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Nickel-Catalyzed Arylative Carboxylation of Alkynes with Arylmagnesium Reagents and Carbon Dioxide Leading to Trisubstituted Acrylic Acids

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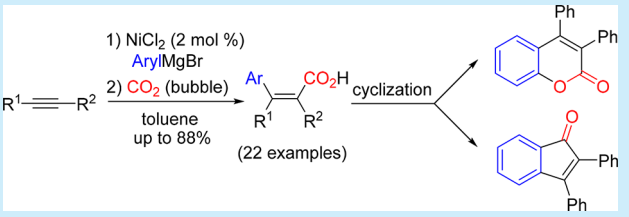
Supporting Information

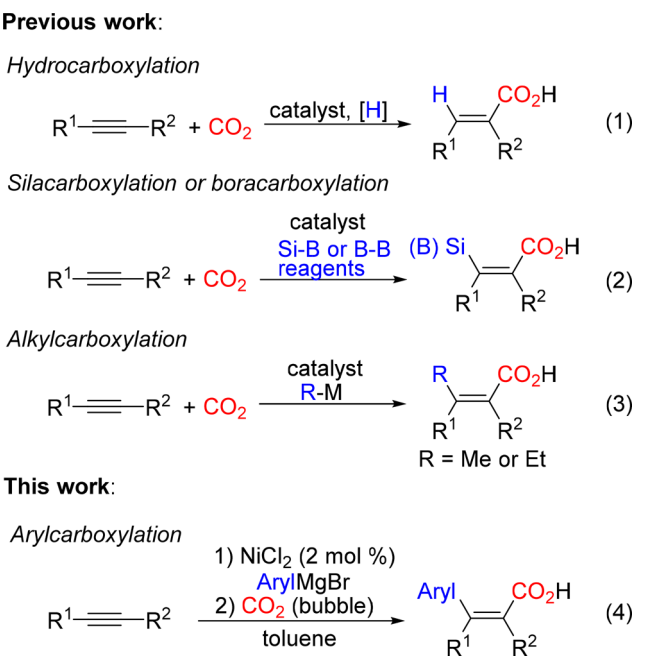
ABSTRACT: Nickel-catalyzed arylcarboxylation of alkynes with arylmagnesium reagents and carbon dioxide (CO_2, 1 atm) was realized in one pot. Various trisubstituted acrylic acids within an aryl group at the β-position have been prepared efficiently with good regioselectivity under mild conditions. The resulting products could be further transformed to benzoannelated cycles retaining CO_2 as a one-carbon synthon.



Acrylic acids are significant building blocks in pharmaceuticals and widely exist in organic synthesis. Moreover, their derivatives such as acrylic amides and esters are also extensively distributed in molecules with biological activity.[1] Consequently, a variety of methodologies has been developed to realize synthesis of the acrylic acids. Conventionally, Doebner−Knoevenagel reaction[2] or Wittig reaction[3] to construct a C═C double bond provide a facile approach to important arcylic acids. More recently, $P(NMe)_2$-mediated alkylation of aroylformate-derived Kukhtin−Ramirez intermediates also offered a method to prepare trisubstituted arcylic acids.[4] Although the desired products could be prepared efficiently, poor *E*/*Z* selectivity in a highly substituted olefin restricts their application, which might be attributed to sensitivity of the intermediate to steric hindrance.

CO_2 is a renewable, abundant, and green chemical. Accordingly, overcoming difficulty in thermodynamics and kinetics, its utilization as a C1 building block for the synthesis of value-added chemicals has attracted increasing attention.[5] In particular, transition-metal-catalyzed or -promoted carboxylation reactions, which afforded carboxylic acids or derivatives from CO_2, have been extensively studied.[6,7] To prepare substituted acrylic acids utilizing CO_2, transformation via five-membered metallocycle intermediates from cycloaddition using alkynes, CO_2 and metal catalysts is a feasible approach.[8] *Syn*-addition of organometallic reagents to alkynes, which deliver new reactive alkenylmetal reagents, is a more general, effective, and flexible method to prepare highly substituted acrylic acids (Scheme 1). Silanes or organometallic reagent as reductants could afford the corresponding hydrocarboxylation products with alkynes and CO_2 (Scheme 1, eq 1).[9] Moreover, Me_2PhSi-B(pin) and $B_2(pin)_2$ were reported to react with alkynes and CO_2 in catalysis of copper catalysts to afford silacarboxylation and boracarboxylation products, respectively (Scheme 1, eq 2).[10] Alkylmetallic reagents such as Me_2Zn, Me_3Al, and EtMgX could also give the alkylcarboxylation product with alkyne and CO_2 in the presence of the proper catalysts (Scheme 1, eq 3).[11] Arylcarboxylation of alkynes still lacks attention and is rarely reported[12] to the best of our knowledge. As part of our ongoing project on CO_2 chemistry,[9d,11c,13] herein we report a nickel-catalyzed arylative carboxylation of alkynes with commercially available aryl

