Ni-catalyzed Regioselective Hydrocarboxylation of Alkynes with CO_2 by Using Simple Alcohols as Proton Sources

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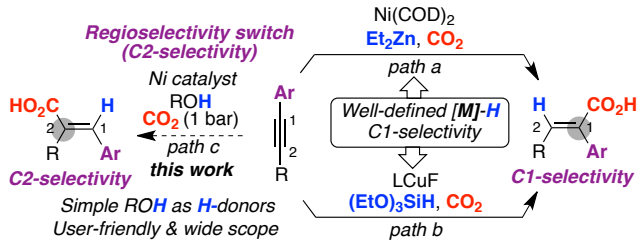
Supporting Information Placeholder

ABSTRACT: A mild and user-friendly Ni-catalyzed regioselective hydrocarboxylation of alkynes with CO_2 (1 bar) is described. This protocol is characterized by a wide scope while obviating the need for sensitive organometallic species and by an unprecedented regioselectivity pattern using simple alcohols as proton sources.

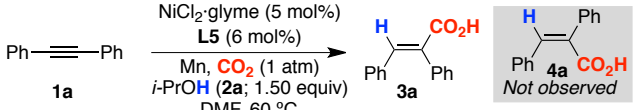
The recent years have witnessed a tremendous progress within the cross-coupling arena, invariably leading to new knowledge in catalytic design.[1] Unfortunately, site-selectivity is oftentimes sacrificed at the expense of discovering new reactivity.[2] Indeed, *the ability to switch the outcome of catalytic endeavors* in a rational and predictable manner still remains a formidable challenge.[1,2] Undoubtedly, such scenario represents a unique opportunity to increase our ever-growing chemical repertoire and improve the flexibility in synthetic design.

Scheme 1. Hydrocarboxylation of Alkynes with CO_2.

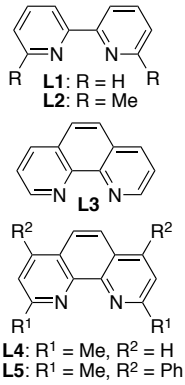


The utilization of carbon dioxide (CO_2) as abundant and inexpensive C1-synthon[3] has gained considerable momentum in catalytic reductive events,[4,5] holding promise for defining new paradigms en route to carboxylic acids, privileged motifs in a myriad of pharmaceuticals.[6] Intriguingly, a limited number of *catalytic* carboxylation protocols of alkynes with CO_2 have been described.[7,8] Among these, hydrocarboxylation events are particularly appealing, providing rapid access to industrially relevant acrylic acids.[9] In 2011, Tsuji[8d] and Ma[8e] independently reported an elegant hydrocarboxylation of alkynes with air-sensitive and pyrophoric Et_2Zn (Scheme 1, *path a*) or well-defined silanes (*path b*) as hydride sources. A close inspection into these procedures, however, indicates that CO_2 insertion preferentially occurs adjacent to aromatic or directing groups;[10] furthermore, low selectivity profiles were found for *sterically unbiased combinations*. While we anticipated that altering such selectivity pattern would be rather problematic, we were attracted to the challenge of providing new knowledge in retrosynthetic analysis while leading to a priori inaccessible building blocks. As part of our studies in CO_2,[11] we report herein an exceedingly practical and user-friendly hydrocarboxylation of alkynes that obviates the need for air-sensitive or organometallic reagents (*path c*).[12] Importantly, the method is characterized by an exceptional chemoselectivity profile at atmospheric pressure of CO_2. While counterintuitive, the inclusion of simple alcohols as proton sources results in an exquisite and predictable selectivity switch, *even for sterically unbiased unsymmetrical alkynes,* exploiting a previously unrecognized opportunity in reductive carboxylation events.

