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Communication

Remote sp^2 C−H Carboxylation via Catalytic 1,4-Ni Migration with CO_2

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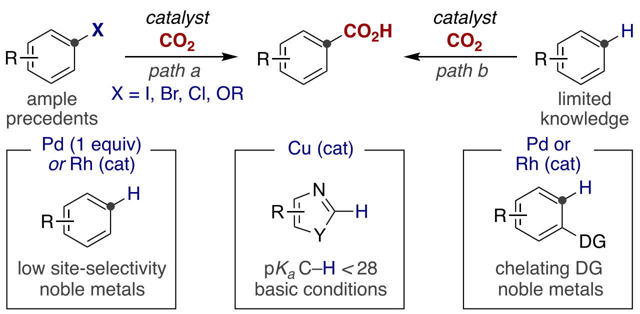
ABSTRACT: A remote catalytic reductive sp^2 C−H carboxylation of arenes with CO_2 (1 bar) via 1,4-Ni migration is disclosed. This protocol constitutes the first catalytic 1,4-Ni migration reported to date, thus offering new vistas in the Ni-catalyzed reductive coupling arena while providing an unconventional new platform for incorporating electrophilic sites at remote sp^2 C−H linkages.

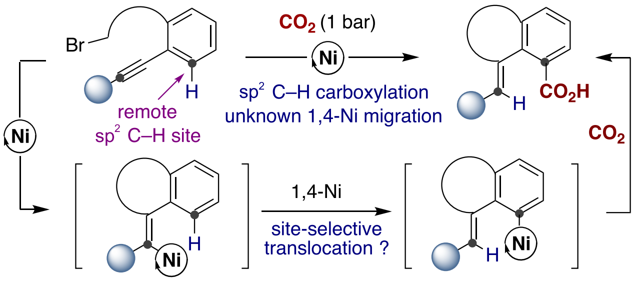
Recent years have witnessed the design of catalytic reductive carboxylations of aryl (pseudo)halides with CO_2 en route to benzoic acids,[1] privileged motifs in biologically active molecules.[2] Although remarkable levels of sophistication have been reached, prefunctionalization at the targeted sp^2 reaction site is required prior to CO_2 insertion (Scheme 1, path a).[1] Beyond any doubt, the pursuit of an alternative catalytic carboxylation at previously unfunctionalized sp^2 C−H sites (path b) might constitute, conceptuality and practicality aside, a worthwhile endeavor for chemical invention.[3]

Scheme 1. sp^2 Carboxylation Reactions with CO_2



Prompted by a seminal work of Fujiwara with stoichiometric amounts of Pd complexes,[4] significant efforts have been made to unlock the potential of sp^2 C−H carboxylations by employing either acidic sp^2 C−H linkages[5] or strategies requiring chelating groups (Scheme 1, bottom).[6] However, extensions to non-acidic sp^2 C−H bonds are beyond reach in the former, whereas the absence of chelating groups results in site-selectivity issues, invariably requiring noble metals and/or stoichiometric organometallic reagents (bottom left).[7] These observations have contributed to the perception that a de novo catalytic sp^2 C−H carboxylation strategy without recourse to noble metals or organometallics might provide fundamentally new knowledge in both sp^2 C−H functionalization and carboxylation processes. Under this premise, we wondered whether a new catalytic blueprint could be designed via a cascade-type process based on a site-selective 1,4-Ni migration,[8] thus setting the stage for a formal CO_2 insertion at remote sp^2 C−H bonds (Scheme 2). At the outset of our investigations, however, it was unclear whether such a strategy could be implemented, as (1) *catalytic* 1,4-Ni translocation[9] remains an unknown cartography in cross-coupling reactions[10−14] and (2) site-selectivity issues might come into play because of competitive catalytic carboxylation at the sp^3 C−Br site[15] or at the alkyne motif.[16] We recognized that, if successful, such a scenario might offer a conceptually new reactivity mode in the reductive cross-coupling arena for tackling the functionalization of otherwise inaccessible sp^2 C−H reaction sites.[17] Herein we report the successful realization of this goal. Our protocol is characterized by its mild conditions, wide substrate scope—including challenging substrate combinations—without the need for handling air- or moisture-sensitive reagents, and an exquisite site-selectivity pattern.

