# Development of an Improved System for the Carboxylation of Aryl Halides through Mechanistic Studies

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## Abstract

The nickel-catalyzed carboxylation of organic halides or pseudohalides using carbon dioxide is an emerging method to prepare synthetically valuable carboxylic acids. Here, we report a detailed mechanistic investigation of these reactions using the carboxylation of aryl halides with $(PPh_3)_2Ni^{II}Cl_2$ as a model reaction. Our studies allow us to understand several general features of nickel-catalyzed carboxylation reactions. For example, we demonstrate that both a Lewis acid and halide source are beneficial for catalysis. To this end, we establish that heterogeneous Mn(0) and Zn(0) reductants are multifaceted reagents that generate noninnocent Mn(II) or Zn(II) Lewis acids upon oxidation. In a key result, a rare example of a well-defined nickel(I) aryl complex is isolated, and it is demonstrated that its reaction with carbon dioxide results in the formation of a carboxylic acid in high yield (after workup). The carbon dioxide insertion product undergoes rapid decomposition, which ca These three oxidation states correspond to the onbe circumvented by a ligand metathesis reaction with a halide source. Our studies have led to both a revised mechanism and the development of a broadly applicable strategy to improve reductive carboxylation reactions. A critical component of this strategy is that we have replaced the heterogeneous Mn(0) reductant typically used in catalysis with a well-defined homogeneous organic reductant. Through its use, we have increased the range of ancillary ligands, additives, and substrates that are compatible with the reaction. This has enabled us to perform reductive carboxylations at low catalyst loadings. Additionally, we demonstrate that reductive carboxylations of organic (pseudo)halides can be achieved in high yields in more practically useful, non-amide solvents. Our results describe a mechanistically guided strategy to improve reductive carboxylations through the use of a homogeneous organic reductant, which may be broadly translatable to a wide range of cross-electrophile coupling reactions.

## Graphical Abstract

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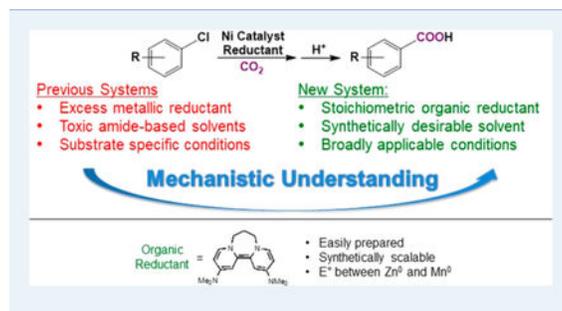
## INTRODUCTION

Carbon dioxide ($CO_2$) is an attractive C1 source because it is renewable, inexpensive, abundant, and nontoxic.[1] The catalytic formation of C–C bonds from $CO_2$ is a particularly interesting class of reactions due to the prevalence of C–C bonds in fuels, commodity chemicals, and pharmaceuticals.[1] For instance, in synthetic chemistry, it would be valuable to use $CO_2$ as a feedstock for the preparation of carboxylic acids,[2] which are commonly found in bioactive molecules and are important intermediates in complex molecule synthesis due to their synthetic versatility and facile purification.[3] Additionally, current methods to generate carboxylic acids, such as the stoichiometric reaction of $CO_2$ with highly reactive organometallic reagents,[4] the oxidation of alcohols and aldehydes,[5] and nitrile hydrolysis,[6] all have poor functional group tolerance and atom economy. Therefore, the development of efficient catalytic methods for the preparation of carboxylic acids from $CO_2$ that are functional group tolerant could have widespread applications in organic synthesis.

Over the past decade, it has been demonstrated that the catalytic reductive coupling of $CO_2$ with unsaturated hydrocarbons[7] and organic halides or pseudohalides[8–12] is a highly chemoselective strategy to generate carboxylic acids. For example, in 2012, Tsuji and co-workers demonstrated that carboxylic acids can be generated from aryl chlorides and $CO_2$ using a well-defined $(PPh_3)_2Ni^{II}Cl_2$ precatalyst (5 mol %), a heterogeneous $Mn^0$ reductant (300 mol %), tetraethylammonium iodide ($Et_4NI$) (10 mol %), and $PPh_3$ (10 mol %) in the amide-based solvent 1,3-dimethylimidazolidinone (DMI) (Figure 1a).[8a] Furthermore, in a series of seminal reports, Martin demonstrated that related Ni-catalyzed systems can be used to couple $CO_2$ with a variety of electrophiles, including aryl, alkyl, and vinyl halides or pseudohalides with high functional group tolerance (Figure 1b).[8b–e,h–l,h] However, despite the impressive progress in Ni-catalyzed carboxylation reactions, there are a number of general problems that are preventing both further development and practical application of this method.[2g] These include (1) the need for super-stoichiometric amounts of heterogeneous $Zn^0$ or $Mn^0$ metallic reductants in most reactions,[13] which give rise to poorly reproducible kinetic profiles, limiting industrial applications and complicating mechanistic studies, (2) the need for synthetically undesirable, highly toxic amide-based solvents,[14]

which are increasingly subject to strict regulation and reduce the number of substrates that are compatible with this method, (3) the need for excess ligand and other inscrutable additives, which complicate mechanistic analysis and make it difficult to predict the outcome of reactions with different substrates, (4) the need for high catalyst loadings (10 mol % Ni is frequently used), (5) the need for different ancillary ligands for even closely related substrates, and (6) limitations in the substrate scope for each particular class of electrophile. For instance, in Tsuji's system, the reaction is restricted to substrates that are not *ortho*, amino, or hydroxy substituted.[8a,15] It is also noteworthy that many of these limitations in Ni-catalyzed carboxylation reactions also apply to Ni-catalyzed cross-electrophile couplings involving substrates other than $CO_2$, such as reductive couplings between alkyl and aryl halides, which are also currently attracting significant attention in synthetic chemistry.[16]

One of the main reasons why the design of improved systems for Ni-catalyzed carboxylation reactions has proven challenging is our relative lack of understanding of the mechanism of these transformations.[2g] Nevertheless, a general mechanism is commonly proposed for all Ni-catalyzed reductive carboxylation reactions. This is summarized in Figure 2 for the Tsuji system.[8a] In the proposed mechanism, precatalyst activation generates a Ni0 active species, which undergoes oxidative addition with an organic halide (or pseudohalide) to form an organometallic Ni[II] halide (or pseudohalide) complex. Subsequent one electron reduction removes the halide (or pseudohalide) and forms an organometallic Ni[I] complex, which is proposed to insert $CO_2$ and generate a Ni[I] carboxylate. Reduction of the Ni[I] carboxylate removes the carboxylate product from the metal and regenerates the catalytically active Ni[0] species. However, with the exception of oxidative addition,[17] there is little experimental precedent for the other elementary steps in the proposed catalytic cycle. In particular, the reactivity and speciation of the proposed Ni[I] intermediates remain largely uninvestigated, and there are no characterized examples of $CO_2$ insertion into well-defined Ni[I] complexes.[18] Additionally, the role of the additives, such as $Et_4NI$ in the Tsuji system, which are typically required for productive catalysis, are not accounted for in the proposed mechanism.

Here, we perform a detailed mechanistic study of the Tsuji carboxylation system. We explain the roles of all of the required additives and propose a modified catalytic cycle. In a key result, we isolate a well-defined Ni[I] aryl complex and demonstrate that reaction with $CO_2$ results in the formation of a carboxylic acid in high yield (after workup). Lewis acids increase the rate of the proposed $CO_2$ insertion, and we show that a Lewis acid, as well as a halide source are beneficial for catalysis. Our mechanistic studies have enabled us to develop a general strategy to improve catalytic systems for aryl halide carboxylation. A central feature of this strategy is that we can replace the superstoichiometric Mn[0] reductant with a well-defined homogeneous organic reductant and an alkali metal halide additive. This has enabled us to decrease the catalyst loading and reaction time, carboxylate more sterically bulky substrates, and perform reactions in more synthetically practical, non-amide solvents. Overall, our results provide fundamental understanding about Ni-catalyzed carboxylation reactions, which may be broadly applicable to improving a variety of cross-electrophile coupling reactions.

# RESULTS AND DISCUSSION

## Empirical Investigation into the Role of Different Reagents in the Tsuji System for Carboxylation.

**Precatalyst Screen.—**To begin our investigation, we compared the catalytic performance of precatalysts in the $Ni^0$, $Ni^I$, and $Ni^{II}$ oxidation states for the carboxylation of 4-chloroanisole to 4-anisic acid using the conditions reported by Tsuji et al. (Table 1).[8a] These three oxidation states correspond to the oxidation states of the Ni intermediates in the mechanism proposed in Figure 2. The amount of free $PPh_3$ ligand added was varied so the overall ratio of $PPh_3$ to $Ni^I$ was always 4:1. The Ni precatalyst, $(PPh_3)_3Ni\,Cl$, gave comparable activity to Tsuji's $Ni^{II}$ precatalyst, $(PPh_3)_2Ni^{II}Cl_2$, with yields of approximately 75% observed in both cases. In contrast, the $Ni^0$ precatalyst, $(PPh_3)_4Ni^0$, gave a lower yield (51%) of 4-anisic yield. This result is surprising as our control experiments suggest that when $(PPh_3)_2Ni^{II}Cl_2$ is used as the precatalyst, $(PPh_3)_4Ni^0$ is the catalyst resting state, which suggests that $PPh_3$ dissociation is likely turnover limiting in catalysis (see SI). When either $(PPh_3)_3Ni^ICl$ or $(PPh_3)_2Ni^{II}Cl_2$ is used as the precatalyst, $MnCl_2$ is presumably generated as a byproduct of precatalyst activation to form the $Ni^0$ active species; however, this step is not required when $(PPh_3)_4Ni^0$ is used as the precatalyst. The addition of 5 mol % $MnCl_2$ to a catalytic reaction using $(PPh_3)_4Ni^0$ as the precatalyst resulted in an increase in product yield from 51% to 81%, which is comparable to results obtained with the $Ni^I$ and $Ni^{II}$ precatalysts. This increase in yield strongly suggests that the $Mn^0$ reductant plays a dual role in catalysis—it not only provides electrons but is also a source of $MnCl_2$, which is beneficial for catalysis. These results may also explain why $Mn^0$ (or $Zn^0$, which presumably generates $ZnCl_2$) has been the reductant of choice for Ni-catalyzed carboxylation reactions and may guide the development of reductive carboxylation systems that employ alternative reductants. This hypothesis is explored further in our reductant screen.

