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Ni-Catalyzed Direct Carboxylation of an Unactivated C−H Bond with CO_2

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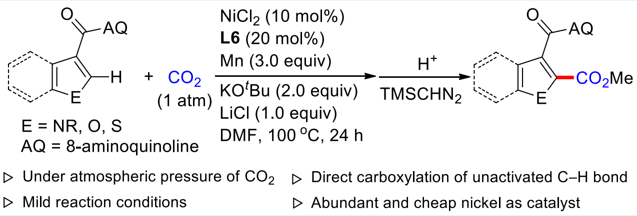
ABSTRACT: The transition-metal-catalyzed direct carboxylation of an unactivated C−H bond is rarely reported, and no example of catalysis using abundant and cheap nickel has been reported. In this work, the first Ni-catalyzed direct carboxylation of an unactivated C−H bond under an atmospheric pressure of CO_2 is reported. This method affords moderate to high carboxylation yields of various methyl carboxylates under mild conditions. Preliminary mechanistic studies reveal that a Ni(0)−Ni(II)−Ni(I) catalytic cycle may be involved in this reaction.



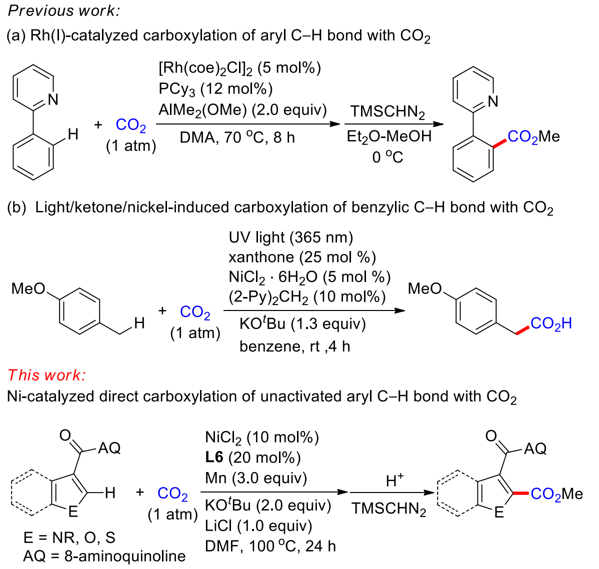
Despite its significant kinetic inertness and thermodynamic stability, CO_2 is an abundant, nontoxic, inexpensive, and renewable C1 feedstock in synthetic chemistry.[1] The conversion of CO_2 into fine chemicals has attracted considerable attention, especially the formation of carboxylic acids,[2,3] which are building blocks in many valuable synthetic compounds.[4]

Compared to traditional coupling methods, the transition-metal-catalyzed C−H functionalization reactions are considered to be a more efficient and atom-economic strategy.[5] Thus, transition-metal-catalyzed C−H carboxylation provides a powerful tool for CO_2 fixation. In recent years, although transition-metal-catalyzed C−H carboxylation with CO_2 has led to great progress in the synthesis of carboxylic acids or their derivatives,[3] the substrates are mainly focused on terminal alkynes, perfluorinated or perchlorinated benzenes, and heteroaromatic rings, which possess acidic C−H bonds or an electron-deficient nature.[6a−d] The carboxylation of these kinds of C−H bonds can be carried out in the presence of a base even without a metal catalyst.[6e−h] The transition-metal-catalyzed direct carboxylation of unactivated aryl C−H bonds is rarely reported. The first carboxylation of unactivated C−H bonds with CO_2 was reported in 1984 by Fujiwara using $Pd(OAc)_2$ as a catalyst, but with limited examples and low turnover numbers.[7] In 2011 and 2014, Iwasawa's group reported Rh(I)-catalyzed direct carboxylation of unactivated aryl C−H bonds with CO_2 (Scheme 1a). In these reactions, insertion of CO_2 into a C−Rh(I) bond is involved and a stoichiometric methyl aluminum complex plays an important role.[8] In 2014, Sato's group reported cobalt-catalyzed allylic C−H carboxylation.[18]

Some elegant works including Pd- or Rh-catalyzed lactonization or lactamization of unactivated alkenyl or aryl C−H bonds with CO_2 assisted by an intramolecular hydroxyl or amino group were also reported by the groups of Iwasawa, Yu, Wang, and Li,[9] but the insertion of CO_2 into the C−M or O−M/N−M bond is ambiguous.

As an abundant and cheap first-row transition metal, nickel has been extensively studied in homogeneous catalysis because

Scheme 1. Transition-Metal-Catalyzed Direct Carboxylation of Unactivated C−H Bonds with CO_2



