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Nickel-catalyzed decarbonylation of *N*-acylated N-heteroarenes†

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Nickel-catalyzed decarbonylation of *N*-acylated N-heteroarenes is developed. This method can be used to produce a variety of *N*-aryl heteroarenes, including pyrroles, indoles, carbazoles and phenoxazines, using benzoic acid derivatives as arylating reagents. Arylnickelamide intermediates that are relevant to the catalytic reaction were characterized by X-ray crystallography. When *N*-acylated benzimidazoles are used as substrates, decarbonylation accompanied 1,2-migration to form 2-arylated benzimidazoles.

Introduction

Because of their widespread utility in medicinal and materials chemistry,[1] methodology for preparing *N*-arylated heteroarenes has continued to be a subject of intense studies. Currently, the most powerful approach to these compounds involves the catalytic cross-coupling of aryl halides with NH-heteroarenes (Scheme 1a).[2,3] If aromatic acids, in place of aryl halides, could be used as aryl sources for the synthesis of *N*-aryl *N*-heteroarenes, several benefits would be expected. For example, aromatic acids are widely available feedstock materials, often with substitution patterns that are difficult to access from the corresponding aryl halides, and therefore the flexibility of synthetic planning would be enhanced. In addition,

a new synthetic strategy, such as orthogonal and late-stage transformation, would be possible if a carboxyl group can serve as a handle with a reactivity profile different from halides. However, despite significant progress made in the decarboxylative cross-coupling,[4] decarboxylative *N*-arylation of NH-heteroarenes has not been reported, to the best of our knowledge.[5] We hypothesized that the use of an aromatic acid in the *N*-arylation of NH-heteroarenes would be possible formally through a two-step sequence, namely, amide formation (*N*-acylation) and decarbonylation of the resulting amide (Scheme 1b). Since a number of reliable methods are available for amide formation,[6,7] the key issue is the development of the latter decarbonylation reaction. Except for 2-azinecarboxamides,[8] catalytic decarbonylation of amides is an unattained transformation, indicating that C(aryl)–N bond formation *via* decarbonylation is clearly not a trivial task. We report herein on the realization of this objective.
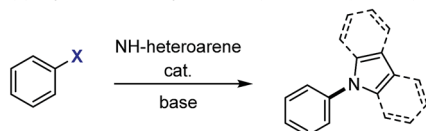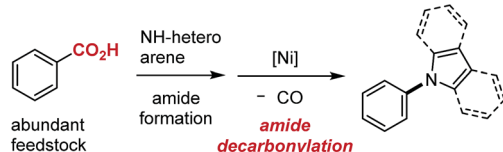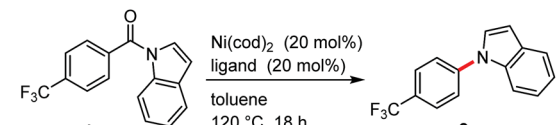

Scheme 1 Approaches to the *N*-arylation of heteroarenes.

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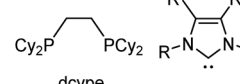
Results and discussion

We initiated our study by examining the decarbonylation of *N*-acylindole **1a**. To promote this reaction, we focused on the use of a nickel catalyst, since it has been successfully used in the activation of amides[9] and in the ketone decarbonylation reaction.[10] A brief screening of ligands revealed that strong σ-donor ligands, such as alkylphosphines and N-heterocyclic carbenes (NHCs), actually afforded the desired decarbonylation product **2a** in 12–31% yield (Table 1, entries 2–7). Although the difference in the yield of **2a** was not significant between the ligands examined, a larger amount of **1a** was recovered from the reactions when phosphine ligands were used than when NHCs were used. Therefore, further optimization was pursued using PCy₃ and 1,2-bis(dicyclohexylphosphino)ethane (dcype). When 1 equiv. of Ni(cod)₂ and PCy₃ were used, the decarbonylation proceeded quantitatively, even at 80 °C (entry 8). The catalytic decarbonylation was accomplished by running the reaction at

Table 1 Development of the nickel-mediated decarbonylation of N-acylindole **1a**[a]

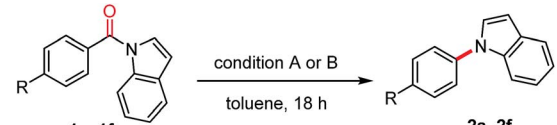|		GC yields (%)	
Entry	Ligand[b]	**2a**	**1a**
1	PPh₃	0	71
2	PCy₃	31	60
3	dcype	16	52
4	ICy	0	46
5	IMes	28	29
6	IMes^Me	27	27
7	IPr	12	25
8[c]	PCy₃	>99 (88)[e]	0
9[d]	PCy₃	19	65
10[c]	dcype	4	86
11[d]	dcype	93 (84)[e]	0

