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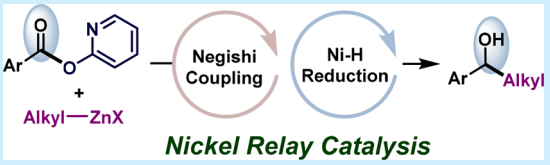
Direct Transformation of Aryl 2-Pyridyl Esters to Secondary Benzylic Alcohols by Nickel Relay Catalysis

Xianqing Wu, Xiaobin Li, Wenyi Huang, Yun Wang, Hui Xu, Liangzhen Cai, Jingping Qu,* and Yifeng Chen*

Key Laboratory for Advanced Materials and Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, School of Chemistry and Molecular Engineering, East China University of Science & Technology, 130 Meilong Road, Shanghai, 200237, China

Supporting Information

ABSTRACT: A direct transformation of aryl esters to secondary benzylic alcohols via tandem Ni-catalyzed cross-coupling reactions of aromatic 2-pyridyl esters with alkyl zinc reagents and carbonyl group reduction by Ni−H species is achieved. Preliminary mechanistic studies reveal that the Ni−H species is generated *in situ* via *β*-hydride elimination of the Negishi reagents. The reaction is catalyzed by bench-stable nickel salts under mild conditions with wide functional group tolerance.



Aromatic esters are easily accessed feedstock starting materials, which are commonly employed in organic synthesis to afford tertiary benzylic alcohols and primary benzylic alcohols via the organometallic reagents addition (Scheme 1a). Recently, transition-metal-catalyzed cross-coupling reactions of aromatic esters have emerged as powerful tools for expedient formation of various carbon−carbon, carbon−heteroatom and carbon−metal bonds in either decarbonylative or nondecarbonylative ways.[1−5] Despite the broad utility of these transformations, the practical, direct forging secondary benzylic alcohols from aromatic esters still remains a significant synthetic challenge. Nevertheless, the most commonly employed strategy relies on the two-step Weinreb amide chemistry[6] or Fukuyama reaction,[7] followed by an additional reducing manipulation, which could result in the potential chemo-unselective side reductions in complex molecular synthesis.[8a] The prevalence of secondary benzylic alcohols in biologically active compounds has driven us to tackle this synthetic gap via the relay catalysis to achieve the step economy and redox economy synthesis.[8] The relay catalysis via metal−organic[9] or dual-metal[10] combinations has emerged as a versatile and powerful strategy in organic synthesis and made remarkable progress over the past years, which possesses substantial advantages in enhancing reactivity and selectivity in more efficient ways. However, a single transition metal catalyst in relay catalysis involving two catalytic cycles through different oxidation state transformation is still very rare.[11]

Aryl 2-pyridyl ester was seminally reported by the Chatani group in a Suzuki−Miyaura reaction through the facile formation of an acyl palladium intermediate through the chelation of a nitrogen atom in the pyridine ring.[12] Compared with the well-established aromatic phenyl esters, research on aryl 2-pyridyl esters has been less developed.[13] Herein, we propose a nickel-catalyzed cross-coupling reaction of aryl 2-pyridyl esters with alkyl zinc reagents to achieve direct transformation of aromatic carboxylic acid derivatives to secondary benzylic alcohols, in which the Negishi reagents act as both coupling partners and the reducing sources (Scheme 1b).[14,15] We speculate the following mechanism (Scheme 1c): the low valent−nickel species undergoes oxidative addition to **1** to form acyl nickel intermediate **A**, which proceeds via transmetalation with the Negishi reagent to form intermediate **B**, followed by reductive elimination to afford the ketone intermediate **3**. Meanwhile, the alkyl zinc reagent serves as the precursor to the hydride species. The alkyl−nickel intermediate **C** proceeds with the *β*-hydride elimination to form the crucial Ni−H species **D**, which then reduces ketone **3** to form intermediate **E**. Ultimately, the alkoxyl nickel species **E** reacts with the Negishi reagent to regenerate **C** in order to form final product **2** after a hydrolytic workup procedure. To enable the catalytic cycle, several issues should be addressed. First, the most common precursors of Ni−H[16] such as silanes,[17] HBpin,[18] and alkyl halides[19] could lead to competing reactions with either acyl metal intermediates or Negishi reagents. Thus, the use of a Negishi reagent as a Ni−H precursor would provide a solution for the problem. Meanwhile, excess Negishi reagent could potentially react with the ketone intermediate to afford the corresponding tertiary alcohol.[20] Furthermore, the intermediate **B** could undergo the direct elimination to afford aldehyde intermediate **G**, followed by the organometallic reagent addition sequence (Scheme 1c, path b).

