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Nickel-Catalyzed 1,2-Carboamination of Alkenyl Alcohols

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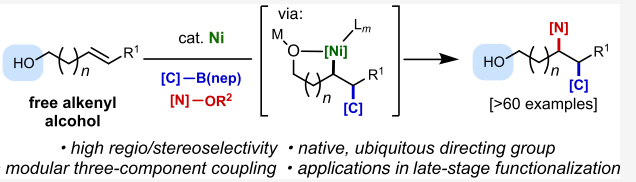
ABSTRACT: An alcohol-directed, nickel-catalyzed three-component umpolung carboamination of unactivated alkenes with aryl/alkenylboronic esters and electrophilic aminating reagents is reported. This transformation is enabled by specifically tailored *O*-(2,6-dimethoxybenzoyl)hydroxylamine electrophiles that suppress competitive processes, including undesired β-hydride elimination and transesterification between the alcohol substrate and electrophile. The reaction delivers the desired 1,2-carboaminated products with generally high regio- and *syn*-diastereoselectivity and exhibits a broad scope of coupling partners and alkenes, including complex natural products. Various mechanistic experiments and analysis of the stereochemical outcome with a cyclic alkene substrate, as confirmed by X-ray crystallographic analysis, support alcohol-directed *syn*-insertion of an organonickel(I) species.



INTRODUCTION

Substituted aliphatic amines are substructures with essential biological importance in medicines, agrochemicals, and natural products.[1] Thus, the invention of methods to prepare such prized motifs from readily available starting materials in a manner that is rapid, selective, and modular is a captivating pursuit. In this context, alkene carboamination, in which a nitrogen substituent and a carbon substituent are added across a C═C bond, has been actively pursued as a strategy with great promise in organic synthesis (Figure 1A). Early pioneering examples of alkene carboamination centered on various two-component strategies. This includes use of carbon/nitrogen functional groups tethered to the alkene of interest. For example, Wolfe and others have developed carboamination reactions using intramolecular azacyclization of nitrogen-tethered alkenes under palladium, copper, or nickel catalysis, which enables facile preparation of various azaheterocycles.[2−4] Additionally, several groups independently demonstrated heteroannulations in which alkenes are coupled with bifunctional coupling partners using different transition metal catalysts.[5] Moreover, use of ambiphilic reagents possessing activatable heteroatom−heteroatom bonds has also enabled carboamination of electronically activated alkenes or 1,3-dienes.[6]

Despite these remarkable achievements, two-component alkene carboamination possesses inherent limitations in terms of modularity and structural diversity since two of the three putative reaction components must be colocalized on the same molecule. Moreover, existing methods generally require use of nonbasic amine coupling partners that are less likely to cause catalyst poisoning, such as sulfonamides, amides, carbamates, and anilines, which limits direct access to valuable *aliphatic* amine products. To address these shortcomings, we and others have endeavored to develop three-component carboamination reactions using various mechanistic paradigms. Such transformations have historically been fraught with issues, including competitive two-component coupling, difficulty in controlling regioselectivity, and formation of undesired side products that arise from unstable alkylmetal or alkyl radical intermediates. Thus, three-component carboamination has been limited to conjugated alkenes,[7,8] strained cyclopropenes,[9] or alkenes bearing directing auxiliary groups.[10−12] For instance, in 2019 our lab developed a nickel-catalyzed umpolung 1,2-carboamination that unites alkenes bearing the strongly coordinating 8-aminoquinoline (AQ) directing auxiliary with electrophilic aminating reagents and alkylzinc nucleophiles (Figure 1B). Although this system offered high regio- and stereoselectivity, the method has an intrinsic limitation in requiring two additional steps for auxiliary installation and removal. In addition, the use of air- and moisture-sensitive alkylzinc reagents, which are less readily available compared with bench-stable alternatives, also diminishes the synthetic flexibility and practical utility of the method. Moreover, C(sp^2) nucleophiles showed poor reactivity under these conditions (a single example, 27% yield), and thus the three-component carboamination of unactivated alkenes with C(sp^2) nucleophiles remains an unresolved problem.

To invent a next-generation carboamination system that overcomes these obstacles, we sought to employ common, readily available alkene starting materials containing only native chemical functionality in conjunction with bench-stable

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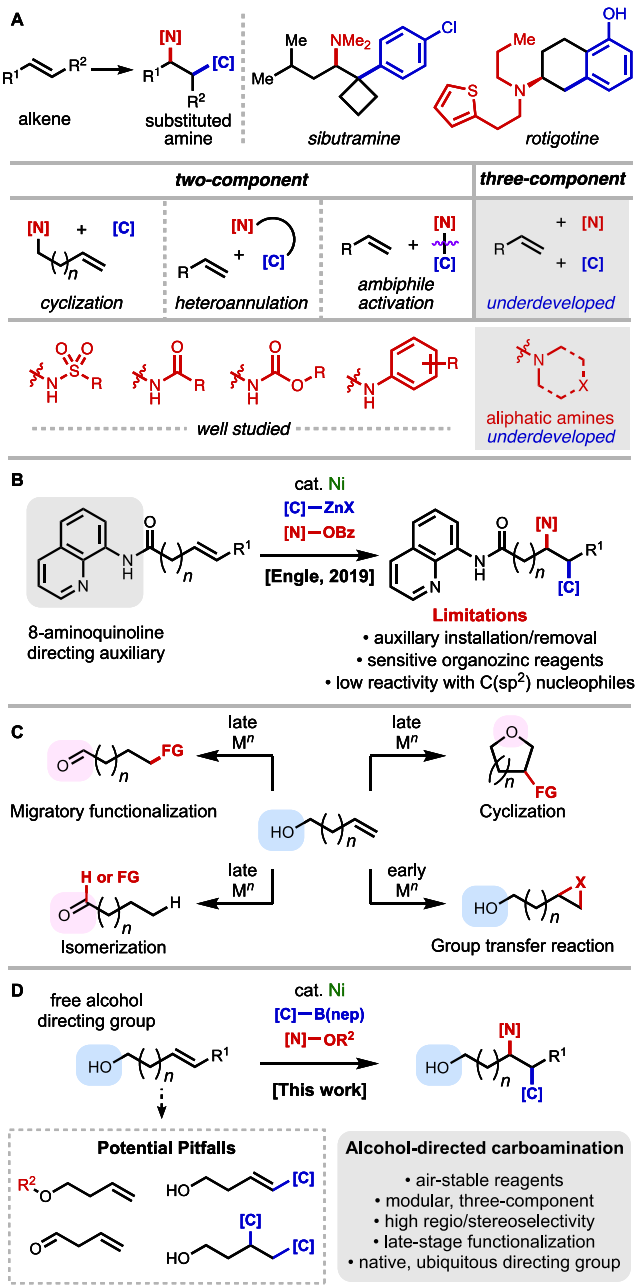