**Reductant Screen.—**Despite the rising interest in reductive coupling reactions, there are limited comparative studies exploring the impact of the nature of the reductant on catalysis. [19] To this end, a diverse series of reductants spanning a range of reduction potentials was evaluated in the carboxylation of 4-chloroanisole with $(PPh_3)_2Ni^{II}Cl_2$ as the precatalyst to explore the effect of reductant speciation and potential on catalyst performance (Table 2). Specifically, we tested the one electron organometallic, homogeneous reductants decamethylcobaltocene $(Cp^*_2Co)$[20] and cobaltocene $(Cp_2Co)$,[21] as well as the organic, homogeneous two-electron reductants tetrakis(dimethylamino)ethylene (TDAE)[22] and DMAP-OED,[23] which is an organic electron donor derived from 4-(dimethylamino)pyridine that was first reported by Murphy and co-workers. These reductants were compared to the standard metallic, heterogeneous two electron reductants $Mn^0$ and $Zn^0$ in catalysis.[24] Under the standard Tsuji conditions, only the two strongest reductants gave significant yields of product (Table 2, column 1). The heterogeneous reductant $Mn^0$ gave a yield of 76%, while the homogeneous reductant $Cp^*_2Co$ generated 4-anisic acid in 40% yield. No weaker reductants formed product in a yield of greater than 12%, demonstrating that strong reductants are critical for catalysis under the Tsuji conditions.

One of the additives that is present in the Tsuji conditions is $Et_4NI$, which is proposed to assist with electron transfer between the heterogeneous $Mn^0$ reductant and the solution-state Ni catalyst.[25] To explore this hypothesis, catalytic reactions were performed with our full series of reductants in the absence of $Et_4NI$ (Table 2, column 2). No significant changes in product yields were observed with homogeneous reductants in the absence of $Et_4NI$. For example, the yield of product using $Cp*_2Co$ as the reductant was 36% in the absence of $Et_4NI$, which is essentially the same as the yield in the presence of $Et_4NI$. In contrast, when $Et_4NI$ was removed from a reaction with the heterogeneous reductant $Mn^0$ the yield diminished entirely to <1%. These results are consistent with the hypothesis that $Et_4NI$ is required to facilitate electron transfer when the reaction is performed using heterogeneous reductants. For that reason, in the remainder of this work, unless otherwise stated, $Et_4NI$ was not present in catalytic reactions using a homogeneous reductant but was added in catalytic reactions using a heterogeneous reductant.

Our previous results showed that $MnCl_2$, which is generated in situ upon oxidation of $Mn^0$, is beneficial in catalysis. To further investigate its role, 100 mol % $MnCl_2$ was added to a series of reactions with different reductants (Table 2, column 3). Upon addition of $MnCl_2$, an increase in yield was observed with all reductants tested except for TDAE, which is incapable of producing catalytically active $(PPh_3)_4Ni^0$, as reaction of $(PPh_3)_3Ni^{II}Cl_2$ with an excess of TDAE only generates $(PPh_3)_3Ni^ICl$ in the presence of 2 equiv of $PPh_3$ (see the SI). Using both homogeneous and heterogeneous reductants, product yields increased with increasing reductant strength. Interestingly, a significant decrease in the reductant strength required for productive catalysis was observed upon addition of $MnCl_2$. This is best illustrated by the fact that the yield obtained using $Cp*_2Co$ as the reductant in the absence of $MnCl_2$ (36%) was the same as the yield obtained using $Cp_2Co$ as the reductant in the presence of $MnCl_2$ (34%). Essentially, the addition of $MnCl_2$ allows for comparable catalytic performance between structurally similar reductants with a 490 mV (13.6 kcal/mol) difference in reduction potential in DMF. This suggests that the addition of $MnCl_2$ changes either the speciation of the catalyst in solution or the reaction mechanism, a topic that is explored further in a subsequent section.

From a practical perspective, the most noteworthy result is that the addition of $MnCl_2$ leads to a significant yield (62%) of product when a stoichiometric amount of DMAP-OED is used as the reductant. This is the first example of an organic reductant being utilized in a reductive carboxylation reaction without concomitant photoredox catalysis.[8n,9d] Additionally, DMAP-OED can be prepared in two steps from relatively inexpensive starting materials (each less than $100/kg) and is a solid at room temperaure,[23] which makes it easier to work with than volatile liquid organic reductants such as TDAE.[19,26] From a mechanistic perspective, no catalysis was observed with DMAP-OED as the reductant in the absence of $MnCl_2$. This indicates that when DMAP-OED is used in catalysis, the source of the electrons is decoupled from the production of $MnCl_2$, unlike when $Mn^0$ is used the reductant. This observation is important because it means that when DMAP-OED is used as the reductant, we can discretely study the role of $MnCl_2$ (and related additives) in catalysis in the absence of in situ generated $MnCl_2$ from the reductant, which provides an opportunity to improve the reaction.

**Additive Screen.—**Metal halide type additives are commonly employed in Ni-catalyzed reductive carboxylation reactions, but the role of such additives has remained unclear.[2g,i] To empirically investigate the role of $MnCl_2$ in catalysis, the metal halide-type additive was systematically varied across catalytic reactions using $(PPh_3)_2Ni^{II}Cl_2$ as the catalyst and a slight excess of DMAP-OED (120%) as the reductant and catalyst performance was monitored (Table 3). When the reaction was performed with $MnCl_2$ as the additive, a 68% yield was obtained. Simple alkali halide salts with high solubility in DMI, such as LiCl and LiBr, performed comparably to $MnCl_2$, giving yields of 68% and 67%, respectively (see SI for a full list of additives that were evaluated). This result is significant in understanding the mechanism of these reactions because it indicates that organometallic Mn (or Zn when it is used as the reductant) species do not play a crucial role in Ni-catalyzed carboxylation reactions as the reaction proceeds in the absence of any Mn-containing species. Previous stoichiometric studies have demonstrated that Ni-mediated carboxylation can occur in significant quantities in the absence of Mn or Zn species;[7f,8a,e,j,k] however, they had not been able to rigorously exclude this hypothesis in catalysis.[2g] As a result, mechanisms in which carboxylation requires species derived from $Mn^0$ could not be excluded.[13] It is also important from a practical perspective because $Li^+$ salts are both available in greater variety and tend to be significantly cheaper than $Mn^{2+}$ salts. For this reason, LiBr (or LiCl) was used in place of $MnCl_2$ in many of our further studies.

It was not clear from our preliminary work if the cation, anion, or both components of LiBr or $MnCl_2$ were crucial for enhancing catalysis. To explore this, we used either $Li^+$ or $Br^-$ additives with generally innocent counterions such as trifluoromethanesulfonate ($OTf^-$), hexafluorophosphate ($PF_6^-$), and tetrafluoroborate ($BF_4^-$) or tetrabutylammonium ($^nBu_4^+$) in catalysis. Reactions using LiOTf, $LiPF_6$, and $LiBF_4$ gave product yields of 15%, 14%, and 36%, respectively, while the reaction using $nBu_4Br$ gave a yield of 3%. The difference in the yields with the different lithium salts may be related to ion-pairing effects between the cation and anion in DMI, which changes the effective concentration of free Li+.[27] The reaction with $LiBF_4$ was repeated using $(PPh_3)_4Ni^0$ as the precatalyst in place of $(PPh_3)_2Ni^{II}Cl_2$ (with 2 equiv of $PPh_3$) to limit the number of halide sources present in the reaction. This decreased the yield to 23%. We note that it is not possible to completely eliminate halide sources from the reaction when 4-chloroanisole is used as the substrate, but catalytic data collected using phenyl triflate as the substrate demonstrated that while a Lewis acid is essential for catalysis, a halide source only increases catalyst performance and is not essential (see the SI for further details). Overall, our results demonstrate that neither $Li^+$ nor $Br^-$ sources with innocent counterions are sufficient to provide catalytic results comparable to those obtained with LiBr, which indicates that both the cation and anion are important in catalysis.

One potential role of $Li^+$ in catalysis is to act as a Lewis acid. To investigate the potential role of Lewis acids, a nonionic Lewis acid, triphenoxyborane ($B(OPh)_3$), was employed as an additive in catalysis, giving a product yield of 17%, which is significantly above the baseline reaction with no Lewis acid. Furthermore, when $B(OPh)_3$ was used as an additive in catalysis with $^nBu_4Br$, an increase in yield to 44% was observed. This result provides evidence that the role of $Li^+$ or $Mn^{2+}$ in catalysis is that of a Lewis acid and further

exemplifies the benefits of both a Lewis acid and halide source in catalysis. *In fact, a review of the literature indicates that every system for the reductive carboxylation of organic halides and pseudohalides reported to date has both a Lewis acid and halide source present in catalysis, demonstrating the critical nature of these reagents to productive catalysis.*[8–11] In most cases, these species have not been added deliberately but form in situ, and there is presumably significant scope for optimizing these reagents to enhance catalysis, especially if the reductant is decoupled from the Lewis acid source. Additionally, despite their ubiquity in carboxylation reactions, only one computational study has proposed any sort of role for Lewis acids and halides (vide infra),[28] and it is noteworthy that in the proposed mechanism for the carboxylation of aryl chlorides (Figure 2), neither a Lewis acid nor an external halide source is involved as a reagent in any elementary reaction. Therefore, we sought to investigate the elementary steps of the proposed catalytic cycle through stoichiometric reactions in order to explore their validity and elucidate the role of Lewis acids and halides in catalysis.

