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Alkyl Bromides as Mild Hydride Sources in Ni-Catalyzed Hydroamidation of Alkynes with Isocyanates

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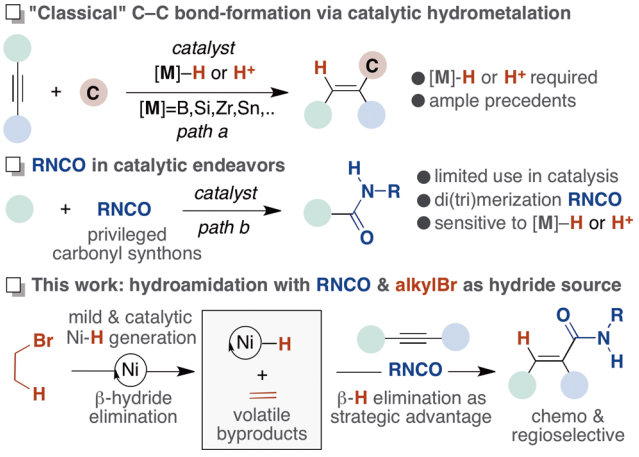
Supporting Information

ABSTRACT: A catalytic hydroamidation of alkynes with isocyanates using alkyl bromides as hydride sources has been developed. The method turns parasitic β-hydride elimination into a strategic advantage, rapidly affording acrylamides with excellent chemo- and regioselectivity.

Hydrometalation of alkynes ranks among the most fundamental reactions in organometallic chemistry, enabling a rapid access to well-defined alkenyl metal species.[1] At present, intermolecular C−C bond-forming reactions via catalytic hydrofunctionalization of alkynes remain confined to the utilization of well-defined metal hydride species, or the presence of acids as hydrogen donors (Scheme 1, path a).[1,2]

Scheme 1. Alkyne Hydrofunctionalization and Isocyanates



Unfortunately, these conditions preclude the use of partners sensitive to either metal hydrides or acidic media. If successful, a new design principle capable of expanding the boundaries of alkyne hydrofunctionalization for C−C bond-formation by using unconventional hydride sources could lead to new knowledge in our ever-growing organometallic arsenal.

Prompted by the utmost synthetic relevance of acrylamides in pharmaceuticals, agrochemicals and polymers,[3] we wondered whether it would be possible to design a catalytic hydroamidation of alkynes by intercepting the *in situ* generated alkenyl metal species with isocyanates, privileged synthons in both industrial and academic laboratories.[4,5] At the outset of our investigations, however, it was unclear whether such a protocol could ever be implemented, as isocyanates have rarely been employed in catalytic endeavors other than cycloaddition events (Scheme 1, path b).[6,7] This is likely due to their exceptional sensitivity to both hydrides and proton sources as well as their strong binding properties to low valent metal species.[8,9] We anticipated that a mild generation of the transient metal hydride would be critical for success.[10] To such end, we questioned whether we could turn β-hydride elimination, traditionally considered a drawback when coupling unactivated alkyl halides,[11] into a strategic advantage, thus offering a novel method capable of delivering metal hydrides under mild conditions while releasing volatile byproducts (Scheme 1, bottom).[12] As part of our interest in heterocumulenes,[13,7a,b] we report herein the successful realization of this new design principle, accessing a wide range of acrylamides in both a chemo- and regioselective manner.

We started our proposed protocol by evaluating the hydroamidation of **1a** with **2a** (Table 1), as the *t*-butyl group in acrylamides could be used as a vehicle for further functionalization.[14] After careful optimization,[15] we found that a combination of $NiBr_2$·diglyme, **L4**, Mn as reducing agent in NMP at rt, and using simple *i*-PrBr as the hydride source provided the best results, resulting in 91% isolated yield of **3a** as a single diastereoisomer (entry 1). In line with our expectations, subtle modifications on the ligand backbone led to profound changes on the reaction outcome, with *ortho*-substituted 1,10-phenanthroline ligands being considerably more reactive than bipyridine motifs (entries 2−6), suggesting that a reasonable steric bulk was critical for stabilizing the transient reaction species. Likewise, other Ni sources, solvents, reducing agents, or related alkyl bromides as hydride sources resulted in lower yields (entries 7−11).[15] As expected, classical hydrometalation techniques based on R_3SiH, H_2, $NaBH_4$ or alcohols as protic sources resulted in the degradation of **2a**, with little of **3a**, if any, being observed in the crude mixtures (entries 12−13). Notably, only traces of reductive amidation of *i*-PrBr were observed, thus showing the unique features of our method.[7a] Control experiments in the absence of Ni catalyst, **L4**, *i*-PrBr or Mn revealed that all these parameters were necessary for the reaction to occur (entry 14).

