Copper-Catalyzed Carbonylation of Alkyl Iodides

BY

Siling Zhao

M.A. University of Virginia, 2015

B.S. Sichuan University, 2014

THESIS

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Defense Committee:

Neal P. Mankad, Chemistry, Chair and Advisor
Donald J. Wink, Chemistry
Justin T. Mohr, Chemistry
Daesung Lee, Chemistry
David A. Nagib, The Ohio State University

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CONTRIBUTION OF AUTHORS

Chapter 1 offers an introduction to carbonylation with metal catalyzed two-electron and radical chemistry. Subchapter 1.3 comes from part of the published mini-review, Zhao, S.; Mankad, N. P., Metal-catalysed radical carbonylation reactions. *Catalysis Science & Technology* **2019,** *9* (14), 3603-3613.

Chapter 2 is adapted from Zhao, S.; Mankad, N. P., Cu-Catalyzed Hydroxymethylation of Unactivated Alkyl Iodides with CO To Provide One-Carbon-Extended Alcohols. *Angewandte Chemie International Edition* **2018,** *57* (20), 5867-5870. I was the primary author of this article and finished all the experimental work and manuscription preparation, while Dr. Mankad contributed to composing the introduction and revision of the paper.

Chapter 3 is adapted from Zhao, S.; Mankad, N. P., Synergistic Copper-Catalyzed Reductive Aminocarbonylation of Alkyl Iodides with Nitroarenes. *Organic Letters* **2019,** *21* (24), 10106-10110. I was the primary author of this article and finished all the experimental work and manuscription preparation, while Dr. Mankad contributed to the revision of the paper.

Chapter 4 is adapted from Cheng, L.-J.; Zhao, S.; Mankad, N. P., One-Step Synthesis of Acylboron Compounds via Cu-Catalyzed Carbonylative Borylation of Alkyl Halides. *Angewandte Chemie International Edition.* Accepted Manuscript. doi:10.1002/anie.202012373. Dr. Cheng was responsible for the reaction optimization, secondary and tertiary alkyl substrates, mechanistic investigation, synthetic utility studies and preparation of manuscript . I was responsible for the synthesis of the primary alkyl iodides and substrate scope with primary alkyl iodides, and the preparation of supporting information.

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BINAS	Bis(diphenylphosphinomethyl)-1,1'-binaphthyl
DMF	Dimethylformamide
NMP	*N*-methyl-2-pyrrolidone
DPPP	1,3-bis(diphenylphosphino) propane
OTf	Triflate
NMR	Nuclear Magnetic Resonance
MS	Molecular sieve
PMP	1,2,2,6,6-Pentamethylpiperidine
DCE	1,2-Dichloroethane
Nu	Nucleophile
BQ	Benzoquinone
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
MeCN	Acetonitrile
p-TsOH	*p*-Toluenesulfonic acid
TON	Turnover number
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
BDTBPMB	1,2-Bis-(ditertiarybutylphosphinomethyl)benzene
MsOH	Methanesulfonic acid
KIE	Kinetic isotope effect
VANOL	3,3'-Diphenyl-2,2'-bi-1-naphthalol
DCM	Dichloromethane
ESI-MS	Electrospray ionization mass spectrometry
$Co_2(CO)_8$	Dicobalt octacarbonyl
MPa	Megapasal
[BMim][Tf_2N]	1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide
Dcfp	1,1'-bis(dicyclohexylphosphino)ferrocene
TMANO	Trimethylamine *N*-oxide dihydrate
cata*CX*ium A	Di-1-adamantyl-*n*-butylphosphane
TFben	Benzene-1,3,5-triyl-triformate
$Mo(CO)_6$	Molybdenum hexacarbonyl
atm	Standard atmosphere
Dcpp	1,3-Bis(dicyclohexylphosphino)propane
eq	Equivalent
DMSO	Dimethyl sulfoxide
DMAc	*N*,*N*-dimethylacetamide

$BuPAd_2$	Di(1-adamantyl)-*n*-butylphosphine
Dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
dba	Dibenzylideneacetone
PCy_3	Tricyclohexylphosphine
TMSCl	Trimethylsilyl chloride
TBAF	Tetra-*n*-butylammonium fluoride
r.t	Room temperature
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
NHC	*N*-Heterocyclic carbene
DMAP	4-Dimethylaminopyridine
PPh_3	Triphenylphosphine
PMHS	Poly(methylhydrosiloxane)
PrCN	Isobutyronitrile
B_2pin_2	Bis(pinacolato)diboron
SET	Single electron transfer
DTBP	Di-*tert*-butyl peroxide
DCP	Dicumyl perioxide
TBHP	*tert*-Butyl hydroperioxide
1,10-phen	1,10-Phenanthroline
DIAD	Diisopropyl azodicarboxylate
DEAD	Diethyl azodicarboxylate
acac	Acetylacetone
COD	1,5-Cyclooctadiene
(*R*)-DTBM-SEGPHOS	(*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
TMDSO	1,1,3,3-Tetramethyldisioxane
TLC	Thin layer chromatography
UV	Ultraviolet
FT-IR	Fourier-transform infrared spectroscopy
LCMS-IT-TOF	Liquid chromatograph mass spectrometer-Ion trap-Time of flight
HRMS	High-resolution mass spectrometry
o/v	Overnight
Rf	Retention factor
Calcd.	Calculated
Cat.	Catalyst
h	Hour
aq.	Aqueous

LDA	Lithium diisopropylamide
KAT	Potassium acyl trifluoroborate
MIDA	*N*-methyliminodiacetyl
NMO	4-Methylmorpholine *N*-oxide
DME	Dimethoxyethane
B_2cat_2	Bis(catecholato)diboron
ATC	Atom transfer carbonylation
Boc	*tert*-Butyloxycarbonyl protecting group

SUMMARY

Chapter 1 summarizes the present state of carbonylation chemistry, including metal catalyzed two-electron and radical carbonylation. Transformations with unsaturated compounds including olefins and alkynes represent one of the main disciplines in metal-catalyzed two-electron carbonylation. It serves as a robust strategy to construct carbonyl-containing compounds. The development of carbonylation with carbon-halide or -pseudohalide bonds and C-H bonds diversifies the product library with various nucleophiles, such as alcohols, amines and organometallic reagents. Furthermore, metal-catalyzed radical carbonylation complements two-electron chemistry by expanding the reactant scope to sp^3-carbon substrates. This subchapter 1.3 on radical carbonylation is partially adapted from the published mini-review Zhao, S.; Mankad, N. P., Metal-catalysed radical carbonylation reactions. *Catalysis Science & Technology* **2019,** *9* (14), 3603-3613.

Chapter 2 represents the work from the reference Zhao, S.; Mankad, N. P., Cu-Catalyzed Hydroxymethylation of Unactivated Alkyl Iodides with CO To Provide One-Carbon-Extended Alcohols. *Angewandte Chemie International Edition* **2018,** *57* (20), 5867-5870. We have developed a reductive carbonylation method by which unactivated alkyl iodides can be hydroxymethylated to provide one-carbo-extended alcohol products under Cu-catalyzed conditions. The method is tolerant of alkyl β-hydrogen atoms, is robust towards a wide variety of functional groups, and was applied to primary, secondary, and tertiary alkyl iodide substrates. Mechanistic experiments indicate that the transformation proceeds by atom-transfer carbonylation (ATC) of the alkyl iodide followed in tandem by two CuH-mediated reductions in rapid succession. This radical mechanism renders the Cu-catalyzed system complementary to precious-metal-catalyzed reductive carbonylation reactions.

The content presented in Chapter 3 closely follows the reference Zhao, S.; Mankad, N. P., Synergistic Copper-Catalyzed Reductive Aminocarbonylation of Alkyl Iodides with Nitroarenes. *Organic Letters* **2019,** *21* (24), 10106-10110. Our findings were reported as the development of a Cu-catalyzed reductive aminocarbonylation of alkyl iodides using nitroarenes as the nitrogen source. The reaction proceeds with a single copper catalyst playing dual roles of synergistically mediating both carbonylation of alkyl iodides and reduction of nitroarenes, providing acyl iodides and anilines as possible reactive intermediates that then do amide coupling spontaneously. A diverse range of secondary *N*-aryl alkylamides are accessible from a variety of primary, secondary, and tertiary alkyl iodides using this method.

Chapter 4 discusses a Cu-catalyzed carbonylative borylation of unactivated alkyl halides, which comes from the reference Cheng, L.-J.; Zhao, S.; Mankad, N. P., One-Step Synthesis of Acylboron Compounds via Cu-Catalyzed Carbonylative Borylation of Alkyl Halides. *Angewandte Chemie International Edition.* Accepted Manuscript. doi:10.1002/anie.202012373. It enables efficient synthesis of aliphatic potassium acyltrifluoroborates (KATs) in high yields by treating *in-situ* formed tetracoordinated acylboron intermediates with aqueous KHF_2. A variety of functional groups are tolerated under the mild reaction conditions, and primary, secondary and tertiary alkyl halides are all applicable. In addition, this method also provides facile access to *N*-methyliminodiacetyl (MIDA) acylboronates as well as α-methylated potassium acyltrifluoroborates in a one-pot manner. Mechanistic studies indicate a radical atom transfer carbonylation (ATC) mechanism to form acyl halide intermediates that are subsequently borylated by (NHC)CuBPin.

1. The present state of carbonylation chemistry

The subchapter 1.3 comes from Zhao, S.; Mankad, N. P., Metal-catalysed radical carbonylation reactions. *Catalysis Science & Technology* **2019,** *9* (14), 3603-3613.

1.1. A glance at carbon monoxide and carbonylation

Carbon monoxide is known for its acute toxicity for living organisms, originating from its 210 times stronger binding affinity to hemoglobin than oxygen, thus cutting oxygen delivery in blood. The production of carbon monoxide comes from oxidations of hydrocarbons; motor vehicle exhaust contributes 70% of the total emission, and it indirectly affects climate change and global warming by offsetting the concentration of stronger greenhouse gas, carbon dioxide and methane. US Environmental Protection Agency has identified carbon monoxide as one the six air pollutants in Clean Air Act since 1990, and continuously regulates and monitors the production of carbon monoxide due to its health and environmental effects. Regardless of its bad reputation, carbon monoxide has been studied recently for the treatment of sepsis,[1] lung fibrosis,[2] cardiovascular disease,[3] and many other diseases.[4-6] Chemists also use carbon monoxide for interesting carbonylation reactions. The first metal carbonyl complex was synthesized by Mond in 1890,[7] and it was used for refining nickel metal.[8] Later on, Gattermann and Koch discovered the formylation of benzene on the basis of Friedel-Craft reaction[9] (Figure 1.1 a). In 1938, the first hydroformylation with alkene and syngas (mixture of H_2 and CO) was disclosed by Roelen using a cobalt-carbonyl based catalyst[10] (Figure 1.1 b). Heck and Breslow further revealed the widely known mechanism for the cobalt carbonyl promoted hydroformylation of olefins, in which cobalt hydrotetracarbonyl serves as active catalyst[11] (Figure 1.1 c). The blooming era of transition-metal catalyzed carbonylation of haloarenes was ignited by Heck's pioneering work in 1974,[12] and it was advanced with a variety of nucleophiles to furnish diverse carboxylic compound derivatives[13-15] (Figure 1.2 a). Complementary to transition-metal catalyzed transformations, free radical-promoted carbonylation has blossomed into a platform to construct alkyl-carbonylated compounds. Tremendous accomplishments have been achieved by Ryu and coworkers in this discipline[16-18] (Figure 1.2 b).

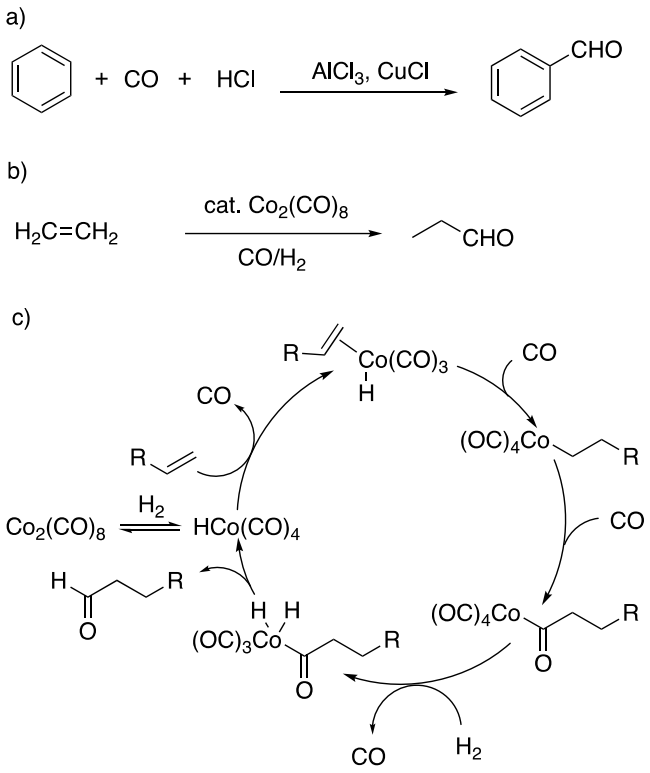


Figure 1.1 a) Gattermann-Koch reaction, b) First hydroformylation by Roelen, c) Heck and Breslow's monometallic pathway for hydroformylation by $HCo(CO)_4$ (linear product only showed here)

Over the past 60 years, carbonylation has attracted much attention in industry. In 1960, a cobalt-based catalytic methanol carbonylation process was commercialized by BASF for manufacturing acetic acid. Thereafter, Monsanto invented the well-known rhodium-catalyzed carbonylation of methanol with a higher selectivity under milder conditions[19] (Figure 1.2 c). BP Chemicals further improved the catalyst stability and lowered the water content in the product by replacing rhodium with iridium, named as Cativa™ process to avoid water gas shift reaction.[20] As one of the most important chemical commodities, acetic acid is broadly used to produce vinyl acetate monomers, a precursor to coatings, adhesives, films, fabrics, et al. It occupied $10.9 billion market in 2016 while forecasting to reach $16.4 billion by 2026. Being one of the most successful applications in industry, the Monsanto process contributes to 75% of the total acetic acid production worldwide.[21] Hydroformylation or oxo process represents another of the largest homogenously catalyzed transformations in industry, and is one of the premier achievements in industrial chemistry in the 20th century. It has been developed by BASF, Exxon, Shell and other corporations concentrating on olefins with different chain lengths ranging from C3 to C15, and mainly relies on cobalt catalysts. There are millions metric tons of oxo chemicals produced every year, including aldehydes, alcohols, carboxylic

compounds and their derivatives. They serve as intermediates to plasticizers, adhesives, and other products, which ubiquitous in everyday life.

