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Article

Ni-Catalyzed Distal-Selective *gem*-Difluorovinylation of Unactivated Alkenes with 2,2-Difluorovinyl Benzoates

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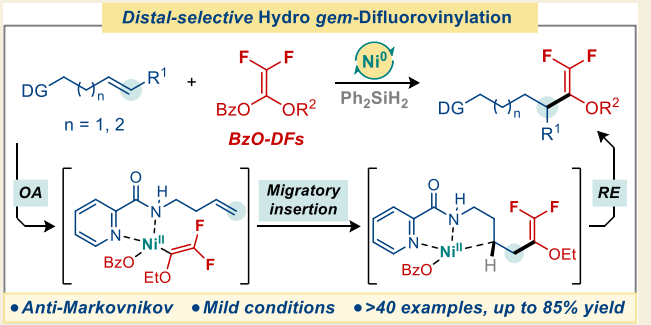
ABSTRACT: The *gem*-difluoroalkene is a bioisostere of the carbonyl group, used for improving the bioavailability of drug candidates. Here, we present an intermolecular Ni-catalyzed strategy for the distal-selective hydro *gem*-difluorovinylation of unactivated alkenes, utilizing 2,2-difluorovinyl benzoates (BzO−DFs) as building blocks for the synthesis of a wide array of *gem*-difluoroenol ethers that are otherwise challenging to produce. Diverse BzO−DF derivatives bearing sensitive functional groups, strained carbocycles, and natural products are prepared from inexpensive bromodifluoroacetates by using metallic zinc as a reductant. The cross-coupling reaction is initiated by Ni(0) oxidative addition to BzO−DFs to form the difluorovinyl Ni(II) complexes as the resting state. The vinyl Ni(II) complexes have been characterized by ESI-MS. The precoordination of the picolinimide auxiliary facilitates the migratory insertion of the difluorovinyl Ni(II) into alkenes, exhibiting exceptional regiocontrol and broad functional group tolerance. Complementary to the methods involving organometallic nucleophiles, this approach employs alkenes as abundant nucleophiles, achieving high distal-selectivity without chain-walked isomerization. The synthetic utility is further demonstrated through late-stage modifications with complex, medicinally relevant molecules.



KEYWORDS: *gem-Difluoroalkene, hydrovinylation, nickel, regioselective, alkene*

INTRODUCTION

As bioisosteres of carbonyl groups, *gem*-difluoroalkenes are privileged scaffolds for drug design.[1] While carbonyl groups are susceptible to reduction by NAD(P)H-dependent reductases due to their high hydrophilicity and electrophilicity, substituting them with *gem*-difluoroalkenes has demonstrated improved metabolic stability, potency, and selectivity (Scheme 1a).[2] The conventional synthesis of *gem*-difluoroalkenes includes the Wittig reaction, Julia−Kocienski reaction, and Horner−Wadsworth−Emmons reaction. Methods involving the elimination of the benzenesulfonyl group from (benzenesulfonyl)-difluoromethide and the defluorination of trifluoromethyl ketones to give *gem*-difluoroalkenes are also reported (Scheme 1b).[3] Recently, transition-metal-catalyzed defluorinative cross-coupling reactions have emerged as a versatile route for *gem*-difluoroalkene synthesis. In this regard, Hu pioneered the Cu-catalyzed defluorinative coupling of trifluoromethylsilane and diazoalkanes; the route includes the formation of Cu-carbene.[4] Later the groups of Murakami, Hayashi, and Lautens developed the Rh-catalyzed defluorinative arylation of α-(trifluoromethyl)styrenes.[5] More recently, Ni-catalyzed defluorinative reductive cross-coupling of *N*-hydroxyphthalimide esters, acetals, cyclobutanone oxime esters, and alkenes has been reported. For example, Wang and coworkers developed a Ni-catalyzed three-component cross-electrophilic coupling using 2-bromo-3,3,3-trifluoropropene as the *gem*-difluoroalkene surrogate.[6] Recently, we accomplished a nondefluorinative approach for the synthesis of *gem*-difluoroenol ethers by employing 2,2-difluorovinyl benzoates (BzO−DFs) as building blocks under Ni catalysis (Scheme 1b).[7] The coupling reaction is initiated by the facile cleavage of the C(vinyl)−O(benzoate) bond facilitated by the Ni(0) catalyst, and the subsequent C−C coupling reaction is achieved by using organometallic reagents.

Recently, NiH-mediated hydrometalations of unactivated alkenes to form reactive alkyl metal complexes have garnered significant attention. The nucleophilic alkyl metal complexes can react with various electrophiles for regioselective C−C and C−X bond couplings.[8] For example, Fu's group has pioneered an enantioconvergent alkyl−alkyl Ni-catalyzed coupling of racemic secondary and tertiary alkyl electrophiles with alkenes using chiral Ni−*bis*(oxazoline) catalysts.[9] Our group independently developed a NiH-catalyzed remote γ-methylene C−