Table 1. Optimization of the Reaction Conditions.[a]



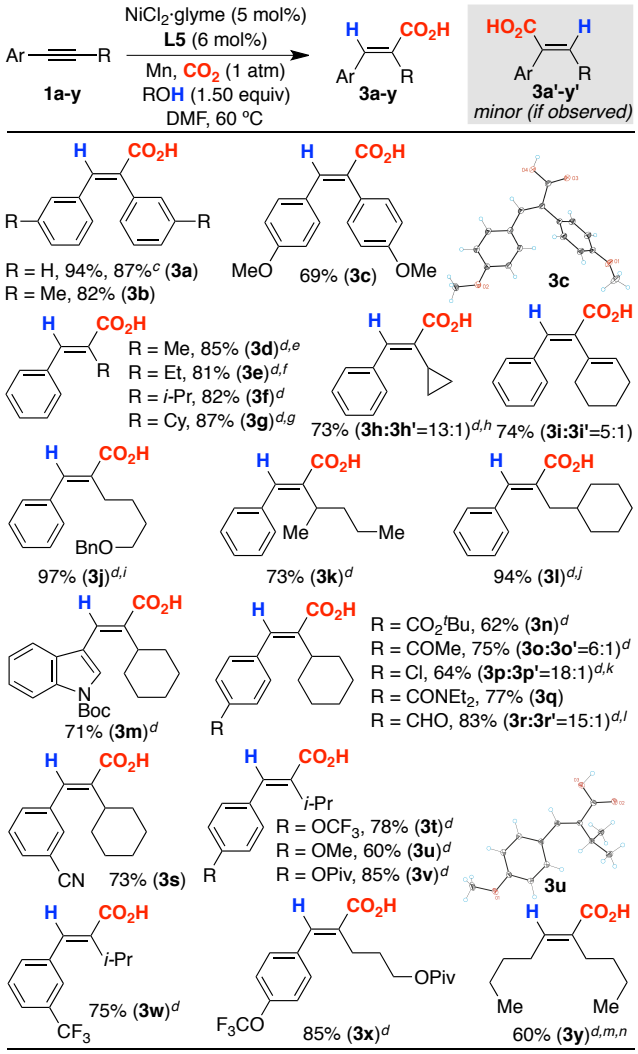
Entry	Change from standard conditions	3a(%)[b]
1	None	99 (94%)[c]
2	$NiCl_2$ (10 mol%) as catalyst at rt	64
3	$Ni(COD)_2$ (10 mol%) as catalyst	78
4	DMA (DMSO) as the solvent	36 (66)
5	Zn as reducing agent	20
6	Using **L1** at rt	0[d]
7	Using **L2** at rt	45[d]
8	Using **L3** at rt	0[d]
9	Using **L4** at rt	66[d]
10	No $NiCl_2$·glyme, **L5**, Mn or **2a**	0
11	HFIP (**2b**) instead of *i*-PrOH (**2a**)	50
12	*t*-BuOH (**2c**) instead of *i*-PrOH (**2a**)	37



[a] **1a** (0.25 mmol), **2** (0.375 mmol), $NiCl_2$·glyme (5 mol%), ligand (6 mol%), Mn (0.375 mmol), DMF (1 mL) at 60 °C. [b] HPLC yield using naphthalene as internal standard. [c] Isolated yield. [d] $NiCl_2$·glyme (10 mol%), **L** (20 mol%).

We initiated our investigations with **1a** as the model substrate and CO_2 (1 bar). After scrupulous evaluation of all reaction parameters,[13] we found that a cocktail consisting of $NiCl_2$·glyme (5 mol%), **L5** (6 mol%), Mn as reducing agent, *i*-PrOH (**2a**) as hydrogen donor in DMF delivered **3a** in 94% isolated yield (Table 1, entry 1). It is worth noting that **4a** was not detected in the crude mixtures. As anticipated, the efficiency was found to be strongly dependent on the nature of the ligand backbone (entries 6-9). Among all ligands analyzed, we found that nitrogen-containing motifs possessing *ortho*-substituents exclusively promoted the targeted transformation, with **L5** providing the best results. Interestingly, inferior results were found with other solvents, catalysts or reducing agent combinations, thus showing the subtleties of our protocol (entries 2-5). Strikingly, the inclusion of HFIP (**2b**) or *t*-BuOH (**2c**) had a deleterious effect, thus revealing a non-innocent behavior of the alcohol structure and suggesting an intimate interplay between electronic and steric effects (entries 11 and 12).[13,14] As expected, control experiments indicated that all reaction parameters were essential for the reaction to occur.[15]