Figure 1. Summary of previous and current work.

coupling partners. Specifically, we were attracted to alkenyl alcohol substrates because these bear the most common, readily available, and synthetically versatile functional group, the hydroxyl group. Employing a hydroxyl group as a directing group in late-transition metal catalysis for reactions beyond hydrogenation is challenging for a number of interrelated reasons (Figure 1C). First, coordination of the hydroxyl group with late-transition metals is relatively weak, meaning the resultant alkylmetal intermediate may not form a rigid metallacycle and may instead possess dynamic coordination chemistry and conformational flexibility. This in turn opens the possibility for β-H elimination resulting in chain-walking processes, where the alcohol can serve as a redox terminating group.[13,14] In addition, the innate nucleophilicity of alcohols (or metal alkoxides) can result in direct nucleophilic attack on the electrophilic coupling partners or cyclization onto the pendant alkene, interfering with the desired transformation.[15] Moreover, many late transition metals are known to directly oxidize alcohols to the corresponding aldehydes or ketones,[16] which can then undergo functionalization at the carbonyl group.[17] For these reasons, seemingly straightforward extension of late-transition-metal-catalyzed alkene functionalization reactions directed by protected amines or carbonyl groups[18] to alkenyl alcohol substrates is generally not possible without introduction of a protecting group or directing auxiliary.[19,20] Indeed, free-alcohol-directed alkene functionalizations have generally been limited to oxophilic early transition metal catalysts, with the most notable success being in epoxidation.[21] Using stoichiometric titanium along with a catalytic chiral ligand, Burns and co-workers have recently achieved three-component dihalogenations and haloazidation reactions of allylic alcohols.[22] To the best of our knowledge, alcohol-directed metal-*catalyzed* three-component alkene difunctionalization has not yet been demonstrated. Herein, we describe the catalytic three-component coupling of alkenyl alcohols, various aliphatic amine electrophiles, and organoboronic acids enabled by the combined use of nickel catalysis and fine-tuned nitrogen activating groups (Figure 1D).

RESULTS AND DISCUSSION

Optimization. We initiated our study with 3-buten-1-ol (**1a**) as the model substrate, *O*-benzoyl hydroxylmorpholine (**2a**) as an electrophilic aminating reagent,[11,23] and $Ni(cod)_2$ as the precatalyst (Table 1). In place of air- and moisture-sensitive organozinc nucleophiles, we opted for PhB(nep) as the standard bench-stable nucleophilic coupling partner. After initial exploratory screening, we were able to observe the desired three-component conjunctive cross-coupling product in 17% yield with *t*-BuOH as solvent and KO*t*-Bu as base. In addition to the desired product, we detected three major side products: (1) styrenyl alcohol product **4**, likely arising from an oxidative Heck pathway, (2) benzoyl ester product **5** from transesterification between the starting material **1a** and the amine electrophile **2a**, and (3) small amounts (5−10% by ^{1}H NMR) of the hydroarylation product of **1a**, 4-phenylbutanol. We envisioned that the yield of the desired 1,2-arylamination product could be improved by suppressing the formation of these side products through the use of sterically and electronically tuned N−O reagents. Introducing a bulky *O*-pivaloyl group on the hydoxylamine (**2b**) successfully inhibited transesterification with the alcohol starting material and increased the desired product yields, although the Heck byproduct **4** was still present. Furthermore, we observed a general trend that more electron-rich benzoyl groups on the electrophile delivered higher yields of desired product (**2c**−**2e**). On the basis of these two observations, we expected that electron-donating groups at the *ortho*-positions of the electrophile would enhance the yield of the desired product by suppressing undesired side product formation both sterically and electronically. Interestingly, use of a sterically bulkier mesityl group on the electrophile (**2g**) gave higher yields of desired product along with only trace amounts of both side products. In addition, more electron-donating substituents on the benzoyl electrophiles (**2h** and **2i**) further increased the product yield. A control experiment with **2f**, which has 2,6-disubstitution but possesses electron-withdrawing fluorine substituents, revealed the importance of both the substitution pattern and electronic properties of the benzoyl activating group. The 2,6-dimethoxybenzoyl activating group (as in **2h**)

