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Nickel-Catalyzed Asymmetric Synthesis of α-Arylbenzamides

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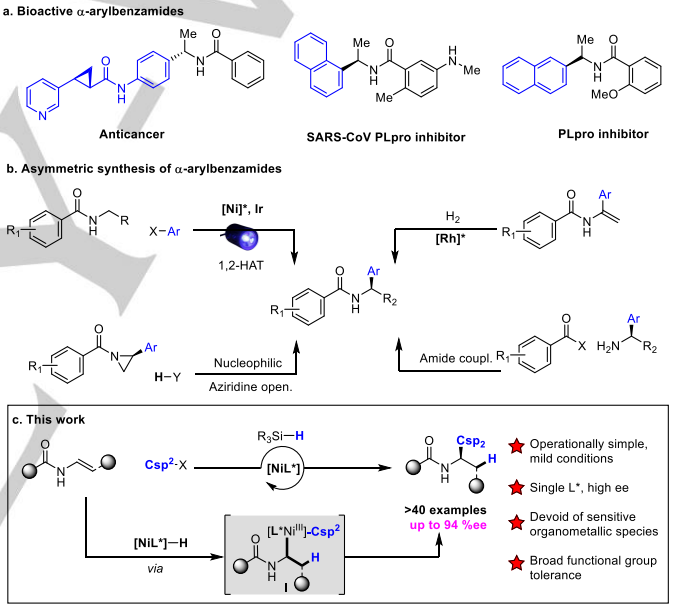
Abstract: A nickel-catalyzed asymmetric reductive hydroarylation of vinyl amides to produce enantioenriched α-arylbenzamides is reported. The use of a chiral bisimidazoline (BIm) ligand, in combination with diethoxymethylsilane and aryl halides, enables regioselective introduction of aryl groups to the internal position of the olefin, forging a new stereogenic center *α* to the N atom. The use of neutral reagents and mild reaction conditions provides simple access to pharmacologically relevant motifs present in anticancer, SARS-CoV PLpro inhibitors and KCNQ channel openers.

α-Arylbenzamides are ubiquitous motifs in bioactive molecules such as anti-cancer agents[1a], SARS-CoV PLpro inhibitors [1b-c] and anti-depressants[1d] among many others[1e-g] (Scheme 1a). Access to enantiomerically enriched versions of these motifs is nonetheless far from straightforward. Rh-catalyzed hydrogenation of vinyl amides[2], C-N coupling between carboxylic acid derivatives and chiral α-aryl substituted amines[3], hydride opening of N-acylaziridines[4] are some of the methods currently at hand to assemble these challenging motifs.[5] Limited reaction scope, relatively harsh conditions and risk of epimerization restrict the applicability of these methodologies in synthesis. Recently, a Ni/photoredox dual catalyzed α-arylation of benzamides has also been realized[6] (Scheme 1b). An alternative disconnection for this motif would stem from a three-component formal hydroarylation reaction involving readily available vinylbenzamides, arene halides and an H source (Scheme 1c).[7] Asymmetric hydroarylation reactions of alkenes are nonetheless scarce. Successful examples have been reported relying on the combination of Pd and/or Cu complexes, and aryl halides or boranes.[8] Recently, highly selective Ni-catalyzed intramolecular cyclizations have been reported. [9] Formal hydroarylations employing boronic acids and aryl iodides under asymmetric Ni catalysis have also proven fruitful.[10] Despite their obvious synthetic utility, these transformations are mostly amenable only to styrene-based substrates and thus, introduction of aryl groups to the α-position to a heteroatom remains an unconquered challenge.

In recent years, our group has explored the use of nickel catalysis towards the efficient difunctionalization of π-systems[11a-b] with a particular focus on olefins[11c-e]. We have recently reported an asymmetric alkene dicarbofunctionalization reaction in which a chiral bisoxazoline ligand and the presence of coordinating sites on the alkene can be synergistically combined to ensure stereodefined Csp^3-Csp^2 bond formation.[12]

Based on these results, we set out to explore the asymmetric formal hydroarylation of functionalized olefins, particularly vinyl amides.

