Nickel-Catalyzed Intermolecular Alkyne Hydrohydrazonation

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ABSTRACT: We report a method for mild and atom-efficient synthesis of ketazines via nickel-catalyzed intermolecular hydroamination of internal alkynes with NH_2-hydrazones. This alkyne hydrohydrazonation process is promoted by $[Ni(cod)_2]$ as a Ni(0) pre-catalyst and IPr as a N-heterocyclic carbene (NHC) ligand. A stoichiometric reaction between *in situ* generated $[Ni(IPr)_2]$ and benzophenone hydrazone ($Ph_2C{=}NNH_2$) led to the isolation of IPr-coordinated and hydroxo-bridged dinuclear Ni(II) hydrazonato complex $[(IPr)Ni(HNN{=}CPh_2)(\mu_2\text{-}OH)]_2$ that displayed high activity as a hydrohydrazonation pre-catalyst. We propose a catalytic cycle involving C−N bond formation via alkyne insertion into the Ni−N linkage of Ni(II) hydrazonato intermediates.

Hydrazones are important building blocks in organic synthesis due to their convenient preparation via hydrazine-carbonyl condensation and versatile reactivity with C=N and N−N functionality.[1] Synthetic applications of hydrazones have conventionally focused on their conversions into carbanion intermediates driven by N_2 release, exemplified by the classic Wolff-Kishner reduction.[2] Recent developments in organometallic catalysis have significantly expanded the scope of hydrazone transformations. In particular, N-functionalized hydrazones are established as activated imine-analogs for catalytic hydrogenations and nucleophilic additions.[1b,1c] For catalytic C−N bond formation with hydrazones, a well-documented approach is the Buchwald-Hartwig amination of aryl halides with N-unsubstituted hydrazones (NH_2-hydrazones).[3] In comparison, limited progress has been made on the hydroamination approach, the formal addition of a hydrazone N−H bond across an un-activated C−C π bond.[4] Reports on such "hydrohydrazonation" mainly involve intramolecular transformations that are thermodynamically driven by stable N-heterocycle formation.[5,6] By contrast, intermolecular hydrohydrazonation with simple alkene/alkyne substrates remains underexplored.[7-9] In comparison to the more successful development of hydroamination with NH_2-hydrazines (i.e. hydrohyrazination),[4,5c,9-11] hydrohydrazonation faces the obstacles of lower reactivity for hydrazones as NH-nucleophiles and base-promoted hydrazone decomposition under heating conditions.[2]

We report herein a nickel/N-heterocyclic carbene (NHC) catalyst system for intermolecular hydrohydrazonation of internal alkynes with NH_2-hydrazones under mild conditions. This work is part of our continuous efforts to develop catalytic hydroamination processes following a prior study on Ni/NHC-catalyzed alkyne hydroimination with N-H ketimines.[12] Recent reports on transition metal-catalyzed intermolecular NH_2-hydrazone/alkyne couplings have focused on [4+2] and [3+2] annulations initiated by hydrazone-directed C−H activation/cyclometalation and subsequent alkyne insertions (Scheme 1a).[7,13,14] Notably, Bertrand and coworkers have reported Au- and Cu-catalyzed hydrohydrazonation of terminal alkynes with methyl ketone-derived NH_2-hydrazones at 100 °C (Scheme 1b),[9] which was proposed to proceed by an outer-sphere pathway via nucleophilic attack to Lewis acidic metal π-alkyne complexes.[4e] In comparison, the current Ni/NHC catalyst enables coupling between various NH_2-hydrazones (**1**) and internal alkynes (**2**) at reduced reaction temperatures of 23-80 °C (Scheme 1c).[15] We also report preliminary mechanistic results that support a migratory insertion pathway for C−N bond formation via Ni(II) hydrazonato intermediates. Thus, the current method expands the scope of base metal-catalyzed hydroamination[4] and provides atom-efficient access to valuable azine products (**3**).[16] Furthermore, this work provides new mechanistic insight into Ni/NHC-catalyzed transformations as a versatile toolbox for organic synthesis.[17]

