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Enantioselective Rhodium-Catalyzed [4+2] Cycloaddition of Alpha, Beta-Unsaturated Imines and Isocyanates

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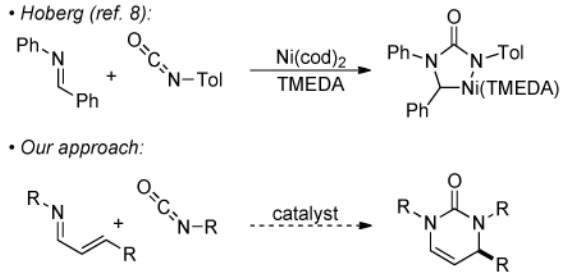
Abstract

A [4+2] cycloaddition of α, β-unsaturated imines and isocyanates catalyzed by a phosphoramiditerhodium complex provides pyrimidinones in good yields and high enantioselectivities.

Pyrimidinones are attractive scaffolds due to their biological activity[1] and their accessibility via multicomponent reactions. Traditionally, this motif is synthesized via the three-component Biginelli reaction.[2] Improvements on Biginelli's initial report[3] include the use of chiral acids to achieve high enantioselectivities[4] and departure from classic components.[5]

Recently, our group has reported asymmetric syntheses of nitrogen-containing heterocycles via rhodium catalysis.[6,7] Inspired by Hoberg's report8 of a nickelacycle generated from an imine and isocyanate, we envisioned using α, β-unsaturated imines9 and isocyanates10 to generate pyrimidinones.[11] By employing α, β-unsaturated imines, we sought to change the typical substitution pattern that accompanies the classic Biginelli reaction. Herein, we report that a rhodium-phosphoramidite complex catalyzes the [4+2] cycloaddition between α, β-unsaturated imines and isocyanates[12] to generate pyrimidinones in good yields and high enantioselectivities.13



We began our investigations by examining nickel catalysts as per the stoichiometric precedent of Hoberg, but found them ineffective at catalyzing the desired reaction (Table 1, entry 2). Wilkinson's catalyst is only marginally effective, but switching to a Taddol phosphoramidite-rhodium complex provides the target material in moderate yield and enantioselectivity (entries 3 and 4). After exploring various phosphoramidites, we found **L2** generates pyrimidinone **3aa** in the highest yield and enantioselectivity (entry 5).[14]

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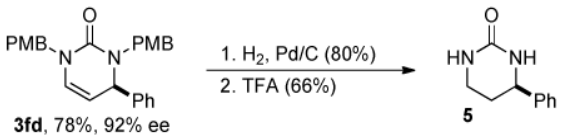
SUPPORTING INFORMATION Experimental procedures, characterization, ^{1}H and ^{13}C NMR spectra, and CIF file for **3ge**. This material is available free of charge via the Internet at http://pubs.acs.org.

With our optimized catalyst system in hand, we explored the scope of this reaction (Chart 1). Electron-deficient aryl imines (**3ca**) furnish slightly higher yields and selectivities over electron-rich aryl imines (**3ba**). Primary alkyl imines generate the highest enantioselectivities with good yield; a secondary alkyl imine is also well-tolerated but provides moderately reduced selectivities (**3da**). Electron-rich aryl substituents at the 4-position provide products in good yields and high enantioselectivities, while electron-deficient aryl substitution leads to higher enantioselectivity with a decrease in yield. Furyl, vinyl, and alkyl substitution also yields product, with the latter furnishing lower selectivities (**3ma**). An increase in size of the alkyl substituent only leads to a slight improvement in yield and enantioselectivity (**3na**). Primary alkyl isocyanates deliver high yields and enantioselectivities.[15] Phenyl isocyanate also generates product, but the yield and selectivity is lower. This reaction has been performed on a 4.5 mmol scale using imine **1g** and benzyl isocyanate **2c** with 2 mol % catalyst loading and the yield and enantioselectivity does not suffer.

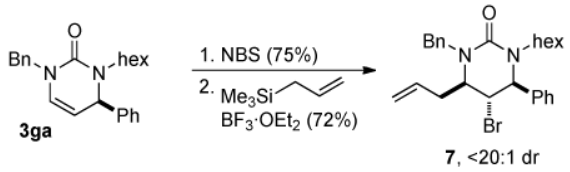
We propose the following mechanism (Scheme 1). Initial coordination of the α, β-unsaturated imine and isocyanate is followed by oxidative cyclization to generate rhodacycle **I**, which resembles the nickelacycle isolated by Hoberg.[8] An η^1-η^3-η^1 shift forms rhodacycle **II** that reductively eliminates to furnish the pyrimidinone and regenerate catalyst. An alternative mechanism involving a [4+1] cycloaddition between the α, β-unsaturated imine and rhodium can also be envisioned. If a [4+1] cycloaddition occurs first, the stereocenter would be set before the isocyanate is incorporated. Variance in enantioselectivities using different isocyanates suggests that oxidative cyclization of the imine and isocyanate takes place before the enantiodetermining step.