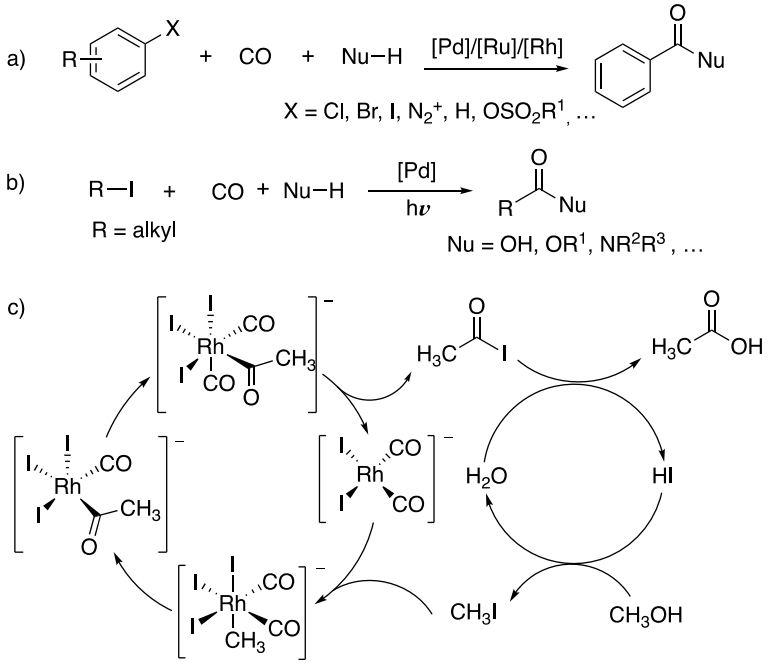


Figure 1.2 a) Transition metal-catalyzed Heck carbonylation, b) Ryu's radical carbonylation of alkyl iodides, c) Monsanto process

1.2. Metal-catalyzed two-electron carbonylation

Carbon monoxide, as one of the cheapest and most available C1 units, is the anchor to thrive the synthesis of carbonylated compounds. Transition-metal catalysts magnified carbonylative transformations with a broad range of substrates. Heck and Sonogashira type carbonylations represent landmarks for the use of palladium catalysts with alkene and alkyne substrates.[22,23] Carbonylation of C(sp^2)-X bonds is another important development in broadening the substrate scope. In addition, the employment of various nucleophiles such as water, alcohols and amines further diversifies the product library.[14] In this subchapter, three main disciplines including carbonylation of olefins, alkynes and C-X bonds will be discussed.

1.2.1. Carbonylation of Olefins

1.2.1.1. Hydroformylation

Although aldehyde is less of interest, it paves the way to produce a broad class of compounds through chemical transformations. One of the major products is alcohol, which can be transformed through hydrogenation, aldolization,

or addition of formaldehyde and hydrogenation in two steps. The major consumption of alcohols is for the production of derivatives of inks, resins, paints, and explosives. It can also undergo oxidation to manufacture carboxylic acids and esters, serving as ingredients in detergent, disinfect, polyesters for different purposes. Amine derivatives can be made via reductive amination. Amines are important intermediate in dyes and pharmaceutical industry (Figure 1.4).

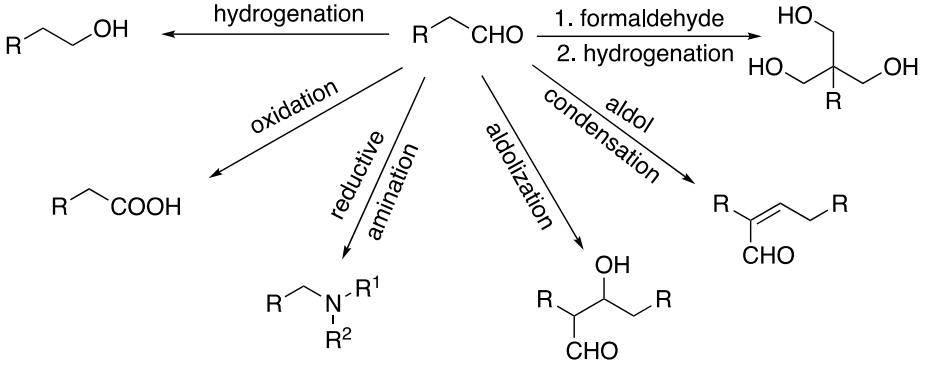


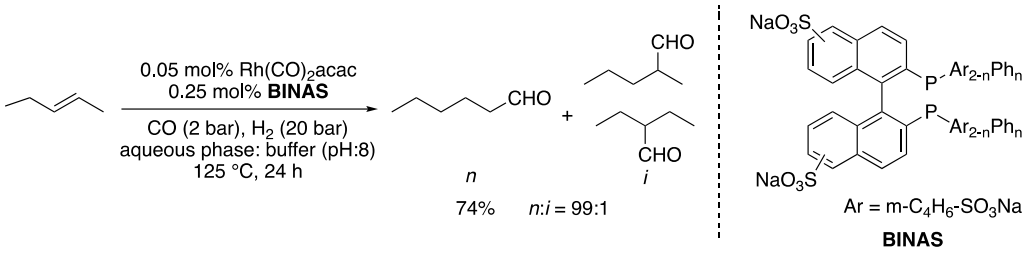
Figure 1.3 Chemical applications of aldehydes

The transformation of addition of syngas to alkenes affording aldehydes is named hydroformylation. The first cobalt-mediated hydroformylation of ethylene was discovered by Roelen in 1938 (Figure1.1b) and the general mechanism is depicted in Figure 1.1c. Typically it operates at 140 ℃ and 200 bar pressure.[24] Since both carbons of ethylene are equally active, only propanal is obtained. However, isomerization take place when longer-chain olefins or internal olefins were applied.[25,26] Among the myriad of catalysts that have been investigated under such topic, rhodium is the candidate that provides better regioselectivity than other metals while operating the transformation under lower pressure and temperature.[27] Rhodium carbonyl is the most reactive metal carbonyl compounds toward hydroformylation as shown below[28]:

Rh >> Co > Ir > Ru > Os ~ Tc > Pt > Pd > Mn > Fe > Ni >> Re

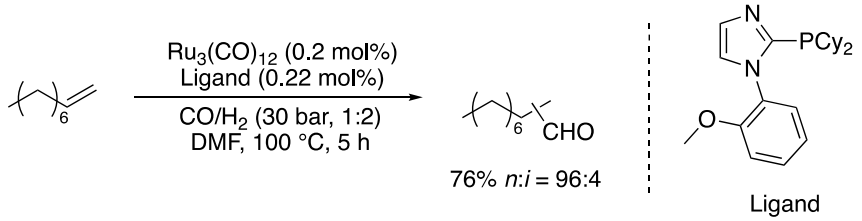
Figure 1.4 Trend of reactivity of unmodified metal carbonyls towards carbonylation

Beller group studied the hydroformylation of internal olefins using a phosphine ligated Rhodium catalyst (Scheme 1.1). The mild condition (2 bar CO and 10 bar H_2 pressure, 125 ℃) afforded excellent regioselectivity as the linear to branched ratio was 99:1. To achieve this highly selective reaction, a sterically demanding phosphine ligand (BINAS)[29] promoted the isomerization of internal alkenes over hydroformylation step.[30]



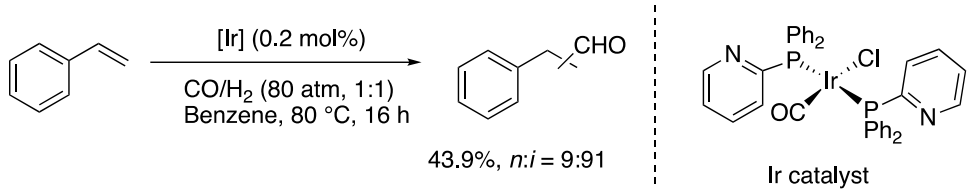
Scheme 1.1 Hydroformylation of 2-butene using Rh catalyst

Although rhodium provided excellent *n*-selectivity, it is expensive to use for plant-scale production in industry.[31] Ruthenium, as the cheapest noble metal, has drawn attention from researchers as a potential replacement. The pioneering work has been done by Wilkinson utilizing a $RuCl_3(PPh_3)_2(CH_3OH)$ complex at 100 atm pressure of syngas and 100 ℃. However, side reactions accompanied desired hydroformylation, including hydrogenation of the corresponding aldehydes, isomerization of internal alkenes, and direct reduction of alkenes, resulting a mixture of products.[32] Recently, Beller and coworkers revealed an advanced ruthenium catalyst system involving a imidazole-substituted monophosphine ligand for hydroxymethylation of olefins, which will be discussed in chapter 2.[33, 34] Based on Beller's study, a continuously operating miniplant for hydroformylation of olefins was developed with Ru catalyst and another imidazole based phosphine ligand.[35] The high regioselectivity for linear aldehydes and good yields were achieved after optimizing reaction conditions. This application also featured the recycling of catalyst via *ex situ* extraction with the addition of branched octane (Scheme 1.2).



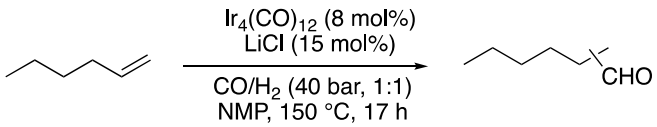
Scheme 1.2 Ru-catalyzed hydroformylation at miniplant scale

Another alternative metal would be iridium for the homogeneous hydroformylation of olefins.[36,37] Although iridium possess lower reactivity towards carbonylation compared to rhodium and cobalt, it exhibits similar coordination geometries and chemical properties. Faranoe and coworkers successfully synthesized *trans*-$[Ir(CO)(Ph_2PPy)_2Cl]$ complex, an analog to Vaska's complex, and employed it for hydroformylation of styrene. This catalyst system favored branched aldehydes over linear products with a high turnover frequency[38] (Scheme 1.3).



Scheme 1.3 Ir-catalyzed hydroformylation favoring branched aldehydes

With regard to hydrogenation occurring as a side reaction during this transformation, Pakkanen and others found that the side reaction can be suppressed by the addition of LiCl salt[39] (scheme 1.4). A series of control experiments showed that the promoting effect is the combined result of the both anions and cations.[40] It also suggested that the addition of the promoting salt could improve the solubility of iridium catalyst, and benefit the formation of the active catalyst, iridium carbonyl halide. Meanwhile, some other evidence showed the hydrogenation could be inhibited by increasing the partial pressure of carbon monoxide.[37]

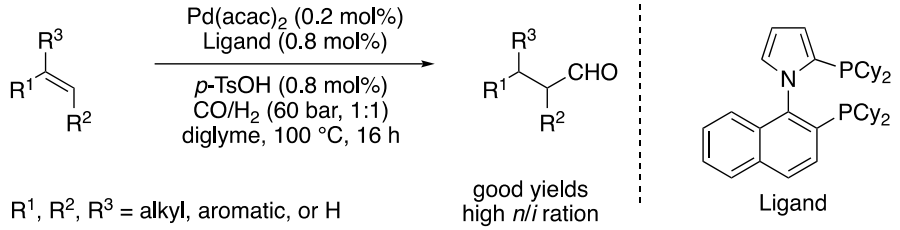


Promoter (mol%)	n-hexanes and isomers (%)	1-heptanal and isomers (%)	1-heptanol and isomers (%)
0	81	-	19
15	27	73	0

Scheme 1.4 Ir-catalyzed hydroformylation of 1-hexene with addition of LiCl

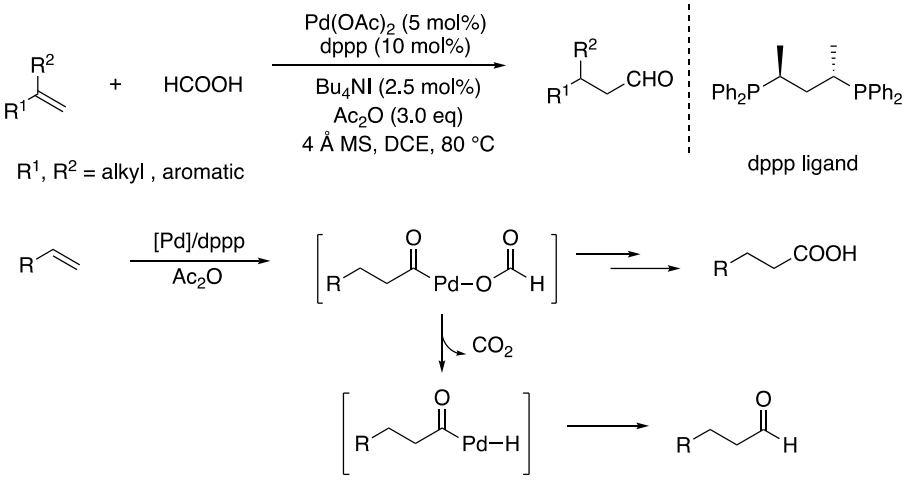
(data in table obtained under optimized conditions)

Although palladium is the most general and versatile catalyst for coupling reactions, it is rarely reported for hydroformylation. Beller group introduced a palladium-catalyst system with a bidentate 2,2'-heteroarylarylphosphine ligand and a cocatalyst, *p*-toluenesulfonic acid.[41] The addition of the cocatalyst promoted hydroformylation over competing side reactions. This catalyst system tolerated a variety of alkyl and aromatic olefins, providing good to excellent chemoselectivity as well as regioselectivity (Scheme 1.5). It's also shown that the low concentration of acid benefitted the regioselectivity for linear aldehydes. The *n*:*i* ratio was 95:5 when 0.075 mol% acid was added, but dropped to 54:46 with the addition of 10 mol% acid. Most recently, they provided another route for the synthesis of aromatic aldehydes from vinyl triflates without the use of any acid additives[42].



