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Merging NiH Catalysis and Inner-Sphere Metal-Nitrenoid Transfer for Hydroamidation of Alkynes

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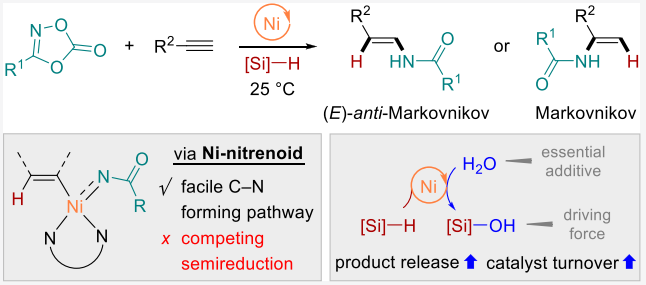
ABSTRACT: The formal hydroamination/hydroamidation utilizing metal hydride is an appealing synthetic tool for the construction of valuable nitrogen-containing compounds from unsaturated hydrocarbons. While significant advances have been made for the functionalizations of alkenes in this realm, the direct hydroamidation of alkynes remains rather limited due to the high feasibility of the key metal-alkenyl intermediate to choose other reaction pathways. Herein, we report a NiH-catalyzed strategy for the hydroamidation of alkynes with dioxazolones, which allows convenient access to synthetically useful secondary enamides in (*E*)-*anti*-Markovnikov or Markovnikov selectivity. The reaction is viable for both terminal and internal alkynes and is also tolerant with a range of subtle functional groups. With H_2O found as an essential component for high catalyst turnovers, the involvement of *inner-sphere* nitrenoid transfer is proposed that outcompetes an undesired semireduction process, thus representing the first example to show the competence of Ni catalysis for metal-nitrenoid formation from dioxazolones.



INTRODUCTION

Enamides are a versatile motif that play a significant role in drug discovery, wherein they serve as a potent pharmacophore in bioactive compounds[1,2] or as an important intermediate for the construction of more valuable nitrogen functionalities.[3,4] Among the diverse range of synthetic strategies,[5,6] the transition-metal-catalyzed hydroamidation of alkynes, that is, addition of an amide N−H bond across the C−C triple bond, represents one of the most atom-economical methods to access such a class of moieties.[7−10] Processes that achieve high levels of chemo-, regio-, and stereoselectivity have been developed within this synthetic platform, especially for an *anti*-Markovnikov addition of secondary amides. Despite these advances, alkyne hydroamidation is generally limited to terminal or activated internal alkynes,[11−13] and to the best of our knowledge, that leading to Markovnikov addition in intermolecular reactions is yet to be achieved. Moreover, primary amides remain as somewhat more challenging reactants for this transformation, mainly due to their low nucleophilicity as well as feasibility of the newly formed secondary enamides for further reactions with alkynes. Only a handful of examples of hydroamidation protocols have been reported for the synthesis of secondary enamides (Scheme 1a),[14,15] all of which are known to give (*Z*)-selective *anti*-Markovnikov addition by either catalyst or substrate control. Although the former example showed that (*E*) secondary enamides can also be obtained via a one-pot isomerization (*Z* to *E*),[14] this sequential process is steric-dependent and often results in low *E*/*Z* selectivities. In addition, the elevating conditions required for the isomerization (110 °C) could be detrimental for certain functional groups. Therefore, the development of a mild alternative that could directly afford (*E*)-*anti*-Markovnikov or Markovnikov addition, as well as that applicable to internal alkynes, is highly sought after.

In this context, we envisaged to develop a new alkyne hydroamidation strategy based on a polarity-reversed reaction mode, utilizing metal hydride in combination with an electrophilic amidating source. This concept of formal hydrofunctionalization has emerged as a powerful synthetic tool in recent years[16−18] and offers thermodynamically differed pathways for complementary reactivity and selectivity to the traditional two-component methodologies. In particular, the pioneering works by Buchwald[19] and Miura[20] established CuH catalysis as a competent handle for a hydroamination or hydroamidation of *alkenes*, and recent developments have further engendered highly efficient, regio- and stereoselective protocols with the exploitation of a variety of electrophilic nitrogen sources.[21−27] While much success has been achieved with alkenes, the direct functionalization of alkynes in this mechanistic approach is, however, limited. This is especially

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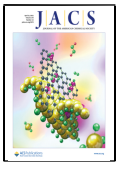

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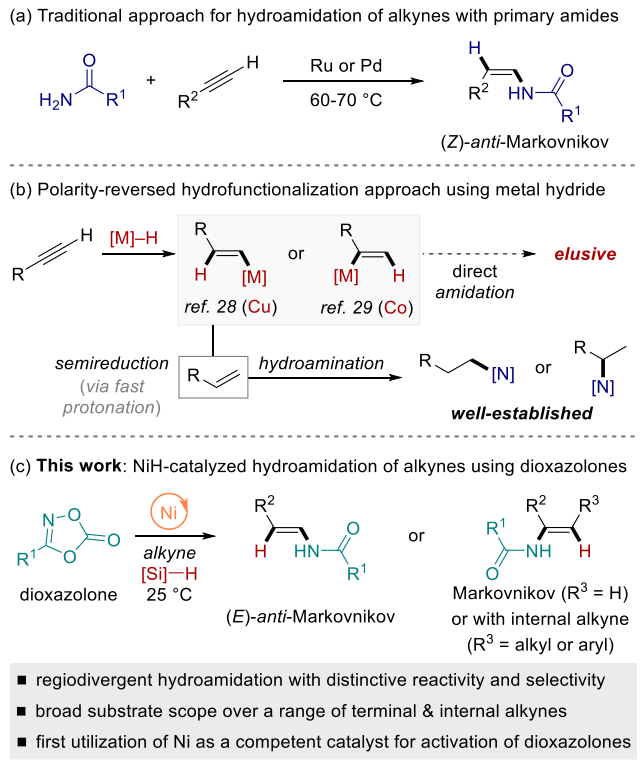
Scheme 1. Synthesis of Secondary Enamides Via Hydroamidation of Alkynes



pertinent for aliphatic alkynes that lack an electronic bias for both reactivity and selectivity, whereas the formal hydroamination of aromatic equivalents is known to some extent.[28] Furthermore, the hydro*amidation* counterpart remains elusive, regardless of the nature of alkynes (Scheme 1b). Alkynes have been more frequently employed as a precursor of alkene intermediates in cascade hydroamination reactions.[28−30] For instance, Buchwald[26,28] and Lu[29] reported Cu- and Co-catalyzed processes, respectively, in which alkylamines are afforded by a hydrometalation of alkynes, followed by protonation (semireduction to alkenes) and then (*anti*)-Markovnikov hydroamination (Scheme 1b). Although highly appealing on its own right, avoiding this facile semireduction pathway would be desirable for achieving the unexplored formal hydroamidation of alkynes to enamides.

