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Nickel-Catalyzed Decarbonylative Borylation and Silylation of Esters

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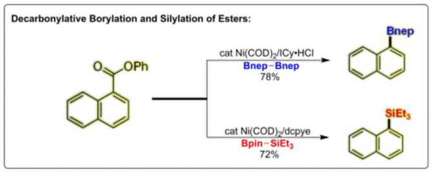
ABSTRACT: A nickel-catalyzed direct borylation and silylation of phenolic ester has been established. The key to this highly efficient acyl C-O bond borylative and silylative cleavage depends on the appropriate choice of different ligands and additives in presence of nickel catalyst. Both transformations exhibit good functional group compatibility and can serve as powerful synthetic tools for late-stage functionalization of complex compounds. The elucidation of key mechanistic features of this newly developed acyl C-O bond activation in esters was confirmed by two well-characterized organonickel(II) intermediates.



KEYWORDS: nickel, borylation, silylation, esters, decarbonylation

INTRODUCTION

The transition-metal-catalyzed functionalization of unreactive bonds is one of the most powerful protocols for practitioners in chemical synthesis.[1] Esters are widely found in broad range of organic molecules, including pharmaceuticals, agrochemicals and organic materials, and their selective functionalization represents a challenge in the field of organometallic chemistry. The utilization of esters in the cross-coupling process is meaningful not only because of avoiding formation of toxic wastes such as halide salts, but also it opens access to a vast number of non-toxic and readily available esters and the precursor carboxylic acids. Among various transition-metals, nickel catalysis[2] play a dominant role in C-O bond activation process in esters.[3] In the early of 1980, Yamamoto et al. demonstrated the first stoichiometric Ni(0)-mediated decarbonylation of aryl carboxylates *via* acyl metal species formation.[4] In recent years, the utilization of acyl C-O electrophiles in Ni-catalyzed cross-coupling reactions has received considerable attention. Itami and Yamaguchi et al. reported important decarbonylative coupling reactions of phenolic esters with 1,3-azoles[5] and arylboronic acids[6] *via* nickel-catalyzed C-O bond cleavage (Figure 1a & b). Garg and Houk et al. also revealed the first catalytic method to synthesize anilide products *via* activating the methyl ester C-O bonds. Interestingly, decarbonylation process does not occur in their reactions (Figure 1c).[7] Although the events of these Ni-catalyzed reactions were supported by DFT calculation,[6-7] there are still many fundamental issues need to be clarified. (1) The transient acylnickel species in these transformations has never been structurally characterized to confirm C-O bond cleavage step; (2) The essential difference between decarbonylative and non-decarbonylative processes need to be investigated; (3) More diversified reactions have not been developed.

Organo-boron[8] and silicon[9] compounds are significantly valuable synthetic intermediates with considerable interest in modern organic synthesis. They are usually prepared from Grignard or organolithium reagents, processes that are not compatible with numerous functional groups according to the traditional routes.[10] Alternatively, the development of transition-metal-catalyzed cross-couplings of organohalides with diborons[11] or disilanes[12] has allowed the synthesis of these compounds under mild conditions. Remarkably, borylation and silylation of unreactive bonds such as C-H,[13-14] C-N,[15] C-O[16], C-F[17] and C-C[18] bonds has shown promises because it confers synthetic versatility of such inert functional groups. For instance, Martin and co-workers developed Ni-catalyzed borylative[19] and silylative[20] cleavage of C-OMe bonds in aryl ethers. Most recently, we have also explored an efficient Ni-catalytic system, which is capable of activating amide C–N bonds for decarbonylative borylation to produce various organoboronates.[21] Despite these reported advances, decarbonylative borylation and silylation process of ester C-O bonds have been virtually unexplored.

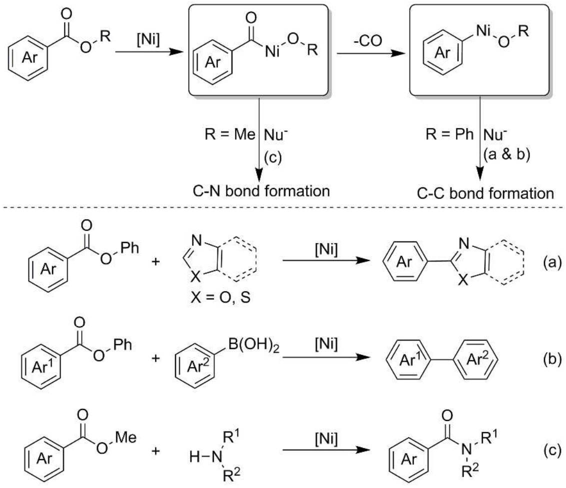


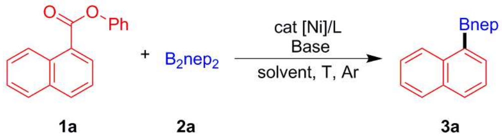
Figure 1. Nickel-Catalyzed Ester C-O Bond Functionalization

Herein, we report the first Nickel-catalyzed decarbonylative borylation and silylation reaction of ester by acyl C-O bond cleavage. Remarkably, this transformation is to cleave a stable ester C−O bond while forming an easily transformable C−B or C-Si bond. Moreover, this new C-B or C-Si bond cross-coupling can be accomplished in high yields with a broad scope of phenolic esters, w the further Suzuki–Miyaura or Hiyama coupling[6, 22] with unconsumed esters. In light of the importance of esters and the advantages offered by nickel catalysis, we expect that this concept will provide an efficient strategy for the application of ubiquitous esters as unconventional electrophiles in synthesis of organoboron and silicon compounds.

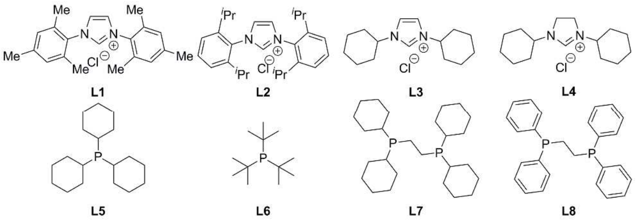
RESULTS AND DISCUSSION

Nickel-catalyzed decarbonylative borylation of esters: Initial studies involved the evaluation of the borylation of phenyl 1-naphthoate (**1a**) with $B_2(nep)_2$ (**2a**) (Table 1). In the presence of 5.0 mol% $Ni(COD)_2$, 10 mol% NHC ligand **L1** and 2.0 equiv NaF as additive, at 160 °C under an Ar atmosphere in 1,4-dioxane. We indeed observed the desired product **3a** in trace amount after 12 h in GC-MS (entry 1). Under these conditions, Na_3PO_4 works better than NaF (entry 2) and 21% yield was observed by employing Na_2CO_3 as the base (entry 3). Among other NHC ligands **L2-L4**, a dramatic effect of ICy·HCl (**L3**) was observed with 71% yield of **3a** (entry 5). We next turned our attention to phosphine ligands, and found that the former success with ligands for activating aryl C-O bonds such as PCy_3 (**L5**),[23] P^tBu_3 (**L6**), dcype (**L7**)[5, 24] and dppe (**L8**) were ineffective for the present decarbonylative borylation coupling (entries 7-10). When both Na_2CO_3 and NaCl (1:1) were added as the additives, we achieved better yield improving up to 81% (entry 11). Other air-stable nickel sources such as $Ni(PCy_3)_2Cl_2$ and anhydrous $Ni(OAc)_2$was also proven successful in this coupling reaction with a high reactivity (entries 12-13). We also examined the ttemperature effect and lower temperature (140 °C) was found to be not optimal (entry 14). Notably, increasing the $Ni(COD)_2$ loading to 10 mol% still resulted in a similar yield (entry 15), and no product was observed in the absence of Ni catalyst (entry 16).