Our study began with a model reaction between benzophenone hydrazone (**1a**) and diphenylacetylene (**2a**). With prior results on alkyne hydroimination,[12] we chose to focus on Ni/NHC catalyst systems with $[Ni(cod)_2]$ (**4**) as a Ni(0) pre-catalyst to evaluate reaction parameters by GC analysis. Key results from the catalyst development are summarized in Table 1 and more details are described in Table S1-S2 in Supporting Information. Under previously reported hydroimination conditions,[12] a reaction between 0.50 mmol **1a** and 1.5 equiv **2a** was promoted by 10 mol% **4**, 22 mol% IPr ligand (**5a**) and 1 equiv Cs_2CO_3 in *m*-xylene to form ketazine product **3a** in 78% yield after heating at 120 °C for 24 hours (entry 1). Replacing IPr with other NHC ligands, such as the structurally related IMes (**5b**), SIPr (**5c**) and IPr*OMe (**5d**),[18] led to significantly reduced catalyst reactivity (entries 2-4). In contrast, removing Cs_2CO_3 or replacing it with various inorganic bases did not have major impacts (entries 5-9). Thus, solvent effects on reactivity were studied without using base additives (entries 9-13), and toluene was found to give the highest **3a** yield of 81%. Further catalyst development involved changing catalyst/ligand loadings, reaction temperatures, and reagent stoichiometry (entries 14-18). In general, **3a** was detected as a dominant (*E*)-stereoisomer (>50:1 selectivity) regarding the deoxybenzoin hydrazone moiety, which is sterically less strained than the corresponding (*Z*)-isomer. The structure of isolated **3a** was established by NMR spectroscopy and X-ray crystallography (*vide infra*). Under the optimized conditions of heating at 80 °C in toluene solvent, reaction between **1a** and **2a** (1.2 equiv) was promoted by 5 mol% **4** and 11 mol% **5a** to form **3a** in 81% yield over 24 hours (entry 15). Small amounts of byproducts (<10%) from hydrazone decomposition and alkyne oligomerization[19] were detected under these conditions. The loadings of **4** and **5a** could be reduced to 1 and 2 mol% to form **3a** in 73% yield over 48 hours (entry 17). In addition, higher loadings of 15 mol% **4** and 31 mol% **5a** promoted the reaction at room temperature (~23 °C) to form **3a** in 79% yield after 96 hours (entry 18). It should be noted that room-temperature intermolecular alkyne hydroamination is only known for Au-based catalysts and limited to terminal alkynes.[10,20] Lastly, the gram-scale hydrohydrazonation was demonstrated with a 10-fold scale-up of the optimized model reaction to give **3a** in 78% yield (entry 19, 1.46 g isolated).

Under the standard reaction conditions at 80 °C, various NH_2-hydrazones (**1**) and internal alkynes (**2**) were studied for Ni-catalyzed hydrohydrazonation (Table 2).[21] In general, the reactions led to selective formation of ketazines (**3**) to the exclusion of possible annulation byproducts,[13,14] and most ketazines were formed as the less sterically strained stereoisomer in high selectivity (>20:1). Alkyne substrate scope and structural effects on hydrohydrazonation reactivity were evaluated with benzophenone hydrazone (**1a**) to generate products **3a**-**g**. Symmetrical diaryl alkynes with electron-donating alkyl substituents at *para*- or *meta*-positions led to ketazine products **3b** and **3c** in high yields. In comparison, the electron-deficient bis(*para*-trifluoromethylphenyl)acetylene displayed high reactivity but low ketazine production due to competitive alkyne trimerization.[19] Thus, a modified procedure of slow alkyne addition and lower reaction temperature of 40 °C was developed to suppress trimerization, giving product **3d** in 81% yield. As a probe for regioselectivity with electronically differentiated diarylacetylenes, a reaction between **1a** and (*p*-anisylethynyl)benzene was subjected to GC analysis.[22] The result indicated formation of two ketazine isomers in 70% overall yield and 1.6:1 ratio (**3e**/**3e'**), favoring C-N bond formation at the benzylic position of electron-rich *para*-anisyl over phenyl group. Reactions with symmetrical dialkylacetylenes face the dual challenges of competitive alkyne trimerization[19] and ketazine instability that hindered isolation attempts. Thus, a moderate yield of 63% for 4-octyne-derived product **3f** was obtained via GC analysis.[22] Similarly, a GC yield of 60% was determined for product **3g** from room-temperature hydrohydrazonation of 1,4-dimethoxy-2-butyne. **3f** and **3g** were both detected as a ~1:1 mixture of E/Z-stereoisomers, which is anticipated with their similar steric environments. Reactions between **1a** and 1-alkyl-2-arylacetylenes (e.g. 1-ethyl-2-phenylacetylene) suffered from dominant alkyne trimerization[19] and generated only traces of desired ketazine products.[23]

