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New trends and applications in carboxylation for isotope chemistry

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Carboxylations are an important method for the incorporation of isotopically labeled $^{14}CO_2$ into molecules. This manuscript will review labeled carboxylations since 2010 and will present a perspective on the potential of recent unlabeled methodology for labeled carboxylations. The perspective portion of the manuscript is broken into 3 major sections based on product type, arylcarboxylic acids, benzylcarboxylic acids, and alkyl carboxylic acids, and each of those sections is further subdivided by substrate.

KEYWORDS
[^{14}C]carbon dioxide, ^{14}C carboxylation, ^{14}C labeling, carbon-14

1 | INTRODUCTION

The common precursor for the synthesis of all ^{14}C-labeled compounds is $Ba^{14}CO_3$. $Ba^{14}CO_3$ can be converted to numerous useful starting materials including ^{14}C cyanides and ^{14}C acetylene, but arguably, the most used of the ^{14}C reagents is $^{14}CO_2$. It can be reduced to afford ^{14}CO, $H^{14}CO_2H$, $H^{14}CHO$, or $^{14}CH_3OH$, and from these, many other 1-carbon synthons can be prepared including $^{14}CH_3I$, $^{14}COCl_2$, and $^{14}CH_3NO_2$. $^{14}CO_2$ can also be used directly to give ^{14}C-labeled carboxylic acids such as ^{14}C-labeled acetate or benzoic acids. This perspective will focus on recent ^{14}C carboxylations and modern methodology that could be applied to ^{14}C carboxylations. Carboxylic acids can also be formed in 1 step via carbonylation, but that will not be considered in this review. Neither will multiple step processes such as cyanation followed by hydrolysis or formylation followed by oxidation. This topic has not been reviewed previously, but a monograph on the synthesis of tritium and ^{14}C-labeled compounds does cover the traditional carboxylation techniques.[1] In addition, there are several literature reviews covering carboxylations which are of potential use in radiochemical applications.[2-4] While this manuscript focuses on the use of $^{14}CO_2$, the methods described could also be applied to $^{13}CO_2$. The focus on $^{14}CO_2$ is intentional as the need to adhere to the use of stoichiometric or near stoichiometric amounts of CO_2 is more critical for C-14 than for C-13 because of the cost of the reagent and the radiochemical waste produced.

2 | HANDLING OF $^{14}CO_2$

$Ba^{14}CO_3$ can be converted to $^{14}CO_2$ by treatment with H_2SO_4[5] or by heating with $PbCl_2$.[6] The later method leads to heavy metal radioactive waste, which is best avoided. Once liberated, $^{14}CO_2$ can easily be manipulated because it is highly volatile (BP −78°C) but has a low vapor pressure when cooled in liquid nitrogen (−196°C).[7] In 2001, Bannwart and coworkers reported a $^{14}CO_2$ manifold system which greatly facilitates the handling of $^{14}CO_2$.[8] The manifold uses $^{14}CO_2$ absorbed on molecular sieves

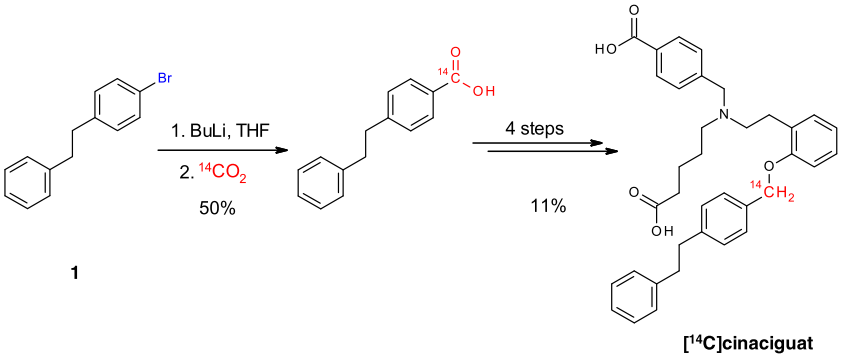
which is stored at room temperature. The $^{14}CO_2$ can be liberated by heating the sieves, and the excess $^{14}CO_2$ can be retrapped onto the molecular sieves. The molecular sieve reservoir is attached to a stainless steel manifold which can be evacuated to very low pressures. The $^{14}CO_2$ released into the manifold can be accurately measured and quantified and the specified amount easily transferred into a reaction flask. This avoids the need to generate $^{14}CO_2$ each time a reaction is run. The manifold greatly improved the speed and efficiency of ^{14}C carboxylation reactions and greatly facilitates reaction optimization. At the same time, it reduces the waste generated by the reaction as the radioactive sulfuric acid waste is only generated when loading the manifold with $^{14}CO_2$ (if $^{14}CO_2$ is not used directly).

3 | RECENT CARBOXYLATIONS USING $^{14}CO_2$

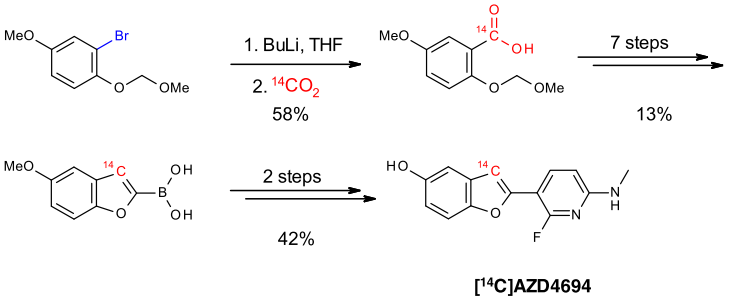
Carboxylation using $^{14}CO_2$ has long been known,[5,9] and it remains a frequently used methodology for the incorporation of ^{14}C into molecules.[1] This is in part because of the robust nature of the reaction, the simplicity of the reaction design, and the relatively low cost of $^{14}CO_2$ compared to other ^{14}C starting materials. Traditional carboxylation reactions—coupling of organolithium or Grignard reagents with CO_2—require harsh reaction conditions thereby requiring early installation of the ^{14}C because of functional group incompatibility. For example, Seidel and Pleiss recently reported the synthesis of [^{14}C]cinaciguat in which bromide **1** was lithiated and the organolithium carboxylated with $^{14}CO_2$ (Scheme 1).[10] The resulting acid was converted to the target compound in 4 steps.

The relative low cost of $^{14}CO_2$ allows for earlier introduction of the ^{14}C label than would otherwise be considered. For example, in a recent report of the synthesis of [^{14}C]AZD4694, a synthesis with 10 radioactive steps and 5% overall yield is reported (Scheme 2).[11] Such a lengthy synthesis would be much less likely to be pursued with an expensive starting ^{14}C source.

