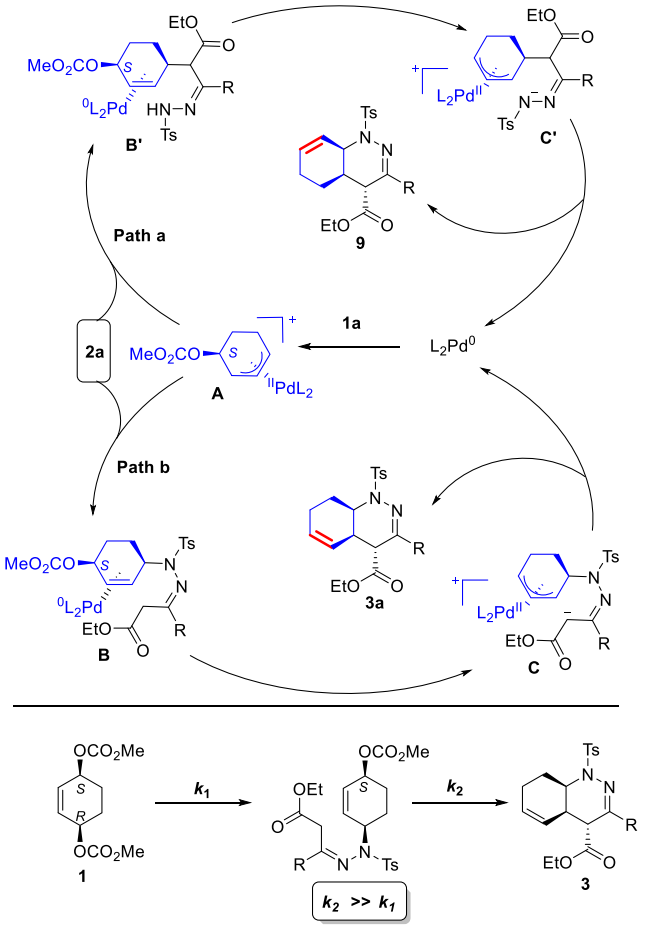
Scheme 4. Proposed Reaction Mechanism



reaction times and epimerization was observed at the chiral center bearing the ester under the basic reaction conditions.[11]

In conclusion, we have developed a RuPHOX/Pd-catalyzed allylic substitution cascade involving a desymmetrization of *meso*-dicarbonatecyclohexene with *β*-hydrazino carboxylic esters, providing chiral hexahydrocinnoline derivatives in up to 95% yield, >20:1 dr, and 96% ee. The protocol could be scaled to gram quantities without any loss of reaction activity and enantioselectivity. Furthermore, the corresponding chiral hexahydrocinnolines can undergo several transformations. Mechanistic studies reveal that the reaction proceeds via a different pathway compared with our previous work and the nitrogen nucleophilic substitution is the rate-determining step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03211.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 2007663 and 2040737 contain 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.

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