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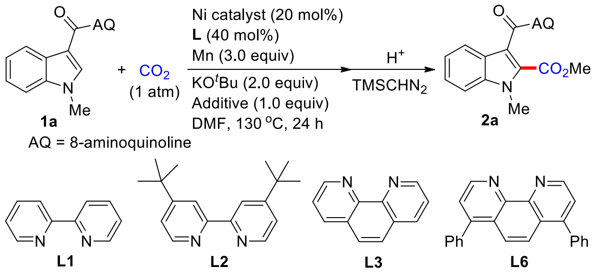
of its distinguishing characteristics.[10] Ni-catalyzed reductive carboxylation of organic (pseudo)halides with CO_2 is one of the most well-established strategies.[2,11] The Ni(0)−Ni(II)−Ni(I) catalytic cycle was suggested for these reactions, and CO_2 was inserted into the more nucleophilic C−Ni(I) bond. Very recently, Murakami reported the carboxylation of benzylic and aliphatic C−H bonds with CO_2 induced by light, ketone, and nickel (Scheme 1b). The mechanism of this reaction involved the formation of benzylic and aliphatic radicals and an R−Ni(I) intermediate, and the substance scope has limitations.[12] Although Ni-catalyzed C−H functionalization reactions have been extensively reported,[13] to the best of our knowledge, Ni-catalyzed direct carboxylation of unactivated C−H bonds with CO_2 remains unreported. Herein, we report for the first time a Ni-catalyzed direct carboxylation of unactivated C−H bonds of indole, benzothiophene, benzofuran, and benzene under an atmospheric pressure of CO_2. The carboxylation products, especially indole-2-carboxylic acids, and their derivatives are ubiquitous structural motifs in pharmaceuticals and natural products.[14]

Our initial attempt was conducted by employing *N*-quinolyl 1-methylindole-3-carboxamide (**1a**) as a model substrate under an atmospheric pressure of CO_2 in the presence of $NiCl_2$ (20 mol %) with KO^tBu (2.0 equiv) as the base and Mn (3.0 equiv) as the reductant in DMF for 24 h; the desired C-2 carboxylation product **2a** was obtained in 50% isolated yield (Table 1, entry 1). Different ligands, including bipyridines and phenanthrolines, were screened first (Table 1, entries 2−5, and Table S1, see the Supporting Information for details). 4,7-Diphenyl-1,10-phenanthroline (**L6**) proved to be the most effective ligand providing **2a** in 63% yield. Then, other simple and readily available nickel catalysts were investigated (Table 1, entries 6−9), and $NiCl_2$ proved to be the most effective. Some inorganic salts were tested as additives (Table 1, entries 10−13), which were often added in Ni-catalyzed carboxylation of aryl halides with CO_2.[11] Addition of LiCl improved the yield to 84%, while addition of KCl had no influence. Addition of $MgCl_2$ even suppressed the reaction totally. LiBr was also investigated and less effective than LiCl. The addition of LiCl may facilitate the carboxylation by accelerating the reduction of Ni(II).[15] The desired product was produced in 87% yield when the temperature was decreased to 100 °C (see Table S1, entry 21). In addition, product **2a** was obtained in 85% isolated yield with 10 mol % catalyst loading (Table 1, entry 14). Notably, product **2a** was detected in only a trace amount in the absence of $NiCl_2$ with recovery of **1a** in 95% yield (Table 1, entry 15), which revealed that the nickel catalyst is essential. Other solvents, reductants, and bases were also screened (see Table S1), and DMF, Mn, and KO^tBu were the best combination, giving an 85% isolated yield.

With the established optimal reaction conditions in hand, the scope of this reaction was investigated (Scheme 2). When indoles possess an electron-donating or electron-withdrawing group at the C-5 position, such as alkyl (-Me), alkoxy (-OMe), trifluoromethyl ($-CF_3$), and fluoro (-F) groups, the carboxylation proceeded smoothly to afford desired products **2b−2e**,

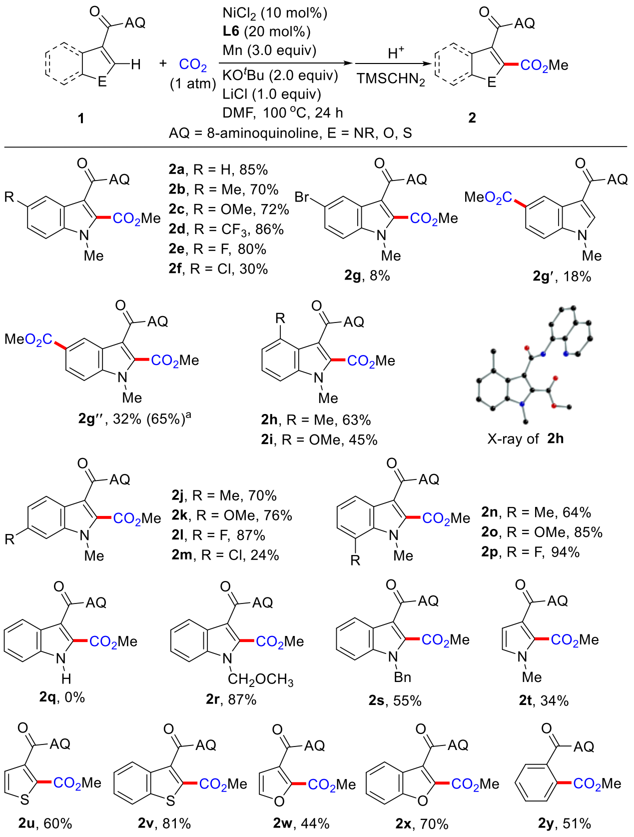
Table 1. Optimization of Reaction Conditions[a]



entry	Ni catalyst	L	additive	yield (%)
1	$NiCl_2$	–	–	50
2	$NiCl_2$	**L1**	–	56
3	$NiCl_2$	**L2**	–	46
4	$NiCl_2$	**L3**	–	58
5	$NiCl_2$	**L6**	–	63
6	$NiBr_2$	**L6**	–	60
7	NiI_2	**L6**	–	57
8	$Ni(COD)_2$	**L6**	–	62
9	$Ni(OTf)_2$	**L6**	–	15
10	$NiCl_2$	**L6**	LiCl	84
11	$NiCl_2$	**L6**	$MgCl_2$	0
12	$NiCl_2$	**L6**	KCl	62
13	$NiCl_2$	**L6**	LiBr	79
14[b]	$NiCl_2$	**L6**	LiCl	85
15[b]	–	**L6**	LiCl	trace