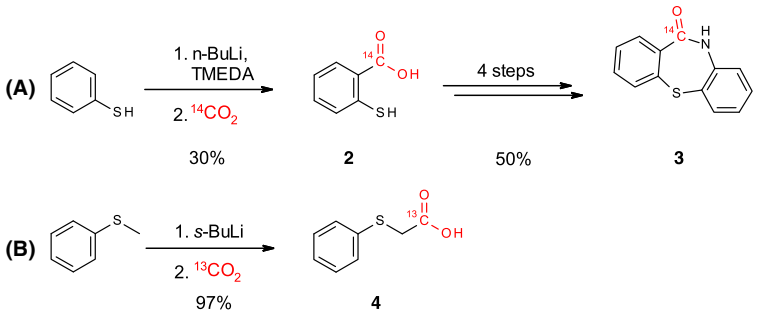
Directed deprotonation still plays a major role in the synthesis of labeled compounds. Elmore and coworkers formed the bisanion of thiophenol and reacted the anion with $^{14}CO_2$ to afford 2-sulfhydrobenzoic acid (**2**) in poor



SCHEME 1 The carboxylation of an aryllithium reagent en route to [^{14}C] cinaciguat[10]



SCHEME 2 The carboxylation of an aryllithium en route to [^{14}C]AZD4694[11]



SCHEME 3 A, Bisdeprotonation of thiophenol and subsequent carboxylation.[12] B, Deprotonation of thioanisole and carboxylation[12]

yield; the product was then converted to thiazepine **3** (Scheme 3).[13] Martinez and coworkers took advantage of the acidity of the protons on the methyl group of thioanisole to generate labeled 2-(phenylthio)[2-^{13}C] acetic acid (**4**).[12]

Modern methods for the preparation of Grignard reagents are now standard practice in radiochemistry labs. Latli and coworkers[14] first formed the enolate of trifluormethylketone **5** using NaH and then the Grignard reagent using the procedure of Knochel[15] (Scheme 4). The Grignard was then reacted with $^{14}CO_2$ and the resulting acid converted to glucocorticoid receptor antagonist **6** in 6 steps.

Similarly, Hickey and coworkers used the Knochel conditions to generate the 2-chlorophenyl Grignard from the corresponding bromide (Scheme 5).[16]

In an analogous fashion, Zhang generated 2-bromo-3-cyanophenyl Grignard from the corresponding iodide (Scheme 6).[17]

While the work of Hickey[16] and Latli[14] could likely have been accomplished using traditional methods, the arylnitrile in the substrate for Zhang[17] might have precluded the formation of a organolithium or Grignard reagent by traditional means.

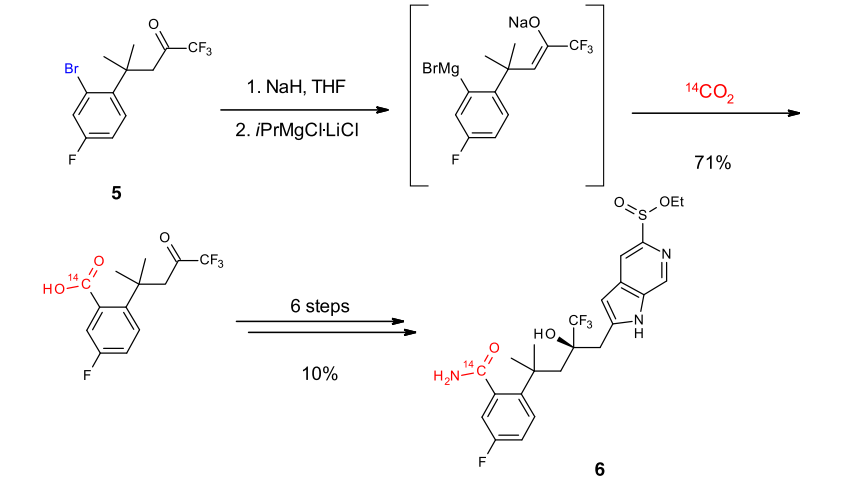
4 | FUTURE OF CARBOXYLATIONS

While Gringard and organolithium reagents react directly with CO_2 to form carboxylic acids, their poor functional group compatibility ultimately limits their use. The incorporation of $^{14}CO_2$ via late stage functionalization would dramatically increase the applicability of this chemistry for the synthesis of labeled materials and avoid multistep conversions via nitrile formation-hydrolysis pathways.[18] We therefore present below a review of the current literature in the context of applicability to ^{14}C carboxylation. The review is organized by product type (aromatic acid, benzylic acid, and aliphatic acid), with each area being subdivided by starting material.

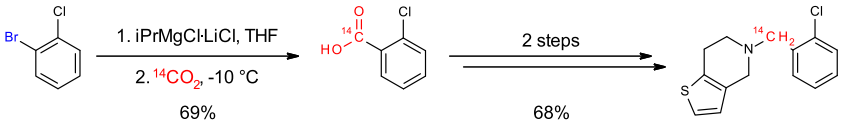
4.1 | Aromatic acids

In 2010, Knochel showed that organozinc reagents, generated from the corresponding bromo starting materials, reacted with CO_2 in the presence of $MgCl_2$ at 1 bar of pressure to give carboxylic acids in good yield (Scheme 7).[19] Esters and nitriles were demonstrated to be compatible with the zinc reagent, but ketones and aldehydes reacted.

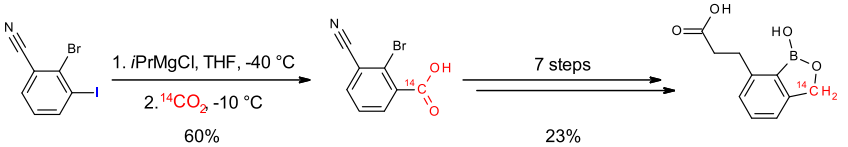
In 2013, Daugulis demonstrated the use of a copper-catalyzed carboxylation of aryl iodides, with a wide range of substrates (Scheme 8).[20] The reaction proceeds at 1 bar of CO_2 with low catalyst loadings, but uses several equivalents of the pyrophoric reagent Et_2Zn. However, the reaction was shown to tolerate a wide range of functional groups, including bromo, fluoro, hydroxy, and ester moieties. Mechanistically, the reaction is believed to proceed



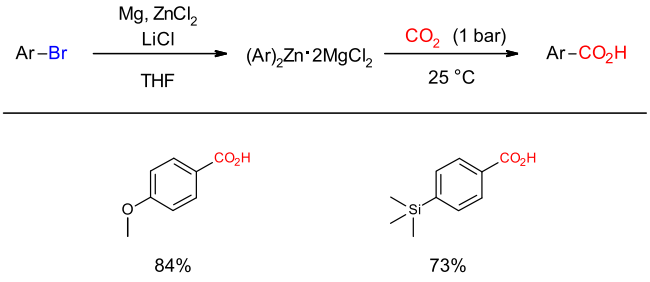
SCHEME 4 Carboxylation of an aryl Grignard reagent en route to glucocorticoid receptor antagonist **6**[14]



