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Enantioselective Nickel-Catalyzed Michael Additions of Azaarylacetates and Acetamides to Nitroalkenes

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Azaarenes are privileged structures that appear in numerous biologically active compounds such as natural products, pharmaceuticals, and agrochemicals. Therefore, the development of new methods for the incorporation of azaarenes into compounds, or to functionalize preexisting azaarenes, are of high value. Our laboratory has recently developed two reactions that utilize alkenylazaarenes as electrophiles for enantioselective addition reactions: copper-catalyzed 1,4-reductions,[1a] and rhodium-catalyzed 1,4-arylations.[1b] These processes rely upon a suitably positioned C=N group in an azaarene to activate an adjacent alkene toward a nucleophilic addition (Figure 1 A).[2,3] These studies led us to consider whether the C=N group of an azaarene could provide a complementary mode of substrate activation through acidification of the protons of an adjacent methylene carbon. Under suitable reaction conditions, deprotonation of this methylene carbon could occur to generate a nucleophile that, under the influence of a chiral catalyst, could undergo enantioselective addition to a carbon electrophile (Figure 1 B).

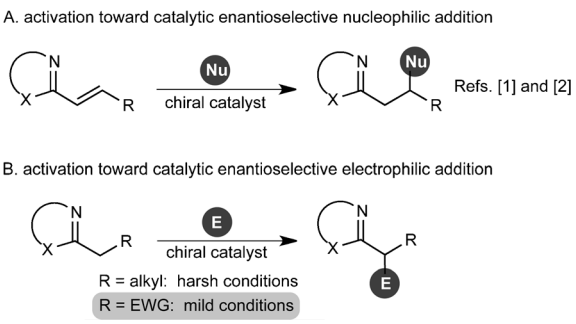

Figure 1. Azaarenes as activating groups for enantioselective catalysis. E = electrophile, EWG = electron-withdrawing group, Nu = nucleophile.

In this context, the Trost group has reported enantioselective palladium-catalyzed allylic alkylations of alkylazaarenes with cyclic allylic carbonates.[4] Although this protocol was effective, stoichiometric quantities of a strong lithium amide base, lithium hexamethyldisilazide (LiHMDS), are required for the reactions to proceed.[4] The development of processes that operate under milder reaction conditions without stoichiometric preactivation of the alkylazaarene[5] is therefore highly desirable, and recent reports have documented initial progress toward this goal.[6] The research groups of Huang,[6a–c] Rueping,[6d] and Matsunaga and Kanai[6e] have reported non-asymmetric metal-catalyzed additions of alkylazaarenes to imines,[6a–d] enones,[6e] and an α,β-unsaturated *N*-acylpyrrole.[6e] A catalyst-free addition of alkylazaarenes to imines was also recently described.[7] Furthermore, there is a body of related work on transition-metal catalyzed cross-coupling reactions involving C–H functionalization of alkylazaarenes.[8] However, because of the relatively low acidity of alkylazarenes, high temperatures and long reaction times are often required to achieve acceptable yields in these reactions, and to our knowledge, no enantioselective variants have been reported.

One strategy for increasing the reactivity of alkylazaarenes is to place an additional acidifying group at the α carbon, which may also serve as a functional handle for further manipulation. Although there are numerous examples of additions of azaarylcarbonyl compounds or azaarylacetonitriles to carbon electrophiles, enantioselective variants are virtually nonexistent. The research group of Melchiorre recently described a secondary-amine-catalyzed asymmetric addition of nitrobenzyl pyridines to enals,[9] a reaction that is conceptually related to work by Cid, Ruano, and co-workers on the use of nitrophenylacetonitriles as pronucleophiles.[10] Given the paucity of such processes, the development of new catalytic enantioselective carbon–carbon bond-forming reactions of alkylazaarene derivatives represents an attractive goal.[11] Herein, we describe catalytic enantioselective Michael additions of azaarylacetates and acetamides to nitroalkenes.[12]

Azaarylacetates **1a–h** were examined first (Table 1). A brief evaluation of selected catalysts employed for the enantioselective addition of 1,3-dicarbonyl compounds to nitroalkenes[13,14] revealed that the nickel(II)-bis(diamine) complex **2** developed by the research group of Evans[14d,e,15] exhibited good activity. Stirring a 1:1 mixture of the azaarylacetate and the nitroalkene with 5 mol% of **2** in dioxane at room temperature in the presence of 3 Å molecular sieves provid-