[a] Reaction conditions: **1a** (0.2 mmol), Ni catalyst (20 mol %), **L** (40 mol %), KO^tBu (2.0 equiv), Mn (3.0 equiv), additive (1.0 equiv), DMF (2.0 mL) at 130 °C for 24 h. The isolated yield is given. [b] At 100 °C. Ni catalyst (10 mmol %), **L** (20 mmol %).

Scheme 2. Substrate Scope of Ni-Catalyzed C−H Carboxylation[b]



[a] **2g′** as the substrate. [b] Reaction conditions: **1a** (0.2 mmol), $NiCl_2$ (10 mol %), **L6** (20 mol %), KO^tBu (2.0 equiv), Mn (3.0 equiv), LiCl (1.0 equiv), DMF (2.0 mL) at 100 °C for 24 h. The isolated yield is given.

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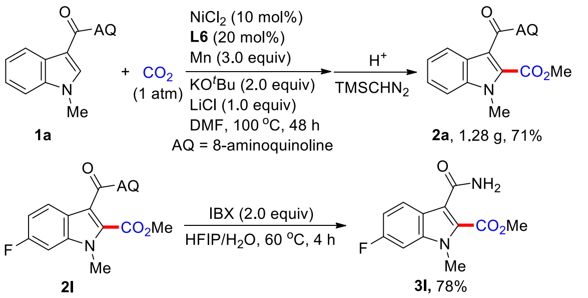
respectively, in 70−86% yields. However, when chloro (-Cl) or bromo (-Br) was introduced at the C-5 position of indole, desired products **2f** (30%) and **2g** (8%) were obtained in low yields. Meanwhile, two byproducts, including 5-carboxylation (**2g′**) and 2,5-dicarboxylation (**2g″**) products, were isolated in 18% and 32% yields, respectively, indicating the presence of C−Br carboxylation as a competition reaction. When an ester group was introduced at the C-5 position (**2g′**), desired product **2g″** was obtained in 65% yield. Indoles with a substituent at the *ortho* position gave the desired products in slightly low yields (**2h**, 63%; **2i**, 45%), possibly due to the steric hindrance. Various functional groups at the C-6 and C-7 positions of indole were well tolerated, affording the desired products **2j**−**2l** and **2n**−**2p**, respectively, in 64−94% yields. The low yield of **2m** (24%) is also due to the presence of C−Cl carboxylation. However, when a vinyl group was introduced at the C-6 position of indole, no reaction was detected, probably because the vinyl group can coordinate with nickel and suppress the carboxylation. The N-protecting groups of indole were next examined. Without the N-protecting group, no carboxylation was observed (**2q**). *N*-MOM- or *N*-Bn-protected indole afforded corresponding carboxylation product **2r** or **2s** in 87% or 55% yield, respectively. In addition to indoles, other nitrogen-, oxygen-, and sulfur-containing heterocycles could also undergo direct carboxylation in 34−81% yields (**2t**−**2x**, respectively). It seems that the fused aromatic substrates may facilitate the carboxylation. When benzamide with more inert C−H bonds was employed as a substrate, the corresponding product **2y** was obtained in 51% yield under standard conditions.

To demonstrate the synthetic potential of this method, a gram-scale reaction was conducted and product **2a** was obtained in 71% yield. Furthermore, the 8-aminoquinoline directing group could be easily removed by using IBX as an oxidant under mild conditions[16] to give the primary amide **3l** in 78% yield (Scheme 3).

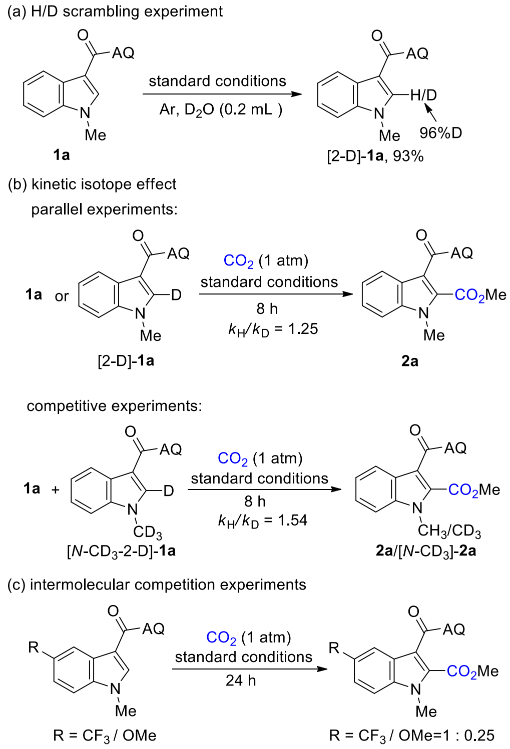
Scheme 3. Gram-Scale Synthesis and Removal of the Directing Group