Scheme 1.5 Pd-catalyzed hydroformylation with acid additives

Later Shi and coworkers reported another palladium-catalyzed hydroformylation of aliphatic and aromatic olefins.[43] In this study, they took advantage of formic acid as carbon monoxide surrogate, thus reactions were operated under milder conditions and in a simple way. The use of 1,3-bis(diphenylphosphino) propane (dppp) ligand was crucial for directing the reaction pathway to hydroformylation instead of hydrocarboxylation (Scheme 1.6).



Scheme 1.6 Pd-catalyzed hydroformylation with HCOOH

1.2.1.2. Heck-type Carbonylation

Heck reaction (Mizoroki-Heck reaction) is a well-known palladium-catalyzed coupling transformation of alkenes and aryl halides.[44] The first palladium-catalyzed copolymerization of carbon monoxide with alkenes was reported in 1982.[45] Subsequently, Negishi and Miller described an intramolecular carbonylation of silylated alkenes under mild carbon monoxide atmosphere.[46] Since then carbonylative Heck reactions have been widely studied both intramolecularly and intermolecularly.[47-49] The general mechanistic cycle is depicted in figure 1.5. Pd(0) undergoes oxidative C-X bond insertion to form an aryl palladium complex. Immediately, the arylpalladium complex undergoes CO and alkene insertion, followed by reductive elimination to release the ketone product and regenerate the active catalyst.

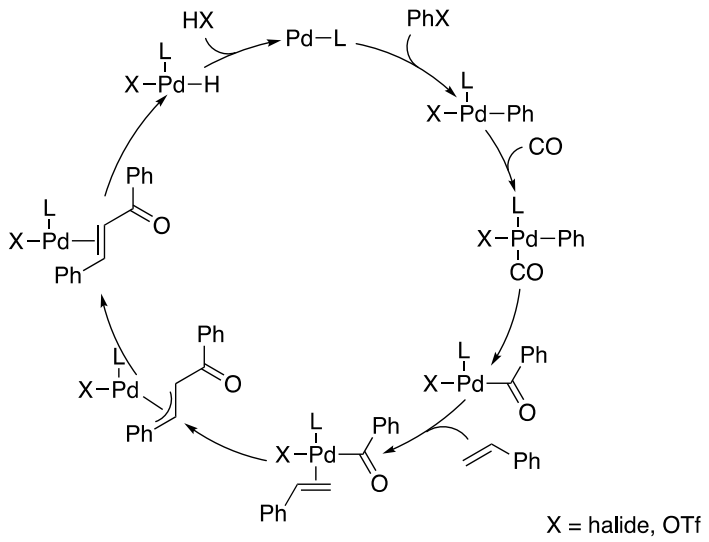
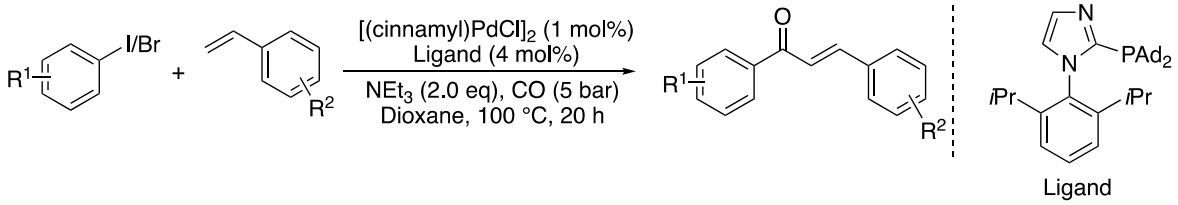


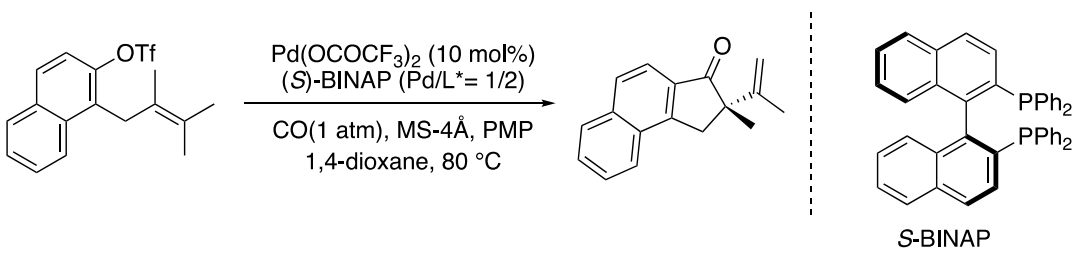
Figure 1.5 General mechanism for a palladium-catalyzed carbonylative Heck reaction

Beller group demonstrated a general palladium-catalyzed carbonylative vinylation of aryl halides and styrenes or vinyl esters, selectively synthesizing α,β-unsaturated ketones in moderate to good yields.[50,51] The key intermediates, aryl- and acylpalladium complexes, were isolated and characterized by NMR spectroscopy and X-ray crystallography, supporting the proposed reaction mechanism. (Scheme 1.7)



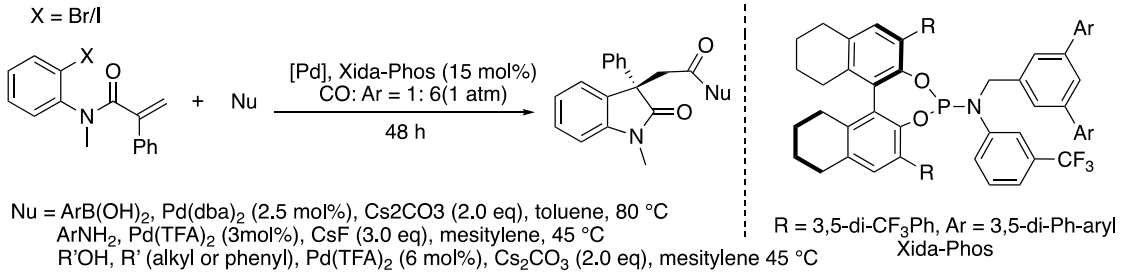
Scheme 1.7 Pd-catalyzed carbonylative Heck reaction

Later on, attempts also have been made to achieve this type of transformation enantioselectively, which often operates with the assistance of a chiral, bidentate bis(phosphine) or bis(oxazoline) ligand.[52-54] Early discoveries were made by Kato and coworkers, illustrating a palladium-based system with *S*-BINAP/dioxane to yield enantiomerically enriched cyclopentenones.[55] (Scheme 1.8) This carbonylative cyclization featured increased enantioselectivities with any substituents introduced to the aromatic moieties.



Scheme 1.8 Pd-catalyzed enantioselective carbonylation with *S*-BINAP ligand

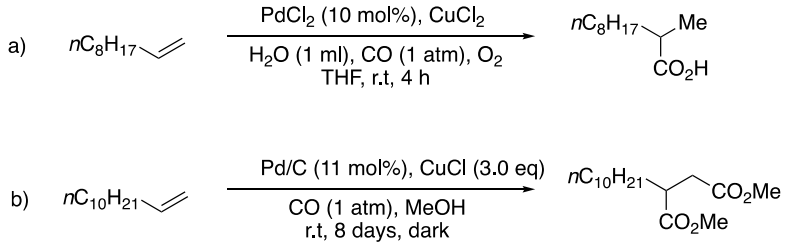
The development of asymmetric Heck carbonylation has been dominated by chelating ligands. It's challenging to achieve such transformation with no "chelate effect" ligand. Very recently, Guan group reported the first enantioselective domino Heck carbonylation with a monodentate phosphine ligand, Xida-Phos.[56] (Scheme 1.9) The authors believed that such monodentate ligand would relieve the competing coordination between the ligand and CO to metal center. This asymmetric carbonylation provided a very efficient route to synthesize β-carbonyl compounds with enantioenriched quaternary carbons. Additionally, the employment of different nucleophiles, like aryl boronic acids, amines, and alcohols, further advanced the application of this method.



Scheme 1.9 Pd catalyzed enantioselective Heck carbonylation with Xida-Phos ligand

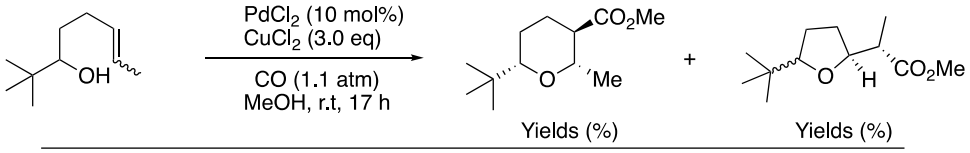
1.2.1.3. Oxidative carbonylation of olefins

The Hoechst-Wacker process (also known as Wacker process) refers to the oxidation of ethylene to produce acetaldehyde in industry. This palladium-catalyzed transformation was first discovered in late 1950s,[57, 58] requiring a catalytic addition of copper(I) chloride to regenerate palladium(II) from palladium(0) in the presence of O_2. Although this is not a carbonylation transformation, Wacker process is an archetype of oxidative carbonylation as it is equipped with all the basic mechanistic steps required for oxidative carbonylation.[59, 60] Smith and coworkers described a completely regiospecific hydrocarboxylation of terminal olefins at very mild conditions to give branched carboxylic acids in the presence of hydrochloric acid[61] (Scheme 1.10a). Later on, Kinoshita group found that the corresponding diesters can be selectively formed when copper(I) chloride was used as oxidant instead of copper(II) chloride in methanol[62] (Scheme 1.10b). The asymmetric catalysis for the formation diesters was achieved later by Inomata, Huang and others.[63,64, 65]



Scheme 1.10 a) Hydrocarboxylation of olefin with $Pd/CuCl_2$ system b) carbonylation of olefins for succinate formation with Pd/CuCl system

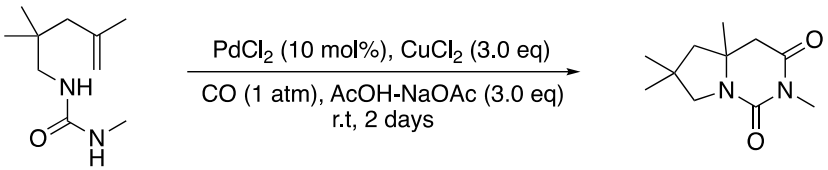
Heterocycles are always of great interest in synthesis. Carbonylation provides a direct path for synthesis of such type of compounds. An intramolecular alkoxypalladation/carbonylation of olefins was reported by Bodurow in 1983.[66] According to their study, the alkene geometry dictated the ring size of cyclized products. *E*-alkenes favored six-member ring formation as a single diastereomer depicted below, while Z-alkenes preferred five-member ring epimers (Scheme 1.11).



