OL Organic Letters

pubs.acs.org/OrgLett Letter

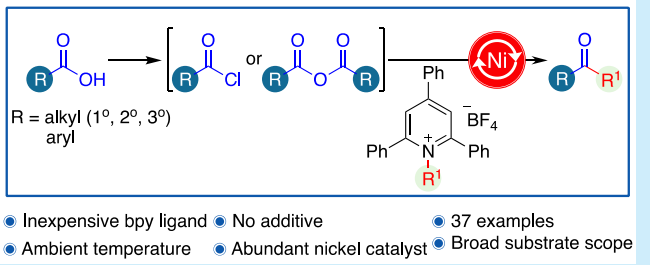
Nickel-Catalyzed Cross-Coupling of Alkyl Carboxylic Acid Derivatives with Pyridinium Salts via C–N Bond Cleavage

Feba Thomas Pulikottil,[†] Ramadevi Pilli,[†] Rohith Valavil Suku, and Ramesh Rasappan*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00554 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The electrophile–electrophile cross-coupling of carboxylic acid derivatives and alkylpyridinium salts via C–N bond cleavage is developed. The method is distinguished by its simplicity and steers us through a variety of functionalized ketones in good to excellent yields. Besides acid chlorides, carboxylic acids were also employed as acylating agents, which enabled us to incorporate acid-sensitive functional groups such as MOM, BOC, and acetal. Control experiments with TEMPO revealed a radical pathway.

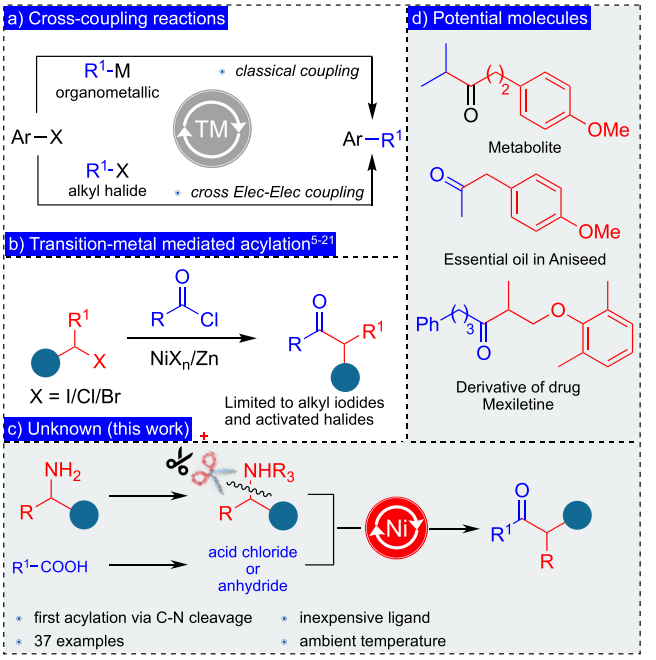


The ubiquity of ketones in pharmaceutical agents, natural products, agrochemicals, and synthetic applications[1−4] has led to the invention of various elegant strategies for accommodating this intrinsic group. A convergent acylation that utilizes carboxylic acid derivatives with preformed organometallic reagents is commonly found in the literature.[3−5] A further improvement to this acylation was achieved using transition metals, in which less reactive organometallic reagents such as organozinc,[6] organomagnesium,[5,7] organotin,[8] organoboron,[9,10] and organosilane[11] were successfully utilized. Despite these advancements, the instability and limited availability of the organometallic reagents drive the researchers to find potent alternative methods. Moreover, the alkyl organometallic reagents consisting of a β-leaving group are more prone to undergoing elimination.[12]

The electrophile–electrophile cross-coupling reactions are an attractive alternative to classical cross-coupling reactions (Scheme 1a). Although the strategy was reported a few decades ago,[2,13,14] it was not developed further until recently when Weix et al., Gong et al., and others showed that the alkyl halides could be cross-coupled with various electrophiles in the presence of nickel,[15−21] cobalt,[22] palladium,[13] and iron catalysts.[23] In this context, acylations via a cross electrophile–electrophile coupling reaction to afford ketone were also reported (Scheme 1a). Carboxylic acids[10,21,24] and their derivatives, including acyl halides,[2,13,18−20] anhydrides,[21,25] and esters,[14,19] were utilized as the source of the acylating agent. Mukaiyama et al. showed that the pyridyl ester could be coupled with alkyl iodides.[14] In the same year, Fujisawa et al. reported a palladium-mediated acylation of benzyl bromide.[13] The direct cross-coupling of carboxylic acids with alkyl halides has also been recently reported wherein the anhydrides were prepared *in situ* from carboxylic acids and Boc_2O.[21,24]

Despite these significant advancements in transition metal-mediated electrophile–electrophile cross-coupling reactions

Scheme 1. Electrophile–Electrophile Cross-Coupling Reactions



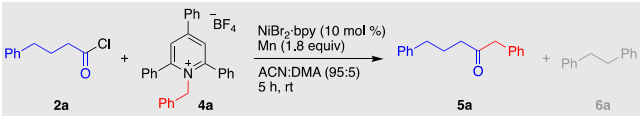
Received: February 11, 2020

(Scheme 1b), the acylation remains confined to the use of alkyl halides. However, the use of amines as an electrophilic coupling partner in transition metal-mediated acylation is unknown (Scheme 1c) despite its widespread availability.[26−28] Activation of kinetically inert C−N bonds in cross-coupling reactions is notoriously difficult, and a significant effort has been made to activate C−N bonds. Transition metal-mediated cleavage of $C(sp^2)$−N and activated $C(sp^3)$−N (strained, allylic, and benzylic) bonds is reported.[29] Recently, Watson,[16,26,30] Glorius,[31] Aggarwal,[32] and Rueping[15] et al. reported the activation of an unactivated $C(sp^3)$−N bond by converting various amines into Katritzky pyridinium salts.[33]

Perceiving the advantage of this approach and in accordance with our interest in nickel-mediated cross-coupling reactions,[34] herein, we demonstrate the feasibility of electrophile−electrophile cross-coupling reaction between amines and acid chlorides as well as carboxylic acids by the synthesis of vital molecules (Scheme1c) in various facets of chemistry.