Table 1. Optimizaion of Decarbonylative Borylation Process[a]

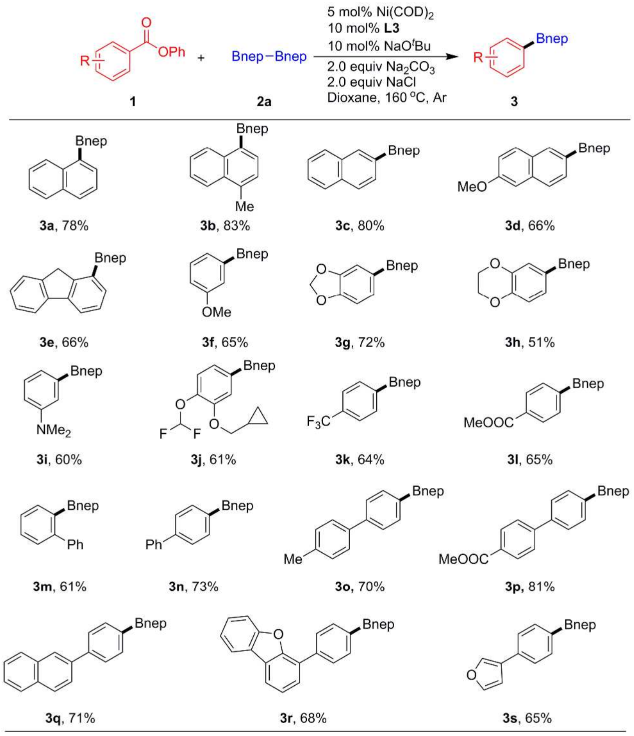


entry	[Ni]	L	additives (equiv)	yield (%)[b]
1	$Ni(COD)_2$	**L1**	NaF (2.0)	8
2	$Ni(COD)_2$	**L1**	Na_3PO_4 (2.0)	15
3	$Ni(COD)_2$	**L1**	Na_2CO_3 (2.0)	21
4	$Ni(COD)_2$	**L2**	Na_2CO_3 (2.0)	9
5	$Ni(COD)_2$	**L3**	Na_2CO_3 (2.0)	71
6	$Ni(COD)_2$	**L4**	Na_2CO_3 (2.0)	0
7	$Ni(COD)_2$	**L5**	Na_2CO_3 (2.0)	6
8	$Ni(COD)_2$	**L6**	Na_2CO_3 (2.0)	4
9	$Ni(COD)_2$	**L7**	Na_2CO_3 (2.0)	32
10	$Ni(COD)_2$	**L8**	Na_2CO_3 (2.0)	15
11	**$Ni(COD)_2$**	L3	**Na_2CO_3 (2.0) + NaCl (2.0)**	**81 (78)**[c]
12	$Ni(PCy_3)_2Cl_2$	**L3**	Na_2CO_3 (2.0) + NaCl (2.0)	66
13	$Ni(OAc)_2$	**L3**	Na_2CO_3 (2.0) + NaCl (2.0)	62
14[d]	$Ni(COD)_2$	**L3**	Na_2CO_3 (2.0) + NaCl (2.0)	74
15[e]	$Ni(COD)_2$	**L3**	Na_2CO_3 (2.0) + NaCl (2.0)	82
16	-	**L3**	Na_2CO_3 (2.0) + NaCl (2.0)	0



[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.80 mmol), 5 mol% of catalyst, 10 mol% of ligand,10 mol% of NaO^tBu (only in **L1**-**L4**), 2.0 equiv of base in dioxane (2.0 mL), at 160 °C, 12 h, under Ar. [b]Determined by GC analysis. [c]Isolated yield. [d]At 140°C. [e]Using 10 mol% $Ni(COD)_2$ and 20 mol% **L3**.

Table 2. Ni-catalyzed Decarbonylative Borylation of Phenolic Esters[a]

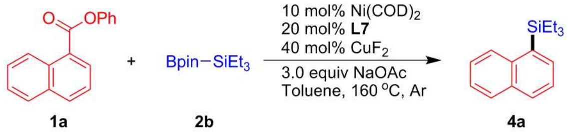


[a]Reaction conditions A: **1** (0.20 mmol), **2a** (0.80 mmol), 5 mol% of $Ni(COD)_2$, 10 mol% of **L3**, 10 mol% of NaO^tBu, 2.0 equiv of Na_2CO_3, 2.0 equiv of NaCl in dioxane (2.0 mL), at 160 °C, 12 h, under Ar; Isolated yields.

To evaluate the utility of this decarbonylative borylation reaction, a series of esters have been carried out (Table 2). As shown, a wide range of electronically and sterically diverse arene carboxylic acid esters underwent cross-coupling with B_2nep_2 (**2a**) in moderate to excellent yields. Polyaromatic substrates, including naphthalenes (**3a-3d**) and 9*H*-fluorene (**3e**) were also shown to exhibit high levels of reactivity. The chemoselectivity profile of this method was nicely illustrated by the fact that ethers (**3d**, **3f-3h**), amines (**3i**) and fluorocontaining compounds (**3j-3k**) could all be equally accommodated to synthesize the desired products. The unique selectivity toward phenolic ester was corroborated by the presence of other types of esters such as -COOMe group (**3l**). Decarbonylative borylation of phenyl [1,1'-biphenyl]-2-carboxylate (**1m**) satisfactorily provided desired product **3m** in 61% yield, inspite of the steric hindrance from the *ortho*-phenyl group. Moreover, a wide variety of π-extended systems,[25] participated in the reaction to afford borylation products **3n-3s** in moderate to high yields. Among them, the presence of substituted oxygen-containing heterocycles (**3r-3s**) did not interfere with productive C–B bond formation. These methods suggested that using a nickel catalyst in combination with a highly nucleophilic boron reagent is a promising approach to achieve the desired decarbonylative borylation of esters.

Nickel-catalyzed decarbonylative silylation of esters. After successful synthesis of arylboronates, we envisioned that aryl silanes could also be derived by a C-Si bond-forming event *via* the decarbonylative process under certain reaction conditions. Our investigation commenced with the cross coupling of phenyl 1-naphthoate (**1a**) and silylborane **2a** to give triethyl(naphthalen-1-yl)silane (**4a**). During experimentation to optimize the reaction condition, the best results were obtained with a catalytic amount of Ni(COD)$_2$ and CuF$_2$ as a multimetallic system,[17c, 20, 26] dcpye (**L7**) as the ligand and NaOAc as the additive in toluene (Table 3, entry 1). Under these conditions, conversion was completed within 48 h at 160 °C with 72% isolated yield. Control experiments revealed that all reaction parameters were critical for the success (entries 2-5), suggesting that a nucleophilic aromatic substitution pathway may not be in effect. Lowering the Ni(COD)$_2$ loading to 5 mol% and **L7** to 10 mol% resulted in a decreased yields (entries 6-7). As expected, the nature of the ligand played a critical role on the reactivity, the best ligand in the borylation reaction (**L3**) provided **4a** only in 18% yield (entry 8). Moreover, a significant erosion in yield was observed when using anhydrous Ni(OAc)$_2$ in this reaction (entry 9). Interestingly, a slight decrease in temperature gave a dramatic change in reactivity, providing **4a** in 55% yield (entry 10).

