

## Communication

## Ligand-Controlled Regioselective Hydrocarboxylation of Styrenes with CO by Combining Visible Light and Nickel Catalysis

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## Ligand-Controlled Regioselective Hydrocarboxylation of Styrenes with CO<sub>2</sub> by Combining Visible Light and Nickel Catalysis

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Supporting Information Placeholder

**ABSTRACT:** The ligand-controlled Markovnikov and anti-Markovnikov hydrocarboxylation of styrenes with atmospheric pressure of CO<sub>2</sub> at room temperature using dual visiblelight-nickel catalysis has been developed. In the presence of neocuproine as ligand, the Markovnikov product is obtained exclusively, while employing 1,4-bis(diphenylphosphino)butane (dppb) as the ligand favors the formation of the anti-Markovnikov product. A range of functional groups and electron-*poor*, *-neutral*, as well as electron-*rich* styrene derivatives are tolerated by the reaction, providing the desired products in moderate to good yields. Preliminary mechanistic investigations indicate the generation of a nickel hydride (H-Ni<sup>II</sup>) intermediate, which subsequently adds irreversibly to styrenes.

Carboxylation with  $CO_2$  as an abundant one-carbon ( $C_1$ ) building block would provide an extremely appealing way to synthetically access valuable carboxylic acids.<sup>1</sup> Among these reactions, the carboxylation of styrenes with CO<sub>2</sub> has been regarded as a simple and atom-economic approach to amethyl phenylacetic acid derivatives, which are frequent structural motifs in synthetic pharmaceuticals, such as Ibuprofen, Naproxen and Fenoprofen.<sup>2</sup> Rovis and co-workers pioneered Ni-mediated catalytic hydrocarboxylation of electron-deficient and -neutral styrene analogues with excellent regioselectivity.<sup>3</sup> Thomas and Greenhalgh used FeCl<sub>2</sub> as catalyst to synthesize a-methyl phenylacetic acids from electron-rich and -neutral styrene derivatives with CO2.4 After that, catalysts based on Ti or Rh have also been employed to realize the transformation of electron-rich or electron-deficient styrene derivatives into the corresponding products.5 Strong reductants, including Et<sub>2</sub>Zn and EtMgBr are necessary, to enable these transformations, thus typically leading to lower functional group tolerance. Martin and co-workers reported an excellent strategy to accomplish the Ni-catalyzed site-selective carboxylation of unsaturated hydrocarbons with tolerance to a wider variety of functional groups by using Mn as the stoichiometric reductant.<sup>6</sup> Notably, all these protocols afford highly selective the Markovnikov hydrocarboxylation of styrenes due to the formation of the more stable  $\eta^3$  benzylic metal species (Scheme 1a). Therefore, selective anti-Markovnikov hydrocarboxylation of styrenes by metal catalysis is challenging and much more difficult to realize. Very recently, Jamison and coworkers developed a photoredox catalytic anti-Markovnikov hydrocarboxylation of styrenes under UV light irradiation of p-terphenyl as photosensitizer (PS) in continuous flow. CO<sub>2</sub> was initially reduced into its anion radical CO2<sup>•-</sup>, which subsequently added to the  $\beta$ -position of styrenes to produce the more stable benzylic radical species, thus ensuring anti-Markovnikov selectivity (Scheme 1b).<sup>7</sup> Herein, we describe a ligand-controlled, regiodivergent hydrocarboxylation of styrenes by combining visible light and Ni catalysis. Both Markovnikov and anti-Markovnikov products can be selectively obtained by the proper choice of ligands, i.e. employing neocuproine as the ligand yields the Markovnikov product (b:l=100:0, b:branched, l: linear), whereas utilizing 1,4-bis(diphenylphosphino)butane (dppb) as the ligand promotes the formation of the anti-Markovnikov product (l:b $\geq$ 97:3) (Scheme 1c).

