Communication

Nickel-Catalyzed Hydroimination of Alkynes

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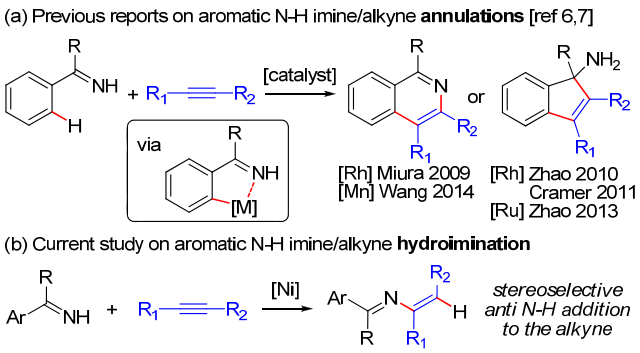
Supporting Information Placeholder

ABSTRACT: A modular and atom-efficient synthesis of 2-aza-1,3-butadiene derivatives has been developed via nickel-catalyzed intermolecular coupling between internal alkynes and aromatic N-H ketimines. This novel alkyne hydroimination process is promoted by a catalyst system of Ni(0) precursor ([Ni(cod)$_2$]), N-heterocyclic carbene (NHC) ligand (IPr), and Cs_2CO_3 additive. The exclusive formation of (Z)-enamine stereoisomers is consistent with a proposed *anti*-iminometalation of alkyne by π-complexation with Ni(0) and subsequent attack by the N-H ketimine nucleophile. A NHC-ligated Ni(0) π-imine complex, [(IPr)Ni(η^1-HN=CPh$_2$)(η^2-HN=CPh$_2$)], was independently synthesized and displayed improved reactivity as the catalyst precursor.

Nitrogen-substituted imines are ubiquitous substrates in transition metal-catalyzed transformations.[1-2] By contrast, catalytic transformations of N-unsubstituted imines (N-H imines) are much less established.[3-8] This is in part because of concerns over their low stability, difficulty for synthesis, and potential complications by *E*/*Z* isomerism and imine-enamine tautomerization. These issues are less pronounced with aromatic N-H ketimines, which are readily accessible via organometallic addition to benzonitriles, usually exist and react as single isomers, and are relatively stable compared to N-H aldimines and aliphatic N-H ketimines. Thus, aromatic N-H ketimines have been successfully explored in a number of catalytic processes such as the Buchwald-Hartwig amination,[3] enantioselective imine hydrogenation,[4] and imine-directed aromatic C-H functionalization.[5-8] However, aromatic N-H ketimines are not known to undergo catalytic hydroamination, the formal addition of a N–H bond across an unactivated C–C π-bond.[9,10] Such "hydroimination" of alkene or alkyne substrates would provide convenient and atom-economical synthesis of imine derivatives with N-alkyl or N-alkenyl substituents.

We report herein the development of a nickel-based catalyst system for intermolecular hydroimination of internal alkynes with aromatic N-H ketimines.[11] To our best knowledge, this is the first example of catalytic hydroimination with unactivated alkynes.[10] Prior studies on catalytic coupling between these two classes of substrates have focused on annulation processes involving cyclometalated imine complexes via imine-directed C-H bond activation (Scheme 1a).[12] Since the first report of such annulation strategy by Miura, Satoh and coworkers in 2009,[6a] several transition metal catalysts have been developed to promote oxidative [4+2] and redox-neutral [3+2] N-H ketimine/alkyne annulations to form isoquinoline and indenamine products respectively.[2a,6,7] In comparison, the current catalyst system promotes alkyne hydroimination via a formal *anti* alkyne addition by the imine N-H bond, leading to the formation of (3*Z*)-2-aza-1,3-butadiene products in high chemo- and stereoselectivity (Scheme 1b). 2-Aza-1,3-dienes are important building blocks in amine and N-heterocycle synthesis due to their versatile reactivity towards a broad range of addition and cycloaddition reactions including the aza-Diels-Alder reaction.[13] Existing procedures for 2-aza-1,3-diene synthesis typically require multiple steps and often involve highly reactive intermediates such as phosphazenes and 2*H*-azirines.[13a] Thus, this work expands the scope of N-nucleophiles for catalytic hydroamination and provides rapid assembly of valuable 2-aza-1,3-diene structures from readily available starting materials. It also paves the way for further development of earth-abundant Ni-based catalysts as a versatile and low-cost alternative to precious metal catalysts for hydroamination.[14,15]

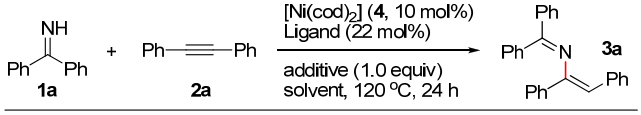
Scheme 1. Transition metal-catalyzed couplings between aromatic N-H ketimines and alkynes.