Scheme 2. sp^2 C−H Carboxylation via 1,4−Ni Migration



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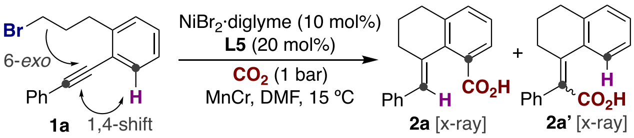
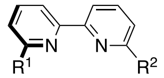
Our investigations began by evaluating the remote sp^2 C−H carboxylation of **1a** with CO_2 (Table 1). As expected, conditions previously employed for the reductive carboxylation of aryl halides failed to provide even traces of **2a**[18] and mainly resulted in statistical mixtures of carboxylic acids arising from CO_2 insertion at the vinyl motif (*E*,*Z*-**2a′**). After a judicious choice of the reaction parameters, a combination of $NiBr_2$·diglyme, **L5**, and $Mn_{89}Cr_{11}$ was found to be critical for success,[19] delivering **2a** in 77% yield with an excellent site-selectivity profile (94:6).[20] As shown in entries 2−5, subtle changes in the electronic or steric environment of the 2,2′-bipyridine core had a non-negligible impact on the reactivity.[21] Strikingly, erosion of both the yield and site selectivity was observed when metal reductants other than $Mn_{89}Cr_{11}$ were employed (entries 6−8).[22] While one might argue that the presence of Cr atoms might dictate the site-selectivity pattern, the results shown in entries 7 and 8 indicate otherwise.[14] At present we have no explanation for this behavior. While inferior results were found with $Ni(cod)_2$ and DMSO (entries 9 and 10), no erosion in yield or selectivity was found when air- and moisture-stable $NiBr_2(\mathbf{L5})_2$ was used, constituting an additional bonus from a user-friendly standpoint (entry 11).

Table 1. Optimization of the Reaction Conditions[a]

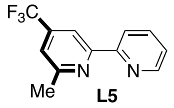


1a **2a** [x-ray] **2a′** [x-ray]

entry	deviation standard conditions	**2a** (%)[b]	**2a′** (%)[b]
1	none	77	5
2	**L1** instead of **L5**	0	0
3	**L2** instead of **L5**	75	8
4	**L3** instead of **L5**	56	6
5	**L4** instead of **L5**	19	7
6	Mn instead of MnCr	40	9
7	using Mn/$CrCl_3$ (10 mol%)	43	14
8	using Mn/$CrCl_2$ (10 mol%)	3	45
9	using $Ni(cod)_2$ as catalyst	64	4
10	DMSO instead of DMF	0	0
11	using $NiBr_2(\mathbf{L5})_2$ (10 mol%)	77 (80%)[c]	5



R^1=H; R^2=H (**L1**)
R^1=Me; R^2=H (**L2**)
R^1=*i*-Pr; R^2=H (**L3**)
R^1=R^2=Me (**L4**)

