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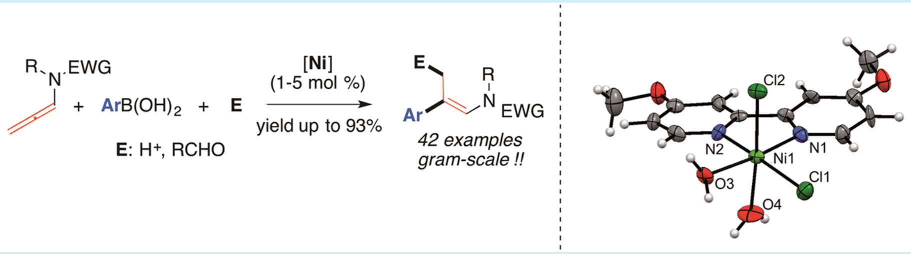
Nickel-Catalyzed Synthesis of Stereochemically Defined Enamides via Bi- and Tricomponent Coupling Reaction

Y. Liu, A. De Nisi, A. Cerveri, M. Monari, and M. Bandini*

Department of Chemistry “G. Ciamician”, Alma Mater Studiorum, University of Bologna, via Selmi 2, 40126 Bologna, Italy

Supporting Information



ABSTRACT: The stereoselective synthesis of (*E*)-trisubstituted tertiary enamides is documented via site-selective Ni-catalyzed β-arylation of allenamides with boronic acids in high yields (up to 89%). The nucleophilic character of the “organo-Ni” intermediates is further exploited to implement a one-pot tricomponent procedure involving the final allylation of aldehydes (yields up to 93%). Mechanistic insights and efficiency on a gram scale process were also documented.

Stereochemically defined enamides are common molecular motifs in numerous naturally occurring compounds and pivotal chemical partners in countless organic transformations.[1] In this direction, growing attention toward the realization of synthetic protocols for enamides with increased chemical efficiency and cost effectiveness/environmental sustainability has been recorded in recent years.[2] Acid catalyzed regio- and stereoselective nucleophilic addition to allenamides (also referred as *N*-allenyl amides)[3] represents an unparalleled approach to access enamides in a straightforward manner, with some limitations related to stereochemical issues and to the employment of second- and third-row soft noble metals as promoters.[3−5]

In order to further expand the synthetic applicability of *N*-allenyl amide derivatives, we envisioned the possibility to create a new reaction channel for the manipulation of allenamides based on a formal inversion of their classic reactivity (Figure 1 upper). In particular, we thought that the overall electronic perturbation performed by the “amidyl” group onto the allenyl unit could guarantee an initial site-selective insertion of nucleophilic organometallic reagents (M−R′ in Figure 1 lower) into the cumulene core (*vide infra*), followed by electrophilic trapping of the resulting allylic organometallic intermediate at the γ-position. In addition, sustainability issues are targeted by replacing conventional noble 4d and 5d transition metals with earth-abundant first-row analogues in the present investigation.[6] At the outset of our study, we considered nickel catalysis being a desirable low-cost first-row transition metal element,[7] which is known to efficiently promote cross-coupling reactions based on nucleophilic organometallic intermediates.

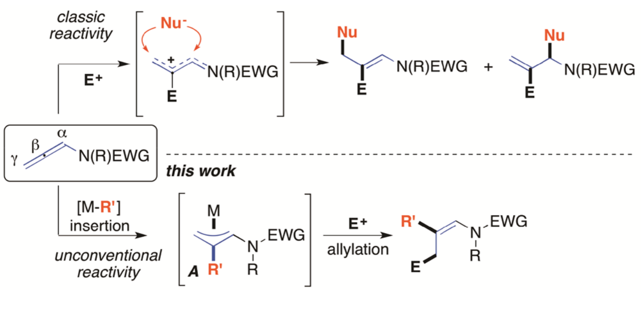


Figure 1. Classic reaction profile of *N*-EWG-allenes (upper). Working plan for the present study (lower).

It is worth mentioning that 3d-metal based activation of allenamides is sporadic[8] and nickel has not been associated with this class of transformations to date.[9]

In order to ascertain the feasibility of the working hypothesis, allenamide **1a** and $PhB(OH)_2$ (**2a**) were elected as model substrates and a range of reaction conditions, such as nickel complexes, bases, solvents, reaction temperatures, and stoichiometry, were assessed (see Supporting Information (SI)).[5,10]

From this survey, parameters reported in Scheme 1 were elected as optimal, namely $[NiCl_2(\mathbf{L})]$ (5 mol %), K_2CO_3 (3 equiv), 1,4-dioxane, 1 h, 90 °C, providing (*E*)-**3aa** in a stereochemically defined manner (X-ray analysis) in 82% isolated yield. It is worth mentioning that every deviation from the listed conditions caused a marked drop in catalytic performance.