Under standard hydrohydrazonation conditions, reactions between **2a** and benzophenone hydrazone derivatives with *para*-methyl, -methoxy and -fluoro substituents gave ketazines **3h**-**j** in good yields. In particular, 4,4'-dimethylbenzophenone hydrazone (**1b**) gave product **3h** in 91% yield, which suggests enhanced hydrazone nucleophilicity by electron-donating alkyl substitution. The high reactivity of **1b** was also displayed in its coupling with diarylacetylenes with *para*-^{i}Pr or -CF_3 substituents that formed ketazine **3k** and **3l** in 93% and 88% yields. In addition, **1b** reacted with di(2-thienyl)acetylene to form ketazine isomers **3m** and **3m'** in 93% combined yield and 3.3:1 stereoselectivity.[24] Similar to benzophenone-derived NH_2-hydrazone, the acetophenone- and benzil-derived analogs displayed good reactivity towards **2a** to form ketazines **3n** and **3o** in high yields. In comparison, the sterically bulky and thermally unstable dicyclohexyl ketone hydrazone led to product **3p** in a moderate yield of 65%. As demonstrated with the solid-state structures of **3a** and **3n-p** by X-ray crystallography, the stereochemistry of diphenylacetylene-derived ketazine products was mainly affected by steric factors to favor (*E*)-stereoisomer regarding the deoxybenzoin hydrazone moiety and twisted *s-trans* conformations.

In-depth reaction mechanism understanding for current hydrohydrazonation is hindered by the lack of suitable probes for regioselectivity[23] as well as stereochemical information, which was due to product detection in ketazine forms rather than isomeric enamines forms that would indicate a formally *syn*- or *anti*-alkyne addition by the N–H bond.[4,25] In our prior study on alkyne hydroimination using a similar Ni/IPr catalyst system, the stereospecific formation of (*Z*)-enamine-type products supported a proposed *anti*-attack at Ni(0)-coordinated alkynes by NH-imine nucleophiles.[12] In addition, a room-temperature reaction between benzophenone imine and *in situ* generated $[Ni(IPr)_2]$ via heating mixed $[Ni(IPr)_2]$/IPr led to the formation of a Ni(0) bis(imine) complex, $[(IPr)Ni(HN{=}CPh_2)_2]$ (**6**), that was catalytically active for alkyne hydroimination (Scheme 2a). In current study, a similar reaction between benzophenone hydrazone (**1a**) and *in situ* generated $[Ni(IPr)_2]$ led to a complex mixture of multiple Ni species. Attempted purification of such mixture by recrystallization did not generate analogous Ni(0) bis(hydrazone) complexes, but instead a hydroxo-bridged, dinuclear Ni(II) hydrazonato complex $[(IPr)Ni(\eta^1\text{-}H_2NN{=}CPh_2)(\mu_2\text{-}OH)]_2$ (**7a**). The solid-state structure of **7a** was established by single crystal X-ray diffraction and featured relatively short Ni–N bond length of 1.83 Å for the Ni(II) hydrazonato moieties.[26] The formation of **7a** was likely initiated by aerobic oxidation of $[Ni(IPr)_2]$ considering the high air-sensitivity of electron-rich, zero-valence metal bis-NHC complexes.[16,27] For example, Stahl and coworkers reported rapid aerobic oxidation of $[Pd(IMes)_2]$ to form an η^2-peroxo complex $[Pd(IMes)_2(O_2)]$.[28] Thus, we propose a similar process of $[Ni(IPr)_2]$ oxidation by trace O_2 in solvent to form $[Ni(IPr)_2(\eta^2\text{-}O_2)]$ (**A**) (Scheme 2b).[29] Subsequent reaction with another equivalent of $[Ni(IPr)_2]$ generated dinuclear Ni(I) oxo complex **B**, which underwent IPr dissociation and dinuclear oxidative addition process with **1a** to form **7a**. Notably, the Sigman group has reported facile aerobic oxidation of a IPr-ligated Ni(II) π-allyl chloro complex to generate $[(IPr)NiCl(\mu_2\text{-}OH)]_2$ as a close structural analog of **7a**.[30]