ICy (R = cyclohexyl, R' = H)
IMes (R = 2,4,6-Me₃C₆H₂, R' = H)
IMes^Me (R = 2,4,6-Me₃C₆H₂, R' = Me)
IPr (R = 2,6-^iPr₂C₆H₃, R' = H)

[a] Reaction conditions: **1a** (0.25 mmol), Ni(cod)₂ (0.050 mmol), ligand (0.050 mmol), in toluene (1.0 mL) for 18 h at 120 °C. [b] N-Heterocyclic carbene ligands were generated *in situ* from the corresponding imidazolium salts by treatment with NaO^tBu (25 mol%). [c] Ni(cod)₂ (0.25 mmol) and the ligand (0.25 mmol) were used at 80 °C. [d] Run at 180 °C. [e] Isolated yield.

Table 2 Electronic effect of the acyl group[a]

A: Ni(cod)₂ (20 mol%), dcype (20 mol%), 180 °C
B: Ni(cod)₂ (100 mol%), PCy₃ (100 mol%), 80 °C

		Isolated yield [%]	
R	σ_p[b]	A	B
CF₃ (**1a**)	0.54	84	—
CO₂Me (**1b**)	0.45	85	—
Ph (**1c**)	−0.01	30[c]	79
H (**1d**)	0	23[c]	71
Me (**1e**)	−0.17	18[c]	63
OMe (**1f**)	−0.27	8[c]	14[d] (33)[c,e]

[a] Condition A: amide (0.25 mmol), Ni(cod)₂ (0.050 mmol), dcype (0.050 mmol) in toluene (1.0 mL) for 18 h at 180 °C; condition B: amide (0.25 mmol), Ni(cod)₂ (0.25 mmol), PCy₃ (0.25 mmol) in toluene (1.0 mL) for 18 h at 80 °C. [b] Substituent constants from ref. 11. [c] GC yield. [d] NMR yield. [e] 3,4-Bis(dicyclohexylphosphino)thiophene (100 mol%) was used instead of PCy₃ and run at 180 °C.

180 °C using dcype as the ligand (entry 11). The reaction was not effective when conducted at 180 °C using 20 mol% of Ni(cod)₂/PCy₃ (entry 9) nor at 80 °C using 1 equiv. of Ni(cod)₂/dcype (entry 10). We therefore decided to use two sets of conditions for investigating the scope and limitations of the reaction: 20 mol% of Ni(cod)₂/dcype at 180 °C (condition A) and 1 equiv. of Ni(cod)₂/PCy₃ at 80 °C (condition B).

The scope of the *N*-acyl group was initially investigated to identify the electronic requirement for this nickel-catalyzed decarbonylation reaction (Table 2). Under the catalytic conditions (condition A), *N*-acylindoles bearing an electron-withdrawing group (*i.e.*, **1a** and **1b**) readily underwent decarbonylation, while electron-neutral (**1c** and **1d**) and electron-rich (**1e** and **1f**) amides were much less reactive.[11] The yields of these less reactive amides could be improved by using condition B, in which Ni(cod)₂/PCy₃ (1 equiv. each) was used.

A diverse array of *N*-acylated N-heteroarenes could be decarbonylated using our nickel-mediated protocol (Table 3). Although a methoxy group can be activated by Ni(0) catalysis,[12] it was compatible with this decarbonylation reaction, as exemplified by efficient reactions when **1i** and **1j** were used. Several other common functional groups, including esters **1g**, amides **1k**, ketones **1l**, nitriles **1m**, and fluorides **1n**, were found to be tolerated and decarbonylation occurred chemoselectively at the indole amide moiety. In addition to benzoic acid derivatives, π-