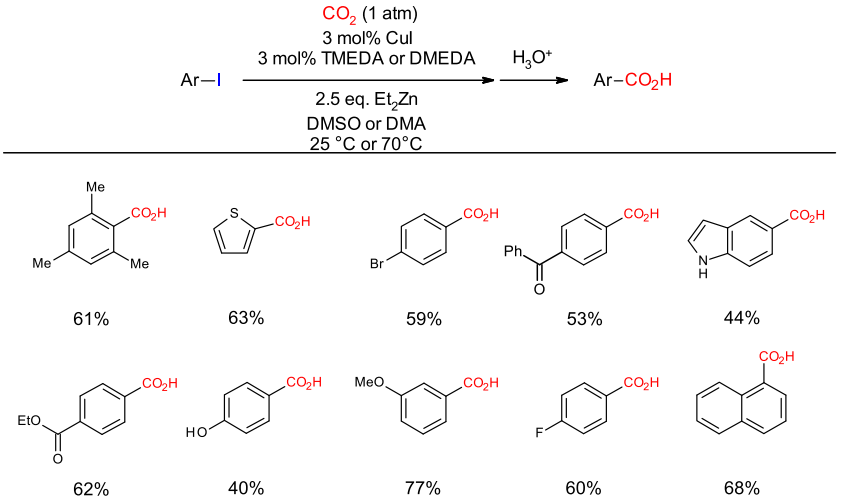
SCHEME 5 Carboxylation of 1-bromo-2-chlorobenzene via the Grignard reagent[16]



SCHEME 6 Carboxylation of 2-bromo-3iodo-benzonitrile via the Grignard reagent[17]



SCHEME 7 Zinc-mediated carboxylation of aryl bromides[19]

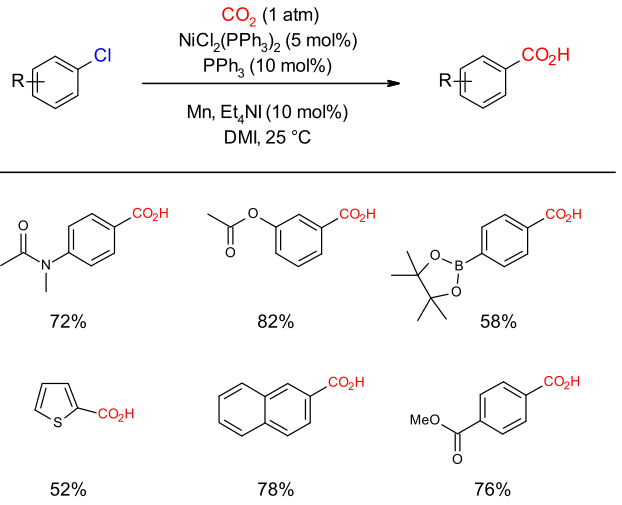


SCHEME 8 Cu-catalyzed carboxylation of aryl iodides[20]

via initial reduction of CuI to Cu(0) with Et_2Zn. Oxidative addition to the aryl iodide and subsequent reaction with CO_2 afford the copper(I) carboxylate. Finally, Et_2Zn reduction regenerates Cu(0) to complete the catalytic cycle.

Correa and Martin also developed a similar methodology using a phosphine containing palladium catalyst to carboxylate aryl bromides with Et_2Zn used to regenerate the catalyst.[21] They investigated the effect of CO_2 pressure on the reaction and found that a pressure of 10 atm afforded the best yield and reduced the amount of proto-debromination. While the reaction showed very good functional group compatibility, the dependence upon CO_2 pressure limits its application for radiochemical uses.

Tsuji and coworkers developed a nickel-catalyzed carboxylation of aryl chlorides (Scheme 9).[22] The method was tolerant of functional groups including esters,



SCHEME 9 Ni-catalyzed carboxylation of aryl chlorides[22]

ketones, 3°-amides, and boronic esters. However, alcohols, 2°-amides, and *ortho*-substituted arenes were not compatible with the reaction conditions. Importantly, the use of aryl chlorides gives access to a much larger supply of commercially available starting materials. Aryl bromides, aryl tosylates, and aryl triflates were also effective substrates for the reaction.

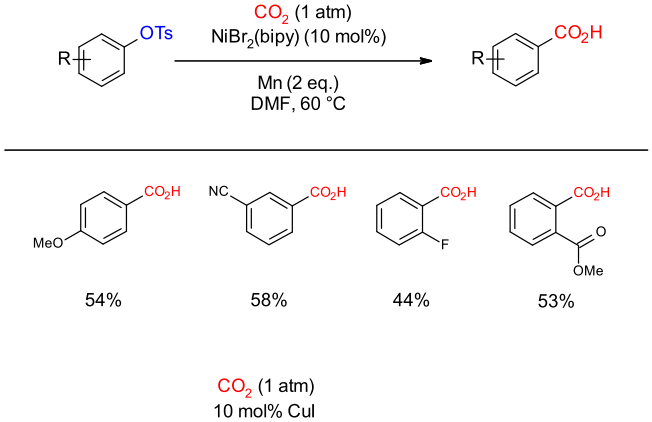
The conversion of aryl tosylates to aryl carboxylic acids has been demonstrated by the group of Durandetti[23] using a catalyst system similar to that described by Tsuji[22] (Scheme 10). The Durandetti method, however, effectively converts *ortho*-substituted tosylates albeit at a slightly elevated temperature. This methodology demonstrates that phenols can be used as precursors for aryl carboxylates. Although not explicitly stated, it is likely that this procedure does not tolerate alcohols or amines. Not surprisingly, the procedures are also efficacious with aryl iodide and aryl bromide substrates.

Cheng and coworkers showed that sodium arylsulfinates serve as efficient precursors of aryl carboxylic acids (Scheme 11).[24] Under CuI catalysis, the aryl sulfinate is desulfinated with concomitant carboxylation or in a stepwise process via an arylcopper intermediate. The procedure requires elevated temperatures and prolonged reaction times in a sealed tube which will likely limit its application to radiochemistry. The reaction also shows some sensitivity to steric bulk as sodium 2,4,6-trimethylbenzenesulfonate was efficiently converted to the corresponding carboxylic acid in 82% yield, but 2,4,6-triisopropylbenzenesulfonate failed to afford the desired product.

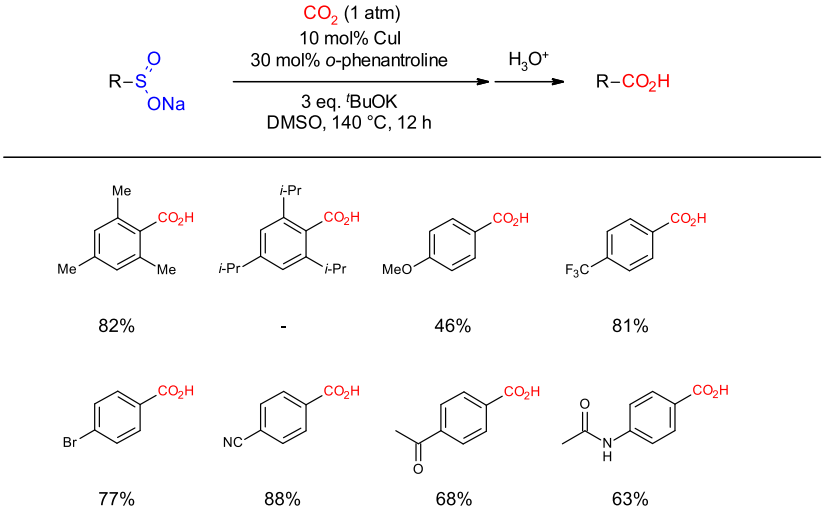
The conversion of 2-aryl-5,5-dimethyl-1,3,2-dioxaborinanes to aryl carboxylic acids has been shown to be effective using CuI catalysis and bisoxazoline ligand **7** (Scheme 12).[25] The reaction was tolerant of functionality, but required 3 equivalents of CsF and 90°C. The yields of the reaction were higher when performed in a sealed tube rather than with a balloon of CO_2; the authors postulated that this was because of the sensitivity of the organometallic intermediate to water and oxygen.