With an optimized set of conditions in hand, we turned our attention to validating the generality of our hydroamidation

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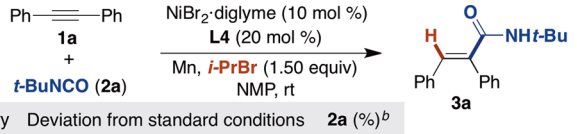
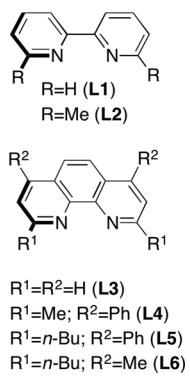
Table 1. Optimization of the Reaction Conditions[a]



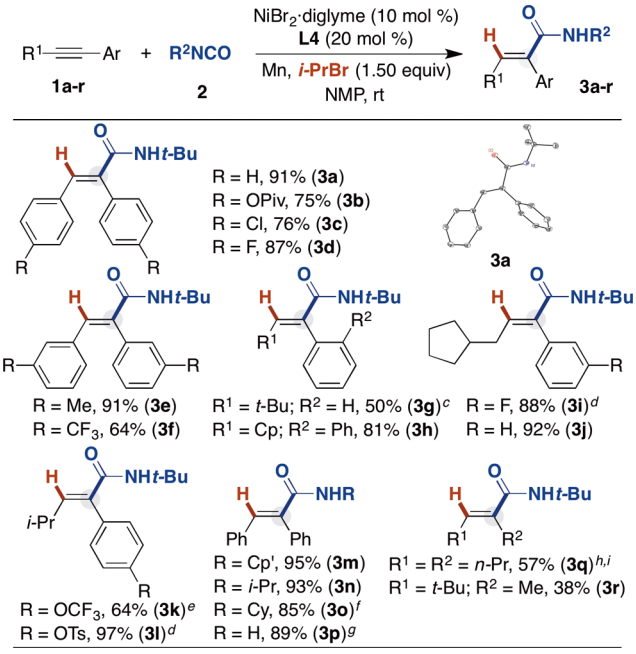
Entry	Deviation from standard conditions	2a (%)[b]
1	None	91[c] (83[d])
2	**L1** instead of **L4**	0
3	**L2** instead of **L4**	45
4	**L3** instead of **L4**	0
5	**L5** instead of **L4**	64
6	**L6** instead of **L4**	66
7	PPh_3 instead of **L4**	38
8	$Ni(COD)_2$ as catalyst	68
9	*t*-BuBr as hydride source	69
10	DMF (DMA) instead of NMP	73 (54)
11	Zn instead of Mn	54[e]
12	$Me(EtO)_2SiH$ (H_2) as hydride source	17[f] (0)
13	$NaBH_4$ (*t*-BuOH) as hydride source	0 (0)
14	No $NiBr_2$·diglyme, no **L4** or no Mn	0



[a]**1a** (0.25 mmol), **2a** (0.38 mmol), $NiBr_2$·diglyme (10 mol %), **L4** (20 mol %), Mn (0.38 mmol), NMP (0.25 M) at rt, 12 h. [b]HPLC yields using naphthalene as internal standard. [c]Isolated yield. [d]$NiBr_2$·diglyme (5 mol %), 24 h. [e]*E*:*Z* = 5:1. [f]Na_2CO_3 (0.75 mmol), no Mn.

protocol. As illustrated in Table 2, a host of different alkyl- or aryl-substituted symmetrical or unsymmetrical acetylenes could

Table 2. Scope of Aryl- and Alkyl-Substituted Acetylenes[a,b]