We commenced our research by investigating the reaction between pyridin-2-yl benzoate **1a** and ^{n}BuZnCl as the Negishi

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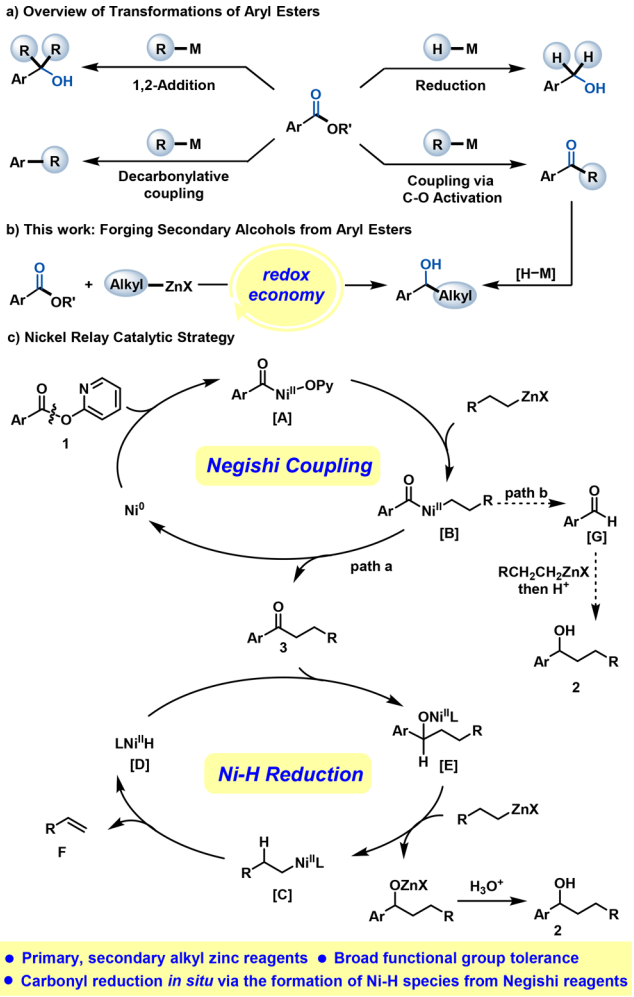
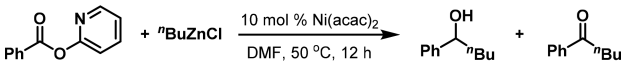
Scheme 1. Development of the Transformation of Aryl Esters to Benzylic Alcohols