Herein, we show that NiH catalysis provides a unique synthetic toolbox for a selective alkyne hydroamidation with 1,4,2-dioxazol-5-ones (dioxazolones) as an electrophilic amidating reagent, which allows the incorporation of a wide range of both terminal and internal alkynes with excellent functional group tolerance (Scheme 1c). Tailoring the catalytic system grants access to either (*E*)-selective *anti*-Markovnikov or Markovnikov addition via hydrometalation and subsequent amidation, thereby furnishing secondary enamides with contrasting selectivities to that obtained by the conventional alkyne hydroamidation with primary amides. This process represents the first utilization of Ni catalyst for the activation of dioxazolones by means of a metal-nitrenoid formation.

RESULTS AND DISCUSSION

Reaction Development. Dioxazolones are attractive *umpolung* surrogates of primary amides in synthesis,[31] as they can be readily prepared from the corresponding carboxylic acids. The Bolm group elegantly showed that these reagents serve as a robust acyl nitrene precursor in sulfur imidations,[32,33] and our group[34−39] as well as others[25,40−48] have since demonstrated their versatility in various types of transition-metal-catalyzed C−N-forming reactions. We visualized to achieve the desired formal hydroamidation by engaging our expertise in this chemistry with metal hydride catalysis (Figure 1). Upon the selective hydrometalation of an alkyne to

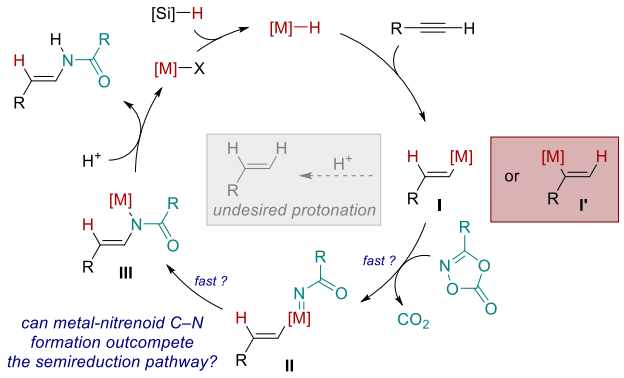


Figure 1. Working hypothesis for formal hydroamidation of alkynes via a merger of hydrometalation and *inner-sphere* metal-nitrenoid transfer.

the metal-alkenyl complex (**I** or **I′**), we envisioned that the incorporation of metal-nitrenoid intermediacy (**II**) would promote a low-energy C−N-forming pathway. This *inner-sphere* nitrenoid transfer would outcompete the typically favorable semireduction process, thus leading to the C−N coupled species **III** and finally an enamide by selective protonation. To successfully furnish this alkyne hydroamidation, the ability to attain a highly selective catalytic cycle would be essential, as there are also a number of other possible side pathways, such as the cyclopolymerization of alkynes[49] and decomposition of dioxazolones.[50]

With these challenges in mind, we started the optimization with but-3-yn-1-ylbenzene **2** as a model alkyne in reaction with methyl dioxazolone **1** (Table 1), given that the success with the challenging aliphatic substrate would deliver a more general strategy. We first tested the CuH[28] and CoH[29] systems that were previously developed for semireduction/hydroamination cascade reactions, as to examine whether the use of dioxazolones under these conditions could simply overturn the reaction to favor the enamide formation (entries 1 and 2). On the one hand, the Cu catalyst was completely ineffective to make a full recovery of the starting materials (entry 1). On the other hand, the alkyne hydrometalation was found to work to some extent with a Co catalyst, but the subsequent protonation was more favored to give a semireduced alkene **2-SP** as the major product (35%) along with a Markovnikov enamide **4** in 9% yield (entry 2). A modified procedure precluding H_2O was not beneficial either, indicating that the competing semireduction process would be a critical hurdle to achieving the desired reaction.

While this issue could probably be addressed by further optimization with the aforementioned catalytic systems, we turned our attention to NiH catalysis considering its rich repertoire for the hydrofunctionalization of alkynes.[51−57] In addition, the compatibility of Ni for a metal-imido formation has been well-recognized,[58−60] although that with dioxazolones remains unexplored. A series of bipyridine-based ligands (7.5

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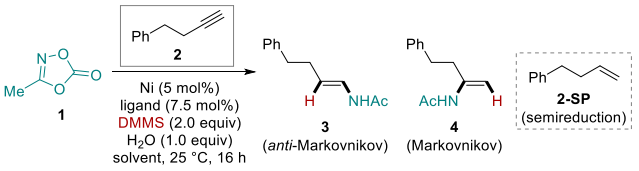
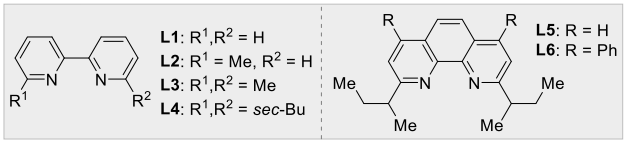
Table 1. Reaction Optimization



entry	1:2 (equiv)	catalysts	solvent	3:4[a] (%)
1	1.5:1.0	CuH (ref 28)	THF	nd
2[b]	1.5:1.0	CoH (ref 29)	THF	<1:9
3	2.0:1.0	$NiCl_2$·glyme, **L1**	acetone	nd
4	2.0:1.0	$NiCl_2$·glyme, **L2**	acetone	11:22
5	2.0:1.0	$NiCl_2$·glyme, **L3**	acetone	53:46
6	2.0:1.0	$NiCl_2$·glyme, **L4**	acetone	56:14
7[c]	1.5:1.0	$NiBr_2$·glyme, **L2**	DMA	8:34
8[c]	1.5:1.0	$NiBr_2$·glyme, **L2**	DMPU	10:78
9	1.5:1.0	$NiCl_2$·glyme, **L4**	DMA	98:<1
10	1.0:1.5	$NiCl_2$·glyme, **L4**	DMA	99:<1
11	1.0:1.1	$NiCl_2$·glyme, **L4**	DMA	95:<1
12	1.0:1.5	$NiCl_2$·glyme, **L5**	DMA	85:<1
13	1.0:1.5	$NiCl_2$·glyme, **L6**	DMA	85:<1
14[d]	1.0:1.5	$NiCl_2$·glyme, **L4**	DMA	89:<1
15[e]	1.0:1.5	$NiCl_2$·glyme, **L4**	DMA	7:<1