## Investigation of Proposed Elementary Steps.

**$L_n Ni^{II}(Ar)(Cl)$ Reduction.—**In all Ni-catalyzed reductive carboxylation reactions involving alkyl or aryl halide or pseudohalide substrates, the reduction of an organometallic $Ni^{II}$ halide or pseudohalide is proposed to be an elementary step (Figure 2).[8] For example, in the Tsuji system the reduction of $(PPh_3)_2 Ni^{II}(Ar)(Cl)$ is proposed to occur as opposed to $CO_2$ insertion into $(PPh_3)_2 Ni^{II}(Ar)(Cl)$.[8a] Two observations from the literature provide support for this step: (i) complexes of the type $L_n Ni^{II}(Ar)(X)$ (X = (pseudo)halide) do not react directly with $CO_2$,[29] an observation which is consistent with our own control experiments using complexes of the form $(PPh_3)_2 Ni^{II}(Ar)(Cl)$; (ii) Tsuji et al. reported that when $(PPh_3)_2 Ni$ In agreement with our hypothesis,$^{II}(C_6H_5)(Cl)$ was treated with a $Mn^0$/$Et_4 NI$ reductant pair iFollowing this precedent, we preparn DMI under an atmosphere of $CO_2$, 47% yield of methylbenzoate was produced after esterification of the product.[8a] Given this precedent, we have not studied the reduction of $Ni^{II}$ to $Ni^{I}$ in detail, although we have performed some experiments exploring the effect of the aryl group on reduction. Specifically, in direct contrast to Tsuji's results with $(PPh_3)_2 Ni^{II}(C_6H_5)(Cl)$, when we stirred $(PPh_3)_2 Ni^{II}(o\text{-}tol)\text{-}(Cl)$ with a $Mn^0$/$Et_4 NI$ reductant pair in DMI under both an $N_2$ and $CO_2$ atmosphere for 1 day, no reaction was observed. However, when $(PPh_3)_2 Ni^{II}(o\text{-}tol)(Cl)$ was treated with 1 equiv of DMAP-OED in DMI under an $N_2$ atmosphere, starting material was consumed rapidly and a black precipitate was formed (see the SI). When the same reaction was performed under a $CO_2$ atmosphere, 2-toluic acid was produced in 42% yield (see the SI for details). Since $Mn^0$ is a stronger reductant than DMAP-OED, these results indicate that kinetic factors, presumably related to the increased steric bulk around the metal center, prevent electron transfer from the $Mn^0$/$Et_4 NI$ reductant pair to $(PPh_3)_2 Ni^{II}(o\text{-}tol)(Cl)$. Our stoichiometric observations are consistent with the inability of the Tsuji system to carboxylate *ortho*-substituted aryl halides and suggest that when DMAP-OED is used as the reductant it may be possible to carboxylate these substrates.[8a] In agreement with our hypothesis, when 2-chlorotoluene was employed as a substrate in catalysis using DMAP-OED as the reductant, $MnCl_2$ as an additive, and $(PPh_3)_2 Ni^{II}Cl_2$ as the catalyst, 2-toluic acid was produced in 53% yield (Table 4). This result demonstrates that in the Tsuji system, the restriction in substrate scope is not intrinsic to the reaction, but is a limitation imposed by

the choice of reductant and suggests that improved and distinct reactivity can be achieved with homogeneous reductants compared to heterogeneous reductants in reductive coupling reactions. Additionally, the $Ni^{II}$ complex $(PPh_3)_2Ni^{II}(o\text{-tol})(Cl)$ performed comparably as a catalyst to the literature $(PPh_3)_2Ni^{II}Cl_2$ precatalyst for the carboxylation of 2-chlorotoluene using DMAP-OED (see the SI for details). This result provides further evidence that complexes of the type $(PPh_3)_2Ni^{II}(Ar)(Cl)$ are intermediates in catalysis.

**Preparation of a $Ni^I$ Aryl Complex and Reaction with $CO_2$.**—One-electron reduction of compounds of the type $L_nNi^{II}(R)\text{-}(X)$ is proposed to generate highly reactive organometallic $L_nNi^I(R)$ intermediates (in this work $(PPh_3)_nNi^I(Ar)$) in catalysis, which are proposed to react with $CO_2$; however, studying this class of complexes is difficult due to their instability.[30] Indeed, the direct reduction of $(PPh_3)_2Ni^{II}(o\text{-tolyl})(Cl)$ with DMAP-OED did not lead to the formation of any organometallic complexes that could be spectroscopically characterized. Recently, it was demonstrated that metastable $Ni^I$ aryl species supported by the bidentate phosphine ligand dppf (dppf = 1,1′-bis(diphenylphosphino)ferrocene) can be synthesized using sterically bulky aryl ligands.[30e] Following this precedent, we prepared $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$, which contains a bulky aryl group, through the treatment of $(PPh_3)_3Ni^I(Cl)$ with 2,4,6-triisopropylmagnesium bromide (Scheme 1). This compound, which is a model for the proposed $Ni^I$ aryl intermediates in the carboxylation of aryl chlorides (Figure 2), is a rare example of a well-defined $Ni^I$ aryl species.[30b,c,e,f] Although $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ decomposes over 5 h in THF at room temperature to 1,3,5-triisopropylbenzene and a mixture of unidentifiable products, we were able to grow single crystals suitable for X-ray diffraction (Scheme 1). The Ni(1)–C(1) bond length of 1.9369(16) Å is similar to those observed in the few previous examples of $Ni^I$ aryl complexes.[30b,c,e,f] The geometry around the Ni center is highly distorted trigonal planar with the P(2)–Ni(1)–C(1) bond angle of 140.72(5)° being significantly larger than either the P(1)–Ni(1)–C(1) or P(1)–Ni(1)–P(2) bond angles, which are 109.22(5) and 109.278(11)°, respectively. The $^1H$ NMR spectrum of $(PPh_\cdot)Ni^I(2,4,6\text{-}^iPr$ $C H_\cdot)$ is consistent with a paramagnetic complex.[31] There is a broad diagnostic resonance integrating to 12 protons at 10.86 ppm in toluene-$d_8$, which enabled us to use NMR spectroscopy to determine the stability of the complex and check if it is present in a reaction mixture (see the SI for details). The rate of decomposition of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ is unaffected by the presence of a strong reductant such as $Cp^*_2Co$, indicating that the $Ni^I$ aryl complex is likely not reduced during catalysis. The decomposition of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ is significantly slower in the presence of 2 equiv of $PPh_3$ (2 days compared to 5 h at room temperature in THF), suggesting that ligand dissociation provides a decomposition pathway and providing a rationale for the need for excess $PPh_3$ in catalysis.[8a] Owing to the instability of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$, we were not able to directly evaluate the competence of an isolated sample of the $Ni^I$ aryl complex as a (pre)catalyst in a catalytic reaction. The E PR spectrum of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ is consistent with the presence of $S = 1/2$ species and is dependent upon the concentration of $PPh_3$. Similar to its dppf congener,[30e] the EPR spectrum shows metal-centered radical character, in agreement with the proposed $Ni^I$ oxidation state (see the SI for details).

In catalysis, the formation of a new C–C bond and the incorporation of $CO_2$ into the catalytic cycle is proposed to occur via $CO_2$ insertion into a $(PPh_3)_nNi^I(Ar)$ species.[8a] Due to the instability of $Ni^I$ aryl species, the only evidence to support this elementary step is from DFT calculations[29a] and there are no examples of reactions of $CO_2$ with $Ni^I$ aryl species resulting in the formation of carboxylic acids.[2g] To this end, a THF solution of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ was placed under 1 atm of $CO_2$ in the presence of 2 equiv of $PPh_3$ (Table 5). The excess $PPh_3$ was added to slow down the background decomposition of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ (vide supra). After 5 h, $^1H$ NMR spectroscopy indicated that all of the $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ had been consumed, and treatment of the reaction mixture with acid gave a 78% yield of 2,4,6-triisopropylbenzoic acid. Efforts to identify the metal-containing product from the reaction of $CO_2$ with $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ prior to treatment with acid are described in a subsequent section. *The carboxylic acid product we obtain after an acid workup clearly establishes for the first time that $L_nNi^I(R)$ complexes are capable of activating $CO_2$, supporting the commonly proposed elementary step in reductive carboxylation reactions.* It also provides evidence against the proposal that Mn or Zn are required for the activation of $CO_2$ and confirms that $Ni^I$ aryl species are highly nucleophilic. This suggests that they may also be able to insert other molecules with polar double bonds such as carbonyls, which could be relevant to cross-electrophile coupling reactions between aryl halides and aryl aldehydes or cyclic anhydrides.[32]

It has previously been demonstrated that Lewis acids, such as $Li^+$, can promote $CO_2$ insertion reactions into transition-metal hydride and methyl bonds.[33] In catalytic carboxylation reactions, this provides a possible role for Lewis acid additives (vide supra). When a THF solution of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ was placed under 1 atm of $CO_2$ in the presence of 2 equiv of $PPh_3$ and 20 equiv of $LiPF_6$, the rate of $CO_2$ insertion increased significantly. All of the $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ was consumed in 20 min, and after the reaction mixture was exposed to acid, the yield of 2,4,6-triisopropylbenzoic acid was 79% (Table 5). To check if the increase in rate was due to a change in the ionic strength of the solution, the reaction was repeated with 20 equiv of $^nBu_4PF_6$ in place of $LiPF_6$. In this case, no rate enhancement was observed. These results demonstrate that $CO_2$ insertion into $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_2H_6)$ is promoted by the presence of $Li^+$, which presumably stabilizes the negative charge which builds up on the incipient carboxylate group in the transition state.[29b,33d] Given the similarities between the calculated transition states for $CO_2$ insertion into $Ni^I$ aryl and alkyl bonds,[28,29] we suggest that this Lewis acid rate enhancement is likely also relevant to carboxylation reactions involving alkyl substrates.