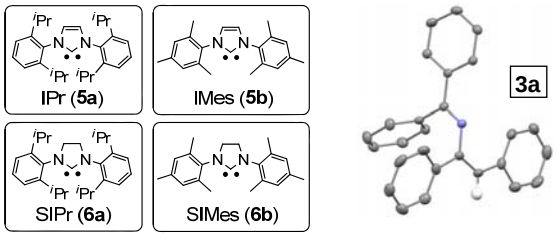
We began our catalyst development with the model reaction between benzophenone imine (**1a** in Table 1) and diphenylacetylene (**2a**). Results from an initial screening of various transition metal complexes led us to focus on Ni(0) complexes as catalyst precursors, which selectively promoted the formation of hydroimination product **3a** over byproducts from [3+2] or [4+2] annulations (Scheme 1).[6,7] Thus, we used [Ni(cod)$_2$] (**4**) as a commercially available Ni(0) precursor to evaluate other reaction parameters such as the ligand, salt additive, and solvent (Table 1). In general, **3a** was formed in

higher yields with N-heterocyclic carbene (NHC) ligands such as IPr (**5a**) (entries 1-4), stoichiometric amount of inorganic base additives (entries 5-12),[16] and nonpolar aromatic solvents (entries 13-19). Under the optimized conditions of 120 °C and using *m*-xylene solvent, reaction between **1a** and **2a** (1.2 equiv) was promoted by 10 mol% **4**, 22 mol% **5a** and 1 equiv Cs_2CO_3 to selectively form **3a** in 91% yield over 24 hours (entry 1). **3a** was detected as a single isomer of (3*Z*)-2-aza-1,3-butadiene derivative by NMR spectroscopy and single crystal X-ray diffraction, suggesting a formal *anti* alkyne addition by the imine N-H bond. Traces of byproducts (<5 %) from alkyne oligomerization[11d,17] were also formed under these conditions, while none of the [3+2] and [4+2] annulation byproducts (Scheme 1a) was detected by GC analysis.

Table 1. Development of the catalytic reaction.[a,b]



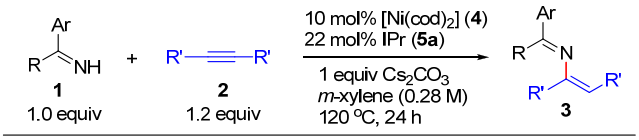
Entry	Ligand	Additive	Solvent	Yield (%)[c]
1	IPr (**5a**)	Cs_2CO_3	*m*-xylene	91
2	SIPr (**6a**)	Cs_2CO_3	*m*-xylene	84
3	IMes (**5b**)	Cs_2CO_3	*m*-xylene	31
4	SIMes (**6b**)	Cs_2CO_3	*m*-xylene	28
5	**5a**	K_2CO_3	*m*-xylene	88
6	**5a**	Na_2CO_3	*m*-xylene	84
7	**5a**	LiOH	*m*-xylene	83
8	**5a**	NaOEt	*m*-xylene	73
9	**5a**	KO^{t}Bu	*m*-xylene	0
10	**5a**	LiHMDS	*m*-xylene	0
11	**5a**	H_2O (5 equiv)	*m*-xylene	71
12	**5a**	none	*m*-xylene	56
13	**5a**	Cs_2CO_3	toluene	82
14	**5a**	Cs_2CO_3	1,4-dioxane	87
15	**5a**	Cs_2CO_3	THF	56
16	**5a**	Cs_2CO_3	hexane	63
17	**5a**	Cs_2CO_3	CH_3CN	44
18	**5a**	Cs_2CO_3	DMF	0
19	**5a**	Cs_2CO_3	DCE	0