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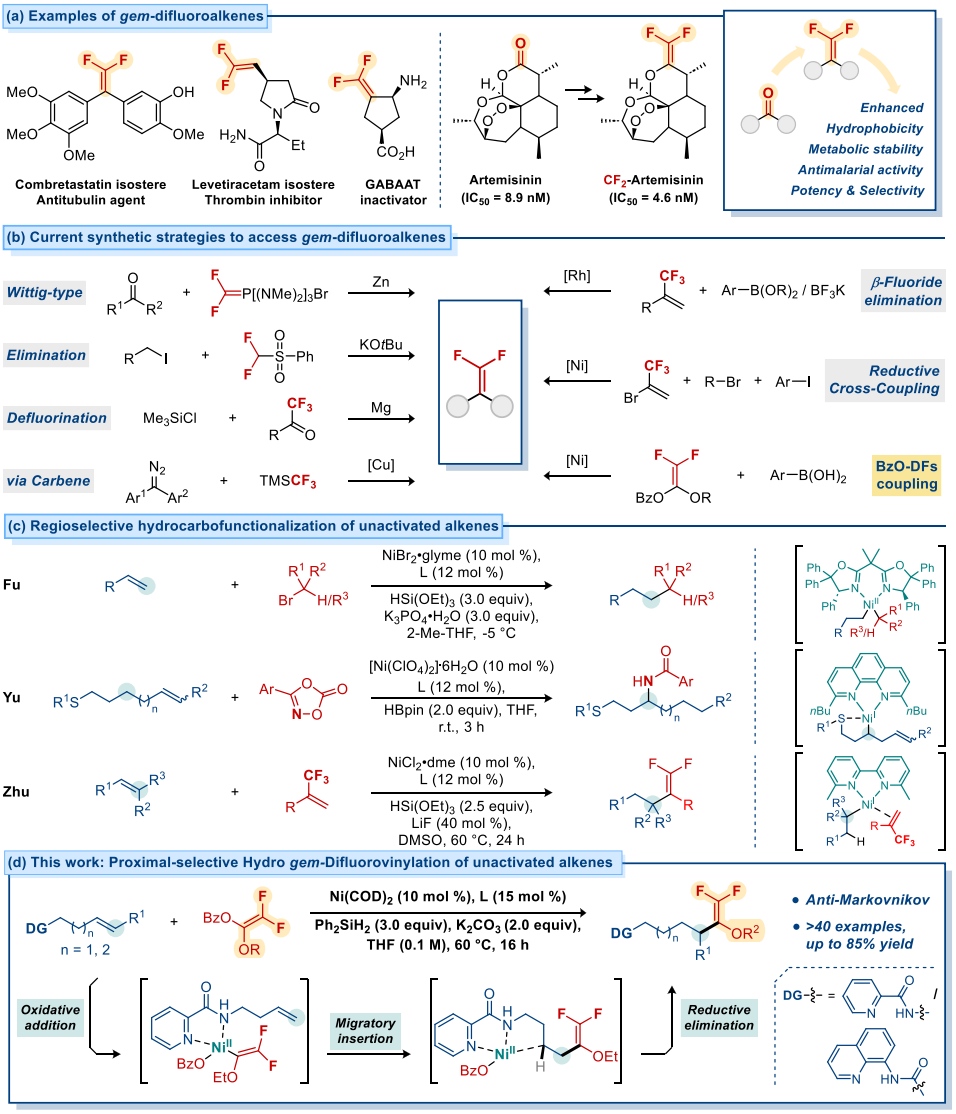
Scheme 1. Examples and Synthetic Strategies to *gem*-Difluoroalkenes



H bond amidation of unactivated alkenes.[10] The thioether group was found to mediate effective five-membered nickelacycle formation, thereby terminating the chain-walking isomerization selectively at the γ-methylene site for amidation by dioxazolones. Regarding difluoroalkene synthesis, Zhu and coworkers have established a NiH-catalyzed migratory defluorinative coupling between unactivated alkenes and α-(trifluoromethyl)styrenes to produce *gem*-difluoroalkenes (Scheme 1c).[11] Despite the advances in the NiH-catalyzed coupling reaction, the direct insertion of a *gem*-difluoroalkene moiety into unactivated alkenes is largely unexplored. Herein, we describe a Ni-catalyzed distal-selective *gem*-difluorovinylation of unactivated alkenes utilizing 2,2-difluorovinyl benzoates as the building block. This method allows for the efficient and regioselective installation of *gem*-difluoroalkene units onto the terminal carbon of the C═C bonds, thereby broadening the synthetic toolbox for constructing fluorinated compounds (Scheme 1d).

METHODS

Reaction Optimization

Based on previous works, *in situ*-generated Ni−H would react with terminal alkenes to form alkyl-Ni complexes, which would further couple with electrophiles to forge C−C and C−N bonds. Initially, we tested a series of terminal alkenes such as styrene with $Ni(ClO_4)_2$, HBpin, and 2,2-difluorovinyl benzoate **2a** in THF at room temperature for 12 h. However, no desired coupled product was observed, with the majority of **2a** remaining unchanged. Nevertheless, further screening of various Ni precursors, hydride reagents, and some alkenes did not yield favorable results.

To account for the ineffective coupling of alkenes with **2a**, we surmised that employing stronger σ-donors coordinating to the alkyl-Ni intermediate might activate the complex toward oxidative addition to **2a**, favoring the coupling reaction. In this regard, when *N*-(but-3-enyl)picolinamide **1a** (0.1 mmol) was treated with 1-ethoxy-2,2-difluorovinyl benzoate **2a** (0.2 mmol), $Ni(COD)_2$ (10 mol %), 4-methoxypyridine **L1** (15 mol %), and K_2CO_3 (2.0 equiv) in THF at 60 °C for 16 h, the desired coupled product **3** was obtained in 85% yield (Table 1, entry 1). Only the linear product was observed, while no branched products were observed in any case. In the absence of $Ni(COD)_2$, no coupled product was obtained, with full recovery of **1a** (entry 2). Using $NiBr_2(DME)$ as the catalyst, the analogous reaction afforded **3** in 54% yield (entry 3).

