NiH-Catalyzed Asymmetric Hydroarylation of *N*-Acyl Enamines: Practical Access to Chiral Benzylamines

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Abstract: The enantio- and regioselective reductive hydroarylation of *N*-acyl enamines has been achieved with a NiH catalyst and a chiral bis-imidazoline ligand. A broad range of structurally diverse, enantioenriched benzylamines, a moiety found in many pharmacologically active molecules, have been synthesized efficiently under mild, operationally simple reaction conditions.

As a privileged structural motif, benzylamines and related amide derivatives are found in many natural products, pharmaceuticals, agrochemicals, and other chemicals (Figure 1a),[1] and efficient strategies for their catalytic, enantioselective synthesis have long been sought.[2] Metal hydride[3] catalyzed reductive hydrofunctionalization from readily available alkene starting materials is a particularly appealing approach to the synthesis of benzylamines. Previously, starting from styrene and an electrophilic amination reagent, Buchwald[4a] and Miura and Hirano[4b] have developed an enantioselective reductive CuH-catalyzed hydroamination method (Figure 1b, left). We recognized that if asymmetric hydroarylation of enamines could be achieved, enantioenriched benzylamines would become accessible (Figure 1b, right).

Benefiting from the economical and facile chain-walking and cross-coupling[5,6], and use of simple ligands, NiH catalysis has emerged in recent years as an efficient means of achieving enantioselective C–C bond formation[7-9]. In these general synthetic processes: 1) both of the starting alkenes and aryl halides/alkyl halides are commercially or synthetically available; 2) no prior generation of organometallic reagents is necessary; and 3) the newly formed sp^3-hybridized stereocenters could potentially be enantioselectively controlled at the carbons originating in the achiral olefins[8e-8h] or at the carbons from racemic alkyl electrophiles[8a-8d]. Recently, we reported the enantioselective hydroarylation[8-10] of styrenes using a novel chiral nickel-bis(imidazoline) catalyst (Figure 1c, i).[8f] In this process, an asymmetric center was generated and controlled at the carbon derived from the olefin. To demonstrate the wide-ranging applicability of this reductive NiH[11] catalysis, we have explored the feasibility of asymmetric hydroarylation with electron-rich alkenes, for example *N*-acyl enamines, which are generally less reactive than styrenes (Figure 1c, ii).

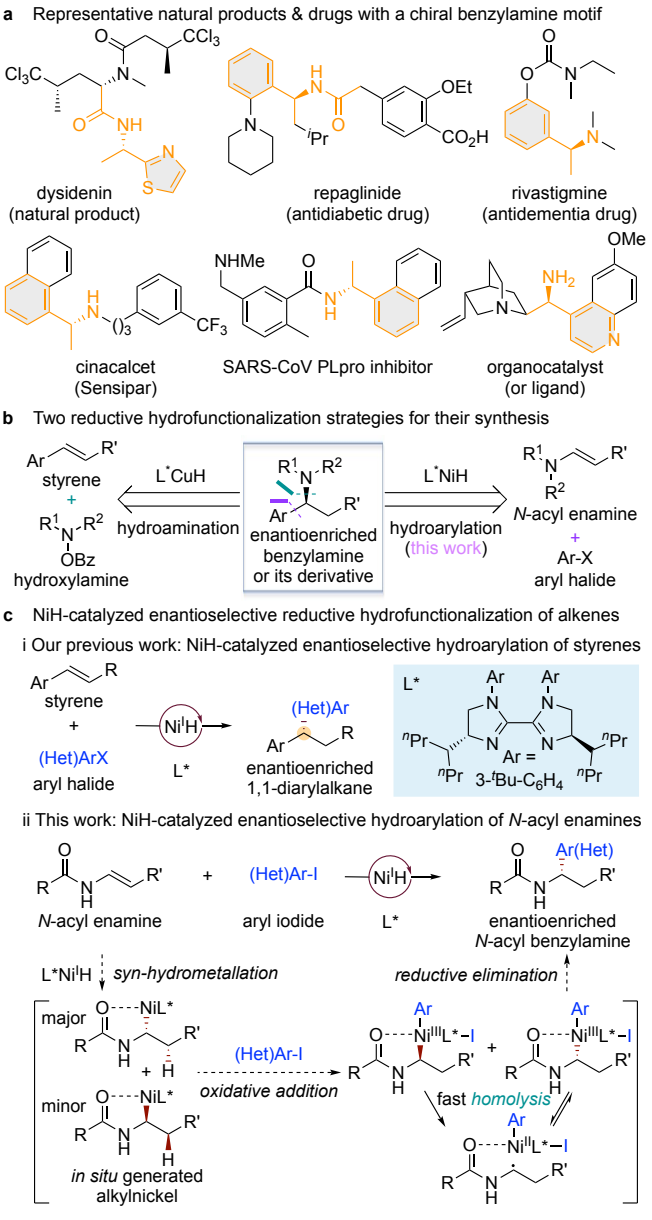
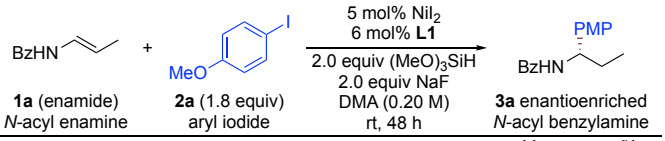