	Yields (%)	Yields (%)
E-alkene	59	25
Z-alkene	10	55

Scheme 1.11 Intramolecular carbonylation of alkene for the formation of tetrahydropyran and tetrahydrofuran derivatives

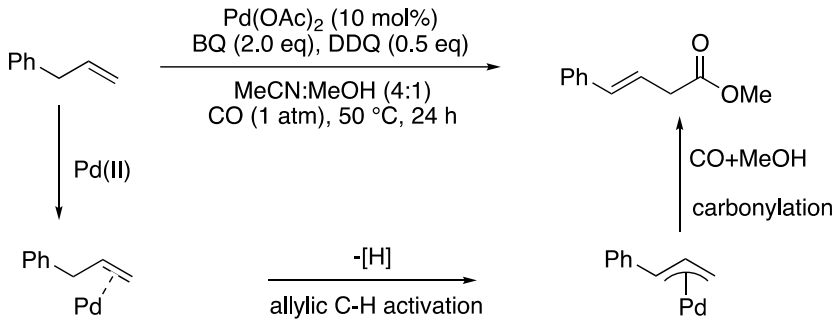
Urea can also serve as nucleophile in oxidative carbonylation to provide *N*-containing heterocycles, imidazolidinones, pyrimidinones, diazabicycles, and others. Yoshida group has illustrated a palladium-catalyzed aminocarbonylation of *N*-protected 4-pentenylamine.[67] In contrast to aprotic solvents, like tetrahydrofuran and dichloromethane, the protic solvents, acetic acid, provided the best conversions and yields. They hypothesized that the acidic environment helped the solvation of chloride ion from the catalyst as well as restrained the coordination of amine to $Pd(2^+)$ by protonation of amine moieties (Scheme 1.12).



Scheme 1.12 Palladium-catalyzed aminocarbonylation of unsaturated amines

Another palladium-catalyzed regioselective carbonylation of olefin was reported by Jiang and coworkers in 2011.[68] They proposed a tandem transformation, allylic C-H activation/carbonylation, for this dehydrogenative

carbonylation shown in Scheme 1.13. The subjection of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) facilitated allylic C-H activation to form the allylpalladium complex first, then carbonylation took place. This prevented from the occurrence of carbonylation earlier than C-H activation, which would lead the formation of diesters. Benzoquinone (BQ) and DDQ were the oxidants responsible for the regeneration of active catalyst (Scheme 1.13). There have been some attempts to use "greener" oxidants, like air, oxygen, or lower loading of oxidants for such transformations.[69,64]



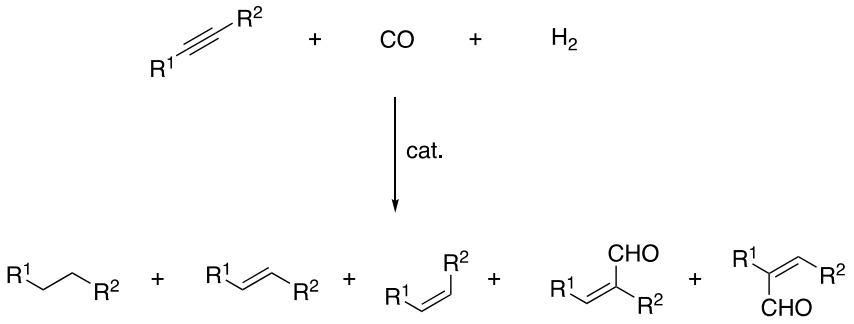
Scheme 1.13 Pd-catalyzed oxidative allylic C-H carbonylation

1.2.2. Carbonylation of Alkynes

α,β-Unsaturated carbonyl compounds are class of important intermediates in organic transformations. Conventionally, they are prepared from phosphonate carbanions and aldehydes, namely Horner-Wadsworth-Emmons reaction, from the well-known aldol condensation between enols and carbonyl compounds, or from Knoevenagle condensation, a more specific type of aldol condensation. Although these methods are well-established, all of them take advantage of a pre-installed carbonyl group, limiting the diversity of accessible products. In this regard, carbonylation of alkynes provides an alternative route to construct α,β-unsaturated carbonyl compounds. Milder carbonylative conditions could benefit a more diversified substrate library.[70]

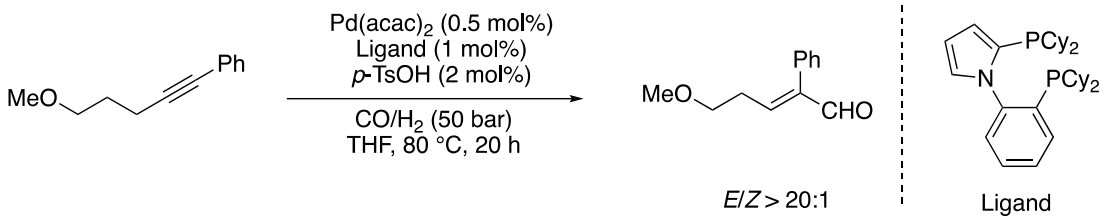
1.2.2.1. Hydroformylation of alkynes

Compared to hydroformylation of alkenes, such transformation of alkynes is largely underdeveloped due to the competing hydrogenation and uncertain regioselectivity. Possible byproducts include alkenes from semihydrogenation, alkanes from complete hydrogenation, and isomers of hydroformylated product (Scheme 1.14).



Scheme 1.14 Possible products from hydroformylation of alkynes

Despite all the challenges, Buchwald and coworkers led research on rhodium-catalyzed hydroformylation of internal alkynes. In their rhodium/bisphosphine ligand system, good chemo- and regioselectivity were achieved to synthesize α,β-unsaturated aldehydes from symmetric alkynes. Their method performed poorly with unsymmetric alkynes in terms of yields and regioselectivity.[71] Recently, Beller group and others[72] carried out related work to deliver the targeting aldehydes in an efficient and selective manner (Scheme 1.15). With the assistance of a *N*-phenylpyrrole-based bisphosphine ligand, the hydrogenation was largely suppressed. Good to excellent yields with good stereoselectivity were obtained with symmetric and unsymmetric internal alkynes.[73]



Scheme 1.15 Pd-catalyzed regio- and stereoselective hydroformylation of alkynes

1.2.2.2. Hydroxycarbonylation of alkynes

Reppe reported a pioneering study on catalytic hydroxycarbonylation of alkynes to produce α,β-unsaturated carboxylic acids in the presence of nickel catalyst.[74, 75] Then Alper followed up with a nickel cyanide catalyzed carbonylation under milder conditions (90 °C, 1 atm CO). This method selectively provided branched α,β-unsaturated carboxylic acids from terminal alkynes under a biphasic environment (toluene/aqueous NaOH) where cetyltrimethylammonium bromide was the phase transfer agent.[76] Most recently, Zhou group disclosed a palladium-catalyzed hydroxycarbonylation of alkynes with high regioselectivity and yields[77] (Figure 1.6). The conversion of alkynes into corresponding acids occurred with turnover numbers (TONs) up to 350. In addition, the reaction operated with the use of formic acid as a carbon monoxide surrogate due to it is safer storage and easier to handle. The formic

acid reacts with anhydride to form the mixed anhydride, which then decomposes to carbon monoxide for carbonylation. Meanwhile, the activated alkyne reacts with formic acid to form the palladium complex **B**. Immediately, CO insertion takes place with this complex to provide complex **C**. Then **C** releases the anhydride **D** through reductive elimination and regenerates the catalyst. Finally, the anhydride **D** decomposes to form the targeting α,β-unsaturated carboxylic acid. In the same manner, Fu and coworkers illustrated a similar nickel catalyzed transformation with formic acid.[78]

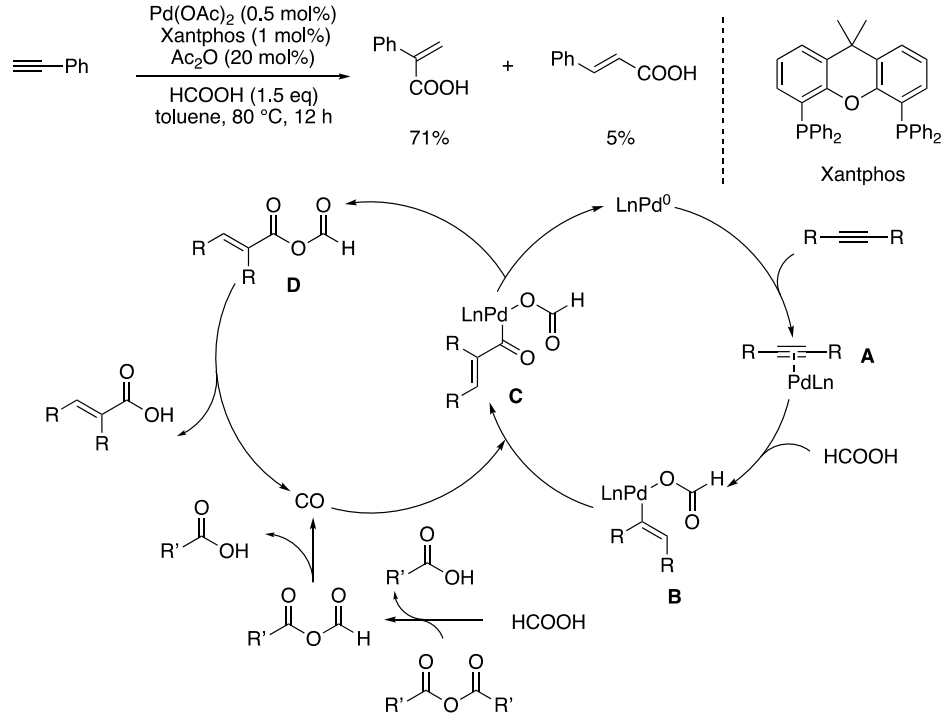


Figure 1.6 Pd-catalyzed hydroxycarbonylation of alkynes with formic acid as CO provider and proposed cycles

Another approach to this reductive carbonylation would be to take advantage of water-gas shift reaction. Related work has been done by Chiuoli with a PdI/KI system[79] (Figure 1.7). In the mixture of carbon monoxide and water, terminal alkyne could undergo cyclocarbonylation, resulting in the formation of furan-2(5*H*)-ones as the major products, and maleic acids as the minor one. However, the authors found carbon dioxide would strongly influence the distribution of products, giving rise to the formation maleic acids.[80] They anticipated that alkyne insertion with I-Pd-CO_2H was followed by a second CO insertion to form an acylpalladium complex **A**. Then hydride exchange with complex **A** occurred with a subsequent reductive cyclization, giving the formation of an allylpalladium complex **C**. The furanone was obtained after the protonolysis of **C**, with the regeneration of catalyst. (Figure 1.7 path a) Or the tautomerization of acylpalladium complex **A** could take place, giving the anhydride as final product and I-Pd-H or Pd (0) (Figure 1.7 path b).

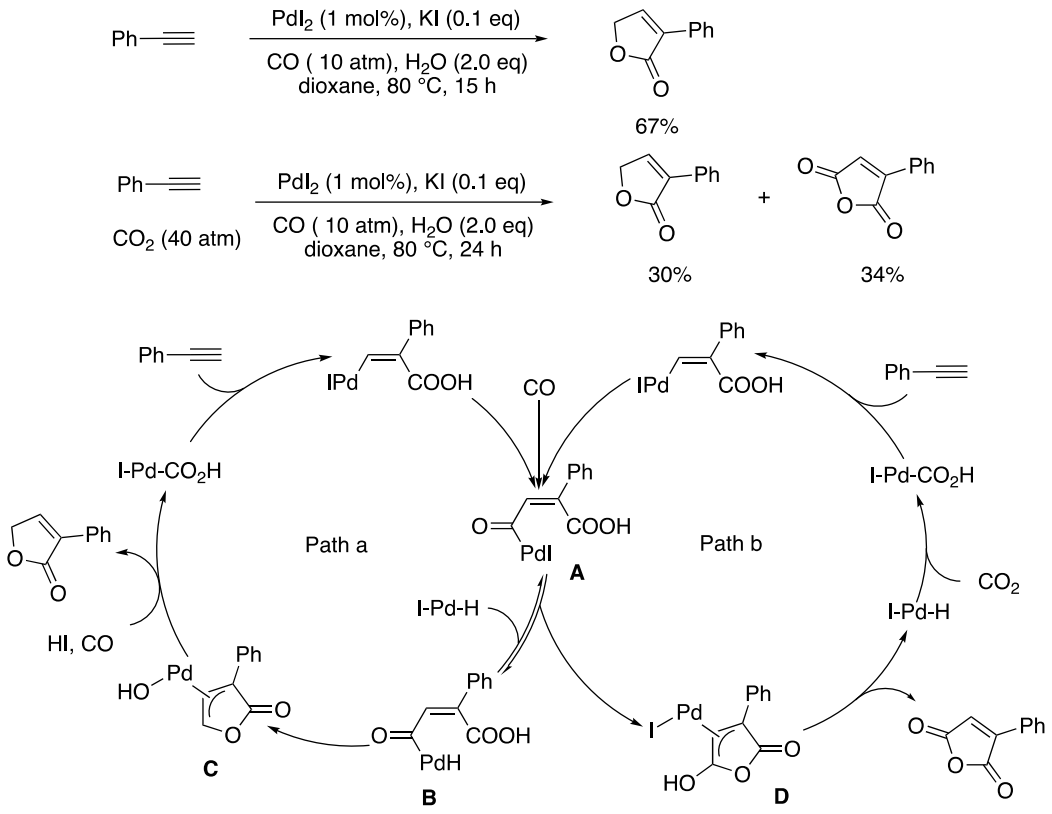
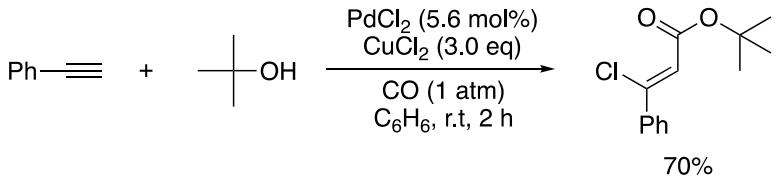