Hou and coworkers developed a procedure using a *N*-heterocyclic carbene copper(I) complex ([(IPr)CuCl], **8**) in refluxing THF to effect the same transformation (Scheme 13).[26] This procedure was demonstrated to have broad functional group compatibility and was performed using a balloon of CO_2.

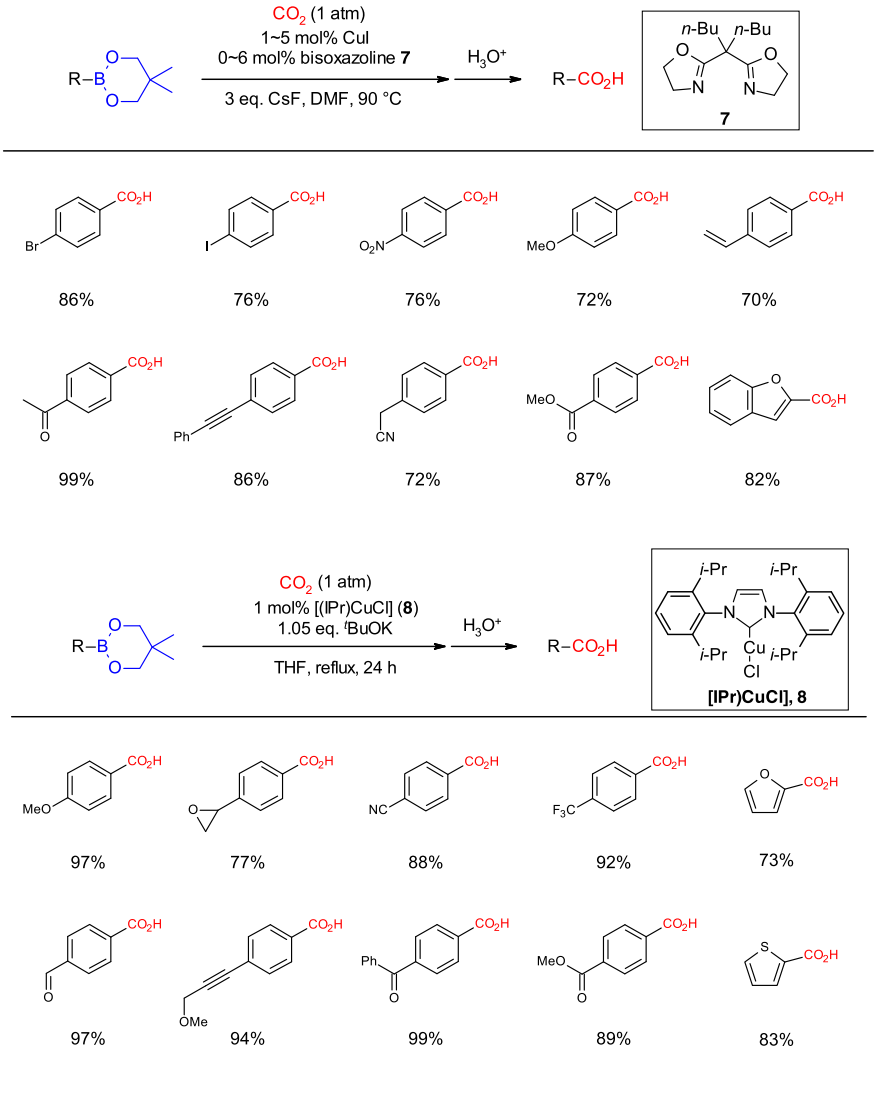
Riss and coworkers extended this methodology to ^{11}C using a mixture of CuI, TMEDA, KF, and cryptofix-222 in DMF (Scheme 14).[27] Bromo, nitrile, nitro, and aldehyde functionalities were compatible with the reaction conditions and afforded products in radiochemical yields over 70%. However, hydroxy and amine containing substrates



SCHEME 10 Ni-catalyzed carboxylation of aryl tosylates[23]

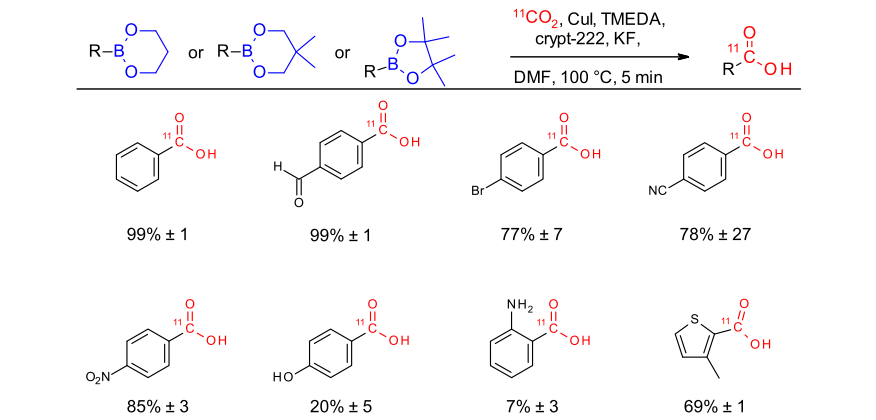


SCHEME 11 Cu-catalyzed carboxylation of aryl sulphinates[24]

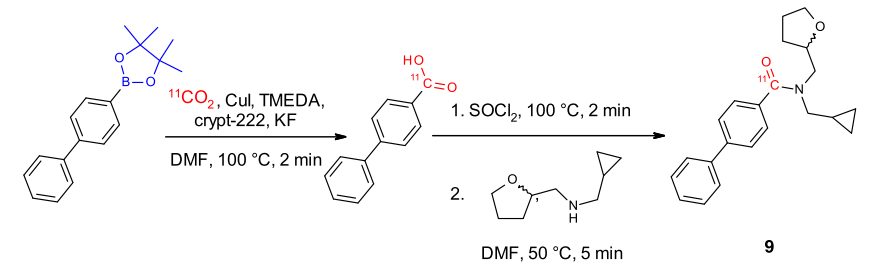


SCHEME 12 Cu-catalyzed carboxylation of arylboronic esters[25]