#### Scheme 1. Hydrocarboxylation of Styrenes with CO2

## Previous works:

А

$$r \sim \underbrace{\begin{array}{c} \text{Ni, Ti, Fe or Rh (Cat.)} \\ \text{Et_2Zn, EtMgBr or Mn} \end{array}} \underbrace{\left[ \begin{array}{c} \text{M} \\ \text{Ar} \end{array} \right] \underbrace{\begin{array}{c} \text{CO}_2 \\ \text{H}^* \end{array}} \\ \text{Ar} \xrightarrow{\begin{array}{c} \text{COOH} \\ \text{H}^* \end{array}}$$

(b) Anti-Markovnikov hydrocarboxylation of styrenes under UV light irradiation

$$Ar \sim + CO_2 \frac{p-terphenyl (PS)}{NR_3, UV light} \left[Ar \sim COO \right] \frac{e}{2H^*} Ar \sim COOH$$

This work:

(c) Ligand-controlled Markovnikov and anti-Markovnikov hydrocarboxylation of styrenes by visible light catalysis

$$\begin{array}{c} \text{LNiB}_{r_2}\left(\text{Cat.}\right) \\ \textbf{L: Neocuproine} \\ \text{Ar} \end{array} \xrightarrow{\text{Ar}} \begin{array}{c} \text{Ni}\left(\text{Cat.}\right) \\ \textbf{dczlPN}\left(\text{PS}\right) \\ \text{visible light} \end{array} \xrightarrow{\text{Ar}} \begin{array}{c} \text{Ni}\left(\text{Cat.}\right) \\ \textbf{dpb}\left(\textbf{L}\right) \\ \text{4CzlPN}\left(\text{PS}\right) \\ \text{visible light} \end{array} \xrightarrow{\text{Ar}} \begin{array}{c} \text{COOH} \\ \text{CO}_2 \end{array} \xrightarrow{\text{Visible light}} \begin{array}{c} \text{Ni}\left(\text{Cat.}\right) \\ \textbf{dczlPN}\left(\text{PS}\right) \\ \text{visible light} \end{array}$$

Building on our recent experience with the direct carboxylation of (pseudo)halides with CO2 by dual visible-light-Ni catalysis,8 we commenced our investigation on hydrocarboxylation of styrene with the developed system. Initially, various solvents and nitrogen ligands were screened; only Markovnikov hydrocarboxylation of styrene was observed and the best result was obtained when using DMF as the solvent and neocuproine as the ligand (Table S1, entries 1-4 and Table S2, entries 1-5). Interestingly, the addition of K<sub>2</sub>CO<sub>3</sub> was not essential for the reaction to proceed, and a similar reactivity was observed when CsF was added as the additive to replace K<sub>2</sub>CO<sub>3</sub> (Table S1, entry 5).<sup>9</sup> Screening of other photosensitizers including dyes and metal complexes demonstrated that only [Ir(ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> and [Ir(dF(Me)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> gave comparable results (Table S2, entries 6-13). It is notable that using  $LNiBr_2$  (L = neocuproine) instead of  $NiBr_2$ ·glyme and neocuproine provides a slightly better yield (Table S1,



# Table 1. Scope of styrene derivatives for the Markovnikov hydrocarboxylation with CO<sub>2</sub><sup>*a*</sup>



<sup>a</sup> All reactions were carried out with styrene derivatives (0.2 mmol),  $K_2CO_3$  (0.2 mmol), 4CzIPN (0.002 mmol),  $LNiBr_2$  (0.02 mmol, L = neocuproine), HEH (0.3 mmol) and 50 mg 4Å MS in anhydrous DMF (2 mL), irradiation with blue LEDs at room temperature with a CO<sub>2</sub> balloon for 24 h. HEH: Hantzsch ester.