There are several reports of acid- or base-promoted C−H carboxylation of indole and benzothiophene.[19] The Lewis acid Me_2AlCl-mediated C−H carboxylation of indole involved the electrophilic substitution of indole to form indolylaluminum species, which then reacted with CO_2 to form aluminum carboxylate. The carboxylation of indole occurred at position 3, and a high pressure (3.0 MPa) is needed to shift the reversible equilibrium to the carboxylation direction.[19a] LiO^tBu-mediated C−H carboxylation of indole could occur at position 3 with an atmospheric pressure of CO_2 but only limited to the unprotected indole.[19b] Copper-catalyzed formal C−H carboxylation of indole and benzothiophene occurred with an atmospheric pressure of CO_2 at position 2, but this is a two-step reaction. The first step is the deprotonative alumination with a mixed alkyl amido lithium aluminate compound $^i Bu_3Al(TMP)Li$. The second step is the NHC copper-catalyzed carboxylation of the resulting arylaluminum species.[19c] Therefore, our work provides an efficient direct C2−H carboxylation strategy for indole and benzothiophene derivatives.

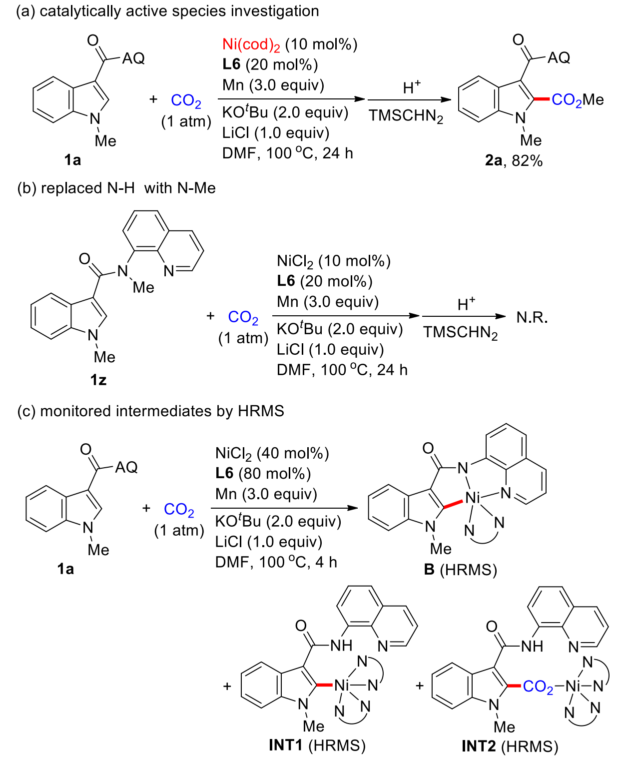
To better clarify the reaction mechanism, some preliminary studies were carried out. First, a H/D scrambling experiment was conducted. Reaction of **1a** with D_2O with a Ni catalyst under Ar instead of CO_2 afforded [2-D]-**1a** with 96% deuteration (Scheme 4a), indicating that C−H activation was reversible. Second, parallel kinetic experiments with **1a** or [2-D]-**1a** (96% D) with CO_2 and a competition experiment between **1a** and [*N*-CD_3-2-D]-**1a** were performed, and k_H/k_D values of 1.25 and 1.54 were obtained, respectively (Scheme 4b), suggesting that the C−H bond cleavage may not be involved in the rate-limiting step. Meanwhile, intermolecular competition experiments between 5-CF_3- and 5-OMe-substituted indoles were conducted. The corresponding carboxylation products were obtained in a ratio of 1:0.25 (Scheme 4c), revealing that the electron-deficient substrate (**1f**) has better reactivity.

Scheme 4. Preliminary Mechanistic Studies



When $Ni(cod)_2$ was used instead of $NiCl_2$ under standard conditions, the carboxylation product was obtained in 82% yield (Scheme 5a), indicating that Ni(0) may be the catalytically active species. When the N−H group of the substrate was protected with methyl (**1z**), no product was observed (Scheme 5b), indicating that the N−H bond in the bidentate directing group also played an important role. The isolation of the cyclonickel intermediate in the reaction was tried, but many attempts failed. Fortunately, when the catalyst loading was increased to 40 mol % and the reaction was stopped at 4 h under the standard conditions, the cyclo-

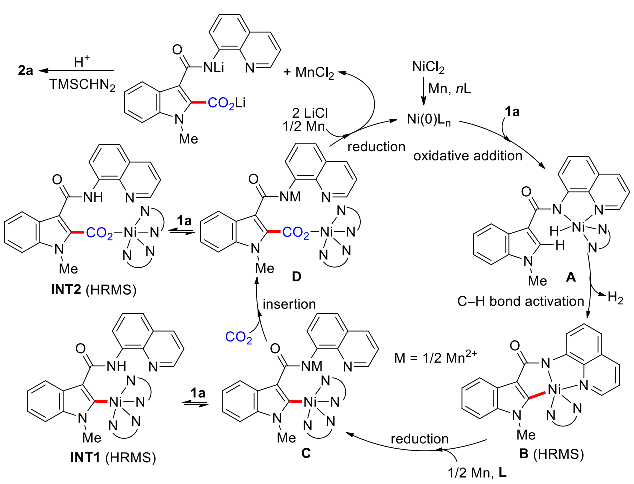
Scheme 5. Control Experiments and Intermediate Studies



metalated Ni(II) complex (**B**) and Ni(I) intermediates **INT 1** and **INT 2** were detected by HRMS (Scheme 5c). The electron paramagnetic resonance experiment (see the Supporting Information for details) was also conducted, but only the signal of Mn^{2+} was detected. The signal of Ni(I) may be covered by the strong signal of Mn^{2+}.