Using complex **7a** to replace mixed $[Ni(cod)_2]$/IPr under hydrohydrazonation conditions (Scheme 2c), the reaction between **1a** and **2a** was effectively promoted at a low catalyst loading of 0.5 mol% **7a** to give **3a** in 83% GC yield (73% isolated). The same catalyst loading also enabled a 5-fold scale-up reaction to give **3a** in 79% isolated yield after heating at 80 °C for 48 hours. By increasing the loading of **7a** to 5 mol%, the scale-up reaction could proceed without heating to give **3a** in 71% yield. Thus, complex **7a** is a more reactive catalyst precursor compared to mixed $[Ni(cod)_2]$/IPr, which presumably led to *in situ* generation of $[Ni(IPr)_2]$ as a common pre-catalyst for Ni/NHC catalysis.[31]

Based on the isolation and high catalytic activity of complex **7a**, we propose a Ni(II)-based catalytic cycle for alkyne hydrohydrazonation as shown in Scheme 2d. Under current catalytic conditions, oxidation by trace O_2 of *in situ* Ni(IPr)$_2$ and subsequent reaction with hydrazone substrate led to dinuclear Ni(II) complex **7**. De-aggregation of **7** generated the IPr-ligated Ni(II) hydroxo hydrazonato monomer **C**, which underwent sequential alkyne coordination and 1,2-insertion into the Ni–N bond to form Ni(II) alkenyl intermediate (**C→D** and **D→E**). Subsequent protonation with NH_2-hydrazone regenerated **C** to complete the catalytic cycle and released N-iminyl enamine product **3'**, which underwent rapid isomerization to form the more stable ketazine **3** as detectable hydrohydrazonation product. We hasten to add that alkyne 1,2-insertion into a late transition metal–nitrogen σ-bond is not well-established as analogous alkene insertions, and the direct observations on such intermolecular amido transfer processes are limited to activated alkynes such as dimethyl acetylenedicarboxylate (DMAD).[32-35] Thus, we cannot exclude the possibility of alternative, Ni(0)/Ni(II)-based hydrohydrazonation mechanisms involving different C–N bond formation processes that have been proposed for catalytic alkyne hydroamination.[4] We are particularly intrigued by the possibility of Ni(0)-mediated N–H oxidative addition of NH_2-hydrazone that forms a Ni(II) hydrido hydrazonato intermediate. Subsequent alkyne insertion into the Ni–H bond and C–N bond formation by reductive elimination from the resulting Ni(II) alkenyl hydrazonate forms the hydrohydrazonation product (**3'**) and regenerates Ni(0) catalyst.[36] This alternative mechanism would resonate with reported mild Buchwald-Hartwig amination with NH_2-hydrazones using a similar Ni/IPr catalyst system, which involved C–N reductive elimination from Ni(II) aryl hydrazonato intermediates.[3d] Getting definitive evidence to distinguish between possible hydrohydrazonation pathways would require a comprehensive mechanism investigation that we wish to pursue in the near future.

In summary, we have developed a Ni/NHC catalyst system for intermolecular hydrohydrazonation of internal alkynes under mild and base-free conditions. Based on the high catalytic activity of an isolated Ni(II)/NHC complex, we propose a rare process of C–N bond formation by alkyne insertion into the Ni–N linkage of Ni(II) hydrazonato intermediates. Future studies will focus on in-depth mechanism understanding of this catalyst system for broader synthetic applications involving N-H bond cleavage and C-N bond formation processes.