[a]Reactions performed on 0.5 mmol scale at 25 °C for 16 h; all reagents were measured under argon atmosphere; nd, not detected; DMMS, dimethoxymethylsilane; THF, tetrahydrofuran; DMA, *N,N*-dimethylacetamide; DMPU, *N,N′*-dimethylpropyleneurea. Yields determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b]Semireduced alkene **2-SP** was formed as the major product (35%). [c]8 h. [d]H_2O (2.0 equiv). [e]H_2O not added.



mol %) were first investigated for the reaction between dioxazolone **1** (2.0 equiv) and terminal alkyne **2** (1.0 equiv), in combination with $NiCl_2$·glyme (5.0 mol %), dimethoxymethylsilane (DMMS, 2.0 equiv), H_2O (1.0 equiv), and acetone solvent at 25 °C for 16 h (entries 3−6). Unsubstituted 2,2′-bipyridine ligand **L1** was found to be completely inefficient (entry 3), and an electronic variation of the ligand by introducing electron-donating or -withdrawing groups at the 4,4′- or 5,5′-positions (**L12**−**L15**, see Supporting Information, Tables S1 and S2) did not promote the desired reactivity either. In sharp contrast, the ligand modulation by installation of a methyl group at the 6-position (**L2**) intriguingly provoked the reactivity to give Markovnikov hydroamidation product **4** as the major isomer albeit in low yield and moderate selectivity (entry 4). This vivid improvement in catalytic activity presumably stems from the introduced steric hindrance, which may facilitate the dissociative formation of an active NiH monomeric species and also stabilize other involved three-coordinate Ni intermediates.[61−63] Similar steric effects have previously been observed in a number of Ni-catalyzed hydrofunctionalization reactions.[54,56,64−66]

It was found that the steric ligand also plays a crucial role for the regioselectivity, which would be governed during the initial hydrometalation step. While the methyl substituent in **L2** might not provide sufficient steric hindrance, thereby favoring the inherently preferred Markovnikov hydrometalation (**I′** in Figure 1), the steric increase could invert the selectivity by directing the metal insertion into the less-hindered terminal carbon (**I** in Figure 1).[28] Indeed, the steric variation of 2,2′-bipyridine ligand with dimethyl (**L3**) or di-*sec*-butyl (**L4**) substituents at the 6,6′-positions gave altered selectivities (entries 5 and 6). In particular, with ligand **L4**, the *anti*-Markovnikov hydroamidation product **3** was afforded as the major isomer in good regioselectivity (entry 6).

To obtain an improved set of orthogonal conditions for both selectivities from these preliminary results, we performed further optimization studies (entries 7−15, see also Supporting Information, Tables S1−S3). Delightfully, modified conditions utilizing dioxazolone **1** (1.5 equiv), alkyne **2** (1.0 equiv), $NiBr_2$·glyme (5 mol %), **L2** (7.5 mol %), and *N,N*-dimethylacetamide (DMA) or *N,N′*-dimethylpropyleneurea (DMPU) solvent afforded the enamide products in higher yields with good selectivities for the Markovnikov addition (**4**) (entries 7 and 8). On the other hand, the catalyst system consisting of $NiCl_2$·glyme (5 mol %) and **L4** (7.5 mol %) was superior for the opposite selectivity, furnishing (*E*)-*anti*-Markovnikov enamide **3** by a *syn* addition, in quantitative yield and excellent regioselectivity (entry 9). The reaction was found to be flexible in terms of the stoichiometries of starting materials, as similar results could also be obtained with reversed stoichiometries (entry 10) or with a reduced amount of alkyne **2** (1.1 equiv, entry 11). 1,10-Phenanthroline-based ligands with analogous substituents (**L5**−**L6**) were also effective but resulted in slightly lower yields (entries 12 and 13, see Figure 4 for the crystal structure of isolated Ni-**L6** complex). Notably, the formation of semireduction adducts was barely observed in most of these conditions, which is in stark contrast to the previously reported Cu or Co system that typically undergoes the protonation pathway in the presence of a protic source. In fact, H_2O was identified as an essential component for the present Ni strategy: the increased amount of H_2O had a negligible effect on the outcome (entry 14), whereas the reaction was inefficient in its absence (entry 15).

Mechanistic Investigation: Intermediacy of Ni-Nitrenoid. With H_2O identified as an inevitable element for the current transformation, we wondered how the typically favored protonation pathway could be effectively suppressed under the protic conditions. For this investigation, we first performed density functional theory (DFT) calculations based on a presupposed catalytic cycle involving Ni(I) as the active species (Figure 2), in consideration of our experimental evidence (vide infra) as well as the previously suggested mechanism for the NiH-catalyzed alkene hydroamination[67,68] and other hydrofunctionalization reactions utilizing silanes as a hydridic source.[69−74]

Taking the *anti*-Markovnikov hydroamidation of substrate **2** as a model reaction, the initial hydrometalation process with Ni(I)−H would lead to Ni-alkenyl complex **int1** (see Supporting Information, Figure S1 for energy profiles of the whole process). While the oxidative N−X insertion mechanism was mostly proposed for the subsequent activation of electrophilic nitrogen sources in the previously reported formal hydroamination procedures,[18] we hypothesized that the participation of Ni-nitrenoid might be liable for empowering the ability to intercept **int1** selectively. Coordination of the dioxazolone is a prerequisite for this pathway, which affords tetrahedral Ni complex **int2** with increase in energy by 6.7 kcal/mol. It was revealed that Ni is indeed highly viable for promoting the subsequent oxidative decarboxylation of