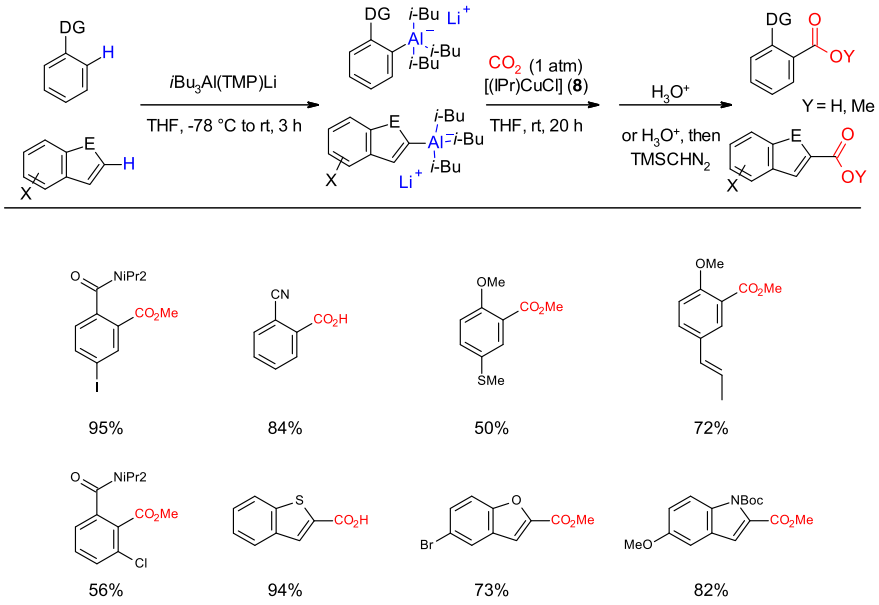
SCHEME 13 Cu-catalyzed carboxylation of arylboronic esters[26]



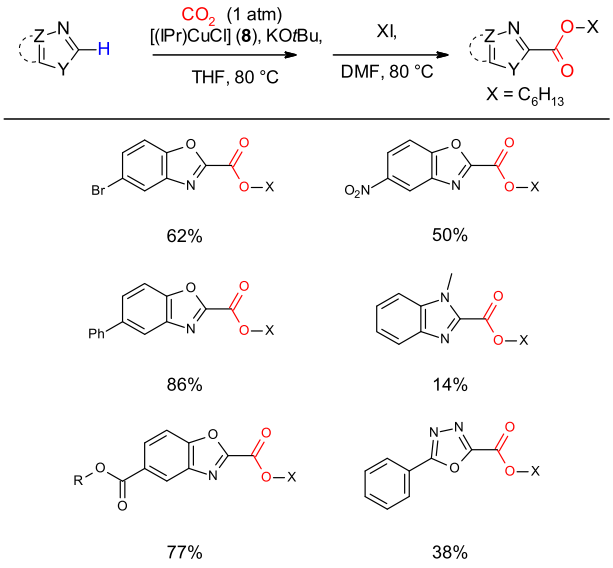
SCHEME 14 Cu-catalyzed ^{11}C carboxylation of arylboronic esters[27]



SCHEME 15 Synthesis of a ^{11}C-labeled oxytocin receptor PET ligand **9**[27]



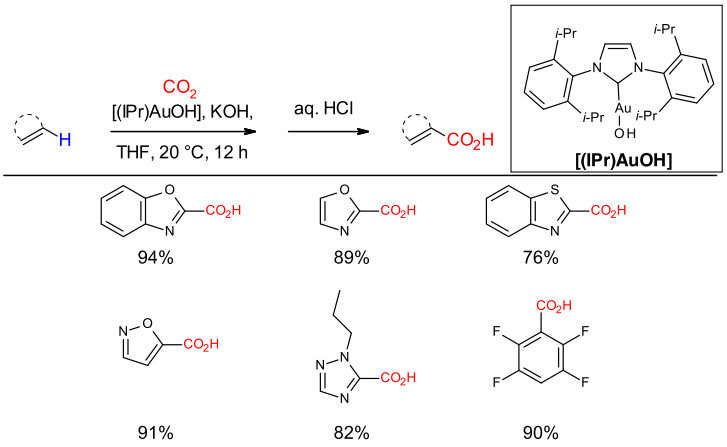
SCHEME 16 Directed deprotonation and Cu-catalyzed carboxylation of arenes[30]



SCHEME 17 Deprotonation and Cu-catalyzed carboxylation of benzoxazoles[31]

gave poor yields. They used this methodology to produce ^{11}C-labeled oxytocin receptor radioligand **9** (Scheme 15). Compehensive reviews of ^{11}C carboxylations have recently been published by Gee and Vasdev.[28,29]

Hou and coworkers demonstrated that a combination of deprotonation *ortho* to a directing group to give an arylaluminum species followed transmetallation with [(IPr)CuCl] (**8**) and subsequent capture of the anion by CO_2 resulted in good to excellent yields of several carboxylic acids (Scheme 16).[30] The reaction affords products with an excellent regioselectivity and modest functional group tolerance; nitriles, diisopropylamides, halides, an alkene, and a *t*-butoxycarbonyl-protected indole were unreactive under the conditions that were used. However, the reaction has a number of potential drawbacks for radiochemical synthesis. The reaction was performed under strict anhydrous conditions (glovebox) and uses triisobutylaluminum, which is very air and moisture sensitive. More significantly, the isobutyl groups of

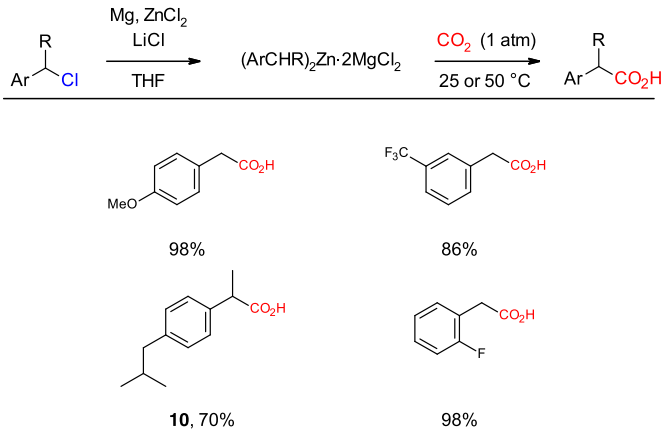


SCHEME 18 Au-catalyzed carboxylation of arenes and heteroarenes[32]

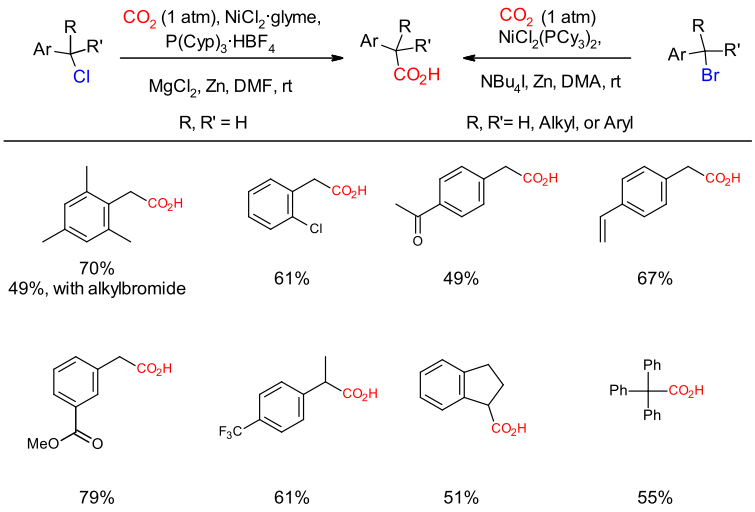
triisobutyl aluminum react with the CO_2 to generate isovaleric acid generating more by-product than desired product (mol/mol). Obviously, this is a serious drawback for radiochemistry purposes, but perhaps the use of CO_2 as the limiting reagent might limit this by-product, and the direct use of an arene is very attractive.