Scheme 1. Transition Metal-Catalyzed Intermolecular Couplings between NH_2-Hydrazones and Alkynes.

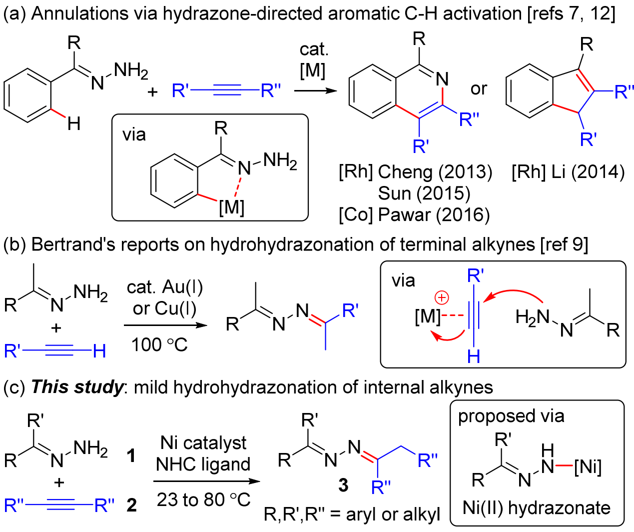
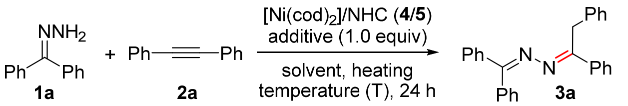
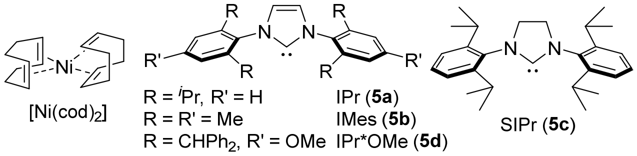


Table 1. Optimization of Alkyne Hydrohydrazonation.[a]