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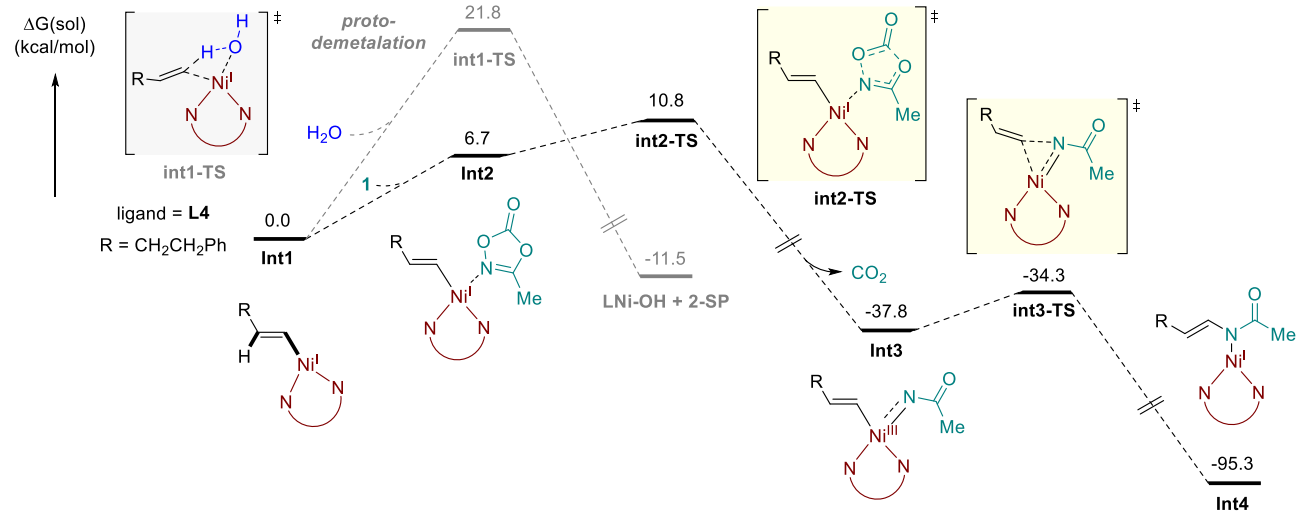
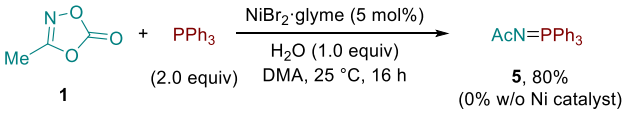


Figure 2. Potential energy surfaces for the formation of Ni-nitrenoid and subsequent C−N formation.

dioxazolone to furnish Ni-nitrenoid **int3**, traversing the transition state **int2-TS** that lies only 4.1 kcal/mol higher in energy than the Ni-dioxazolone adduct **int2**. On the other hand, protodemetalation of **int1** to semireduced alkene **2-SP** was found to be substantially less favorable with the activation barrier of 21.8 kcal/mol (**int1-TS**).

In addition, the C−N formation leading to the Ni-enamido complex **int4** via *inner-sphere* nitrenoid transfer of **int3** was energetically highly feasible, with the transition state **int3-TS** being located only at 3.5 kcal/mol higher in energy. This low activation barrier clarifies the observations that other known transformations of metal-nitrenoid are precluded in the current reaction system. Adversely, the direct experimental validation of such an intermediacy was proven highly challenging. Nevertheless, the reaction between dioxazolone **1** and PPh_3(2.0 equiv) in the presence of $NiBr_2$·glyme (5 mol %) gave an imidophosphorane **5** in 80% yield (Scheme 2), which

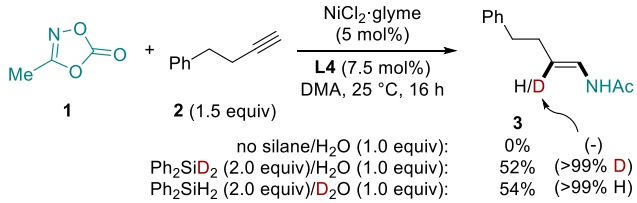
Scheme 2. Capture of Nitrenoid Intermediate by Formation of Imidophosphorane with PPh_3



is a well-known adduct derived from a nitrene transfer to phosphines.[43] Although this nitrenoid capture does not provide direct evidence for the existence of Ni-nitrenoid **int3**, it somehow proves the competence of Ni to activate dioxazolone by means of a metal-nitrenoid formation. In combination with the DFT calculations, this experimental result should therefore give a good indication that the proposed nitrenoid transfer would be viable in the current hydroamidation reaction.

Mechanistic Investigation: Role of H_2O. With the Ni-nitrenoid intermediate pinpointed as an essential mechanistic piece that enables surpassing the conventional semireduction pathway, in a process seemingly necessitating H_2O as an imperative additive, we next wished to scrutinize the role of H_2O. It is well-established that protic reagents, such as H_2O or alcohols, could often act as a formal hydride source in alternative types of Ni-catalyzed hydrofunctionalization reactions,[54,57,75−78] and therefore, we wondered whether our reaction also proceeds via this pathway. Although DMMS was identified to be the most efficient silane source for the current system (see Supporting Information, Table S1), control experiments were performed by alternatively using diphenylsilane (Ph_2SiH_2 and Ph_2SiD_2), due to the commercial availability of the deuterated reagent (Scheme 3). Once again, we took our

Scheme 3. Deuterium Experiments to Investigate the Feasibility of H_2O as a Formal Hydride Source



anti-Markovnikov-selective hydroamidation as a model reaction for this investigation, and it was soon found that H_2O is not likely the source of hydrogen that is inserted into the unsaturated carbon. The reaction was completely ineffective in the absence of a silane reagent, indicating that a hydridic source is certainly required for productive outcomes. Furthermore, deuterium experiments using either Ph_2SiD_2/H_2O or Ph_2SiH_2/D_2O also showed that the incorporation of D or H takes place exclusively from the silane source.

Further to the above scenario, the addition of protic reagents is often required in silane-based hydrofunctionalization reactions.[18] Their role in those processes is not entirely understood, but such a requisite was generally attributed to the need for a protonation source to enhance the product release that could bypass the slow transmetalation.[79] In our system, the transmetalation between Ni-enamido complex (**III** in Figure 1) and hydrosilane (DMMS) might also be kinetically or thermodynamically unfavorable otherwise, and H_2O would provide an alternative route to facilitate the product liberation and catalyst regeneration. Indeed, the reactions employing higher catalyst loadings (20−100 mol %) consistently showed catalyst turnover numbers of ∼1 (0.8−1.4) when H_2O was not added (Figure 3a, entries 1−4), indicating that there may exist a catalyst inhibition presumably by the hydroamidated species.