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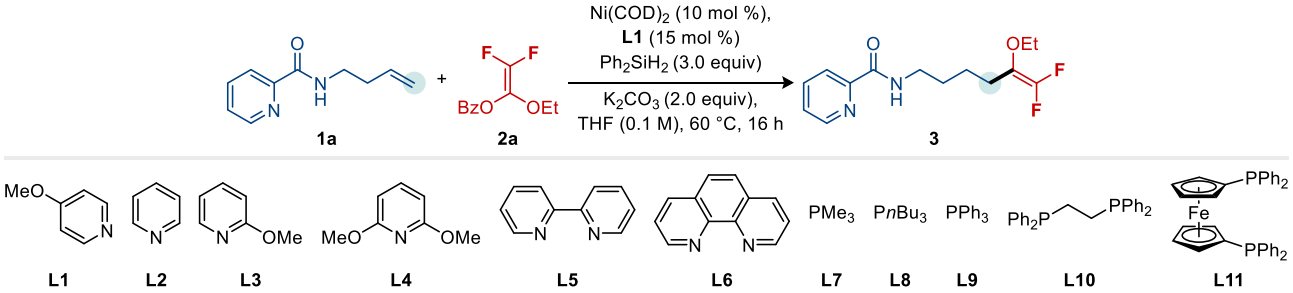
Table 1. Reaction Optimization[ab]



entry	variation from standard conditions	yield (%)[b]
1	none	85
2	without $Ni(COD)_2$	0
3	$NiBr_2(DME)$ instead of $Ni(COD)_2$	54
4	without ligand	43
5	**L2** instead of **L1**	60
6	**L3** instead of **L1**	46
7	**L4** instead of **L1**	44
8	**L5** instead of **L1**	21
9	**L6** instead of **L1**	39
10	**L7** instead of **L1**	48
11	**L8** instead of **L1**	42
12	**L9** instead of **L1**	52
13	**L10** instead of **L1**	27
14	**L11** instead of **L1**	66
15	without Ph_2SiH_2	0
16	Et_3SiH instead of Ph_2SiH_2	trace
17	DCM	22
18	Toluene	33
19	MeCN	61
20	without K_2CO_3	60
21	Na_2CO_3 instead of K_2CO_3	60
22	KF instead of K_2CO_3	60
23	DBU instead of K_2CO_3	trace
24	Et_3N instead of K_2CO_3	44
25	T = 20 °C instead of 60 °C	4
26	T = 40 °C instead of 60 °C	59
27	T = 80 °C instead of 60 °C	45

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Ni(COD)_2$ (0.01 mmol), 4-methoxypyridine **L1** (0.015 mmol), Ph_2SiH_2 (0.3 mmol), K_2CO_3 (0.2 mmol), THF (1 mL), 60 °C, 16 h. [b]NMR yield (CH_2Br_2 as internal standard).

As depicted in Table 1, the ligand-free conditions afforded **3** in significantly lower yield (entry 4). While simple pyridine (**L2**) promotes the coupling reaction with a 60% product yield (entry 5), other pyridine derivatives **L3** and **L4** bearing methoxy substituent(s) at the *ortho*-position(s) are less effective ligands for the coupling reaction (ca. < 50% yield; entries 6−7). The use of bidentate ligands such as 2,2'-bipyridine (**L5**) and 1,10-phenanthroline (**L6**) resulted in poor product yields of less than 40% (entries 8−9). Other σ-donor ligands, such as trimethylphosphine (**L7**) and tributylphosphine (**L8**) performed similarly with 40−50% product yields (entries 10−11). Triphenylphosphine (**L9**) is an ineffective ligand (entry 12). Bidentate phosphine ligands 1,2-*bis*(diphenylphosphino)ethane (**L10**) led to 27% product yields (entry 13), while dppf (**L11**) shows a promising 66% product yield (entry 14).

Removal of diphenylsilane did not lead to any product formation, with the starting materials remaining unchanged (entry 15). Substituting diphenylsilane with triethylsilane yielded a trace amount of the desired coupling product; instead, hydrogenation of the alkene was observed (entry 16). Conducting the reaction in nonpolar solvents such as dichloromethane (22%, entry 17) or toluene (33%, entry 18) resulted in low product yields. However, the product yield improved to 61% when acetonitrile was used as the solvent (entry 19). Conducting the reaction without K_2CO_3 or with alternatives (e.g., Na_2CO_3 or KF) led to lower product yields (entries 20−22). Additionally, organic bases such as DBU and triethylamine were found to be less effective additives (entries 23−24). Temperature screening revealed that performing the reaction at 20 °C resulted in a low yield of 4%. Increasing the temperature to 40 °C significantly improved the yield to 59%, whereas further heating to 80 °C caused the yield to decrease to 45% (entries 25−27).