**Formation of a Putative $Ni^I$ Carboxylate Species.**—Monomeric $Ni^I$ carboxylate complexes, formed via the insertion of $CO_2$ into $Ni^I$ organometallic complexes, are proposed as intermediates in all Ni-catalyzed reductive carboxylation reactions of organic halides or pseudohalides, even though there are no structurally characterized examples.[8,34] In an effort to spectroscopically observe a $Ni^I$ carboxylate species, we monitored the reaction of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ with $CO_2$ in the presence of excess $PPh_3$ (vide supra) using NMR and EPR spectroscopy. Upon consumption of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$, no new paramagnetic species were present according to $^1H$ NMR (in THF) or EPR spectroscopy (in 2-MeTHF) in the presence of 20 equiv of LiOTf (Scheme 2, step 1). This suggests that if

$CO_2$ insertion is resulting in a monomeric $Ni^I$ carboxylate it is unstable. Upon complete consumption of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$, the only signals observed in the $^{31}P$ NMR spectrum were consistent with the generation of $(PPh_3)_4Ni^0$ and $(PPh_3)_2Ni^0(\kappa^2\text{-}OCO)$, which is known to form reversibly through the reaction of $(PR_3)_2Ni^0$ complexes with $CO_2$ (see the SI).[35] The observation of these $Ni^0$ products suggests that decomposition of the putative $Ni^I$ carboxylate occurs alongside an electron-transfer process. We hypothesized that the $Ni^I$ carboxylate could undergo a disproportionation reaction to generate 1 equiv of $Ni^0$ and 1 equiv of a $Ni^{II}$ species containing two carboxylate ligands, which was not detected by either NMR or EPR spectroscopy (Scheme 2, step 2). It is possible that the proposed $Ni^{II}$ species was not observed because it is paramagnetic with an integer spin state. This could be caused by the formation of dimeric or higher order species. For example, dimeric $Ni^{II}$ paddlewheel complexes featuring four bridging carboxylate units and a capping phosphine ligand are known.[34]

To explore if the putative $Ni^I$ carboxylate was undergoing disproportionation, we sought to quantify the products. However, since $(PPh_3)_4Ni^0$ exhibits a broad signal by $^{31}P$ NMR spectroscopy that is difficult to integrate accurately, especially in the presence of free $PPh_3$, and we could not spectroscopically observe the proposed $Ni^{II}$ biscarboxylate complex, trapping experiments were designed to quantify the products of disproportionation (Scheme 2). After the reaction between $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ and $CO_2$ had reached full conversion as determined by $^1H$ NMR spectroscopy, $(PPh_3)_2Ni^{II}Br_2$ was added to selectively react with the observed $Ni^0$ products. This resulted in a comproportionation reaction,[36] which generated $(PPh_3)_3Ni^IBr$ in a 74% yield. Two equivalents of $(PPh_3)_3Ni^IBr$ are formed in the comproportionation reaction: 1 equiv from the $Ni^0$ products formed after decomposition of the $Ni^I$ carboxylate and 1 equiv from the $(PPh_3)_2Ni^{II}Br_2$ trapping reagent (Scheme 2, step 3). Therefore, if the trapping reaction is quantitative, 37% of the $Ni^I$ carboxylate species generates $Ni^0$ products after decomposition. Next, LiBr was added to the reaction mixture to react selectively with the proposed $Ni^{II}$ product of disproportionation, the $Ni^{II}$ biscarboxylate complex, through a ligand metathesis reaction. This generated $(PPh_3)_2Ni^{II}Br_2$ in a 41% yield, as well as presumably $Li\{OC(O)(2,4,6\text{-}^iPr_3C_6H_2)\}$, which, when treated with acid, generated 2,4,6-triisopropylbenzoic acid in 83% yield (Scheme 2, step 4). The high mass balance and nearly 1:1 ratio of the trapped $Ni^0$ and $Ni^{II}$ species formed after the reaction of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ with $CO_2$ provide strong evidence for disproportionation as the major decomposition pathway for a putative $Ni^I$ carboxylate species. At this time, the speciation of the proposed $Ni^{II}$ species with two carboxylate ligands remains unclear, although when it is treated with acid it presumably generates 2,4,6-triisopropylbenzoic acid (vide supra). It is possible that this species forms under our catalytic conditions, and if it does form, it is probably an off-cycle species.

Our catalytic results indicate that a halide source is beneficial for high catalytic activity. One potential role of a halide source is to trap the $Ni^I$ carboxylate before it undergoes disproportionation. To probe this hypothesis, $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ was treated with $CO_2$ in THF in the presence of 2 equiv of $PPh_3$ and 20 equiv of LiCl. We expected that the LiCl might allow us to trap the $Ni^I$ carboxylate as the known, stable complex $(PPh_3)_3Ni^ICl$ through a ligand metathesis reaction (Scheme 3). Complete consumption o f $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ was observed in less than 10 min, and $(PPh_3)_3Ni^ICl$ was formed

in 83% yield, alongside a colorless precipitate, which is presumably Li{OC(O)-(2,4,6-$^{i}Pr_3C_6H_2$)}. Subsequent treatment of the reaction mixture with acid generated 2,4,6-triisopropylbenzoic acid in 75% yield, indicating that the Ni that underwent the $CO_2$ insertion was trapped as $(PPh_3)_3Ni^ICl$. These results are consistent with (1) an unstable $Ni^I$ carboxylate complex being a catalytic intermediate; (2) ligand metathesis of a $Ni^I$ carboxylate complex with a metal halide salt to generate $(PPh_3)_3Ni^IX$ and a metal carboxylate salt being a plausible elementary reaction in catalysis, especially given that halide salts are beneficial in catalysis; and (3) ligand metathesis with a halide salt being faster than the decomposition of the putative $Ni^I$ carboxylate via disproportionation (Scheme 2).

Given the apparent instability of $Ni^I$ carboxylate complexes, it was not possible to investigate the ligand exchange reaction of a $Ni^I$ carboxylate with a halide in stoichiometric reactions. We note that several alternative synthetic routes, which did not involve $CO_2$ insertion into a $Ni^I$ aryl complex, were pursued in order to prepare $Ni^I$ carboxylates and did not give tractable products (see SI). However, our catalytic data provide some insight into the ligand substitution reaction. When DMAP-OED is used as the reductant in the presence of a halide source but in the absence of a Lewis acid, no catalytic activity was observed (Table 3). Although the Lewis acid assists with $CO_2$ insertion, we have shown that $CO_2$ insertion can still occur in the absence of a Lewis acid, albeit at a slower rate (vide supra). It is, therefore, surprising that almost no product is generated in catalysis without a Lewis acid. In fact, these results suggest that the Lewis acid also helps with another step in catalysis. Previous computational studies have suggested a strong Lewis acid–base interaction between the $Mg^{2+}$ cation of $MgCl_2$ with the noncoordinated oxygen atom of a $\kappa^1$-carboxylate ligand on a $Ni^I$ center supported by two tricyclopentylphosphine ligands.[28] These calculations suggest that a cationic Lewis acid may play a role in catalysis by stabilizing the $Ni^I$ carboxylate intermediate toward disproportionation. Additionally, Lewis acids have been shown to interact with $\kappa^1$-carboxylate ligands and to induce a change in binding mode of carboxylate ligands from $\kappa^2$ to $\kappa^1$, both of which can lead to changes in reactivity or reduction potential (see the reductant screen section in the SI for further discussion).[37] At this stage, we do not have enough evidence to unequivocally determine whether Lewis acids are playing a role in altering the reactivity of the putative $Ni^I$ carboxylate in our systems but in light of our results this hypothesis seems plausible.

In Tsuji's mechanism for the carboxylation of aryl halides, it is proposed that a $Ni^I$ carboxylate is directly reduced during catalysis (Figure 2). Our catalytic results indicate that when a strong reductant such as $Cp^*_2Co$ is used, turnover is observed in the absence of a Lewis acid. This suggests that direct reduction of a $Ni^I$ carboxylate can occur under strong reducing conditions. However, when a weaker reductant such as DMAP-OED is used, catalytic activity is only observed in the presence of a Lewis acid and higher yields are obtained when a halide source is present. Therefore, we suggest that DMAP-OED is not a strong enough reductant to reduce the $Ni^I$ carboxylate intermediate by itself. As a consequence, with DMAP-OED and weaker reductants, reduction only occurs if the $Ni^I$ carboxylate is primed for reduction by a Lewis acid (vide supra). In agreement with this hypothesis, weaker reductants can be utilized in catalysis in the presence of a Lewis acid (see the SI). Additionally, if a halide source is present the $Ni^I$ carboxylate can be converted

into a $Ni^I$ halide, which is presumably easier to reduce, and leads to the best catalytic performance. Our studies provide insight into the role of a putative $Ni^I$ carboxylate intermediate in catalysis; however, a well-defined system, which will likely be difficult to synthesize, is required to rigorously investigate the structure and reactivity of $Ni^I$ carboxylate complexes.

**Revised Mechanistic Proposal.**—Based on our catalytic and stoichiometric studies, we propose a modified catalytic cycle for the nickel catalyzed reductive carboxylation of aryl chlorides compared to that typically proposed in the literature (Figure 3). Initially, precatalyst activation of $(PPh_3)_2Ni^{II}Cl_2$ occurs through reduction with $Mn^0$, which requires $Et_4NI$, to generate a catalytically active $Ni^0$ species and $MnCl_2$. The formation of $MnCl_2$ is crucial because it subsequently acts as a catalytically beneficial Lewis acid and halide source in catalysis. The catalytically active $Ni^0$ species is in equilibrium with $(PPh_3)_4Ni^0$ due to the presence of excess $PPh_3$. We propose that $(PPh_3)_4Ni^0$ is the catalyst resting state, which must lose one or more $PPh_3$ ligands to generate the catalytically active $Ni^0$ species. This $Ni^0$ species undergoes oxidative addition with the aryl chloride electrophile to generate a $(PPh_3)_2Ni^{II}(Ar)$-(Cl) intermediate, which is reduced by one electron by $Mn^0$ to generate a highly reactive $(PPh_3)_nNi^I(Ar)$ species. The $Ni^I$ aryl species is unstable but the presence of free $PPh_3$ decreases the rate of its decomposition. In the key step, $CO_2$ inserts into $(PPh_3)_nNi^I(Ar)$ to generate a new C–C bond. This process is assisted by the presence of a Lewis acid, which increases the rate of insertion. The product of $CO_2$ insertion is presumably a $Ni^I$ carboxylate, which is highly unstable. At this point the mechanism diverges and the $Ni^I$ carboxylate can undergo two different processes. First, in the presence of a strong reductant, such as $Mn^0$, direct reduction of the $Ni^I$ carboxylate regenerates the catalytically active $Ni^0$ species and releases the carboxylated product from the Ni center. It is likely that in the presence of a Lewis acid there is a decrease in required reducing power for this elementary reaction, so weaker reductants can be used with a Lewis acid. Alternatively, the $Ni^I$ carboxylate can undergo a ligand metathesis reaction with a halide source to generate a more stable $(PPh_3)_3Ni^ICl$ intermediate and release the carboxylated product from the Ni center. The $Ni^I$ halide complex, $(PPh_3)_3Ni^ICl$, is readily reduced by $Mn^0$ to regenerate the active $Ni^0$ species. We suggest that our revised mechanism is likely to be general to nickel-catalyzed reductive carboxylations of other organic halides and pseudohalides and possibly to the broader field of cross-electrophile coupling, where Lewis acids and halide sources are also commonly used.[16,32] Additionally, our revised mechanism provides guidance on how to improve reductive carboxylation reactions, a topic which is addressed in the following section.