extended analogues, such as **1o** and **1p**, also served as good substrates for forming *N*-arylated products. The alkenyl amide **1q** could be used to produce *N*-alkenylindole **2q** in excellent yield under condition B. Heteroarene-based carboxylic acids can also be used in this decarbonylation reaction, as demonstrated in the reaction of **1r**. The scope of the N-heteroarene moiety was also investigated. Substituents on the indole ring had no significant effect on the efficiency of the reaction, thus permitting a variety of indole derivatives to be produced *via* decarbonylation (**1s–1ab**). This decarbonylation is not limited to indole derivatives and pyrroles **1x**, carbazoles **1y** and azaindoles **1z** also participated in this decarbonylation reaction, allowing rapid access to a diverse array of arylated heteroarenes from the corresponding carboxylic acids. Moreover, the non-aromatic six-membered phenoxazine derivative **1aa** was decarbonylated successfully, whereas the *N,N*-diphenyl amide was much less reactive (10% yield, see ESI† for details). These results indicate that there is a threshold for the pK_a value of the parent amine in determining whether or not the reaction will proceed (pK_a in DMSO: pyrrole 23, indole 21, carbazole 20, phenoxazine 22, and diphenylamine 25).[13] This seems to be reasonable since the C(=O)–N bond becomes stronger as the parent amine becomes more basic, leading to a lower reactivity in this decarbonylation reaction. In agreement with this conclusion, a substrate derived from an electron-deficient diphenylamine (*i.e.*, **1ab**) exhibited a significantly improved reactivity for this decarbonylation reaction.

This decarbonylative *N*-arylation allows for the orthogonal introduction of azoles into halogen and carboxylic acid functionalities. For example, the *N*-arylation of carbazole using ethyl 3-iodobenzoate (**3**) occurs at the iodide site when the common copper-catalyzed method is used,[2] and the

Table 3 Scope of the nickel-catalyzed decarbonylation of *N*-acylated heteroarenes[a]
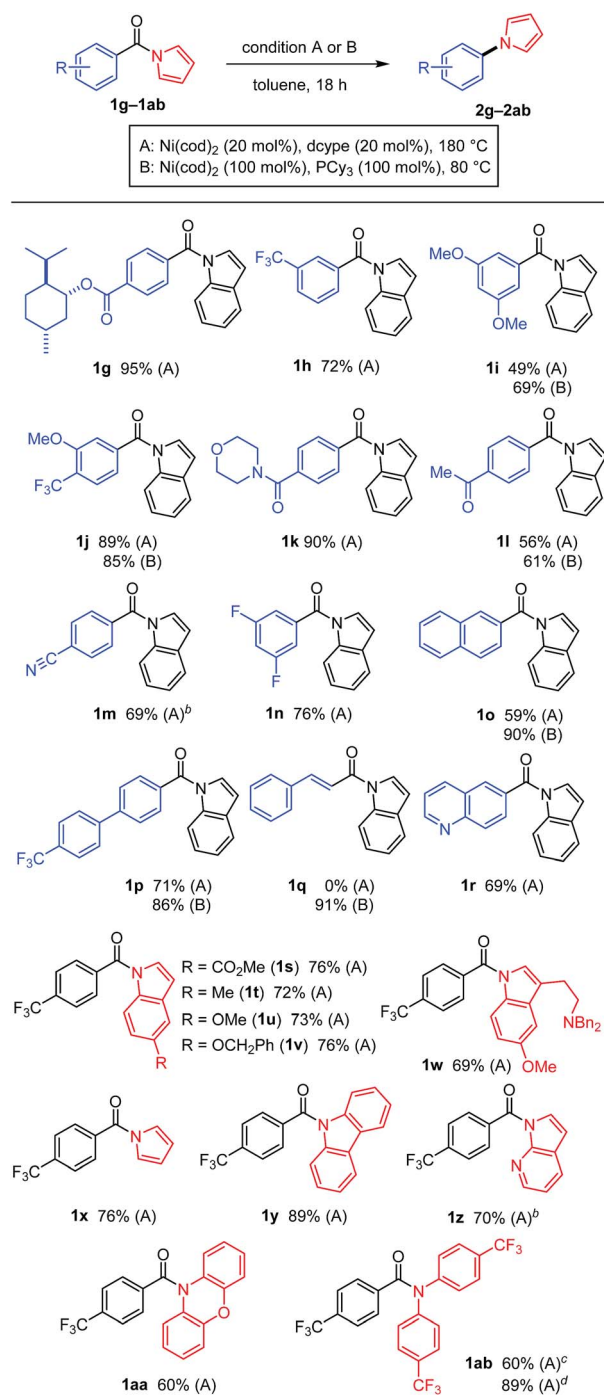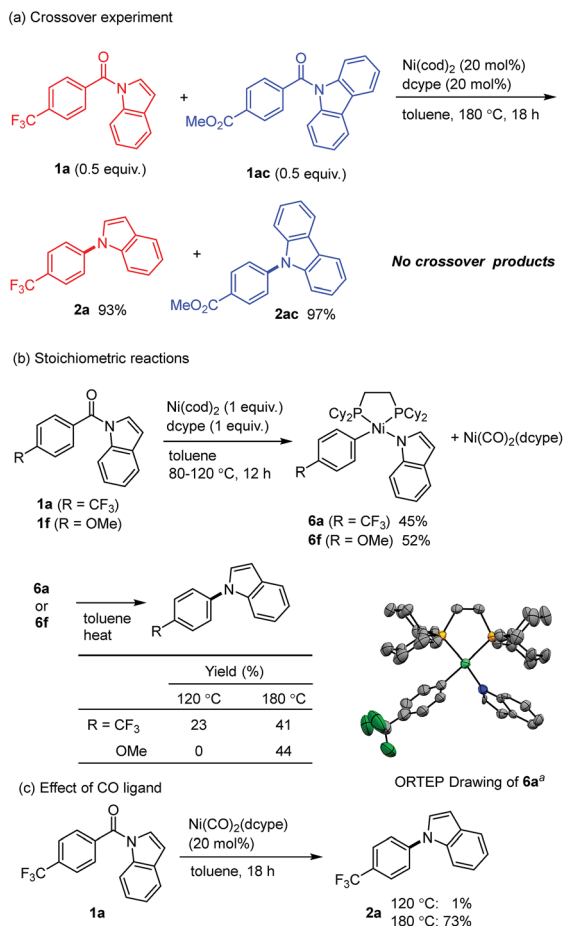

