Enantioselective Nickel-Catalyzed Michael Additions of 2-Acetylazaarenes to Nitroalkenes

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2-Acetylazaarenes undergo catalytic enantioselective Michael additions to nitroalkenes in the presence of a chiral Ni(II)-bis(oxazoline) complex. The process is tolerant of a range of azines or azoles in the pronucleophilic component, resulting in Michael products in moderate to high enantioselectivities.

The ubiquitous occurrence of azaarenes in chiral, biologically active compounds and other functional molecules renders the development of new catalytic enantioselective methods to prepare chiral azaarene-containing compounds a valuable objective. In this context, recent work from our group has targeted the utilization of the C=N moiety embedded within various azaarenes for the activation of adjacent alkenyl or alkyl groups in several catalytic enantioselective processes.¹ To increase the range of potential transformations that may be developed, we became interested in processes in which the C=N moiety of an azaarene could participate in other modes of substrate activation.

Recently, the use of 1,2-dicarbonyl compounds as pronucleophiles in catalytic enantioselective reactions has received increasing attention.² We therefore questioned whether the homology between 1,2-dicarbonyls and 2-acylazaarenes could be exploited in the development of catalytic enantioselective processes that employ the latter compounds as pronucleophiles. In a similar manner to 1,2-dicarbonyl compounds in related processes,³ twopoint binding of a 2-acylazaarene to a chiral metal complex would be expected to facilitate α -deprotonation with a basic counterion to generate a chiral metal enolate that could then participate in an enantioselective addition to an electrophile (Scheme 1). To our knowledge, the use of 2-acylazaarenes in this manner has not been reported previously.⁴ Such a process would be attractive, as the resulting chiral azaarene-containing products could serve as valuable building blocks for synthesis. In this paper, we describe the successful realization of this strategy with the development of enantioselective nickel-catalyzed Michael additions of 2-acetylazaarenes to nitroalkenes.^{5–7}

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Scheme 1. Soft Enolization of 2-Acylazaarenes and Reaction with Electrophiles



Given the successful use of 1,2-dicarbonyls in metalcatalyzed enantioselective additions to nitroalkenes by the groups of Sodeoka,^{3g} Shibasaki,^{3h} and Huang,³ⁱ our preliminary experiments focused upon the enantioselective reaction of the commercially available compounds 2-acetylpyridine (**1a**) and nitroalkene **2a**.⁸ After a survey of chiral metal complexes and reaction conditions,⁹ we were pleased to find that treatment of a mixture of **1a** (1.2 equiv) and **2a** (1.0 equiv) with the complex composed of Ni(OAc)₂. 4H₂O (5 mol %) and the bis(oxazoline) ligand L**1**^{10,11} in

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Figure 1. Enantioselective nickel-catalyzed additions of 2-acetylazaarenes to nitroalkene **2a**. Reactions were conducted using 0.60 mmol of acetylazaarene and 0.50 mmol of **2a** in 5 mL of *i*-PrOH. Yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis.

i-PrOH at room temperature afforded the Michael adduct **3a** in 86% yield and 93% ee (Figure 1).¹² Further investigation revealed that, in addition to **1a**, 2-acetylazaarenes containing quinoline, pyrazine, thiazole, benzothiazole, or *N*-methylimidazole groups reacted smoothly with **2a** to provide products **3b**-**3f**, respectively, in 64–94% yield and 94–99% ee. Unfortunately, replacement of the methyl ketone in the pronucleophile with higher homologues such as an ethyl ketone was problematic; although good reactivity was observed with these substrates, the resulting products were prone to epimerization at the stereogenic center adjacent to the ketone during handling and purification, resulting in unwieldy mixtures of diastereomers.

The requirement for the C=N moiety in the azaarene to be adjacent to the carbonyl group for reactivity was confirmed by the attempted reaction of 4-acetylpyridine (**1g**) with **2a**, which gave no Michael product under our reaction conditions (eq 1).¹³



The Michael additions of 1a-1f to various other (hetero)aryl-substituted nitroalkenes also proceeded

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⁽¹²⁾ The absolute configurations of the products in this study were assigned by analogy to that of **4g**, which was determined by X-ray crystallography (Figure 3).

⁽¹³⁾ In addition, no reaction was observed using 3-acetylpyridine, 2-acetylthiophene, or acetophenone as the pronucleophile.