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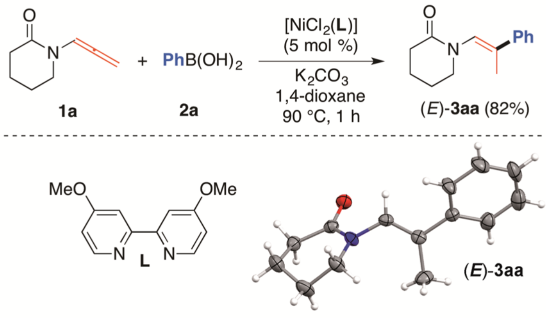
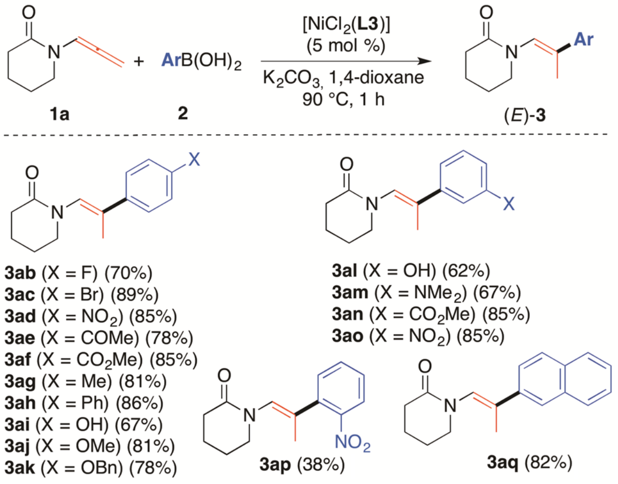
Scheme 1. Optimal Reaction Conditions



Having established the optimal catalytic system, we verified the potential of the present cross-coupling protocol with a range of boronic acids (**2b**–**q**), and the results obtained are summarized in Scheme 2. The methodology turned out to be highly robust (yields: 62–89%) concerning aromatic boronic acids with remarkable tolerance toward electron-withdrawing (e.g., F, Br, COMe, CO_2Me, NO_2) and electron-donating substituents (Me, OMe, OBn, OH, NMe_2) in different positions (*ortho*, *meta* and *para*) of the phenyl ring. Additionally, the 2-naphthyl boronic acid **2q** performed satisfyingly, providing the corresponding enamide **3aq** in 82% yield. It is noteworthy that high stereospecificity toward the formation of the *E*-isomer was always recorded. However, the process faced some limitations in the inertness of the *ortho,ortho*-dimethylphenyl boronic acid and 3-pyridyl analogue that could be rationalized in terms of steric hindrance and poisoning of the Ni-catalyst, respectively.

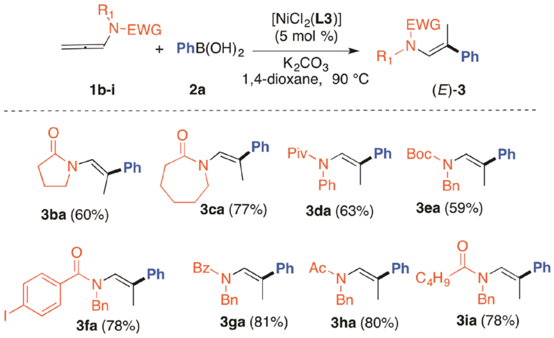
Scheme 2. Scope of the Reaction Focusing on Boronic Acids[a]



[a]Compounds **3** were isolated with an *E*/*Z* ratio >20:1 (reaction crude by ^1H NMR).

Interestingly, the protocol did not appear limited to cyclic allenamides. In fact, *N*-Boc, *N*-Bz, *N*-Ac and *N*-Piv based compounds (**3d**–**i**) took part in the coupling processes to a moderate to good extent (yields: 63–81%, Scheme 3) always guaranteeing high stereospecificity toward the *trans*-adduct. Notably, the methodology proved tolerant toward the iodo-substituted benzene derivative **1f**. This evidence emphasizes the complementarity of our method with that of the Pd-catalysis previously reported[11] and it excludes the existence of [Ni(0)] intermediates that would promote the deiodination of the allenyl precursor or perhaps the Suzuki coupling on the aryl unit.

Scheme 3. Reaction Scope on Allenamides[a]



[a]Compounds **3** were isolated in a *E*/*Z* ratio >20:1 (reaction crude by ^1H NMR).