Figure 1. Design plan: asymmetric hydroarylation of *N*-acyl enamines to access chiral benzylamines.

As shown in Figure 1c, ii, the *syn*-hydrometallation of an L*NiH species into an *N*-acyl enamine would generate two alkyl-nickel enantiomers. These could undergo oxidative addition with an aryl iodide, affording two high-valent Ar-Ni(III)-alkyl enantiomers which would experience rapid homolysis and sequential stereoselective radical recombination prior to a selective reductive elimination.[12] In the presence of a suitable chiral ligand, the radical recombination process could be enantioselectively controlled and deliver a single Ar-Ni(III)-alkyl enantiomer in an enantioconvergent fashion. Subsequent reductive elimination would deliver the enantiopure arylation product. Notably, the amide group in the enamine substrate would also play a key role, enhancing both the regio- and the enantioselectivity. Here we describe the successful execution of this strategy. During the preparation of this report, similar work was reported by Nevado et al.[8h]

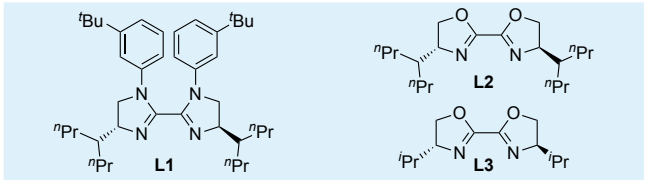
On the basis of our previously reported asymmetric hydroarylation of styrenes[8f], we attempted the enantioselective hydroarylation of enamide (**1a**) with 4-iodoanisole (**2a**), and obtained the results summarized in Table 1. After extensive examination of nickel sources, ligands, silanes, bases, and solvents, we found that NiI_2 and our previously used chiral bis-imidazoline ligand (**L1**)[8f] can provide the desired hydroarylation product in good yield as a single regioisomer with high enantioselectivity (99% ee, entry 1). Other nickel sources such as $NiBr_2$ led to lower yields with almost no change in *ee* (entry 2). Evaluation of ligands showed that both the imidazoline skeleton (entry 3 vs entry 1) and the remote steric effects of the substituent on the imidazoline skeleton (entry 4 vs entry 3) have a dramatic influence on the enantioselectivity. Dimethoxymethylsilane (DMMS) was shown to be an unsuitable silane (entry 5) and KF was shown to be an unsuitable base (entry 6). Use of DMF as solvent also led to a significantly lower yield (entry 7) and use of the less polar THF as solvent produced no desired arylation product (entry 8). Reducing the reaction time from 48 h to 24 h led simply to incomplete conversion (entry 9).

Table 1: Variation of reaction parameters.