[a] Condition A: amide (0.25 mmol), Ni(cod)₂ (0.050 mmol), dcype (0.050 mmol) in toluene (1.0 mL) for 18 h at 180 °C; condition B: amide (0.25 mmol), Ni(cod)₂ (0.25 mmol), PCy₃ (0.25 mmol) in toluene (1.0 mL) for 18 h at 80 °C. [b] 1,3-Bis(dicyclohexylphosphino)propane (0.050 mmol) was used instead of dcype. [c] Run for 48 h. [d] Ni(cod)₂ (0.25 mmol) and dcype (0.25 mmol) were used.

resulting carboxylic acid moiety can be converted to another azole ring through an amidation/decarbonylation protocol (Scheme 2).

Several mechanistic experiments were conducted. A nickel-catalyzed reaction using a mixture of **1a** and **1ac** provided the corresponding decarbonylation products **2a** and **2ac** without the formation of any crossover products, indicating that this reaction proceeds *via* an intramolecular pathway (Scheme 3a). The reaction of amide **1a** with 1 equivalent of Ni(cod)₂ and dcype was monitored by ³¹P NMR, which revealed that a signal derived from the Ni(CO)₂(dcype) (64.0 ppm, singlet) and two sets of doublets (57.9 ppm and 60.7 ppm, *J* = 13.1 Hz) appeared upon heating the mixture at 80 °C.[14] These results indicate that a relatively stable organometallic intermediate is formed. Additional stoichiometric experiments resulted in the isolation of the arylnickelamide complex **6a**, the structure of which was unambiguously determined by X-ray crystallography (Scheme 3b).[15] Interestingly, the corresponding arylnickelamide complex **6f** can also be formed from a methoxy-substituted amide **1f** under similar conditions, although the amide **6f** was much less reactive under the catalytic conditions used. These results indicate that, the reductive elimination from the arylnick-elamide species to form a C–N bond has higher activation barrier than the prior C–N and C–C(=O) bond cleavage processes. Indeed, a higher temperature (>120 °C) was required for this reductive elimination to occur to form an *N*-arylated product.[16] Since Ni(CO)₂(dcype) is also formed as the decarbonylation reaction proceeds, its catalytic activity was investigated (Scheme 3c). The Ni(CO)₂(dcype) was found to catalyze the decarbonylation of **1a** at 180 °C, whereas only a trace amount of the product was formed at 120 °C. These results suggest that heating at 180 °C is necessary for the dissociation of a CO ligand to occur to generate a catalytically active nickel species.