We commenced our study with acid chloride **2a**, which was readily prepared from the corresponding carboxylic acid **1a**. The pyridinium salt **4a** was prepared from benzyl amine in two steps. The optimized condition requires the use of $NiBr_2$·bpy (10 mol %), 1.8 equiv of Mn, and 2.0 equiv of acid chloride **2a** in a 95:5 CH_3CN/DMA mixture at room temperature. Under this ideal condition, we were delighted to obtain the ketone **5a**, a photochromic dye, in 92% isolated yield (Table 1, entry 1). Nickel complexes $NiBr_2$·bpy[35] and $NiBr_2$·bpy_2[36] offered excellent catalytic activity with similar yields, stressing that the coordination environment around the nickel center did not alter the reaction efficiency (entries 1 and 2, respectively),

Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from standard conditions	6a (%)[b]	5a (%)[b]
1	none	ND[g]	93, 92[c]
2	$NiBr_2$·bpy_2 instead of $NiBr_2$·bpy	5	90
3	NiI_2·bpy	18	55[d]
4	$Ni(acac)_2$ + bpy	42	34
5	$NiBr_2$ in the absence of bpy	5	42[d]
6	*in situ* $NiBr_2$·$3H_2O$ + bpy	ND[g]	89
7	*in situ* $NiCl_2$ + bpy	27	20[d]
8	without $NiBr_2$·bpy	ND[g]	0
9	Zn instead of Mn	3	56[d]
10	no Mn	ND[g]	0[d]
11	1 equiv of **2a**	8	74[d]
12	1.2 equiv of Mn	trace	49[d]
13	CH_3CN alone	ND[g]	48,[d] 65[d,e]
14	DMA alone	6	67
15	5 mol % $NiBr_2$·bpy	2	89
16	1 mol % $NiBr_2$·bpy	ND[g]	60[f]
17	anhydride instead of acid chloride	ND[g]	72
18	*in situ* **2a** from oxalyl chloride	3	60
19	*in situ* **2a** from thionyl chloride	ND[g]	32

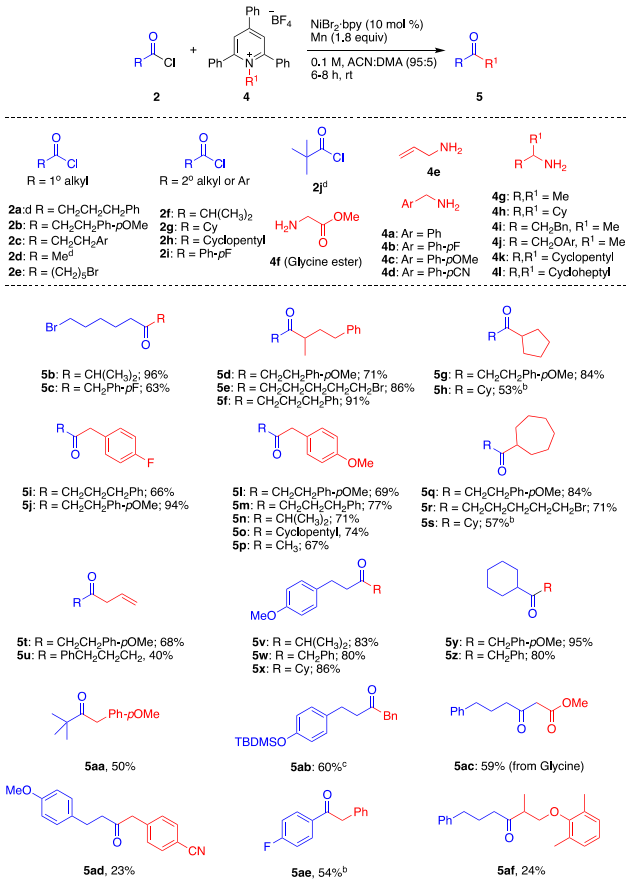
[a]Reaction conditions: 0.295 mmol of **4a**, 0.59 mmol of **2a**, 0.0295 mmol of $NiBr_2$·bpy, 0.53 mmol of Mn, 0.1 M CH_3CN/DMA solution (95:5). [b]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]Leftover **4a** was seen in TLC. [e]After 20 h. [f]Carried out with 2.06 mmol of **4a**. [g]Not detected.