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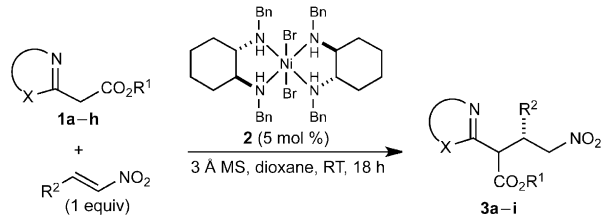
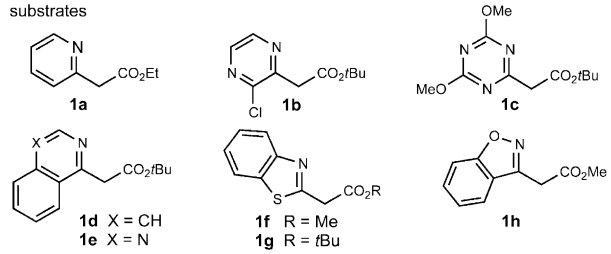
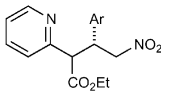
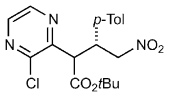
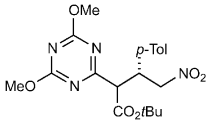
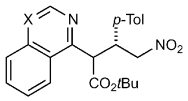
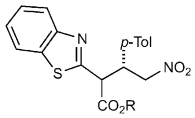
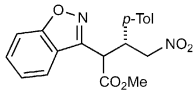
Table 1. Addition of azaarylacetates to nitroalkenes.[a]



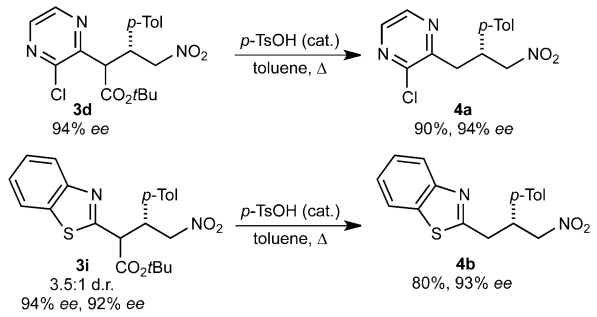
substrates



	Product		Yield [%][b]	d.r.[c]	*ee* [%][d]
1		**3a** Ar = *p*-Tol	71	12:1	89
2		**3b** Ar = *p*-MeOC$_6$H$_4$	88	7.5:1	80
3		**3c** Ar = 2-furyl	98	5:1	91 (45)
4		**3d**	66[e]	7:1[f]	94
5[g]		**3e**	50[h]	9:1[h]	90
6		**3f** X = CH	78[e]	9:1[f]	99
7		**3g** X = N	60[e,i]	6:1[f]	88
8		**3h** R = Me	94	2:1	96 (96)
9		**3i** R = *t*Bu	91	3.5:1	94 (92)
10		**3ja**, **3jb**	59 (39)[j]	1.6:1[f]	93 (82)

[a] Reactions were conducted using 0.30 mmol of **1a**-**h**. [b] Yields of inseparable isolated mixtures of diastereomers. [c] Unless stated otherwise, diastereomeric ratios of isolated product mixtures as determined by ^{1}H NMR analysis. [d] Enantiomeric excess of the major diastereomer as determined by HPLC analysis on a chiral stationary phase. Numbers in parentheses refer to the *ee* value of the minor diastereomer. [e] Yield of isolated pure major diastereomer. [f] Diastereomeric ratio of the unpurified reaction mixture as determined by ^{1}H NMR analysis. [g] Reaction conducted at 50 °C. [h] Product **3e** slowly epimerized to a 1:1 mixture of diastereomers upon standing. [i] A 1:1 mixture of diastereomers of **3g** was also isolated in 28 % yield. [j] Yield of isolated pure major and minor diastereomers. Bn = benzyl, MS = molecular sieves, Tol = tolyl.