Table 2. Scope of the Hydrocarboxylation Event.[a,b]



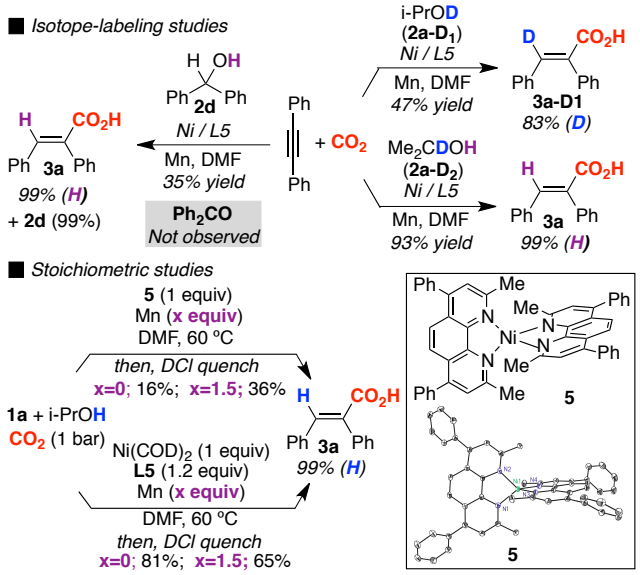
[a] As for Table 1 (entry 1) but at 0.5 mmol scale. [b] Isolated yields, average of at least two independent runs. [c] **1a** (1.10 g). [d] *t*-BuOH (**2c**) was used instead of **2a**. [e] With **2a**: 74% yield (**3d:3d'**=4:1). [f] With **2a**: 85% yield (**3e:3e'**=4:1). [g] With **2a**: 84% yield (**3g:3g'**=4:1). [h] With **2a**: 81% yield (**3h:3h'**=3:1). [i] With **2a**: 77% yield (**3j:3j'**=5:1). [j] With **2a**: 82% yield (**3l:3l'**=4:1). [k] $NiCl_2$·glyme (10 mol%) at rt. [l] The corresponding 1,3-dioxolane was used as coupling partner. [m] $NiCl_2$·glyme (15 mol%) at 80 °C. [n] *E*:*Z* = 15:1.

Encouraged by these findings, we set out to explore the preparative scope of our Ni-catalyzed regioselective hydrocarboxylation event (Table 2). As expected, the coupling of symmetrical alkynes posed no problems (**3a-3c**). Notably, the reaction could be executed on a gram scale, delivering **3a** in 87% isolated yield. As shown in Table 2, our protocol exhibited a remarkable chemoselectivity profile, as a host of substrates containing alkenes (**3i**), carbamates (**3m**), esters (**3n, 3v, 3x**), ketones (**3o**), amides (**3q**), acetals (**3r**), nitrogen-containing heterocycles (**3m**) and nitriles (**3s**) were perfectly accommodated.[16] Importantly, an *exquisite regioselectivity profile* was found for a wide variety of unsymmetrical alkynes, even without significant steric bias (**3d-3x**). As