Based on the mechanistic studies described in Scheme 3, we propose a catalytic cycle shown in Scheme 4. *In situ* generated Ni(dcype) **A**[17] serves as the catalytically active species, which initially activates a C(acyl)–N bond of the amide **1d** *via* oxidative addition[18] to form an acylnickelamide intermediate **B**. The subsequent extrusion of CO from the acyl ligand in **B** leads to the formation of the carbonylnickel species **C**, in which one of the phosphorus atoms of dcype is dissociated. The dissociation of the CO ligand in **C** is facilitated by the recovery of the bidentate coordination of dcype to form the arylnickelamide complex **D**, which is one of the resting states of the catalyst. C–N bond forming reductive elimination from **D** is one of the
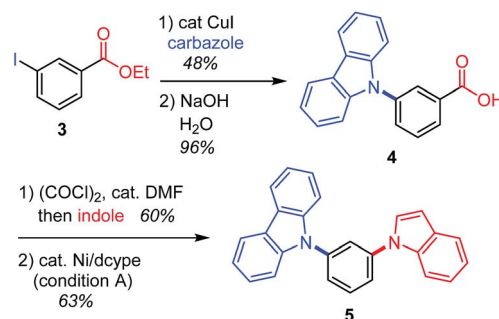
Scheme 2 Sequential C–N bond formation using halogen and carboxyl groups as orthogonal handles.

(a) Crossover experiment

1a (0.5 equiv.) + 1ac (0.5 equiv.)

Ni(cod)₂ (20 mol%)
dcype (20 mol%)
toluene, 180 °C, 18 h

2a 93% + 2ac 97%   *No crossover products*

(b) Stoichiometric reactions

1a (R = CF₃)
1f (R = OMe)

Ni(cod)₂ (1 equiv.)
dcype (1 equiv.)
toluene
80–120 °C, 12 h

6a (R = CF₃) 45%
6f (R = OMe) 52%   + Ni(CO)₂(dcype)

6a or 6f → toluene heat

	Yield (%)	
	120 °C	180 °C
R = CF₃	23	41
OMe	0	44

ORTEP Drawing of 6a[a]

(c) Effect of CO ligand

1a

Ni(CO)₂(dcype)
(20 mol%)
toluene, 18 h

2a   120 °C: 1%
     180 °C: 73%

Scheme 3 Mechanistic Studies. [a]Thermal ellipsoids set at the 50% probability level. All hydrogen atoms are omitted for clarity.[15]

A (P = PCy₂)

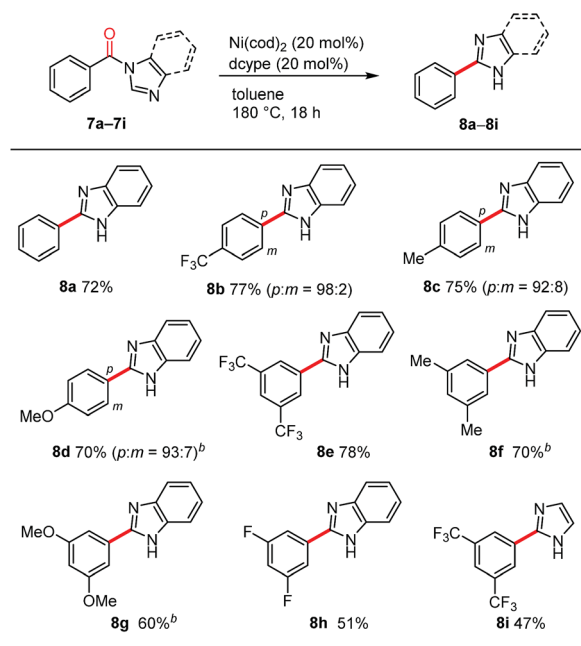2d ← Ni/P P → + 1d

D → B

C

A ↑↓ −A
CO
Ni(CO)₂(dcype)
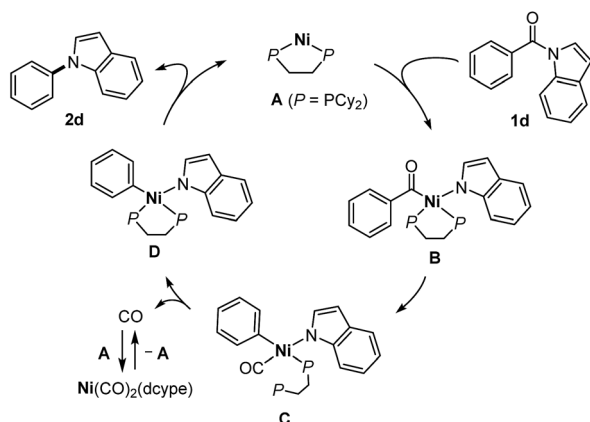
Scheme 4 Proposed mechanism.

