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Enantioselective Rhodium-Catalyzed Isomerization of 4-Iminocrotonates: Asymmetric Synthesis of a Unique Chiral Synthon

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Abstract

An enantioselective isomerization of 4-iminocrotonates catalyzed by a rhodium(I)/phosphoramidite complex is described. This reaction uses widely available amines to couple with 4-oxocrotonate to provide a convenient access to a central chiral building block in good yield and high enantioselectivity. Although the mechanism of this new transformation remains unclear, both Rh and the phosphoramidite play a central role.

Graphical Abstract

As a source of optically active *N*-acyliminium ion precursors,^{1,2} chiral 5-alkoxy-3-pyrrolin-2-ones are important building blocks for the synthesis of biologically active natural products and pharmaceuticals.^{3–5} Current strategies for preparing enantiomerically-enriched 5-alkoxy-3-pyrrolin-2-ones rely heavily on derivatization of enantiopure starting materials provided by nature (eq 1, Scheme 1)⁶ or enzymatic resolution of racemic substrates (eq 2).⁷ While these methods are useful, a catalytic asymmetric synthesis of this key building block remains unreported. Herein, we describe that a rhodium(I)/phosphoramidite complex catalyzes an intramolecular cyclization of 4-iminocrotonates to give 5-alkoxy-3-pyrrolin-2-ones in good yields and high enantioselectivities (eq 3).

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ASSOCIATED CONTENT

Supporting Information

Experimental procedures, additional experiments, and new compounds' characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interests.

Our group has been interested in the development of rhodium-catalyzed asymmetric syntheses of nitrogen-containing heterocycles.^{8,9} In 2011, we reported an asymmetric [4 + 2] cycloaddition of α,β -unsaturated imines and isocyanates catalyzed by a rhodium(I)/phosphoramidite (**L1**) complex.^{9e} This reaction allows facile access to pyrimidinones in good yields and high enantioselectivities. Surprisingly, when ethyl 4-iminocrotonate (**1a**) is used as a substrate under the same reaction conditions, the reaction gives no pyrimidinone product. Instead, 5-ethoxy-3-pyrrolin-2-one **2a**, formed from intramolecular cyclization of **1a**, is isolated in good yield (Table 1, entry 1). Although the enantioselectivity is low when Taddol phosphoramidite ligand **L1** is used, we recognized that optimization of this reaction would offer a novel and promising method to synthesize enantiomerically-enriched 5-alkoxy-3-pyrrolin-2-ones.

Investigation of the effect of the alkoxy group on reaction enantioselectivity revealed that isopropyl 4-iminocrotonate (**3a**) reacts with higher enantioselectivity than ethyl 4-iminocrotonate, albeit in lower yield (entry 2, and SI).

Ligand was also found to have a profound effect on reaction enantioselectivity. Use of previously developed Guiphos (**L2**)^{9c-d} gives a sharp increase in selectivity (entry 3). Moreover, substitution of the 3,3'-position in Guiphos with more bulky silyl groups led to the discovery of an optimal ligand, TIPS-Guiphos (**L6**) for this reaction. This TIPS-substituted phosphoramidite further improves enantioselectivity to 94% ee for **4a** (entry 7). It is noteworthy that neither $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ nor TIPS-Guiphos alone gives product (entries 8 and 9), which clearly demonstrates the catalytic role of the rhodium(I)/phosphoramidite complex. Further optimization of the reaction conditions (See SI) established that treatment of **3a** with 10 mol % $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ and 20 mol% TIPS-Guiphos in toluene at 110 °C for 24 h (entry 10) provides **4a** in high yield and excellent enantioselectivity.

We propose a possible mechanism for the transformation in Scheme 2. Upon coordination of 4-iminocrotonate **3** initially to the rhodium(I)/phosphoramidite complex, **3** isomerizes from *E* to *Z* configuration. At this point, the imine nitrogen is poised for intramolecular attack on the carbonyl group, affording *N*-acyliminium intermediate **B**.¹⁰ A resultant trapping of **B** by alkoxide delivers 5-alkoxy-3-pyrrolin-2-one **4** and regenerates catalyst. Rhodium precatalysts bearing norbornadiene or cyclooctadiene ligands give no product (see SI). Presumably, these strongly coordinating diene ligands impede coordination of the 4-iminocrotonate, thereby preventing the catalyst from entering into the catalytic cycle. Although 5-alkoxy-3-pyrrolin-2-ones generally produce *N*-acyliminiums in the presence of a Lewis acid catalyst, control experiments reveal that alkoxide attack on acyliminium ion **B** is irreversible under the reaction conditions (see SI). It is worth noting that intermediate **B** in the absence of Rh coordination is putatively antiaromatic, which may be a further role for Rh in this reaction.