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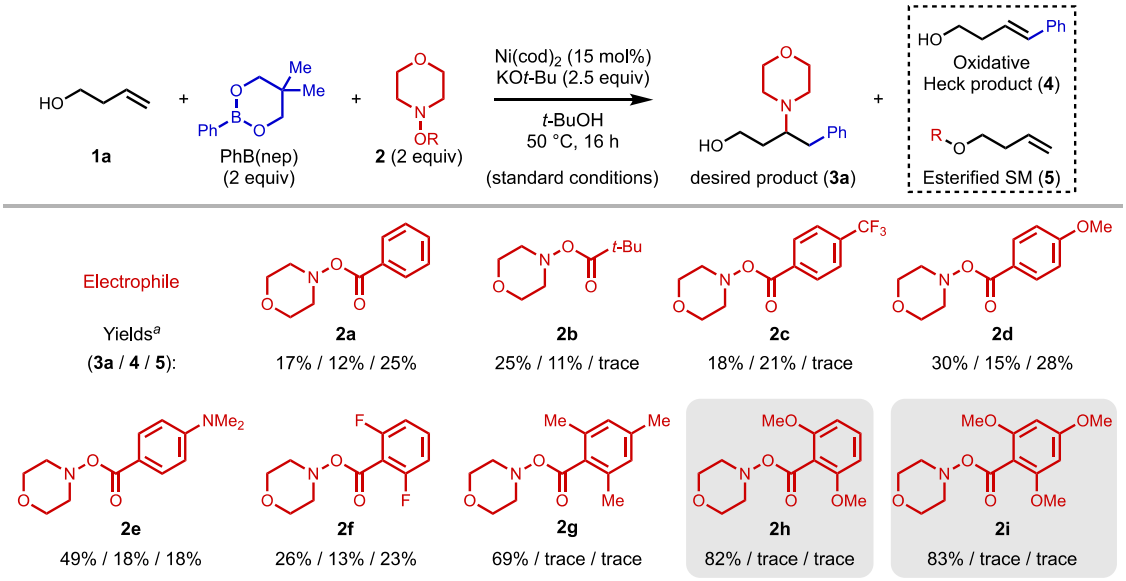
Table 1. Optimization of Reactions



entry	variation from standard conditions (with **2h**)	yield (**3a**)[a]	yield (**4** + **5**)[a]
1	$PhB(OH)_2$ instead of PhB(nep)	43% [66%][b]	trace
2	PhB(pin) instead of PhB(nep)	33%	trace
3	rt/70 °C instead of 50 °C	60%, 72%	trace
4	5 mol %/25 mol % $Ni(cod)_2$ instead of 15 mol %	72%, 71%	trace
5	KOH instead of KO*t*-Bu	nd	trace
6	LiO*t*-Bu/NaO*t*-Bu instead of KO*t*-Bu	70%, 82%	trace
7	2 equiv of KO*t*-Bu instead of 2.5 equiv of KO*t*-Bu	67%	trace
8	$NiBr_2$·glyme (without glovebox) instead of $Ni(cod)_2$	79%	trace

[a]Percentages represent ^{1}H NMR yields using 1,3,5-trimethoxybenzene as internal standard. See Supporting Information for details regarding additional optimization tables. [b]The yield in brackets was obtained using 2 equiv of NaO*t*-Bu instead of 2.5 equiv of KO*t*-Bu.

was ultimately selected for further study due to its comparative ease of installation. Notably, the Buchwald group has previously documented the benefits of using electron-rich benzoyl activating groups for accelerating L_nCuH regeneration in copper-catalyzed umpolung alkene hydroamination.[24] Our data expand upon these earlier findings to encompass alternative catalytic manifolds, demonstrating that precisely tailored activating groups on the electrophile can not only increase product yield but also allow for control of pathway selectivity (i.e., product distribution) in a complex multicomponent nickel-catalyzed reaction system (*vide infra*).

The reaction was further evaluated under different conditions. Corresponding $PhB(OH)_2$ and PhB(pin) nucleophiles also delivered the desired product, albeit in lower yields than standard PhB(nep) (entries 1 and 2). Lower (room temperature) or higher temperature (70 °C) did not improve the product yield (entry 3).

We found that lower catalyst loading (5 mol %) also gave an excellent yield, but higher catalyst loading (25 mol %) did not further increase the yield (entry 4). In addition, the weaker base, potassium hydroxide, was found to be incompatible, while *tert*-butoxide salts with varying countercations were nearly equally effective (entries 5 and 6). Importantly, the bench-stable precatalyst, $NiBr_2$·glyme, could be used in place of $Ni(cod)_2$, allowing the reaction to be performed without an inert atmosphere glovebox with only slightly diminished yield (entry 8, see Supporting Information for additional details).

Nucleophile and Electrophile Scope. Having identified the optimal reaction conditions, we next examined the scope of nucleophilic coupling partners (Scheme 1). Arylboronic ester nucleophiles bearing electron-donating substituents in the *para* position reacted in excellent to good yields (**3b**−**3d**). In addition, fluoro-, chloro, and protected amino substituents were compatible under the reaction conditions (**3e**−**3g**). On the other hand, arylboronic ester nucleophiles bearing electron-withdrawing groups in the *para* position resulted in lower yields, presumably due to less favorable migratory insertion of the arylnickel species in these cases (**3h**−**3j**). Several *ortho*- and *meta*-substituted aryl nucleophiles also gave the desired product in moderate yields (**3k**−**3p**). Gratifyingly, alkenylboronic ester nucleophiles worked well to yield homologated alkenyl alcohol products with only slightly lower yields than those of aryl nucleophiles (**3q**−**3u**). On the other hand, alkyl-, highly electron-deficient aryl-, and heterocycle-containing B(nep) coupling partners were ineffective under the reaction conditions.