On the basis of our preliminary investigations and previous reports on Ni-catalyzed C−H bond activation[17] and reductive carboxylation of organic (pseudo)halides with CO_2,[11] a plausible mechanistic pathway via a Ni(0)−Ni(II)−Ni(I) catalytic cycle was postulated (Scheme 6). First, a catalytically active Ni(0) species is formed in situ by the reduction of $NiCl_2$ with Mn. Then, the pyridine nitrogen of amide **1a** coordinates to Ni(0) and promotes the oxidative addition of an N−H bond to afford nickel hydride intermediate **A**. The *ortho*-C−H bond is activated via σ-bond metathesis, providing cyclometalated Ni(II) intermediate **B** (detected by HRMS). The detection of H_2 by gas chromatography during the reaction (see the Supporting Information) supported this process. Reduction of **B** by Mn via SET reaction forms Ni(I) species **C**, which can occur via a proton exchange with substrate **1a** to produce intermediate **INT 1** (detected by HRMS). Then CO_2 is inserted into the C−Ni(I) bond to produce carboxylate Ni(I) intermediate **D**, which also can occur via a proton exchange to produce intermediate **INT 2** (detected by HRMS). Finally, **D** is reduced to Ni(0) by Mn for the next catalytic cycle. Meanwhile, lithium salts of carboxylate and amide anion are formed in the presence of LiCl and further acidified and reacted with $TMSCHN_2$ to afford product **2a**. KO^tBu played a vague but indispensable role in the catalytic cycle (see Table S1, entries 18−20). It may facilitate the insertion of CO_2 into the C−Ni(I) bond because CO_2 might react with KO^tBu to generate $^tBuOCO_2K$, which is more active than CO_2.[9b,e,f] The use of an excess of KO^tBu may also suppress the undesired decarboxylation side reaction.[19b]

Scheme 6. Proposed Mechanistic Pathway



In summary, we developed the first Ni-catalyzed direct carboxylation of the unactivated C−H bond of indoles using an 8-aminoquinoline auxiliary under an atmospheric pressure of CO_2. Various methyl carboxylates were accessed easily. This straightforward and novel carboxylation strategy will provide a new approach to CO_2 fixation. Further exploration of this reaction with other types of substrates and the capture of reaction intermediates are being carried out in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02429.

> Experimental details, optimization studies, and characterization data (PDF)

Accession Codes

CCDC 1977331 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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REFERENCES

(1) For selected books and reviews, see: (a) Aresta, M. *Carbon Dioxide as Chemical Feedstock*; Wiley-VCH: Weinheim, Germany, 2010. (b) Centi, G.; Perathoner, S. *Green Carbon Dioxide*; Wiley-VCH: Hoboken, NJ, 2014. (c) Scibioh, M. A.; Viswanathan, B. *Carbon Dioxide to Chemicals and Fuels*; Elsevier: Amsterdam, 2018. (d) Liu, Q.; Wu, L.; Jackstell, R.; Beller, M. Using Carbon Dioxide as a Building Block in Organic Synthesis. *Nat. Commun.* **2015**, *6*, 5933. (e) Beydoun, K.; Klankermayer, J. Recent Advances on CO_2 Utilization as C1 Building Block in C−N and C−O Bond Formation. *Top. Organomet. Chem.* **2018**, *63*, 39−76.

(2) For selected reviews of transition-metal-catalyzed C−X carboxylation, see: (a) Huang, K.; Sun, C.-L.; Shi, Z.-J. Transition-Metal-Catalyzed C−C Bond Formation through the Fixation of Carbon Dioxide. *Chem. Soc. Rev.* **2011**, *40*, 2435−2452. (b) Zhang, L.; Hou, Z. N-Heterocyclic Carbene (NHC)-Copper-Catalysed Transformations of Carbon Dioxide. *Chem. Sci.* **2013**, *4*, 3395−3403. (c) Moragas, T.; Correa, A.; Martin, R. Metal-Catalyzed Reductive Coupling Reactions of Organic Halides with Carbonyl-type Compounds. *Chem. - Eur. J.* **2014**, *20*, 8242−8258. (d) Yu, D.; Teong, S. P.; Zhang, Y. Transition Metal Complex Catalyzed Carboxylation Reactions with CO2. *Coord. Chem. Rev.* **2015**, *293−294*, 279−291. (e) Borjesson, M.; Moragas, T.; Gallego, D.; Martin, R. Metal-Catalyzed Carboxylation of Organic (Pseudo)halides with CO_2. *ACS Catal.* **2016**, *6*, 6739−6749. (f) Ahamed, M.; Verbeek, J.; Funke, U.; Lecina, J.; Verbruggen, A.; Bormans, G. Recent Progress in Metal Catalyzed Direct Carboxylation of Aryl Halides and Pseudo Halides Employing CO2: Opportunities for ^{11}C Radiochemistry. *ChemCatChem* **2016**, *8*, 3692−3700.