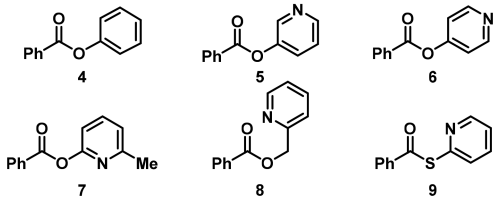
reagent. The reaction proceeded smoothly when catalyzed by 10 mol % bench-stable $Ni(acac)_2$ in DMF at 50 °C for 12 h without additional ligand, delivering the desired product **2a** in 87% isolated yield. Under these conditions, the corresponding intermediate **3a** was not observed in the crude reaction mixture (Table 1, entry 1). It should be pointed out that the isomerization of the **1a** to corresponding *N*-benzoyl-2-pyridone is not observed. The 2-hydroxypyridine was also not obtained during the workup manipulation, which indicated that the 2-pyridione may coordinate with the excess zinc salts. Optimization of the leaving group revealed the importance of the 2-pyridyl functional group in this tandem Negishi/Ni−H reduction sequence. The employment of commercially available phenyl benzoate **4** was unsuccessful, and no desired product could be obtained (Table 1, entry 2). The substitution effect on the pyridine ring was also critical for this nickel relay catalysis. A minimal amount of **2a** was obtained while using 3- or 4- substituted pyridyl esters **5** and **6** (Table 1, entries 3 and 4), which revealed that the chelation of the 2-substituted pyridine ring presumably promoted the tandem sequence.[21] Moreover, steric effects on the pyridine were also significant; the efficiency dropped dramatically with the introduction of a methyl group at the 6-position (Table 1, entry 5). When 2-pyridinemethanol was utilized as the ester group, the corresponding benzyl ester failed to afford **2a** (Table 1, entry

Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from above	conv. of **1a**%[b]	yield of **2a**%[b]	yield of **3a**%[b]
1	none	100	87[c]	0
2	**4** instead of **1a**	43	0	<5
3	**5** instead of **1a**	72	0	<5
4	**6** instead of **1a**	100	7	9
5	**7** instead of **1a**	100	32	29
6	**8** instead of **1a**	78	0	<5
7	**9** instead of **1a**	100	0	71
8	$Ni(COD)_2$ instead of $Ni(acac)_2$	100	54	15
9	$NiCl_2(DME)$ instead of $Ni(acac)_2$	100	69	0
10	$Pd(OAc)_2$ instead of $Ni(acac)_2$	100	0	26
11	THF instead of DMF	100	30	48
12	added 20 mol % SIPr•HCl	100	52	12
13	2.0 equiv nBuZnCl instead of 3.0 equiv	100	31	38

Representative carboxylic acid derivatives:



[a]Reaction conditions: **1a** (0.2 mmol), nBuZnCl (0.6 mmol), $Ni(acac)_2$ (0.02 mmol), DMF (1 mL), 50 °C, 12 h. [b]Corrected GC yield. [c]Isolated yield at 1.0 mmol scale.

6). The Fukuyama type product **3a** was solely observed in the reaction mixture using 2-pyridyl thioester **9** as starting material (Table 1, entry 7). The investigation of other commercially available nickel catalysts, including the air/moisture sensitive $Ni(COD)_2$ and $NiCl_2(DME)$, led to inferior results (Table 1, entries 8 and 9). Intriguingly, switching the nickel catalyst to palladium catalyst $Pd(OAc)_2$ failed to provide any desired product (Table 1, entry 10). Additionally, attempts to improve the efficiency by changing the solvent from DMF to THF was also ineffective (Table 1, entry 11). The strongly coordinating ligand SIPr·HCl was also detrimental to the reaction, indicating the possibility of ligand effects between pyridine-2-olate and the nickel metal center,[21] which would lead to acceleration of the Ni−H reduction step (Table 1, entry 12).[22] Decreasing the amount of Negishi reagent from 3.0 to 2.0 equiv resulted in a lower yield (Table 1, entry 13).

With the optimized conditions in hand, we explored the scope of the aryl 2-pyridyl esters with the alkyl zinc reagents (Scheme 2). Various substituted aryl 2-pyridyl esters containing both electron-donating and -withdrawing groups on the aryl rings could be tolerated, affording the corresponding benzylic alcohols in moderate to good yield (51−94%). The reaction proceeds well with a variety of functional groups, including substituted phenols (**2d**, **2j**, **2k**, **2l**), a trifluoromethyl group (**2h**), fluorines (**2e**, **2i**), a tertiary carbamate (**2m**), a tertiary aniline group (**2t**), and a benzoxazole group (**2u**). Interestingly, it was found that the substitution at the *meta*- or *para*- position of the aryl ring had minimal effect (**2d**−**2o**) on the reaction, while the yields dropped with introduction of groups *ortho*- to the aryl 2-pyridyl esters (**2b**, **2c**), probably due to the disfavored steric