We next explored the nitrogen electrophile scope. Pharmaceutically relevant six-membered azaheterocycles, including piperidine, *N*-Boc-protected piperazine, and thiomorpholine-derived electrophiles, gave excellent to moderate yields (**3v**−**3x**). Additionally, various substituted cyclic amines also delivered the corresponding products in excellent to synthetically viable yields (**3y**−**3ac**). Notably, the piperidine in product **3z** could be used as a primary amine surrogate through simple deprotection, and a commercial drug (paroxetine) derived electrophile was also compatible with the reaction conditions (**3ac**). Moreover, five- and seven-membered cyclic amine electrophiles were also successful, although with diminished

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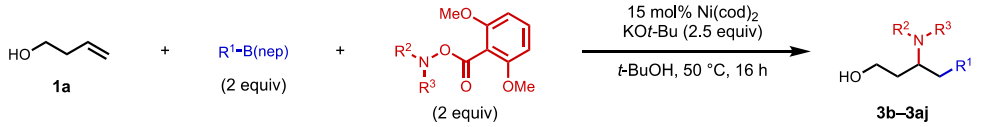
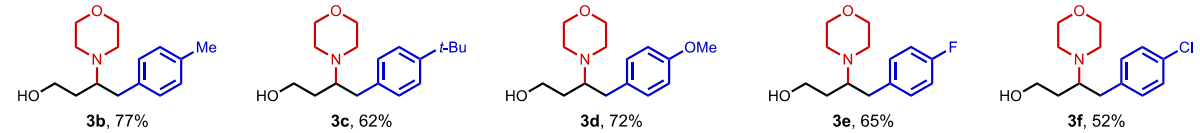
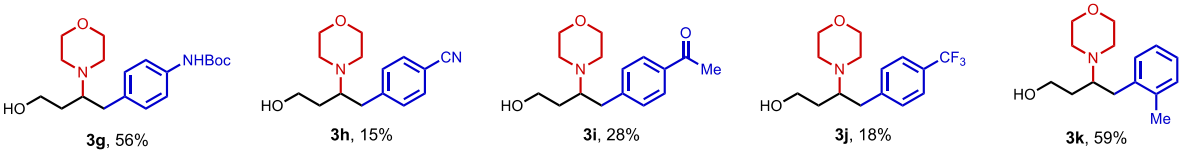
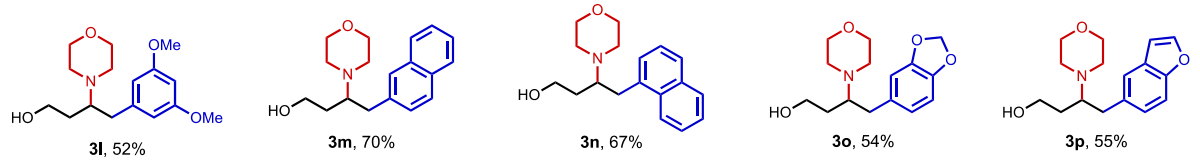
Scheme 1. Nucleophile and Electrophile Scope[b]