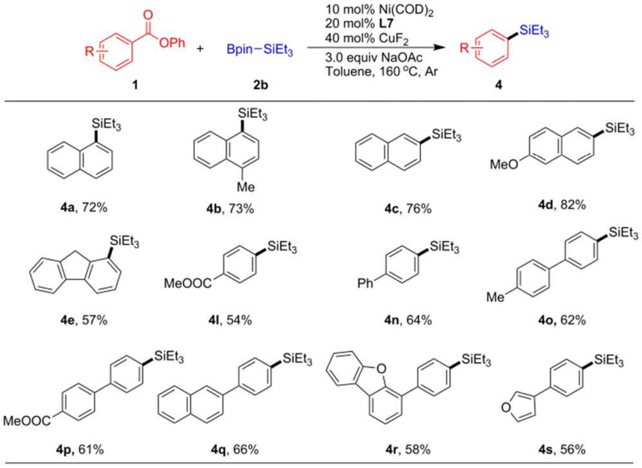
Table 3. Optimization of Reaction Conditions[a]



entry	Variation from the “standard conditions”	Yield of **4a** (%)[b]
1	none	78 (72)[c]
2	without Ni(COD)$_2$	0
3	without **L7**	0
4	without CuF$_2$	0
5	without NaOAc	trace
6	Using 5 mol% Ni(COD)$_2$	32
7	10 mol% **L7**	26
8	**L3** instead of **L7**	18
9	Ni(OAc)$_2$ instead of Ni(COD)$_2$	25
10	At 140 °C	55

[a]Reaction conditions: **1a** (0.20 mmol), **2b** (0.50 mmol), Ni(COD)$_2$ (10 mol%), **L7** (20 mol%), CuF$_2$ (40 mol%), NaOAc (0.6 mmol), toluene (1.0 mL), 160 °C, 48 h, under Ar. [b]Determined by GC analysis. [c]Values in parentheses indicate isolated yield.

Table 4. Ni-catalyzed Decarbonylative Silylation of Phenolic Esters[a]

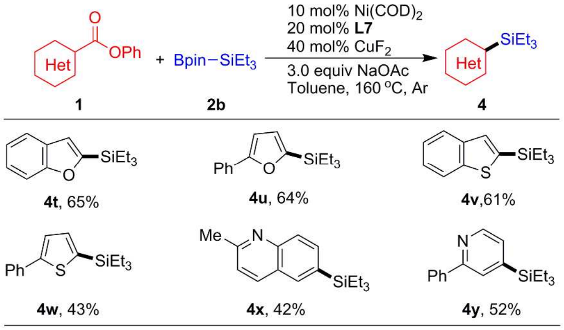


[a]Reaction conditions B: **1** (0.20 mmol), **2b** (0.50 mmol), 10 mol% of Ni(COD)$_2$, 20 mol% of **L7**,40 mol% of CuF$_2$, 3.0 equiv of NaOAc, in toluene (1.0 mL), at 160 °C, 48 h, under Ar; Isolated yields.

As outlined in Table 4, we have found that a broad range of aryl rings can be selectively coupled with silylborane **2a** using this multimetallic system. The coupling of naphthoic acid derivatives was performed very well to afford the desired products in good efficiency, irrespective of the ester group location either at 1- or at 2-positions (**4a-4d**). This Ni/Cu-cocatalyzed silylation event could be even extended to the use of simpler, yet challenging phenyl esters. For instance, the ester (**4l**) and phenyl groups (**4n**) did not affect in desired outcome of the process. In addition, the reaction of extended π systems can also afforded desired products **4o-4s** in 56-66% yields.

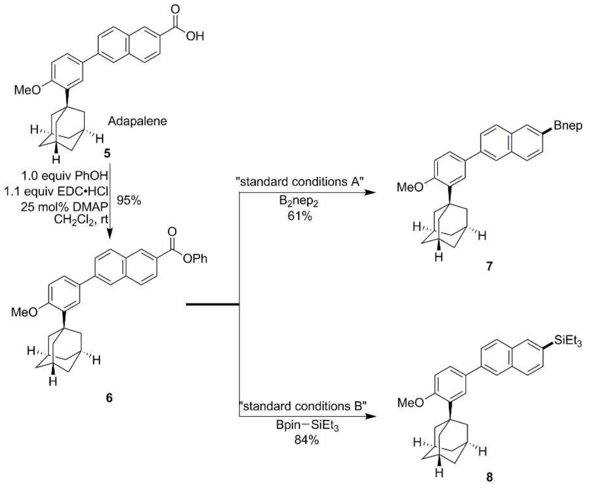
Since most heteroarylboronates are inherently unstable, which can’t be synthesized by this present Ni-catalyzed method.[27] However, a great variety of heteroaryl esters can be transformed into the corresponding silanes under the optimized reaction conditions (Table 5). Heteroaryl esters bearing a benzofuran (**4t**), furan (**4u**), benzo[*b*]thiophen (**4v**), thiophen (**4w**), quinolone (**4x**) and pyridine (**4y**) which are often found in bioactive compounds, participated in the reaction, affording the corresponding products in acceptable yields.

Table 5. Ni-Catalyzed Decarbonylative Silylation of Heteroaryl Esters[a]



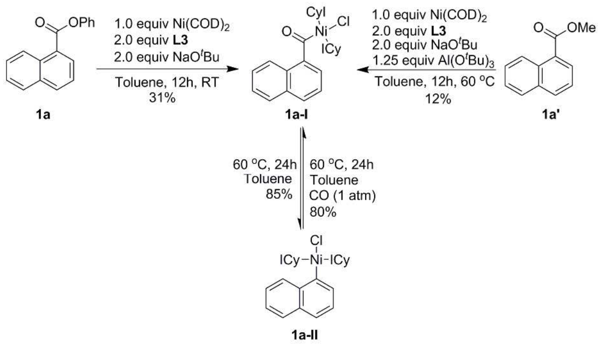
[a]Reaction conditions B: **1** (0.20 mmol), **2b** (0.50 mmol), 10 mol% of Ni(COD)$_2$, 20 mol% of **L7**,40 mol% of CuF$_2$, 3.0 equiv of NaOAc, in toluene (1.0 mL), at 160 °C, 48 h, under Ar; Isolated yields.

Late-stage decarbonylative borylation and silylation of Adapalene. Late-stage modification of naturally significant molecules to access new bioactive compounds has been an promising concept in organic chemistry.[28] Encouraged by this successful decarbonylative borylation and silylation process, we also turned our attention to utilize the method as a key step for selective functionalization of a complex molecule, Adapalene **5**, a second-generation topical retinoid primarily used in the treatment of mild-moderate acne.[29] This compound could be converted to the corresponding ester **6** by the treatment of PhOH in excellent yield. Under the standard condition A, the formed ester **6** could be subjected to decarbonylative borylation with $B_2(nep)_2$ (**2a**) to produce the arylboronate **7** in 61% isolated yield. Alternatively, this substrate can also be subjected to standard condition B to take place the decarbonylative silylation with silylborane **2a** generating arylsilane **8** in 84% yield (Scheme 1).



Scheme 1. Late-stage Decarbonylative Borylation and Silylation of Adapalene.

Synthesis, isolation and identification of nickel intermediates. Previously, we reported the synthesis of acylnickel^{II} complexes from oxidative addition of Ni^0 to amide C-N bond.[21] However, as a key intermediate, the transient acylnickel^{II} species has never been structurally characterized in acyl C–O bond cleavage. According the above investigation, NHC ligand **L3** is beneficial for the Ni-catalyzed borylation of esters, but fundamental understanding of the ligand effect on acyl C−O bond cleavage has been limited by the challenges associated with the isolation of acylnickel^{II} intermediates.



