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

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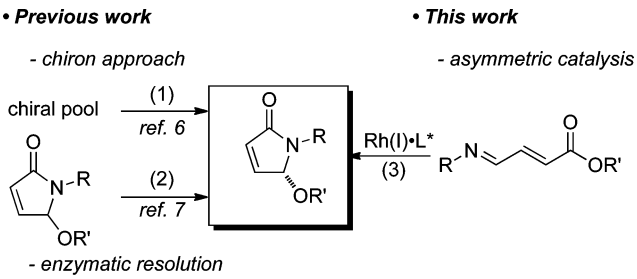
Supporting Information

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.

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

Scheme 1. Access to 5-Alkoxy-pyrrolinones

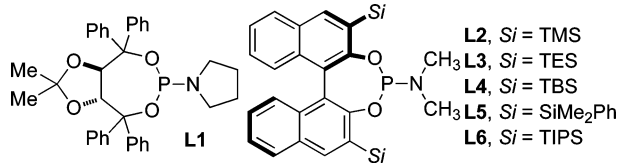


of racemic substrates (eq 2).[7] While these methods are useful, a catalytic asymmetric synthesis of this key building block remains unreported. Herein, we describe that a rhodium(I)/phosphoramidite complex catalyzes an intramolecular cyclization of 4-iminocrotonates to give 5-alkoxy-3-pyrrolin-2-ones in good yields and high enantioselectivities (eq 3).

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

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



[a]Conditions: **1a** or **3a** (0.2 mmol), $[Rh(C_2H_4)_2Cl]_2$ (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). [d]In the absence of **L6**. [e]In the absence of rhodium source. [f]$[Rh(C_2H_4)_2Cl]_2$ (10 mol %), **L6** (20 mol %), 24 h.

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 Supporting Information (SI)).

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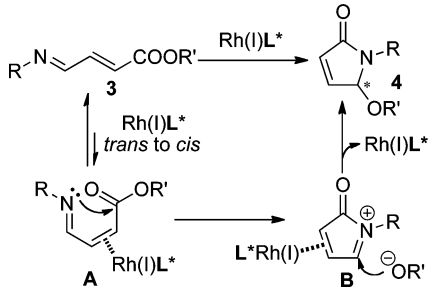
The ligand was also found to have a profound effect on reaction enantioselectivity. Use of previously developed Guiphos (**L2**)[9c,d] gives a sharp increase in selectivity (entry 3). Moreover, substitution of the 3,3′-position in Guiphos with more bulky silyl groups led to the discovery of an optimal 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 $[Rh(C_2H_4)_2Cl]_2$ 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 % $[Rh(C_2H_4)_2Cl]_2$ 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

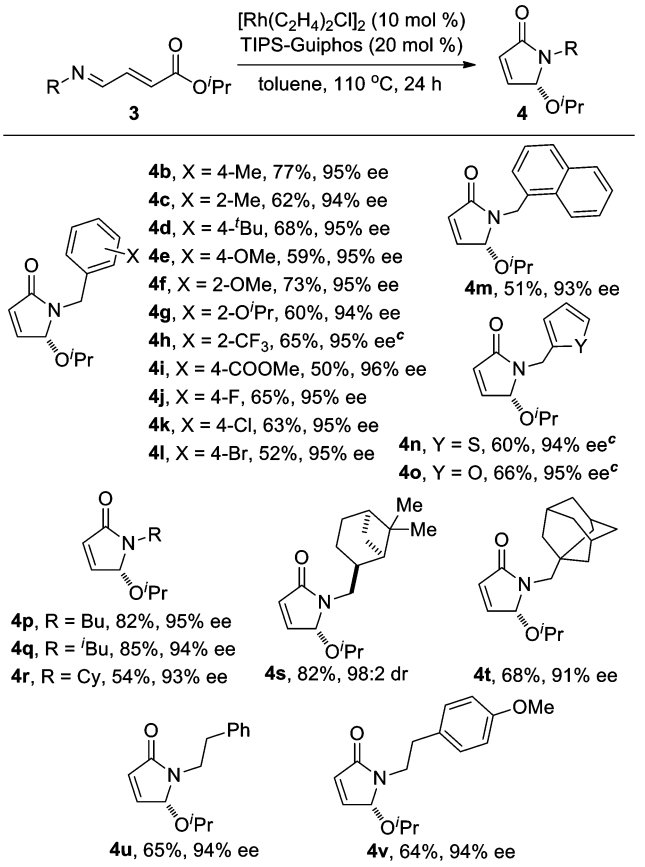
Scheme 2. Possible Mechanism



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-

Chart 1. Reaction Scope[a,b]



[a]Conditions: **3** (0.2 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.02 mmol), TIPS-Guiphos (0.04 mmol), toluene, 110 °C, 24 h. [b]Isolated yield. [c]48 h.

(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 OsO_4 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 erosion of enantiopurity. 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 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 aminal, 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

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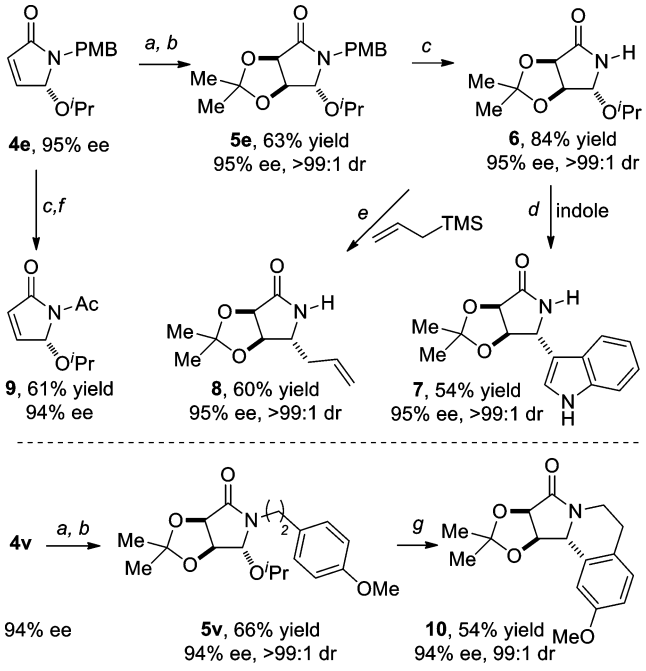
Scheme 3. Derivatization of the Products[a]



[a]Reaction conditions: (a) cat. OsO_4, NMO, acetone/H_2O, rt, 18 h. (b) 2,2-Dimethoxypropane, cat. TsOH, acetone, rt, 18 h. (c) CAN, CH_3CN/H_2O, 0 °C to rt, 1 h. (d) Cat. AuCl/AgOTf, indole, DCM, 40 °C, 24 h. (e) $BF_3{\cdot}OEt_2$/TMSOTf, allyltrimethylsilane, DCM, 40 °C, 18 h. (f) Ac_2O, pyridine, cat. DMAP, rt, 2 h. (g) Cat. AuCl/AgOTf, CH_3CN, 80 °C, 24 h.

stereodefined amides in high enantio- and diastereoselectivity by reactions with various carbon nucleophiles.

■ 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.

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Notes

The authors declare no competing financial interest.

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