1a (enamide) *N*-acyl enamine | **2a** (1.8 equiv) aryl iodide | **3a** enantioenriched *N*-acyl benzylamine

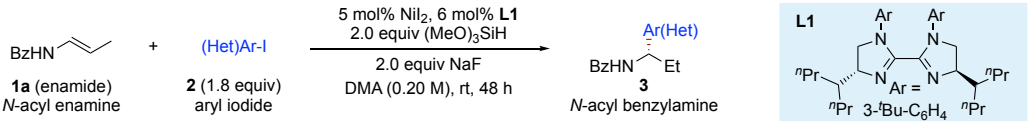
Entry	Variation from standard conditions	Yield [%][a]	*ee* [%][b]
1	none	80 (81)	99
2	$NiBr_2$, instead of NiI_2	65	98
3	**L2**, instead of **L1**	48	85
4	**L3**, instead of **L1**	71	64
5	DMMS, instead of $(MeO)_3SiH$	9	97
6	KF, instead of NaF	8	ND
7	DMF, instead of DMA	3	ND
8	THF, instead of DMA	0	–
9	24 h, instead of 48 h	71	98



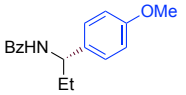
[a] Yields determined by crude ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard, the yield in parentheses is the isolated yield. [b] Enantioselectivity was determined by chiral HPLC analysis. DMPU = *N*,*N*-dimethylacetamide; DMMS = dimethoxymethylsilane; DMF = *N*,*N*-dimethylformamide; PMP = *p*-methoxyphenyl.

Having established the optimal conditions, we explored the scope of the aryl iodide coupling partner (Table 2) and found that a wide range of aryl and heteroaryl iodides are tolerated. The aryl substituent can be substituted at the *ortho*, *meta* or *para* position (**2a**–**2p**). Electron-rich (**2a**–**2e**) as well as electron-withdrawing (**2h**–**2p**, **2w**–**2z**) aryl iodides work well in the reaction. In case of the latter, $Ni(ClO_4)_2{\cdot}6H_2O$ was found to be a superior catalyst and only 1.5 equiv of aryl iodide was needed. A variety of functional groups, including ethers (**2a**, **2e**, **2h**, **2i**, and **2y**), esters (**2b**, **2k**, **2w**, and **2x**), a carbamate (**2c**), an amide (**2d**), a trifluoromethyl group (**2j**), aryl fluorides (**2n**, **2z**), as well as a ketal (**2x**), are all readily accommodated. Notably, sensitive functional groups such as an easily reduced aldehyde (**2l**) and ketone (**2m**, **2z**), a chloride (**2o**, **2y**) and a triflate (**2p**) commonly used for subsequent cross-coupling all remained unchanged under the exceptionally mild reaction conditions of the reaction. Compounds containing heterocycles such as thiophene (**2q**, **2z**), pyridine (**2r**, **2s**, and **2t**), pyrrole (**2t**), pyrimidine (**2u**), and imidazopyridine (**2v**) are also competent coupling partners. With this protocol, several core structures of bioactive and pharmaceutical molecules, such as L-menthol (**2w**), glucose (**2x**), empagliflozin (**2y**), and canagliflozin (**2z**), could be readily introduced in an enantioselective fashion, irrespective of the existing chiral centers and complex structures.

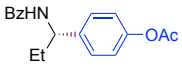
Table 2: Scope of aryl iodide coupling partner.[a,b]



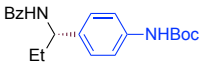
a) from aryl iodides



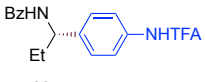
3a 81% yield, 99% ee



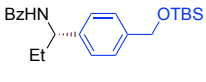
3b 51% yield, 98% ee



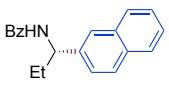
3c 99% yield, 97% ee



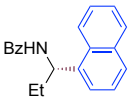
3d[c] 69% yield, 98% ee



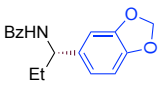
3e 66% yield, 99% ee



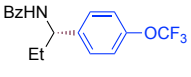
3f 86% yield, >99% ee



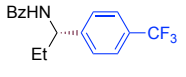
3g[c] 65%yield, >99% ee



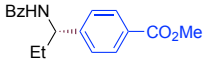
3h 51% yield, 99% ee



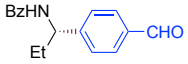
3i[c] 69% yield, >99% ee



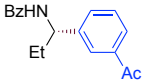
3j[c] 75% yield, >99% ee



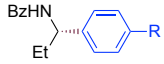
3k[c] 76% yield, 99% ee



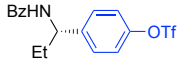
3l[c] 82% yield, >99% ee



3m[c] 84% yield, 98% ee

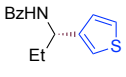


3n[c] R = F, 78% yield, >99% ee
3o[c] R = Cl, 72% yield, >99% ee

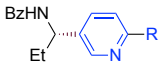


3p[c] 86% yield, >99% ee

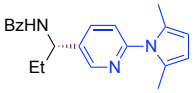
b) from heteroaryl iodides



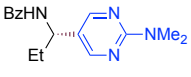
3q 67% yield, 97% ee



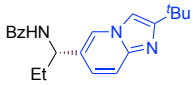
3r[c] R = OMe, 45% yield, 98% ee
3s[c] R = F, 72% yield, 98% ee