Scheme 2. Stoichiometric Reactions of Ester 1a with $Ni(COD)_2$

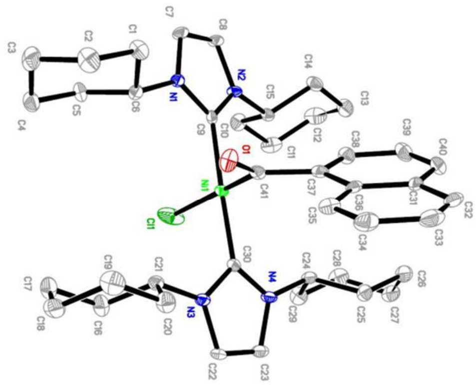


Figure 2. Molecular Structure of 1a-I Shown with 30% Probability Ellipsoids

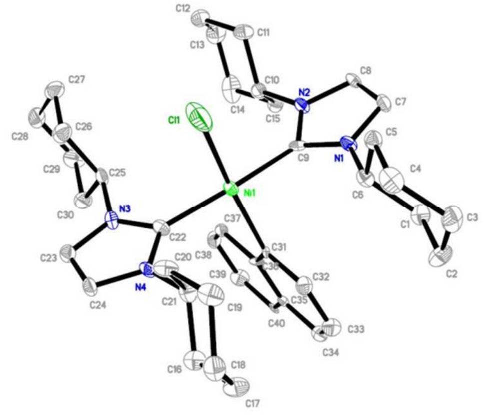
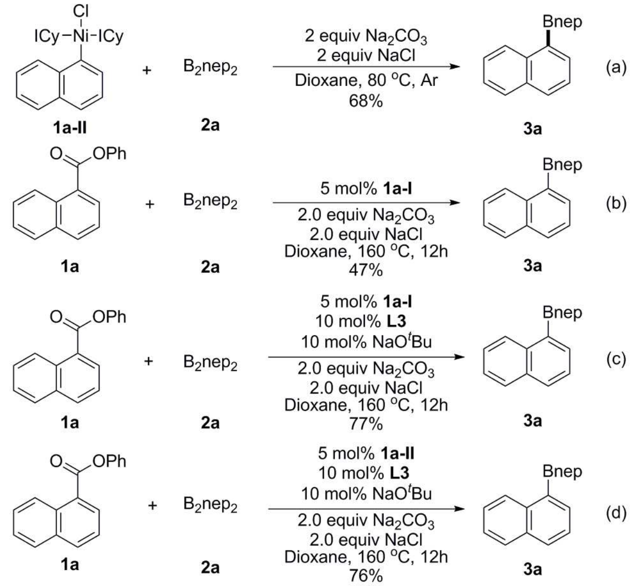


Figure 3. Molecular Structure of 1a-II Shown with 30% Probability Ellipsoids

We prepared (1-naphthoyl)NiCl$(ICy)_2$ (**1a-I**) by treatment of ester **1a** with $Ni(COD)_2$, NHC ligand **L3** and NaO^tBu in toluene at room temperature (Scheme 2). The molecular structures of complexes **1a-I** in the solid state was shown in Figure 2, and the structure refinement data are given in supporting information. In **1a-I**, two carbene ligands are coordinated to nickel mutually in *trans* position to each other with one 1-naphthoyl group and a chlorine atom, building up the formal coordination number to 4 and displaying a square planar geometry. Under these conditions, the acyl C-O bonds of methyl ester **1a'** seems infective to generate **1a-I** through an oxidative addition process. According to the DFT calculation from Garg, Houk and coworkers, the addition of Lewis acid $Al(O^tBu)_3$ can lower the kinetic barrier for activating the acyl C-O bonds of methyl esters.[7] To prove the theoretical study, 1.25 equiv $Al(O^tBu)_3$ was added to the system and the desired acylnickel^{II} species **1a-1** was indeed formed in 12% isolated yield. Furthermore, the decarbonylative process was also observed. Complex **1a-1** undergoes decarbonylation to produce an arylnickel intermediate **1a-II** with 85% isolated yield at 60 °C. This complex was obtained in pure form after column chromatography, which was also confirmed by NMR and X-ray analysis (Figure 3). We next investigated the reactivity of this isolated arylnickel complex towards the reversible path. Upon heating at 60°C for 12 hours under 1 atm CO atmosphere, complex **1a-II** underwent carbonylation to produce acylnickel intermediate **1a-I** in high yield. Treatment of the stoichiometric reactions of complex **1a-II** with B_2nep_2

in presence of Na_2CO_3 and NaCl at 80°C in dioxane gave the corresponding arylboronate **3a** in 68% yield (Scheme 3a). Nickel complexes **1a-I** and **1a-II** were also capable of effecting the catalytic borylation approximately in identical efficiency (Scheme 3b-3d), suggesting the intermediacy of these complexes in the catalytic cycle.



Scheme 3. Studies Designed to Support the Mechanism

On the basis of these investigations, we have hypothesized that the mechanism outlined in Figure 4 is operative when ester **1** is employed as electrophile. This reaction triggered by oxidative addition of the nickel^0 catalyst into ester C−O bond generates an *cis* acylnickel^{II} intermediate **A**.[30] This complex can easily undergo ligand exchange with Cl^- (or other anionic reagents in the system such as AcO^-, $^tBuO^-$) generating *trans* acyl nickel species **B**, followed by decarbonylation to provide aryl nickel species **C**. Decarbonylation of **B** to trans aryl nickel species **C**, followed by boryl transfer assisted by the base and subsequent *cis* reductive elimination delivers the target product **3** and regenerates the $Ni(ICy)_2$ species.

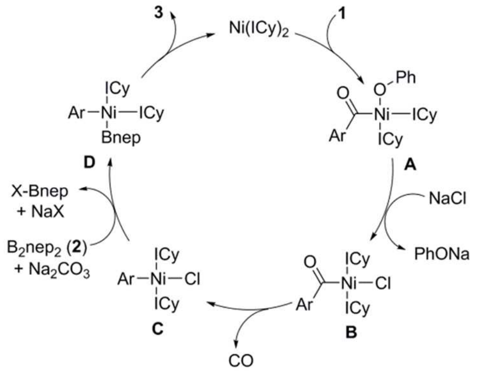


Figure 4. Proposed Catalytic Cycle for Decarbonylative Borylation of Esters

Probably due to unstability of nickel intermediates using dcype as the ligand in decarbonylative silylation of esters, we could not isolate the desired acylnickel and arylnickel intermediates at the current stage. Although detailed mechanism requires further studies, we believe that these two reactions have a lot of similarities (Figure 5). In this silylation process, the formed aryl nickel species **C** undergoes transmetalation with in situ generated copper silane intermediate **D**, followed by a reductive elimination that delivers the final product and regenerates the active Ni^0 catalytic species.

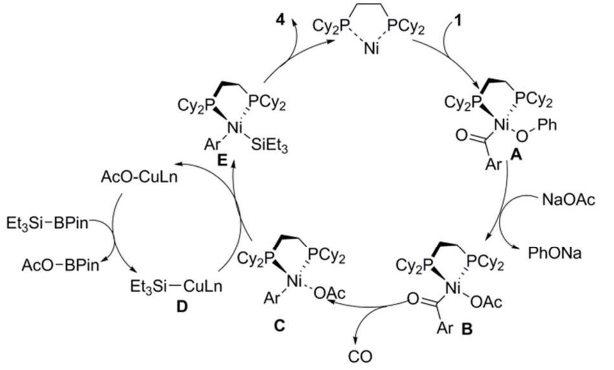


Figure 5. Proposed Catalytic Cycle Decarbonylative Silylation of Esters

CONCLUSION

In summary, we have developed two efficient Ni-catalyzed systems capable of activating ester C–O bonds for decarbonylative borylation and silylation to produce various aryl boronates and silanes. In view of the widespread ester group and its precursors in chemicals, this method offers a meaningful tool to enable them as valuable building blocks. The elucidation of key mechanistic features of this newly developed reaction was confirmed by two well-characterized Ni intermediates. Further mechanistic details of this borylation and silylation process as well as expansion of the scope of the transformation are in progress in our laboratory.