The Hou group has developed a method to carboxylate aromatic systems with relatively acidic protons (pKa = 25) (Scheme 17).[31] The *N*-heterocyclic carbene-copper(I) complex [(IPr)CuCl] (**8**) deprotonates the arene to generate an arylcuprate which reacts with CO_2 to give the corresponding acid. While this works well for benzoxazoles (yields 50%-86%) and tolerates halides, esters, nitros, and nitriles, it is much less effective for substrates with less acidic protons such as benzimidazoles, benzothiazoles, benzofurans, and 1,3,4-oxadiazoles.

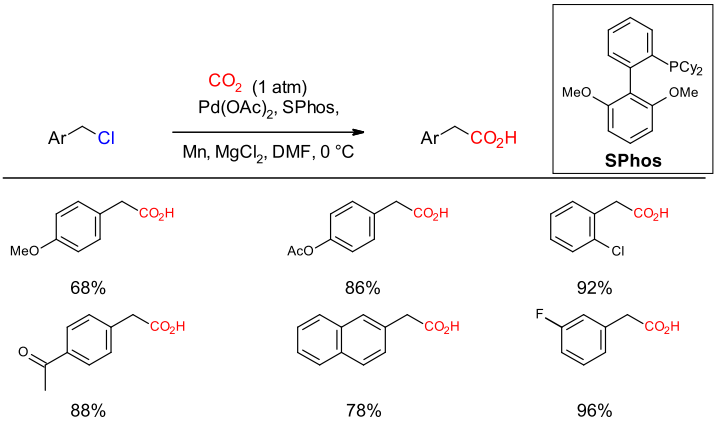
A more general method for carboxylating acidic heterocycles has been reported by Boogaerts and Nolan



SCHEME 19 Zinc-mediated carboxylation of benzyl chlorides[19]



SCHEME 20 Ni-catalyzed carboxylation of benzyl chlorides and bromides[34]



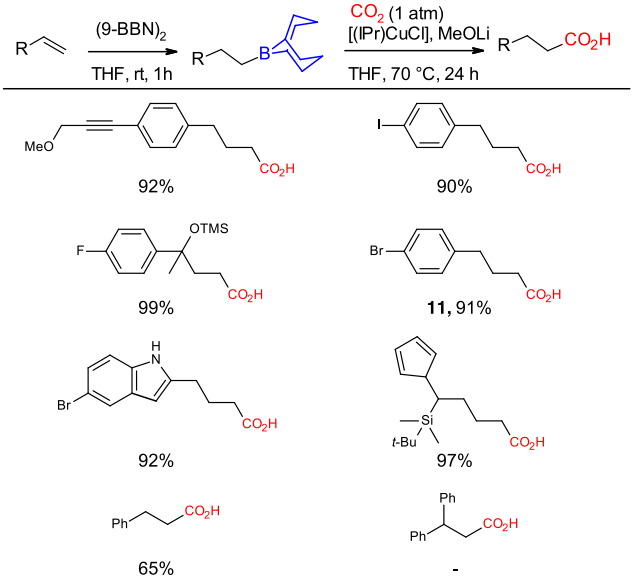
SCHEME 21 Pd-catalyzed carboxylation of benzyl chlorides[35]

(Scheme 18).[32] Under a pressure of 1.5 bar of CO_2, the *N*-heterocyclic carbene gold(I) hydroxide complex [(IPr)AuOH] successfully carboxylates a range of heterocycles including oxazole, isoxazole, benzoxazole, thiazole, and *N*-methylimidazole. The methodology was also extended to electron-deficient arenes. The functional group capability for this reaction was not investigated.

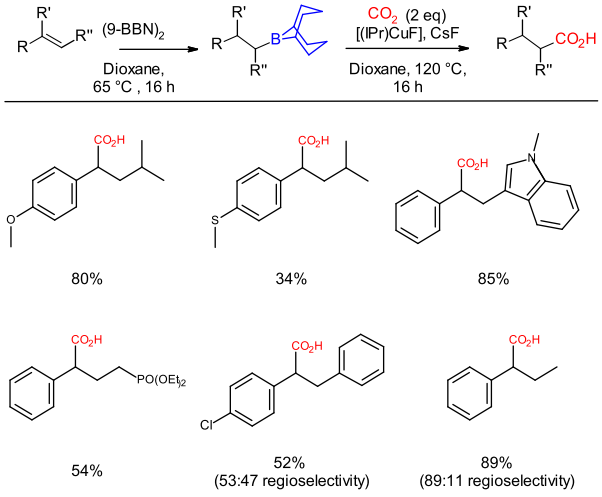
Cazin and coworkers also investigated the application of the *N*-heterocyclic carbene-copper(I) hydroxide complex [Cu(IPr)(OH)] for the same transformation, because of its ease of synthesis.[33] Comparable results were achieved for benzoxazole, benzothiazole, oxazole, and electron-deficient arenes. An inherent drawback for carboxylation of acidic substrates in labeled syntheses is the potential for the products to decarboxylate. However, the products may still prove useful as synthetic intermediates.

4.2 | Benzylic acid

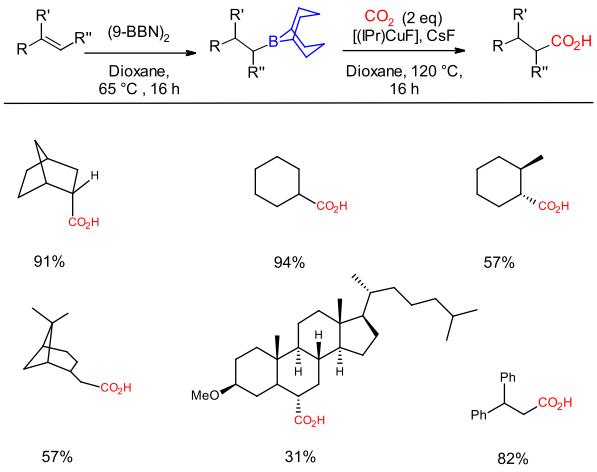
The method reported in Section 4.1.1 was also used by Knochel and coworkers to convert benzylic chlorides to phenylacetic acids (Scheme 19).[19] The method was used to synthesize ibuprofen (**10**) from 1-(1-chloroethyl)-4-isobutyl-benzene.