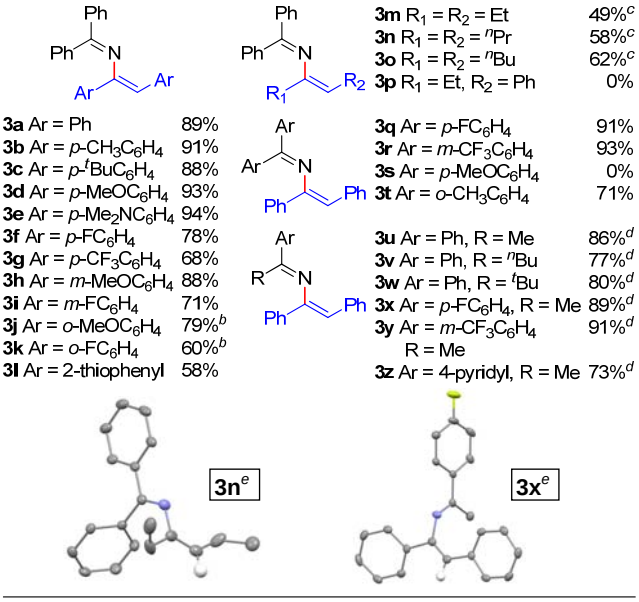


[a] General conditions: **1a** (0.28 mmol, 1.0 equiv), **2a** (1.2 equiv), [Ni(cod)$_2$] (**4**, 0.10 equiv), ligand (0.22 equiv), additive (1.0 equiv), solvent (1.0 mL), 120 °C, 24h. [b] Ligand structures and the ORTEP diagram of **3a** (40% probability; all aromatic H emitted for clarity) are shown below. [c] GC yields.

With the standard reaction conditions established, various aromatic N-H ketimines (**1**) and internal alkynes[18] (**2**) were studied for Ni(0)-catalyzed hydroimination (Scheme 2). In general, 2-aza-1,3-butadienes (**3**) were formed in high chemoselectivity, with small amounts of byproducts from alkyne oligomerization. All of the azadiene products were detected and isolated as a single isomer of (*Z*)-enamine structures (*vide infra*). Scope of the alkyne substrates was studied with benzophenone imine (**1a**) as the reaction partner. For symmetrical diarylacetylenes, high product yields of 88-94% were achieved with those having electron-donating substituents at *para* or *meta* positions (**3b-e**, **3h**). In comparison, diarylacetylenes with *para* F/CF_3 or *meta* F groups led to slightly lower yields of 68-78% (**3f**, **3g**, **3i**). Diarylacetylenes with *ortho* OMe or F groups required a longer reaction time of 36 h to reach 60-79% yields (**3j**, **3k**). Di(2-thiphenyl)-acetylene also reacted with **1a** to give product **3l** in 58% yield. Symmetrical dialkylacetylenes were significantly less reactive than diarylacetylenes under standard reaction conditions. Thus, 2 equiv of **1a** was required to promote complete conversion with dialkylacetylenes as the limiting reagents and gave products **3m-o** in 49-62% yields. Notably, aryl alkyl alkynes such as 1-phenyl-1-propyne failed to give the desired hydroimination product (e.g. **3p**) but instead formed a mixture of alkyne oligomers.[11d,17,19] Scope of the ketimine substrates was studied by reactions with diphenylacetylene (**2a**), and high reactivity was observed for electron-poor diaryl N-H ketimines with *para* F or *meta* CF_3 groups (**3q**, **3r**). By contrast, the *electron-rich* di(*p*-anisyl) N-H ketimine failed to react with **2a** to give the desired product **3s**. Interestingly, the electron-rich *and* sterically hindered di(*o*-tolyl) N-H ketimine did react with **2a** to give azadiene **3t** in 71% yield. Alkyl-substituted (hetero)aromatic N-H imines with phenyl, electron-poor aryl, or 4-pyridyl groups showed slightly lower reactivity and required 1.5 equiv of **2a** to give products **3u-z** in 73-91% yields. As demonstrated with the solid-state structures of **3n** and **3x** by X-ray crystallography, the regio- and stereochemistry of the (3*Z*)-2-aza-1,3-diene structure from formal *anti* N-H addition was maintained for products with alkyl substituents at 1-, 3- or 4-positions. Thus, it appeared that no E/Z isomerization or imine-enamine tautomerization occurred under current reaction conditions.