Scheme 1. Typical Carboxylation of Alkynes with CO_2



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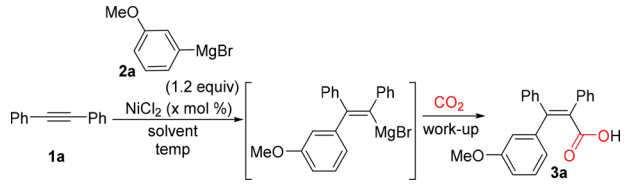
Grignard reagents and CO_2 (1 atm) to synthesize trisubstituted arcylic acids with an aryl group at the β position with good efficiency and high regioselectivity (Scheme 1, eq 4). Furthermore, the resulting products could be transformed into benzoannelated cycles retaining CO_2 as a one-carbon synthon.

On the basis of previous nickel-catalyzed carbometalation of alkynes[14] and carboxylation with in situ generated Grignard reagents[9c,15] we began our experiment utilizing 1,2-diphenylethyne **1a** as a substrate and 5 mol % of $NiCl_2$ as a catalyst in the presence of (3-methoxyphenyl)magnesium bromide **2a** at 60 °C in toluene for 2 h to afford triarylalkenylmagnesium bromide. Subsequently, the reaction was bubbled with CO_2 at room temperature and delivered the corresponding acrylic acids **3a** in 80% NMR yield (Table 1, entry 1). Different

Table 1. Arylcarboxylation of Alkynes with CO_2[a]



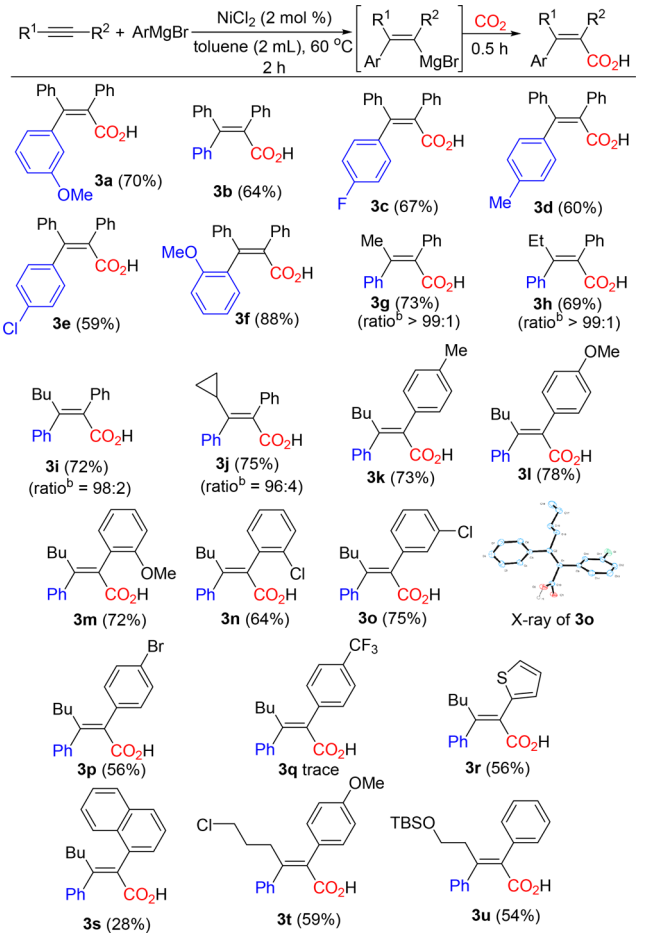
entry	X (mol %)	temp (°C)	solvent	yield[b] (%)
1	5	60	toluene	80
2	5	30	toluene	14
3	5	90	toluene	72
4	5	120	toluene	40
5	5	60	THF	27
6	5	60	Et_2O[c]	11
7	2	60	toluene	83 (70)