entry 6). Control experiments confirmed the dual catalytic nature of the Markovnikov hydrocarboxylation of styrene, as no reaction was observed in the absence of reaction components (Table S2, entries 14-18). Particularly, only 11% yield of the desired product is obtained in the absence of 4Å MS, which is explained by the fact that 4Å MS absorbs the water produced in situ from the reaction of K<sub>2</sub>CO<sub>3</sub> and the proton released from Hantzsch ester (HEH; Table S2, entry 19). After that, we attempted to selectively realize an anti-Markovnikov hydrocarboxylation of styrene. As ligands can control the regiodivergent functionalization,10 a variety of phosphine ligands were tried instead of neocuproine (Table S1, entries 7-14). To our delight, the desired linear product is observed when bis(diphenylphosphino)methane (dppm) was used as the ligand, albeit the yield and regioselectivity are low (Table S1, entry 12). Linear products were obtained exclusively and with increased efficiencies when 1,3-bis(diphenylphosphino)propane (dppp) and 1,4-bis(diphenylphosphino)butane (dppb) were used as ligand, respectively (Table S1, entries 13 and 14). Further optimizations including solvents and additives demonstrated that the use of lithium acetate promoted the efficiency and 41% yield of the desired product was formed (Table S1, entry 15 and Table S3, entries 1-14). Gratifyingly, decreasing the amount of the reductant enhanced the formation of the linear product, which was ascribed to a less efficient styrene hydrogenation; ethyl benzene was confirmed as the main byproduct in the reaction (Table S1, entry 16). In the absence of 4Å MS as drying agent or by adding 1 equiv. of  $H_2O$ , the efficiency of the reaction decreased (Table S3, entries 19 and 20). Finally, a 62% yield of the anti-Markovnikov hydrocarboxylation of styrene was obtained when 4-Me-HEH was used as the reductant, whereas other reductants gave lower efficiencies (Table S1, entry 17 and Table S3, entries 15-18).

# Table 2. Scope of styrene derivatives for anti-Markovnikov hydrocarboxylation with CO2<sup>a</sup>



<sup>a</sup> All reactions were carried out with styrene derivatives (0.2 mmol), 4CzIPN (0.002 mmol), NiBr<sub>2</sub>·glyme (0.02 mmol), dppb (0.04 mmol), LiOOCCH<sub>3</sub> (0.2mmol), 4-Me-HEH (0.2 mmol) and 50 mg 4Å MS in anhydrous DMF (2 mL), irradiation with blue LEDs at room temperature with a CO<sub>2</sub> balloon for 24 h (l: linear, b: branched). 4-Me-HEH: 4-Me-Hantzsch ester.

Having identified the optimal reaction conditions for the hydrocarboxylation of styrene by this dual visible-light-Ni catalysis, we then aimed to explore the generality of our methodology. Firstly, it was found that Markovnikov hydrocarboxylation of several different styrene derivatives bearing electron-neutral (2a, 2b and 2e-2h), -donating (2c, 2i and 2o) or withdrawing substituents (2d, 2i-2n and 2p-2r) at para-, metaor ortho- positions proceeds well under our protocol, giving the desired products in moderate to good yields (shown in Table 1). A range of functional groups including fluoro (2d and 2p), aliphatic and aromatic carboxylic esters (2h, 2l and 2q), amide (2j), ketone (2k), cyano (2m) and trifluoromethyl (2n and 2r) are tolerated. Particularly, unprotected primary and secondary alkyl hydroxyl groups were also applicable affording the corresponding products in 56% and 67% yields, respectively (2f and 2g). To demonstrate the application of our newly developed method further, Ibuprofen was synthesized and Estrone was derivatized. First, 4-isobutyl styrene was synthesized as the starting material by Ni-catalyzed Kumada coupling reaction.<sup>11</sup> Then a 62% yield of Ibuprofen was obtained under our standard conditions (2s). Moreover, a vinyl group was introduced efficiently into the Estrone scaffold by triflate activation of its hydroxyl group and subsequent Pd-catalyzed Heck coupling reaction.<sup>12</sup> The vinyl compound was transformed into the desired  $\alpha$ -carboxylic acid in 71% yield (2t). It is important that all reactions herein provided only the Mar-

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kovnikov hydrocarboxylation products, which confirms an excellent regioselectivity.