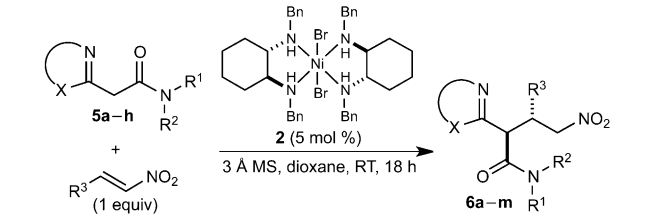
ed the Michael products with high enantioselectivities.[16,17] Unsurprisingly, the stereocenter α to the ester carbonyl group in many of the Michael adducts was prone to epimerization, and these products were isolated as inseparable mixtures of diastereomers. Ethyl 2-pyridylacetate (**1a**) underwent addition to a variety of β-(hetero)aryl-substituted nitroalkenes[18] with reasonable to high enantioselectivities (80–91 % *ee*, entries 1–3). Substrates containing other azines are also effective partners for (*E*)-4-methyl-β-nitrostyrene as demonstrated by the successful reaction of substrates bearing chloropyrazine (Table 1, entry 4), dimethoxytriazine (Table 1, entry 5), isoquinoline (Table 1, entry 6), and quinazoline (Table 1, entry 7) moieties, providing products in 88–99 % *ee*. Dimethoxytriazine **1c** was poorly reactive, and a slightly elevated temperature of 50 °C was required to provide **3e** in 50 % yield, but in 90 % *ee* (Table 1, entry 5). Azoles such as benzothiazole (Table 1, entries 8 and 9) and benzisoxazole (Table 1, entry 10) are also tolerated. In contrast to the other examples, the diastereomers of products **3d**, **3f**, **3g**, and **3j** were configurationally stable and separable. Furthermore, decarboxylation of **3d** and **3i** was readily achieved with no loss of enantiopurity upon heating with catalytic *p*-TsOH·H$_2$O in toluene (Scheme 1).

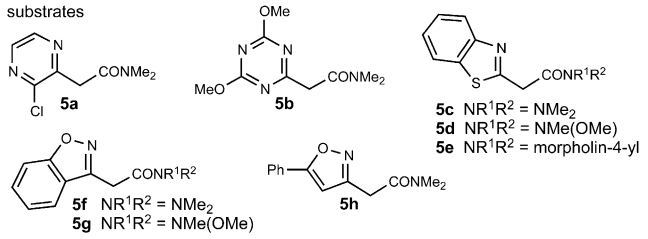


Scheme 1. Decarboxylation of Michael products. Ts = toluenesulfonyl.

The process is not limited to azaarylacetates; azaaryl tertiary acetamides are also viable substrates (Table 2).[17] In these cases, the products are configurationally stable, an observation that can be rationalized by the well-known resistance of tertiary amides containing an acidic stereocenter at the α position to undergo enolization, because of the significant $A_{1,3}$ strain that would develop.[19] Therefore, the indicated diastereomeric ratios likely reflect the inherent kinetic diastereoselectivities of these reactions. Under reaction conditions identical to those employed in Table 1, azaaryl *N*,*N*-dimethylacetamides containing chloropyrazine (Table 2, entry 1), dimethoxytriazine (Table 2, entry 2), benzothiazole (Table 2, entries 3–10), benzisoxazole (Table 2, entries 11 and 12), or 5-phenylisoxazole (Table 2, entry 13) groups underwent Michael additions to give the corresponding products in generally good yields and reasonable to high *ee* values. With substrate **5c**, the β substituent of the nitroalkene may be varied from *p*-tolyl (Table 2, entry 3) to *p*-methoxyphenyl (Table 2, entry 5), *p*-fluorophenyl (Table 2, entry 6), *p*-bromophenyl (Table 2, entry 7), or 2-furyl (Table 2, entry 8) without a major impact on diastereo- or enantioselectivities. However, a sterically more demanding *o*-tolyl group led to **6d** in somewhat diminished selectivities

Table 2. Addition of azaarylacetamides to nitroalkenes.[a]