[a]Reaction conditions: (i) **1a** (0.5 mmol), $NiCl_2$ in 2 mL of toluene, 3-methoxyphenylmagnesium bromide **2a** (0.6 mmol, 0.6 mL, 1 M in THF), under N_2, 2 h. (ii) CO_2 bubbled at room temperature for 0.5 h; [b]NMR yield, trichloroethylene as the internal standard, isolated yield in parentheses. [c]Conducted in sealed tube.

temperatures were examined (Table 1, entries 1−4), and 60 °C was selected as the best choice (Table 1, entry 1). Screening solvents such as THF and Et_2O (Table 1, entries 1, 5, and 6) revealed that toluene was the optimized solvent. When the catalyst amount was reduced to 2 mol %, no obvious decrease in yield was demonstrated (Table 1, entry 7).

With optimized reaction conditions in hand, the substrate scope was investigated. Initially, different arylmagnesium bromides were tested (Scheme 2). Electron-deficient and -rich arylmagnesium bromides could afford the corresponding acrylic acids in good yields (**3a−f**). Then unsymmetrical alkynes bearing various functional groups were examined as well. When one aryl group was replaced with an alkyl group, such as methyl, ethyl, butyl, and cyclopropyl, the reaction delivered arylcarboxylation product successfully in high regioselectivity (**3g−j**) in which the carboxyl group connected to the sp^2 carbon atom bearing the phenyl group as a major product in good yield. The reaction worked well with substrates containing an electron-donating group such as −OMe and −Me to afford the corresponding acrylic acids in satisfactory yield (**3k−m**). Unsymmetrical alkynes bearing an electron-withdrawing group, such as Cl, at the *ortho*- and *meta*-positions of phenyl gave the corresponding products in 64% (**3n**) and 75% (**3o**) yields, respectively. To our delight, the crystal of **3o** was suitable for single-crystal analysis, and its structure was fully characterized by X-ray diffraction analysis.

Scheme 2. Substrate Scope of Arylcarboxylation of Alkynes[a]



[a]Isolated yield of major product. [b]NMR ratio of regioisomers.

This result supported the regioselectivity and *syn*-addition process in this reaction. Notably, bromide could survive in this transformation (**3p**), while an unsymmetrical alkyne **3q** bearing a CF_3 group on the phenyl did not generate the corresponding acrylic acid due to failure in arylmetalation of alkyne. Furthermore, thienyl- and naphthyl-substituted alkyne could also be achieved in this reaction, and the corresponding products were obtained in 56% (**3r**) and 28% (**3s**) yields, respectively. When (5-chloropent-1-yn-1-yl)benzene was applied, the reaction was conducted smoothly in 59% yield (**3t**). Additionally, TBS(*tert*-butyldimethylsilyl)-protected 4-phenylbut-3-yn-1-ol gave the corresponding acid **3u** in 54%. Notably, when an unsymmmetric diarylalkyne such as 1-methoxy-2-(phenylethynyl)benzene was employed, a mixture of two products was observed without regioselectivity. It should be noted when a dialkylacetylene such as 5-decyne was treated under the optimized conditions, no corresponding product was observed and 5-decyne remained.

To further understand the mechanism of this reaction, additional experiments were performed (Scheme 3). After reaction of $NiCl_2$ (1 equiv), hex-1-yn-1-ylbenzene **1i** (1 equiv), and PhMgBr (1 equiv) under the optimized conditions, **1i** still retained (Scheme 3, eq 1). This result excludes the Ni(II)-catalyzed direct arylmetalation pathway. When the reaction was treated with $NiCl_2$ (0.5 equiv), **1i** was also retained and diphenyl was obtained in 92% yield (Scheme 3, eq 2), which may be attributed to fast reductive elimination of Ni(II) to