Figure 1.7 Pd-catalyzed cyclocarbonylation of alkynes with and without CO_2. Path a, catalytic cycle for the formation of furanone; path b, catalytic cycle for the formation of maleic acid

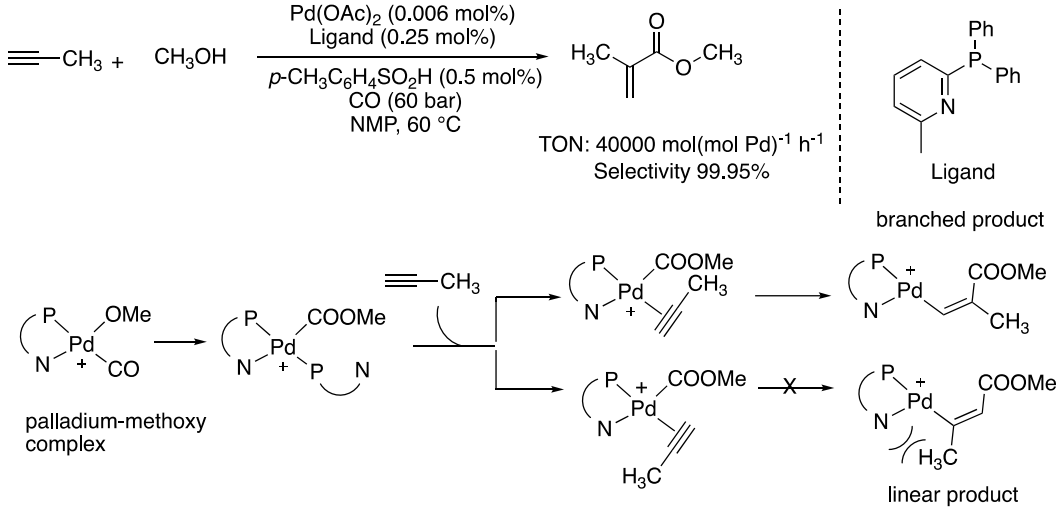
1.2.2.3. Alkoxycarbonylation of alkynes

Alkoxycarbonylation requires alcohols as nucleophiles instead of water. In 1980, Tsuji has studied carbonylation of terminal acetylenes based on a $PdCl_2/CuCl_2$ system. The reactions were run in methanol and NaOAc, and afforded acetylenecarboxylates as products.[81] When HCl was added to methanol instead of the base, unsaturated diesters were observed as products.[82] Later on, Jiang and coworkers developed a highly regio- and stereospecific oxidative chlorocarboxylation of terminal acetylenes with different aliphatic alcohols (Scheme 1.16). The polarity of the solvent was found to be very critical for the selectivity. Only in a less polar solvent (methanol/benzene) (*Z*)-3-chloroacrylates predominated in the products.[83]



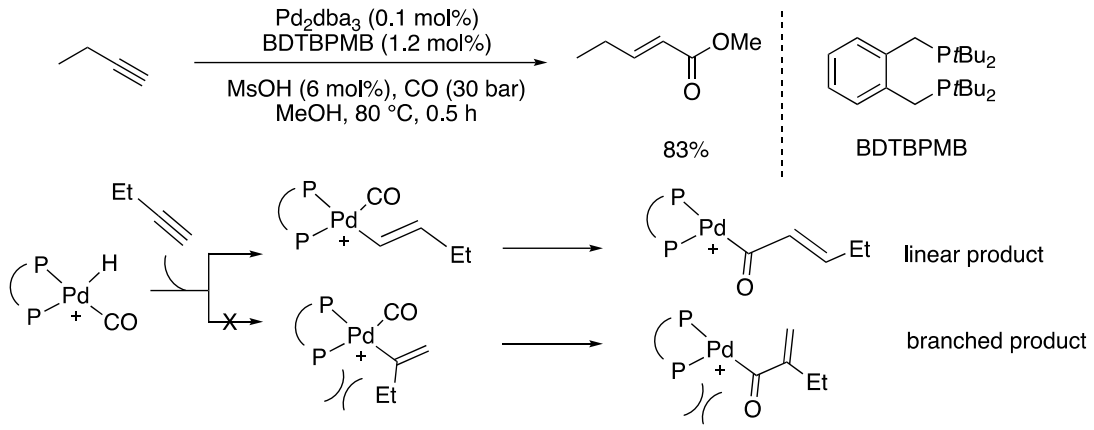
Scheme 1.16 Pd-catalyzed stereospecific chlorocarbonylation of terminal acetylene

Since then, many efforts had been made to improve this transformation.[84-86] Regarding the regioselectivity, Drent and others revealed a quite stereospecific alkoxycarbonylation of alkynes under mild conditions.[87] This method featured a remarkable TONs of more than 40000 as well as selectivity towards branched methacrylates of up to 99.95%. They postulated that this transformation was realized through a carbomethoxy mechanism, in which the regioselectivity was determined by steric factor in a *cis* coordination fashion between the palladium-methoxy complex and an alkyne (Scheme 1.17). The addition of a proton source with weakly coordinating anions (*p*-toluenesulfonic acid) also contributed to the successful transformation.



Scheme 1.17 Pd-catalyzed alkoxycarbonylation of alkynes for efficient synthesis of branched methacrylates

The different regioselectivity was achieved by Cole and coworkers in 2010. In a palladium and bisphosphine catalytic system, linear α,β-unsaturated carboxylates were mainly produced with a good turnover frequency (1700 mol (mol Pd)$^{-1}$ h^{-1}) only after 30 min.[88] A quantitative amount of α,β-diesters were observed if left the reaction for a longer time (> 3 h). The high selectivity has been attributed to a hydride mechanism instead of the carbomethoxy pathway mentioned above. The steric effect between the bulky 1,2-bis-(ditertiarybutylphosphinomethyl)benzene (BDTBPMB) ligand and the substituent on the alkyne played an important role during the regio-determining step (Scheme 1.18). There are also other excellent works on regioselective alkoxycarbonylation with the use of aryl formates as the CO source by Tsuji[89] and Liang.[90]



Scheme 1.18 Pd-catalyzed methoxycarbonylation of alkynes for the synthesis of linear esters

Sonogashira type carbonylation is a highly efficient protocol to establish ynones in one step. The general scheme is illustrated in Figure 1.8a starting with terminal alkynes and aryl halides.[91,92] Extensive efforts have been made by Bäckvall on cyclocarbonylation of enallenes.[93-95] In 2015, they reported a beautiful cascade carbonylation-carbocyclization-carbonylation-alkynation with exclusive chemoselectivity[96-98] (Figure 1.8b). A proposed mechanism started with a coordination between palladium, allene and olefin. Then allene attack took place to yield the vinyl palladium complex **B**. The complex **B** underwent CO insertion, olefin insertion and a second CO insertion, resulting an acyl palladium speices **E**. Subsequently, the alkyne insertion and reductive elimination led to the final product. KIE study indicated that the first allenylic C-H bond cleavage was the rate-determining step. Later, they successfully advanced this method to asymmetric catalysis with the chiral VANOL phosphoric acid as the cocatalyst.[99,100]

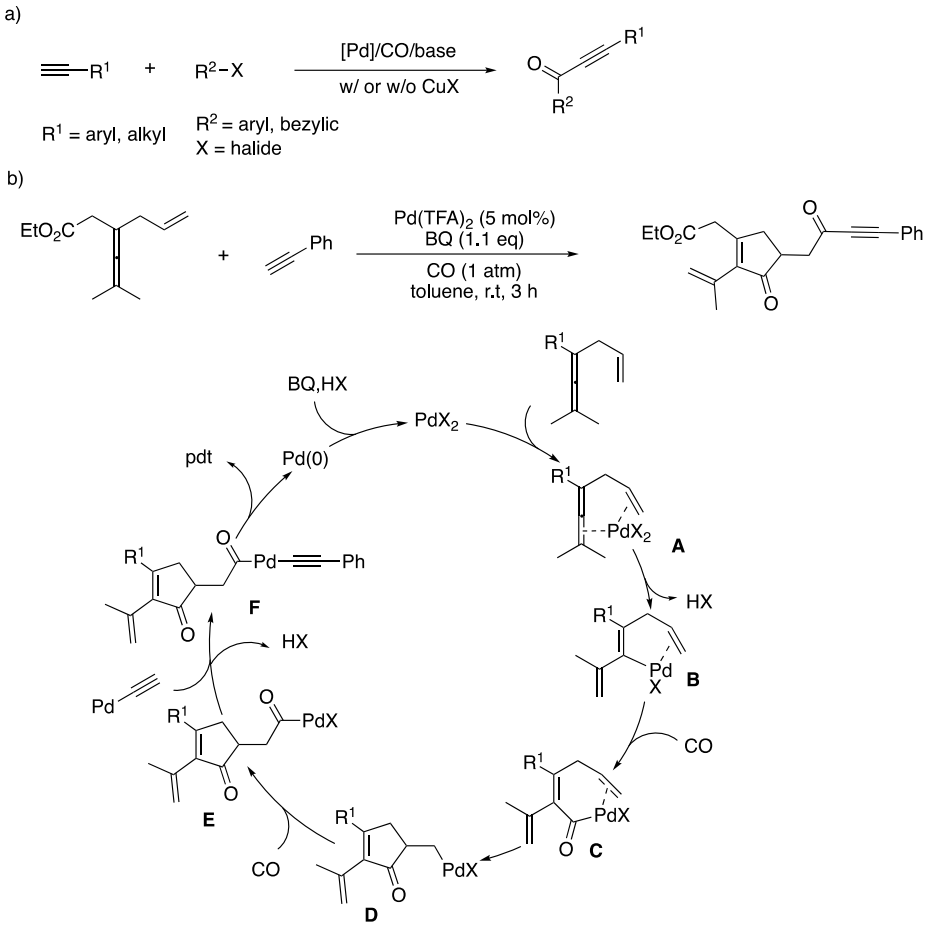
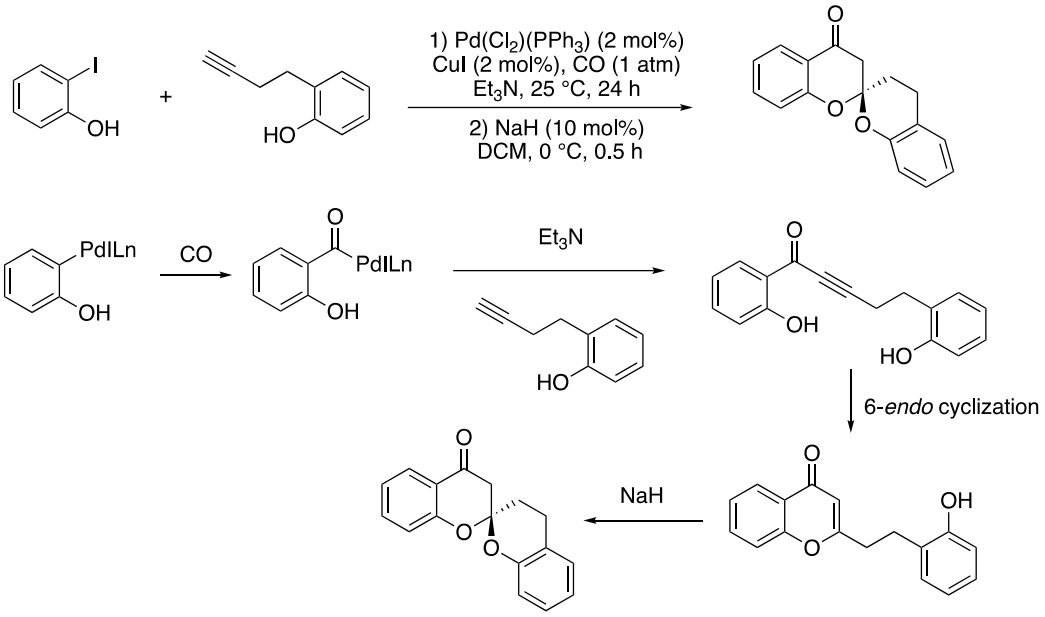


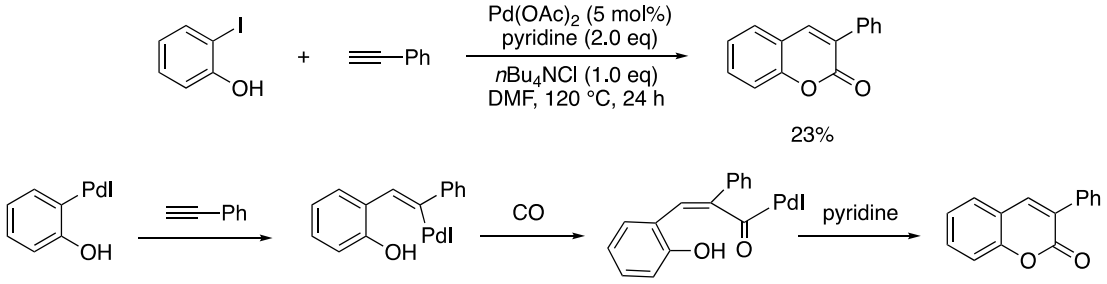
Figure 1.8 a) General scheme of carbonylative Sonogashira coupling reactions; b) Pd-catalyzed oxidative carbonylation of enallenes; BQ: benzoquinone

Besides the mentioned examples, other interesting Sonogashira type carbonylaitons were also investigated by other researchers.[101-104] With *ortho*-iodophenols and terminal alkynes, 5- or 6-membered rings (aurones or chromones) could be obtained under palladium catalytic system and CO atmosphere. Li and coworkers believed that it went through a Sonogashira-type coupling right after CO insertion to result in an ynone first, then cyclized to afford the aurone or chromone derivatives.[105,106] Then it was followed by a second annulation to produce spiroketals in one-pot strategy (Scheme 1.19).