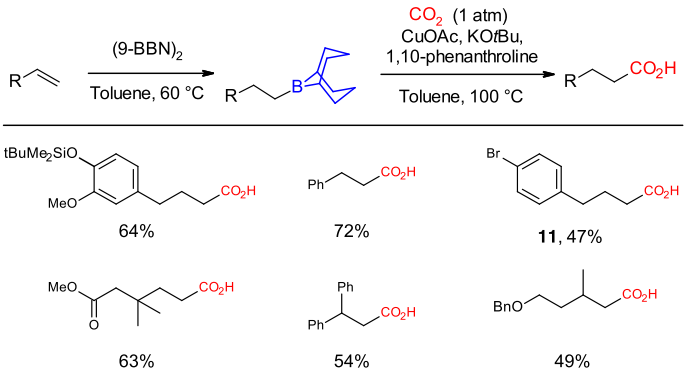
SCHEME 24 Cu-catalyzed carboxylation of alkyl-9-BBN compounds[38]



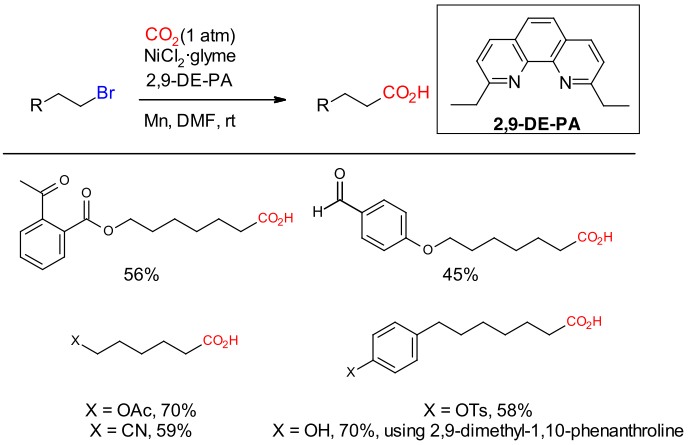
SCHEME 22 Cu-catalyzed carboxylation of benzyl-9-BBN compounds[36]



SCHEME 25 Cu-catalyzed carboxylation of primary and secondary alkyl-9-BBN compounds

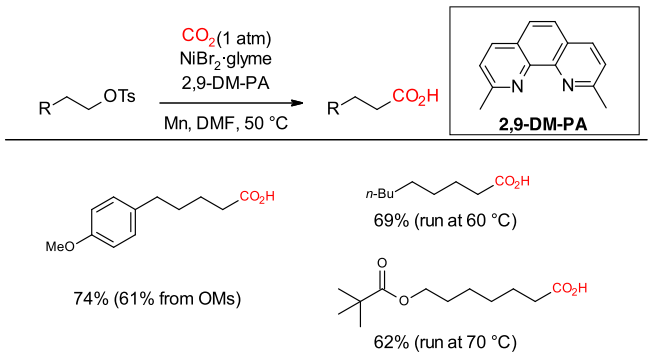


SCHEME 23 Cu-catalyzed carboxylation of alkyl-9-BBN compounds[37]



SCHEME 26 Ni-catalyzed carboxylation of alkyl bromides[39]

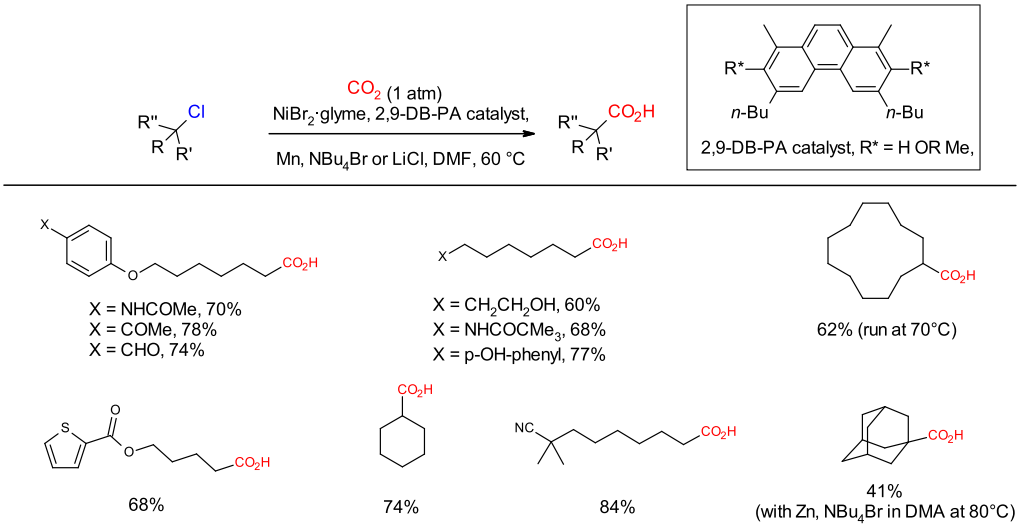
Martin and coworkers also have developed a Ni-catalyzed carboxylation of benzylic halides to afford phenyl acetic acids (Scheme 20).[34] The method uses catalytic $NiCl_2$-dimethoxyethane with zinc dust as the stoichiometric oxidant and tricyclopentylphosphine tetrafluoroborate to ligate the zinc. The reaction is run in DMF or DMA at room temperature. The addition of 2 equivalents of $MgCl_2$ improved the yield substantially, but the role of the metal is not clear. These conditions were not effective for secondary benzylic substrates, but substitution of tetrabutylammonium iodide for $MgCl_2$ and DMA for DMF gave modest yield of the target acids.



SCHEME 27 Ni-catalyzed carboxylation of alkyl tosylates[39]

He and coworkers have demonstrated that benzyl chlorides can be carboxylated to afford phenylacetic acids using Pd catalysis (Scheme 21).[35] The reaction is conducted with catalytic $Pd(OAc)_2$ ligated with 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos) and a large excess of $MgCl_2$ and Mn in DMF at 0°C under 1 bar of CO_2. The reaction has a similar functional group compatibility to the Ni-catalyzed reaction as substrates containing a chloride, an ester, a ketone, and a vinyl group were demonstrated to give good yields.

The Ni-catalyzed method of Martin[34] and the Pd-catalyzed reaction of He[35] give similar yields, have comparable functional group compatibility, and, operationally, appear to be of the same complexity. Therefore, for a primary benzylic chloride, either method is an appropriate choice.



SCHEME 28 Ni-catalyzed carboxylation of alkyl chlorides[40]

TABLE 1 Target acid with the methods reported and the demonstrated functional group compatibilities of the described methods

Target	Substrate	Method	Functional Group Tolerance										Incompatibility/ Drawbacks	References
			Ester	Amide	Aldehyde	Ketone	Nitrile	Halide	Alkene	Alkyne	Nitro	Other		
Aromatic														
ArCO_2H	ArI/ArBr	Zn activated by Mg	L	L				F				$SiMe_3$, $OSiR_3$, NMe_2		Ref. 19
	ArI	CuI, $ZnEt_2$	X			X		X				ArOH, indole NH		Ref. 20
	ArCl or ArBr	$NiCl_2$, Mn	X	X		X		F				Boronic ester, $OSiR_3$	Ortho substitution, alcohols, amines prohibited	Ref. 22
	ArOTs	$NiCl_2$, Mn	X			X	X	F					Likely alcohols and amines	Refs. 22,23
	ArOTf	$NiCl_2$, Mn	X	X		X		F				Boronic ester, $OSiR_3$	Ortho substitution, alcohols, and amines prohibited	Ref. 22
	ArSO_2Na	CuI		X		X	X	Cl, Br					Requires sealed tube, 140°C	Ref. 24
	Ar$B(OR)_2$	CuI	X			X	X	X	X	X	X		90°C, sealed tube (maybe), CsF	Ref. 25
		CuI	X	X	X	X	X	X	X	X	X	Epoxide, NR_2, $OSiR_3$, ArOH, $ArNH_2$	KOtBu can lead to transesterification	Refs. 26,27
	Directed C-H insertion	Al, Cu		If sterically congested			X	X	X			SMe	$Al(iBu)_3$, glove box	Ref. 30
HetCO_2H	Benzoxazoles	Cu	X				X	X			X		KOtBu can lead to transesterification	Ref. 31
HetCO_2H	Heterocycles with pH < 30	Au											Functional group compatibility not probed, but esters will likely hydrolyze because of use of KOH	Ref. 32