After that, we turned our attention to explore the generality of styrene derivatives for anti-Markovnikov hydrocarboxylation with CO<sub>2</sub>. As shown in Table 2, *ortho*-substituted styrene is compatible with this protocol, leading to the desired product with high regioselectivity (**3b**). In the case of *meta*-substituted styrenes, reactions also proceeded well to give the corresponding products in moderate yields (**3c**-**3f**). Notably, *para*substituted styrenes including fluoro, ester and un-protected hydroxy groups were tolerated under our conditions, affording anti-Markovnikov hydrocarboxylation products with excellent regioselectivity (**3g**-**3i**). However, none of the desired anti-Markovnikov products and only small yields of the Markovnikov products were obtained with electron-withdrawing substituents, such as nitrile or ester, present in the styrene core.<sup>13</sup>

Scheme 2. Deuterium-Labelling Experiments for Markovnikov Hydrocarboxylation of Styrene with CO<sub>2</sub>



Scheme 3. Deuterium-Labelling Experiments for Anti-Markovnikov Hydrocarboxylation of Styrene with CO<sub>2</sub>

	4CzIPN (1 mol%) NiBr <sub>2</sub> •glyme (10 mol%) dppb (20 mol%)	2M HCI_		(4)
	4-Me-HEH (1.0 equiv.) 4 Å MS (50 mg), CO <sub>2</sub> (balloor	1)	Pn H T H	
1a	LiOOCCH3 (1 equiv.), d <sup>7</sup> -DMF blue LEDs, 24h, r.t.	=	<b>3a, yiel</b> d: 38%	
	4CzIPN (1 mol%) NiBr₂glyme (10 mol%) dppb (20 mol%) 4Me+HEH (1.0 equiv.) 4 Å MS (50 mg), cO₂ (balloor LiOOCCH₂ (1 equiv.) DMF	2M HCI		(2)
1a'	blue LEDs, 24h, r.t.		<b>3a'</b> , yield: 53%	
	4CzIPN (1 mol%) NiBr₂glyme (10 mol%) dppb (20 mol%) 4-Me-HEH (1.0 equiv.) 4 A MS (50 mg), CO <sub>2</sub> (balloor	- <u>2M HCI</u> ► Ph		(3)
1a : 1a' = 1:1	LiOOCCH3 (1 equiv.) DMF, blue LEDs, 24h, r.t.		3a : 3a' = 2.3:1, yield: 52%	

To gain information on the reaction mechanism, we initially carried out dihydrogen generation experiments. We detect trace amount of dihydrogen under our reaction conditions, while no dihydrogen was generated in the absence of the Ni catalyst or 4CzIPN, confirming that the combination of the Ni catalyst and 4CzIPN can produce dihydrogen, likely via a H-Ni<sup>II</sup> intermediate (Scheme S1). Combined with facts that the main by-product of the reaction was ethyl benzene, it is likely that the H-Ni<sup>II</sup> species adds to styrene, giving rise to an intermediate Ni species for subsequent carboxylation. Furthermore, deuterium experiments demonstrated that there was no H/D scrambling when d7-DMF or d3-styrene was used, which shows that the hydrogen atom for the hydrocarboxylation comes from the reductant HEH or 4-Me-HEH, and the addition of the H-Ni<sup>II</sup> species on styrene is irreversible (Scheme 2, equation 1 and 2; Scheme 3, equation 1 and 2). Additionally, a normal secondary kinetic isotope effect (KIE) is observed when a 1:1 ratio of styrene and d<sup>3</sup>-styrene were used as starting materials for the Markovnikov hydrocarboxylation. A larger secondary KIE is observed for the anti-Markovnikov hydrocarboxylation of styrene, indicating that the addition of the H-Ni<sup>II</sup> species to styrene or the subsequent CO<sub>2</sub> inserting into the Ni-R bond are rate limiting (Scheme 2, equation 3 and Scheme 3, equation 3). Finally, radical inhibitors, such as butylated hydroxytoluene (BHT) and 9,10-dihydroanthracene (DHA) were added and all reactions proceeded well, thus supporting that radical intermediates are not essential for the process (Scheme S2, equation 1 and 2; Scheme S3, equation 1 and 2). However, the use of TEMPO reduced the reactivity presumably due to the oxidation of HEH (Scheme S2, equation 3 and Scheme S3, equation 3).<sup>14</sup>