Scheme 1.19 Pd-catalyzed carbonylative Sonogashira annulation to construct spiroketals in one pot

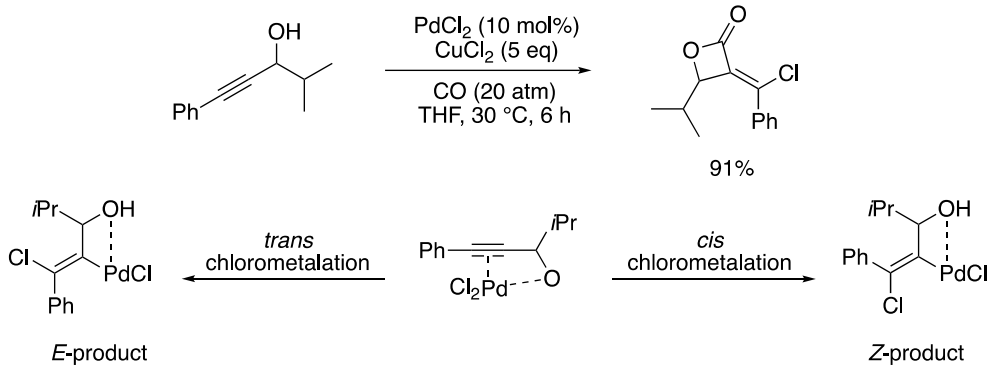
In contrast, Larock reported a carbonylation with totally different selectivity. Under a similar condition, a palladium catalyst and pyridine system, *ortho*-iodophenols and terminal alkynes delivered coumarins as the only products instead of chromones, although with poor yields. In this study, it was indicated that the formation of a vinyl palladium complex occurred instead of the Sonogashira-type coupling mentioned above. Then carbonylation and cyclization took place to furnish the final product, coumarin (Scheme 1.20). The same group also explored this transformation with internal alkynes under a similar condition.[107]



Scheme 1.20 Pd-catalyzed carbonylative annulation of alkynes for the synthesis of coumarins and derivatives

Cyclocarbonylation is considered as an effective method prepare heterocyclic compounds.[108] When the above reactions take place in propargylic alcohols, corresponding lactones can also be obtained as expected. Such transformation is realizable to produce strained β,γ,δ-lactones,[109,110] which represent an important class of biologically active compounds. In 2004, Zhao group reported a good regioselective cyclocarbonylation of propargylic alcohols to afford α-haloalkylidene-β-lactones with particular stereochemistry.[111] Products with *Z*-conformation was mainly

formed, which was originated from the *cis*-chlorometalation of the triple bond (Scheme 1.21). Chiral β-lactones can also be prepared through this route from readily available optically active α-alkynols. In some cases, double carbonylation was also observed.[112,113]



Scheme 1.21 Pd-catalyzed cyclocarbonylation of propargylic alcohols for the synthesis of (*Z*)-α-alkylidene-β-lactones and stereo-determining step

1.2.2.4. Aminocarbonylation of alkynes

In the vein of alkoxycarbonylation, amines can also serve as nucleophiles in carbonylative transformations, providing an efficient route to 2-ynamides from terminal alkynes and amines.[114] Since the early studies have been done by Hoberg with stoichiometric addition of the nickel catalyst in 1983,[115] many improvements have been made on this subject.[116-118] Recently, Xia group reported a facile oxidative aminocarbonylation of alkynes and secondary alkyl amines in the presence of a palladium-*N*-heterocyclic carbene complex.[119] ESI-MS studies supported the formation the amino-palladium complex **A** and the acyl palladium complex **B**. Then a displacement occurred with alkyne under basic condition gave the acyl-palladium alkynyl species **C**. Lastly, 2-ynamide was furnished after elimination (Figure 1.9). Very recently, Zhu and Wu improved the method by switching to a different carbonyl source, $Co_2(CO)_8$.[120] The reaction was conducted at room temperature and in air. It also worked smoothly with bromoalkynes and terminal alkynes.

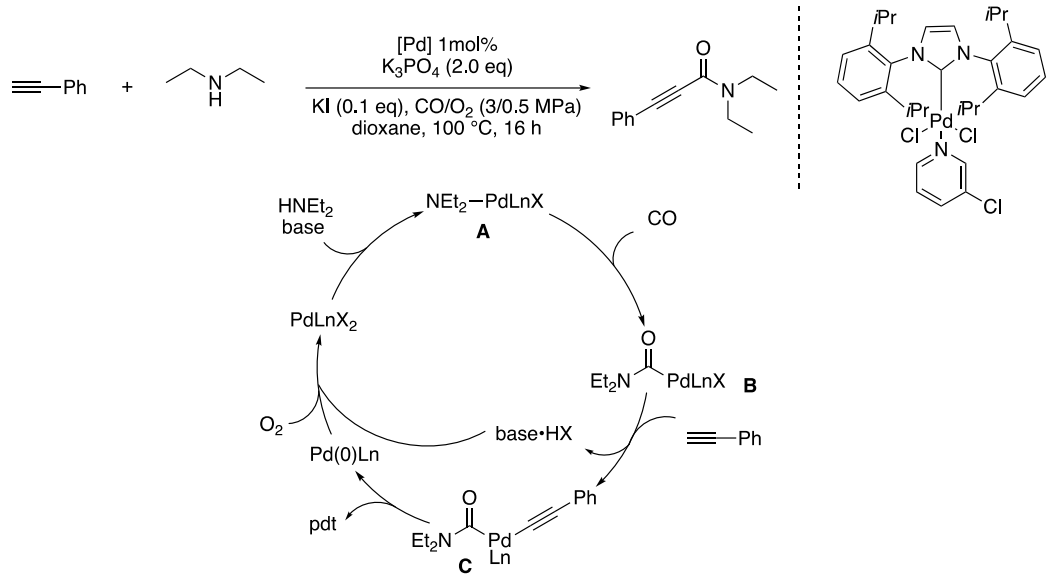
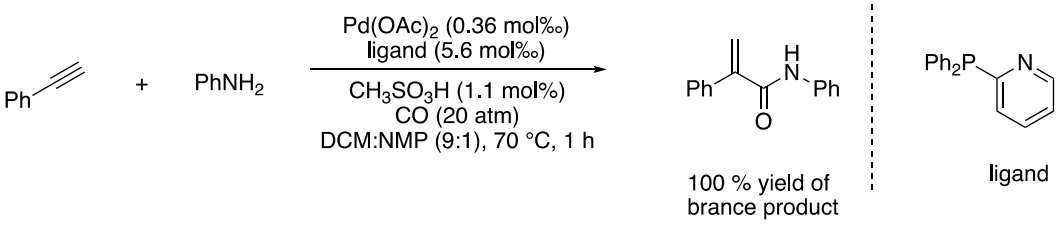


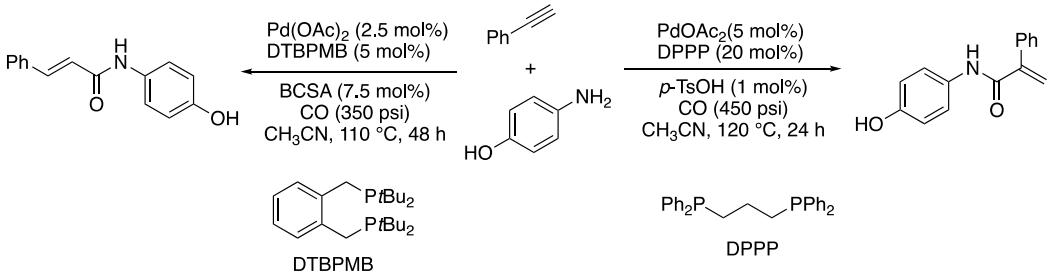
Figure 1.9 Pd-*N*-heterocyclic carbene-catalyzed dehydrogenative aminocarbonylation of terminal alkynes

Starting from the same chemicals, another important class of compounds, α,β-unsaturated amides, can be established under similar conditions. During such transformations, α-methylene amides were mainly produced under most of the catalyst systems.[121] In 2004, Matteoli revealed a selective aminocarbonylation of alkynes with a palladium acetate and (2-pyridyl)diphenylphosphine system for the synthesis of branched acrylamides.[122] The best performance involved use of catalyst accompanied by the addition of methanesulfonic acid. Control experiments were carried out to show that the mixed solvent system of dichloromethane and *N*-methylpyrrolidinone was the optimal to achieve the highest reaction rates. However, this reaction was operated at a relatively high CO atmosphere, 20 atm (Scheme 1.22). Later, Alper and Yu reported a similar transformation with a bidentate phosphine ligand, 1,3-bis(diphenylphisphino)propane, in an ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide [BMim][Tf_2N] without assistance of any acid additives.[123] This methodology worked with a broader scope of alkynes and amines. Another feature of this method was that the catalyst can be recycled five times without loss of catalytic activity.



Scheme 1.22 Pd-catalyzed aminocarbonylation of alkynes for the synthesis of α-methylene amides

To achieve different regioselectivity, Alper and Sha developed an interesting ligand and additive-controlled catalytic systems to deliver two different α,β-unsaturated amides.[124] The combination of boronic acid and 5-chlorosalicyclic acid would provide the rare linear products with 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) as the ligand; the branched amides could be accessed with *p*-toluenesulfonic acid and DPPP as the ligand. Another advantage is that this method demonstrated good tolerance to different functional groups, such as vinyl and carboxy groups. Even with the presence of phenol group, the method exhibited excellent chemoselectivity (Scheme 1.23). According to their mechanistic study, the authors believed that the reactions were operated through two different mechanism: with the *p*-toluenesulfonic acid and dppp ligand, there was a formation of an arylcarbamyolpalladium complex, then the alkyne reacted with this complex to yield the final branched product; with BCSA and DTBPMB, a hydride mechanism was favored, in which the palladium hydride was established first, then inserted to the alkyne, followed by CO insertion and amination. The regioselectivity was mainly affected due to steric reason during the migration step.



Scheme 1.23 Ligand and additive controlled selective aminocarbonylation with alkynes to divergently synthesize acrylamides; BCSA: the mixture of 1.0 eq $B(OH)_3$ and 2.0 eq salicylic acid

For the transformations with primary amines, cyclized double carbonylation was observed to yield the very important succinimide compounds, reported by Liu and Dyson in 2014.[125] In the presence of *p*-toluenesulfonic acid and Pd(xantphos)Cl_2, variety of alkyl and aryl amines with either terminal or internal alkynes were transformed to succinimide and its derivatives in good yields. With the lack of a detailed mechanism, the authors anticipated aminocarbonylation of an alkyne happened first, in the similar manner of hydroformylation to result in α,β-unsaturated amides (Figure 1.10 left cycle). Then the double bond in the unsaturated amides was further activated by the palladium hydride catalyst, and carbonylated to furnish the final cyclized product (Figure 1.10 right cycle).

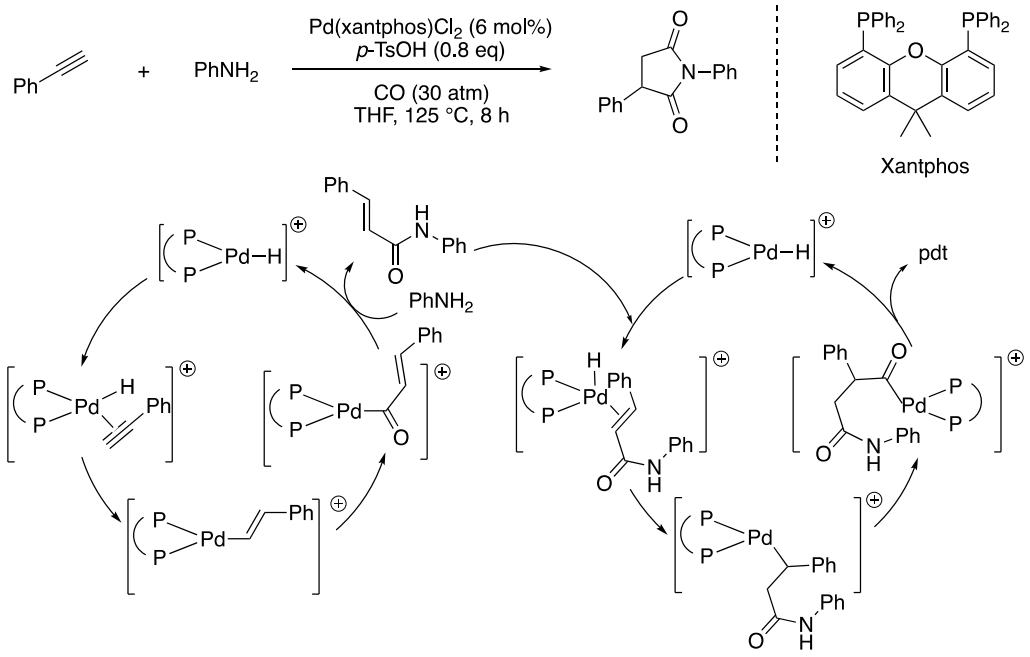


Figure 1.10 Pd-catalyzed aminocarbonylation of alkynes for the synthesis of succinimides

In addition to primary and secondary amines, tertiary amines can also be employed as a good nitrogen source due to its lower binding affinity to metal centers. Direct functionalization with tertiary amines has attracted much attention, and significant advancement has been made over the past ten years.[126-128] In 2017, Huang developed a hydroaminocarbonylation of alkynes and tertiary amines to produce branched acrylamides selectively[129] (Figure 1.11). The C-N bond activation required the use of di-*tert*-butylperoxide. They proposed the reaction started with the formation of a palladium hydride species **A**. Then addition of species A to alkyne in Markovnikov rule afforded the branched alkenyl palladium complex **B**, followed by CO insertion to have the acyl palladium complex **C** formed. Meanwhile, tertiary amine was cleaved in the presence of peroxide, and intercepted with complex **C** to give intermediate **D**. The last step was the release of amide product and regeneration of the catalyst.