(Continues)

TABLE 1 (Continued)

Target	Substrate	Method	Functional Group Tolerance										Incompatibility/ Drawbacks	References
			Ester	Amide	Aldehyde	Ketone	Nitrile	Halide	Alkene	Alkyne	Nitro	Other		
Benzylic														
$ArCH_2CO_2H$	$ArCH_2Cl$	Mg, $ZnCl_2$	L	L				F				$SiMe_3$, $OSiR_3$, NMe_2		Ref. 19
		$NiCl_2$, $MgCl_2$, Zn	X			X		F, cl	X	X		$OSiR_3$		Ref. 34
		$Pd(OAc)_2$, $MgCl_2$, Mn	X			X		F, cl	X					Ref. 35
$ArCHRCO_2H$	ArCHRCl	Mg, $ZnCl_2$	L	L				F						Ref. 19
	ArCRHBr	$NiCl_2$, $MgCl_2$, Zn,	X			X		X						Ref. 34
$ArCR_2CO_2H$	$ArCR_2Br$	$NiCl_2$, $MgCl_2$, Zn,											Only 1 example: Ph_3Br	Ref. 34
$ArCH(CO_2H)CRR'$	$ArCH{=}CRR'$ or ArCH (9-BBN) CRR′	CuI				X		F, Cl				Thioether, phosphonate, indole	Silyl ethers, carbon-carbon double and triple bonds.	Ref. 36
Alkyl														
$RR'CHCH_2CO_2H$	$RR'CHCH_2$ (9-BBN) or $RR'C{=}CH_2$	Cu(I)	X	X				X		X		$OSiR_3$		Refs. 37,38
$RCH(CO_2H)CRR'$	RR′CHCHR″ (9-BBN) or RR′C=CR″H	CuI				X		F, Cl				Thioether, phosphonate, indole	Silyl ethers, carbon-carbon double and triple bonds.	Ref. 36
$RCH_2CH_2CO_2H$	RCH_2CH_2Br	$NiCl_2$, Mn	X	Secondary	X	X	X	F, Cl				OTs, $SnBu_3$, OH,		Ref. 39
	RCH_2CH_2OTs	$NiCl_2$, Mn	X										Functional group compatibility not probed, but should be similar to bromide	Ref. 39
	RCH_2CH_2Cl	$NiCl_2$, Mn	X	X	X	X	X	F	X			$OSiR_3$, OH,		Ref. 40

X indicates that the compatibility was demonstrated. L indicates that while the carboxylation reaction was not probed with these functional groups, a very similar reaction is reported in which they are tolerated. For halides, *X* indicates that all F, Cl, Br, and I are stable to the conditions; otherwise, the specific halide that is tolerated is depicted.

However, for a secondary or tertiary benzylic halide, the method of Martin has been demonstrated to work while the method of He will presumably lead to β-elimination.

The Skrydstrup group (Scheme 22) have developed a method to carboxylate benzyl-9-borabicyclononane (benzyl-9-BBN) compounds using copper(I) catalysis (Scheme 22).[36] Using 2 equivalents of CO_2 and [(IPr)CuF] formed in situ from CuI, 1,3-bis-(2,6-diisopropylphenyl)imidazolinium, and 3 equivalents of CsF, they demonstrated that styrenes and stilbenes could be successfully carboxylated (via the benzyl-9-BBN adduct). The reaction was run at elevated temperatures and tolerated a wide range of substrates including phosphonates, thioethers, boronic acids, halides, and methylindoles. The regioselectivity is derived from the regiospecificity of the initial hydroboration.

4.3 | Aliphatic acid

Sawamura and coworkers developed a method to carboxylate alkyl-9-borabicyclononane (alkyl-9-BBN) compounds by using copper(I) catalysis (Scheme 23).[37] The procedure consists of the addition of the alkyl-9-BBN compound in toluene to a solution of CuOAc, 1,10-phenylanthroline, and KO*t*Bu under 1 bar of CO_2. The reaction is heated at 100°C for 12 h to afford modest to good yields of the target alkyl acids. The main side product results from the protic deborylation. The reaction was demonstrated to tolerate silyl-protected alcohols, esters, an acetal, a phthalimide, and a bromide. Secondary alkylboranes do not react under these conditions.

A similar method has been developed by Hou which also uses copper(I) catalysis to convert alkyl-9-BBN compounds to acids (Scheme 24).[38] In this case, [(IPr)CuCl] (**8**) was used as the catalyst with MeOLi as base in THF at 70°C. The functional group compatibility is the same as the Sawamura method[37] with the exception that an aryl iodide, a diaryl ketones, an aryl alkynes, and a thiophene were also demonstrated to be stable to the reaction conditions. In general, the yields were higher for this method; for example, aryl bromide **11** gave a 91% yield with the method of Hou versus 47% with that of Sawamura. However, 9-BBN adduct of 1,1-diphenylethylene gave a 54% yield using the method of Sawamura while the method of Hou failed to carboxylate the compound.

The methodology of Skrydstrup reported in Section 4.2.2 has also been applied to affect the carboxylation of primary and secondary alkyl-9-BBN compounds (Scheme 25).[36] The regioselectivity of the carboxylation is determined by the regiochemistry of the boronic acid.

Martin and coworkers have developed a method for the conversion of alkyl chlorides, bromides, and tosylates to alkylacids.[39] While the procedure differs slightly for each substrate, the dimethoxyethane complex of $NiCl_2$ is used catalytically with a substituted phenanthroline ligand and Mn as the stoichiometric oxidant in DMF (chlorides and tosylates) or DMA (bromides) under 1 bar pressure of CO_2. The optimal conditions for the reaction with bromides (Scheme 26)[39] occurred at room temperature; that of tosylates (Scheme 27)[39] required heating to 50°C while chlorides (Scheme 28)[40] required heating to 60°C and the addition of tetrabutylammonium bromide. The reaction of bromides was demonstrated to tolerate a wide range of functionality as was the reaction of chlorides. It is likely that the functional group tolerance of the reaction of tosylates will be similar to that of the chlorides, but that was not demonstrated. Three secondary and 1 tertiary chloride were also successfully carboxylated using the conditions similar to that developed for primary chlorides.

5 | CONCLUSION

The use of modern chemical methods to incorporate $^{14}CO_2$ has been very limited. However, the progress made over the past 10 years, detailed herein, demonstrates that excellent methods for late-stage incorporation of labeled CO_2 exist. Method development will be required because all of these methods with the exception of that reported by Riss[27] use an excess amount of CO_2; however, it is likely that at least a few of these methods will be useful with stoichiometric quantities. All catalysts are commercially available thereby removing a frequent barrier to the use of the chemistry. A table summarizing the methods reported in this manuscript is presented herein (Table 1), indexed by reaction product and substrate. It details the functional group compatibility for each method.

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