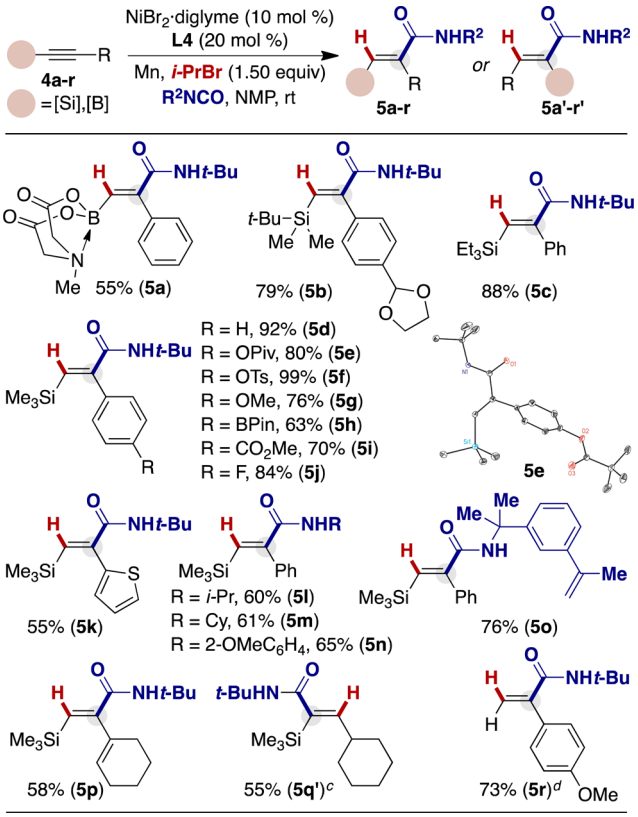


[a]As Table 1 (entry 1), at 0.50 mmol scale. [b]Isolated yields, average of at least two independent runs. [c]35 °C, 72 h. [d]*E*/*Z* = 14:1. [e]*E*/*Z* = 15:1. [f]*E*/*Z* = 13:1. [g]Subsequent TFA treatment at reflux. [h]Using neocuproine (20 mol %) as ligand at 10 °C. [i]*E*/*Z* = 6:1. Cp = cyclopropyl, Cp′ = cyclopentyl.

participate well in the targeted reaction.[16] Notably, similar results were obtained regardless of the electronic and steric parameters of the substituents on the alkyne terminus. In all cases, a single regioisomer with high levels of diastereoselectivity was obtained, with the amide function located adjacent to the aromatic motif, an observation corroborated by X-ray crystallography (**3a**, **3l**).[15] Particularly interesting was the ability to accommodate aryl halides (**3c**, **3d**, **3i**), pivalates (**3b**) or tosylates (**3l**), as these motifs have successfully been used as counterparts in Ni-catalyzed cross-coupling reactions,[17] thus providing an additional handle for further derivatization. Notably, the coupling of isocyanates other than **2a** posed no problems, and **3m**−**3o** could all be prepared in high yields. Upon simple exposure to TFA,[15] we found that primary amides could be within reach (**3p**), thus effectively using the *t*-butyl group as a masked form of hydrogen while leading to *a priori* inaccessible building blocks via classical alkyne hydroamidation processes.[1,5] Importantly, the hydroamidation could also be applied to aliphatic internal alkynes (**3q**, **3r**), albeit in slightly lower yields.

Encouraged by these results, we questioned whether we could extend the scope of our protocol to silyl- or boryl-substituted acetylenes, as these motifs have shown to be versatile intermediates in organic synthesis.[18] As shown in Table 3, this turned out to be the case. As for the results

Table 3. Scope of Silyl- and Boryl-Substituted Acetylenes[a,b]



[a]As Table 1 (entry 1), at 0.50 mmol scale. [b]Isolated yields, average of two independent runs. [c]*E*/*Z* = 1.8:1. [d]Using **1r** followed by TBAF (1.20 equiv).

compiled in Table 2, the amide function in **5a**−**5p** was invariably located adjacent to the aromatic or vinylic motif, as ultimately confirmed by X-ray crystallography (**5e**). The absence of a π-component on the alkyne terminus resulted in **5q′**, a selectivity switch that is attributed to the electropositivity of Si and hyperconjugation into the adjacent Si−C σ^* orbital.[19] As shown for **5n**, the reaction could be extended to aromatic isocyanates with similar ease. Interestingly, desilylation with TBAF yielded **5r**, thus accessing compounds that formally