The pyrimidinones generated from this reaction may serve as useful chiral building blocks. After reduction of **3fd**, the resulting bis(4-methoxybenzyl)-tetrahydropyrimidinone can be deprotected using neat trifluoroacetic acid (eq 1). In the presence of N-bromosuccinimide and wet dimethylformamide, **3ga** generates the bromohydrin that can be converted to **7** using boron trifluoride etherate and allyltrimethylsilane (eq 2).[5b]



3fd, 78%, 92% ee **5**

(1)



3ga **7**, <20:1 dr

(2)

In conclusion, we report the synthesis of pyrimidinones from α, β-unsaturated imines and isocyanates using a rhodiumphosphoramidite catalyst, affording a substitution pattern complementary to that of Biginelli adducts. This reaction proceeds in moderate to good yields and high enantioselectivities, and the products are useful chiral building blocks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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14. The ^{1}H NMR of the unpurified reaction mixture typically shows unreacted starting material and product only, with occasional urea derived from isocyanate hydrolysis.
15. Cyclohexyl isocyanate provides trace product and tert-butyl isocyanate does not generate any product.

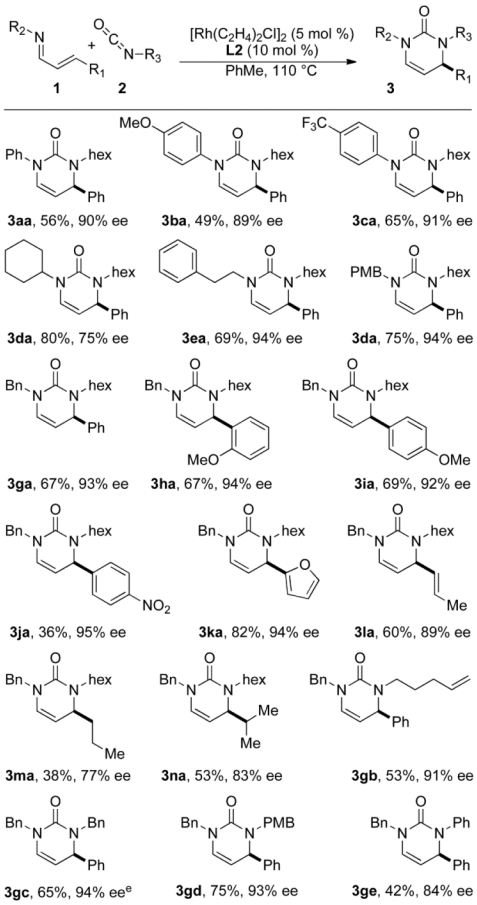
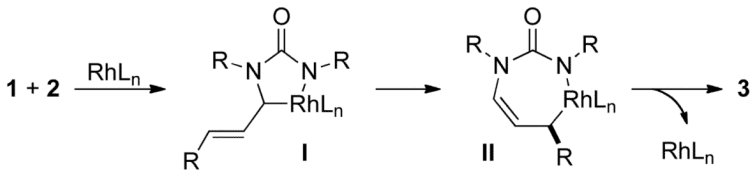


Chart 1.

Reaction scope.[a]

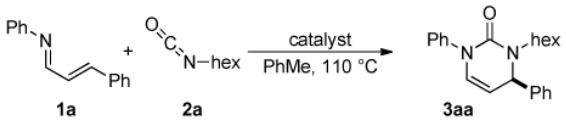
[a] Conditions: **1** (0.3 mmol), **2** (1.25 equiv), $[Rh(C_2H_4)_2Cl]_2$ (5 mol %), and **L2** (10 mol %) in PhMe at 110 °C for 12 h. [b] Isolated yield. [c] Enantiomeric excess determined by HPLC using a chiral stationary phase. [d] Absolute configuration assigned by analogy to (*R*)-**3af** (established by X-ray analysis – see SI). [e] On 4.5 mmol scale with $[Rh(C_2H_4)_2Cl]_2$ (1 mol %) and **L2** (2 mol %): 71% yield and 94% ee.



Scheme 1.
Mechanistic Proposal.

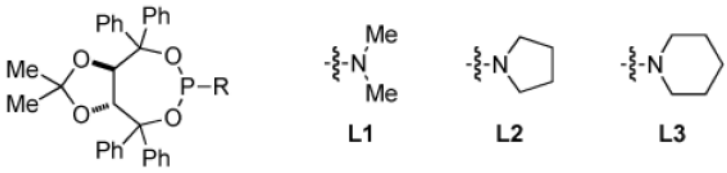
Table 1

Catalyst Screen.[a]



1a 2a 3aa

entry	catalyst	yield (%)[b]	ee (%)[c,d]
1	none	0	-
2	$Ni(cod)_2$ (10 mol %), TMEDA (10 mol %)	0	-
3	$Rh(PPh_3)_3Cl$ (10 mol %)	<5	-
4	$[Rh(C_2H_4)_2Cl]_2$ (5 mol %), **L1** (10 mol %)	29	81
5	$[Rh(C_2H_4)_2Cl]_2$ (5 mol %), **L2** (10 mol %)	56	90
6	$[Rh(C_2H_4)_2Cl]_2$ (5 mol %), **L3** (10 mol %)	22	79
7	**L2** (10 mol %)	0	-



L1 L2 L3

[a] Conditions: **1** (0.3 mmol), **2** (1.25 equiv), and catalyst in PhMe at 110 °C for 12 h.

[b] Isolated yield.

[c] Enantiomeric excess determined by HPLC using a chiral stationary phase.

[d] Absolute configuration assigned by analogy to (*R*)-**3af** (established by X-ray analysis – see SI).