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Ni-Catalyzed Divergent Cyclization/Carboxylation of Unactivated Primary and Secondary Alkyl Halides with CO_2

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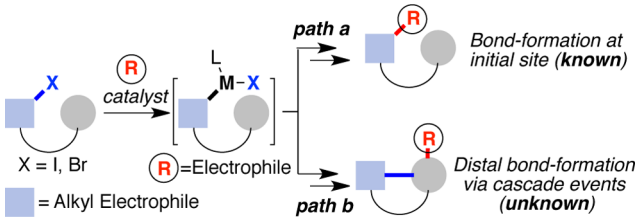
Supporting Information

ABSTRACT: A user-friendly Ni-catalyzed reductive cyclization/carboxylation of *unactivated* alkyl halides with CO_2 is described. The protocol operates under mild conditions with an excellent chemoselectivity profile and a divergent syn/anti selectivity pattern that can be easily modulated by the substrate utilized.

Catalytic reductive coupling reactions of organic halides have evolved from mere curiosities to robust tools that rapidly build up molecular complexity from simple precursors.[1] At present, this field of expertise remains essentially confined to bond-formation events at the initial site (Scheme 1, *path a*).

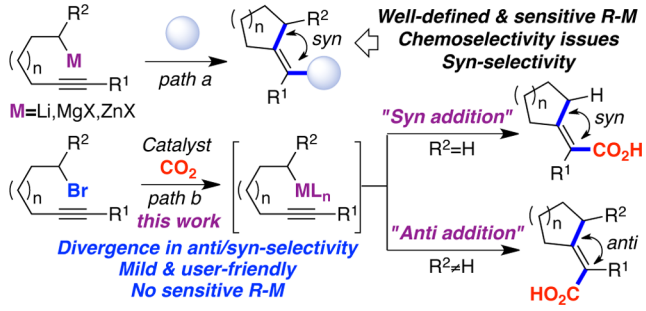
Scheme 1. Bond Formation via Electrophile Couplings



Intriguingly, the ability to promote cascade reactions of *unactivated alkyl electrophiles* via multiple C−C bond formations (*path b*) has been virtually unexplored.[2,3] If successful, such protocols would offer a unique opportunity to increase our chemical portfolio for rapidly preparing carbocyclic skeletons while dealing with bond-formation events at *distal sites*.

In recent years, we[4] and others[5] have designed new catalytic techniques for reductive carboxylation of organic halides using CO_2, probably the greenest C1 synthon in nature.[6] Unlike the utilization of stoichiometric amounts of organometallic complexes,[7] many of these protocols operate under mild conditions in the absence of sensitive reagents, thus representing a straightforward, yet practical, alternative for preparing carboxylic acids, privileged motifs in a myriad of pharmaceuticals.[8] At the outset of our investigations, however, it was unclear whether CO_2 could participate in cascade reductive coupling reactions via multiple bond-forming reactions.[9] Although we anticipated that reductive cascade processes based on the use of *unactivated* alkyl halides,[10] probably the most challenging substrates in the cross-coupling arena, would be rather problematic, we were attracted to the challenge.[11] Specifically, such a route would offer the unique opportunity to control parasitic β-hydride elimination pathways[10] while resulting in carboxylated carbocyclic skeletons from simple precursors via *distal catalytic CO_2 fixation*. We speculated that a technique capable of modulating, at will, the anti/syn selectivity of the cyclization event would set the standards for catalytic biomimetic cascade carboxylation events.[12] Herein, we report a mild and user-friendly reductive cyclization/carboxylation of *unactivated alkyl halides* with CO_2 en route to elusive tetrasubstituted olefins (Scheme 2, path b).[13] In sharp contrast to syn-carbometalation techniques using stoichiometric, well-defined, and in many instances air-sensitive organometallics (Scheme 2, path a),[14] our protocol is characterized by its exquisite chemoselectivity profile while obviating the need for sensitive species. Importantly, this transformation is distinguished by an unconventional divergence in syn/anti- selectivity that can be easily dictated by the ligand backbone or substrate utilized.