RESULTS AND DISCUSSION

Scope Study

With the optimized conditions, we examined the scope of *gem*-difluoroalkenes with *N*-(but-3-enyl)picolinamide **1a** as the coupling partner (Scheme 2a). Effective coupling of *gem*-difluoroalkenes bearing alkoxy substituents such as ethoxy, dodecyloxy, cyclopropylmethoxy, and cyclopentylmethoxy furnished **3**−**6** in 57−85% yields. *gem*-Difluoroalkenes with various benzyloxy substituents reacted successfully to give the corresponding *gem*-difluoroenol ethers **7**−**12** in 66−72% yields. Comparable results were obtained for a gram-scale

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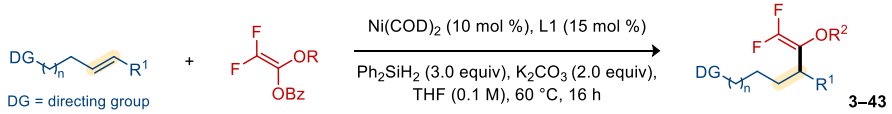
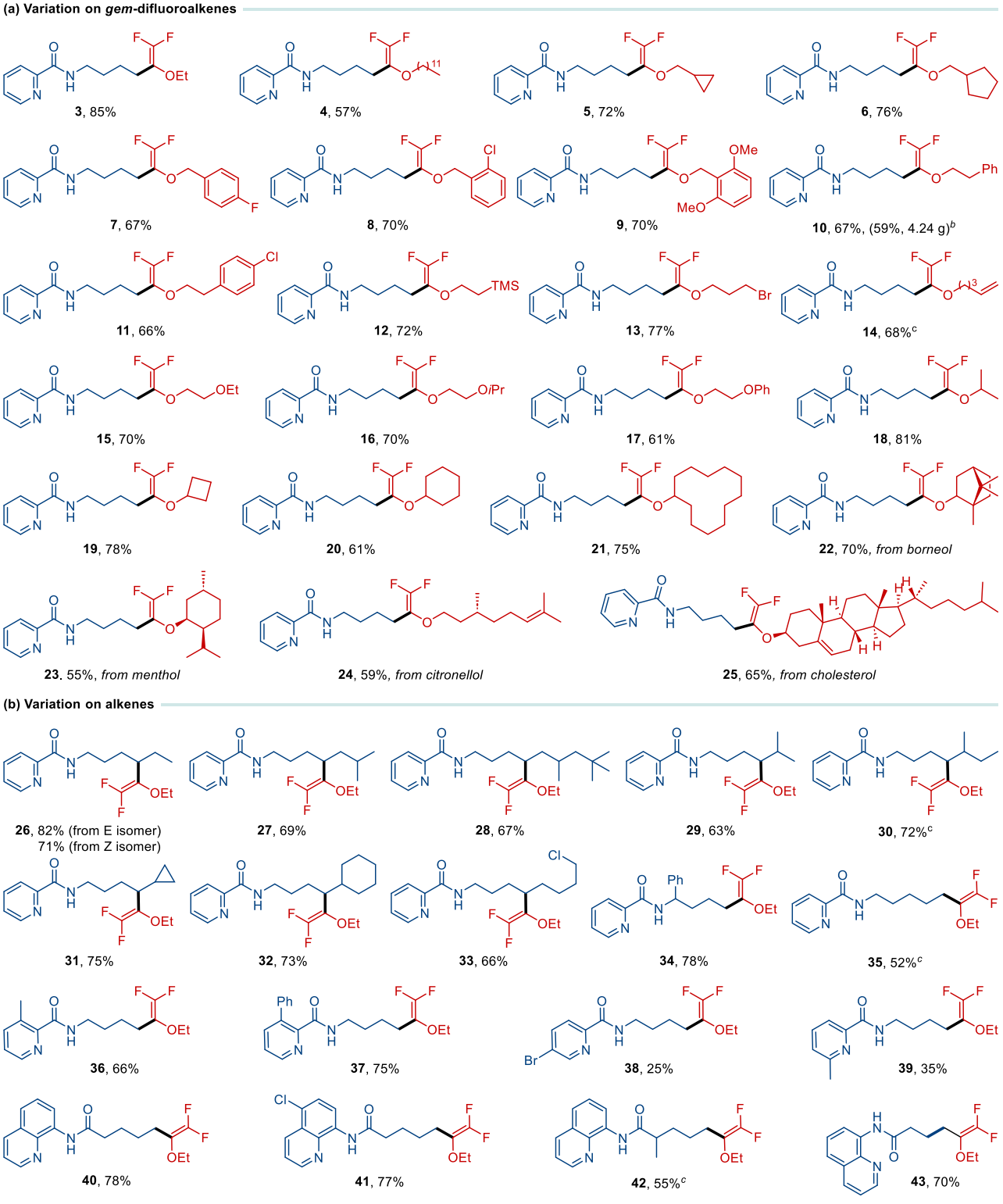
Scheme 2. Substrate Scope Study[a]





[a]Reaction conditions: alkene (0.1 mmol), 2,2-difluorovinyl benzoate (0.2 mmol), $Ni(COD)_2$ (0.01 mmol), 4-methoxypyridine **L1** (0.015 mmol), Ph_2SiH_2 (0.3 mmol), K_2CO_3 (0.2 mmol), THF (1 mL), 60 °C, 16 h. [b]Large-scale reaction with **1a** (20 mmol), **10** was furnished in 59% yield, 4.24 g. [c]Mixture containing <10% impurities.