Based on the above results and in combination with our previous work,8 a preliminary mechanism is proposed in Scheme 4. Irradiation of 4CzIPN with visible light yields a long-lived photoexcited state \*4CzIPN ( $\tau = 5.1 \pm 0.5 \ \mu s$ ), which oxidizes HEH affording 4CzIPN<sup>-</sup> ( $E_{1/2}^{red} = -1.21$  V vs SCE).<sup>15</sup> The active Ni<sup>0</sup>L<sub>n</sub> species A is generated in situ via two single electron transfer (SET) steps  $[E_{1/2}^{red} (Ni^{II}/Ni^0) = -1.2 V vs SCE]$ under the photocatalytic reduction conditions.<sup>16</sup> Subsequent regioselective hydrometalation of styrene is supported by DFT calculations (see discussion in the supporting information). When L2 (neocuproine) was used as the ligand, protonation by HEH<sup>++</sup> produces a Ni hydride complex **B**, *i.e.* H-Ni<sup>II</sup>L<sub>n</sub>. Then L2-ligated H-Ni<sup>II</sup>L<sub>n</sub> creates a transient two-coordinated geometry with less steric hindrance, thus leading to the formation of a more stable organonickel complex C. After accepting one electron from the reduced form of 4CzIPN,<sup>17</sup> the insertion of  $CO_2$  into **D** proceeds smoothly,<sup>18</sup> leading to the generation of a nickel carboxylate intermediate E, followed by further reduction to give the desired product and regenerate A for the next cycle. When L12 (dppb) was employed as the ligand, a transient Ni<sup>0</sup> species A combined with two ligands were generated, which can be supported by the observation that a 1:1 ratio of NiBr<sub>2</sub>·glyme and L12 gave none or much lower yield of the desired product (Table S3, entries 21 and 22), while a 1:2 ratio of NiBr2 glyme and L12 still catalyzes the transformation with varying effectivity (Table S3, entries 23-26). This Ni<sup>0</sup> species A may coordinate with CO<sub>2</sub> first,<sup>19</sup> giving rise to intermediate F, which subsequently inserts into styrene to generate a 5membered cyclic intermediate G. Upon accepting one electron from the reduced form of 4CzIPN, a nickel carboxylate intermediate E' was produced. Finally, the desired product is released by further reduction. As experimentally supported by

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deuterium experiments, both hydrometalation of styrene and insertion of **F** into styrene are irreversible.

In conclusion, we have developed a dual visible-light-Ni catalysis accomplishing an operationally simple, mild and highly regioselective hydrocarboxylation of aryl alkenes using CO<sub>2</sub> as the C1-feedstock. Particularly, employing different ligands can promote selective Markovnikov and anti-Markovnikov hydrocarboxylation of styrenes with tolerance of many functional groups. Mechanistic investigations indicated that a H-NiL<sub>n</sub> species is generated during the process and adds irreversible to styrene. Further investigations on the reaction mechanism and the development of an efficient version to realize anti-Markovnikov hydrocarboxylation of electron-deficient styrenes are in progress.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, methods and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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1 2 3 4 5 6 7 8 9 10 11	TOC: Ar b:l = 100:0; 42-83% yields Markovnikov	LNiBr <sub>2</sub> (Cat.) <b>:: Neocuproine</b> Donor-acceptor visible light	Ar (+ + CO <sub>2</sub>	Ni (Cat.) dppb (L) Donor-acceptor visible light	Ar I:b ≥ 97:3; 40-62% yields anti-Markovnikov
13 14 15 16 17 18 19 20 21 22 23 24					
25 26 27 28 29 30 31 32 33 34 35 36					
37 38 39 40 41 42 43 44 45 46 47 48					
49 50 51 52 53 54 55 56 57 58 59					