evident from careful NMR spectroscopic analysis,[13] CO_2 insertion took place predominantly *distal* to the aromatic site. Such observation was univocally confirmed by X-ray crystallography of **3u**. These results are in contrast with the opposite selectivity pattern or the significant erosion in regioselectivity observed in previous hydrocarboxylation events for sterically unbiased alkynes,[8d,8e] thus showing the genuine potential of our protocol. Strikingly, the nature of the alcohol motif exerted a profound influence on site-selectivity for unsymmetrical substrates. While a regime based on *i*-PrOH (**2a**) resulted in low regioselectivity profiles, the utilization of *t*-BuOH (**2c**) dramatically improved the selectivity pattern, delivering single regioisomers in virtually all cases analyzed, albeit with some exceptions (**3h** and **3o**). At present, we do not have an explanation for such distinctive selectivity pattern depending on the substrate utilized. Care, however, must be taken when generalizing this since single regioisomers were found for **3q** and **3s** by using *i*-PrOH (**2a**), thus showing the subtleties of our system. Although tentative, we believe these results reinforce the notion that the alcohol utilized is not a mere spectator and that interacts with the putative reaction intermediates. Interestingly, no carboxylation occurred at electrophilic sites amenable to Ni-catalyzed coupling reactions such as aryl chlorides[5f] (**3p**) or aryl pivalates (**3v**),[10c] thus providing a handle for further manipulation. Notably, the reaction could be extended to internal alkynes possessing aliphatic motifs at both ends (**3y**).[17] Taken together, we believe these results clearly demonstrate that our exceedingly practical Ni-catalyzed regioselective hydrocarboxylation protocol might pave the way for future reductive CO_2 fixation techniques into organic matter.

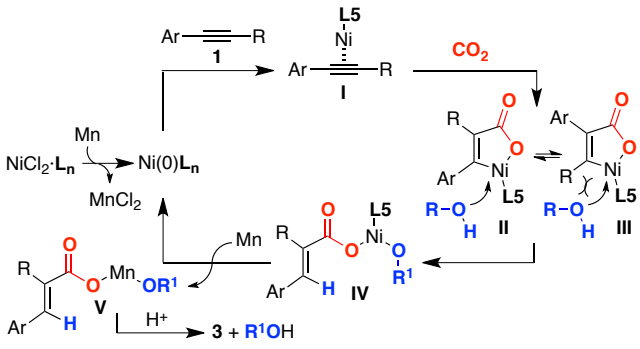
Although an in-depth mechanistic discussion should await further investigations, the utilization of alcohols as hydrogen donors exhibits features reminiscent of a number of elegant hydrogen borrowing strategies reported in the literature.[18] In order to shed light on the mechanism, we decided to gather indirect evidence by studying the reactivity of **2a-D$_1$** and **2a-D$_2$** (Scheme 2). While **2a-D$_1$** reacted at a significantly lower rate than **2a-D$_2$**, **3a-D$_1$** was exclusively observed with a protocol based on **2a-D$_1$** (Scheme 2, *top right*).[19] Interestingly, we observed a $k_H/k_D = 1.1$ when comparing the initial rates of **1a** with **2a** or **2a-D$_1$**.[13] Importantly, **2d** was fully recovered en route to **3a** with not even traces of benzophenone detected in the crude mixtures (Scheme 2, *top left*).[20] Overall, the results depicted in Scheme 2 reinforce the notion that a hydrogen borrowing strategy does not come into play[21] and suggests that alcohols might be acting with dual roles, both as proton sources and as reagents that interact with reaction intermediates within the catalytic cycle. This interpretation gains credence by the markedly distinct selectivity pattern observed in Table 2 under a **2c** or **2a** regime.[22] Next, we set out to explore the reactivity of **5**[23] or Ni(COD)$_2$/**L5** with **1a** and **2a** in a stoichiometric fashion followed by DCl quench (Scheme 2, *bottom*).[24,25] As shown, we found that **3a** was invariably formed regardless of whether Mn was present or not.[26]

Scheme 2. Isotope-labeling and Stoichiometric Studies.



The regioselectivity profile shown in Table 2 does not match the inherent propensity of metal hydride complexes to undergo *cis*-addition across the alkyne motif with the incoming hydride located at the most sterically hindered position (**3d'-x'**).[27] Although tentative, we support a mechanistic scenario consisting of the intermediacy of nickelalactones (**II** and **III**)[28] that are likely in equilibrium upon CO_2 extrusion via **I** (Scheme 3). We propose that **II** reacts preferentially with the alcohol donor in order to avoid the clash with the alkyl substituent on the alkyne terminus of **III**.[29] Subsequently, a protonolysis might occur at the C–Ni(II) bond, generating **IV** that precedes a reduction event to afford manganese carboxylate **V** while regenerating the propagating Ni(0)**L5$_n$** species.[30] A final hydrolytic workup would deliver the targeted acrylic acid and the corresponding alcohol.