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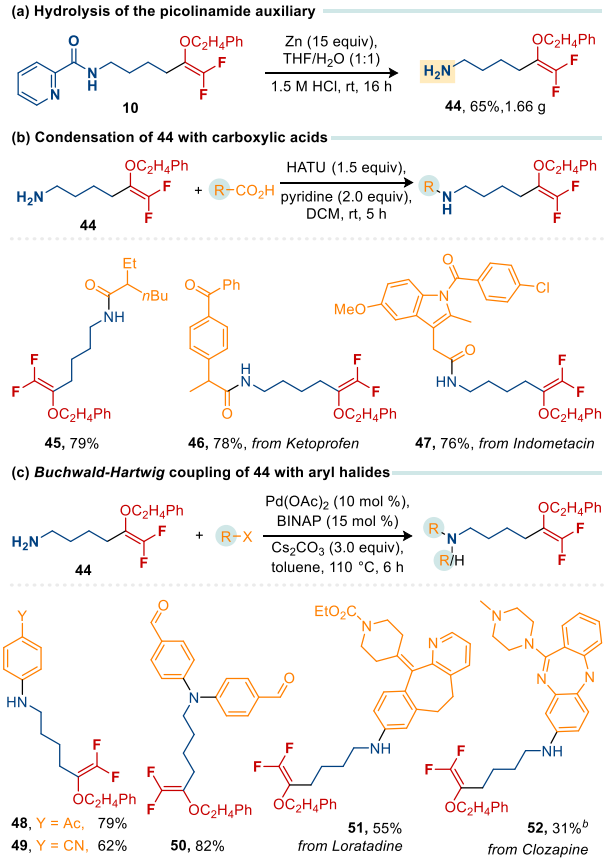
reaction, furnishing **10** in a 59% yield (4.24 g). Notably, 3-bromopropoxy and pent-4-enyloxy groups are compatible with the Ni-catalyzed conditions, and the desired compounds **13** and **14** were obtained in 77% and 68% yields, respectively. Similarly, the ether moiety on the alkoxy substituent gave **15**–**21** in 61–81% yields. *gem*-Difluoroalkenes derived from natural products such as borneol (**22**), menthol (**23**), citronellol (**24**) and cholesterol (**25**) were transformed into the corresponding *gem*-difluoroenol ethers in 55–70% yields.

Apart from terminal alkenes, some internal alkenes incorporating a picolinamide auxiliary were investigated for the difluorovinylation reaction (Scheme 2b). Under the Ni-catalyzed conditions, both (*E*)- and (*Z*)-*N*-(hex-3-enyl)-picolinamide substrates afforded the same product **26**, with yields of 82% and 71%, respectively. Furthermore, alkenes possessing longer or more substituted alkyl chains were effectively converted to products **27**–**30**, with yields ranging from 63% to 72%. Substrates containing cycloalkyl groups, including cyclopropyl and cyclohexyl substituents, reacted efficiently to produce products **31** and **32** in yields of 75% and 73%, respectively. Importantly, the primary chloroalkyl group demonstrated compatibility with the nickel-catalyzed conditions, resulting in the synthesis of compound **33** in 66% yield. The scope of the terminal alkenes was also explored. Consistent with *N*-(but-3-enyl)picolinamide **1a**, the presence of a phenyl group adjacent to the picolinamide moiety did not hinder the coupling reaction, yielding the corresponding product **34** with a yield of 78%. Reaction of *N*-(pent-4-enyl)picolinimide produced **35** in 52% yield regioselectively, along with nearly 40% *N*-pentylpicolinamide as the hydrogenation product.

Regarding the effect of the substituents, substrates containing the 3′-methyl and phenyl picolinamide auxiliaries reacted to give **36** (66%) and **37** (75%). Yet, the analogous reactions for substrates with 5-bromo (**38**) and 6-methyl (**39**) substituents were less effective, presumably due to steric hindrance affecting substrate coordination. Reactions with *N*-(quinolin-8-yl)acetamide as an auxiliary also gave favorable results, and products **40** and **41** were formed in ca. 77% yields despite the halogen substituents on the quinolinyl group. Comparatively, the coupling reaction became sluggish with a methyl substituent adjacent to the directing group, and **42** was obtained in a 55% yield. The reaction was also effective with *N*-(quinolin-8-yl)but-3-enamide furnishing the corresponding product **43** in 70% yield.

According to the literature, the picolinamide auxiliary can be deprotected to yield a free amine by hydrolysis (Scheme 3).[12] In this study, *gem*-difluoroalkene **10** was converted to compound **44** with a 65% yield (1.66 g) through Zn–HCl hydrolysis (Scheme 3a). Utilizing the amino group as a functional handle, compound **44** was coupled with 2-ethylhexanoic acid to produce the corresponding amide **45** in 79% yield (Scheme 3b). Condensation reactions with ketoprofen and indomethacin were also successful, yielding compounds **46** and **47** in 78% and 76% yields, respectively.[13] The synthetic utility of **44** was further explored by subjecting the compound to Buchwald–Hartwig coupling reactions with various aryl halides (Scheme 3c).[14] Under Pd-catalyzed conditions, effective coupling of 1-(4-chlorophenyl)ethan-1-one and 4-bromobenzonitrile with **44** afforded secondary amines **48** and **49** in yields of 79% and 62%, respectively. An analogous reaction with 4-bromobenzaldehyde resulted in the formation of tertiary amine **50** in 82% yield. Additionally, the

