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

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Ⓢ *Supporting Information*

ABSTRACT: A [4 + 2] cycloaddition of α,β-unsaturated imines and isocyanates catalyzed by a phosphoramidite—rhodium 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 report[8] of a nickelacycle generated from an imine and isocyanate, we envisioned using α,β-unsaturated imines[9] and isocyanates[10] 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]

• *Hoberg (ref. 8):*

• *Our approach:*
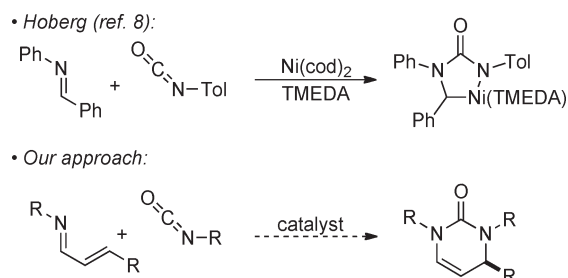
We began our investigations by examining nickel catalysts as per the stoichiometric precedent of Hoberg but found them ineffective at catalyzing the desired reaction (Table 1, entry 2). Wilkinson's catalyst is only marginally effective, but switching to a Taddol phosphoramidite—rhodium complex provides 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]

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

Table 1. Catalyst Screen[a]

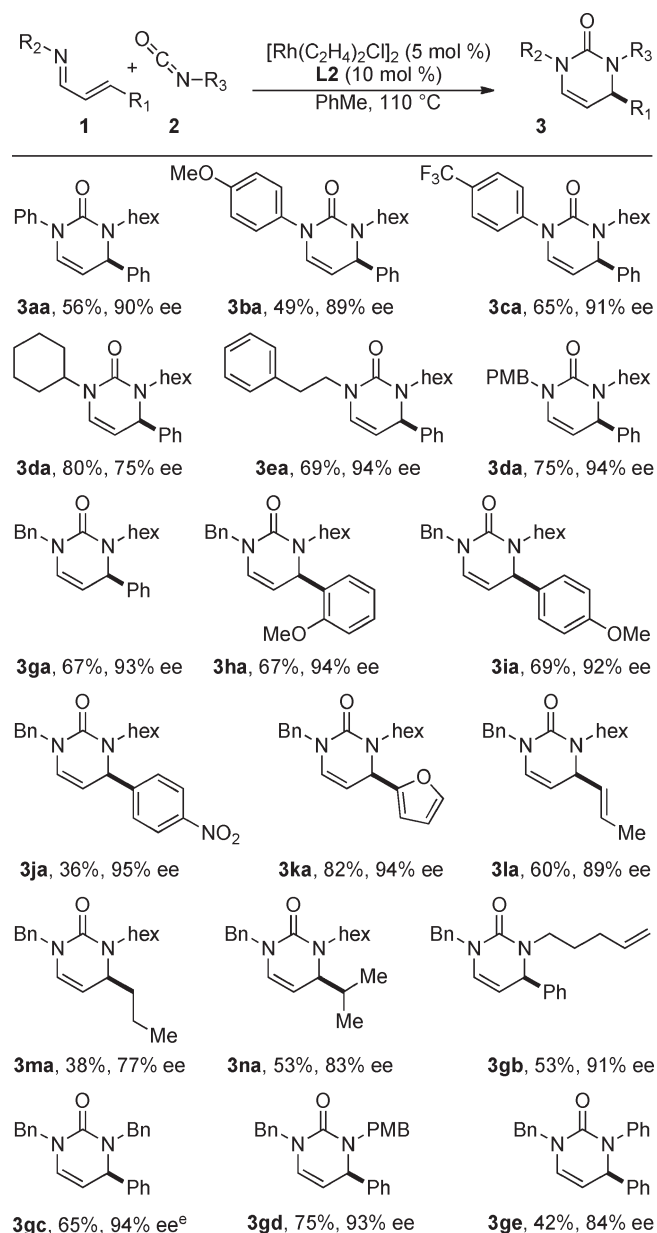| entry	catalyst	yield (%)[b]	ee (%)[c,d]
1	none	0	-
2	Ni(cod)$_2$ (10 mol %), TMEDA (10 mol %)	0	-
3	Rh(PPh$_3$)$_3$Cl (10 mol %)	<5	-
4	[Rh(C$_2$H$_4$)$_2$Cl]$_2$ (5 mol %), **L1** (10 mol %)	29	81
5	[Rh(C$_2$H$_4$)$_2$Cl]$_2$ (5 mol %), **L2** (10 mol %)	56	90
6	[Rh(C$_2$H$_4$)$_2$Cl]$_2$ (5 mol %), **L3** (10 mol %)	22	79
7	**L2** (10 mol %)	0	-

[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).

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 a 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 a product, but the yield and selectivity are 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 do 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

Chart 1. Reaction Scope[a−d]

3aa, 56%, 90% ee   **3ba**, 49%, 89% ee   **3ca**, 65%, 91% ee

3da, 80%, 75% ee   **3ea**, 69%, 94% ee   **3da**, 75%, 94% ee

3ga, 67%, 93% ee   **3ha**, 67%, 94% ee   **3ia**, 69%, 92% ee

3ja, 36%, 95% ee   **3ka**, 82%, 94% ee   **3la**, 60%, 89% ee

3ma, 38%, 77% ee   **3na**, 53%, 83% ee   **3gb**, 53%, 91% ee

3gc, 65%, 94% ee[e]   **3gd**, 75%, 93% ee   **3ge**, 42%, 84% ee

[a]Conditions: **1** (0.3 mmol), **2** (1.25 equiv), [Rh(C₂H₄)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(C₂H₄)₂Cl]₂ (1 mol %) and **L2** (2 mol %): 71% yield and 94% ee.

Scheme 1. Mechanistic Proposal
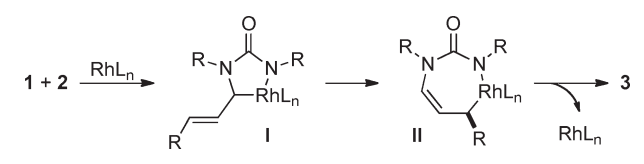
resembles the nickelacycle isolated by Hoberg.[8] An η^1-η^3-η^1 shift forms rhodacycle **II** that reductively eliminates to furnish the

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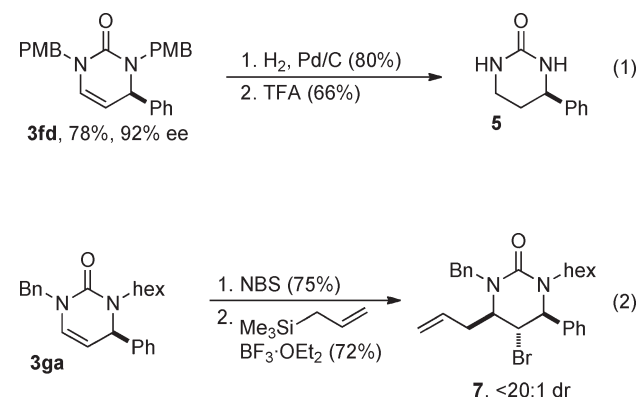
In conclusion, we report the synthesis of pyrimidinones from α,β-unsaturated imines and isocyanates using a rhodium–phosphoramidite catalyst, affording a substitution pattern complementary to that of Biginelli adducts. This reaction proceeds in moderate to good yields and high enantioselectivities, and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

■ ASSOCIATED CONTENT

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

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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 a trace product, and *tert*-butyl isocyanate does not generate any product.