3t[c] 67% yield, 99% ee

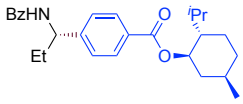


3u[c] 46% yield, 98% ee

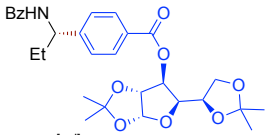


3v[c] 54% yield, 98% ee

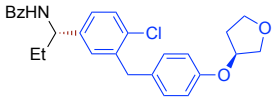
c) pharmaceutical and biological compounds



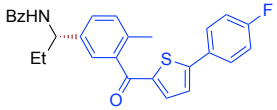
3w[c,d] 82% yield, >20:1 dr
menthol derivative



3x[c,d] 86% yield, >20:1 dr
glucose derivative



3y[c,d] 68% yield, >20:1 dr
empagliflozin derivative

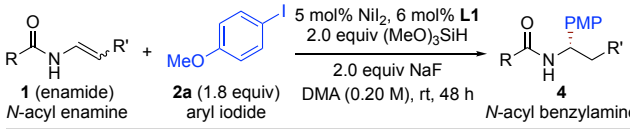


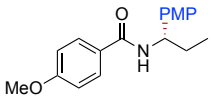
3z[c] 73% yield, 99% ee
canagliflozin derivative

[a] Yield under each product refers to the isolated yield of purified product (0.20 mmol scale, average of two runs), >95:5 regioisomeric ratio (rr) unless otherwise noted. [b] Enantioselectivities were determined by chiral HPLC analysis. [c] 5 mol% $Ni(ClO_4)_2 \cdot 6H_2O$, DMA (0.10 M), 1.5 equiv ArI. [d] Diastereoisomeric ratio (dr) was determined by crude ^1H NMR analysis.

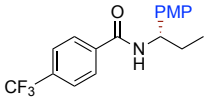
As shown in Table 3, the scope of the enamide is also fairly broad. In general, high levels of enantioselectivity are delivered by the reaction. For *N*-benzoyl enamine substates, an electron-deficient substituent on the aromatic ring of the benzoyl group led to a higher yield than electron-rich substituents (**1c** vs **1b**). The less sterically hindered *N*-acetyl enamine (**1e**) was more reactive than *N*-pivaloyl enamine (**1d**). The β-unsubstituted enamide (**1d**) was also shown to be a viable substrate. Enamides with a range of different functionalized alkyl substituents at the β-position underwent asymmetric hydroarylation smoothly (**1h**–**1m**). A diverse spectrum of functional groups were compatible, including ethers (**1i**, **1j**), esters (**1k**, **1l**), and an alkyl chloride (**1m**). Additionally, both *E* and *Z* isomers of the enamide substrates produced the same enantiomeric product with the same level of enantioselectivity ((*E*)-**1h** vs (*Z*)-**1h**).

Table 3: Scope of the *N*-acyl enamine component.[a]

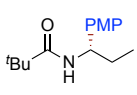




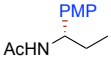
from (*Z*)-**1b**
4b 63% yield, 99% ee



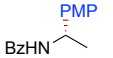
from (*Z*/*E* 6.6:1)-**1c**
4c 88% yield, 99% ee



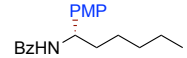
from (*Z*)-**1d**
4d[13] 55% yield, 95% ee



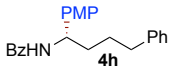
from (*Z*)-**1e**
4e 81% yield, 97% ee



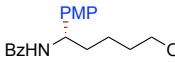
4f 61% yield, 97% ee



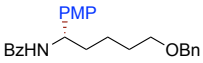
from (*E*)-**1g**
4g 88% yield, 99% ee



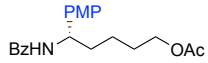
4h
from (*E*)-**1h**, 83% yield, 98% ee
from (*Z*)-**1h**, 88% yield, 98% ee