Scheme 2. Cyclization/Functionalization of Alkyl Halides



We began our investigations by studying the catalytic cascade cyclization/carboxylation reaction of **1aa** with CO_2 (1 atm) utilizing $NiCl_2$·glyme as the catalyst and Mn as the reductant in *N*,*N*-dimethylformamide at room temperature (Table 1).[15] As for related catalytic reductive coupling processes,[1] we anticipated that subtle differences in the ligand backbone would exert a profound influence on the reaction outcome. As shown in Table 1, this turned out to be the case; while **L1**−**L4** predominantly resulted in nonproductive β-hydride elimination pathways (entries 1−4), the inclusion of ortho substituents in the phenanthroline backbone cleanly produced **2a**. Among them, **L5** and **L6** allowed **2a** to be obtained in respectable yields of 33% and 39%, respectively, with no observable side

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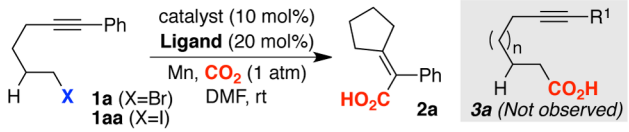
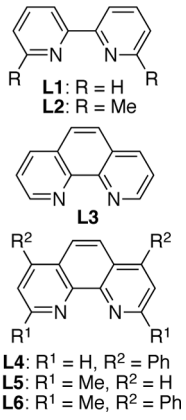
Table 1. Optimization of the Reaction Conditions[a]

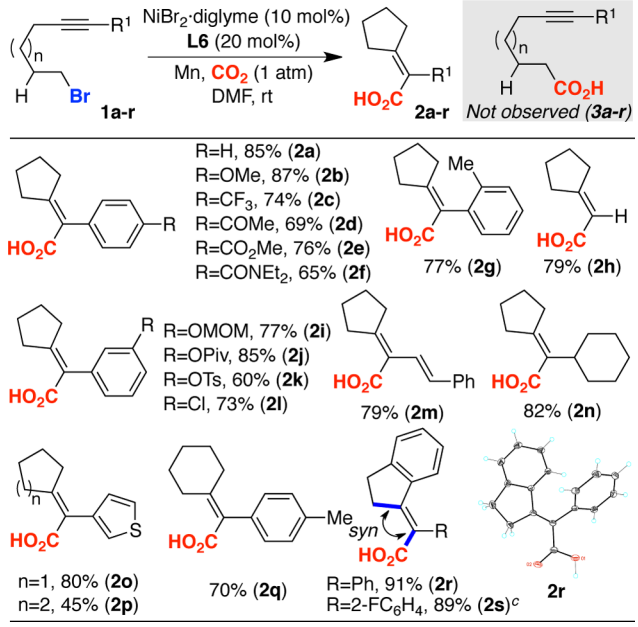


Entry	Catalyst	Ligand	2a(%)[b]
1	$NiCl_2$·glyme	**L1**	0
2	$NiCl_2$·glyme	**L2**	0
3	$NiCl_2$·glyme	**L3**	0
4	$NiCl_2$·glyme	**L4**	0
5	$NiCl_2$·glyme	**L5**	33
6	$NiCl_2$·glyme	**L6**	39
7	$NiBr_2$·glyme	**L6**	63
8	$NiBr_2$·diglyme	**L6**	72,57[c]
9	$Ni(COD)_2$	**L6**	24
10	***$NiBr_2$·diglyme***	***L6***	***85***[d],0[e]
11	$NiBr_2$·diglyme	**L6**	0[f]
12	$NiBr_2$·diglyme	**L6**	3[g]
13	None	None	0



[a]**1aa** (0.30 mmol), Ni catalyst (10 mol %), **L** (20 mol %), Mn (2.20 equiv), DMF (0.15 M), and CO_2 (1 atm) at rt overnight. [b]Determined by HPLC using naphthalene as an internal standard. [c]$NiBr_2$·diglyme (5 mol %). [d]Using **1a** (0.30 mmol); isolated yield. [e]Without Mn or with Zn as the reductant. [f]DMA as the solvent. [g]MeCN as the solvent.