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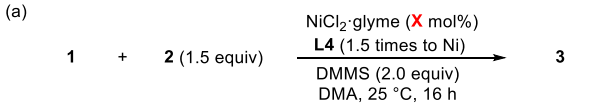
(a)



entry	Ni (X mol%)	3 (%)	turnover number
1	20	28	1.4
2	40	34	0.9
3	50	41	0.8
4	100	81	0.8
5	0.5 + H_2O (1.0 equiv)	85	170

(b)

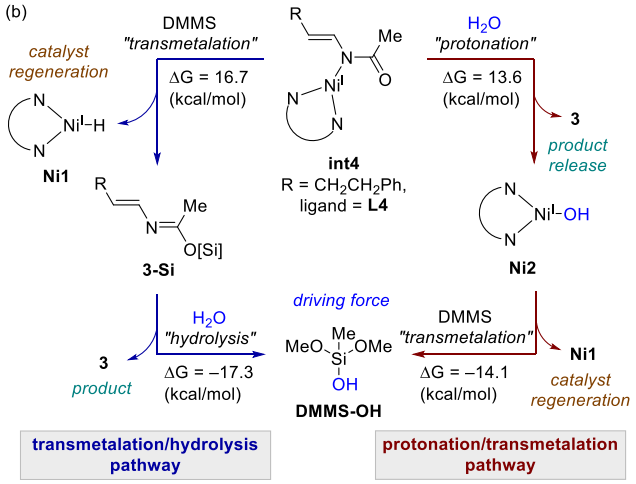


Figure 3. (a) Effects of H_2O additive on catalyst turnovers. (b) Thermodynamics of the product release and catalyst regeneration from **int4** via a transmetalation/hydrolysis or protonation/transmetalation pathway.

Consistent with this hypothesis, Ni-enamido **int4** could be observed by mass spectroscopy (MS) under the above H_2O-free conditions (see Supporting Information). These results are in stark contrast to the procedure with 1.0 equiv of H_2O additive, in which high catalyst turnover numbers of up to 170 could be achieved using 0.5 mol % of $NiCl_2$·glyme (Figure 3a, entry 5).

To understand this explicit effect of H_2O on the substantially enhanced catalyst turnovers, DFT calculations were performed. First, the transmetalation between Ni-enamido **int4** and hydrosilane (DMMS) leading to nickel hydride **Ni1** and silyl-enamidate **3-Si** was computed to be highly endergonic (ΔG = 16.7 kcal/mol, Figure 3b, left). This thermodynamic reluctance may indeed lead to the catalyst inhibition in the absence of any additional mechanistic handles, which conforms to the case of H_2O-free reactions giving poor catalyst turnovers. For the H_2O additive system, we alternatively considered a stepwise process in which the product is released by the protonation of **int4** with the catalyst being regenerated by a subsequent transmetalation (as depicted in Figure 1, X = OH). However, the initial protonation of **int4** was also found to be thermodynamically uphill (ΔG = 13.6 kcal/mol, Figure 3b, right), which indicates a strong affinity of the enamidate moiety to the Ni complex. This outcome suggested that the major role of H_2O for the improved catalyst turnovers is not as a proton source. Although the protonation might indeed provide a kinetically more favored pathway, we tentatively attribute the beneficial effects of H_2O mainly to the ease of thermodynamic disfavor by an irreversible Si–O bond formation. Both the hydrolysis of silyl-enamidate **3-Si** (Figure 3b, left) and transmetalation between nickel hydroxide **Ni2** and DMMS (Figure 3b, right) were energetically downhill by ΔG = −17.3 kcal/mol and ΔG = −14.1 kcal/mol, respectively, and we believe that this thermodynamic driving force would be responsible for the improved transmetalation in either case.

The assumption that the transmetalation of hydride is accelerated by H_2O was further evaluated by X-band electron paramagnetic resonance (EPR) spectroscopy, using a Ni(II) complex **6** prepared from $NiBr_2$·glyme and ligand **L6** (Figure 4). It is known that the Ni(I) species can be generated from

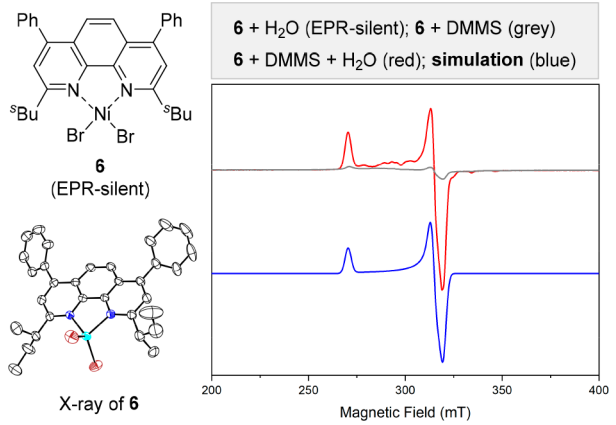


Figure 4. Experimental X-band EPR spectra of **6** + DMMS in DMA (gray) and **6** + DMMS + H_2O in DMA (red); measured at 100 K, and simulated EPR spectrum (blue); simulation parameters: g = [2.094 81, 2.126 59, 2.475 39].

Ni(II) precursors in combination with silanes,[67−74,80] likely via a transmetalation of hydride followed by a reductive elimination/comproportionation,[62] and we hypothesized that the access to such an active catalyst in our system should also be facilitated in a similar manner. As expected, the X-band EPR spectrum of Ni(II) complex **6** was EPR-silent and so was its mixture with H_2O. Interestingly, a mixture of **6** and DMMS gave only negligible signals (gray), indicating that the formation of a Ni(I) species might not be so efficient for this combination. On the other hand, an addition of H_2O to the mixture of **6** and DMMS gave significantly intensified signals (red) that show almost an identical shape to those observed for previously reported Ni(I) complexes.[63,81,82] Moreover, the corresponding mass of the anticipated Ni(I) hydride monomer was detected by MS (see Supporting Information). Although more comprehensive studies are required for the full mechanistic descriptions, the above EPR and MS analyses implicate that the presence of H_2O might indeed enhance the transmetalation between Ni and DMMS by Si–O bond formation as the driving force,[80] thereby leading to the effectual production of Ni(I) species. The formation of a Si–O bond may occur via a stepwise process as shown in Figure 3b or in a concerted manner during transmetalation.[83] Furthermore, it was also found that H_2O could be replaced by alcohols (e.g., MeOH or EtOH, see Supporting Information, Table S2), which are expected to play a similar role in the current transformation.