## Development of an Improved System for the Carboxylation of Aryl Halides and Pseudohalides.

**Optimization of Reaction Conditions in DMI.**—As described in the Introduction, there are several major limitations associated with the conditions and reagents typically used in Ni-catalyzed reductive carboxylation reactions. Our discovery that DMAP-OED can be used as the reductant instead of the combination of $Mn^0/Et_4NI$ has several advantages beyond the fact that it is a homogeneous reductant. Specifically, when DMAP-OED is used as the reductant instead of $Mn^0/Et_4NI$: (1) only a slight excess of the reductant is required,

(2) the substrate scope is expanded to include *ortho* substituted aryl chloride substrates, and (3) there is a greater range of additives and ancillary ligands that can promote the carboxylation reaction, which provides more opportunities to improve the reaction conditions (see the SI for more details). For example, when (dppf)Ni$^{II}$Cl$_2$, a complex featuring a bidentate ancillary ligand, was used as the precatalyst for the carboxylation of 4-chloroanisole with Mn$^0$/Et$_4$NI as the reductant under Tsuji's conditions, no product was observed (see SI). In contrast, when (dppf)Ni$^{II}$Cl$_2$ was used as the precatalyst for the same reaction using DMAP-OED as the reductant and MnCl$_2$ as an additive it outperformed the literature precatalyst (PPh$_3$)$_2$Ni$^{II}$Cl$_2$. In light of these findings, a system for carboxylation was optimized in DMI using (dppf)Ni$^{II}$Cl$_2$ as the precatalyst, near-stoichiometric equivalents of DMAP-OED as the reductant, and a slight excess of LiCl as a cost-effective additive for the carboxylation of 4-chloroanisole (see the SI for the full optimization). Notably, the reaction proceeded with high yields in the absence of excess ligand, which the Tsuji system required for high selectivity.[8a] In fact, under our optimized conditions, high yields could be obtained with catalyst loadings as low as 1 mol %, which is the lowest catalyst loading reported for a reductive carboxylation reaction of any organic halide or pseudohalide (Figure 4a). Addition-ally, at 5 mol % catalyst loading reaction times could be reduced to 30 min, which is the shortest reported time for any catalytic reductive carboxylation reaction (Figure 4b). These results demonstrate that despite the higher cost of DMAP-OED compared to heterogeneous reductants such as Mn$^0$ or Zn$^0$, there is a clear improvement in the catalyst loading and reaction time when using DMAP-OED in combination with ancillary ligands and additives that are incompatible with Mn$^0$ or Zn$^0$. As a result, our findings should translate well to the synthesis of high value products such as the incorporation of $^{13}$C- and $^{14}$C-labeled carbon atoms into pharmaceutically relevant molecules via reductive carboxylation recently described by Baran et al.[38]

**Role of Amide-Containing Solvents in Catalysis.**—The most significant synthetic challenge associated with reductive carboxylation reactions is the requirement of an amide-based solvent. In fact, every reductive carboxylation reaction of an organic halide or pseudohalide reported to date has been performed in a highly undesirable amide-based solvent.[8–11] Therefore, we sought to understand the critical nature of amide-based solvents in catalysis. As part of our mechanistic work, we established that the MnCl$_2$ generated in situ upon oxidation of Mn$^0$ plays a critical role in catalysis. Similarly, when DMAP-OED was used as the reductant, addition of MnCl$_2$ (or a related soluble alkali metal salt) was necessary for appreciable amounts of product to be formed. However, while MnCl$_2$ is highly soluble in amide-based solvents such as DMI, it is only sparingly soluble in more synthetically desirable solvents such as THF. On this basis, we hypothesized that the reason catalytic activity is not observed in non-amide-based solvents is because the MnCl$_2$, which is both the required Lewis acid and halide source in carboxylation, is not soluble in these solvents. Our previous results showed that simple alkali metal salts such as LiCl, which are soluble in THF, can be used instead of MnCl$_2$ to promote carboxylation in DMI. Given these results, we performed a carboxylation reaction in THF using 4-chloroanisole as the substrate, (dppf)Ni$^{II}$Cl$_2$ as the precatalyst, DMAP-OED as the reductant, and LiCl as the additive. Consistent with our hypothesis the reaction was successful and an 86% yield of 4-anisic was obtained (Figure 5). *This reaction is the first reported example of a successful*

*reductive carboxylation of any organic halide or pseudohalide performed in a non-amide-containing solvent.* Interestingly, with the proper choice of additive (LiI), catalysis can also be performed in THF using $Mn^0$ as the electron source (see SI). It is likely that our observation that carboxylation reactions involving aryl halides can be performed in non-amide-containing solvent if the Lewis acid and halide sources are soluble extends to other reductive carboxylation reactions. As a result, our method of employing DMAP-OED as a reductant and LiCl as an additive may be a broadly applicable strategy for performing this class of reactions in more synthetically desirable solvents. Additionally, since reductive carboxylation reactions involve related intermediates to those invoked in other reductive coupling reactions, such as $sp^3$–$sp^2$ couplings, DMAP-OED may also find utility as a reductant in the broader class of cross-electrophile coupling.[16]

**Substrate Scope.—**Using $(dppf)Ni^{II}Cl_2$ as the precatalyst, DMAP-OED as the reductant, and LiCl as an additive, the scope of the reaction was explored in THF (Figure 6). Aryl chlorides containing both electron-donating and -withdrawing groups were carboxylated in high yields (1a–c). Aryl chlorides bearing simple electron-donating groups, such as 4-chloroanisole, could be carboxylated at 2.5 mol % catalyst loadings at 25°C, whereas elevated temperatures and catalyst loadings were required for substrates with electron-withdrawing groups. The carboxylation of *ortho*-substituted aryl bromides,[8n,9a,d] iodides,[11] and triflates[8g] have been reported; however, carboxylation of less expensive and more commercially available aryl chlorides bearing *ortho* substitution had not been successful. To this end, in contrast to Tsuji's carboxylation system,[8a] our system is able to carboxylate *ortho*-substituted aryl chloride electrophiles for the first time owing to the use of the homogeneous reductant DMAP-OED (vide supra). In fact, both mono-*ortho*-substituted aryl chlorides and di-*ortho*-substituted aryl bromides were carboxylated in good yields (1d–f). A reaction with a di-*ortho*-substituted aryl chloride was unsuccessful. Pseudohalide electrophiles, including synthetically valuable phenol derivatives, were readily carboxylated under our reaction conditions. For example, similar to Tsuji's initial report,[8a] phenyl triflate and tosylate could be carboxylated to benzoic acid in good yields (1g, 1h), with successful reactions of phenyl triflate occurring at 25 °C with a catalyst loading of 2.5 mol %. Additionally, aryl sulfamates and pivalates could be carboxylated in moderate yields (1i, 1j). Martin also demonstrated carboxylation of 1j;[8c] however, this is the first report of a sulfamate electrophile, which can be used as a directing group for C–H activation of aryl substrates,[36c] being utilized in any cross-electrophile coupling reaction, demonstrating the broad applicability of our system to various pseudohalide substrates.

Although our $(dppf)Ni^{II}Cl_2$ precatalyst is effective for the carboxylation of a range of sterically congested aryl halide electrophiles, low selectivity is observed when using a substrate with a functional group, such as an ester. In this reaction, a significant amount of biaryl homocoupling product is formed from the electrophile. We observed that, in this case, using Tsuji's precatalyst and 2 equiv of $PPh_3$ in place of $(dppf)Ni^{II}Cl_2$ provides higher selectivity for the desired carboxylated product over the biaryl product. We suggest that this difference in selectivity arises because of the stabilizing effect that excess $PPh_3$ has on $(PPh_3)_2Ni^{II}(Ar)(Cl)$ and $(PPh_3)_nNi^I(Ar)$ intermediates in catalysis (vide supra). This effect is not observed when using an excess of the bidentate ligand dppf and the $(dppf)Ni^{II}Cl_2$

precatalyst. Using Tsuji's precatalyst, we are able to carboxylate an aryl chloride bearing an ester functional group (1l), which suggests that the high chemoselectivity that has been observed in reductive carboxylation reactions in amide-based solvents with metallic reductants is preserved when performing the same reactions in THF with an organic reductant.

The observation that Tsuji's precatalyst is effective under our newly developed conditions, with an organic reductant and non-amide-containing solvent, is significant, as it raises the possibility that our conditions may be directly translatable to carboxylation reactions with other substrates that are facilitated by different catalysts. This would enable us to carboxylate a range of substrates without needing to fully reoptimize the system to accommodate the organic reductant, LiCl additive, and change in solvent. To explore this hypothesis, we performed catalysis with the $sp^3$-hybridized substrate 9-bromofluorene (1m), using the literature precatalyst $((PCy_3)_2Ni^{II}Cl_2)$ under our conditions.[8b] The desired carboxylic acid was isolated in 51% yield, which is comparable to the yield previously reported in the literature (60%). This result suggests that previous work identifying the optimal metal–ligand combination for a specific carboxylation reaction using metallic reductants and amide containing solvents can simply be translated to our new conditions, which are potentially broadly applicable for performing reductive carboxylation reactions under more synthetically desirable conditions.