Scheme 3. Application Studies on Selected Transformations[a]



[a]Reaction conditions: (a) Hydrolysis of **10**: **10** (10 mmol), Zn (15 equiv), THF/H_2O (1:1), HCl (1.5 M), rt, 16 h. (b) Condensation of **44**: **44** (0.1 mmol), acid (1.5 equiv), HATU (1.5 equiv), pyridine (2.0 equiv), DCM (0.1 M), rt, 5 h. (c) Buchwald–Hartwig coupling to **48**–**50**: **44** (0.1 mmol), aryl halide (2.0 equiv), [$Pd(OAc)_2$] (10 mol %), BINAP (15 mol %), Cs_2CO_3 (3.0 equiv), toluene (0.1 M), 110 °C, 6 h. Buchwald–Hartwig coupling to **51**–**52**: **44** (0.1 mmol), aryl halide (2.0 equiv), [$Pd(dba)_2$] (10 mol %), DavePhos (15 mol %), *t*BuOK (1.5 equiv), toluene (0.1 M), 110 °C, 24 h. [b]Compound **52** gives the ^1H NMR yield by using CH_2Br_2 as an internal standard.

coupling of **44** with loratadine and clozapine furnished products **51** (55%) and **52** (31%), demonstrating its applicability to late-stage drug modification.

Mechanistic Study

Regarding the reaction mechanism, we sought to elucidate the resting state of the catalyst. Thus, we conducted the coupling reaction of **1a** and **2a** under stoichiometric conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Ni(COD)_2$ (1.0 equiv), 4-methoxypyridine **L1** (1.5 equiv), Ph_2SiH_2 (3.0 equiv), K_2CO_3 (2.0 equiv), in THF (0.1 M) at room temperature for 0.5 h (Scheme 4a). HRMS analysis of the reaction mixture revealed a characteristic molecular ion cluster peak at m/z = 463.0974, which was assigned as the vinyl Ni(II) complex (**Ni–A**) ($[M + H]^+$ = 463.0981), based on the mass value and isotopic distribution pattern. Extending the reaction time to 16 h resulted in the formation of cross-coupled product **3** in 45% yield. The role of the auxiliary is then examined. In an attempt to isolate the vinyl Ni complex, we conducted the analogous reaction using *N*-(but-3-en-1-yl)-[2,2′-bipyridine]-6-carboxamide (**53**), where the carboxamide group could stabilize the

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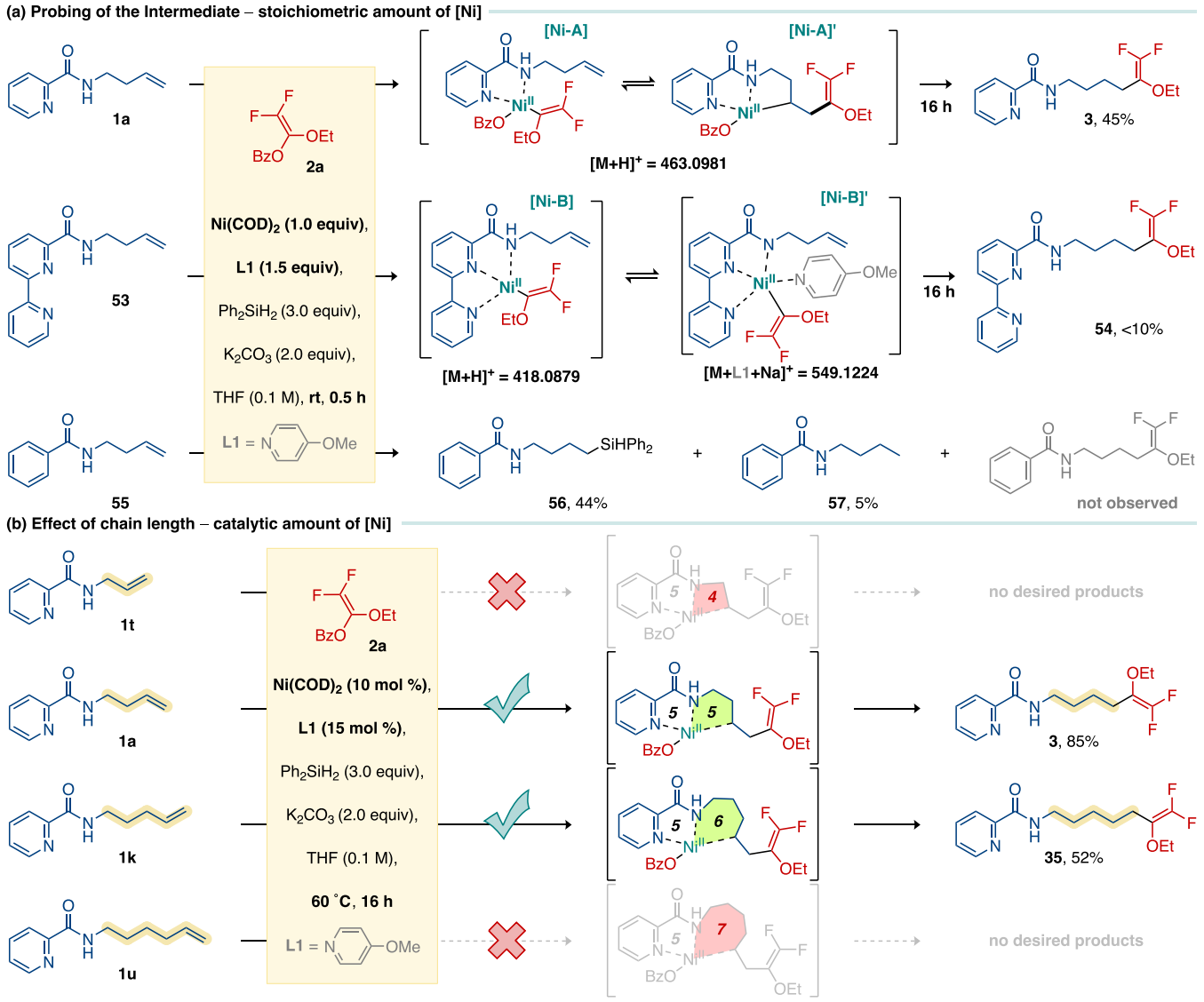
Scheme 4. Mechanistic Study: Probing of Reaction Intermediates and Effect of Chain Length of Alkenes[a]