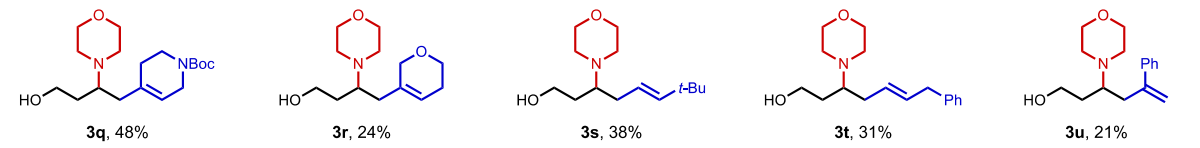


Nucleophile Scope

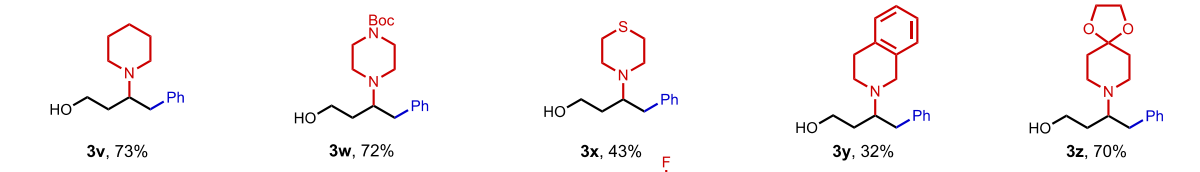


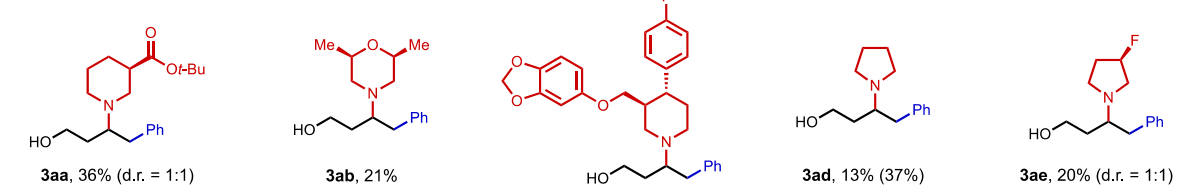


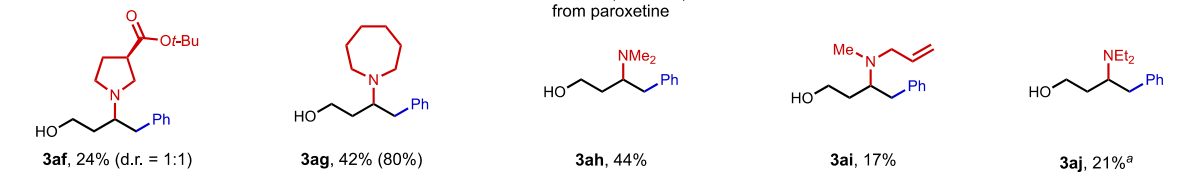




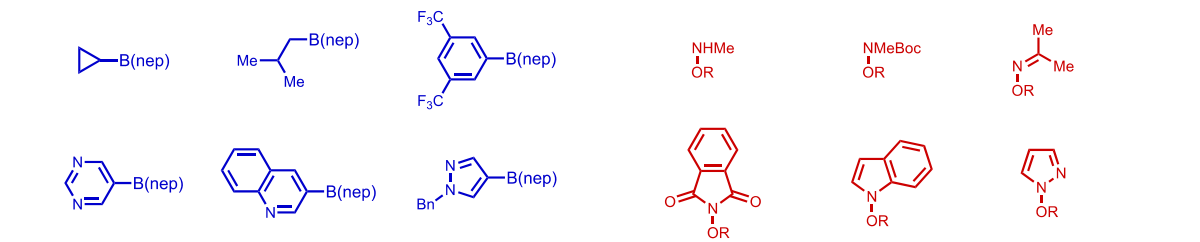
Electrophile Scope







Limitations (<10% yield)



[a]*N,N*-Diethyl-*O*-(2,4,6-trimethylbenzoyl)hydroxylamine was used as the electrophile. [b]Reaction conditions: **1a** (0.1 mmol), aryl/alkenylB(nep) (0.2 mmol), N−O electrophile (0.2 mmol), KO*t*-Bu (0.25 mmol), $Ni(cod)_2$ (0.015 mmol), *t*-BuOH (1 mL), 50 °C, 16 h. Percentages represent isolated yields. Values in parentheses are ^{1}H NMR yields using CH_2Br_2 as internal standard.

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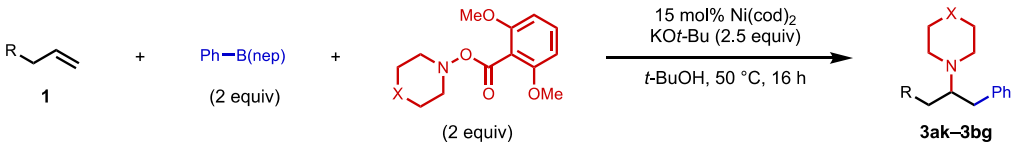
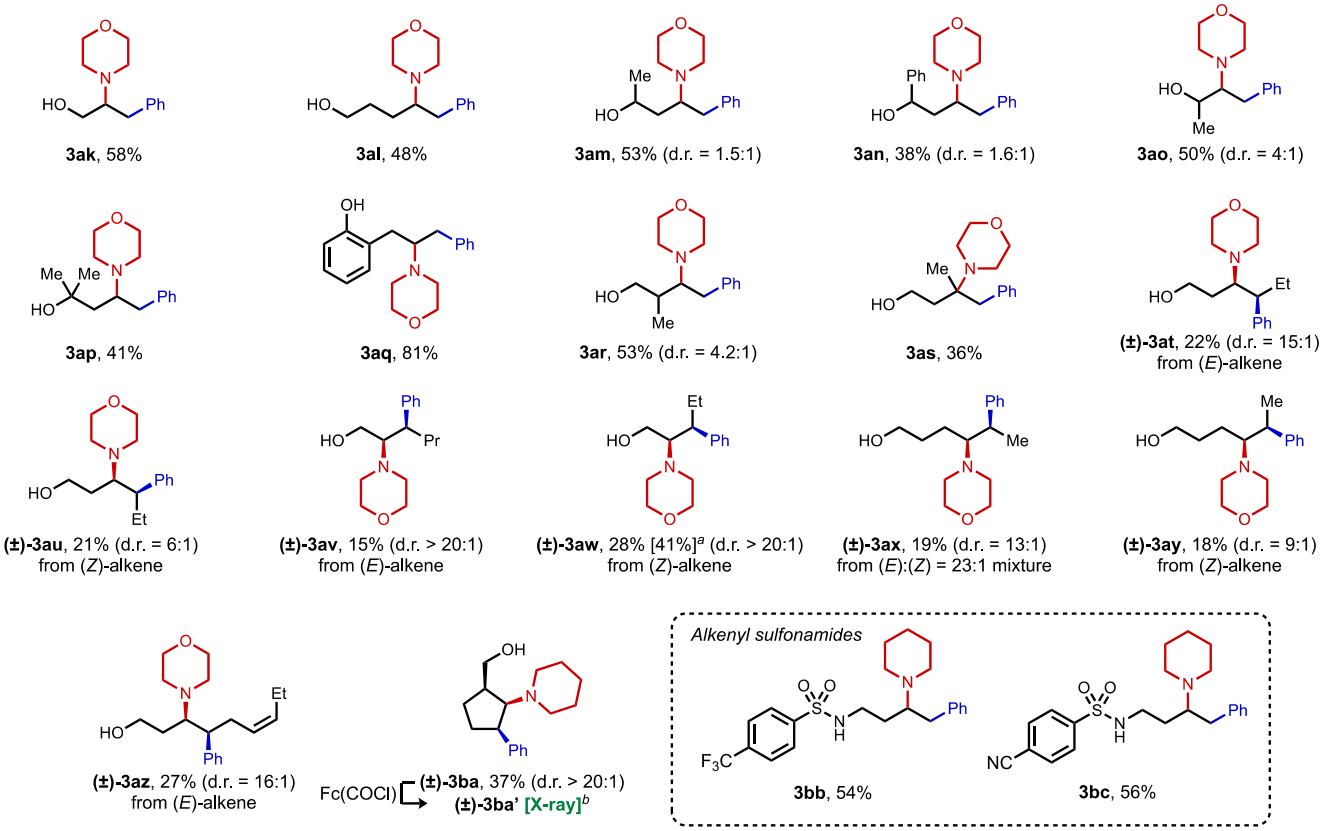
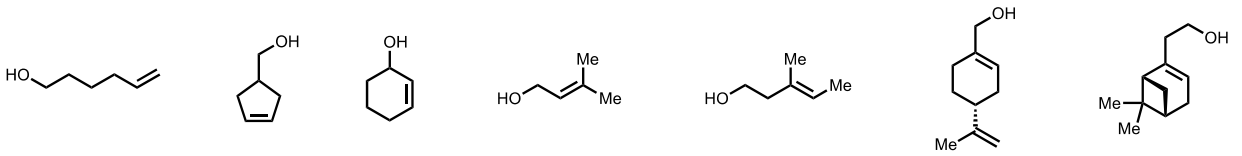
Scheme 2. Alkene Scope[c]