Table 2. Scope Unactivated Primary Alkyl Bromides[a,b]



[a]Conditions: see Table 1, entry 10. [b]Isolated yields (averages of at least two independent runs) are shown. [c]E/Z = 19:1.

products (entries 5 and 6). Strikingly, the choice of precatalyst (entries 7–9), solvent (entries 11 and 12), and reductant (entry 10) had a non-negligible effect on the reactivity, suggesting an intimate interplay among all of the reaction parameters. While not anticipated, we obtained the best results with the a priori less activated alkyl bromide **1a** (entry 10 vs 8), which gave **2a** in 85% isolated yield.[16] Importantly, not even a trace of **3a** was found in the crude reaction mixtures. In line with our expectations, control experiments revealed that all of the reaction parameters ($NiBr_2$·diglyme, **L6**, Mn, and DMF) were critical for success.[15]

Encouraged by these results, we turned our attention to the preparative scope of our catalytic cyclization/carboxylation reaction (Table 2). Particularly noteworthy was the functional group tolerance of our protocol, as ketones (**2d**), ethers (**2b**, **2i**), esters (**2e**, **2j**), amides (**2f**), alkenes (**2m**), and heterocycles (**2o**, **2p**) all were perfectly accommodated. Undoubtedly, the exquisite chemoselectivity profile of our transformation represents a bonus compared with classical carbometalation techniques based on the utilization of organolithium or Grignard reagents, among others (Scheme 2, path a).[14] As shown for **2g**, the inclusion of ortho substituents on the aromatic motif did not hamper the reaction. Interestingly, we found that the cyclization/carboxylation event could even be conducted in the presence of electrophilic partners that are suited for Ni-catalyzed reductive carboxylation reactions, such as aryl chlorides (**2l**),[5c] tosylates (**2k**), or pivalates (**2j**);[4c] notably, no traces of the corresponding benzoic acids derived from C–Cl or C–O bond cleavage were detected in the crude reaction mixtures, thus providing ample opportunities for further functionalization. While one might argue that such a protocol would essentially be restricted to five-membered rings or alkyne residues possessing aromatic motifs, the preparation of **2n**, **2o**, **2p**, and **2q** clearly indicates otherwise. Strikingly, free alkynes posed no problems (**2h**); such a finding is certainly remarkable in view of the proclivity of terminal alkynes to react via competitive trimerization pathways.[17] As anticipated from a classical syn-carbometalation reaction via in situ generated alkyl nickel species,[14,18] we obtained **2r** and **2s**. The structure of **2r** was unequivocally established by X-ray crystallographic analysis.[15]

Next, we focused our attention on a more challenging scenario dealing with *unactivated secondary alkyl halides*.[10] These substrates are particularly problematic because of their reluctance to undergo oxidative addition and their propensity to undergo nonproductive β-hydride elimination, thus constituting an opportunity to explore the robustness of our cyclization/carboxylation event (Table 3). Strikingly, the reaction of **4a** using **L6** under conditions otherwise similar to those of Table 2 resulted in an unexpected selectivity switch (**5a**:**5a′** = 3.3:1). In a formal sense, **5a** can be derived from a rather elusive anti-carbometalation event.[19] Although **5a** was fully characterized by NMR spectroscopic analysis, X-ray crystallography unambiguously identified the abnormal anti-selective motion.[15] It is worth noting that the preparation of **5a** represents the first reductive carboxylation that can be conducted with *unactivated* secondary alkyl electrophiles. Interestingly, the anti selectivity could be modulated by the choice of ligand. Specifically, we found that **L5** uniquely afforded **5a**, with only small amounts of **5a′** being present in the crude mixtures (**5a**:**5a′** = 12.5:1). At present, we have no explanation for this intriguing behavior.[20]

On the basis of these results, we wondered whether the observed anti-selectivity switch for **5a** could be applied to other substrate combinations. As shown in Table 3, this was indeed the case, and a host of differently substituted secondary alkyl bromides could be coupled in high yields with high anti selectivities.[21] Notably, six-membered carbocyclic skeletons could also be accommodated, albeit in lower yields (**5f**). A simple comparison of **5a** vs **5b** and **5c** clearly shows that the anti selectivity is favored with bulkier substituents on the side chain. A similar effect was found with ortho-substituted aromatic motifs (**5d** vs **5a**). Less counterintuitive was the