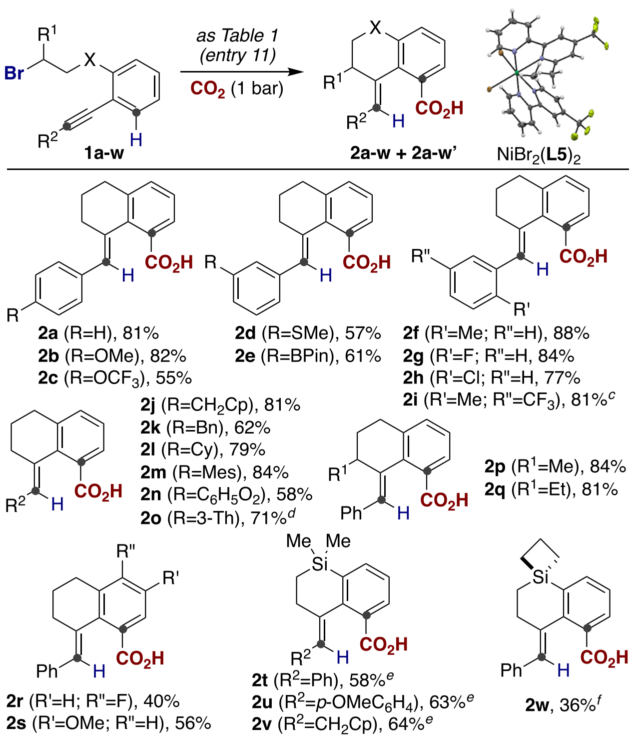


L5

[a]Conditions: **1a** (0.20 mmol), $NiBr_2$·diglyme (10 mol %), **L5** (20 mol %), and MnCr alloy (0.25 mmol) in DMF (0.2 M) at 15 °C under CO_2 (1 atm). [b]Determined by ^{1}H NMR analysis using trimethoxybenzene as an internal standard. [c]Isolated yields.

Encouraged by these findings, we turned our attention to studying the generality of our cascade process with a host of unactivated alkyl bromides. As evident from the results compiled in Table 2, structures containing thioethers (**2d**), methoxy arenes (**2b**), trifluoromethylated derivatives (**2c** and **2i**), or heterocycles (**2o**) could perfectly be tolerated. Even aryl halides (**2g**, **2h**, and **2r**) or organoboranes (**2e**) could be accommodated, thus constituting an orthogonal gateway for subsequent manipulation via cross-coupling reactions. Notably, acetylenes end-capped with either sterically hindered arenes (**2m**) or aliphatic motifs (**2j**−**l**) posed no problems. Equally relevant was the observation that the targeted carboxylation occurred regardless of the steric properties at the acetylene backbone or the employment of secondary unactivated alkyl bromides (**2p** and **2q**). Interestingly, the inclusion of different substitution patterns on the arene backbone did not interfere with productive 1,4-migration, albeit in lower yields (**2r** and **2s**).[23] The successful carboxylation of silicon-tethered alkyl bromides is particularly important, as the corresponding carboxylic acids **2t**−**w** could be homologated via C−Si cleavage at later stages, thus easily accessing nonfused analogues (Scheme 4, bottom).

Table 2. sp^2 C−H Carboxylation of Alkyl Bromides[a,b]



1a-w **2a-w + 2a-w′** $NiBr_2(\mathbf{L5})_2$

2a (R=H), 81%
2b (R=OMe), 82%
2c (R=OCF_3), 55%

2d (R=SMe), 57%
2e (R=BPin), 61%

2f (R′=Me; R″=H), 88%
2g (R′=F; R″=H, 84%
2h (R′=Cl; R″=H, 77%
2i (R′=Me; R″=CF_3), 81%[c]

2j (R=CH_2Cp), 81%
2k (R=Bn), 62%
2l (R=Cy), 79%
2m (R=Mes), 84%
2n (R=$C_6H_5O_2$), 58%
2o (R=3-Th), 71%[d]

2p (R^1=Me), 84%
2q (R^1=Et), 81%

2r (R′=H; R″=F), 40%
2s (R′=OMe; R″=H), 56%

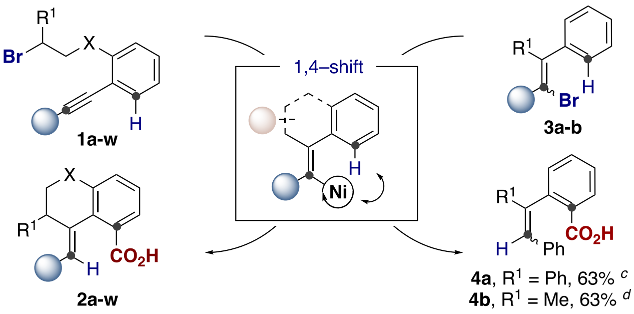
2t (R^2=Ph), 58%[e]
2u (R^2=*p*-$OMeC_6H_4$), 63%[e]
2v (R^2=CH_2Cp), 64%[e]

2w, 36%[f]

[a]Conditions: as in Table 1, entry 11. [b]Isolated yields, averages of two runs, **2a**−**w**:**2a′**−**w′** ≥ 90:10. [c]**2i**:**2i′** = 87:13. [d]**2o**:**2o′** = 76:26. [e]**L2** (20 mol %) and MnCr (2.5 equiv). [f]$NiBr_2$·diglyme (15 mol %)/**L2** (30 mol %) and MnCr (2.5 equiv), **2w**:**2w′** = 80:20.