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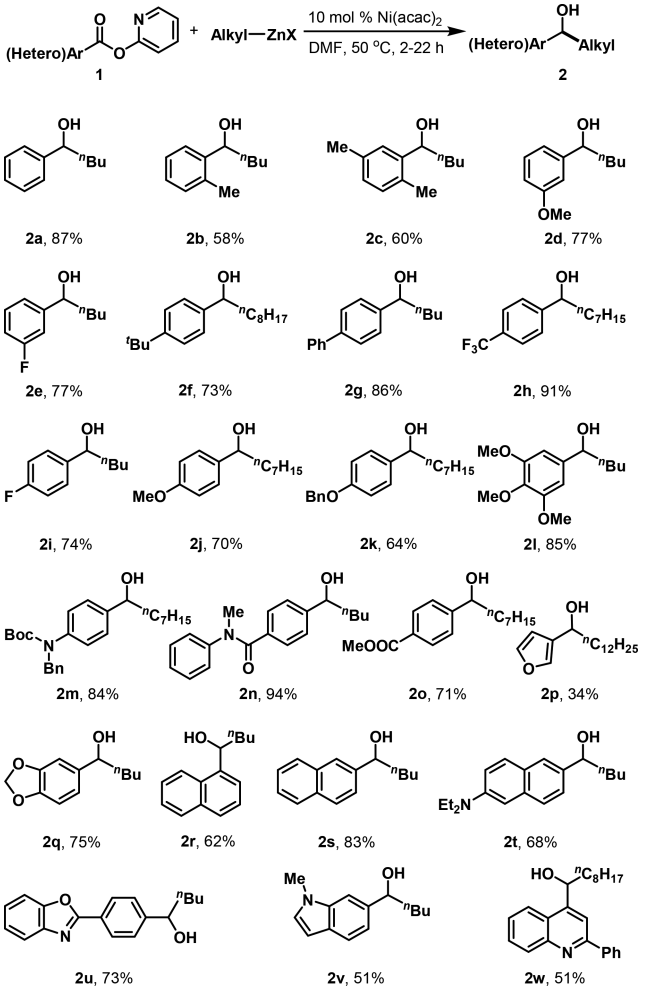
Scheme 2. Scope of 2-Pyridyl Esters for Nickel-Catalyzed (Hetero)Aryl 2-Pyridyl Ester with Alkyl Zinc Reagent[a]