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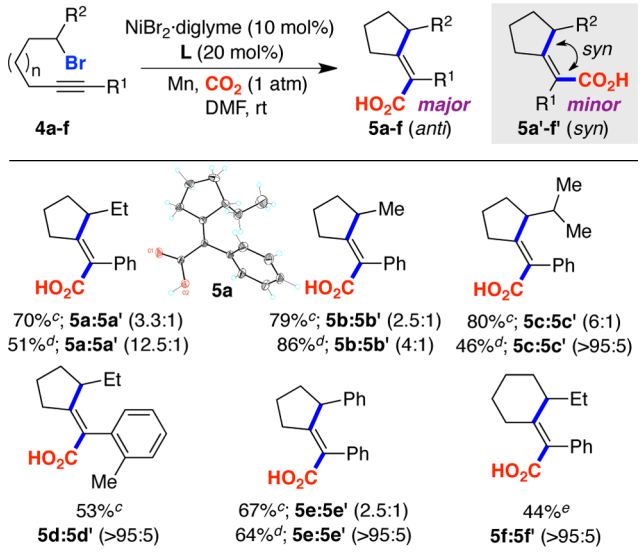
Table 3. Scope Unactivated Secondary Alkyl Bromides[a,b]

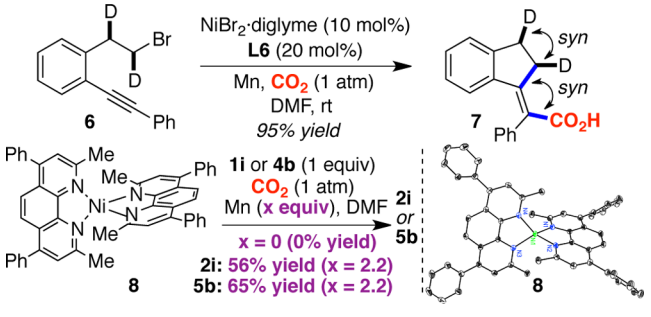


[a]Conditions: see Table 1, entry 10. [b]Isolated yields (averages of at least two independent runs) are shown. [c]**L6** was used as the ligand. [d]**L5** was used as the ligand. [e]**L4** was used as the ligand.

observation that the ligand backbone exerted a profound influence on the selectivity pattern, with **L5** or **L4** providing the best anti/syn selectivities, thus showing the subtleties of our system.[20] At present, we believe that the anti-selectivity switch in secondary alkyl bromides might be attributed to the intermediacy of vinyl radical species that undergo rapid isomerization prior to recombination with Ni(I)Br**L*n*** species.[22−25] Taken together, the data shown in Tables 2 and 3 illustrate the prospective impact of our Ni-catalyzed reductive cyclization/carboxylation event from simple building blocks by promoting *distal* CO_2 *fixation* while controlling the syn/anti selectivity pattern of the cyclization event.

Although a detailed picture requires further studies, we decided to shed light on the mechanism by studying the

Scheme 3. Mechanistic Experiments



stereochemical course of **6** (Scheme 3, *top*). As shown, careful ^{1}H NMR spectroscopic analysis revealed that the reaction exclusively afforded **7**,[15] an observation that is consistent with a scenario consisting of an initial oxidative addition with inversion of configuration.[26,27] Next, we turned our attention to the reactivity of air-sensitive **8**, which is easily accessible simply by reacting $Ni(COD)_2$ with **L6** in tetrahydrofuran (Scheme 3, *bottom*).[28] Importantly, while no reaction took place upon exposure of **8** to either **1i** or **4b** in the absence of Mn, the targeted cyclization/carboxylation product (**2i** or **4i**) was cleanly produced in the presence of the reducing agent. Although premature, we believe that these experiments tacitly suggest that the carboxylation event does not occur from in situ generated Ni(II) species but rather from putative Ni(I) reaction intermediates.[22,29]

In conclusion, we have developed a mild, robust, and user-friendly Ni-catalyzed cascade reductive cyclization/carboxylation using CO_2 at atmospheric pressure in which the selectivity pattern is dictated by an appropriate substrate and/or ligand selection. Further investigations into related processes as well as the development of an asymmetric version are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03340.

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Notes

The authors declare no competing financial interest.

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