Reaction Scope. With a better understanding of the mechanistic aspects, we next investigated the reaction scope of the current NiH-catalyzed hydroamidation. We first explored the *anti*-Markovnikov selective process by utilizing optimized conditions consisting of $NiCl_2$·glyme (5 mol %) and **L4**

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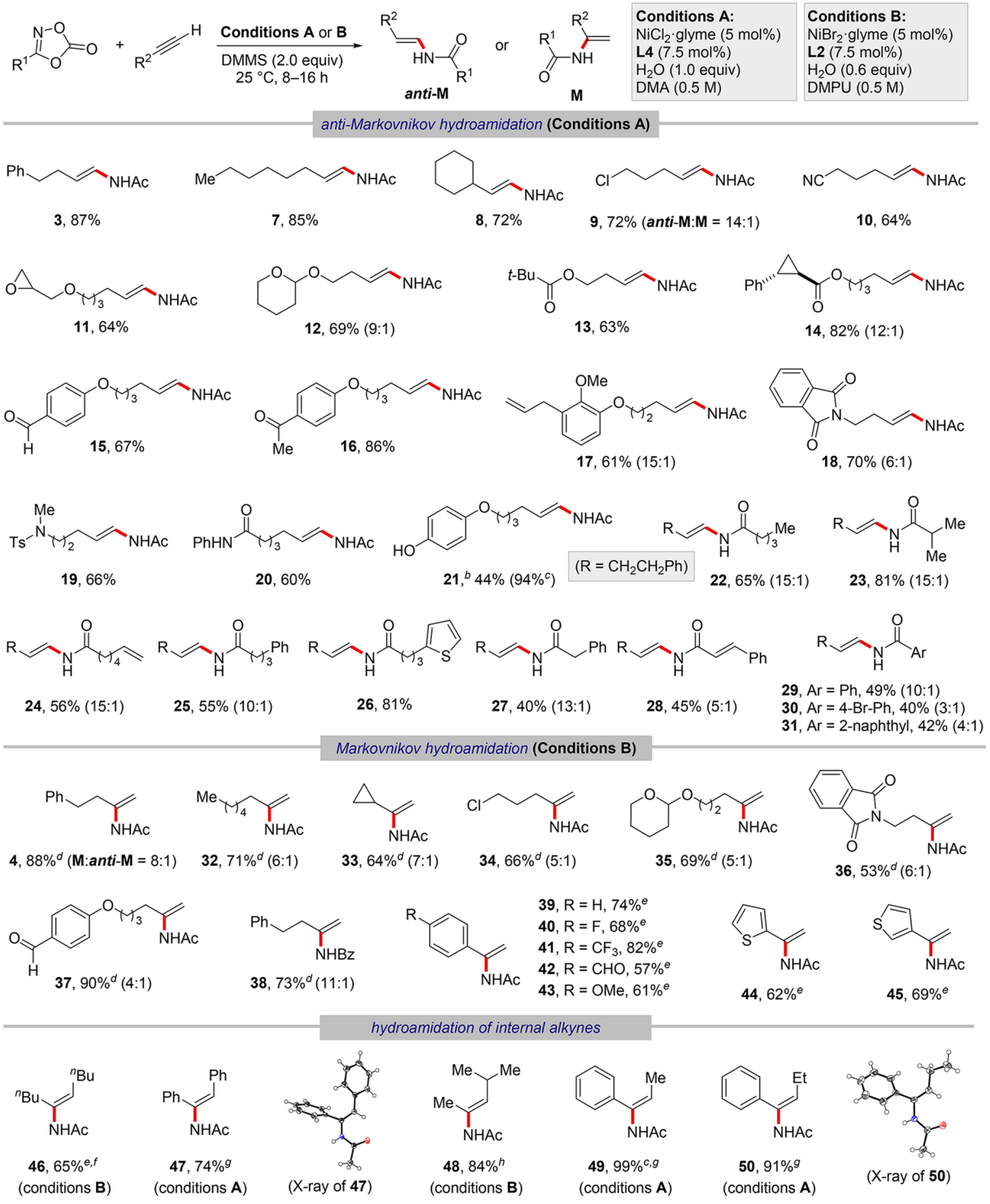
Scheme 4. Reaction Scope of the NiH-Catalyzed Hydroamidation of Alkynes with Dioxazolones[a]



[a]**Conditions A**: Dioxazolone (0.5 mmol), alkyne (1.5 equiv), $NiCl_2$·glyme (5 mol %), **L4** (7.5 mol %), DMMS (2.0 equiv), H_2O (1.0 equiv), and DMA (1.0 mL), 25 °C, 16 h. **Conditions B**: Alkyne (0.5 mmol), dioxazolone (1.5 equiv), $NiBr_2$·glyme (5 mol %), **L2** (7.5 mol %), DMMS (2.0 equiv), H_2O (0.6 equiv), and DMPU (1.0 mL), 25 °C, 8 h. Unless otherwise stated, greater than 20:1 regioselectivity was obtained, and isolated yields of the major isomers are reported. Regioisomeric ratios given in parentheses were determined by crude ^{1}H NMR. All reagents were measured under an argon atmosphere. [b]No H_2O additive. [c]NMR yields using 1,1,2,2-tetrachloroethane as an internal standard. [d]The corresponding Markovnikov enamides were found to be extremely unstable, giving inconsistent and diminished yields after purification on silica or alumina. Combined NMR yields of the two isomers are reported, with **M**/*anti*-**M** ratios given in parentheses. [e]Dioxazolone (1.0 equiv) and alkyne (1.5 equiv). [f]$NiCl_2$·glyme instead of $NiBr_2$·glyme. [g]**L3** instead of **L4**. [h]$NiBr_2$·glyme (10 mol %), **L2** (15 mol %) and alkyne (3 equiv).

(Scheme 4). A wide range of alkynes could be efficiently hydroamidated in high yields and excellent selectivities (**3**, **7**–**21**) with exceptional functional group tolerance: alkyl chloride (**9**), nitrile (**10**), epoxide (**11**), acetal (**12**), ester (**13**),

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cyclopropyl (**14**), aldehyde (**15**), ketone (**16**), alkene (**17**), amides (**18**−**20**), and hydroxyl group (**21**) could all be well-tolerated.