[a]Reaction conditions: (a) alkene (0.1 mmol), **2a** (0.2 mmol), $Ni(COD)_2$ (0.1 mmol), 4-methoxypyridine **L1** (0.15 mmol), Ph_2SiH_2 (0.3 mmol), K_2CO_3 (0.2 mmol), THF (1 mL), rt, 0.5 h. (b) Alkene (0.1 mmol), **2a** (0.2 mmol), $Ni(COD)_2$ (0.01 mmol), 4-methoxypyridine **L1** (0.015 mmol), Ph_2SiH_2 (0.3 mmol), K_2CO_3 (0.2 mmol), THF (1 mL), 60 °C, 16 h.

intermediates.[15] Two notable peaks were observed in the HRMS analysis: one at m/z = 418.0883, corresponding to the vinyl Ni(II) complex (**Ni−B**) ($[M + H]^+$ = 418.0879), and another at m/z = 549.1224, which can be assigned to the vinyl Ni(II) complex coordinated with the 4-methoxypyridine ligand (**L1**), designated as **Ni−B′** ($[M + Na]^+$ = 549.1224). This implies that the ligand promotes the oxidative addition by stabilizing the Ni(II) complex. When changing the picolinamide auxiliary to benzamide (**55**), no desired product was observed. Instead, a 44% yield of the linear hydrosilylation product was detected by GC-MS, while the majority of **2a** decomposed. These findings suggest that the Ni(II) resting state of the reaction requires stabilization by a strong chelating directing group.

With the vinyl Ni(II) intermediate as the resting state, the migratory insertion into the alkene was studied at various tether lengths of the alkene (Scheme 4b). When *N*-propylpicolinamide was subjected to the coupling reaction, no difluorovinyl-coupled product was formed. This can be attributed to the ring strain associated with the formation of bicyclic 5,4-membered nickelacycles during the migratory vinyl insertion. In contrast, reactions with *N*-butenylpicolinamide and *N*-pentenylpicolinamide yielded the corresponding coupled products in 85% and 52% yields, respectively. These transformations likely proceed through 5,5- and 5,6-membered bicyclic nickelacycle intermediates, which are relatively favorable. The lack of reactivity observed with *N*-hexylpicolinamide is consistent with the hypothesis that the formation of a 5,7-membered nickelacycle is disfavored under the current conditions.[16]

To assess whether any radical intermediates are involved in the cross-coupling reactions, we conducted the catalytic reaction in the presence of BHT and (1-cyclopropylvinyl)-benzene (3.0 equiv) as radical scavengers. The formation of **3** proceeded with yields of 82% and 72%, respectively, without significant inhibition from radical scavengers (Scheme 5a). This finding is inconsistent with a mechanism involving carbon radicals. Deuterium labeling studies were also performed by

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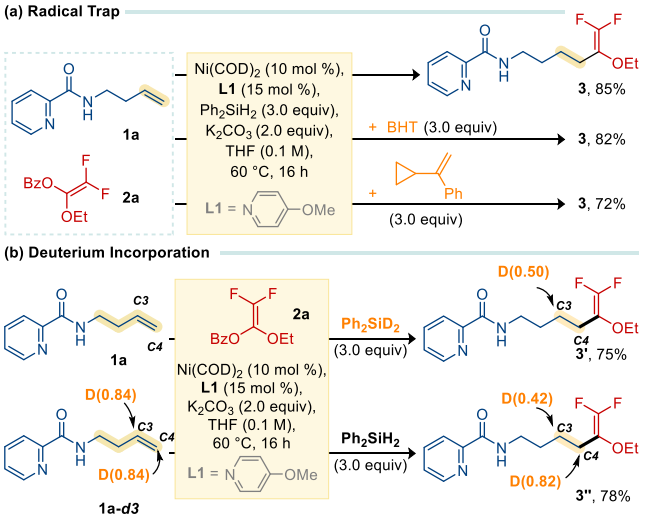
Scheme 5. Mechanistic Study: Radical Traps and Deuterium Labelling Studies[a]



[a]Reaction conditions: (a) alkene (0.1 mmol), **2a** (0.2 mmol), $Ni(COD)_2$(0.01 mmol), 4-methoxypyridine **L1** (0.015 mmol), Ph_2SiH_2 (0.3 mmol), K_2CO_3 (0.2 mmol), THF (1 mL), radical scavenger (0.3 mmol), 60 °C, 16 h. (b) Alkene (or deuterated alkene) (0.1 mmol), **2a** (0.2 mmol), $Ni(COD)_2$(0.01 mmol), 4-methoxypyridine **L1** (0.015 mmol), Ph_2SiH_2 (or deuterated silane) (0.3 mmol), K_2CO_3 (0.2 mmol), THF (1 mL), 60 °C, 16 h.