With the aim of gaining preliminary information on the possible activation modes of the nickel complexes, a single-crystal X-ray analysis was carried out on [$NiCl_2$(**L3**)]. The X-ray structure depicted in Figure 2 shows that the Ni(II)-species was isolated as an aquo-complex (e.g., [$NiCl_2(H_2O)_2$(**L3**)]) in which the Ni atom adopts a distorted octahedral geometry being coordinated by two N atoms of a disubstituted *bis*-pyridyl ligand, two chlorides, and two oxygen atoms belonging to water molecules. The Ni–N distances are slightly different [2.049(7) and 2.058(6) Å] being the longer one in *trans* position with respect to Cl1. Interestingly both the two water molecules and the two chloro ligands are in mutual *cis* position, an unusual geometry that has not been found in crystal structures of analogous mononuclear nickel(II) complexes in the CSD (Cambridge Structural database).[12] The absence of coordinating water in the native [$NiCl_2$L] complexes was ascertained via solid ATR-FTIR spectroscopy.

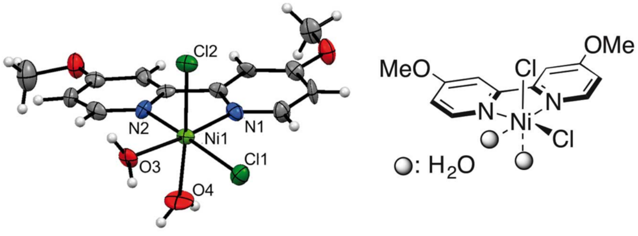
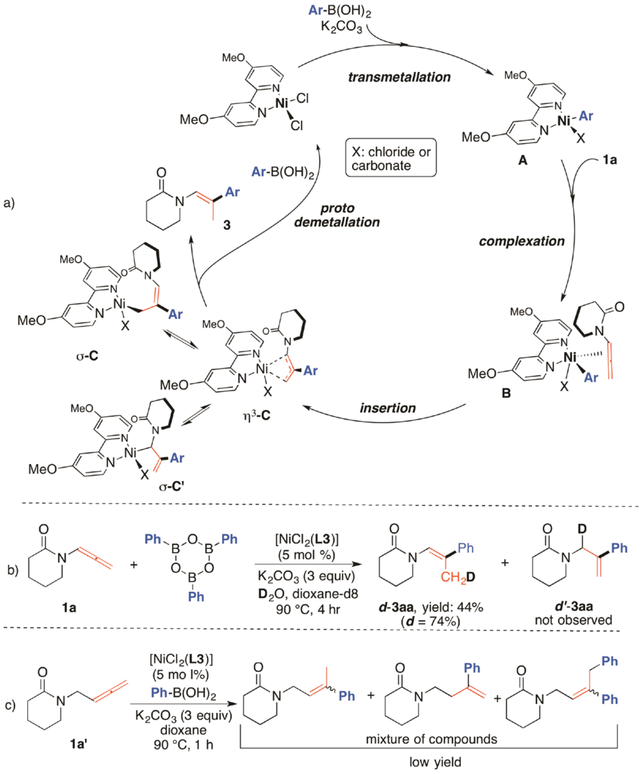


Figure 2. ORTEP drawing of [$Ni(H_2O)_2Cl_2$(**L3**)] (thermal ellipsoids are at 30% of the probability level).

Mechanistically, although a conclusive picture is not available, the tentative catalytic cycle depicted in Scheme 4 is proposed. The initial transmetalation step between the [Ni(II)] complex and the $ArB(OH)_2$ would lead to the [Ni]–Ar intermediate **A**. Complexation of **A** with the allenamide would trigger the regioselective insertion of the Ni–Ar bond into the C=C of the allenyl unit (**B**) providing the allylic-Ni intermediate **C** with concomitant transfer of the aryl unit at the central carbon atom of the π-system.[13]

Finally, proto-demetalation of the resulting allyl organonickel **C** by one molecule of boronic acid would result in the release of product **3** with concomitant restoring of the precatalytic nickel species **A**. The recorded inertness of

Scheme 4. (a) Hypothetical Mechanistic Cycle; (b) Labeling Experiment; (c) Attempted Two-Component Cross-Coupling with Allene 1a'