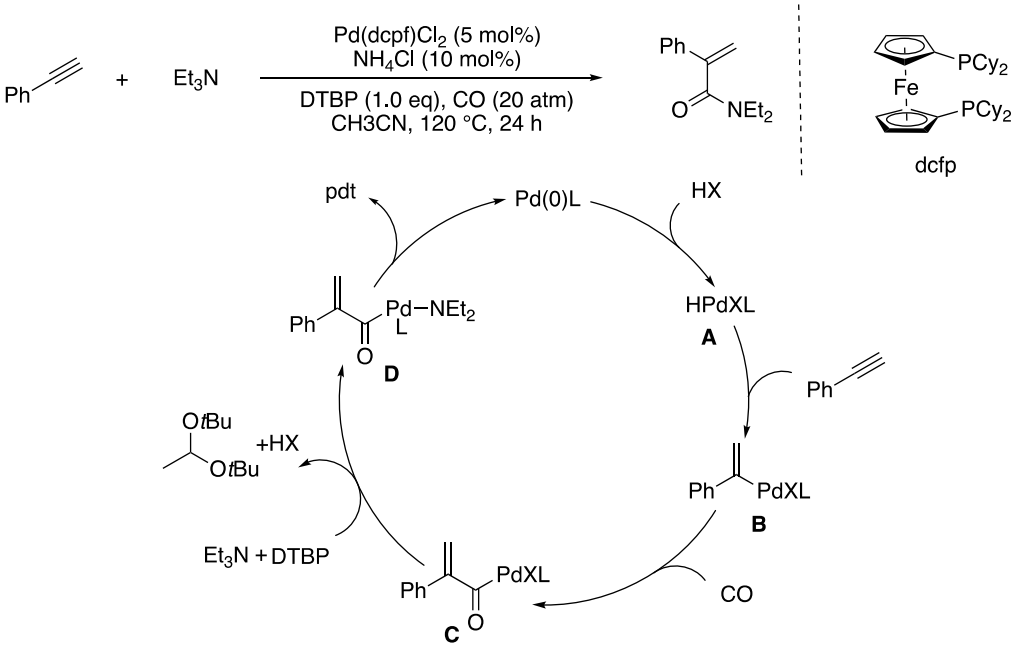


Figure 1.11 Pd-catalyzed hydroaminocarbonylation of alkynes and tertiary amines to branched amides synthesis. dcfp: 1,1'-bis(dicyclohexylphosphino)ferrocene

In the past decades, chemists explored more catalytic systems for this transformation. It was investigated that cyclic imides could be delivered with the stoichiometric addition of $Fe_3(CO)_{12}$ or $Fe(CO)_5$ and excess primary amines.[130] In continuing efforts, Beller et al. had enabled such transformation catalytically with the same metal carbonyls, $Fe_3(CO)_{12}$ or $Fe(CO)_5$, and amines or ammonia.[131] One year later, the same group published another work on selectively synthesis of linear acrylamides using the same catalyst and a diimine ligand[132] (Figure 1.12). They proposed two independent mechanisms for the two distinct regioisomers. For the monocarbonylation, they suspected the involvement of the iron hydride **A**. Then it underwent alkyne addition in anti-Markovnikov manner and CO insertion to give the acyliron complex **B**. After the nucleophilic attack of amine, the linear acrylamide was delivered. For the double carbonylation, it was processed by a concerted double CO insertion with the formation of the cyclic acyliron complex **D**, and reaction with amine to furnish the desired succinimide compound.

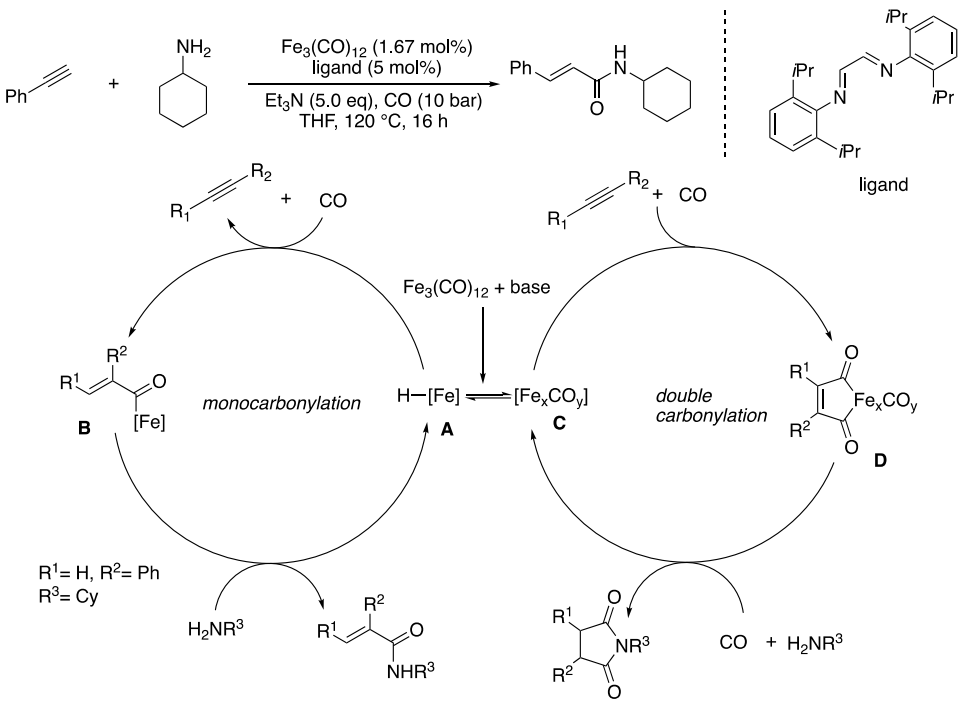
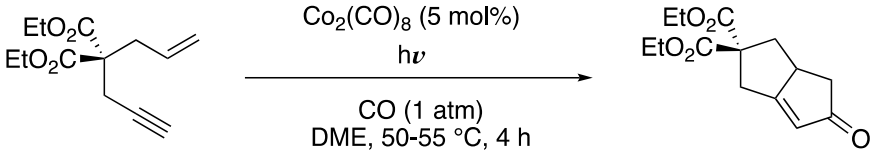


Figure 1.12 Pd-catalyzed selective carbonylation for selective synthesis of linear arcylamides; catalytic cycles for monocarbonylation and double carbonylation

1.2.2.5. Pauson-Khand reaction

Pauson-Khand reaction describes a [2+2+1] cycloaddition with a triple bond, a double bond, and carbon monoxide to construct cyclopentenones.[133] The first Pauson-Khand reaction was reported as the reaction between a stoichiometric alkynedicolbalt hexacarbonyl complexes with bicyclo[2,2,1]hepta-2,5-dienes.[134] Soon after, the first catalytic approach was discovered by Pauson in 1973 using ethylene, norbornene and catalytic amount of octacarbonyldicobalt.[135] In 1996, the first intramolecular Pauson-Khand reaction was reported by Livinghouse, which required a photochemical activation of the $Co_2(CO)_8$ at mild conditions (50-55 °C and 1 atm CO)[136] (Scheme 1.24). A highly pure $Co_2(CO)_8$ was used due to the poor reproducibility of this reaction. To overcome this problem, several additives were studied.[137] Amine *N*-oxide was first used by Kerr at ultrasound conditions.[138] Trimethylamine *N*-oxide dihydrate (TMANO) was subjected to the reaction condition, almost quantitative yield was achieved at room temperature just in 10 min. However, it was accompanied by the formation of amine as the side product. Recently, Geary et al. employed nitrous oxide (N_2O) as the promoter with stoichiometric catalyst addition. In this case, only gaseous byproduct nitrogen (N_2) was produced.[139] Meanwhile, other additives were also documented, such as phosphine oxide[140] and methyl sulfide.[141]



Scheme 1.24 Co-catalyzed intramolecular Pauson-Khand reaction with photoactivation

The general cycle for cobalt-catalyzed intermolecular Pauson-Khand reaction is depicted in Figure 1.13.[142, 143] First is the oxidative addition of hexacarbonyl dicobalt to the alkyne substrate, resulting in the alkyne dicobalt carbonyl complex **A**. After the ligand substitution with the alkene substrate and alkene insertion, complex **C** is formed. Then, CO insertion takes place, followed by two consecutive reductive elimination steps. The final product, cyclopentenone, is established and the hexacarbonyl dicobalt remains for the next cycle. Although $Co_2(CO)_8$ is mainly used for Pauson-Khand reaction, it must be handled at quite inert atmosphere because it easily catches fire in contact with air. Other metals for Pauson-Khand reaction have also been studied.[144-146] Rhodium was reported to be more active than cobalt.[147, 148] However, Rh is normally not effective for intermolecular transformations. The bimetallic systems, such as Co nanoparticles and $Ru_3(CO)_{12}$,[149] or Rh_2Co_2 nanoparticles on charcoal,[150] are proved to be efficient for both inter- and intramolecular cyclocarbonylation. The catalysts can be recycled five times without loss of activity.

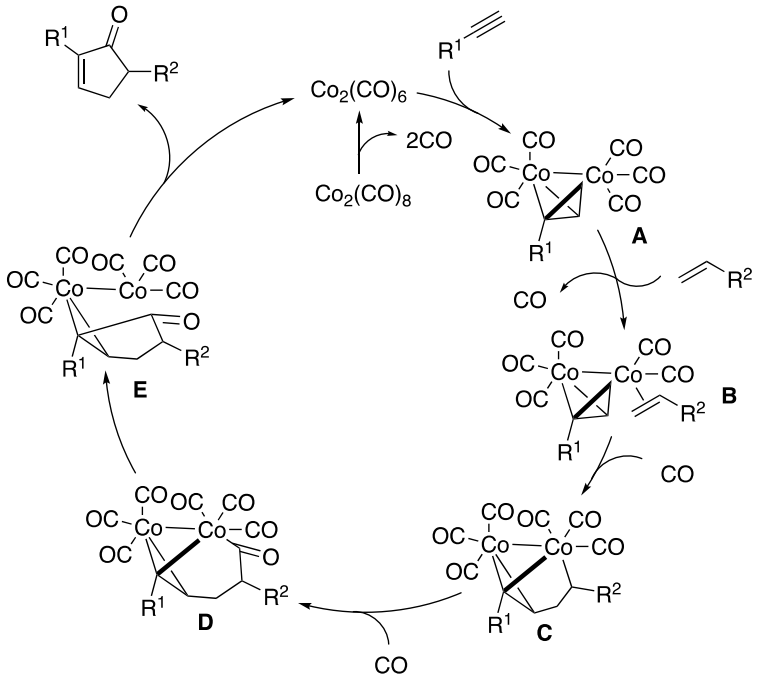


Figure 1.13 General mechanistic cycle for catalytic Pauson-Khand reaction catalyzed by $Co_2(CO)_8$

1.2.3. Carbonylation of C-X bonds

1.2.3.1. Carbonylation of carbon-(pseudo)halogen bonds

Transition metal catalyzed oxidative addition of aryl halides has attracted extensive attention for C-C bond or C-X bond formation. Carbonylation of aryl halides constitutes an important branch under this umbrella. The earliest formylation of aryl halides was documented by Schoenberg and Heck in 1974. Aryl or vinylic halides were formylated with synthesis gas (1100 psi) at 80-150 ℃ by a palladium catalyst.[151] Later, other catalytic systems were investigated with silane as hydrogen donor[152] or under a Pd-Co bimetallic system.[153, 154] However, these reactions required hash conditions, such as high pressure (> 50 atm). It was also found that hydrodehalogenation always accompanied as the side reaction. In 2006, an efficient protocol for formylation of (hetero)aryl bromides was presented by Beller[155] (Figure 1.14). The reaction was run at 100 ℃ in the presence of 5 bar of syn gas. Only 0.1 mol% catalyst loading was required for smooth transformation. Furthermore, the ligand, di-1-adamantyl-*n*-butylphosphane (cata*CX*ium A), used for the reductive formylation is quite stable in air, thus it enabled that it is the first industrial application of formylation of aryl bromides in the scale of more than 1000 kg. Computation study and experiments indicated the reaction went through oxidative addition, carbonylation and hydrogenolysis of acyl complex **B** to yield the formylated product.[156] Other compounds, such as solid aryl formates and formic acids[157] employed as CO source for carbonylation of aryl halides were also investigated by researchers in an effort to avoid gas manipulation. For example, *N*-formylsaccharin developed by Manabe,[158, 159] aryl formates by Tsuji[160], benzene-1,3,5-triyl-triformate (TFben)[161] and $Mo(CO)_6$[162] are all easy to synthesize and robust for carbonylative transformations.