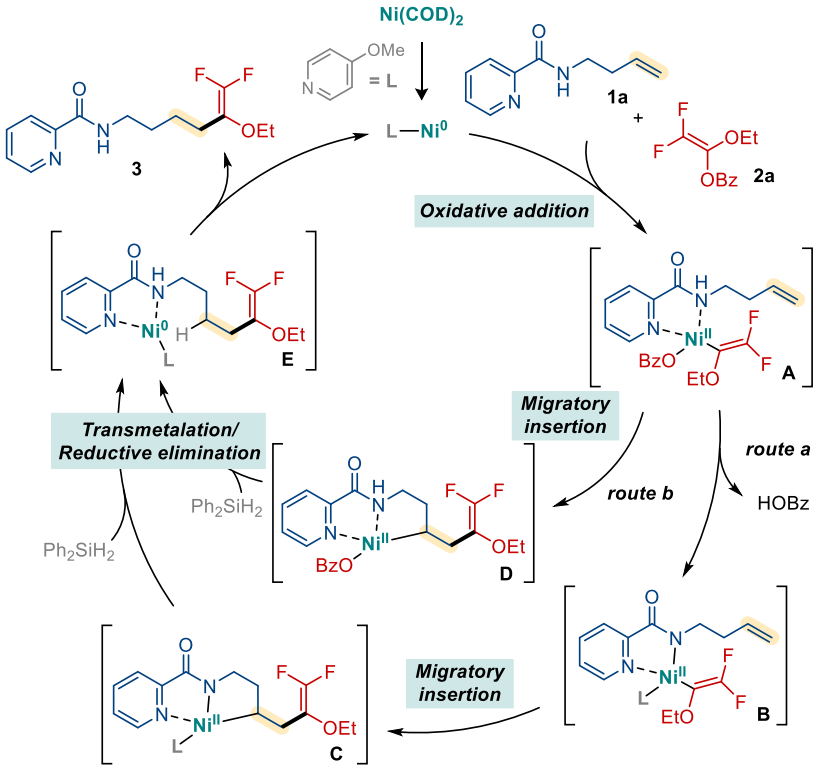
using Ph_2SiD_2 instead of Ph_2SiH_2. Analysis by ^1H NMR and HRMS revealed the formation of deuterated product **3′** (75% yield, 50% deuterium incorporation at the C3 position). Taken together with the HRMS results, which support the vinyl Ni(II) complex as the resting state, the silane reduction of the Ni(II) complex is likely critical for product and catalyst turnovers. A control experiment with *N*-(but-3-en-1-yl-3,4,4-*d3*)picolinamide **1a**-*d3* under the standard conditions was also performed. A 42% deuterium incorporation at the C3 position in **3′′** was observed, which is the same as the expected 42% (84%/2) retention of deuterium at this position. This finding further supports the proposed mechanism.

Scheme 6 illustrates the proposed mechanism for the hydrodifluorovinylation reaction. The reaction begins with the coordination of **1a** to the Ni(0) catalyst, followed by the oxidative addition of **2a**, leading to the formation of Ni(II) intermediate **A**. Intermediate **A** then eliminates a HOBz molecule to form Ni(II) intermediate **B**. Subsequent migratory insertion results in complex **C**. The silane transmetalation/reductive elimination of Ni(II) complex **C** produces Ni(0) complex **E**. Alternatively, complex **A** could undergo migratory insertion directly to form complex **D**, which, upon silane transmetalation/reductive elimination, also yields the Ni(0) complex **E**. Finally, the desired product **3** is released from the catalytic cycle.[14,17]

CONCLUSION

In summary, we have developed a new intermolecular Ni-catalyzed distal-selective hydro *gem*-difluorovinylation of unactivated alkenes with 2,2-difluorovinyl benzoates (BzO–DFs) as building blocks for the modular synthesis of *gem*-difluoroenol ethers. Unlike the previous method relying on the use of organometallic nucleophiles, this work employs alkenes as nucleophiles for effective coupling with a difluorovinyl Ni(II) complex. Our study shows that the precoordination of the picolinimide auxiliary enables distal-selective difluorovinylation of alkenes. A high degree of distal selectivity was observed for substrates bearing terminal and internal alkenes.

Scheme 6. Proposed Mechanism



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No chain-walked isomerized products were formed. The synthetic utility of this method was further demonstrated by the late-stage modification of the coupled product with complex and medicinally relevant molecules.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.5c00522.

Experimental procedures, physical characterization data (^{1}H,^{13}C, and ^{19}F NMR spectra) of the substrates and products (PDF)

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Notes

The authors declare no competing financial interest.

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