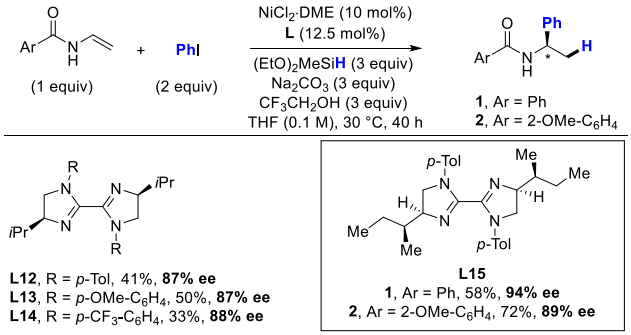


Scheme 1. α-Arylbenzamides: examples of bioactive molecules and general strategies towards their asymmetric synthesis.

Mechanistically, our design relies on the activation of a silane with nickel to produce, upon addition to the double bond, a chiral Csp^3-Ni(I) intermediate. Further, the Csp^2-X precursors are activated via oxidative addition, forming a chiral alkylarylNi(III) complex (**I** in Scheme 1c), and outcompeting the potential direct reduction of the aryl precursors.[13] The C-C bond-forming reductive elimination occurs at the internal position of the olefin delivering the new stereogenic center with high levels of stereocontrol. Thus, Csp^2-halides and a hydride are added to vinyl benzamides with high regio- and stereoselectivity. This process avoids sensitive organometallic reagents and proceeds at room temperature, delivering enantioenriched α-arylbenzamides, whose subsequent derivatization enables the straightforward assembly of pharmacologically relevant scaffolds.[1]

To select the appropriate chiral ligand, vinyl benzamide and phenyl iodide were chosen as benchmark reaction partners using

$NiCl_2$·DME (10 mol%), diethoxymethylsilane (3 equiv), sodium carbonate (3 equiv) and trifluoroethanol[15] (3 equiv) in THF, as these had been found to deliver the desired benzamide **1** in racemic form. Different chiral bisoxazoline, pyridine-oxazoline and isoquinoline-oxazoline ligands (**L1-11**[14], 12.5 mol%) were tested, however, no more than 64% ee was achieved. When we turned our attention to bisimidazoline ligands (BIm), which have recently gained attention in asymmetric nickel catalysis[16], we were delighted to see that different aromatic substituents on the nitrogen atoms and an isopropyl side chain (Scheme 2, **L12-14**) resulted in the formation of the chiral benzamide **1** in moderate yields with high levels of stereocontrol (up to 88%ee).