ASSOCIATED CONTENT

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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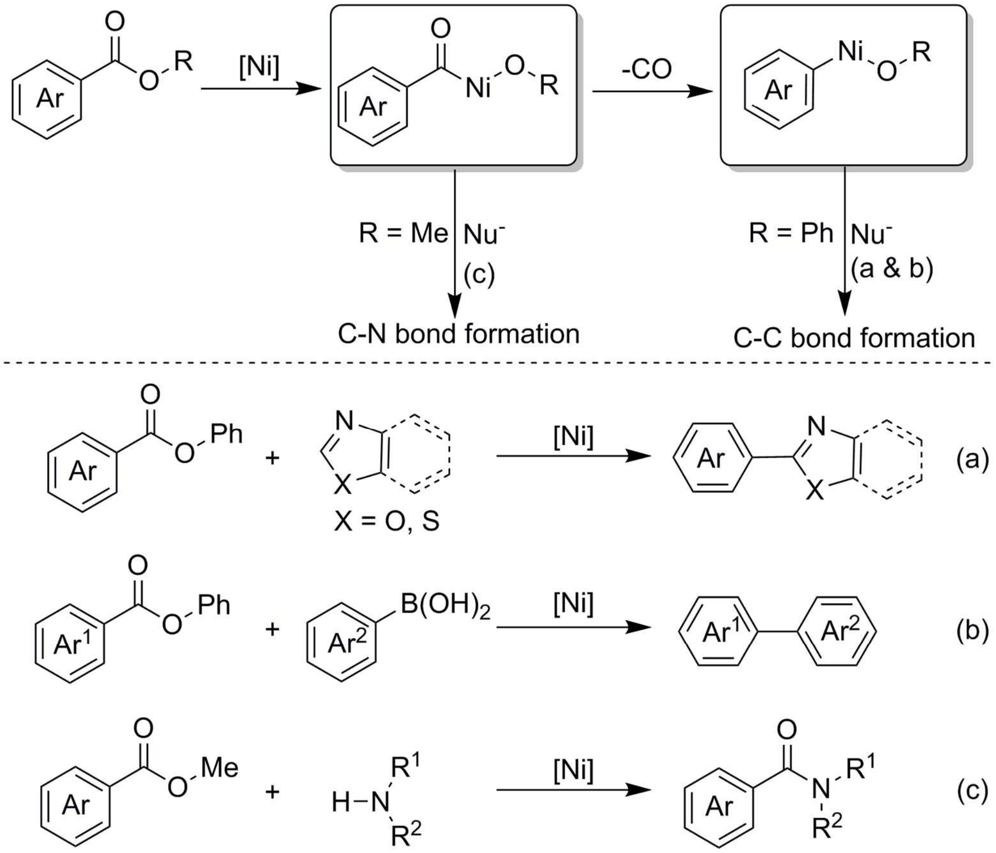

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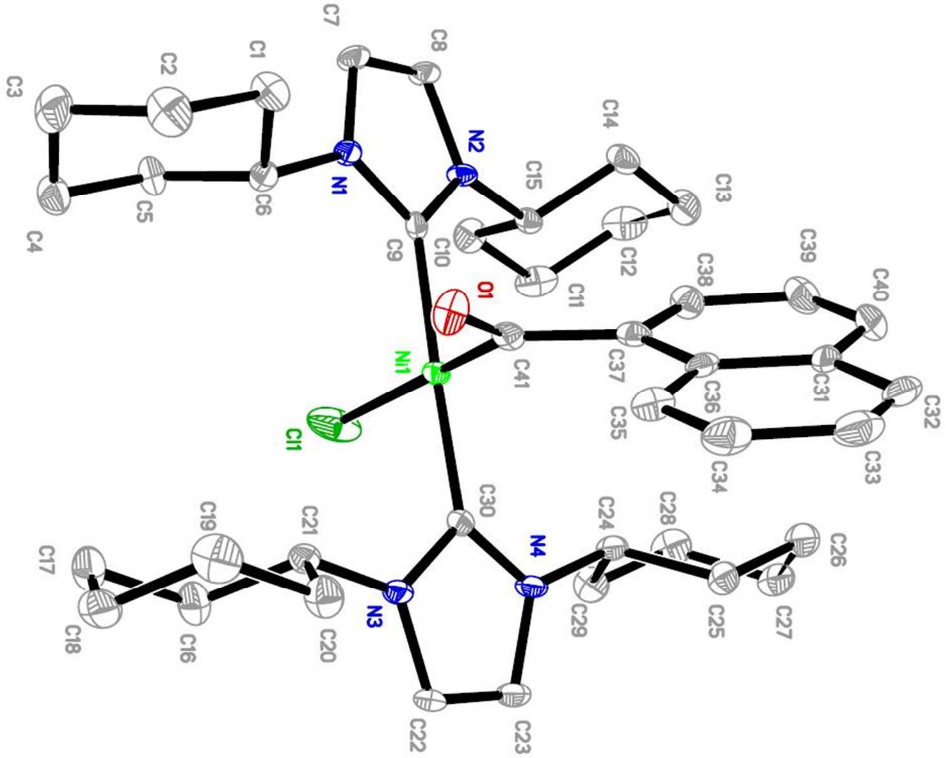

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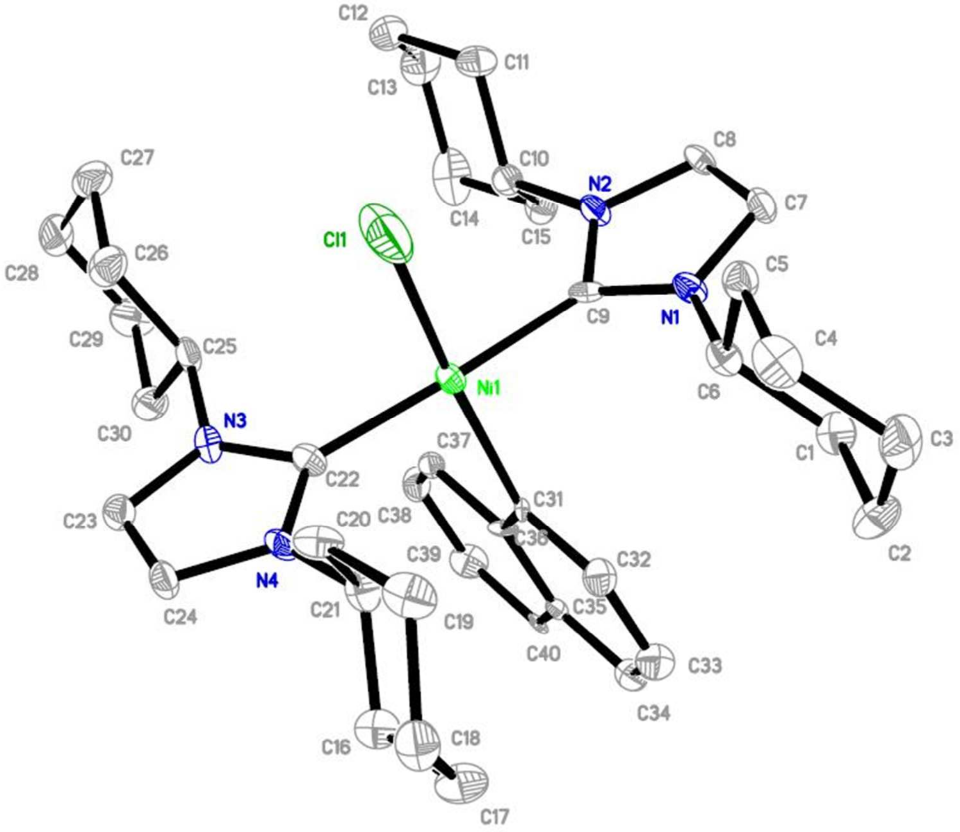