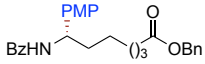
from (*E*)-**1i**
4i 72% yield, 98% ee



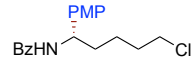
from (*E*)-**1j**
4j 82% yield, 99% ee



from (*E*)-**1k**
4k 67% yield, 94% ee



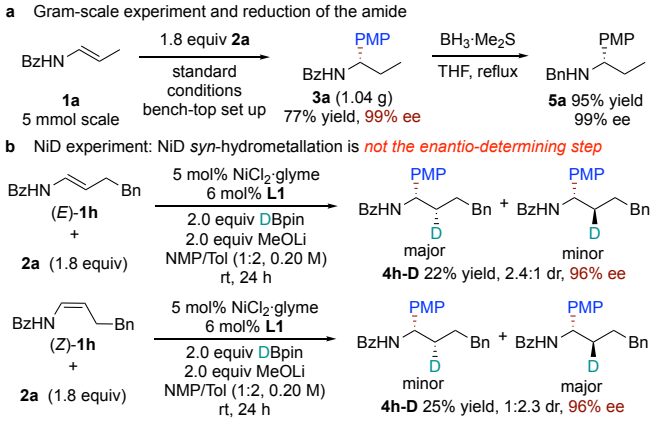
from (*E*)-**1l**
4l 42% yield, 98% ee



from (*E*)-**1m**
4m 67% yield, 98% ee

[a] Yield and ee are as defined in Table 2.

The robustness and synthetic utility of this catalytic system were further demonstrated by gram-scale synthesis and subsequent derivatization of the product (Scheme 1a). A 5 mmol-scale hydroarylation was performed successfully and the product (**3a**) was readily converted into the tertiary amine (**5a**) without racemization. To shed light on the hydrometallation process, deuterium-labeling experiments were carried out with deuteropinacolborane (Scheme 1b). From both *E* and *Z* isomers of the enamide substrates, a diastereomeric mixture of deuterated products were obtained with an opposite dr ratio. If the *syn*-hydrometallation of NiD to *N*-acyl enamine is the enantio-determining step, then a diastereomerically pure **4h-D** should be formed. The observed formation of both diastereoisomers in each case indicates that the NiD insertion is not the enantio-determining step. On the other hand, the same level of enantioselectivity for deuterated products in both cases of *E* and *Z* olefinic substrates (Scheme 1b) is consistent with a mechanism in which rapid homolysis of Ni(III) to Ni(II) and the subsequent enantioselective radical recombination serves as an enantio-determining step (Figure 1c, ii).



Scheme 1. Gram-scale, derivatization, and deuterium-labelling experiments.

In conclusion, we have developed an enantioselective hydroarylation of *N*-acyl enamines which provides access to an array of enantioenriched benzylamines, a biologically active pharmacophore. This reaction is based on a reductive NiH-catalysis strategy. A wide range of functional groups on both the *N*-acyl enamine and aryl iodide components are well-tolerated. Preliminary studies of the mechanism suggest that the hydrometallation of NiH is not the enantio-determining step. Development of a migratory version of this transformation and investigations of the mechanism are currently in progress.

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Keywords: alkenes • asymmetric catalysis • hydroarylation • nickel • regioselectivity

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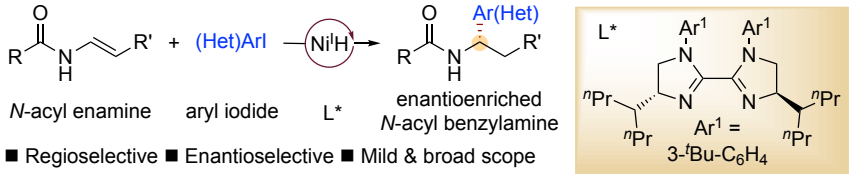
[13] CCDC 2036489 (**4d**, absolute configuration) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Entry for the Table of Contents



Regio- and enantioselective hydroarylation of *N*-acyl enamines with reductive NiH catalysis has been achieved. This practical process provides an efficient access to a wide variety of chiral benzylamines, a structure found in a number of biologically active compounds.