difficult steps of this catalytic cycle. The higher reactivity of electron deficient amides is in agreement with the general trend in which C(aryl)–N bond reductive elimination proceeds more efficiently with an aryl ligand bearing an electron-withdrawing group.[19] The dissociated CO is captured by **A** to form Ni(CO)₂(-dcype), which is catalytically inactive but can regenerate **A** upon

heating to temperatures over 180 °C. The use of a PCy₃ ligand instead of dcype generates a more active complex that can more easily mediate all the elementary steps required for the conversion of the amide **1d** to the amine **2d** (*i.e.*, oxidative addition, extrusion of CO, and reductive elimination). However, unlike the case of dcype, there is no driving force available for the CO dissociation step, which hampers catalyst turnover when PCy₃ is used. A similar contrast between PCy₃ and dcype was also reported in the catalytic decarbonylative cross-coupling of phenyl esters.[20]

During the course of our investigations into the decarbonylation of *N*-acylated N-heteroarenes, we examined the benzimidazole derivative **7a**. To our surprise, an *N*-arylation product was not formed in the Ni/dcype-catalyzed reaction of **7a** but rather, C2-arylation occurred to afford **8a** (Table 4). The overall reaction involves decarbonylation and 1,2-migration of the *N*-substituent.[21,22] Although the detailed mechanism for this intriguing transformation remains elusive at present, the results of several preliminary mechanistic studies are noteworthy. First, a crossover experiment using two different *N*-acylated benzimidazole derivatives resulted in the formation of crossover products, suggesting that, unlike the decarbonylation of *N*-acylated indoles shown in Scheme 3a, an intermolecular pathway is likely to be operative. Second, when benzimidazoles bearing a *para*-substituted benzoyl group on the nitrogen atom, such as **8b**, **8c** and **8d**, were used as substrates, small amounts of *meta* isomers were also formed in addition to the expected *para*-substituted 2-arylbenzimidazoles.[23] This type of

Table 4 Nickel-catalyzed 1,2-migratory decarbonylation of *N*-acylbenzimidazole[a]

7a–7i

Ni(cod)₂ (20 mol%)
dcype (20 mol%)
toluene
180 °C, 18 h

8a–8i

8a 72%
8b 77% (p:m = 98:2)
8c 75% (p:m = 92:8)
8d 70% (p:m = 93:7)[b]
8e 78%
8f 70%[b]
8g 60%[b]
8h 51%
8i 47%

[a] Amide (0.25 mmol), Ni(cod)₂ (0.050 mmol), dcype (0.050 mmol) in toluene (1.0 mL) for 18 h at 180 °C. [b] Ni(cod)₂ (0.10 mmol) and dcype (0.10 mmol) were used.

rearrangement was not observed in the case of the other heteroarene-based substrates shown in Table 3. Third, neither N-phenylbenzimidazole (S17) nor 2-benzoylbenzimidazole (S18) were converted into the 2-phenylbenzimidazole (8a) under these nickel-catalyzed conditions, excluding the intermediacy of these compounds in this migrative decarbonylation reaction. Finally, labelling experiments using a substrate having deuterium at the 2-position of a benzimidazole ring revealed that the cleavage of the C(2)–H bond is not involved in a turnover-limiting step.[24] meta-Disubstituted substrates 8e–8h underwent this decarbonylation to form the corresponding 2-arylated products without forming regioisomers. The reaction can also be applied to N-acylimidazole 8i, albeit in a lower yield.

Conclusions

In conclusion, we have developed the first decarbonylation of N-acylated N-heteroarenes, which allows benzoic acid derivatives to be used as arylating agents for N-heteroarenes. Arylnickelelamide complexes were successfully isolated and characterized as viable catalytic intermediates. 1,2-Migratory decarbonylation occurred when N-acylated benzimidazoles were used as substrates. We expect that the capacity of employing feedstock chemicals in synthesizing N-arylated heteroarenes will find utility across a number of research fields. Further studies directed at the development of new catalytic decarbonylation reactions using simple carbonyl compounds are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 (a) Reductive elimination from the MeO-substituted complex 6f required a higher temperature (180 °C) than that needed for reaction of the CF$_3$-substituted complex 6a; (b) Under catalytic conditions, the rate of product formation is expected to be much less since 6f is generated only in a catalytic amount; (c) The yield of 2a by the reductive elimination of 6a increased to 51% when the

reaction was conducted in the presence of Ni(CO)$_2$(dcype) (1 equiv.), indicating that CO could accelerate the reductive elimination under catalytic conditions.

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