Figure 2. Enantioselective nickel-catalyzed additions of 2-acetylazaarenes to various β -(hetero)aryl-substituted nitroalkenes. Reactions were conducted using 0.60 mmol of acetylazaarene and 0.50 mmol of nitroalkene in 5 mL of *i*-PrOH. Yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis.

smoothly, providing products in uniformly high enantioselectivities (92–99% ee, Figure 2). Nitroalkenes with β -phenyl groups containing 2-methyl (products **4e** and **4k**), 4-methoxy (products **4d** and **4i**), 4-fluoro (product **4f**), 4-bromo (product **4g**), 3-nitro (product **4c**), or 4-trifluoromethyl groups (product **4a**) were effective reaction partners. Furthermore, nitroalkenes containing 1-naphthyl (products **4h** and **4l**) or 2-thienyl groups (products **4b** and **4j**) were also tolerated. The absolute stereochemistry of product **4g** was confirmed by X-ray crystallography (Figure 3).



Figure 3. X-ray structure of Michael adduct 4g.

Next, additions to β -alkyl-substituted nitroalkenes were evaluated. We found that these substrates were significantly less reactive than the (hetero)aryl-substituted nitroalkenes in our process; under the conditions shown in Figures 1 and 2, no reaction was observed using



Figure 4. Enantioselective nickel-catalyzed additions of 2-acetylazaarenes to β -alkyl-substituted nitroalkenes **2j** and **2k**. Reactions were conducted using 0.60 mmol of acetylazaarene and 0.50 mmol of nitroalkene in 1 mL each of PrOH and CH₂Cl₂. Yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis.

 β -alkyl-substituted nitroalkenes, even after extended reaction times.¹⁴ Fortunately, increasing the concentration of the reaction from 0.1 to 0.5 M with respect to the nitroalkene was found to be beneficial for reaction rates, and a 1:1 mixture of *i*-PrOH/CH₂Cl₂ proved to be optimal to maintain good solubility of the reactants. These conditions enabled the addition of 2-acetylazaarenes **1a**–**1f** to nitroalkenes **2j** and **2k** in reasonable yields (Figure 4). However, the enantioselectivities of these reactions (65–82% ee) were lower than those obtained using β -(hetero)-aryl-substituted nitroalkenes.¹⁴

These Michael reactions are also effective on larger scales. For example, additions of 1b-1d to 2a on 10.0 mmol scales (with respect to 2a) using only 1 mol % of catalyst in 1:1 *i*-PrOH/CH₂Cl₂ (0.5 M with respect to 2a) provided Michael adducts in 66–81% yield and 95–99% ee after 72 h (Figure 5).

To illustrate the potential utility of the products, further transformations of **3b** were conducted. Treatment of **3b**

⁽¹⁴⁾ The lower reactivity and enantioselectivities afforded by β -alkylsubstituted nitroalkenes compared with their β -aryl counterparts in related nickel-catalyzed Michael additions of 1,3-dicarbonyl compounds have been observed previously; see ref 5d, 5e.



Figure 5. Larger scale Michael additions. Reactions were conducted using 12.0 mmol of acetylazaarene and 10.0 mmol of 2a in 10 mL each of *i*-PrOH and CH₂Cl₂. Yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis.

with Noyori's RuCl[(*S*,*S*)-TsDPEN](*p*-cymene] complex¹⁵ in the presence of HCO₂H/Et₃N in DMF at room temperature led to highly diastereoselective (>19:1 dr) reduction of the ketone to provide secondary alcohol **6a** in >95% yield (Scheme 2).¹⁶ Use of the enantiomeric complex gave diastereomeric alcohol **6b** with similarly high yield and high diastereoselectivity (>19:1 dr). The high diastereoselectivities of these reactions demonstrate that catalyst control is dominant, and the existing stereocenter in **3b** has little effect on the stereochemical outcome.

In summary, we have developed the enantioselective Michael addition of 2-acetylazaarenes to nitroalkenes, catalyzed by a chiral Ni(II)-bis(oxazoline) complex. The process is tolerant of a range of azaarenes in the pronucleophile, and the reactions proceed under mild, Scheme 2. Asymmetric Transfer Hydrogenation of Product 3b



experimentally convenient conditions. Although the enantioselectivities are modest with β -alkyl-substituted nitroalkenes, a range of β -(hetero)aryl-substituted nitroalkenes react smoothly to give products in much higher enantiopurity (93–99% ee). Further investigations of C=N-containing azaarenes as activating groups for enantioselective catalysis are ongoing and will be reported in due course.

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Supporting Information Available. Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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