The Rh(I)/TIPS-Guiphos catalyst promotes the enantioselective synthesis of different 5-isopropoxy-3-pyrrolin-2-ones very efficiently (Chart 1). 4-(Benzylimino)crotonates bearing a wide range of functional groups including electron-donating alkyl and alkoxy and electron-withdrawing trifluoromethyl and methoxycarbonyl substituents all react smoothly to afford the corresponding cyclization products **4b–4i** in good yields and high enantioselectivities.

Electronic and steric modulations of the *N*-benzyl substituents have no substantial effect on the enantioselectivity of the transformation (**4a–4l**). Substrates containing thiophene and furan give the desired product **4n** and **4o** in satisfactory yields with a prolonged reaction time. Not surprisingly, primary alkyl-substituted 4-(imino)crotonates participate in the cyclization reaction quite efficiently to provide the corresponding products in good yields and high enantioselectivities (**4p**, **4q**, and **4s–4v**). The use of 4-(cyclohexylimino)crotonate **3r** gives a moderate yield and enantioselectivity comparable to primary alkyl-substituted substrates. Aryl substituted 4-iminocrotonate compounds are inert under these conditions.

The products obtained in this reaction can serve as useful chiral synthons (Scheme 3). After dihydroxylation of **4e** with OsO₄ and NMO, protection of the diol with 2,2-dimethoxypropane and removal of the PMB group with CAN, amide **6** undergoes C-C bond forming reactions with indole and allyltrimethylsilane in the presence of Lewis acids in excellent diastereoselectivities and with no significant loss of enantio-purity. Direct removal of the PMB group of **4e** and subsequent acylation provides **9**, which is an effective partner for diastereoselective 1,3-dipolar cycloaddition^{3b} and Diels-Alder reactions.^{6d} Compound **5v**, which is obtained by dihydroxylation of **4v** and subsequent protection, undergoes an intramolecular Friedel-Crafts reaction catalyzed by AuOTf to furnish tetracycle **10** in moderate yield and excellent enantio- and diastereoselectivity.

In conclusion, we have developed an enantioselective rhodium(I)/phosphoramidite-catalyzed intramolecular cyclization reaction of 4-iminocrotonates. This process provides a convenient access to electronically and sterically diverse 5-isopropoxy-3-pyrrolin-2-ones in good yield and high enantioselectivity. Further, this constitutes an example of a catalytic asymmetric synthesis of an amina, examples of which are still relatively rare.¹¹ The products obtained by this method are useful chiral building blocks, and they are rapidly elaborated to stereodefined amides in high enantio- and diastereoselectivity by reactions with various carbon nucleophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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• Previous work

- *chiron approach*

- *enzymatic resolution*

• This work

- *asymmetric catalysis*

Scheme 1.
Access to 5-Alkoxy-pyrrolinones

Scheme 2.
Possible Mechanism

Scheme 3. Derivatization of the Products

Reaction conditions: a) cat. OsO₄, NMO, acetone/H₂O, rt, 18 h. b) 2,2-dimethoxypropane, cat. TsOH, acetone, rt, 18 h. c) CAN, CH₃CN/H₂O, 0 °C to rt, 1 h. d) cat. AuCl/AgOTf, indole, DCM, 40 °C, 24 h. e) BF₃•OEt₂/TMSOTf, allyltrimethylsilane, DCM, 40 °C, 18 h. f) Ac₂O, pyridine, cat. DMAP, rt, 2h. g) cat. AuCl/AgOTf, CH₃CN, 80 °C, 24 h.

Chart 1.

Reaction Scope a,b

^a Conditions: **3** (0.2 mmol), [Rh(C₂H₄)₂Cl]₂ (0.02 mmol), TIPS-Guiphos (0.04 mmol), toluene, 110 °C, 24 h. ^b Isolated yield. ^c 48 h.

Table 1

Reaction Optimization^a

entry	product	ligand	yield (%) ^b	ee (%) ^c
1	2a	L1	79	20
2	4a	L1	18	59
3	4a	L2	15	85
4	4a	L3	22	89
5	4a	L4	20	66
6	4a	L5	23	72
7	4a	L6	20	94
8 ^d	4a	NA	<1	ND
9 ^e	4a	L6	<1	ND
10 ^f	4a	L6	78	94

^aConditions: **1a** or **3a** (0.2 mmol), [Rh(C₂H₄)₂Cl]₂ (0.01 mmol), ligand (0.02 mmol), toluene, 110 °C, 12 h.

^b Isolated yield.

^c Enantioselectivities determined by HPLC analysis on a chiral stationary phase. Absolute configuration assigned by analogy (see SI).

^dIn the absence of **L6**.

^e In the absence of rhodium source.
$$f_{[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2 \text{ (10 mol \%), } \mathbf{L6} \text{ (20 mol \%), 24 h.}$$