## CONCLUSIONS

In this work, we have used a model system to study the mechanism of nickel-catalyzed carboxylation reactions of organic halides and pseudohalides. Our results explain why certain reagents and additives are required for catalysis. For instance, we show that in previous examples of nickel-catalyzed carboxylation reactions involving aryl halides, heterogeneous reductants, such as $Mn^0$ or $Zn^0$, were required because they generate $MnCl_2$ or $ZnCl_2$ salts upon oxidation, which act as necessary sources of a Lewis acid and halide in catalysis. The Lewis acid assists with $CO_2$ insertion, which we demonstrate by establishing that Lewis acids increase the rate of $CO_2$ insertion into a $Ni^I$ aryl complex to generate a carboxylic acid (after workup). The halide source is proposed to undergo a ligand-exchange reaction and facilitate reduction of the proposed $Ni^I$ carboxylate to $Ni^0$, which regenerates the active catalyst. On the basis of these experiments, we propose a revised mechanism for carboxylation in which we have strong evidence for most of the elementary reactions and an understanding of the factors that are important for promoting catalysis. In the case of nickel-catalyzed carboxylation of aryl halides, we used our mechanistic insight into provide strategies to address many of the current challenges associated with these reactions. For example, by using LiCl as a cost-effective additive, which provides both a Lewis acid and halide source, we can, for the first time, perform catalysis using a stoichiometric amount of an easily prepared solid organic reductant instead of a vast excess of a heterogeneous metallic reductant. The use of a homogeneous organic reductant should allow carboxylation reactions to be performed on scale in situations where the use of heterogeneous reductants is problematic. Additionally, by using LiCl as an additive, we can perform catalytic reactions in non-amide-based solvents, such as THF, because the required Lewis acid and halide source is now soluble under the reaction conditions. The fact that previous systems for

carboxylation could only operate in non-amide-based solvents was a major limitation and our advance should also assist in making carboxylation reactions more practical. Our mechanistic studies have also enabled us to lower the catalyst loadings required and increase the substrate scope. Furthermore, in preliminary studies we have demonstrated that our use of an organic reductant in a non-amide-based solvent is generalizable to carboxylation reactions involving alkyl halides. This suggests that it may be possible to apply our findings to many other carboxylation reactions. Finally, our results are likely also relevant to cross-electrophile coupling reactions that do not involve $CO_2$, as the use of superstoichiometric amounts of metallic reductants has also been a problem in these reactions. In the future, our laboratory intends to more fully evaluate the scope of cross-electrophile coupling reactions that can be facilitated through the combination of a solid organic reductant and soluble Lewis acid source.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENTS

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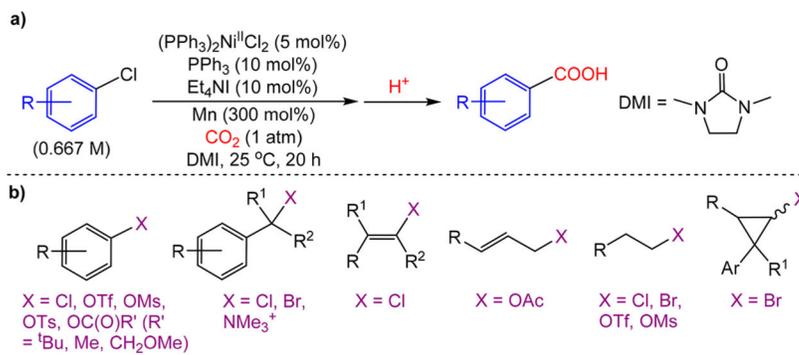
**Figure 1.**
(a) Generic scheme showing Tsuji's carboxylation of aryl halides. (b) Range of electrophiles that can be used in Ni-catalyzed carboxylation reactions.
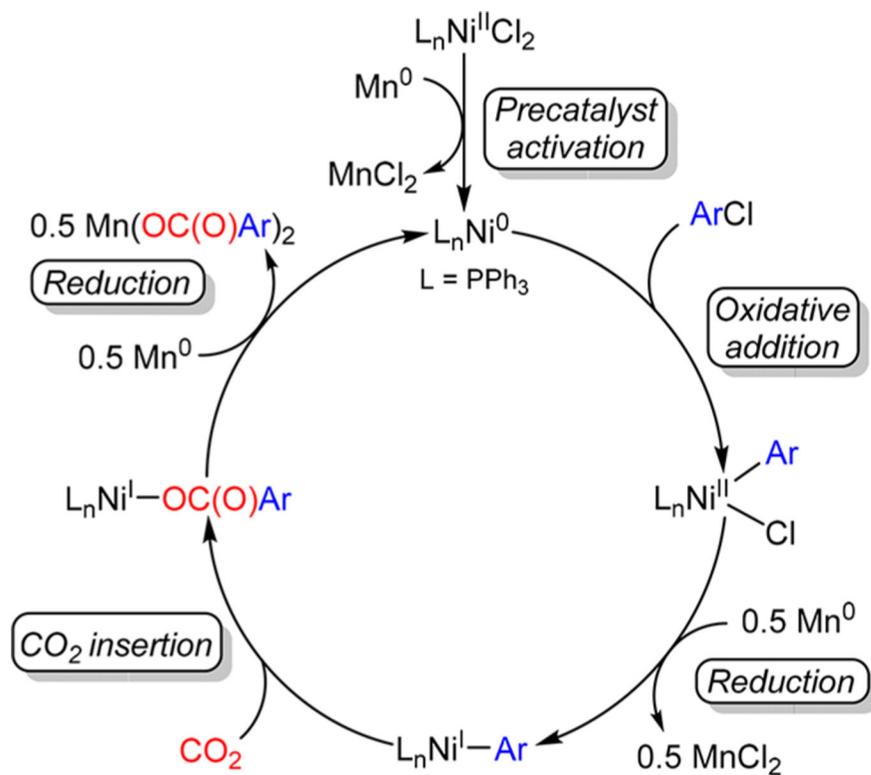
**Figure 2.**
Proposed catalytic cycle for the carboxylation of aryl chlorides using $(PPh_3)_2Ni^{II}Cl_2$.
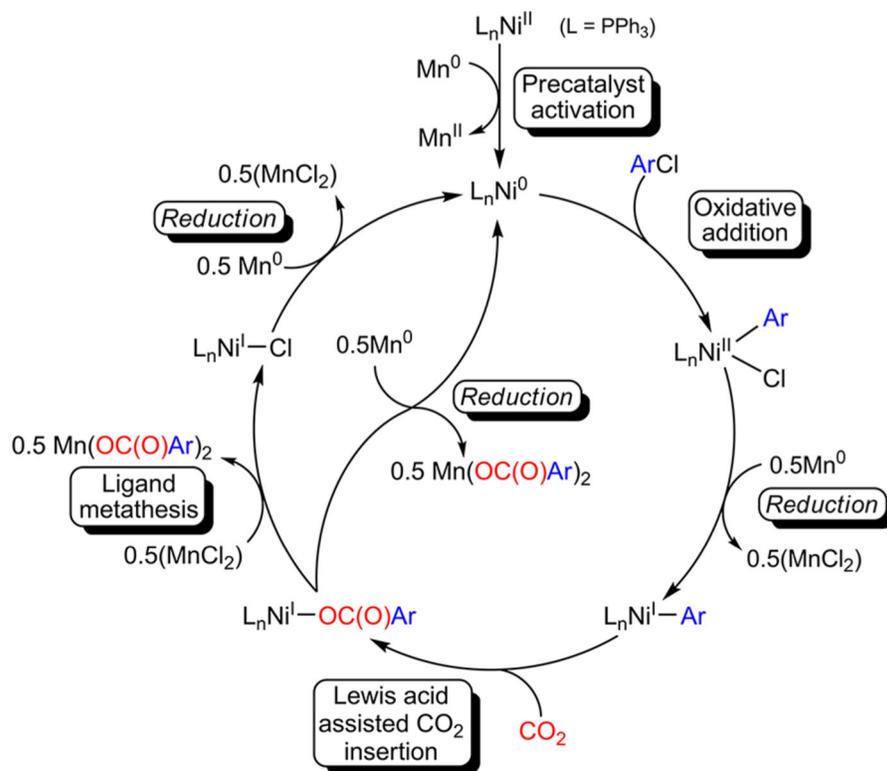
**Figure 3.**
Revised catalytic cycle for the carboxylation of aryl chlorides with $(PPh_3)_2Ni^{II}Cl_2$ and $Mn^0$ as the reductant.
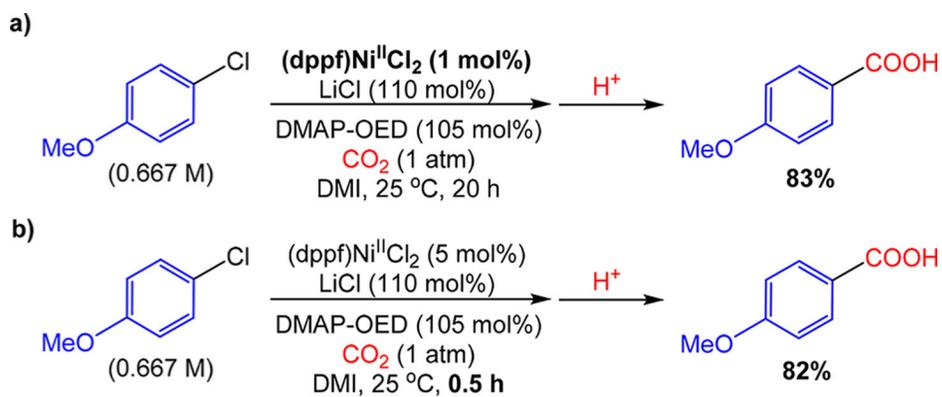
**Figure 4.**
Carboxylation of 4-chloroanisole (0.25 mmol) with $CO_2$ (1 atm) using DMAP-OED (105 mol %) as the reductant and LiCl (110 mol %) as an additive in DMI (0.375 mL) at 25 °C under optimized reaction conditions for (a) low catalyst loadings (1 mol % (dppf)Ni$^{II}$Cl$_2$ for 20 h) and (b) short reaction times (5 mol % (dppf)Ni$^{II}$Cl$_2$ for 0.5 h). Yields are reported as the average of two trials and were determined by integration of $^1$H NMR spectra against a hexamethylbenzene external standard.
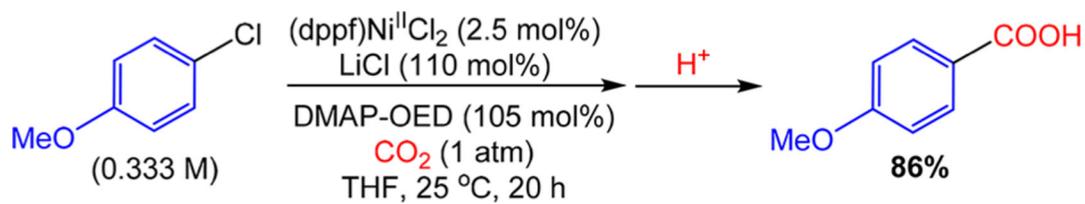
**Figure 5.**
Carboxylation of 4-chloroanisole (0.25 mmol) with $CO_2$ (1 atm) using (dppf)Ni$^{II}$Cl$_2$ (2.5 mol %) as the precatalyst, DMAP-OED (105 mol %) as the reductant, and LiCl (110 mol %) as an additive in THF (0.75 mL) at 25 °C for 20 h. Volume of THF was increased to accommodate LiCl solubility. Yields are reported as the average of two trials and were determined by integration of $^1$H NMR spectra against a hexamethylbenzene external standard.
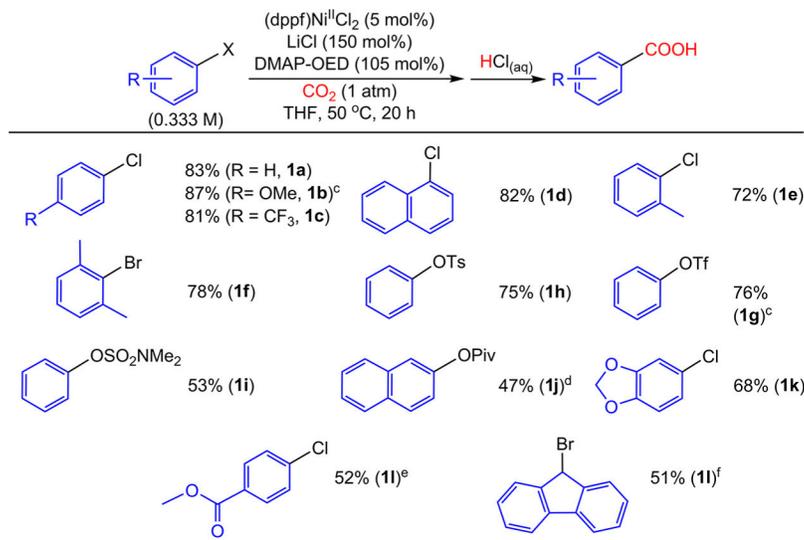
**Figure 6.**
Isolated yields of products for the carboxylation of aryl halides and pseudohalides. (a) Yields are reported as the average of two trials. (b) Reaction conditions: substrate (0.25 mmol), (dppf)Ni$^{II}$Cl$_2$ (0.0125 mmol), LiCl (0.375 mmol), DMAP-OED (0.2625 mmol), CO$_2$ (1 atm) in THF (0.750 mL) at 50 °C for 20 h. (c) (dppf)Ni$^{II}$Cl$_2$ (0.00625 mmol) at 25 °C. (d) (dppf)Ni$^{II}$Cl$_2$ (0.025 mmol) for 40 h. (e) (PPh$_3$)$_2$Ni$^{II}$Cl$_2$ (0.0125 mmol) and PPh$_3$ (0.025 mmol) instead of (dppf)Ni$^{II}$Cl$_2$. (f) (PCy$_3$)$_2$Ni$^{II}$Cl$_2$ (0.025 mmol) instead of (dppf)Ni$^{II}$Cl$_2$.
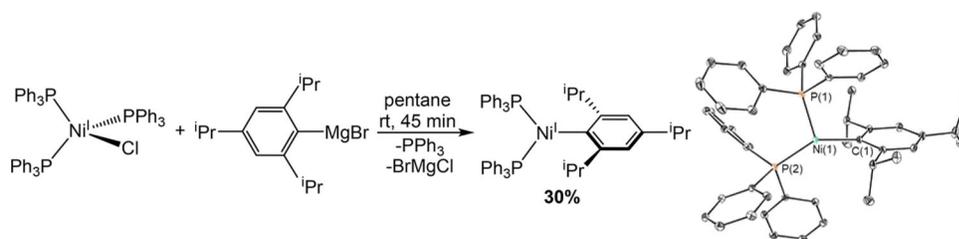
**Scheme 1.**
Synthesis and ORTEP of $(PPh_3)_2Ni^I(2,4,6-^iPr_3C_6H_2)^a$
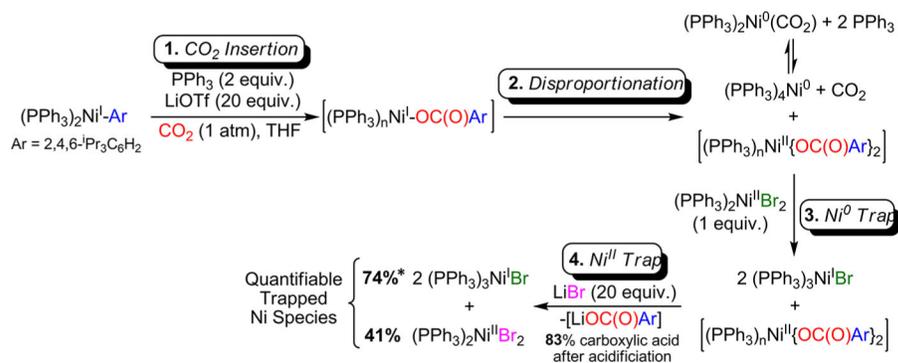
**Scheme 2.**