Scheme 2. Substrate scope of N-H ketimines and internal alkynes for Ni-catalyzed hydroimination.[a]





3a Ar = Ph	89%	**3m** R_1 = R_2 = Et	49%[c]
3b Ar = *p*-$CH_3C_6H_4$	91%	**3n** R_1 = R_2 = ^{n}Pr	58%[c]
3c Ar = *p*-^{t}BuC_6H_4	88%	**3o** R_1 = R_2 = ^{n}Bu	62%[c]
3d Ar = *p*-MeOC_6H_4	93%	**3p** R_1 = Et, R_2 = Ph	0%
3e Ar = *p*-$Me_2NC_6H_4$	94%		
3f Ar = *p*-FC_6H_4	78%	**3q** Ar = *p*-FC_6H_4	91%
3g Ar = *p*-$CF_3C_6H_4$	68%	**3r** Ar = *m*-$CF_3C_6H_4$	93%
3h Ar = *m*-MeOC_6H_4	88%	**3s** Ar = *p*-MeOC_6H_4	0%
3i Ar = *m*-FC_6H_4	71%	**3t** Ar = *o*-$CH_3C_6H_4$	71%
3j Ar = *o*-MeOC_6H_4	79%[b]	**3u** Ar = Ph, R = Me	86%[d]
3k Ar = *o*-FC_6H_4	60%[b]	**3v** Ar = Ph, R = ^{n}Bu	77%[d]
3l Ar = 2-thiophenyl	58%	**3w** Ar = Ph, R = ^{t}Bu	80%[d]
		3x Ar = *p*-FC_6H_4, R = Me	89%[d]
		3y Ar = *m*-$CF_3C_6H_4$, R = Me	91%[d]
		3z Ar = 4-pyridyl, R = Me	73%[d]

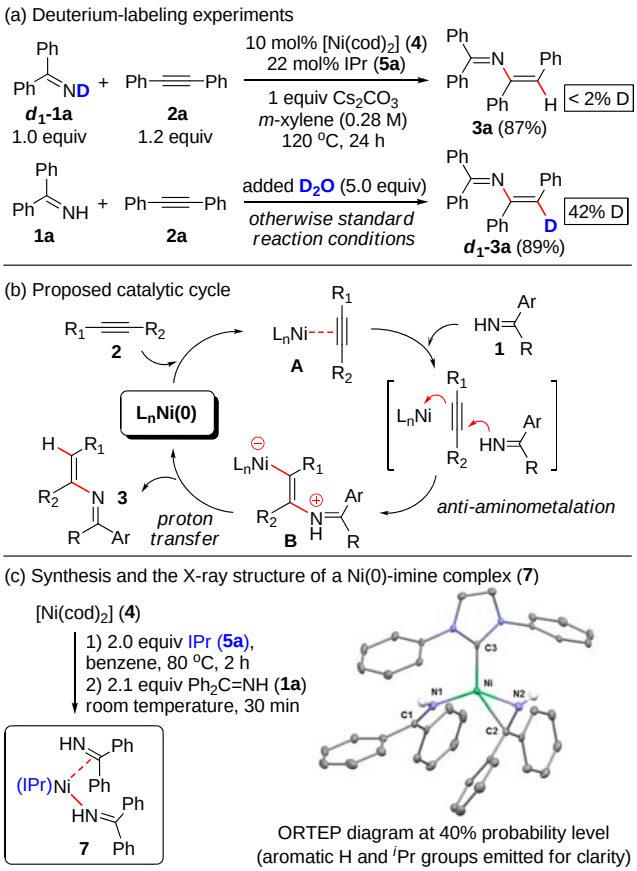
[a] General conditions: **1** (0.28 mmol, 1.0 equiv), **2** (1.2 equiv), **4** (0.10 equiv), **5a** (0.22 equiv), Cs_2CO_3 (1.0 equiv), *m*-xylene (1.0 mL), 120 °C, 24 h; averaged yield of isolatd products from two runs. [b] Reaction time was 36 h. [c] Using 0.61 mmol of **2** and 2.0 equiv of **1**. [d] Using 1.5 equiv of **2**. [e] ORTEP diagram at 40% probability level; all non-vinylic H atoms emitted for clarity.