The successful preparation of **2a**−**w** suggested that an otherwise similar 1,4-Ni migration scenario could be within reach by the use of simple vinyl halides as substrates. As shown in Scheme 3, this turned out to be the case, and vinyl bromides containing either alkyl or aromatic substituents could trigger the targeted sp^2 C−H carboxylation en route to **4a** and **4b** regardless of whether *E*/*Z* mixtures of **3a** and **3b**, respectively, were utilized.[24] While tentative, this observation suggests an initial *E*/*Z* isomerization of the oxidative addition Ni(II) species prior to 1,4-Ni migration, probably via the

Scheme 3. sp^2 C−H Carboxylation of Vinyl Bromides[a,b]



1a-w **3a-b** **2a-w**

4a, R^1 = Ph, 63% [c]
4b, R^1 = Me, 63% [d]

[a]Conditions: as in Table 1, entry 11, using DMA. [b]Isolated yields, averages of two independent runs. [c]*Z*:*E* = 2.4:1. [d]*Z*:*E* = 3.3:1.

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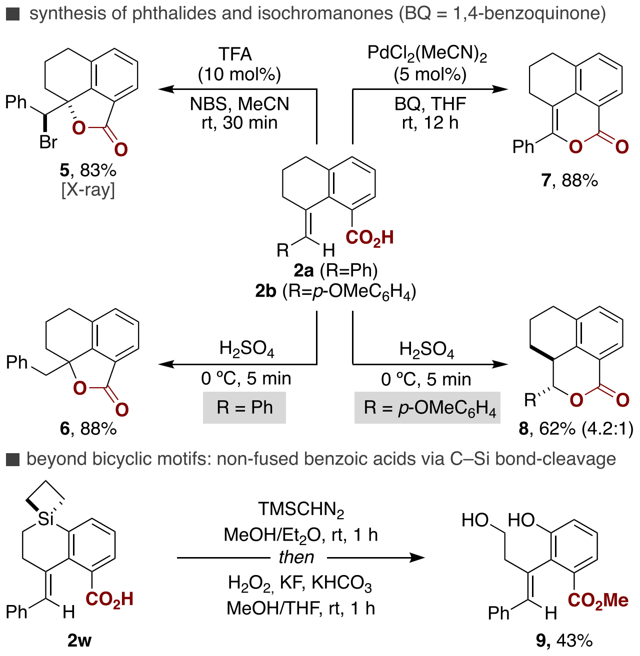
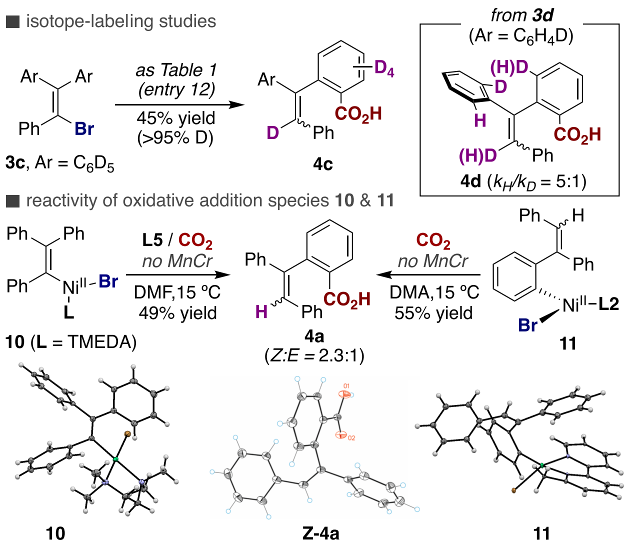
intermediacy of carbene-type species.[25] The prospective impact of our 1,4-Ni migration technique is further illustrated in Scheme 4. As shown, complex molecular isochromanone or phthalide architectures could be accessed from **2a** or **2b** depending on the reaction conditions utilized. Thus, bromolactonization to obtain **5** was easily accomplished by exposing **2a** to NBS in TFA,[26] whereas clean formation of phthalide **6** was observed with H_2SO_4 instead.[27] Similarly, while isochromenone **7** could be obtained via Pd-catalyzed oxidative regimes,[28] the saturated isochromanone analogue **8** was within reach from **2b** instead. More importantly, the successful preparation of **9** in an unoptimized 43% yield tacitly indicates that the presence of silicon fragments can be turned into a strategic advantage to access functionalized polyhydroxylated carboxylic acids, thus expanding the application profile of our technology.[29]