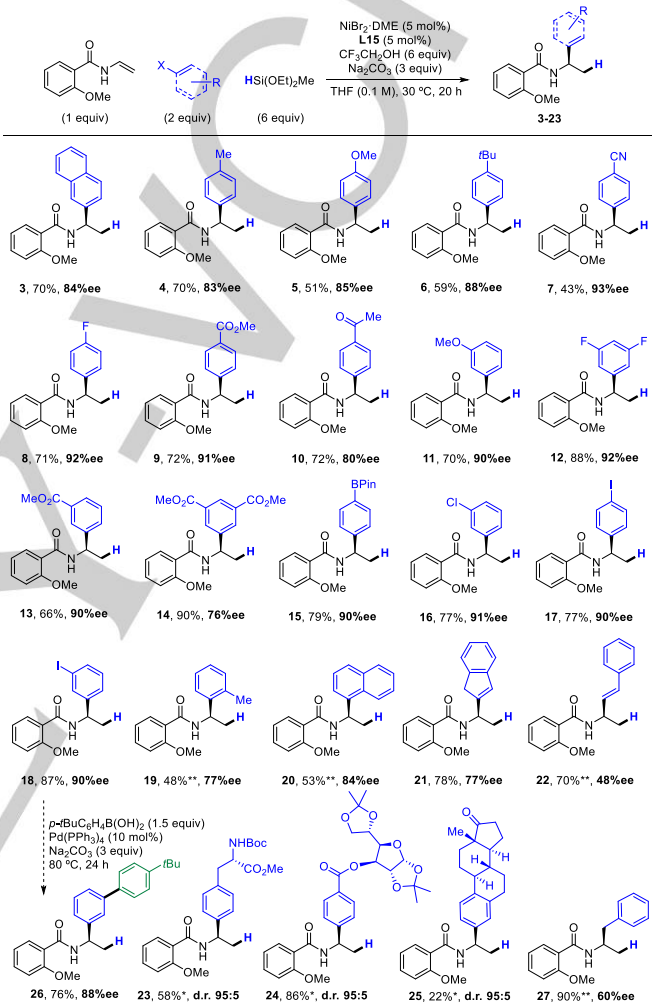


Scheme 2. Ligand screening. Unless otherwise stated, reactions were carried under the indicated conditions. Isolated yields are shown. The enantiomeric excess was determined by chiral HPLC. For detailed experimental conditions, see SI.[14]

Finally, implementation of an isoleucine-derived side chain in ligand **L15** resulted in the formation of the desired amide **1** in 58% yield and 94 ee%. The same conditions were applied to 2-methoxy-N-vinylbenzamide furnishing chiral amide **2** in 72% yield and 89% ee.

After additional optimization of the reaction conditions in order to reduce the catalyst loading,[14] we set out to explore the scope of this transformation (Scheme 3). First, we assessed the reactivity of different aryl iodides with 2-methoxy-*N*-vinylbenzamide as the olefin. Reaction with 2-naphthyl iodide delivered the corresponding α-naphthylbenzamide **3** in 75% yield and 84% ee. Different phenyl iodides were tested next. Both electron-donating (Me, OMe, *t*Bu) and electron-withdrawing (CN, F, CO_2Me, COMe) groups in the *para* position of the aromatic ring were tolerated, as demonstrated by the isolation of the corresponding benzamides **4-10** in good yields and high ee. *Meta* substituents (methoxy, 3,5-difluoro and 3-fluoro and 3,5-dimethyl dicarboxylate) were equally tolerated delivering the corresponding chiral amides **11-14** with good stereocontrol and in high yields. Next, we aimed to explore the compatibility of our protocol with functional groups typically used in classical cross coupling reactions. To our delight, the reaction of 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 1-chloro-3-iodobenzene was completely chemoselective for the Csp^2-I bond, delivering the corresponding boron- and chloro-containing amides **15** and **16** in 83% and 82% yield with 90% ee and 91% ee, respectively. Interestingly, mono-reaction took place in the case of 1,4- and 1,3-diiodobenzenes, delivering the iodo-containing chiral amides **17** and **18**, respectively, in excellent yield. Prolonged reaction times and 4 equiv. of the aryl iodides, 2-iodotoluene and 1-iodonaphthalene furnished the amides **19** and **20** in yields of 53% and 55% with 77% ee and 84% ee, respectively.

It is important to note that activated Csp^2-bromides such as 2-bromo-1H-indene could also be converted into the desired product under the standard reaction conditions as demonstrated by the successful isolation of amide **21**. Interestingly, amide **22** could be obtained from β-bromostyrene, albeit with low stereoselectivity.