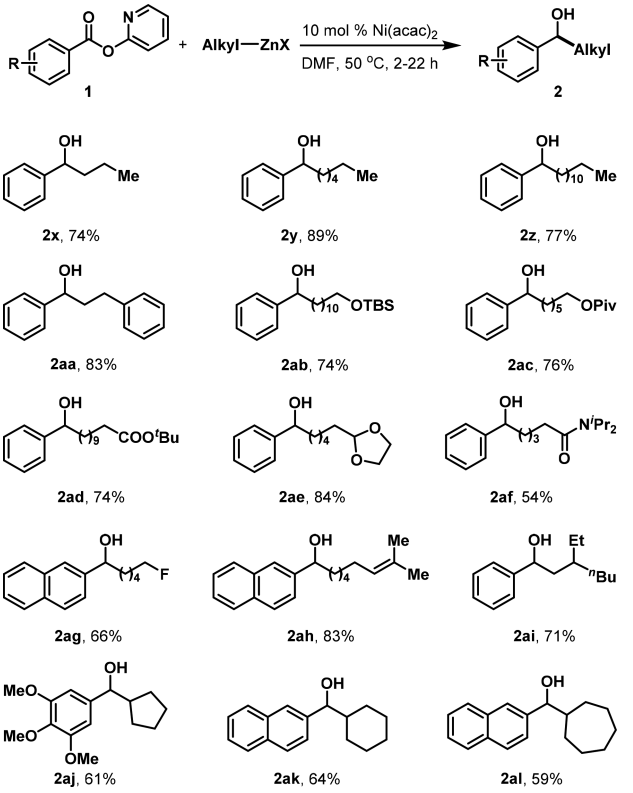


[a]All reactions were performed with **1** (1.0 equiv), RZnX (3.0 equiv), and $Ni(acac)_2$ (10 mol %) in DMF at 50 °C; isolated yields were reported.

repulsion during the Ni−H reduction process. To further show the tolerance of carbonyl functionalities in the reaction, both *N*,*N*-disubstituted amide (**2n**) and methyl ester (**2o**) containing products could be obtained in 94% and 71% isolated yield, respectively, which elucidated that the nickel catalyst preferentially underwent oxidative addition with the more reactive 2-pyridyl ester group. Some heteroaromatic 2-pyridyl esters including furan (**2p**), indole (**2v**), and quinoline (**2w**) were also suitable substrates for this cascade reductive Negishi reaction, albeit in diminished yields (34−51%).

To further explore the robustness of the reaction, we investigated the scope of the Negishi reagents (Scheme 3). It was shown that the easily accessible linear primary alkylated zinc reagents worked well with phenyl 2-pyridyl ester **1a**, affording the corresponding alcohols **2x**−**2aa** in high yields (74−89%). The Negishi nucleophiles with functionality such as OTBS (**2ab**), OPiv (**2ac**), COO^tBu (**2ad**), acetal (**2ae**), tertiary amide (**2af**), fluoride (**2ag**), and alkene (**2ah**) were also tolerated. Additionally, the introduction of an ethyl group at the β-substituent on the alkyl chain of the nucleophile has a subtle impact on the overall efficiency, affording **2ai** in 71% isolated yield. Notably, the cyclic alkyl Negishi reagents

Scheme 3. Scope of Negishi Reagents for Nickel-Catalyzed (Hetero)Aryl 2-Pyridyl Ester with Alkyl Zinc Reagent[a]

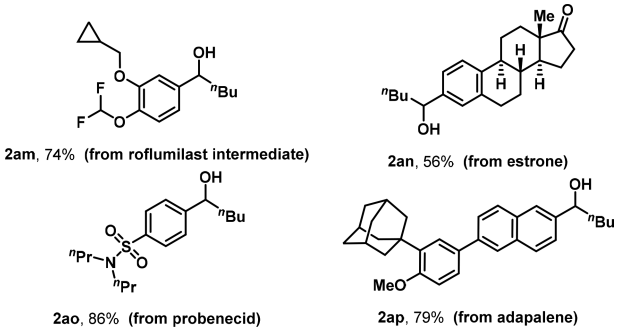


[a]All reactions were performed with **1** (1.0 equiv), RZnx (3.0 equiv), $Ni(acac)_2$ (10 mol %) in DMF at 50 °C; isolated yields were reported.

containing five-membered to seven-membered rings could also serve dual roles as nucleophile and precursor of the reducing reagent (**2aj**−**2al**).

Additionally, biologically active roflumilast intermediate (**2am**), estrone (**2an**), probenecid (**2ao**), and adapalene (**2ap**) derivatives all worked well under the standard conditions, illustrating the potential utility in complex molecule synthesis (Scheme 4). Moreover, the ketone

Scheme 4. Application to Biologically Active Compounds



functional group of **2an** was not only tolerated by Negishi reagents but also tolerated under Ni−H reduction conditions, suggesting that the Ni−H species selectively reduced the more reactive benzyl ketone intermediate in the presence of cyclic ketone functionality.