whereas NiI_2 and $Ni(acac)_2$ yielded moderate results (entries 3 and 4, respectively) with the significant formation of byproduct **6a**. In the absence of a bipyridine ligand (entry 5), a substantial drop in the level of acylation (42% yield) was observed, suggesting the crucial role of a bipyridine ligand. The *in situ*-generated $NiBr_2$·bpy from the trihydrated nickel(II) bromide offered a slightly lower yield (entry 6), whereas the *in situ*-generated $NiCl_2$·bpy from nickel(II) chloride offered a poor yield with significant formation of byproduct **6a** (entry 7). Control experiments reveal that $NiBr_2$·bpy and Mn are essential (entries 8 and 10, respectively), and a detrimental effect was observed when Mn was replaced with Zn (entry 9), demonstrating the potential role of Mn as a reductant to generate low-valent nickel and/or an alkyl radical intermediate from pyridinium salt. Decreasing the amount of either Mn or acid chloride decreased the yield (entry 11 or 12, respectively), presumably due to the partial hydrolysis of acid chloride. A brief screening of solvents showed that the cosolvent system CH_3CN and DMA was the best in terms of chemical yield for acylation (entries 13 and 14, respectively), and a 95:5 solvent ratio (CH_3CN:DMA) was optimal (see the Supporting Information). Remarkably, 5 mol % $NiBr_2$·bpy offered a yield that was slightly lower than that of 10 mol % $NiBr_2$·bpy (entry 15). A further decrease in catalyst load to 1 mol % reduced the yield of acylated product **5a** (entry 16). Because an anhydride can also be used as an acylating agent,[21,25] we employed the purified anhydride **3a** in place of acid chloride **2a** and obtained **5a** in 72% yield (entry 17). It is also necessary to purify the acid chloride **2a** prior to the reaction, or the undistilled crude acid chloride **2a** generated by the reaction of either oxalyl chloride or thionyl chloride offered moderate yields (entry 18 or 19, respectively). The reaction was also carried out with 1 mmol of **4a** and produced **5a** in 95% isolated yield with 10 mol % nickel catalyst and 87% isolated yield with 5 mol % nickel catalyst.

Having an optimized condition in hand, we further expanded the substrate scope, and the results are summarized in Table 2. A broad range of acid chlorides (10 in total) were conveniently prepared from the corresponding carboxylic acids, and the pyridinium salts (12 in total) were made from the corresponding amines via pyrylium salts (see the Supporting Information). Although the purified acid chloride **2a** offered a yield higher than that of the undistilled acid chloride (Table 1), some of the acid chlorides in Table 2 were utilized as a crude because they are prone to undergo decomposition during distillation. A range of acid chlorides, including the primary **2a−e** and secondary alkyl acid chlorides **2f−i**, smoothly underwent cross-coupling reactions with various pyridinium salts **4** to obtain the cross-coupled product in good to excellent yields. The sterically hindered tertiary alkyl acid chloride **2j** offered the cross-coupled product **5aa** in moderate yield. Aryl carboxylic acid chloride **2i** was also compatible to offer the coupled product **5ae** in 54% yield and can also be extended to various aryl acid chlorides, which is not within the scope of this paper. Strikingly, a substrate bearing alkyl bromide was also well tolerated, although the alkyl halides are also known to undergo cross-coupling reactions with acid halides.[37] The alkyl acid chloride **2e** underwent chemoselective cross-coupling reaction to afford the acylated products **5b** and **5c** in 96% and 63% yields, respectively. Various functional groups, including fluoride **2i**, alkene **4e**, ether **2b**, and carbonyl **4f**, were undeterred. The silyl-protected alcohol **2c** was also compatible and underwent smooth cross-coupling to afford

https://dx.doi.org/10.1021/acs.orglett.0c00554
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Scope of Carboxylic Acid Chlorides as an Acylating Source[a]

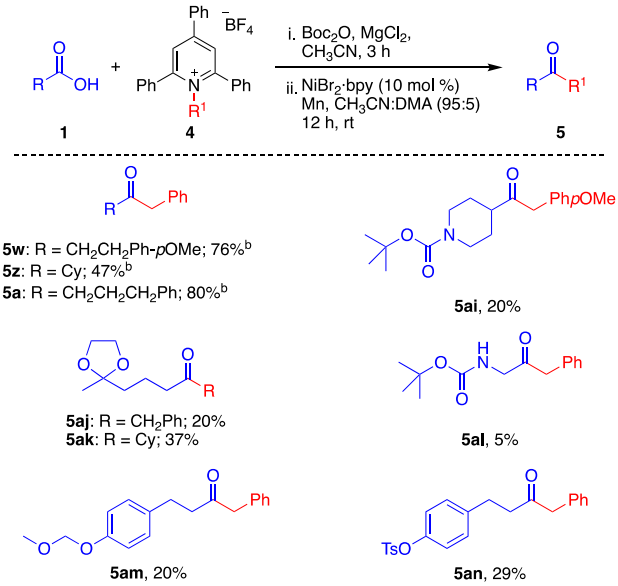


[a]Reaction conditions: 1 equiv of **4**, 2 equiv of **2**, 10 mol % $NiBr_2$·bpy, 1.8 equiv of Mn, 0.1 M CH_3CN/DMA solution (95:5), 6−8 h, rt, isolated yield. [b]Reduced to the corresponding alcohol using $NaBH_4$ (3 equiv). [c]With 1.4 equiv of **2c**. [d]Commerical. Acid chlorides **2a**, **2b**, **2d**, and **2i** were purified by distillation, and **2e**, **2g**, and **2h** were used as crude acid chloride.

product **5ab** in 60% isolated yield. This provides an opportunity for further functionalization of the cross-coupled products. Given the importance of amino acids across various disciplines and their greater accessibility, glycine ester **4f** was successfully cross-coupled into the corresponding acylated product **5ac**. Ketones **5h**, **5s**, and **5ae** were reduced to the corresponding alcohols with $NaBH_4$ for successful isolation from the otherwise inseparable byproduct (triphenylpyridine). We also obtained **5p**, a naturally occurring essential oil in Aniseed,[38] and **5v**, a metabolite, in high yields.[39] It is noteworthy to mention that **5af**, a derivative of antiarrhythmic drug Mexiletine, was also prepared in 24% yield using this method.