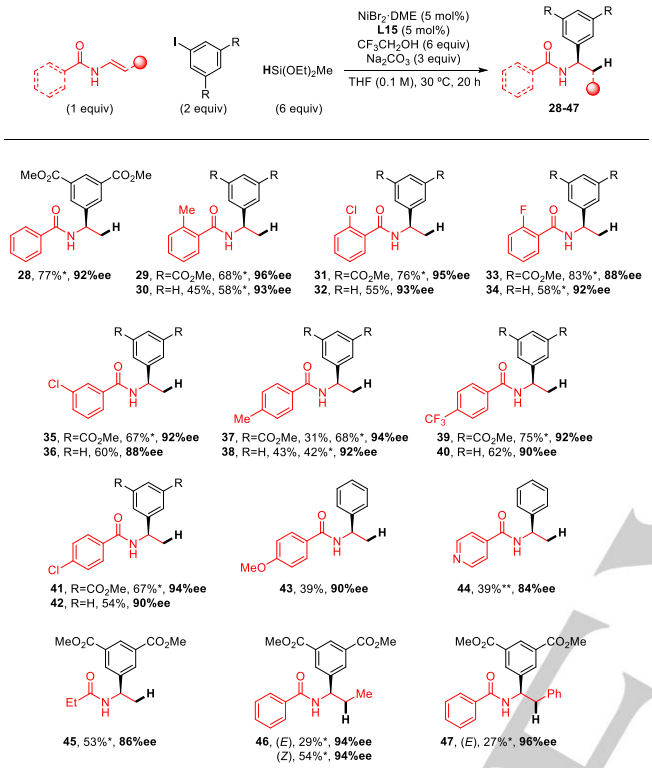


Scheme 3. Reaction scope on the Csp^2-X. For detailed experimental conditions, see SI. * Reactions run for 40 h. ** Reactions run for 40 h with 4 equiv of aryl or benzyl halide.

More complex substrates bearing additional stereocenters were also compatible with this mild reductive hydroarylation protocol. L-Phenylalanine-, estrone- and D-glucose-derived aryl iodides delivered products **23-25** with excellent diastereomeric ratios (≥95:5 d.r.). Finally, derivatization of the Csp^2-I bond in adduct **18** under classical Pd-catalyzed cross-coupling reaction conditions delivered analogue **26** in 76% yield without noticeable erosion of the enantiomeric purity. Interestingly, benzyl bromide could also be used for the reaction to deliver the amide **27** in 90% yield, albeit with only 60% ee.

Next, a variety of vinyl amides were examined (Scheme 4). Unsubstituted (**28**) as well as *ortho*-substituted vinyl benzamides were excellent substrates for this formal hydroarylation. Thus,

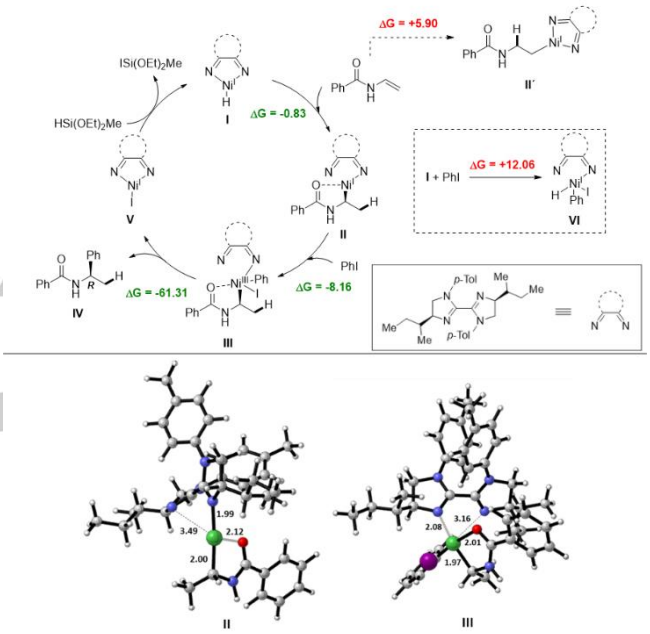
vinyl- and *ortho*-methyl substituted benzamides reacted with phenyl iodide and dimethyl 5-iodoisophthalate to deliver amides **29** and **30** in 68% and 58% yield and 96% and 93% ee, respectively. Both *ortho*- and *meta*-chloro- as well as *ortho*-fluoro-containing substrates afforded products **31-36** in high yields and with excellent ee. *Para*-substitution of the benzamide, with both electron-donating (OMe, Me) and electron-withdrawing groups (CF_3, Cl) delivered adducts **37-43** with similar efficiency in terms of yield and absolute stereocontrol.



Scheme 4. Reaction scope on the vinyl amide.* Reactions run for 40 h. ** Reactions run for 40 h at 40 ºC. For detailed experimental conditions, see SI.