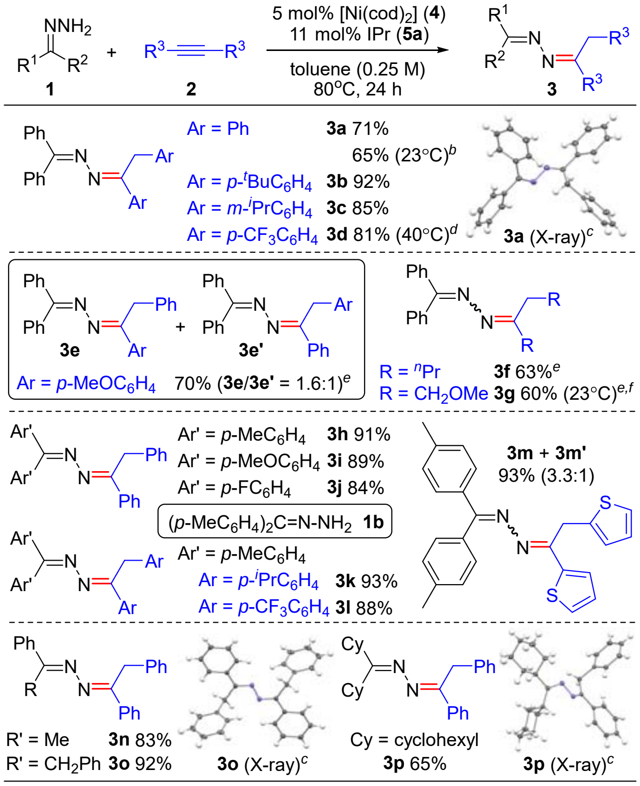


Entry	NHC	Additive	2a equiv.	4/5 equiv.	Solvent	T (°C)	Yield (%)[b]
1	**5a**	Cs_2CO_3	1.5	0.10/0.22	*m*-xylene	120	78
2	**5b**	Cs_2CO_3	1.5	0.10/0.22	*m*-xylene	120	0
3	**5c**	Cs_2CO_3	1.5	0.10/0.22	*m*-xylene	120	23
4	**5d**	Cs_2CO_3	1.5	0.10/0.22	*m*-xylene	120	25
5	**5a**	K_2CO_3	1.5	0.10/0.22	*m*-xylene	120	75
6	**5a**	Na_2CO_3	1.5	0.10/0.22	*m*-xylene	120	78
7	**5a**	KO^{t}Bu	1.5	0.10/0.22	*m*-xylene	120	63
8	**5a**	NaOEt	1.5	0.10/0.22	*m*-xylene	120	69
9	**5a**	none	1.5	0.10/0.22	*m*-xylene	120	78
10	**5a**	none	1.5	0.10/0.22	1,4-dioxane	120	71
11	**5a**	none	1.5	0.10/0.22	THF	100	56
12	**5a**	none	1.5	0.10/0.22	DMF	120	39
13	**5a**	none	1.5	0.10/0.22	toluene	120	81
14	**5a**	none	1.5	0.05/0.11	toluene	80	81
15	**5a**	**none**	**1.2**	**0.05/0.11**	**toluene**	**80**	**81**
16	**5a**	none	1.0	0.05/0.11	toluene	80	72[c]
17	**5a**	none	1.2	0.01/0.02	toluene	80	73[c]
18	**5a**	none	1.2	0.15/0.31	toluene	23	79[d]
19	**5a**	none	1.2	0.05/0.11	toluene	80	78[e]



[a]General conditions: **1a** (0.50 mmol, 1.0 equiv), **2a**, [Ni(cod)$_2$] (**4**), NHC ligand (**5**), additive (1.0 equiv), solvent (2.0 mL), 24 h. [b]Yields determined by GC analysis. [c]48 h reaction time. [d]96 h reaction time. [e]Isolated yield (1.46 g) from a scale-up reaction with 5.0 mmol **1a**, 10 mL toluene and 18 h reaction time.

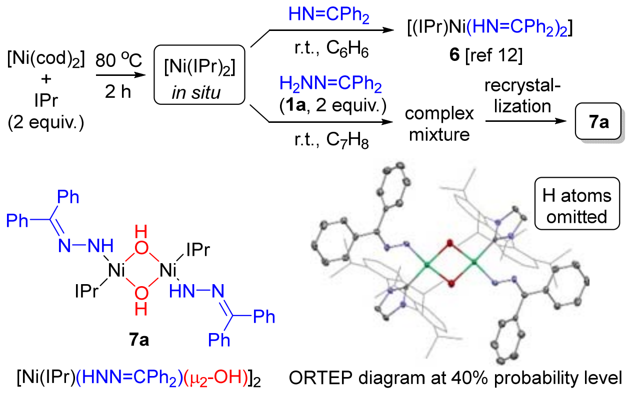
Table 2. Scope of Ketazine Products from of Ni-Catalyzed Alkyne Hydrohydrazonation.



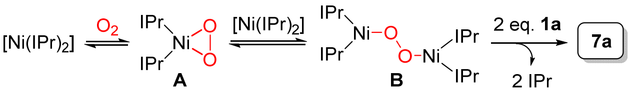
[a]General conditions: **1** (0.50 mmol, 1.0 equiv), **2** (1.2 equiv), **4** (0.05 equiv), **5a** (0.11 equiv), toluene (2.0 mL), 80 °C, 24 h; averaged isolated yield from two runs. [b]Room-temperature reaction with 1.0 mmol **1**, 1.2 mmol **2**, 10 mol% **4**, 21 mol% **5a**; 96 h. [c]ORTEP diagram displayed as 40% probability ellipsoids. [d]Slow addition protocol: alkyne was added portion-wise (4 x 0.3 equiv) over 6 h; 40 °C reaction temperature. [e]Yield is based on GC analysis of corresponding ketone from hydrolysis of ketazine product. [f]Room-temperature reaction with 2.0 equiv **2**; 48 h.

Scheme 2. Results from Reaction Mechanism Studies.