Several experiments were performed to elucidate the mechanism of this relay process (Scheme 5). The kinetic

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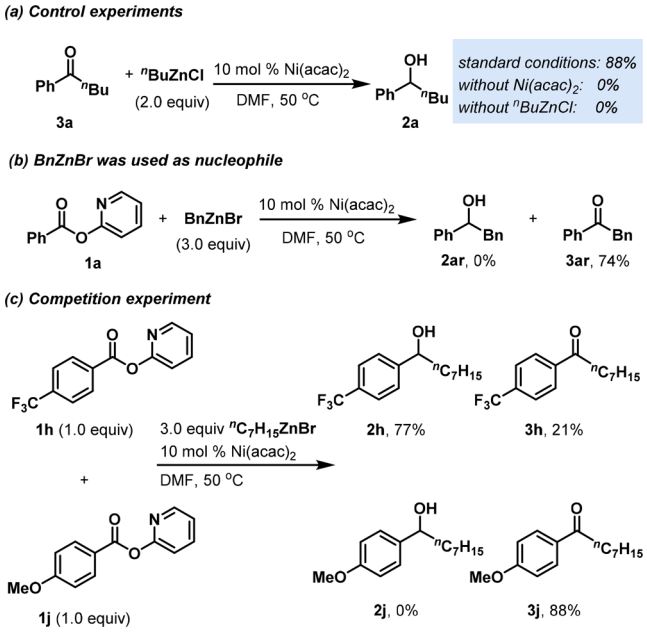
Scheme 5. Preliminary Mechanistic Studies



experiment revealed that phenyl 2-pyridyl ester **1a** was consumed extremely fast to generate **3a**, which was converted to **2a** upon extension of the reaction time as observed by GC.[23] The observation of ketone **3a** eliminates the possibility of formation of an aldehyde intermediate (Scheme 1c, path b). Several control experiments were carried on to determine the reduction step: **3a** was smoothly converted to the desired product **2a** using 2.0 equiv of ^{n}BuZnCl in the standard Ni-catalyzed process, while no product was obtained with the omission of either $Ni(acac)_2$ or ^{n}BuZnCl, which excluded the possibility of formation of a six center transition state between the ketone and Negishi reagent.[24] This suggests the importance of the nickel catalyst in the reduction step and indicates that the hydride species likely arise from the Negishi reagents (Scheme 5a). To gain further insight into the identity and formation of the Ni−H intermediate, benzyl zinc bromide was used as the nucleophile (Scheme 5b). Under these conditions, benzyl ketone **3ar** was formed as the single product, while the desired product **2ar** was not formed. The lack of a β-hydride in the benzyl nucleophile precludes β-hydride elimination, which is necessary for formation of the Ni−H species. We then performed a competition experiment (Scheme 5c), in which esters **1h** and **1j** were subjected to the standard reaction conditions with 3.0 equiv of $^{n}C_7H_{15}ZnBr$ as a nucleophile. Whereas benzylic alcohol product **2h** was formed, benzylic alcohol **2j** was not observed; instead, ketone intermediate **3j** was the main product resulting from ester **1j**. This product distribution suggested that Ni−H as a nucleophile in the reduction step was more facile with the electron-deficient aryl ketone intermediate.

In conclusion, this report details a nickel relay catalysis strategy that enables the tandem Negishi cross-coupling of aryl 2-pyridyl esters, followed by Ni−H (generated *in situ*) reduction of the corresponding ketone intermediates, achieving the direct transformation from aromatic esters to secondary benzylic alcohols in a single synthetic step. In addition, a broad substrate scope is possible due to the mild reaction conditions using functionalized alkyl zinc reagents. The 2-pyridyl group is essential for the reduction sequence, and the detailed reasons for this are currently under investigation in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00774.

Detailed experimental procedures, characterization data, and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: qujp@dlut.edu.cn.
*E-mail: yifengchen@ecust.edu.cn.

ORCID

Jingping Qu: 0000-0002-7576-0798
Yifeng Chen: 0000-0003-3239-6209

Notes

The authors declare no competing financial interest.

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