Scheme 4. Application Profile



Intrigued by the favorable reactivity profile shown in Table 2 and Schemes 2 and 3, we conducted experiments with isotopically labeled substrates (Scheme 5, top). As shown, full deuterium incorporation at the vinyl position (>95% D) was observed in **4c** when **3c** was exposed to our optimized $NiBr_2$/**L5** regime, thus corroborating that a [1,4]-Ni migration occurs at the *ortho* sp^2 C−H bond prior to CO_2 insertion. Interestingly, while a significant intramolecular kinetic isotope effect was observed in the reductive carboxylation of **3d** (k_H/k_D = 5:1; Scheme 5, top right), no intermolecular kinetic isotope effect was found by comparison of the rates of **3a** and **3c**.[19] Although tentative, this observation suggests a rate-determining step that occurs before or after the 1,4-migration event.[30] Still, however, there was a reasonable doubt about whether [1,4]-Ni migration and the subsequent CO_2 insertion occurred at Ni(I) or Ni(II) centers. Thus, we turned our attention to unraveling such mechanistic intricacies by isolating the putative oxidative addition species at either the vinyl or aryl terminus. Interestingly, **10** and **11** could be prepared by reacting the aryl (vinyl) halide with $Ni(cod)_2$ and TMEDA or **L2** in THF.[31] The structures of these complexes in the solid state are depicted in Scheme 5 (bottom).[32] As anticipated, the carboxylation of **10** occurred only *in the presence* of **L5**, thus illustrating the importance of 2,2′-bipyridine ligands in the targeted carboxylation reaction. More importantly, **4a** could be obtained from **10** or **11** *in the absence of external metal reductant*, strongly suggesting that both 1,4-Ni migration and CO_2 insertion occur at Ni(II) centers.[33] This observation can hardly be underestimated, as it challenges the prevailing perception that CO_2 insertion occurs at Ni(I)−carbon bonds[34] and that a 1,4-shift should take place at Ni(I) centers,[9] thus opening up new knowledge about catalyst design, particularly in the reductive cross-coupling arena.[17] Whether CO_2 insertion occurs at four-coordinate or six-coordinate species via octahedral complexes is a subject of ongoing studies in this laboratory.[35]

Scheme 5. Preliminary Mechanistic Studies



In summary, we have documented the first catalytic 1,4-nickel migration as a vehicle to enable CO_2 insertion at remote and previously unfunctionalized sp^2 C−H reaction sites, an unrecognized opportunity in both the carboxylation and reductive cross-coupling arena. The salient features of this protocol are the exquisite chemo- and site selectivity, mild conditions, and application profile. Further extensions to other cross-couplings initiated by 1,4-Ni migration are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c08810.

Crystallographic data for **2a**′ (CCDC 1992996) (CIF)

Crystallographic data for **2a** (CCDC 1992997) (CIF)

Crystallographic data for **4a** (CCDC 1992998) (CIF)

Crystallographic data for **5** (CCDC 1992999) (CIF)

Crystallographic data for **10** (CCDC 1993000) (CIF)

Crystallographic data for $NiBr_2$(**L5**)$_2$ (CCDC 1993001) (CIF)

Experimental procedures and spectral and crystallographic data (PDF)

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Notes

The authors declare no competing financial interest.

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(24) Similar yields were obtained regardless of whethe the reaction started with *Z*- or *E*-vinyl bromide **3b.** Control experiments were conducted to understand the origin of the *E*/*Z* isomerization found for **4a**−**d**.[19]

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