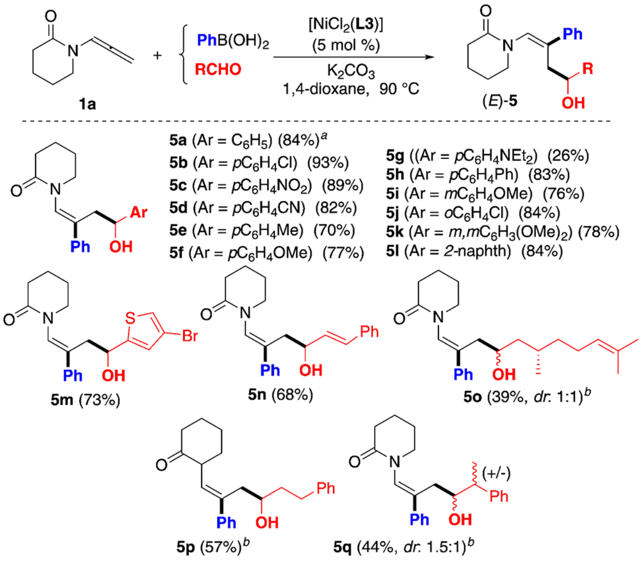
phenylboronic acid pinacol ester in the present approach could account for the role played by boronic acid in the conclusive events of the catalytic cycle.[14]

The presence of an organo-nickel intermediate **C** was proven by a labeling experiment in which allenamide **1a** was coupled with triphenylboroxin (0.5 equiv) and D_2O (4 equiv). Compound ***d*-3aa** was isolated in 44% yield with deuterium incorporation of 73% at the γ-position, exclusively. This outcome could be tentatively rationalized in terms of the more extended conjugate π-system as well as lower steric congestion of σ-**C** with respect to σ-**C**′. Finally, indirect evidence for the pivotal role played by the conjugate amidyl unit on the overall reaction profile was gained by subjecting allene **1a**′ (Scheme 4c) to optimal conditions that failed in promoting the two-component cross-coupling. In fact, a complex mixture of regio- and stereoisomers was isolated from the reaction crude in low yield.

This evidence prompted us to further expand the synthetic utility of the protocol in order to realize a three-component process in which a suitable electrophilic partner could intercept the transient organo-nickel intermediate **C**.

As a proof of concept, we tested PhCHO (**4a**, 2 equiv) as a third component in the one-pot protocol. To our delight, the corresponding homoallylic alcohol **5a** was obtained in 84% yield after 1 h of reaction with a *trans*-stereochemically defined carbon−carbon double bond. The generality of the multi-component Suzuki-type cross-coupling/allylation reaction sequence was then assessed[15] by screening a range of aldehydes (Scheme 5). Also encouraging was the fact that the scope of aromatic aldehydes proved to be significantly broad with tolerance toward electron-withdrawing (**5b−d,j**) as well as electron-donating (**5e−i,k**) groups at different positions (e.g., *ortho*, *meta*, *para*) of the arene. Additionally, also the heterocyclic aromatic aldehyde **4m** proved competent in the methodology providing the corresponding enamidyl-alcohol **5m** in 73% yield. Finally, both aliphatic and α,β-unsaturated aldehydes coupled effectively with the organo-nickel intermediate providing the expected compounds in moderate to good yields (39−68%). Structural confirmation as well as configuration assignment of the C═C in the three-component products **5** was performed via X-ray analysis of compound **5c** (see SI).

Scheme 5. Three-Component Ni-Catalyzed Cross-Coupling



[a] Reaction performed on 5 mmol scale of **1a** (70 min reaction time, 1 mol % [NiCl$_2$(**L3**)]). [b] The product was isolated as TMS-ether.

Interestingly, the present multicomponent reaction did not require external additives (e.g., hard Lewis acids, organometallic reagents, or reducing agents) and attempts to perform the protocol by using the two-component product **3aa** as the staring material failed in providing **5a** with benzaldehyde. This evidence supports the direct involvement of the *in situ* formed organo-nickel intermediate **C** in the final allylating event. Finally, the synthetic potential of the methodology was further supported by running the three-component Suzuki-type coupling/allylation sequence on gram-scale (5 mmol of **1a**) by employing 1 mol % of [NiCl$_2$(**L3**)], 1.39 g of stereochemically defined (*E*)-**5a** (84% yield) were obtained in 70 min reaction time.

In conclusion, the reactivity profile of synthetically relevant allenamides has been revisited by exploiting the nucleophilic character of allyl-Ni species obtained *in situ* through the site-selective stereoselective condensation of boronic acids on allenamides (β-arylation of allenamides). A range of stereochemically defined trisubstituted enamides were obtained in excellent yields via two- and three-component reaction methodologies. Attempts to extend the present protocol to other nucleophilic as well as electrophilic reaction partners are currently ongoing in our laboratories and will be presented in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02166.

Synthetic procedures (PDF)
NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: marco.bandini@unibo.it.

ORCID

M. Bandini: 0000-0001-9586-3295

Notes

The authors declare no competing financial interest.

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