Despite the success of acid chlorides as an acylating source, acid-sensitive protecting groups such as MOM, BOC, and acetals were not compatible in the synthesis of acid chlorides. Encouraged by the literature findings,[21,24] we anticipated that the carboxylic acids could be directly utilized via the *in situ* generation of anhydrides. Moreover, if successful, the acid-sensitive functional groups could be incorporated to diversify the functional group tolerance. We carried out a detailed investigation to optimize the *in situ* generation of anhydride using Boc_2O and $MgCl_2$ in either THF or CH_3CN (see the Supporting Information).[40] The subsequent cross-coupling reaction proceeded smoothly in the presence of $NiBr_2$·bpy (10 mol %) and Mn (1.8 equiv) to afford the ketones **5w** and **5a** in 76% and 80% yields, respectively. We then subjected the carboxylic acids, containing acid-sensitive protecting groups, including MOM, BOC, OTs, and acetal, to the optimized reaction condition and obtained the cross-coupled products in poor to moderate yields as shown in Table 3. These results can

Table 3. Scope of Carboxylic Acids as an Acylating Source[a]



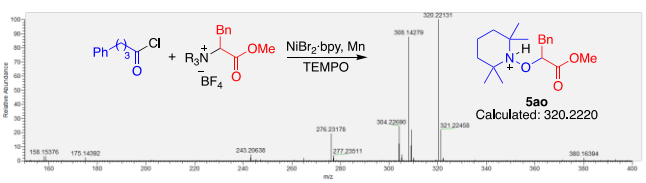
[a]Reaction conditions: 0.885 mmol of **2** (acid), 0.294 mmol of $MgCl_2$, 1.03 mmol of Boc_2O, and 0.9 mL of CH_3CN (1 M) in step i. In step ii, 0.295 mmol of **4**, 0.0295 mmol of $NiBr_2$·bpy, 0.53 mmol of Mn, 1.9 mL of CH_3CN, and 0.15 mL of DMA were added (overall 0.1 M). [b]Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard, and **5a** was synthesized using THF instead of CH_3CN.

be attributed to the formation of byproducts (biphenyl ethane and *tert*-butyl ester of the carboxylic acids) and the unstable nature of these acid-sensitive substrates.

In accordance with the literature, we expected the generation of an alkyl radical intermediate from pyridinium salt.[15,30,32] Hence, we introduced TEMPO under the optimized reaction condition and observed the complete inhibition of the reaction with consequent formation of TEMPO adduct **5ao**, which was confirmed by ^1H NMR (see the Supporting Information) and MS analysis (Scheme 2). The reaction was also inhibited when the reaction was carried out in the presence of radical inhibitor 1-chloro-2,4-dinitrobenzene.

It has been proposed in the literature that the nickel-catalyzed cross-coupling reactions may follow different path-

Scheme 2. Radical Trap Experiment with TEMPO



https://dx.doi.org/10.1021/acs.orglett.0c00554
Org. Lett. XXXX, XXX, XXX−XXX

ways rather than a universal catalytic cycle. Although we are working on a dedicated mechanistic study to identify the actual intermediates and mechanistic pathway (Figure 1), we present

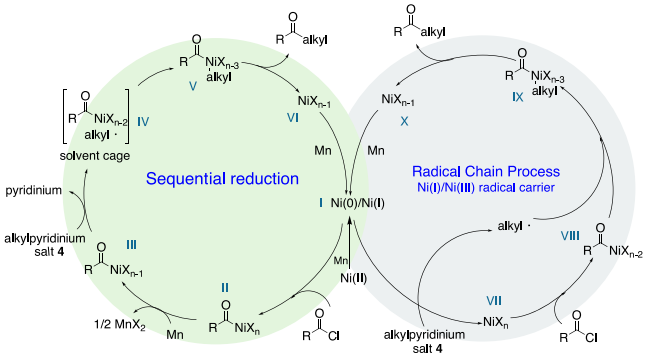


Figure 1. Mechanistic proposal.

here two possible mechanistic pathways based on the preceding literature: (i) sequential reduction and (ii) radical chain process. It has been proposed that the exposure of $Ni(II)X_2$ to Zn or Mn will lead to the low-valent nickel [either Ni(0) or Ni(I)];[15,17a,41,42] subsequently, it can follow two different mechanistic pathways. In sequential reduction, the low-valent nickel can undergo oxidative addition with acid chloride and resultant intermediate **II** could be reduced to intermediate **III**, which will in turn reduce the pyridinium salt **4** to intermediate **V** in a stepwise manner. Reductive elimination of intermediate **V** and further reduction with Mn could regenerate the active nickel species **I**. In the case of a radical chain process,[17a,42,43] the low-valent nickel species **I** may reduce pyridinium salt **4** to generate the intermediate **VII**, and subsequent oxidative addition with acid chloride will lead to the intermediate **VIII**, which in turn will combine with an alkyl radical to generate the intermediate **IX**. Subsequent reductive elimination followed by the Mn-mediated reduction could regenerate the active nickel species.

In summary, we have presented a nickel-mediated acylation of pyridinium salt for the first time. A broad range of acid chlorides, including sterically hindered, and pyridinium salts with varied functional groups underwent cross-coupling reactions to offer the acylated products in good yields. This protocol accommodates inexpensive bipyridine ligand, requires no additives, and proceeds at ambient temperature. We also showed that the carboxylic acids can be used directly in place of acid chloride to incorporate acid-sensitive functional groups, although the yields of these reactions ranged from poor to high. The presence of the radical intermediate is confirmed by the identification of the TEMPO adduct through NMR and MS analysis. We have presented two possible mechanistic pathways, namely, sequential reduction and radical chain process for the acylation via C−N bond cleavage. The process of finding the actual intermediates and mechanistic pathway is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00554.