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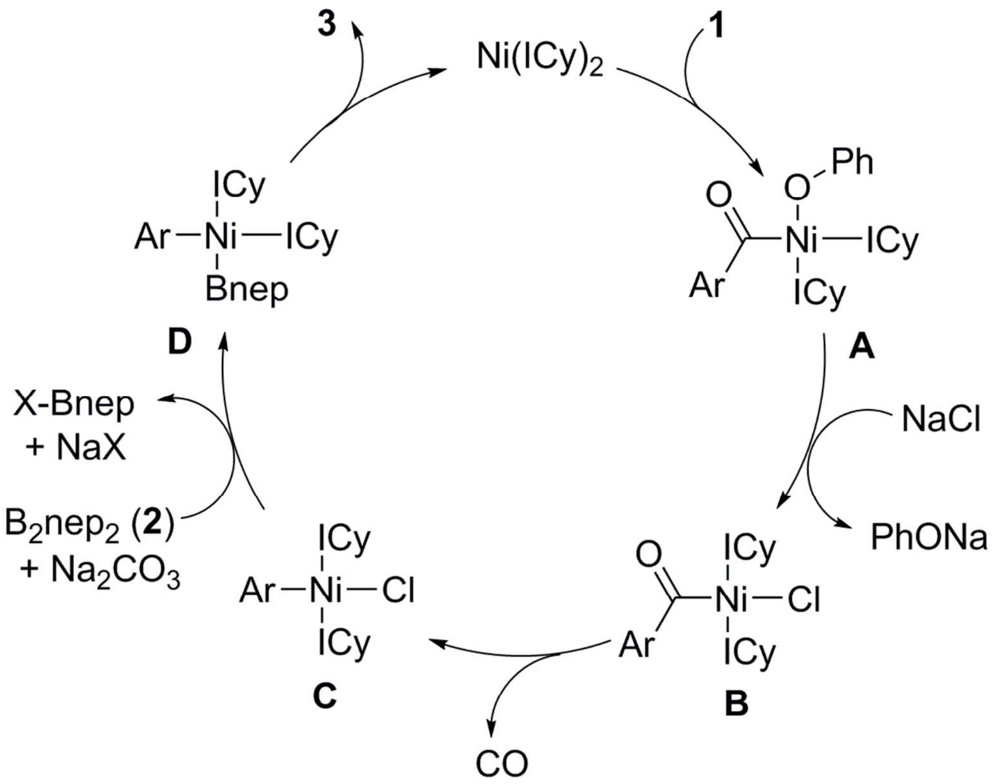

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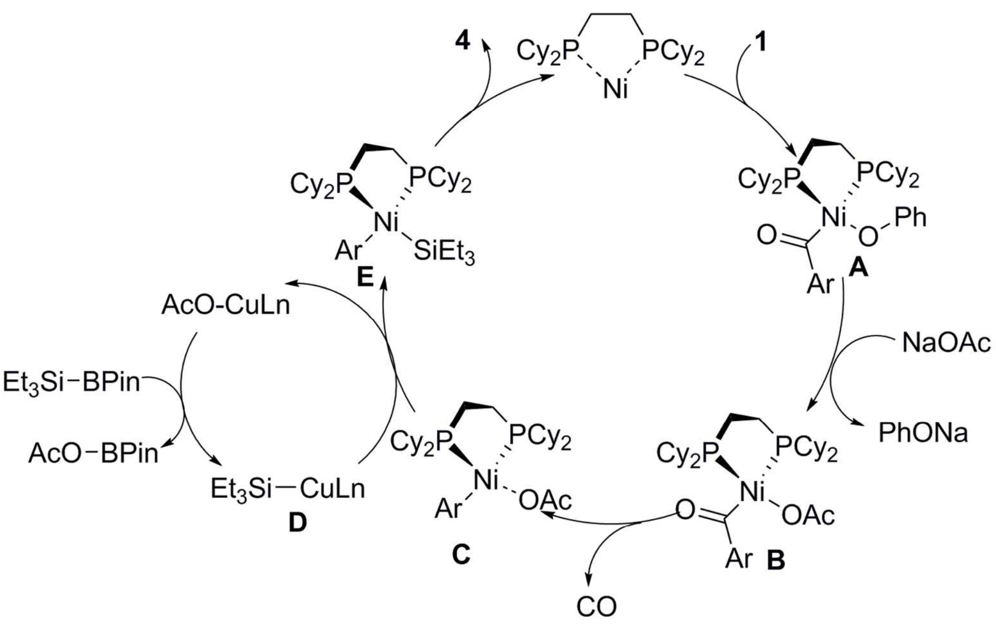

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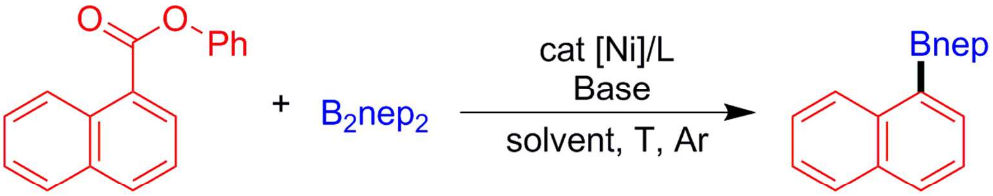

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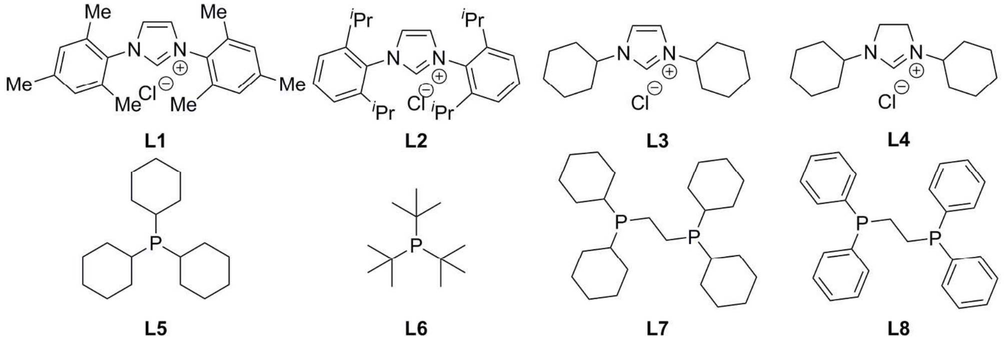

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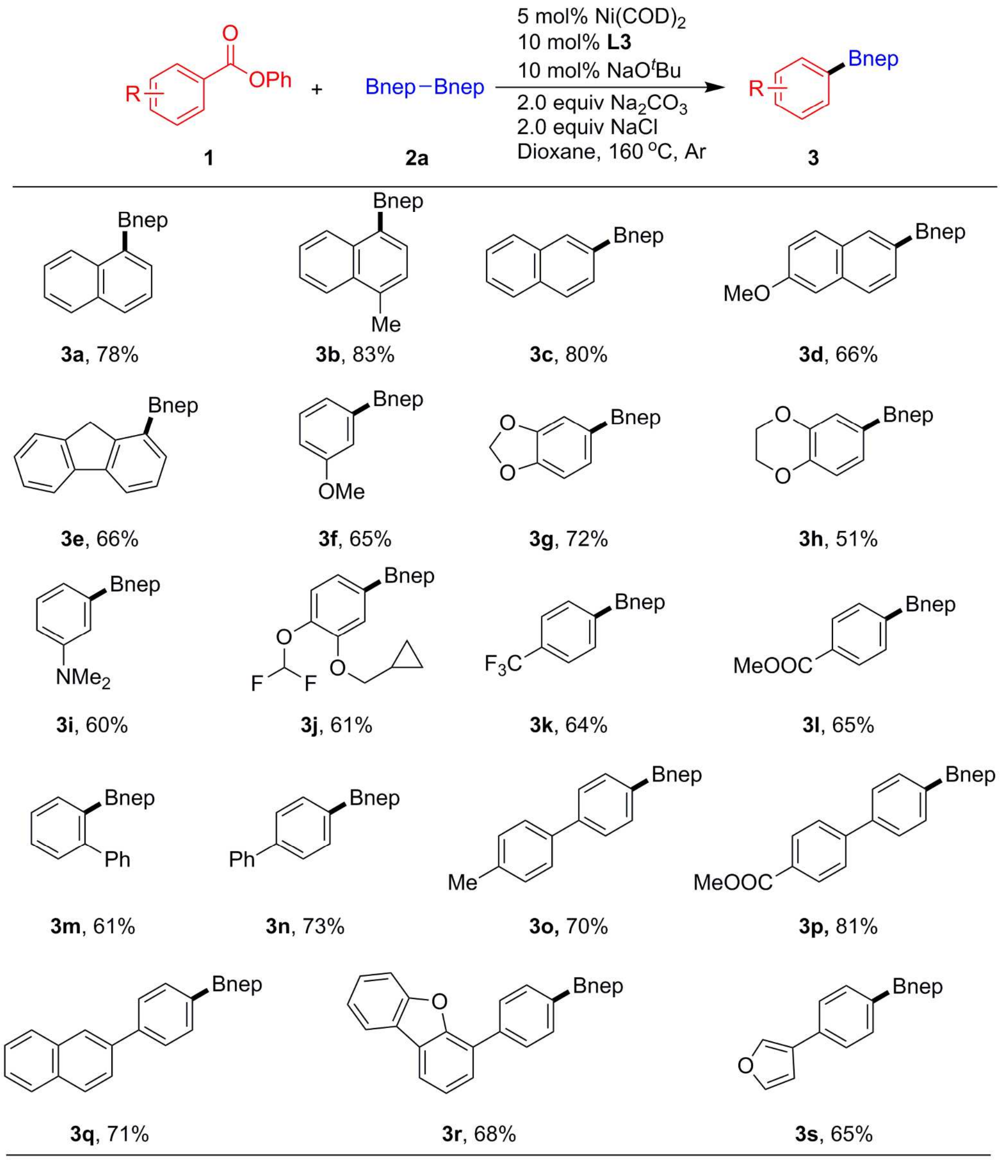