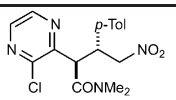
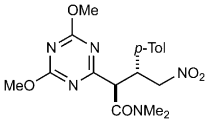
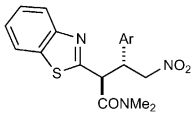
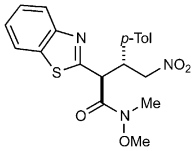
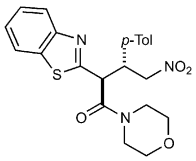
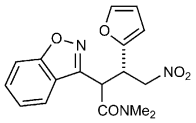
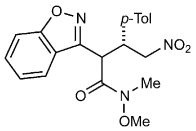
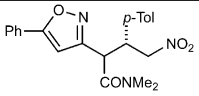
	Product		Yield [%][b]	d.r.[c]	*ee* [%][d]
1		**6a**	83	>19:1	83
2		**6b**	99[e]	10:1	93
3		**6c** Ar = *p*-Tol	79	>19:1	95
4		**6d** Ar = *o*-Tol	64	6:1	66
5		**6e** Ar = *p*-$MeOC_6H_4$	74	>19:1	86
6		**6f** Ar = *p*-FC_6H_4	78	>19:1	95
7		**6g** Ar = *p*-BrC_6H_4	84	>19:1	89
8[f]		**6h** Ar = 2-furyl	95	>19:1	>99
9		**6i**	85	>19:1	96
10		**6j**	87	>19:1	95
11		**6k**	73[g]	2:1[g]	88 (66)
12		**6la**, **6lb**	43 (44)[h]	1:1	81 (89)

Table 2. (Continued)

	Product		Yield [%][b]	d.r.[c]	*ee* [%][d]
13		**6ma**, **6mb**	49 (49)[h]	1:1	99 (99)

[a] Reactions were conducted using 0.30 mmol of **5a–h**. [b] Unless stated otherwise, yields are of isolated pure major diastereomers. [c] Diastereomeric ratio of the unpurified reaction mixtures as determined by ^{1}H NMR analysis. [d] Enantiomeric excess of the major diastereomer as determined by HPLC analysis on a chiral stationary phase. Numbers in parentheses refer to the *ee* value of the second diastereomer. [e] Yield of an isolated inseparable mixture of diastereomers. [f] Reaction conducted using 2.5 mmol each of **5c** and nitroalkene. [g] Product **6k** was isolated as a 1.3:1 mixture of diastereomers. [h] Yields of isolated pure separated diastereomers.

(Table 2, entry 4). The reactions are equally effective at larger scales; for example, reaction of **5c** with a 2-furyl-substituted nitroalkene on a 2.5 mmol scale provided **6h** in 95% yield, greater than 19:1 d.r., and greater than 99% *ee* after a single recrystallization of the crude product (Table 2, entry 8). Other amide groups such as Weinreb amides **5d** (Table 2, entry 9) and **5g** (Table 2, entry 12), and morpholine amide **5e** (Table 2, entry 10) are tolerated. In contrast to the majority of examples in Table 2, substrates **5f–h** underwent reactions with low diastereoselectivities (Table 2, entries 11–13).

Using substrate **5c** for illustrative purposes, Figure 2 depicts plausible transition state models that lead to the four possible stereoisomers of the products. These models are based upon the following assumptions:[14e] 1) catalyst **2** releases one diamine ligand that deprotonates the azaarene substrate to form the reactive enolate; 2) binding of the eno-

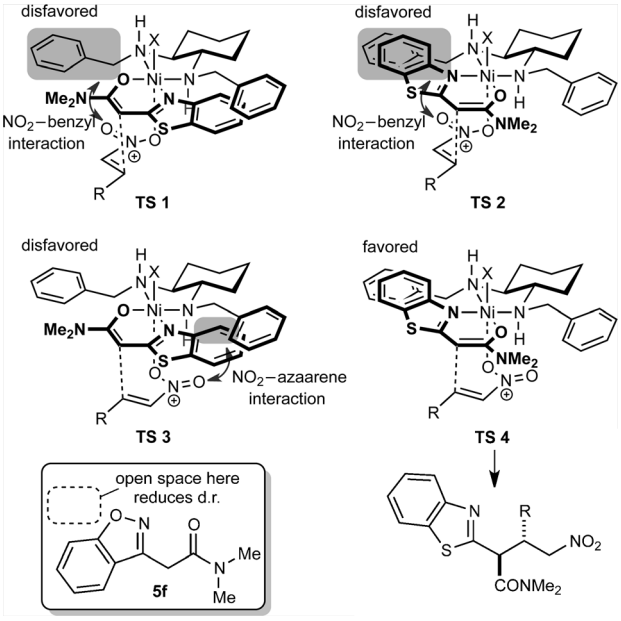


Figure 2. Model for stereochemical induction.