Additional supporting information (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Ramesh Rasappan − *School of Chemistry, Indian Institute of Science Education and Research Thiruvananthapuram, Thiruvananthapuram, Kerala 695551, India;* orcid.org/0000-0002-3209-3315; Email: rr@iisertvm.ac.in

Authors

Feba Thomas Pulikottil − *School of Chemistry, Indian Institute of Science Education and Research Thiruvananthapuram, Thiruvananthapuram, Kerala 695551, India*

Ramadevi Pilli − *School of Chemistry, Indian Institute of Science Education and Research Thiruvananthapuram, Thiruvananthapuram, Kerala 695551, India*

Rohith Valavil Suku − *School of Chemistry, Indian Institute of Science Education and Research Thiruvananthapuram, Thiruvananthapuram, Kerala 695551, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00554

Author Contributions

†F.T.P. and R.P. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Science and Engineering Research Board, Ramanujan Fellowship SB/S2/RJN059/2015, and IISER-Trivandrum for financial support. F.T.P., R.P., and R.V.S. acknowledge IISER, Trivandrum, for fellowships.

■ REFERENCES

(1) (a) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley, 2004. (b) Brunet, J.-J.; Chauvin, R. Synthesis of diarylketones through carbonylative coupling. *Chem. Soc. Rev.* **1995**, *24* (2), 89. (c) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley, 2004. (d) Martin, S. F. Synthesis of Aldehydes, Ketones, and Carboxylic Acids from Lower Carbonyl Compounds by C-C Coupling Reactions. *Synthesis* **1979**, *1979*, 633−665. (e) Müller, M.; Wolberg, M.; Schubert, T.; Hummel, W. Enzyme-catalyzed regio- and enantioselective ketone reductions. *Adv. Biochem. Eng./Biotechnol.* **2005**, *92*, 261−87. (f) Sletten, E.; Bertozzi, C. Bioorthogonal chemistry: fishing for selectivity in a sea of functionality. *Angew. Chem., Int. Ed.* **2009**, *48* (38), 6974−98. (g) Veech, R. Ketone esters increase brown fat in mice and overcome insulin resistance in other tissues in the rat. *Ann. N. Y. Acad. Sci.* **2013**, *1302*, 42−48. (h) Wong, M. K.; Yip, Y. C.; Yang, D. Asymmetric Epoxidation Catalyzed by Chiral Ketones. In *Asymmetric Catalysis from a Chinese Perspective: Topics in Organometallic Chemistry*; Springer: Berlin, 2011; pp 123−152. (i) Wong, O. A.; Shi, Y. Chiral Ketone and Iminium Catalysts for Olefin Epoxidation. In *Topics in Current Chemistry: Asymmetric Organocatalysis*; Springer: Berlin, 2009; pp 201−232. (j) Wu, X.; Neumann, H.; Beller, M. Palladium-catalyzed carbonylative coupling reactions between Ar-X and carbon nucleophiles. *Chem. Soc. Rev.* **2011**, *40* (10), 4986−5009.

(2) Marzouk, H.; Rollin, Y.; Folest, J. C.; Nédélec, J. Y.; Périchon, J. Electrochemical synthesis of ketones from acid chlorides and alkyl and aryl halides catalyzed by nickel complexes. *J. Organomet. Chem.* **1989**, *369* (3), C47−C50.

(3) Lawrence, N. J. Aldehydes and ketones. *J. Chem. Soc., Perkin Trans. 1* **1998**, No. 10, 1739−1750.

(4) Dieter, R. K. Reaction of acyl chlorides with organometallic reagents: A banquet table of metals for ketone synthesis. *Tetrahedron* **1999**, *55* (14), 4177−4236.