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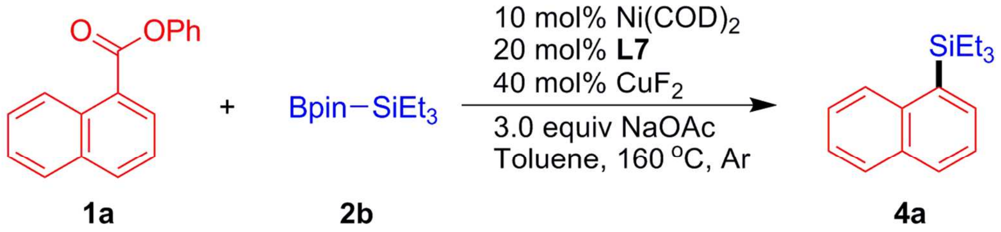

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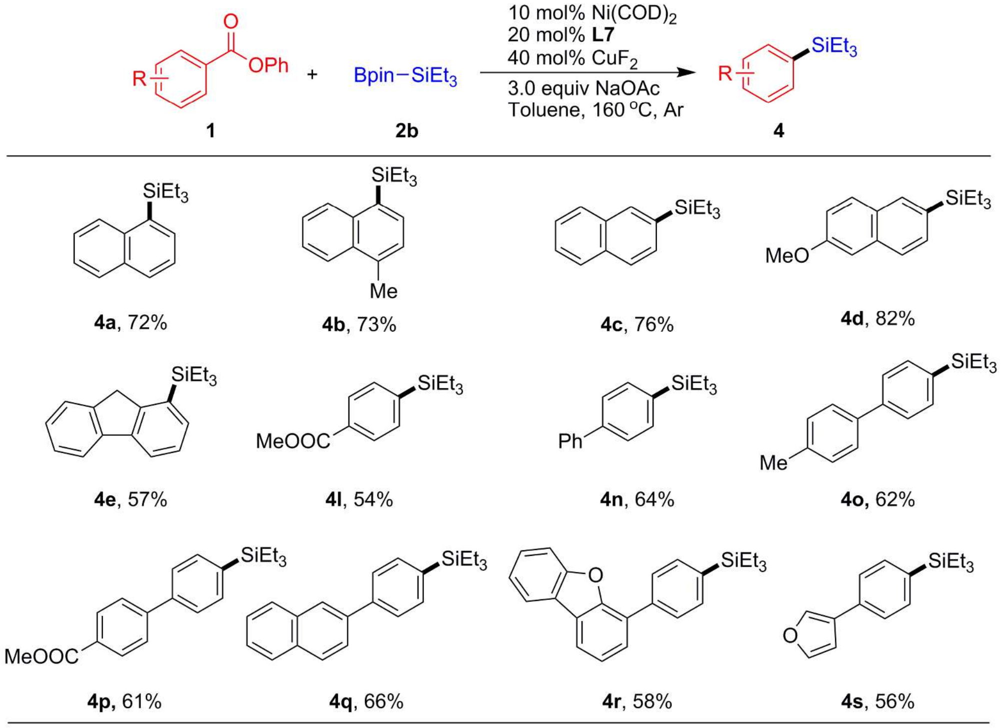

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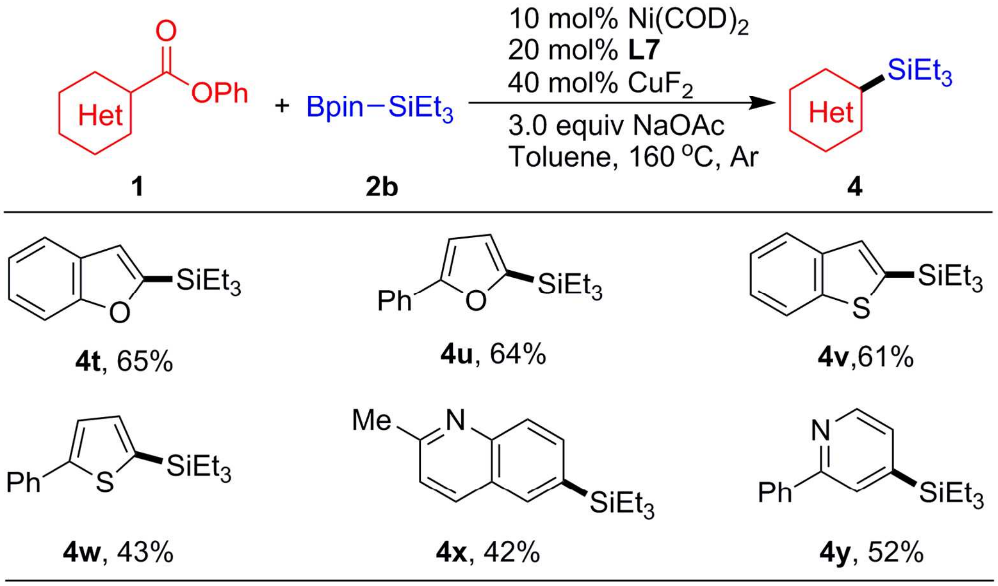