Alkene Scope



Limitations (<10% yield)



[a]The value in brackets corresponds to ^{1}H NMR yield from an experiment in which a second batch of the reagents and catalyst were added after 16 h. [b]Fc = ferrocenyl; see Supporting Information for X-ray crystallography data. [c]Reaction conditions: **1** (0.1 mmol), PhB(nep) (0.2 mmol), N−O electrophile (0.2 mmol), KO*t*-Bu (0.25 mmol), Ni(cod)$_2$ (0.015 mmol), *t*-BuOH (1 mL), 50 °C, 16 h. Percentages represent isolated yields.

yields (**3ad**−**3ag**). We also investigated the acyclic amine scope and observed attenuated reactivity, especially for bulky acyclic amine electrophiles. Indeed, using dimethylamine as electrophile gave a moderate yield, but slightly bulkier methylallylamine and diethylamine electrophiles showed low yields (**3ah**−**3aj**). In addition, a secondary amine, *N*-Boc-protected amine, imines, electron-deficient phthalimide, and other heterocyclic electrophiles did not afford desired product under the reaction conditions.

Alkene Scope. Next, we examined the scope of alkenyl alcohols. The reaction performed well with allyl and bis-homoallyl alcohols (**3ak** and **3al**), demonstrating tolerance for varying chain lengths. Additionally, secondary alcohols (**3am**−**3ao**), tertiary alcohols (**3ap**), and phenol (**3aq**) were viable native directing groups that deliver the desired products in moderate to excellent yields. We then investigated disubstituted alkene substrates, which pose a formidable challenge compared to terminal alkenes due to the sterically encumbered nature of the migratory insertion step. A representative 1,1-disubstituted alkene was compatible under the reaction conditions (**3as**), and various 1,2-disubstituted alkenes also delivered the corresponding products with excellent diastereoselectivity, albeit in low yields (**3at**−**3ba**). The relative all-*cis*-stereochemistry of **3ba** was confirmed by single-crystal X-ray diffraction, establishing unambiguously that the reaction is *syn*-stereoselective and alcohol-directed. In addition to alkenyl alcohol substrates, we demonstrated that our reaction is compatible with sulfonamide directing groups,[18i] which can be further deprotected and diversified to give interesting diamine structures (**3bb** and **3bc**). On the other hand, 5-hexen-1-ol,