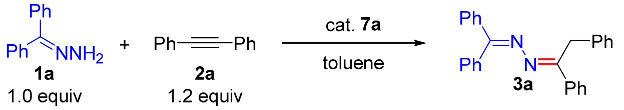
(a) Isolation of an IPr-ligated Ni(II) hydrazonate dimer (**7a**)



(b) Proposed mechanism for formation of hydrazonate **7a**

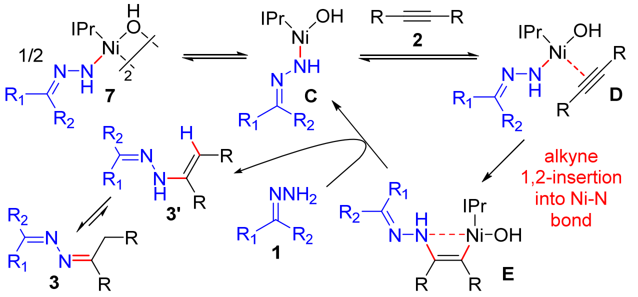


(c) Evaluation of **7a** as pre-catalyst for alkyne hydrohydrazonation



1a Amount	Toluene Volume	**7a** Loading	Temp.	Time	GC yield	Isolated Yield
0.50 mmol	2 mL	0.5 mol%	80 °C	24 h	83%	73%
2.50 mmol	5 mL	0.5 mol%	80 °C	48 h	84%	79% (740 mg)
2.50 mmol	5 mL	5 mol%	r.t. (23 °C)	48 h	78%	71% (664 mg)

(d) Proposed catalytic cycle with Ni(II) hydrazonate dimer (**7**) as pre-catalyst



ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, spectral data, and CIF files for reported single crystals.

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Author Contributions

J.W., J.L. and R.S.M. performed the reported experiments and data analysis. T.K. assisted in substrate preparation and initial catalyst development. A.U. conducted X-ray crystallography tests and data analysis. Y.P. and Z.Y. provided technical support on Ni complex characterization. J.W., R.S.M. and P.Z. designed the catalytic sequence and developed the reaction conditions. P.Z. prepared this manuscript with feedback from J.W. and J.L.

Notes

The authors declare no competing financial interests.

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(22) Ketazine products that were unstable or isolated as inseparable isomeric mixtures were hydrolysed to generate corresponding ketones, which were analysed by calibrated GC for yield determination.

(23) GC analysis indicated high regioselectivity (>10:1) that favors anti-Markovnikov hydrohydrazonation products from aryl-alkyl alkynes. However, further catalyst development is needed to improve ketazine yields and enable reliable determination of regioselectivity.

(24) The mixture of **3m**/**3m'** was inseparable and the product ratio was determined by ^{1}H NMR without assignment of absolute configurations. The (*E*)-isomer is likely the major product due to its higher stability considering similar (yet less pronounced) steric factors as observed with other ketazine products.

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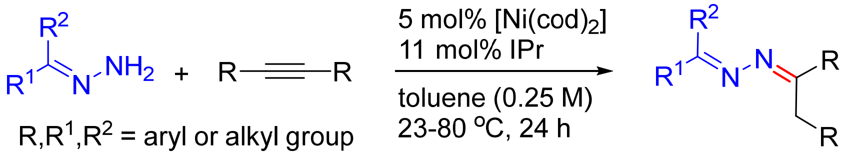
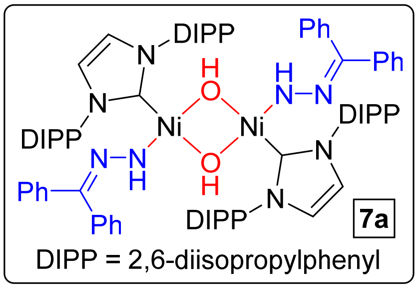
(36) See Schemes S1 and S2 in Supporting Information for description of alternative catalytic cycles and corresponding regiochemistry comparison for alkyne hydrohydrazonation.

Table of Content (TOC) Graphic

Nickel-Catalyzed Intermolecular Alkyne Hydrohydrazonation





- 16 examples; up to 93% isolated yield
- atom-efficient synthesis of ketazines
- proposed C-N bond formation by alkyne insertion into Ni-N bond
- isolated [Ni(IPr)(HNN=CPh$_2$)(μ_2-OH)]$_2$ (**7a**) as highly active catalyst precursor