Some of the examined functional groups are noteworthy, as they would often suffer in other types of reactions for enamide synthesis. For example, carbonyl moieties, such as aldehydes (**15**) or ketones (**16**), might encounter issues in the classical condensation-type strategies whereby those functional groups are transformed in reaction with amides.[84] The tolerance of a secondary amide also deserves a special mention (**20**), as this kind of functional group within the alkyne motif could prompt an undesired intramolecular reaction if the traditional hydroamidation protocols were utilized.[85,86] The compatibility with the hydroxyl group is another interesting feature, albeit isolated in reduced yield due to the instability of enamide **21**. Despite the superior functional group tolerance, a few alkynes were found to be unsuited, including those containing propiolate, enyne, or unprotected aniline moiety (see Supporting Information, Figure S4).

A range of dioxazolones could also be employed, giving *anti*-Markovnikov enamides in similar efficiencies to the standard substrate. Dioxazolones with simple aliphatic functionality (**22** and **23**), alkene functionality (**24**), alkyl benzene (**25**), alkyl thiophene (**26**), and benzylic (**27**) groups were compatible, furnishing the corresponding (*E*)-enamides in good to excellent selectivities. Hydroamidation with styryl (**28**) and aryl (**29**−**31**) dioxazolone reactants were also feasible, however, giving somewhat diminished yields and lower regioselectivities. The attenuated efficiency in these cases is attributed to the relative instability of conjugated dioxazolones under the current Ni conditions, in which their decomposition may also disturb the selectivity-determining hydrometalation step by altering the active catalyst.

On the basis of our initial results that the regioselectivity of the current Ni-catalyzed alkyne hydroamidation can be switched by the choice of ligands (Table 1), we next explored the generality of the Markovnikov hydroamidation using $NiBr_2$·glyme (5 mol %) and **L2** (7.5 mol %) in DMPU. This part of the investigation was highly challenging, as α-alkyl-substituted terminal enamides expected from the Markovnikov selectivity are extremely unstable, which may affect the reaction efficiency and selectivity. Indeed, to our knowledge, there are no general methods to access such a class of enamides, thus explicating the lack of their presence in synthetic applications contrarily to their aromatic counterparts.[3]

Despite this challenge, we could take advantage of the mild conditions applied in our NiH catalytic system, affording the aliphatic enamides in good yields and decent selectivities (**4**, **32**−**38**). Alkyl (**4** and **32**), cyclopropyl (**33**), alkyl chloride (**34**), acetal (**35**), imide (**36**), and benzaldehyde (**37**) on the alkyne substrate were tolerated, as well as phenyl dioxazolone giving rise to *N*-benzoyl enamide **38** in good yield. However, the isolation of these enamide products was found to be difficult because of their instability. In addition, the regioselectivity was generally lower in comparison to those achieved for an *anti*-Markovnikov addition, which could be partly ascribed to some decomposition of the Markovnikov products. Nonetheless, the obtained efficiency and selectivity were gratifying in our case, especially considering the aforementioned issues with α-alkyl-substituted terminal enamides. The current strategy for Markovnikov selectivity is, thus, expected to find useful synthetic applications, for instance, by utilizing it in sequential derivatizations (vide infra).

In contrast, (hetero)aromatic derivatives were found to be relatively more stable than the aforementioned aliphatic terminal enamides. Significantly, (hetero)aromatic terminal alkynes favored a Markonikov hydroamidation irrespective of the ligand used, but the complete selectivities were obtained with the use of a less bulky ligand **L2** (**39**−**45**). Phenylacetylene (**39**) and analogous substrates installed with fluoro (**40**), trifluoromethyl (**41**), aldehyde (**42**), and methoxy (**43**) groups were effectively transformed to the Markovnikov enamide products in good yields and complete regioselectivity. Likewise, 2- and 3-ethynylthiophenes were viable substrates to afford enamides **44** and **45**, respectively.

The reaction was not limited to terminal alkynes but could also be applied to internal substrates to furnish α,β-disubstituted (*E*)-enamides by a *syn* addition (**46**−**50**). Symmetric alkynes bearing alkyl (**46**) or phenyl (**47**) substituents could be successfully converted to the corresponding enamides with (*E*)-selectivity. For unsymmetrical internal alkynes, the regioselectivity could be controlled by either sterics (**48**) or electronics (**49** and **50**), with the amide functionality being inserted into the sterically less-demanding site or that bearing aromatic rings. With these promising results, it is worthwhile mentioning that the obtained (*E*)-configured α,β-disubstituted secondary enamides are challenging to synthesize in a selective fashion by other means,[87,88] as they are thermodynamically less stable than the (*Z*)-counterparts. Therefore, the ability to incorporate internal alkynes to access these challenging enamides is one of the appealing features of our protocol.

Synthetic Utility. The practicality of the current NiH-catalyzed strategy was next demonstrated by a gram-scale hydroamidation of alkyne **2**, which furnished enamide **3** in good yield (Scheme 5a). With this practical procedure in hand, the synthetic utility was subsequently explored by derivatizations of enamide **3**. The direct alkyne functionalization by means of hydroamidation certainly offers a synthetic diversity in comparison to the semireduction sequential processes, as enamides represent common access points for the synthesis of value-added nitrogen-containing compounds.[3] In particular, secondary enamides have been utilized as a versatile intermediate in various organic transformations. For example, the acid-catalyzed reaction with indole nucleophile and *rac*-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **PA1** as a catalyst (5 mol %) gave the arylation product **51** in 86% yield (Scheme 5a). The functionalization of the β-carbon of enamides by a treatment with a suitable electrophile is also a well-known strategy, and indeed, the Cu-catalyzed oxy-trifluoromethylation using Togni's reagent (CF_3^+)[89] and MeOH, followed by a reduction with hydrosilane, successfully afforded the β-trifluoromethylated product **52**. The acid-catalyzed Povarov reaction of enamide **3** was also investigated with a range of in situ generated imines, which resulted in the tetrahydroquinoline products as single diastereomers (**53**−**55**).[90]

We next examined the hydrogenation of α-alkyl-substituted terminal enamides obtained from the Markovnikov hydroamidation of aliphatic alkynes. We considered this worthy of investigation given that such a class of enamides is underpresented in the related chemistry.[3] As aforementioned, this is ascribed to the lack of methods for their syntheses, presumably due to the issues encountered by the instability. Therefore, we conceived to prove the viability of our NiH approach for the