(5) Nahm, S.; Weinreb, S. M. N-methoxy-n-methylamides as effective acylating agents. *Tetrahedron Lett.* **1981**, *22* (39), 3815−3818.
(6) (a) Bercot, E. A.; Rovis, T. A Mild and Efficient Catalytic Alkylative Monofunctionalization of Cyclic Anhydrides. *J. Am. Chem. Soc.* **2002**, *124* (2), 174−175. (b) Havlik, S.; Simmons, J.; Winton, V.; Johnson, J. Nickel-mediated decarbonylative cross-coupling of phthalimides with *in-situ* generated diorganozinc reagents. *J. Org. Chem.* **2011**, *76* (9), 3588−93. (c) Johnson, J.; Yu, R.; Fink, P.; Bercot, E.; Rovis, T. Selective substituent transfer from mixed zinc reagents in Ni-catalyzed anhydride alkylation. *Org. Lett.* **2006**, *8* (19), 4307−10. (d) Kunchithapatham, K.; Eichman, C.; Stambuli, J. Synthesis of diaryl ketones via a phosphine-free Fukuyama reaction. *Chem. Commun.* **2011**, *47*, 12679−81. (e) Mori, Y.; Seki, M. A novel procedure for the synthesis of multifunctional ketones through the Fukuyama coupling reaction employing dialkylzincs. *Tetrahedron Lett.* **2004**, *45* (39), 7343−7345. (f) Shimizu, T.; Seki, M. A novel synthesis of functionalized ketones via a nickel-catalyzed coupling reaction of zinc reagents with thiolesters. *Tetrahedron Lett.* **2002**, *43* (6), 1039−1042. (g) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. A novel ketone synthesis by a palladium-catalyzed reaction of thiol esters and organozinc reagents. *Tetrahedron Lett.* **1998**, *39* (20), 3189−3192.
(7) Duplais, C.; Bures, F.; Sapountzis, I.; Korn, T.; Cahiez, G.; Knochel, P. An efficient synthesis of diaryl ketones by iron-catalyzed arylation of aroyl cyanides. *Angew. Chem., Int. Ed.* **2004**, *43* (22), 2968−70.
(8) (a) Milstein, D.; Stille, J. K. A general, selective, and facile method for ketone synthesis from acid chlorides and organotin compounds catalyzed by palladium. *J. Am. Chem. Soc.* **1978**, *100* (11), 3636−3638. (b) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. Ketone synthesis under neutral conditions. Cu(I) diphenylphosphinate-mediated, palladium-catalyzed coupling of thiol esters and organostannanes. *Org. Lett.* **2003**, *5* (17), 3033−5.
(9) (a) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. Synthesis of Unsymmetrical Ketones by Palladium-Catalyzed Cross-Coupling Reaction of Carboxylic Anhydrides with Organoboron Compounds. *Bull. Chem. Soc. Jpn.* **2002**, *75* (1), 137−148. (b) Liebeskind, L. S.; Srogl, J. Thiol Ester−Boronic Acid Coupling. A Mechanistically Unprecedented and General Ketone Synthesis. *J. Am. Chem. Soc.* **2000**, *122* (45), 11260−11261. (c) Savarin, C.; Srogl, J.; Liebeskind, L. S. Thiol Ester−Boronic Acid Cross-Coupling. Catalysis Using Alkylative Activation of the Palladium Thiolate Intermediate. *Org. Lett.* **2000**, *2* (20), 3229−3231. (d) Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. Catalytic cross-coupling reaction of esters with organoboron compounds and decarbonylative reduction of esters with $HCOONH_4$: a new route to acyl transition metal complexes through the cleavage of acyl-oxygen bonds in esters. *J. Org. Chem.* **2004**, *69* (17), 5615−21. (e) Yu, Y.; Liebeskind, L. S. Copper-Mediated, Palladium-Catalyzed Coupling of Thiol Esters with Aliphatic Organoboron Reagents. *J. Org. Chem.* **2004**, *69* (10), 3554−3557.
(10) Goossen, L.; Ghosh, K. Palladium-Catalyzed Synthesis of Aryl Ketones from Boronic Acids and Carboxylic Acids or Anhydrides. *Angew. Chem., Int. Ed.* **2001**, *40* (18), 3458−3460.
(11) Yamane, M.; Uera, K.; Narasaka, K. Rhodium-Catalyzed Acylation of Vinylsilanes with Acid Anhydrides: Application to the Transformation of α-Acyloxy Vinylsilanes to Unsymmetrical 1,2-Diketones. *Chem. Lett.* **2004**, *33* (4), 424−425.
(12) Steib, A.; Thaler, T.; Komeyama, K.; Mayer, P.; Knochel, P. Highly diastereoselective iron-mediated $C(sp^2)$-$C(sp^3)$ cross-coupling reactions between aryl Grignard reagents and cyclic iodohydrine derivatives. *Angew. Chem., Int. Ed.* **2011**, *50* (14), 3303−7.
(13) Sato, T.; Naruse, K.; Enokiya, M.; Fujisawa, T. Facile Synthesis Of Benzyl Ketones By The Reductive Coupling Of Benzyl Bromide And Acyl Chlorides In The Presence Of A Palladium Catalyst And Zinc Powder. *Chem. Lett.* **1981**, *10* (8), 1135−1138.