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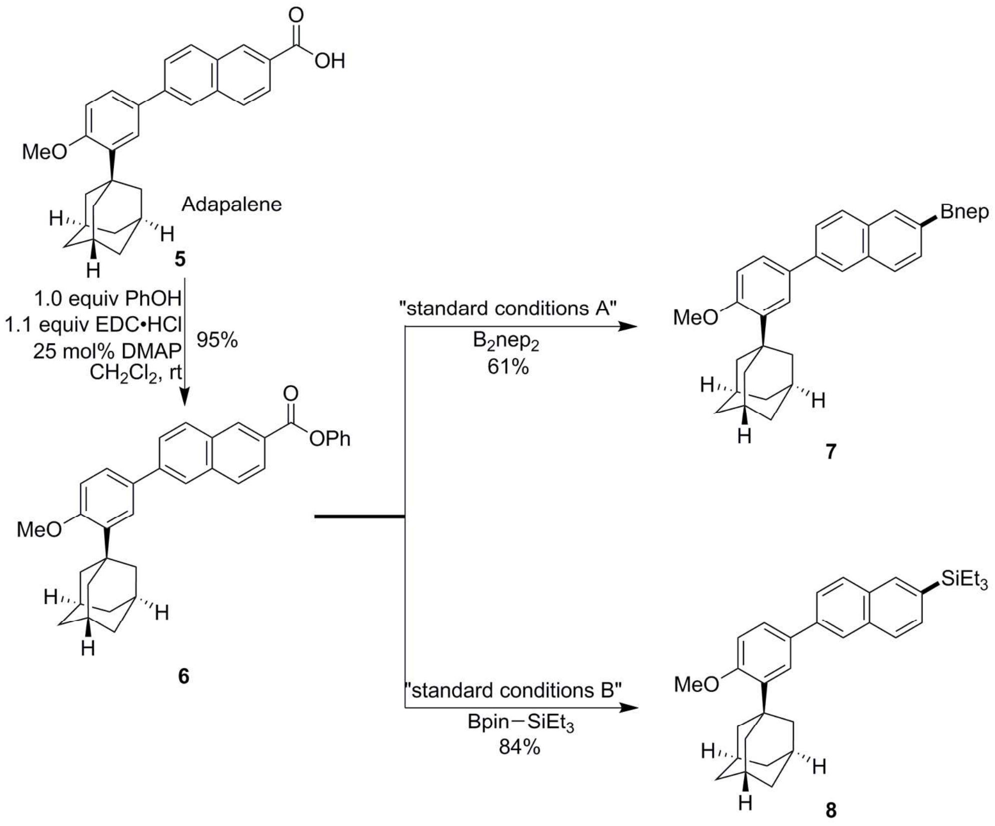

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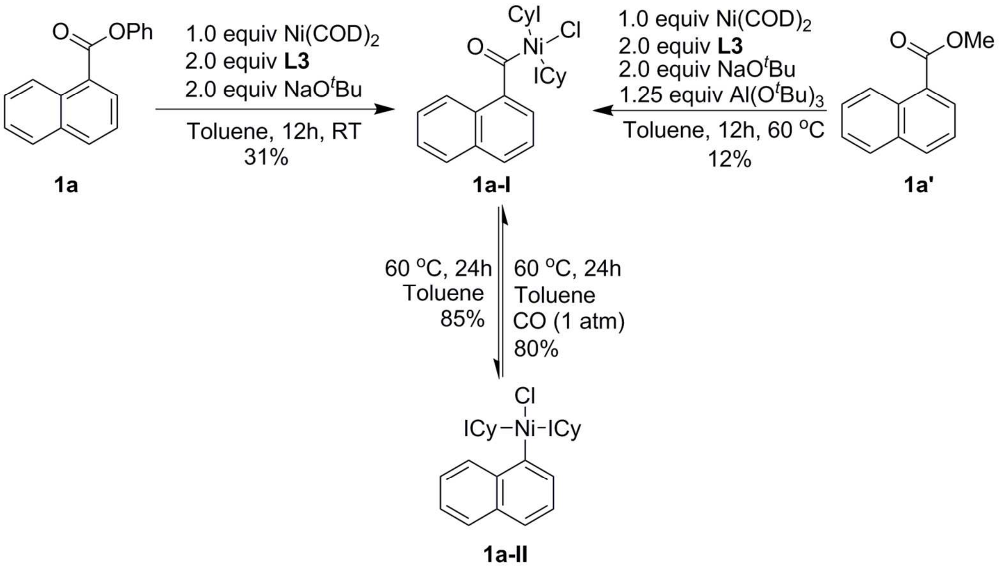

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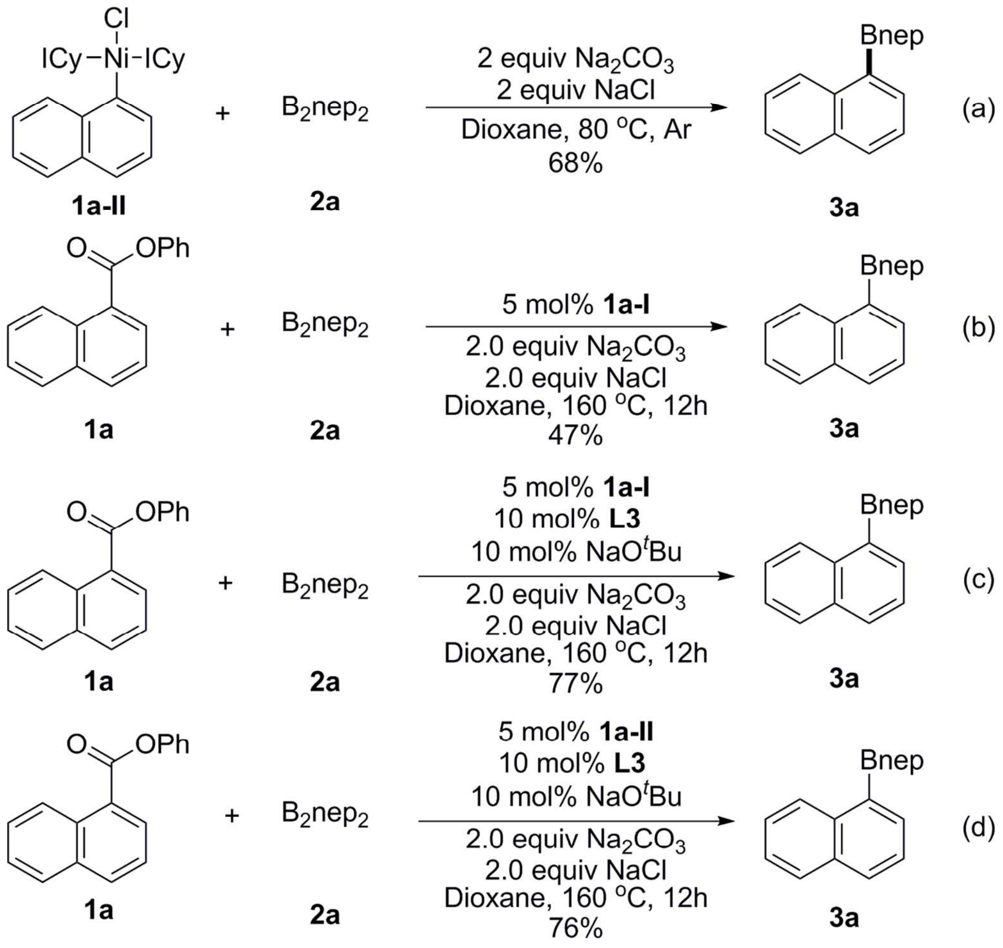

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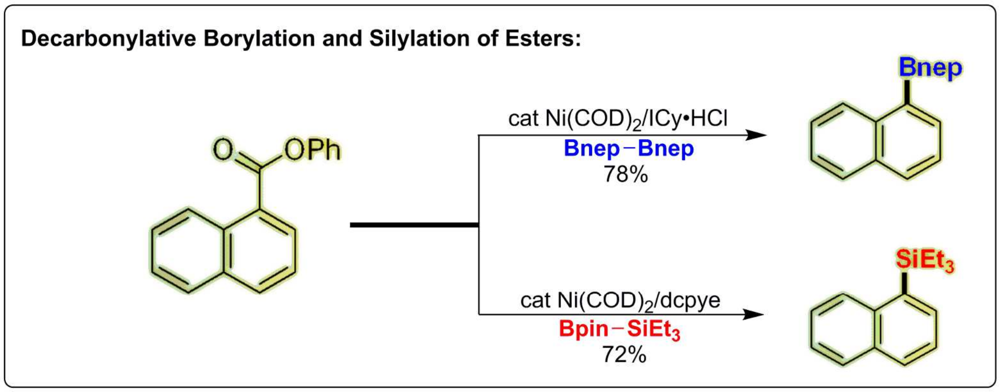

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