late to the nickel(II) center occurs through the amide oxygen and azaarene nitrogen atoms, and 3) the nitroalkene is bound to the nickel(II) center to stabilize the incipient nitronate anion. The facial selectivity with respect to the nitroalkene may be explained by unfavorable nonbonding interactions of the nitro group with a benzyl group of the ligand that are present in **TS 1** and **TS 2** but are absent in **TS 3** and **TS 4**. In turn, the high diastereoselectivities observed with **5c** (Table 2, entries 3 and 5–8) may be rationalized by an unfavorable interaction of the nitro group with the benzene ring of the benzothiazole present in **TS 3**, an interaction that is absent in the favored transition state **TS 4**. Similar considerations may be invoked to explain the high diastereoselectivities observed with substrates **5a**, **5b**, **5d**, and **5e** (Table 2, entries 1, 2, 9, and 10). Finally, the low to nonexistent diastereoselectivities observed with substrates **5f–h** (Table 2, entries 11–13) may be accounted for by the relatively open space in the vicinity of the oxygen atom of the (benz)isoxazole rings; this open space diminishes the unfavorable NO_2–azaarene interaction in **TS 3** and thus reduces the energy difference between **TS 3** and **TS 4**.

In conclusion, we have demonstrated that azaarylacetates and acetamides, which, to our knowledge, have not been utilized previously in catalytic asymmetric synthesis, undergo highly enantioselective Michael additions to nitroalkenes in the presence of a chiral nickel(II)-bis(diamine) complex **2**. A wide variety of azaarenes that includes pyridines, pyrazines, triazines, isoquinolines, quinazolines, benzothiazoles, and benz(isoxazoles) are compatible with this process, suggesting it could be a useful method for the preparation of enantioenriched chiral azaarene-containing building blocks. As well as serving as a further demonstration of the versatility of nickel complex **2** in stereoselective carbon–carbon bond construction,[20] this study suggests that the analogy between the carbonyl group and the C=N moiety in azaarenes may serve as a rich platform for the development of additional catalytic enantioselective reactions. Studies in this area are ongoing in our laboratories, and will be reported in due course.

Experimental Section

General procedure for nickel-catalyzed Michael additions: A mixture of the azaarylacetate or azaarylacetamide (0.30 mmol), 3 Å MS (60 mg), and nickel catalyst **2** (12 mg, 0.015 mmol) in 1,4-dioxane (5 mL) was stirred at room temperature for 5 min before addition of the nitroalkene (0.30 mmol) in dioxane (1 mL) dropwise over 5 min. The mixture was stirred for 18 h at room temperature, filtered through a short plug of silica using EtOAc (30 mL) as eluent, and the solvent was removed in vacuo. Purification of the residue by column chromatography using silica gel afforded the Michael adduct.

Acknowledgements

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Keywords: asymmetric catalysis · enantioselectivity · Michael addition · nickel · nitroalkenes

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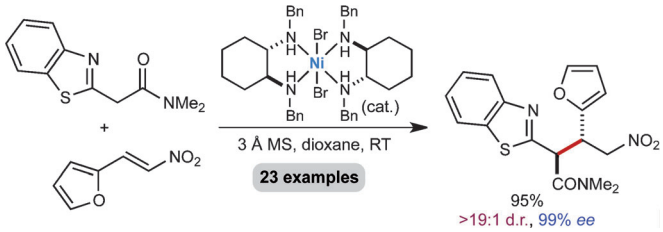
Asymmetric Catalysis

*C. Fallan, H. W. Lam** ..... ▮▮▮▮–▮▮▮▮

Enantioselective Nickel-Catalyzed Michael Additions of Azaarylacetates and Acetamides to Nitroalkenes



Put a nickel in it: Azaarylacetates and acetamides, which have been neglected as substrates in catalytic asymmetric synthesis, undergo highly enantioselective Michael additions to nitroalkenes in the presence of a chiral nickel(II)-bis(diamine) complex (see scheme; Bn = benzyl, MS = molecular sieves). This process is tolerant of a wide variety of azaarenes in the pronucleophile.