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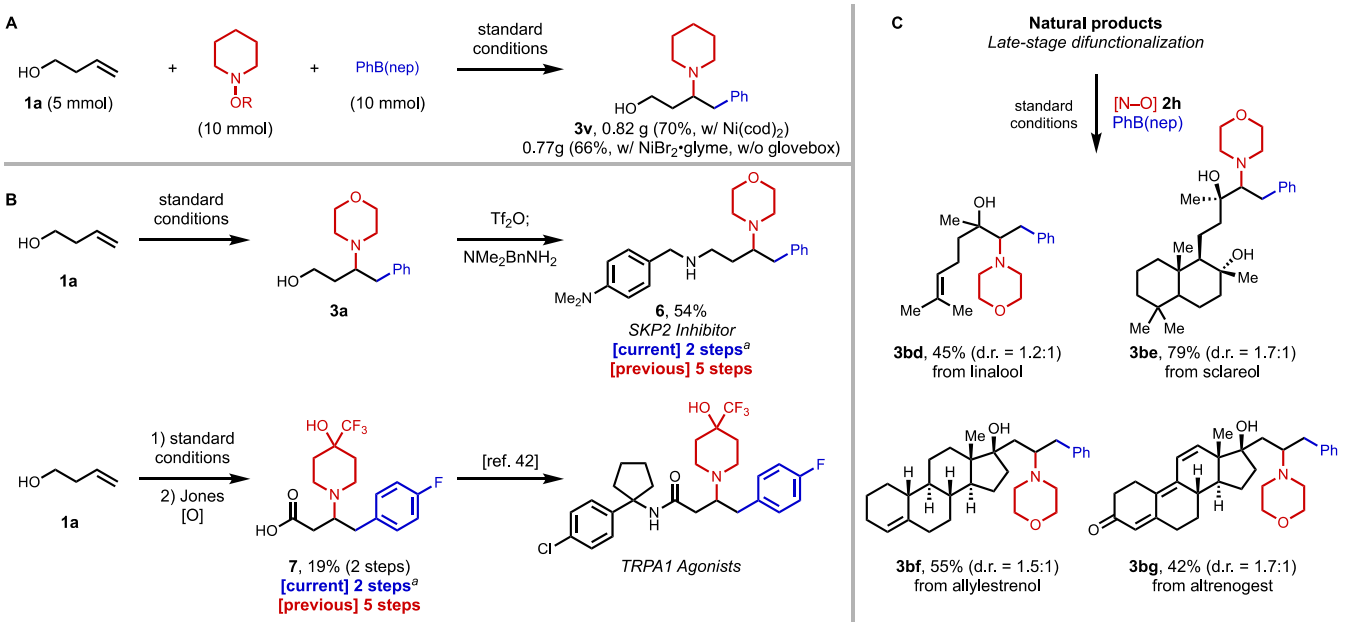
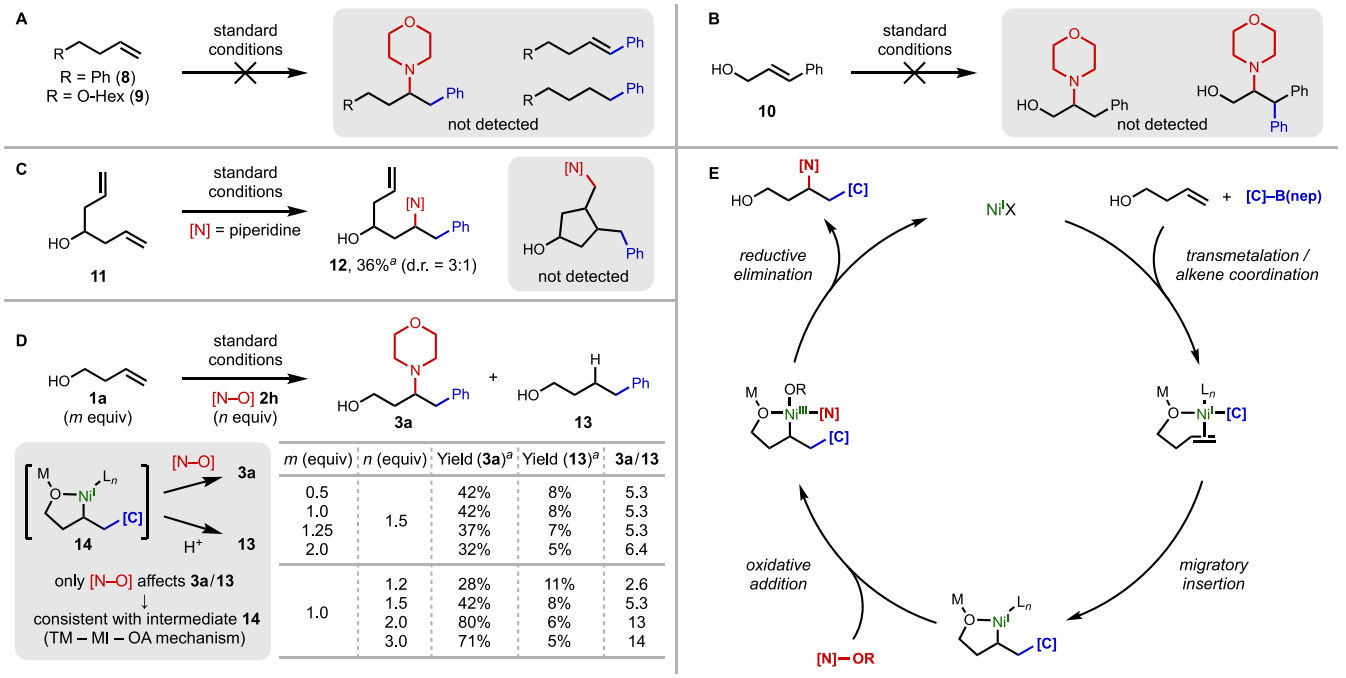
Scheme 3. Large-Scale Reaction and Synthetic Application[b]



[a]Linear step count from alkene substrate **1a**, four steps total including N–O reagent synthesis. [b]See Supporting Information for details regarding scale and specific conditions.

Scheme 4. Mechanistic Investigations and Proposed Catalytic Cycle[b]



m (equiv)	*n* (equiv)	Yield (**3a**)[a]	Yield (**13**)[a]	**3a**/**13**
0.5	1.5	42%	8%	5.3
1.0		42%	8%	5.3
1.25		37%	7%	5.3
2.0		32%	5%	6.4
1.0	1.2	28%	11%	2.6
	1.5	42%	8%	5.3
	2.0	80%	6%	13
	3.0	71%	5%	14

[a]Percentages represent ^{1}H NMR yields using 1,3,5-trimethoxybenzene as internal standard. [b](A) Directing group control experiments. (B) Control experiment with potential intermediate. (C) Radical clock experiment. (D) Substrate loading experiments and product-determining step. (E) Proposed catalytic cycle. M = K, H, or free lone pair (overall anionic complex).

cyclopentenol, cyclohexenol, and several trisubstituted alkenes were found to be ineffective substrates. Here it is worth noting that all alkenyl alcohol substrates used in Scheme 2 were obtained directly from commercial suppliers, illustrating the widespread availability of this substrate class.

Large-Scale Reaction and Synthetic Application. To illustrate the synthetic utility of this alcohol-directed 1,2-carboamination reaction, we performed a large-scale reaction and showcased several real-world applications preparing bioactive molecules (Scheme 3). Indeed, the desired carboaminated product **3v** was successfully obtained on a 5 mmol scale from 3-buten-1-ol (**1a**) in good yield (Scheme 3A). Additionally, two bioactive molecules in the literature were successfully synthesized from the same homoallylic alcohol using our method followed by functionalization of the versatile hydroxyl group (Scheme 3B). First, the hydroxyl group of

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aminoalcohol **3a** was triflated *in situ* and further reacted with an amine nucleophile to give the desired SKP2 inhibitor **6** in only two total steps.[25] In addition, the TRPA1 agonist precursor **7** was synthesized in two steps using the presented 1,2-arylamination followed by oxidation of the alcohol to the carboxylic acid.[26] These routes not only are step-economical but also provide new divergent synthetic pathways that are amenable toward rapid structural diversification of the carboamination products for drug discovery.