(3) For selected reviews of transition-metal-catalyzed C−H carboxylation, see: (a) Manjolinho, F.; Arndt, M.; Gooßen, K.; Gooßen, L. J. Catalytic C−H Carboxylation of Terminal Alkynes with Carbon Dioxide. *ACS Catal.* **2012**, *2*, 2014−2021. (b) Tommasi, I. Direct Carboxylation of C(sp^3)−H and C(sp^2)−H Bonds with CO_2 by Transition-Metal-Catalyzed and Base-Mediated Reactions. *Catalysts* **2017**, *7*, 380. (c) Luo, J.; Larrosa, I. C−H Carboxylation of Aromatic Compounds through CO_2 Fixation. *ChemSusChem* **2017**, *10*, 3317−3332. (d) Wu, X.-F.; Zheng, F. Synthesis of Carboxylic Acids and Esters from CO_2. *Top. Curr. Chem.* **2017**, *375*, 4. (e) Tortajada, A.; Juliá-Hernández, F.; Börjesson, M.; Moragas, T.; Martin, R. Transition-Metal-Catalyzed Carboxylation Reactions with Carbon Dioxide. *Angew. Chem., Int. Ed.* **2018**, *57*, 15948−15982. (f) Hong, J.; Li, M.; Zhang, J.; Sun, B.; Mo, F. C−H Bond Carboxylation with Carbon Dioxide. *ChemSusChem* **2019**, *12*, 6−39.

(4) Maag, H. *Prodrugs of Carboxylic Acids*; Springer: New York, 2007.

(5) For selected books and reviews, see: (a) Dixneuf, P. H.; Doucet, H. *C−H Bond Activation and Catalytic Functionalization I*; Springer, 2016. (b) Dixneuf, P. H.; Doucet, H. *C−H Bond Activation and Catalytic Functionalization II*; Springer, 2016. (c) Rouquet, G.; Chatani, N. Catalytic Functionalization of C(sp^2)−H and C(sp^3)−H Bonds by Using Bidentate Directing Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743. (d) Yang, L.; Huang, H. Transition-Metal-Catalyzed Direct Addition of Unactivated C−H Bonds to Polar Unsaturated Bonds. *Chem. Rev.* **2015**, *115*, 3468−3571. (e) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. Transition-Metal-Catalyzed C−H Bond Addition to Carbonyls, Imines, and Related Polarized π Bonds. *Chem. Rev.* **2017**, *117*, 9163−9227.

(6) (a) Fukue, Y.; Oi, S.; Inoue, Y. Direct Synthesis of Alkyl 2-Alkynoates from Alk-l-ynes, CO_2, and Bromoalkanes Catalysed by Copper(I) or Silver(I) salt. *J. Chem. Soc., Chem. Commun.* **1994**, 2091. (b) Boogaerts, I. I. F.; Nolan, S. P. Carboxylation of C−H Bonds using N-Heterocyclic Carbene Gold(I) Complexes. *J. Am. Chem. Soc.* **2010**, *132*, 8858−8859. (c) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R.; Cazin, C. S.; Nolan, S. P. Carboxylation of N−H/C−H Bonds using N-Heterocyclic Carbene Copper(I) Complexes. *Angew. Chem., Int. Ed.* **2010**, *49*, 8674−8677. (d) Zhang, L.; Cheng, J. H.; Ohishi, T.; Hou, Z. M. Copper-Catalyzed Direct Carboxylation of C−H Bonds with Carbon Dioxide. *Angew. Chem., Int. Ed.* **2010**, *49*, 8670−8673. (e) Vechorkin, O.; Hirt, N.; Hu, X. Carbon Dioxide as the C1 Source for Direct C−H Functionalization of Aromatic Heterocycles. *Org. Lett.* **2010**, *12*, 3567−3569. (f) Dingyi, Y.; Yugen, Z. The Direct Carboxylation of Terminal Alkynes with Carbon Dioxide. *Green Chem.* **2011**, *13*, 1275−1279. (g) Yoo, W. J.; Capdevila, M. G.; Du, X.; Kobayashi, S. Base-Mediated Carboxylation of Unprotected Indole Derivatives with Carbon Dioxide. *Org. Lett.* **2012**, *14*, 5326−5329. (h) Fenner, S.; Ackermann, L. C−H Carboxylation of Heteroarenes with Ambient CO_2. *Green Chem.* **2016**, *18*, 3804−3807.

(7) Sugimoto, H.; Kawata, I.; Taniguchi, H.; Fujiwara, Y. Palladium-Catalyzed Carboxylation of Aromatic Compounds with Carbon Dioxide. *J. Organomet. Chem.* **1984**, *266*, c44−c46.

(8) (a) Mizuno, H.; Takaya, J.; Iwasawa, N. Rhodium(I)-Catalyzed Direct Carboxylation of Arenes with CO_2 via Chelation-Assisted C−H Bond Activation. *J. Am. Chem. Soc.* **2011**, *133*, 1251−1253. (b) Suga, T.; Mizuno, H.; Takaya, J.; Iwasawa, N. Direct Carboxylation of Simple Arenes with CO2 through a Rhodium-Catalyzed C−H Bond Activation. *Chem. Commun.* **2014**, *50*, 14360−14363. (c) Suga, T.; Saitou, T.; Takaya, J.; Iwasawa, N. Mechanistic Study of the Rhodium-Catalyzed Carboxylation of Simple Aromatic Compounds with Carbon Dioxide. *Chem. Sci.* **2017**, *8*, 1454−1462.