The reaction mechanism for Ni(0)-catalyzed alkyne hydroimination was investigated by several deuterium-labeling

experiments and stoichiometric observations (Scheme 3). Under standard catalytic conditions, N-deuterated benzophenone imine (***d*₁-1a**) reacted with diphenylacetylene (**2a**) to give 2-aza-1,3-diene product **3a** in 87% yield and with only trace of deuterium incorporation (< 2%) at the 4-position. In comparison, reaction between non-deuterated **1a** and **2a** in the presence of 5 equiv D_2O additive led to 42% deuterium incorporation at the 4-position of the product (***d*₁-3a**, 89% yield). These results suggested that the catalytic hydroimination pathway likely involved intermolecular proton transfer processes, which led to rapid H/D exchange between reactive intermediates and the reaction media. Based on the deuterium-labeling and stereochemistry results, we proposed that Ni(0)-catalyzed alkyne hydroimination was initiated by formation of a Ni(0)-alkyne π-complex (**A** in Scheme 3b), followed by stereospecific anti-attack by the N-H imine nucleophile (**1**) to form a zwitterionic alkenylnickel iminium intermediate **B**. Subsequent proton dissociation from iminium and protonation of the Ni-alkenyl linkage released the hydroimination product (**3**) and formed a coordinatively unsaturated Ni(0) intermediate, which was stabilized by π-complexation with an alkyne substrate (**2**) and regenerated intermediate **A**. The beneficial effects of added inorganic bases or water on catalytic reactivity (Table 1) suggested that the proposed proton transfer processes with intermediate **B** were possibly assisted by external Brønsted acids or bases, which also led to the observed H/D exchange during deuterium labeling studies. This proposed nucleophilic attack on a coordinate alkyne was based on the well-established "alkyne activation" pathway for catalytic hydroamination,[9,20] and the observed stereochemistry was consistent with an outer-sphere, *anti*-aminometalation process rather than an inner-sphere nucleophilic attack.[21]

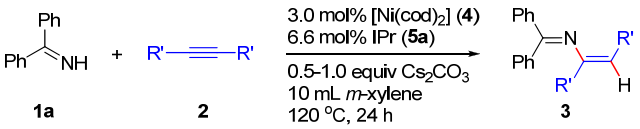
To gain further mechanistic insights, we sought to isolate or independently synthesize the proposed Ni(0)-π-alkyne intermediate (**A**) with attached IPr ligand and evaluate its catalytic activity. Unfortunately, our efforts were hindered by instability of the target Ni-alkyne complexes and formation of alkyne oligomers during attempted synthesis (see Supporting Information for details).[11d,17] Thus, we switched our synthetic target to IPr-ligated Ni(0)-imine complexes as a potential catalyst precursor (Scheme 3c). A 1:2 mixture of $[Ni(cod)_2]$ and IPr in benzene was stirred at 80 °C for 2 h before reacting with 2.1 equiv of benzophenone imine (**1a**) at room temperature to generate a dark violet-colored complex, $[(IPr)Ni(Ph_2C{=}NH)_2]$ (**7**). The solid-state structure of complex **7** was studied by single crystal X-ray diffraction to reveal a σ-imine as well as a π-imine ligand.[22] Using complex **7** as a catalyst precursor to replace $[Ni(cod)_2]$ and without added IPr ligand, a reaction between **1a** and **2a** was effectively promoted at a reduced catalyst loading of 3 mol% to give **3a** in 87% yield (Scheme 3d). Thus, IPr-ligated Ni(0)-imine complexes were likely involved in the alkyne hydroimination process as activated catalyst precursors. With a relatively weak π-imine ligand, these Ni-imine intermediates appeared to favor a single π-imine replacement by an alkyne substrate to form the proposed π-alkyne intermediate **A** while keeping the σ-imine ligand intact.[23] In consequence, the desired alkyne hydroimination was selectively promoted over alkyne oligomerization, which probably required two π-alkynes on a Ni(0) center for C-C bond formation via oxidative cyclization.[17]

Scheme 3. Results from reaction mechanism studies.



To demonstrate the potential of current method for practical synthesis, we carried out a preliminary study on gram-scale alkyne hydroimination with benzophenone imine (**1a**) (Scheme 4). With a reduced catalyst loading of 3 mol% $[Ni(cod)_2]$ and 6.6 mol% IPr, reactions with diphenylacetylene (**2a**) and 4-octyne (**2b**) could be scaled up 15- to 20-fold to produce isolated products **3a** and **3n** in gram quantities, although the yield percentages were lower than those acquired under the standard catalytic conditions (Scheme 2).

Scheme 4. Gram-scale hydroimination reactions.