(14) Onaka, M.; Matsuoka, Y.; Mukaiyama, T. A Convenient Method for the Direct Preparation of Ketones From 2-(6-(2-Methoxyethyl)pyridyl)carboxylates and Alkyl Iodides by Use of Zinc Dust and a Catalytic Amount of Nickel Dichloride. *Chem. Lett.* **1981**, *10* (4), 531−534.
(15) Yue, H.; Zhu, C.; Shen, L.; Geng, Q.; Hock, K.; Yuan, T.; Cavallo, L.; Rueping, M. Nickel-catalyzed C-N bond activation: activated primary amines as alkylating reagents in reductive cross-coupling. *Chem. Sci.* **2019**, *10* (16), 4430−4435.
(16) Liao, J.; Basch, C. H.; Hoerrner, M. E.; Talley, M. R.; Boscoe, B. P.; Tucker, J. W.; Garnsey, M. R.; Watson, M. P. Deaminative Reductive Cross-Electrophile Couplings of Alkylpyridinium Salts and Aryl Bromides. *Org. Lett.* **2019**, *21* (8), 2941−2946.
(17) (a) Biswas, S.; Weix, D. J. Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135* (43), 16192−16197. (b) Cherney, A.; Reisman, S. Nickel-catalyzed asymmetric reductive cross-coupling between vinyl and benzyl electrophiles. *J. Am. Chem. Soc.* **2014**, *136* (41), 14365−8. (c) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134* (14), 6146−6159. (d) Everson, D. A.; Shrestha, R.; Weix, D. J. Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 920−921. (e) Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. New ligands for nickel catalysis from diverse pharmaceutical heterocycle libraries. *Nat. Chem.* **2016**, *8* (12), 1126−1130. (f) Kadunce, N.; Reisman, S. Nickel-Catalyzed Asymmetric Reductive Cross-Coupling between Heteroaryl Iodides and α-Chloronitriles. *J. Am. Chem. Soc.* **2015**, *137* (33), 10480−3. (g) Konev, M.; Hanna, L.; Jarvo, E. Intra- and Intermolecular Nickel-Catalyzed Reductive Cross-Electrophile Coupling Reactions of Benzylic Esters with Aryl Halides. *Angew. Chem., Int. Ed.* **2016**, *55* (23), 6730−3. (h) Molander, G.; Traister, K.; O'Neill, B. Reductive cross-coupling of nonaromatic, heterocyclic bromides with aryl and heteroaryl bromides. *J. Org. Chem.* **2014**, *79* (12), 5771−80. (i) Wang, X.; Wang, S.; Xue, W.; Gong, H. Nickel-Catalyzed Reductive Coupling of Aryl Bromides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2015**, *137* (36), 11562−5. (j) Xue, W.; Xu, H.; Liang, Z.; Qian, Q.; Gong, H. Nickel-catalyzed reductive cyclization of alkyl dihalides. *Org. Lett.* **2014**, *16* (19), 4984−7.
(18) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. Ketone Formation via Mild Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Aryl Acid Chlorides. *Org. Lett.* **2012**, *14* (12), 3044−3047.
(19) Wotal, A. C.; Weix, D. J. Synthesis of Functionalized Dialkyl Ketones from Carboxylic Acid Derivatives and Alkyl Halides. *Org. Lett.* **2012**, *14* (6), 1476−1479.
(20) Cherney, A.; Kadunce, N.; Reisman, S. Catalytic asymmetric reductive acyl cross-coupling: synthesis of enantioenriched acyclic α,α-disubstituted ketones. *J. Am. Chem. Soc.* **2013**, *135* (20), 7442−5.
(21) Jia, X.; Zhang, X.; Qian, Q.; Gong, H. Alkyl−aryl ketone synthesis via nickel-catalyzed reductive coupling of alkyl halides with aryl acids and anhydride acylations. *Chem. Commun.* **2015**, *51*, 10302−10305.
(22) (a) Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. Cobalt co-catalysis for cross-electrophile coupling: diarylmethanes from benzyl mesylates and aryl halides. *Chem. Sci.* **2015**, *6*, 3633. (b) Amatore, M.; Gosmini, C. Direct method for carbon-carbon bond formation: the functional group tolerant cobalt-catalyzed alkylation of aryl halides. *Chem. - Eur. J.* **2010**, *16* (20), 5848−52. (c) Beng, T.; Sincavage, K.; Silaire, A.; Alwali, A.; Bassler, D.; Spence, L.; Beale, O. Direct access to functionalized benzotropones, azepanes, and piperidines by reductive cross-coupling of α-bromo enones with α-bromo enamides. *Org. Biomol. Chem.* **2015**, *13* (19), 5349−53. (d) Qian, X.; Auffrant, A.; Felouat, A.; Gosmini, C. Cobalt-catalyzed reductive allylation of alkyl halides with allylic acetates or carbonates. *Angew. Chem., Int. Ed.* **2011**, *50* (44), 10402−5.
(23) Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. Domino iron catalysis: direct aryl-alkyl cross-coupling. *Angew. Chem., Int. Ed.* **2009**, *48* (3), 607−610.