Proposed Decomposition of a Putative Ni$^I$ Carboxylate Formed from the Reaction of (PPh$_3$)$_2$Ni$^I$(2,4,6-$^i$Pr$_3$C$_6$H$_2$) with CO$_2$ and Trapping Experiments of the Proposed Decomposition Products[a]
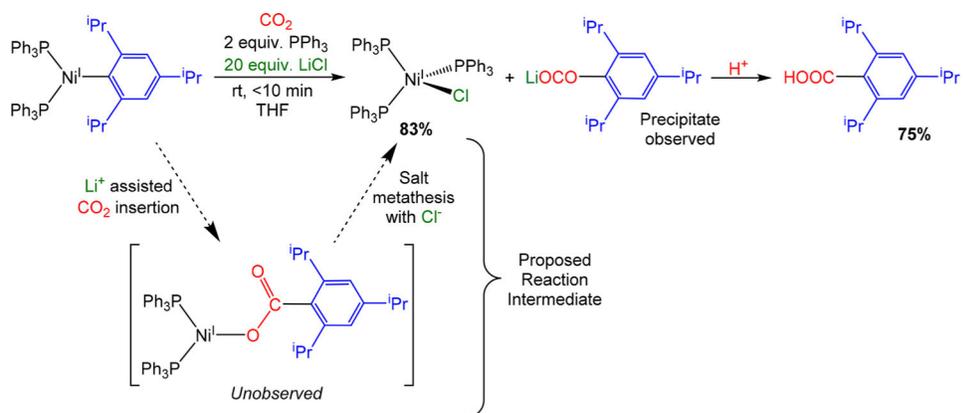
**Scheme 3.**
Reaction of $(PPh_3)_2Ni^I(2,4,6-^iPr_3C_6H_2)$ with $CO_2$ in the Presence of LiCl and Proposed Reaction Pathway

**Table 1.**

Carboxylation of 4-Chloroanisole with $CO_2$ Using $PPh_3$-Supported Nickel Precatalysts in Different Oxidation States[a]



| Ni source | $PPh_3$[b] (mol %) | yield[c] (%) |
|---|---|---|
| $(PPh_3)_2Ni^{II}Cl_2$ | 10 | 76 |
| $(PPh_3)_3Ni^{I}Cl$ | 5 | 73 |
| $(PPh_3)_4Ni^{0}$ | 0 | 51 |
| $(PPh_3)_4Ni^{0}$ with 5 mol % $MnCl_2$ | 0 | 81 |

[a]Reaction conditions: 4-chloroanisole (0.25 mmol), Ni source (0.0125 mmol), PPh3 (Ni[II]: 0.025 mmol; NiI: 0.0125 mmol; Ni0: 0 mmol), Et4NI (0.025 mmol), Mn (0.75 mmol), $CO_2$ (1 atm) in DMI (0.375 mL) at 25 °C for 20 h.

[b]Added PPh3 was varied to maintain a 4:1 ratio of PPh3 /Ni across reactions.

[c]Yields are reported as the average of two trials and were determined by integration of ^{1}H NMR spectra against a hexamethylbenzene external standard.

**Table 2.**

Carboxylation of 4-Chloroanisole with $CO_2$ Using a Variety of Reductants of Differing Strength under Various Reaction Conditions[a]
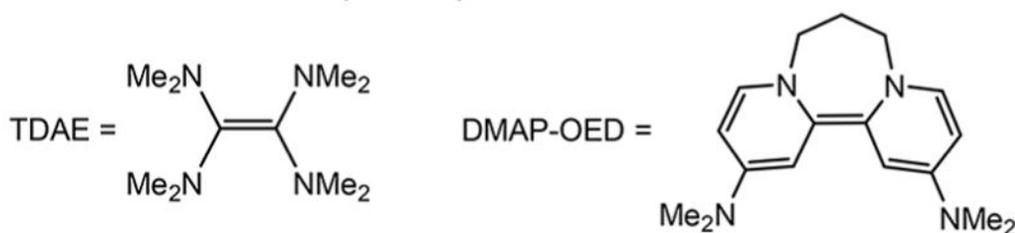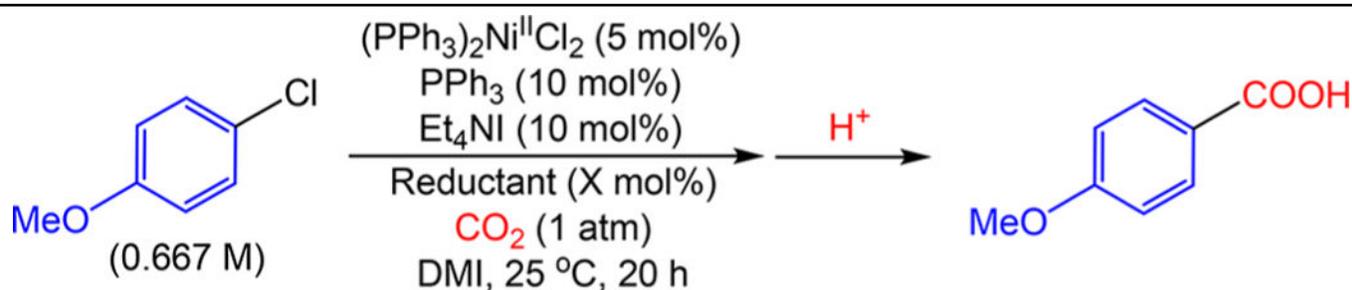


| homogeneous reductant | $E°^d$ (V) | yield[f] (%) | yield without Et4NI[f] (%) | yield without Et4NI and with 100 mol % MnCl2[f] (%) |
|---|---|---|---|---|
| Cp*2Co | −1.16[18] | 40 | 36 | 83[g] |
| DMAP-OED | −1.00[19] | <1 | 7 | 62[h] |
| Cp2Co | −0.67[20] | 1 | 1 | 34 |
| TDAE | −0.57[21] | 0 | 1 | <1 |
| heterogeneous reductant | $E°^e$ (V) | yield (%)[f] | yield without Et4NI[f] (%) | yield with Et4NI and 100 mol % MnCl2[f] (%) |
| Mn0 | −1.19[22] | 76 | <1 | 86 |
| Zn0 | −0.76[22] | 12 | 3 | 35 |