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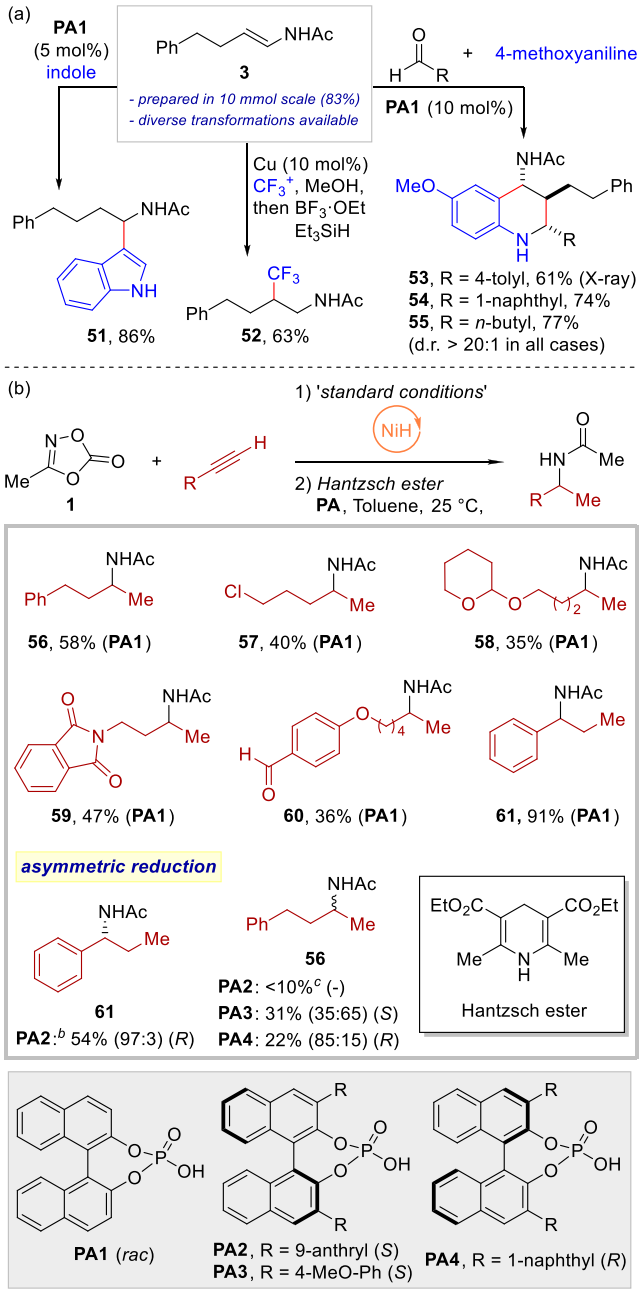
Scheme 5. Synthetic Utility[a]



[a]Isolated yields are reported; d.r., diastereomeric ratio; e.r., enantiomeric ratio (see Supporting Information for details of the reaction conditions). [b]The hydrogenation step was performed at 50 °C. [c]NMR yields using dibromomethane as an internal standard.

incorporation in a sequential reduction transformation, without the isolation of the unstable species.

While transition-metal-based procedures employing hydrogen gas have been most broadly investigated for the hydrogenation of aromatic- or sterically encumbered enamides,[3] we envisioned that an organocatalysis offering milder conditions would be more suited for the subtle aliphatic enamides.[91] Pleasingly, the use of a Hantzsch ester as a reducing reagent and phosphoric acid as a catalyst was effective for achieving the desired sequential transformation (Scheme 5b). Aliphatic enamides were first obtained using our standard procedure and, after a simple workup, were subsequently subjected to the reduction conditions using hydrogen phosphate **PA1** as a catalyst (10 mol %). A range of aliphatic terminal alkynes could be efficiently converted to the corresponding alkylamides albeit in moderate yields over two steps (**56**–**60**). The successful result with an aromatic-based internal alkyne further demonstrated the generality of this sequential transformation (**61**).

Furthermore, we briefly investigated an asymmetric version by using chiral phosphoric acids possessing bulky substituents. The conditions previously established for aryl-substituted enamides[91] were effectively combined with our strategy to convert 1-phenyl-1-propyne to enamide (*R*)-**61** in good yield and excellent enantioselectivity (54%, e.r. = 97:3), by using an (*S*)-phosphoric acid **PA2** (3.5 mol %, 50 °C). However, the standard aliphatic alkyne **2** was found to be ineffective under the same conditions; hence, slightly modified procedures with **PA3** or **PA4** (2.0 mol %, 25 °C) were consequently employed. Notably, differing enantioselectivities were obtained in comparison to the aromatic substrate: the use of an (*S*)-phosphoric acid (**PA3**) resulted in (*S*)-**56** as the major enantiomer (31%, e.r. = 35:65), whereas the opposite atropisomeric catalyst (**PA4**) furnished (*R*)-**56** in good enantioselectivity (22%, e.r. = 85:15). Although the reaction efficiency and stereoselectivity of this aliphatic example are not at satisfactory levels at this stage, the proven viability should stimulate further developments for tandem asymmetric transformations of prochiral alkynes by utilizing the current system, especially considering the importance and challenges in constructing chiral alkylamides of such type.

CONCLUSION

We have developed a NiH-catalyzed strategy for a formal hydroamidation of alkynes, which surpasses the highly susceptible semireduction pathway through the involvement of low-energy *inner-sphere* nitrenoid transfer. A ligand-controlled hydrometalation granted access to both (*E*)-*anti*-Markovnikov and Markovnikov hydroamidations in good to excellent regioselectivities, with a wide range of functional groups well-tolerated under mild and convenient conditions. The addition of H_2O was found to be essential for achieving high catalyst turnovers, and the combined experimental and theoretical investigations suggested that H_2O is engaged in facilitating the transmetalation step. With the improved catalytic efficiency, not only aliphatic- and aromatic-terminal alkynes but also internal alkynes could be employed. The virtue of the present synthetic approach was demonstrated by a number of postmodifications, which led to the construction of synthetically valuable alkylamide moieties, even in an asymmetric fashion. This development offers a complementary reactivity and selectivity that allows the synthesis of underexplored classes of enamides and, thus, should find broad synthetic applications. Moreover, the unique mechanistic platform acquired by the Ni-nitrenoid intermediacy should engender new methodology developments for other types of C–N bond-forming processes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01138.

Experimental procedures, characterization of new compounds, information about computational studies,

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X-ray crystallographic data for compounds **6**, **47**, **50**, and **53** (PDF)

Accession Codes

CCDC 2059010−2059012 and 2071245 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written by S.S. and S.C., and all authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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