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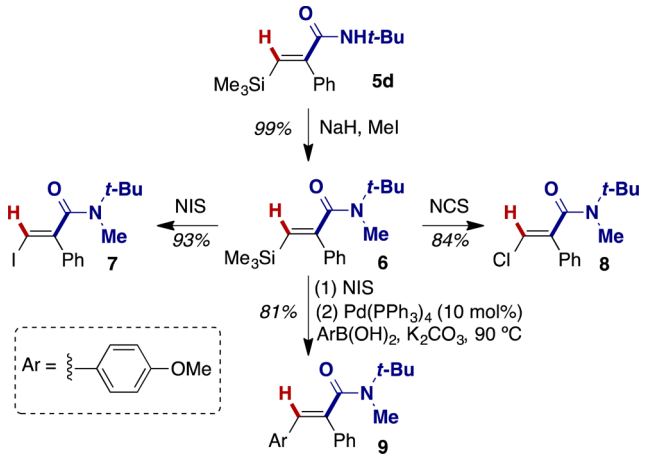
derive from a hydroamidation of free alkynes. As anticipated, the chemoselectivity posed no problems, as acetals (**5b**), esters (**5i**), aryl boronates (**5h**), heteroaromatics (**5k**), aryl fluorides (**5j**) or alkenes (**5o**, **5p**) could perfectly be tolerated. As for Table 2, groups amenable for Ni-catalyzed C−O cleavage such as aryl pivalates (**5e**) or tosylates (**5f**) did not compete with the efficacy of our hydroamidation event.[20] The usefulness of our synthetic method is illustrated in Scheme 2, by rapidly

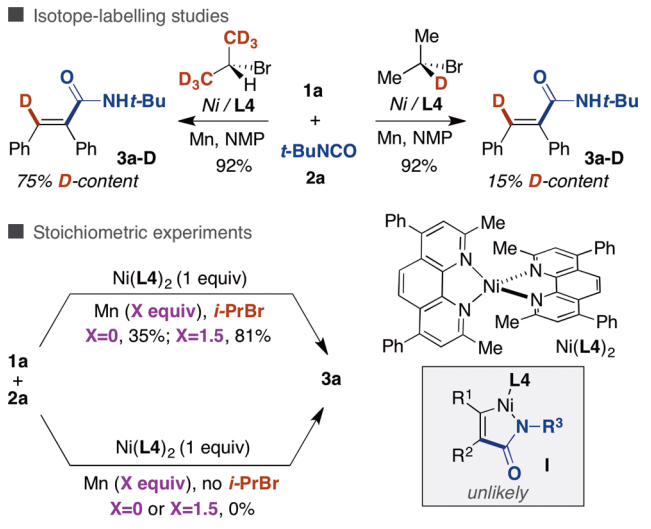
Scheme 2. Synthetic Applicability



preparing synthetically relevant **7** and **8** in high yields by an *N*-alkylation/*ipso*-halogenation sequence.[15] The versatility of our method is further highlighted by the synthesis of **9**,[15] accessing acrylamides that would be beyond reach otherwise with such a high regioselectivity via classical hydroamidation of alkynes possessing two different aromatic residues without steric bias.[1,5,21]

Next, we decided to perform deuterium-labeling experiments to gather evidence about the mechanism of our Ni-catalyzed hydroamidation protocol (Scheme 3, top pathway). As shown, **3a-D** was prepared in high yields from either $(CD_3)_2CHBr$ or $(CH_3)_2CDBr$ with 75% and 15%-D content, respectively, suggesting that a β-hydride elimination/migratory insertion might occur at some extent prior to alkyne binding.[22] The stoichiometric experiments with Ni(**L4**)$_2$ are particularly

Scheme 3. Mechanistic Experiments



illustrative (Scheme 3, bottom);[23] specifically, we found that **3a** was solely obtained in the presence of *i*-PrBr, thus ruling out an oxidative cyclization of Ni(0), **1a** and **2a** en route to **I**.[6] Although further studies are needed, we currently propose a pathway consisting of a hydrometalation with *in situ* generated Ni(II)-hydride, single electron transfer (SET) mediated by Mn en route to a Ni(I) intermediate[24] followed by RNCO insertion[25] and a final SET to recover the Ni(0) species. At present, we cannot rule out a RNCO insertion into a vinyl-Ni(II) species or a comproportionation event to generate the corresponding Ni(I) intermediates, as a non-negligible yield of **3a** was obtained in the absence of Mn (Scheme 3, bottom).[26]

In summary, we have discovered a conceptually new and mild hydroamidation of alkynes with isocyanates by using *in situ* generated nickel hydrides from light bromoalkanes, turning parasitic β-hydride elimination into a strategic advantage. The method is characterized by its generality and excellent chemo- and regioselectivity, suggesting that mechanistically distinct protocols could be initiated via β-hydride elimination. Further investigations along these lines are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10351.

Data for $C_{19}H_{21}NO$ (CIF)
Data for $C_{23}H_{29}NO_4S$ (CIF)
Data for $C_{21}H_{33}NO_3Si$ (CIF)
Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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