The established protocol was applied to a pyridine-containing substrate to afford the desired chiral amide **44**, albeit in moderate yield. Alkyl vinyl amides could also be asymmetrically hydroarylated, as shown by the isolation of amide **45,** although extended reaction time was required in this case. Finally, we also explored the substitution pattern at the terminal position of the olefin. It is well established that metal-mediated insertions as well as radical additions to olefins are sensitive to the terminal substituents.[7j],[17] Interestingly, (*E*)- and (*Z*)-N-(prop-1-en-1-yl)-benzamides displayed markedly different reactivity: while the former offered the product in only 29% yield[14], the *cis* substrate furnished the desired chiral amide **46** in good yield (54%) with excellent levels of stereocontrol (94% ee). Similarly, (*E*)-N-styrylbenzamide delivered amide **47** in comparatively moderate yield, but with excellent enantioselectivity (96% ee).

Control experiments and DFT calculations were performed to unravel the reaction mechanism. The presence of radical scavengers had no significant impact on the reaction outcome.[14] Previous reports have also described the reaction of silanes with Ni complexes to produce Ni hydride species.[18] Further, such hydrides have been invoked in recent reports of cross-couplings and carboxylation reactions among other transformations.[19],[20] Stoichiometric treatment of pre-formed **L15**NiX_2 complex (X = Cl, Br, I) with $Me(OEt)_2SiH$ produced a significant broadening of the ^1H NMR signals and a rapid color change of the reaction to dark blue-purple, possibly indicating the formation of reactive intermediates[21]. DFT calculations were performed using vinylbenzamide, phenyl iodide, $Me(OEt)_2SiH$ and **L15** as model structures to gain additional insights onto the regio- and stereochemical outcome of this process (Scheme 5).[14] These studies confirm the pivotal role of the amide group for the high stereo- and regioselectivity and lead to a plausible mechanistical proposal involving an olefin insertion before oxidative addition and reductive elimination.



Scheme 5. Mechanistic proposal including DFT calculations. Reaction free energies (kcal/mol) calculated at UB3LYP/6-31G(d) (C,H,N), LANL2DZ (Ni, I) level. Indicated distances are given in Å. [13]

In summary, we present here a highly efficient asymmetric reductive hydroarylation of vinyl amides. A variety of readily available Csp^2-halides are added across the corresponding alkenes at room temperature in a highly regio- and enantioselective manner. The reaction proceeds through an alkyl Ni(III)-intermediate involving a chiral bisimidazoline ligand (BIm). DFT calculations confirm that the amide group plays a crucial role in stabilizing the Ni center, contributing to stereodefined Csp^3-Csp^2 bond formation. Our method represents a de novo approach towards the efficient assembly of chiral α-arylbenzamides, pharmacologically relevant motifs present in anticancer, SARS-CoV PL proteosome inhibitors and KCNQ channel openers.

Acknowledgements

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Keywords: Nickel • Hydroarylation • Asymmetric • α-Aryl amides • Vinyl amides

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[14] For additional experimental details, see Supporting Information. Configuration of the products was confirmed by direct comparison with previously reported (*R*)-1-phenylethylbenzamide prepared by reaction of benzoyl chloride and (*R*)-1-phenylethylamine.

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[21] Applying a similar procedure using an α-diimine ligand, two signals in the negative ppm range were observed in ^{1}H-NMR. For additional details, see Supporting Information

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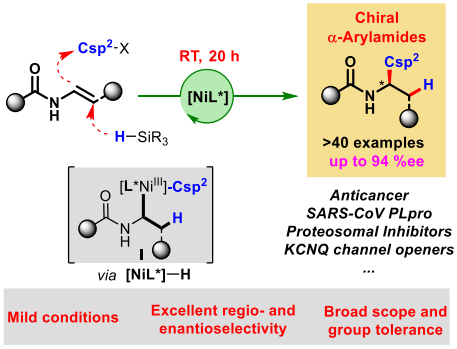

A novel approach towards the efficient assembly of chiral α-arylbenzamides is presented here based on an enantioselective, nickel-catalyzed reductive hydroarylation protocol. The use of neutral reagents and mild reaction conditions enabled the synthesis of α-arylbenzamides in high enantiomeric purity providing an alternative access to pharmacologically relevant motifs present in anticancer, SARS-CoV PLpro inhibitors and KCNQ channel openers.