Scheme 3. Mechanistic Rationale.



In summary, we have described a novel, mild and user-friendly Ni-catalyzed hydrocarboxylation of alkynes at atmospheric pressure of CO_2 that occurs with an exquis-

ite regioselectivity profile using commercially available alcohols as proton sources. We anticipate this study will find widespread use, leading to new knowledge in catalytic reductive carboxylation reactions. Further mechanistic investigations and the extension to a wide variety of π-systems are currently ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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No competing financial interests have been declared.

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(13) See Supporting information for details

(14) The utilization of TFA, triflic acid or benzoic acid as proton sources resulted in no conversion to products.

(15) Under the limits of detection, we did not observe even traces of the corresponding cyclic anhydride via double carboxylation, see: Fujihara, T.; Horimoto, Y.; Mizoe, T.; Sayyed, F. B.; Tani, Y.; Terao, J.; Sakaki, S.; Tsuji, Y. *Org. Lett*. **2014**, *16*, 4960.

(16) While terminal acetylenes resulted in competitive trimerization pathways, diarylacetylenes bearing a *p*-CF_3-C_6H_4 and *p*-OMe-C_6H_4 groups resulted in 15% yield in a 1:1 regioisomeric ratio. The utilization of trimethylsilyl phenyl acetylene resulted in cinnamyl acid in 33% yield via competitive desilylation.

(17) Although not fully optimized, the Ni-catalyzed carboxylation of 4,4-dimethylpent-2-yne (**1z**) with CO_2 and **2c** exclusively resulted in (*E*)-2,4,4-trimethylpent-2-enoic acid (**3z**; 21% yield).

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(19) The carboxylation of **1a** with **2a** as proton source in DMF-d^7 resulted in the exclusive formation of **3a**.

(20) N reductive coupling of **1a** with *in situ* generated benzophenone was observed in the crude reaction mixtures.

(21) These results are in sharp contrast with a recent elegant work reported by Matsubara in which *i*-PrOH (**2a**) was utilized in Ni-catalyzed reductive couplings via a hydrogen borrowing strategy en route to allylic alcohols: Nakai, K.; Yoshida, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2014**, *136*, 7797.

(22) A rather illustrative correlation between regioselectivity pattern and the size of the alcohol utilized was found for the reaction of **1d** with CO_2: MeOH (76% yield, **3d:3d'**=1.5:1); EtOH (73% yield, **3d:3d'**=2:1); BnOH (81% yield, **3d:3d'**=2:1); *i*PrOH-**2a** (**3d:3d'**=4:1); *t*BuOH-**2b** (85% yield **3d**, single regioisomer).

(23) (a) ref. 11a. (b) Powers, D. C.; Anderson, B. L.; Nocera, D. G. *J. Am. Chem. Soc.* **2013**, *135*, 18876.

(24) At present, we do not have a rationale for the lower yield of **3a** when using **5** as compared to the $Ni(COD)_2$/**L5** regime.

(25) The reaction of **1a** with **5** using **2d** as proton source followed by DCl quench resulted in **3a** in 50% yield (not even traces of **3a-D$_1$** in the crude mixtures) while recovering back **2d**.

(26) While these results might support a scenario based on Ni(II) species, we cannot completely rule out the intermediacy of Ni(I) intermediates generated upon single electron transfer reduction. See, for example: (a) see ref. 5f, 15, (b) Duñach, E.; Esteves, A. P.; Medeiros, M. J.; Olivero, S. *New J. Chem.* **2005**, *29*, 633. (c) Nadal, M. L.; Bosch, J.; Vila, J. M.; Klein, G.; Ricart, S.; Moretó, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 10476.

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(29) Care must be taken when invoking that the regioselectivity pattern is merely attributed to a steric model since the observed outcome for **3i** or **3o**, among others, might indicate that other factors come into play.

(30) Although radical intermediates might also account for the observed reactivity, we found no significant inhibition in the presence of BHT or related radical scavengers.