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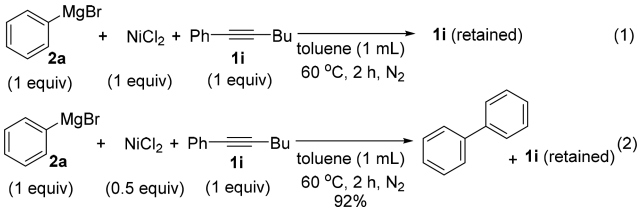
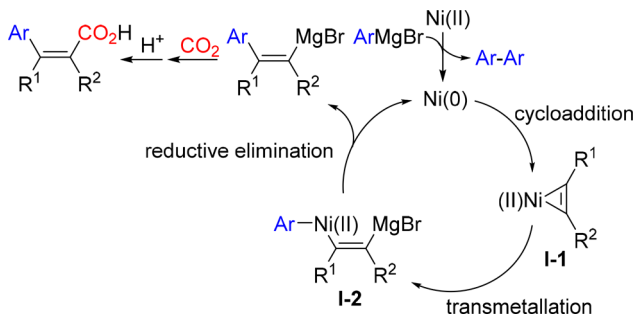
Scheme 3. Controlled Experiments



Ni(0) with PhMgBr. These results suggested that Ni(0) generated from $NiCl_2$ and PhMgBr rather than Ni(II) species might be important in the catalytic cycles.

In combination with known facts[16] and our results, a possible mechanism is proposed in Scheme 4. Initially, Ni(II)

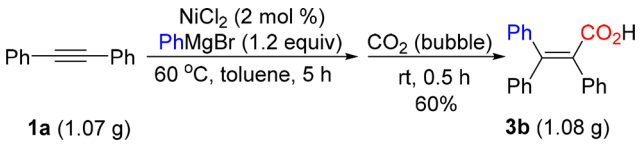
Scheme 4. Plausible Mechanism



was reduced by Grignard reagents to deliver Ni(0), which undergoes cycloaddition with alkyne to gives Ni(II) complex **I-1**. Then the aryl Grignard reagent triggers transmetalation to afford new Ni(II) complex **I-2**. Finally, reductive elimination takes place to generate the arylmagnesium-substituted alkene, which gives acrylic acid **3** after addition of CO_2 and hydrolysis.

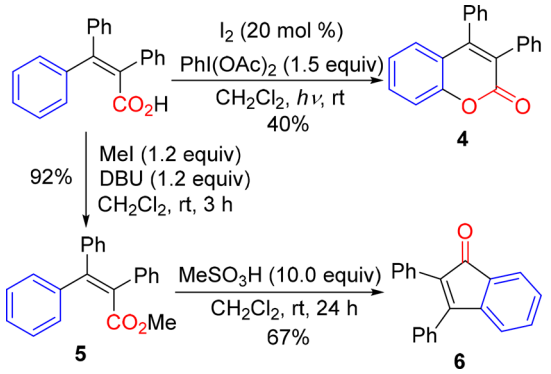
Moreover, we realized this reaction in gram-scale amounts (Scheme 5). When 6 mmol of 1,2-diphenylethyne **1a** was utilized, the corresponding carboxylic acid **3b** was obtained in 60% yield with formation of **3b** (1.08 g).

Scheme 5. Gram-Scale Reaction



Since the β-arylacrylic acids and their derivatives, such as esters, amides, alcohols, and other heterocycles, possess great applications, we further explored the functionalization of the β-arylacrylic acids. Besides the well-known esterification, amination, and reduction reactions, trisubstituted acrylic acids could generate different cycles of incorporation of the β-aryl substituent (Scheme 6). When 2,3,3-triphenylacrylic acid **3b** was exposed to blue LED in the presence of $PhI(OAc)_2$ and I_2, oxidative cross coupling between C−H and O−H took place to afford the coumarin **4** in 40%.[17] Moreover, the corresponding carboxylic ester **5** could be formed in 92% isolated yield after esterification of the resulting **3b** using MeI. Furthermore, product **5** could be easily annulated to indenones in 67% yield with aid of $MeSO_3H$.

Scheme 6. Application of Arylcarboxylated Product



In summary, we developed ligand-free nickel-catalyzed arylcarboxylation of alkyne with aryl Grignard reagents and CO_2 to afford β-arylacrylic acids with high regioselectivity. The reaction provides an efficient approach to trisubstituted β-arylacrylic acids, which could be further transformed to functionalized cycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01693.

Experimental procedures; NMR spectra; crystal data and structure of **3o** (PDF)

Accession Codes

CCDC 1850204 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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