https://dx.doi.org/10.1021/acs.orglett.0c00554
Org. Lett. XXXX, XXX, XXX−XXX

(24) Zhao, C.; Jia, X.; Wang, X.; Gong, H. Ni-catalyzed reductive coupling of alkyl acids with unactivated tertiary alkyl and glycosyl halides. *J. Am. Chem. Soc.* **2014**, *136* (50), 17645−51.
(25) Yin, H.; Zhao, C.; You, H.; Lin, K.; Gong, H. Mild ketone formation via Ni-catalyzed reductive coupling of unactivated alkyl halides with acid anhydrides. *Chem. Commun.* **2012**, *48* (56), 7034−6.
(26) Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. Harnessing Alkyl Amines as Electrophiles for Nickel-Catalyzed Cross Couplings via C−N Bond Activation. *J. Am. Chem. Soc.* **2017**, *139* (15), 5313−5316.
(27) (a) Liu, Y.; Ge, H. Site-selective C−H arylation of primary aliphatic amines enabled by a catalytic transient directing group. *Nat. Chem.* **2017**, *9* (1), 26−32. (b) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87* (12), 1348−1349. (c) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C−N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116* (19), 12564−12649.
(28) Acylation using aromatic amides was recently published: Yu, C. G.; Matsuo, Y. Nickel-Catalyzed Deaminative Acylation of Activated Aliphatic Amines with Aromatic Amides via C-N Bond Activation. *Org. Lett.* **2020**, *22* (3), 950−955.
(29) (a) Basch, C.; Cobb, K.; Watson, M. Nickel-Catalyzed Borylation of Benzylic Ammonium Salts: Stereospecific Synthesis of Enantioenriched Benzylic Boronates. *Org. Lett.* **2016**, *18* (1), 136−9. (b) Hu, J.; Sun, H.; Cai, W.; Pu, X.; Zhang, Y.; Shi, Z. Nickel-Catalyzed Borylation of Aryl- and Benzyltrimethylammonium Salts via C-N Bond Cleavage. *J. Org. Chem.* **2016**, *81* (1), 14−24. (c) Huang, C.-Y. D.; Doyle, A. G. Nickel-Catalyzed Negishi Alkylations of Styrenyl Aziridines. *J. Am. Chem. Soc.* **2012**, *134* (23), 9541−9544. (d) Maity, P.; Shacklady-McAtee, D.; Yap, G.; Sirianni, E.; Watson, M. Nickel-catalyzed cross couplings of benzylic ammonium salts and boronic acids: stereospecific formation of diarylethanes via C-N bond activation. *J. Am. Chem. Soc.* **2013**, *135* (1), 280−5. (e) Shacklady-McAtee, D.; Roberts, K.; Basch, C.; Song, Y.; Watson, M. A General, Simple Catalyst for Enantiospecific Cross Couplings of Benzylic Ammonium Triflates and Boronic Acids: No Phosphine Ligand Required. *Tetrahedron* **2014**, *70* (27−28), 4257−4263.
(30) (a) Guan, W.; Liao, J.; Watson, M. Vinylation of Benzylic Amines via C-N Bond Functionalization of Benzylic Pyridinium Salts. *Synthesis* **2018**, *50* (16), 3231−3237. (b) Hoerrner, M.; Baker, K.; Basch, C.; Bampo, E.; Watson, M. Deaminative Arylation of Amino Acid-derived Pyridinium Salts. *Org. Lett.* **2019**, *21* (18), 7356−7360. (c) Liao, J.; Guan, W.; Boscoe, B.; Tucker, J.; Tomlin, J.; Garnsey, M.; Watson, M. Transforming Benzylic Amines into Diarylmethanes: Cross-Couplings of Benzylic Pyridinium Salts via C-N Bond Activation. *Org. Lett.* **2018**, *20* (10), 3030−3033. (d) Plunkett, S.; Basch, C.; Santana, S.; Watson, M. Harnessing Alkylpyridinium Salts as Electrophiles in Deaminative Alkyl-Alkyl Cross-Couplings. *J. Am. Chem. Soc.* **2019**, *141* (6), 2257−2262.
(31) (a) Klauck, F.; James, M.; Glorius, F. Deaminative Strategy for the Visible-Light-Mediated Generation of Alkyl Radicals. *Angew. Chem., Int. Ed.* **2017**, *56* (40), 12336−12339. (b) Klauck, F. J. R.; Yoon, H.; James, M. J.; Lautens, M.; Glorius, F. Visible-Light-Mediated Deaminative Three-Component Dicarbofunctionalization of Styrenes with Benzylic Radicals. *ACS Catal.* **2019**, *9* (1), 236−241. (c) Pitzer, L.; Schäfers, F.; Glorius, F. Rapid Assessment of the Reaction-Condition-Based Sensitivity of Chemical Transformations. *Angew. Chem., Int. Ed.* **2019**, *58* (25), 8572−8576. (d) Sandfort, F.; Strieth-Kalthoff, F.; Klauck, F.; James, M.; Glorius, F. Deaminative Borylation of Aliphatic Amines Enabled by Visible Light Excitation of an Electron Donor-Acceptor Complex. *Chem. - Eur. J.* **2018**, *24* (65), 17210−17214.
(32) (a) Wu, J.; Grant, P. S.; Li, X.; Noble, A.; Aggarwal, V. K. Catalyst-Free Deaminative Functionalizations of Primary Amines by Photoinduced Single-Electron Transfer. *Angew. Chem., Int. Ed.* **2019**, *58* (17), 5697−5701. (b) Wu, J.; He, L.; Noble, A.; Aggarwal, V. K. Photoinduced Deaminative Borylation of Alkylamines. *J. Am. Chem. Soc.* **2018**, *140* (34), 10700−10704.
(33) (a) Bapat, J. B.; Blade, R. J.; Boulton, A. J.; Epsztajn, J.; Katritzky, A. R.; Lewis, J.; Molina-Buendia, P.; Nie, P.-L.; Ramsden, C. A. Pyridines as leaving groups in synthetic transformations: Nucleophilic displacements of amino groups, and novel preparations of nitriles and isocyanates. *Tetrahedron Lett.* **1976**, *17* (31), 2691−2694. (b) Katritzky, A. R.; De Ville, G.; Patel, R. C. Carbon-alkylation of simple nitronate anions by N-substituted pyridiniums. *Tetrahedron* **1981**, *37*, 25−30. (c) Katritzky, A. R.; Marson, C. M. Pyrylium Mediated Transformations of Primary Amino Groups into Other Functional Groups. New Synthetic Methods (41). *Angew. Chem., Int. Ed. Engl.* **1984**, *23* (6), 420−429.
(34) Murugesan, V.; Balakrishnan, V.; Rasappan, R. Nickel-catalyzed cross-coupling reaction of carbamates with silylmagnesium reagents. *J. Catal.* **2019**, *377*, 293−298.
(35) Khrizanforov, M.; Khrizanforova, V.; Mamedov, V.; Zhukova, N.; Strekalova, S.; Grinenko, V.; Gryaznova, T.; Sinyashin, O.; Budnikova, Y. Single-stage synthetic route to perfluoroalkylated arenes via electrocatalytic cross-coupling of organic halides using Co and Ni complexes. *J. Organomet. Chem.* **2016**, *820*, 82−88.
(36) Yakhvarov, D.; Trofimova, E.; Sinyashin, O.; Kataeva, O.; Budnikova, Y.; Lonnecke, P.; Hey-Hawkins, E.; Petr, A.; Krupskaya, Y.; Kataev, V.; Klingeler, R.; Buchner, B. New dinuclear nickel(II) complexes: synthesis, structure, electrochemical, and magnetic properties. *Inorg. Chem.* **2011**, *50* (10), 4553−8.
(37) Knappke, C.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. Reductive cross-coupling reactions between two electrophiles. *Chem. - Eur. J.* **2014**, *20* (23), 6828−42.
(38) Anastasopoulou, E.; Graikou, K.; Ganos, C.; Calapai, G.; Chinou, I. Pimpinella anisum seeds essential oil from Lesvos island: Effect of hydrodistillation time, comparison of its aromatic profile with other samples of the Greek market. Safe use. *Food Chem. Toxicol.* **2020**, *135*, 110875.
(39) Feunang, Y. D. Cheminformatics Tools for Enabling Metabolomics. Ph.D. Thesis, University of Alberta, Edmonton, AB, 2017.
(40) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Marcantoni, E.; Melchiorre, P.; Sambri, L. Reaction of Dicarbonates with Carboxylic Acids Catalyzed by Weak Lewis Acids: General Method for the Synthesis of Anhydrides and Esters. *Synthesis* **2007**, *2007*, 3489−3496.
(41) Panahi, F.; Bahmani, M.; Iranpoor, N. Nickel-Catalyzed Reductive Benzylation of Aldehydes with Benzyl Halides and Pseudohalides. *Adv. Synth. Catal.* **2015**, *357* (6), 1211−1220.
(42) Lin, Q.; Diao, T. Mechanism of Ni-Catalyzed Reductive 1,2-Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2019**, *141* (44), 17937−17948.
(43) Yin, H.; Fu, G. C. Mechanistic Investigation of Enantioconvergent Kumada Reactions of Racemic alpha-Bromoketones Catalyzed by a Nickel/Bis(oxazoline) Complex. *J. Am. Chem. Soc.* **2019**, *141* (38), 15433−15440.

https://dx.doi.org/10.1021/acs.orglett.0c00554
Org. Lett. XXXX, XXX, XXX−XXX