(9) (a) Sasano, K.; Takaya, J.; Iwasawa, N. Palladium(II)-Catalyzed Direct Carboxylation of Alkenyl C−H Bonds with CO_2. *J. Am. Chem. Soc.* **2013**, *135*, 10954−10957. (b) Song, L.; Zhu, L.; Zhang, Z.; Ye, J.-H.; Yan, S.-S.; Han, J.-L.; Yin, Z.-B.; Lan, Y.; Yu, D.-G. Catalytic Lactonization of Unactivated Aryl C−H Bonds with CO_2: Experimental and Computational Investigation. *Org. Lett.* **2018**, *20*, 3776−3779. (c) Song, L.; Cao, G.-M.; Zhou, W.-J.; Ye, J.-H.; Zhang, Z.; Tian, X.-Y.; Li, J.; Yu, D.-G. Pd-Catalyzed Carbonylation of Aryl C−H Bonds in Benzamides with CO_2. *Org. Chem. Front.* **2018**, *5*, 2086−2090. (d) Yan, K.; Jin, J.; Kong, Y.; Li, B.; Wang, B. Palladium-Catalyzed Inert C−H Bond Activation and Cyclocarbonylation of Isoquinolones with Carbon Dioxide Leading to Isoindolo[2,1-*b*]isoquinoline-5,7-Diones. *Adv. Synth. Catal.* **2019**, *361*, 3080−3085. (e) Cai, Z.; Li, S.; Gao, Y.; Li, G. Rhodium(II)-Catalyzed Aryl C−H Carboxylation of 2-Pyridylphenols with CO_2. *Adv. Synth. Catal.* **2018**, *360*, 4005−4011. (f) Fu, L.; Li, S.; Cai, Z.; Ding, Y.; Guo, X.-Q.; Zhou, L.-P.; Yuan, D.; Sun, Q.-F.; Li, G. Ligand-Enabled Site-Selectivity in a Versatile Rhodium(II)-Catalysed Aryl C−H Carboxylation with CO_2. *Nat. Catal.* **2018**, *1*, 469−478. (g) Gao, Y.; Cai, Z.; Li, S.; Li, G. Rhodium(I)-Catalyzed Aryl C−H Carboxylation of 2-Arylanilines with CO_2. *Org. Lett.* **2019**, *21*, 3663−3669.

(10) For selected reviews, see: (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. Nickel-Catalyzed Cross-Couplings Involving Carbon−Oxygen Bonds. *Chem. Rev.* **2011**, *111*, 1346−1416. (b) Han, F.-S. Transition-Metal-Catalyzed Suzuki−Miyaura Cross-Coupling Reactions: A Remarkable Advance from Palladium to Nickel Catalysts. *Chem. Soc. Rev.* **2013**,

42, 5270−5298. (c) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent Advances in Homogeneous Nickel Catalysis. *Nature* **2014**, *509*, 299−309. (d) Ananikov, V. P. Nickel: The "Spirited Horse" of Transition Metal Catalysis. *ACS Catal.* **2015**, *5*, 1964−1971. (e) Wang, X.; Dai, Y.; Gong, H. Nickel-Catalyzed Reductive Couplings. *Top. Curr. Chem.* **2016**, *374*, 43. (f) Zimmermann, P.; Limberg, C. Activation of Small Molecules at Nickel(I) Moieties. *J. Am. Chem. Soc.* **2017**, *139*, 4233−4242.

(11) For selected works, see: (a) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. Nickel-Catalyzed Carboxylation of Aryl and Vinyl Chlorides Employing Carbon Dioxide. *J. Am. Chem. Soc.* **2012**, *134*, 9106−9109. (b) Leon, T.; Correa, A.; Martin, R. Ni-Catalyzed Direct Carboxylation of Benzyl Halides with CO_2. *J. Am. Chem. Soc.* **2013**, *135*, 1221−1224. (c) Correa, A.; Leon, T.; Martin, R. Ni-Catalyzed Carboxylation of $C(sp^2)$− and $C(sp^3)$−O Bonds with CO_2. *J. Am. Chem. Soc.* **2014**, *136*, 1062−1069. (d) Liu, Y.; Cornella, J.; Martin, R. Ni-Catalyzed Carboxylation of Unactivated Primary Alkyl Bromides and Sulfonates with CO_2. *J. Am. Chem. Soc.* **2014**, *136*, 11212−11215. (e) Borjesson, M.; Moragas, T.; Martin, R. Ni-Catalyzed Carboxylation of Unactivated Alkyl Chlorides with CO_2. *J. Am. Chem. Soc.* **2016**, *138*, 7504−7507. (f) Julia-Hernandez, F.; Moragas, T.; Cornella, J.; Martin, R. Remote Carboxylation of Halogenated Aliphatic Hydrocarbons with Carbon Dioxide. *Nature* **2017**, *545*, 84−88. (g) Charboneau, D. J.; Brudvig, G. W.; Hazari, N.; Lant, H. M. C.; Saydjari, A. K. Development of an Improved System for the Carboxylation of Aryl Halides through Mechanistic Studies. *ACS Catal.* **2019**, *9*, 3228−3241.

(12) Ishida, N.; Masuda, Y.; Imamura, Y.; Yamazaki, K.; Murakami, M. Carboxylation of Benzylic and Aliphatic C−H Bonds with CO_2 Induced by Light/Ketone/Nickel. *J. Am. Chem. Soc.* **2019**, *141*, 19611−19615.