[a]Reaction conditions: 4-chloroanisole (0.25 mmol), (PPh3)2Ni$^{II}$Cl2 (0.0125 mmol), PPh3 (0.025 mmol), Et4NI (0 or 0.025 mmol), reductant (see fnts [b] and [c]), CO2 (1 atm) in DMI (0.375 mL) at 25 °C for 20 h.

[b]When using homogeneous reductants a stoichiometric number of electron equivalents was added relative to 4-chloroanisole and (PPh3) Ni$^{II}$Cl2 (which presumably needs to be reduced as part of the activation process): Cp*2Co and Cp2Co (0.525 mmol, 210 mol %), DMAP-OED and TDAE (0.2625 mmol, 105 mol %).

[c]Three equivalents of electrons relative to 4-chloroanisole was added when using heterogeneous reductants: Zn0 and Mn0 (0.75 mmol, 300 mol %).

[d]Values reported in DMF vs NHE.

[e]Values reported as potentials at the metal surface vs NHE.

[f]Yields are reported as the average of two trials and were determined by integration of $^1$H NMR spectra against a hexamethylbenzene external standard.

[g]Control experiments showed that Cp*$_2$Co could not reduce MnCl$_2$ in DMI, as determined by ^{1}H NMR spectroscopy.

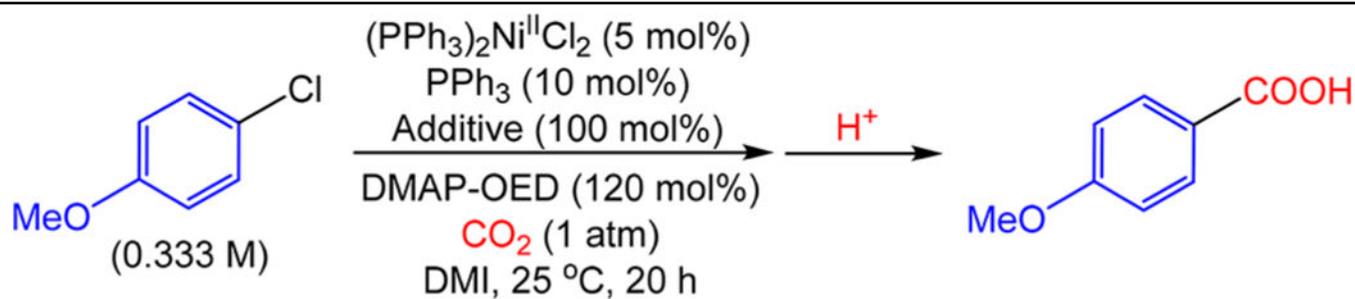[h]Control experiments showed no catalysis in the absence of a Ni catalyst.

**Table 3.**

Carboxylation of 4-Chloroanisole with $CO_2$ Using Various Additives[a,b]



| additive | yield[c] (%) |
|---|---|
| $MnCl_2$ | 68 |
| LiCl | 68 |
| LiBr | 67 |
| LiOTf | 15 |
| $LiPF_6$ | 14 |
| $LiBF_4$ | 36 (23[d]) |
| $^nBuBr$ | 3 |
| $B(OPh)_3$ | 17 |
| $B(OPh)_3$ with 100 mol % $^nBu_4Br$ | 44 |

[a]Reaction conditions: 4-chloroanisole (0.25 mmol), $(PPh_3)_2Ni^{II}Cl_2$ (0.0125 mmol), $PPh_3$ (0.025 mmol), DMAP-OED (0.30 mmol), $CO_2$ (1 atm) in DMI (0.750 mL) at 25 °C for 20 h.

[b]Reactions were performed at more dilute concentrations to ensure additive solubility and with a slight excess of reductant to ensure it was not the limiting reagent.

[c]Yields are reported as the average of two trials and were determined by integration of $^1H$ NMR spectra against a hexamethylbenzene external standard.

[d]Reaction performed with 5 mol % $(PPh_3)_4Ni^0$ (0.0125 mmol) in place of $(PPh_3)_2Ni^{II}Cl_2$ and $PPh_3$.

**Table 4.**

Carboxylation of 2-Chlorotoluene with $CO_2$ Using $Mn^0/Et_4NI$ and DMAP-OED Reductants[a]
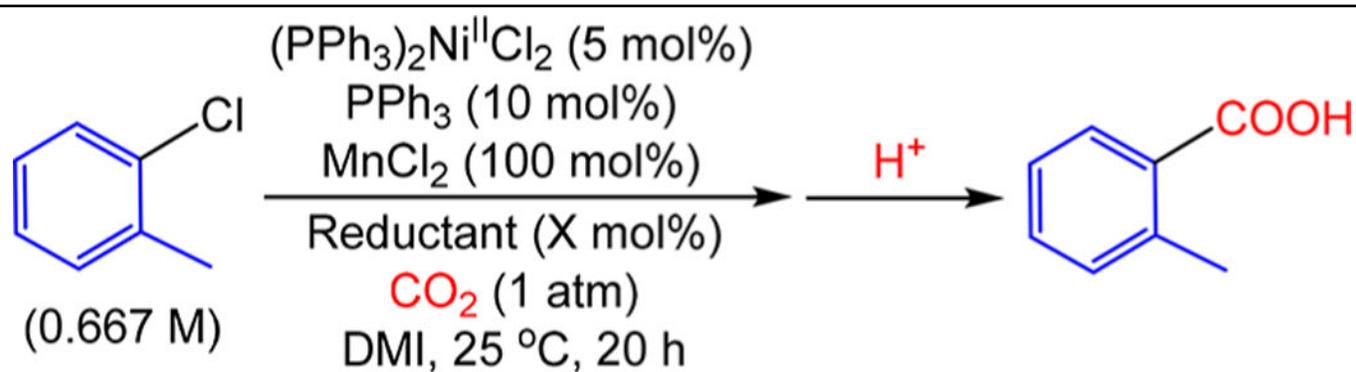


| reductant | yield[d] (%) |
|---|---|
| $Mn^0/Et_4NI$[b] | 0 |
| DMAP-OED[c] | 53 |

[a]Reaction conditions: 2-chlorotoluene (0.25 mmol), $(PPh_3)_2Ni^{II}Cl_2$ (0.0125 mmol), $PPh_3$ (0.025 mmol), reductant (see fnts [b] and [c]), $CO_2$ (1 atm) in DMI (0.375 mL) at 25 °C for 20 h.

[b]300 mol % $Mn^0$ (0.75 mmol) and 10 mol % $Et_4NI$ (0.025 mmol) were utilized.

[c]105 mol % DMAP-OED (0.2625 mmol) was utilized.

[d]Yields are reported as the average of two trials and were determined by integration of $^1H$ NMR spectra against a hexamethylbenzene external standard.

**Table 5.**

Time required for Complete Consumption of $(PPh_3)_2Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ under 1 atm of $CO_2$ in the Presence of Different Additives[a]
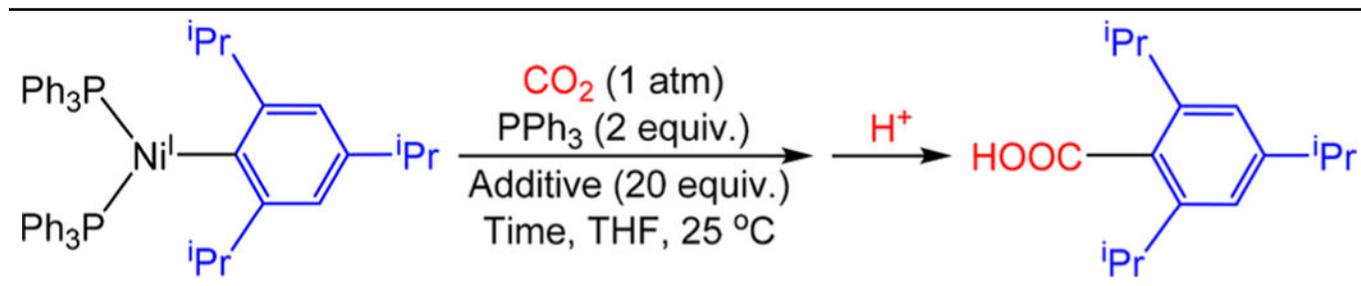


| additive | time[b] (h) | yield[c] (%) |
|---|---|---|
| none | 5 | 78 |
| $LiPF_6$ | 0.33 | 79 |
| $^nBuPF_6$ | 5 | 86 |

[a]Reaction conditions: $(PPh_3)_2$ $Ni^I(2,4,6\text{-}^iPr_3C_6H_2)$ (0.0032 mmol), $PPh_3$ (0.0064 mmol), additive (0.064 mmol), $CO_2$ (1 atm) in THF (0.50 mL) at 25 °C.

[b]Time until consumption of starting material.

[c]Yields were determined by integration of $^1H$ NMR spectra against a hexamethylbenzene external standard.