R' = Ph (**2a**):	5.5 mmol **1a** (1.0 equiv), 1.2 equiv **2a** 0.5 equiv Cs_2CO_3	**3a**: 64% (1.3 g isolated)
R' = ^{n}Pr (**2b**):	9.1 mmol **2b** (1.0 equiv), 2.0 equiv **1a** 1.0 equiv Cs_2CO_3	**3n**: 43% (1.1 g isolated)

In summary, we have developed a Ni(0)/NHC-based catalyst system for the first example of alkyne hydroimination with aromatic N–H ketimines. Stereochemistry and preliminary mechanistic results supported a proposed mechanism of alkyne activation via π-complexation with Ni(0) and subse-

quent nucleophilic attack by the N-H ketimine. Future studies will focus on mechanism-guided catalyst improvement for expanded substrate scopes and synthetic applications of the 2-aza-1,3-diene products.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data, and CIF file for reported single crystals. This material is available free of charge via the Internet at http://pubs.acs.org.

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15. For early transition metal or rare earth metal-catalyzed intermolecular alkyne hydroamination, see ref 9 and the following: (a) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.*, **1992**, *114*, 1708. (b) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770. (c) Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3389. (d) Shi, Y.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 3967. (e) Li, C.; Thomson, R. K.; Gillon, B.; Patrick, B. O.; Schafer, L. L. *Chem. Commun*. **2003**, 2462. (f) Kim, H.; Livinghouse, T.; Shim, J. H.; Lee, S. G.; Lee, P. H. *Adv. Synth. Catal*. **2006**, *348*, 701.

16. Adding H_2O led to slightly improved yield for **3a** compared to reactions without any additives (entries 11, 12) and generated only trace amount of benzophenone (<5%) by GC analysis. However, imine hydrolysis with added H_2O became much more significant with less stable N-H ketimines. Thus, our catalyst development efforts focused on using base additives rather than added H_2O.

17. (a) Alphonse, P.; Moyen, F.; Mazerolles, P. *J. Organomet. Chem.* **1988**, *345*, 209. (b) Eisch, J. J.; Ma, X.; Han, K. I.; Gitua, J. N.; Krueger, C. *Eur. J. Inorg. Chem.* **2001**, 77. (c) Ogata, K.; Murayama, H.; Sugasawa, J.; Suzuki, N.; Fukuzawa, S.-I. *J. Am. Chem. Soc.* **2009**, *131*, 3176. (d) Horie, H.; Kurahashi, T.; Matsubara, S. *Chem. Commun.* **2010**, *46*, 7229.

18. Terminal alkynes such as phenylacetylene led to alkyne oligomerization instead of desired hydroimination; see refs 17c and 17d.

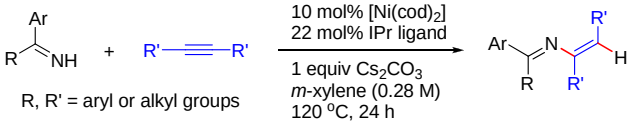
19. It is not clear to us why aryl alky alkyne substrates display such high chemoselectivity towards oligomerization (e.g. cyclotrimerization) over desired hydroimination. Alkyne reactivity for catalytic cyclotrimerization and hydroamination is known to depend on both steric and electronic factors and can be difficult to predict. See ref 11d for an example of chemoselective alkyne hydroamination vs. cyclotrimerization using Ni(II) vs. Ni(0) catalyst precursors.

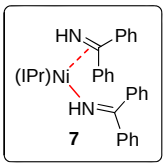
20. Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **2000**, *1*, 170.

21. Formation of the (*Z*)-enamine product could also be explained by *E*/*Z* isomerization of an initial (*E*)-enamine product from *syn*-hydroamination pathways. Such a scenario cannot be ruled out at this point, but the lack of observation for any *syn*-addition products suggested that it was unlikely to be the major reaction pathway.

22. Hoberg, H.; Goetz, V.; Krueger, C.; Tsay, Y. H. *J. Organomet. Chem.* **1979**, *169*, 209.

23. The lack of reactivity for electron-rich diaryl N-H ketimines was probably due to strong Ni-imine complexation that prevented imine replacement by alkyne substrates. Such catalyst deactivation by strongly nucleophilic amines are known for catalytic alkyne hydroamination. See ref 9c and the following example: Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640.





- 24 examples; 49-93% isolated yield
- atom-efficient synthesis of 2-aza-1,3-dienes
- stereoselective formation of (Z)-enamine structures via proposed *anti*-iminometalation
- isolated Ni(0)-(σ-imine)(π-imine) complex (**7**) as a reactive catalyst precursor