(13) For selected reviews: (a) Cai, X.-H.; Xie, B. Recent Advances on Nickel-Catalyzed C−H Bonds Functionalized Reactions. *ARKIVOC* **2015**, 184−211. (b) Johnson, S. A. Nickel Complexes for Catalytic C−H Bond Functionalization. *Dalton Trans* **2015**, *44*, 10905−10913. (c) Yamaguchi, J.; Muto, K.; Itami, K. Nickel-Catalyzed Aromatic C−H Functionalization. *Top. Curr. Chem.* **2016**, *374*, 55. (d) Chatani, N. Nickel-Catalyzed C−H Bond Functionalization Utilizing an N,N'-Bidentate Directing Group. *Top. Organomet. Chem.* **2015**, *56*, 19−46. (e) Harry, N. A.; Saranya, S.; Ujwaldev, S. M.; Anilkumar, G. Recent Advances and Prospects in Nickel-Catalyzed C−H Activation. *Catal. Sci. Technol.* **2019**, *9*, 1726−1743. (f) Arun, V.; Mahanty, K.; De Sarkar, S. Nickel-Catalyzed Dehydrogenative Couplings. *ChemCatChem* **2019**, *11*, 2243−2259.

(14) (a) Baron, B. M.; Cregge, R. J.; Farr, R. A.; Friedrich, D.; Gross, R. S.; Harrison, B. L.; Janowick, D. A.; Matthews, D.; McCloskey, T. C.; Meikrantz, S.; Nyce, P. L.; Vaz, R.; Metz, W. A. CoMFA, Synthesis, and Pharmacological Evaluation of (E)-3-(2-Carboxy-2-arylvinyl)-4,6-dichloro-1H-indole-2-carboxylic Acids: 3-[2-(3-Aminophenyl)-2-carboxyvinyl]-4,6-dichloro-1H-indole-2-carboxylic Acid, a Potent Selective Glycine-Site NMDA Receptor Antagonist. *J. Med. Chem.* **2005**, *48*, 995−1018. (b) Friberg, A.; Vigil, D.; Zhao, B.; Daniels, R. N.; Burke, J. P.; Garcia-Barrantes, P. M.; Camper, D.; Chauder, B. A.; Lee, T.; Olejniczak, E. T.; Fesik, S. W. Discovery of Potent Myeloid Cell Leukemia 1 (Mcl-1) Inhibitors Using Fragment-Based Methods and Structure-Based Design. *J. Med. Chem.* **2013**, *56*, 15−30. (c) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. Simple Indole Alkaloids and Those with a Non-Rearranged Monoterpenoid Unit. *Nat. Prod. Rep.* **2013**, *30*, 694−752.

(15) Huang, L.; Ackerman, L. K. G.; Kang, K.; Parsons, A. M.; Weix, D. J. LiCl-Accelerated Multimetallic Cross-Coupling of Aryl Chlorides with Aryl Triflates. *J. Am. Chem. Soc.* **2019**, *141*, 10978−10983.

(16) Zhang, Z.; Li, X.; Song, M.; Wan, Y.; Zheng, D.; Zhang, G.; Chen, G. Selective Removal of Aminoquinoline Auxiliary by IBX Oxidation. *J. Org. Chem.* **2019**, *84*, 12792−12799.

(17) (a) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. Nickel-Catalyzed Chelation-Assisted Transformations Involving Ortho C−H Bond Activation: Regioselective Oxidative Cycloaddition of Aromatic Amides to Alkynes. *J. Am. Chem. Soc.* **2011**, *133*, 14952−14955. (b) He, Z.; Huang, Y. Diverting C−H Annulation Pathways: Nickel-Catalyzed Dehydrogenative Homologation of Aromatic Amides. *ACS Catal.* **2016**, *6*, 7814−7823. (c) Omer, H. M.; Liu, P. Computational Study of the Ni-Catalyzed C−H Oxidative Cycloaddition of Aromatic Amides with Alkynes. *ACS Omega* **2019**, *4*, 5209−5220.

(18) Michigami, K.; Mita, T.; Sato, Y. Cobalt-Catalyzed Allylic $C(sp^3)$−H Carboxylation with CO_2. *J. Am. Chem. Soc.* **2017**, *139*, 6094−6097.

(19) (a) Nemoto, K.; Tanaka, S.; Konno, M.; Onozawa, S.; Chiba, M.; Tanaka, Y.; Sasaki, Y.; Okubo, R.; Hattori, T. Me2AlCl-Mediated Carboxylation, Ethoxycarbonylation, and Carbamoylation of Indoles. *Tetrahedron* **2016**, *72*, 734−745. (b) Yoo, W.-J.; Capdevila, M. G.; Du, X.; Kobayashi, S. Base-Mediated Carboxylation of Unprotected Indole Derivatives with Carbon Dioxide. *Org. Lett.* **2012**, *14*, 5326−5329. (c) Ueno, A.; Takimoto, M.; Wylie, W. N. O.; Nishiura, M.; Ikariya, T.; Hou, Z. Copper-Catalyzed Formal C−H Carboxylation of Aromatic Compounds with Carbon Dioxide through Arylaluminum Intermediates. *Chem. - Asian J.* **2015**, *10*, 1010−1016.