We next performed the late-stage difunctionalization of complex natural products that contain allylic/homoallylic alcohol moieties (Scheme 3C). Gratifyingly, linalool, sclareol, allylestrenol, and altrenogest were successfully carboaminated in good to excellent yields (**3bd**−**3bg**) without having to install an additional directing auxiliary or any protecting groups.

Mechanistic Studies and Proposed Catalytic Cycle. The high pathway selectivity of this three-component coupling process and the importance of the tailored N−O electrophile prompted us to investigate the reaction mechanism. To this end, we first examined the importance of the alcohol directing group through a series of control experiments. Notably, 4-phenyl-1-butene (**8**) and a representative alkenyl ether (**9**), both of which lack an alcohol directing group, did not result in any product formation (Scheme 4A). Moreover, Heck or hydroarylated products were not observed in either case, signaling a significant role of the alcohol directing group in the migratory insertion step. We next tested cinnamyl alcohol (**10**) as a starting material, and in this case, we did not observe any hydroaminated or carboaminated product, with unreacted **10** detected as the major component of the crude reaction mixture (Scheme 4B). This result rules out a stepwise mechanism consisting of oxidative Heck arylation followed by hydroamination of the resulting styrenyl intermediate. Finally, a radical clock experiment using 1,6-heptadien-4-ol (**11**) was performed to probe the generation of a carbon-centered radical intermediate (Scheme 4C). Interestingly, acyclic carboaminated product **12** was observed as the major product, and no evidence of the cyclized product was observed. This result is consistent with a nonradical pathway or, alternatively, a radical pathway involving a radical capture rate faster than that of the radical cyclization step ($>10^5$ M^{-1} s^{-1}).[27]

With a general picture of the mechanism established, we next considered all of the different possible orders in which the three key elementary steps (TM, transmetalation; OA, oxidative addition; MI, migratory insertion) could take place prior to C−N reductive elimination (see Supporting Information for details). The three most plausible pathways are (1) TM−MI−OA, (2) OA−TM−MI, and (3) TM−OA−MI. To evaluate the viability of these possible sequences, we analyzed the ratio of carboaminated product (**3a**) to hydroarylated side product (**13**), the latter of which was obtained in 6% yield under the standard conditions, as a function of reagent concentrations. In a sequence in which MI precedes OA, both the desired product (**3a**) and hydroarylated product (**13**) would be generated from a common alkylnickel(I) intermediate (**14**); in this case the product ratio should be determined by the relative rates of bimolecular oxidative addition versus protodemetalation (both of which are expected to be irreversible)[28] and should thus be dependent on the concentration of the N−O reagent. In an alternative OA-first mechanism, the thusly generated alkylnickel(III) intermediate would already bear the amido ligand, and the product ratio should be independent of the N−O reagent concentration. Interestingly, we observed that the carboaminated (**3a**) to hydroarylated (**13**) product ratio increased when the N−O reagent concentration was increased, while alkene concentration does not affect the product ratio (Schemes 4D, S1, and S2). These data show that the N−O reagent, and not the alkene, is involved in the product-determining step, which provides support for pathway 1, the TM−MI−OA sequence.

On the basis of these experiments and literature precedents, a plausible catalytic cycle is proposed in Scheme 4E.[11,28,29] Here we propose a Ni(I)/Ni(III) catalytic cycle based on the observed erosion of stereospecificity (**3at**, **3au**, **3ax**, and **3ay**), which may arise from a competitive process involving reversible alkyl−Ni(III) homolysis to generate an alkyl radical and Ni(II), followed by recombination.[30] The proposed catalytic cycle initiates with formation of an organonickel species via transmetalation of the carbon nucleophile. Next, alcohol-directed *syn*-1,2-migratory insertion occurs to afford a putative alcohol-coordinated alkyl nickelacycle. This intermediate then oxidatively adds to the electrophilic aminating reagent, setting up the final carbon−nitrogen reductive elimination step that delivers the 1,2-carboaminated product.

CONCLUSIONS

In summary, we have demonstrated an alcohol-directed, nickel-catalyzed three-component 1,2-carboamination of unactivated alkenes. Sterically and electronically modulated *O*-(2,6-dimethoxybenzoyl)hydroxylamine electrophiles are critical in enabling productive three-component coupling and minimizing undesired pathways. This method tolerates various aryl/alkenylboronate nucleophiles and amine electrophiles as coupling partners, with the nucleophile scope complementing previous amide-directed methodology from our group that employs alkylzinc reagents.[11] In addition, diverse alkene substrates, including alkenyl alcohols of varying chain lengths, secondary alcohols, tertiary alcohols, disubstituted alkenes, natural products, and sulfonamide-protected alkenylamines, react to furnish the corresponding 1,2-carboaminated products with high regio- and diastereoselectivity. On the basis of the all-*cis*-conformation of cyclopentene-derived product **3ba** and the results of various control experiments, hydroxyl groups were shown to function as directing groups for the nickel catalyst, thereby controlling chemo- and regioselectivity. Finally, a gram-scale reaction and applications to construct bioactive compounds exemplify the synthetic utility of this alcohol-directed alkene 1,2-carboamination.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c07112.

Experimental details, NMR, X-ray, and other data (PDF)

NMR data in MNova format (ZIP)

Accession Codes

CCDC 2061172 contains 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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Notes

The authors declare no competing financial interest.

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