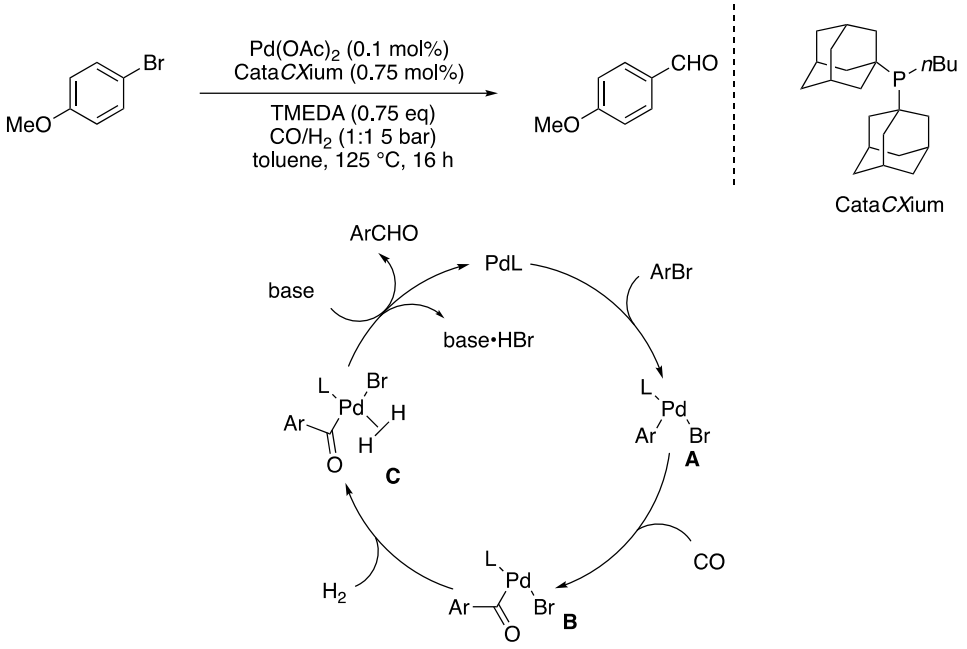
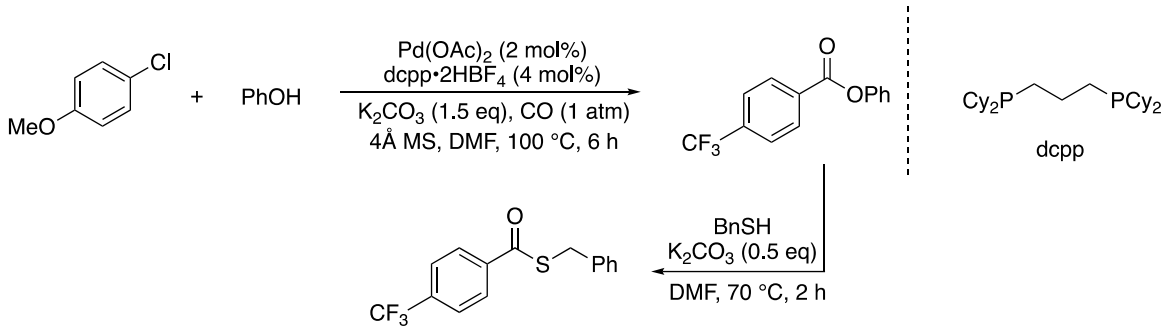


Figure 1.14 General Pd-catalyzed formylation of aryl bromide with air stable Cata*CX*ium phosphine ligand; TMEDA: tetramethylethylenediamine

Alkoxycarbonylation of aryl halides is a straightforward method to prepare (hetero)aromatic carboxylates and their derivatives.[163] Buchwald demonstrated a general protocol to produce such compounds via carbonylation of aryl chlorides and alcohols at atmospheric pressure of CO[164] (Scheme 1.25). The mild condition broadened the reaction tolerance, while it was compatible with alcohols with low boiling points, like methanol and ethanol, to provide methyl or ethyl aromatic esters. The esters can serve as intermediates to derivatize to many other carboxylate derivatives, such as thiol and allyl esters.



Scheme 1.25 Pd-catalyzed carbonylation of aryl chlorides to prepare phenyl esters as acyl transfer reagent

Attempts have been made to develop novel catalyst without phosphine ligands due to their relative instability in oxidative conditions. Sugi and coworkers developed a covalently bonded Pd(II) complex with a cyclometallated oxime ligand as shown in figure 1.15,[165] which is more efficient toward less reactive phenols.

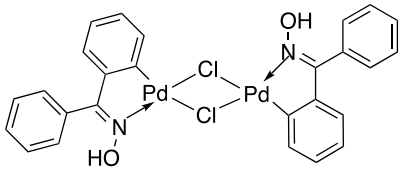


Figure 1.15 Novel dimeric cyclometallated oxime palladium catalyst for carbonylation of aryl iodides

In 2007, Buchwald successfully developed the first general method of aminocarbonylation of aryl chlorides.[166] In this system, bulky electron-rich phosphine ligand dcpp proved to be the optimal ligand. Sodium phenoxide was found not only to serve as base additive for the promotion of carbonylative cycle, but also as an acyl transfer agent for the subsequent aminocarbonylation, in the same manner as described in Scheme 1.25. Like all other palladium-catalyzed carbonylation, the acyl palladium complex was formed then intercepted with sodium phenoxide to yield the phenyl ester compound **D**, which is critical to allow for low temperature operation. Then sodium phenoxide once again catalyzed the amination with amine as a Brønsted base to deliver the corresponding amides (Figure 1.16). Some advanced cascade research was carried out based on this subject. Recently, Wu group presented a Pd-catalyzed aminohomologation of aryl halides and amines for the synthesis of benzylic amines.[167] The reaction proceeded a Pd-catalyzed carbonylation of aryl halide to deliver aromatic aldehydes. Then it was followed by an imine formation with amines and a reduction of the imine with formic acid to yield the final product. The other versions of aminocarbonylation of aryl halides with $Mo(CO)_6$ are also well established.[162,168]

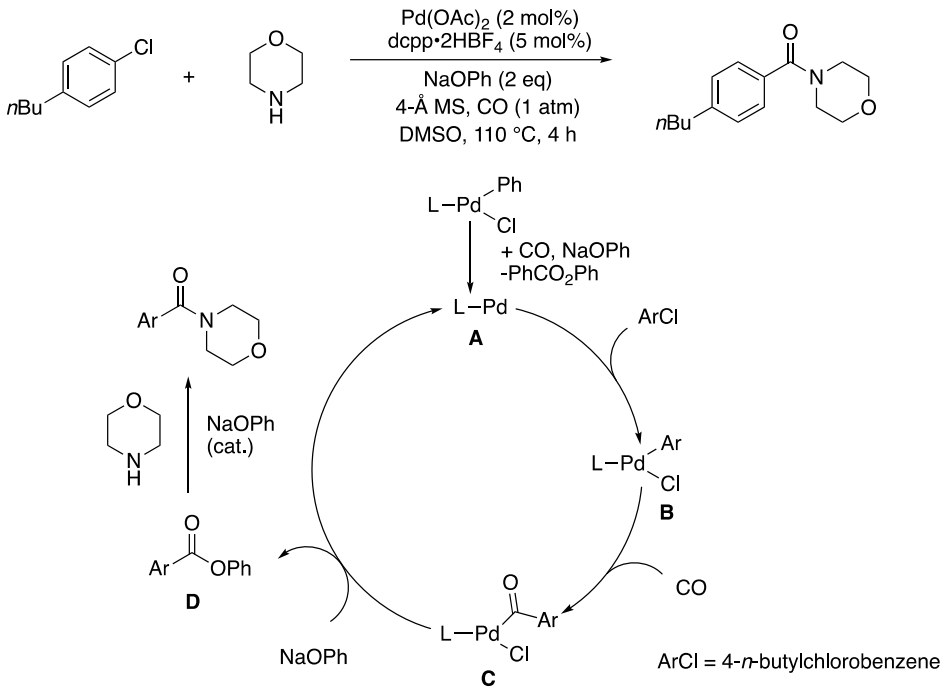


Figure 1.16 Pd-catalyzed aminocarbonylation of aryl chlorides with sodium phenoxide additive

The above carbonylation could also occur twice with a single aryl halide substrate, thus providing routes to construct more complex molecules.[169,170] In 2015, Wu at el. reported a decarbonylative synthesis of tetracycle quinazolines from simple 2-bromoanilines and 2-bromobenzyl amines[171] (Figure 1.17). Under the palladium-catalyzed system, the widely existing 4(3*H*)-quinazoline skeleton could be achieved via one step in good yields and in a selective fashion. However, this method is not compatible with heteroaromatic amines and halides. According their investigation and literature precedents, a possible mechanism was suggested. It started with a palladium oxidative addition and CO insertion to produce the acyl complex **B**. Then after reductive elimination, complex **C** reacted with the second amine substrate to yield the stable intermediate **D**. Then **D** entered another palladium catalytic cycle to furnish the final product. In addition to halide groups, other pseudohalides are also employed during carbonylation for interesting transformations, including azides,[172] tosylates,[173] sulfonyl chlorides,[174] and triflates[175].

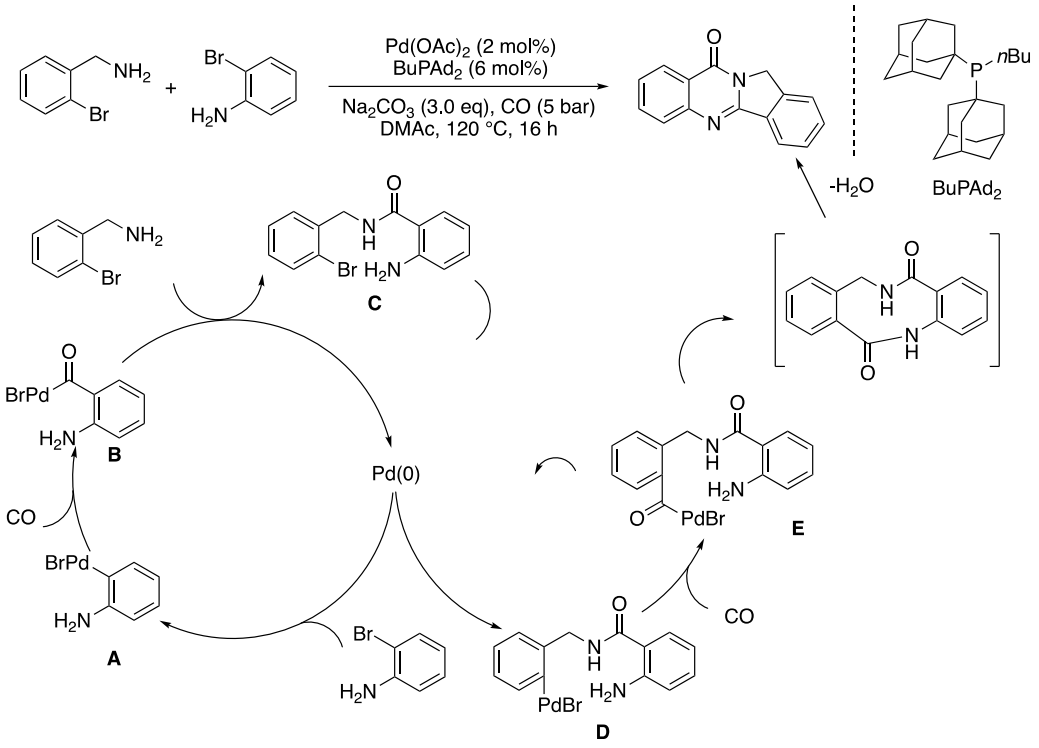


Figure 1.17 Pd-catalyzed dicarbonylation to for the synthesis of tetracycle quinazolines. DMAc: *N*,*N*-dimethylacetamide

1.2.3.2. Carbonylation with organometallic reagents

In addition to the hydrogen, alcohol and amine nucleophiles mentioned previously, organometallic reagents are popular nucleophiles in carbonylative cross couplings. Similar to the traditional cross-coupling reactions, the multicomponent carbonylative cross couplings with carbon monoxide and organometallic reagents complement the ketone synthesis.[13] These useful and convenient carbonylative cross couplings underwent rapid development with aryl halides and became popular to synthesize carbonyl-containing compounds with different carbon nucleophiles.[176,177]

Back in 1988, the carbonylative Stille coupling was reported by Echavarren and Stille with aryl triflates and organostannanes.[178] The reaction had a good tolerance on the aryl triflate side: alcohol, nitro, and ester groups worked well. In contrast, electron-deficient groups like ester and alcohol groups on the tin part led to the decomposition of the starting material. This reaction required the use of lithium chloride, which facilitates the transmetallation between acyl palladium complex and organotin compounds (Figure 1.18). In other scenarios, copper(I) iodide[179] or tetrabutylammonium iodide[180] were used.

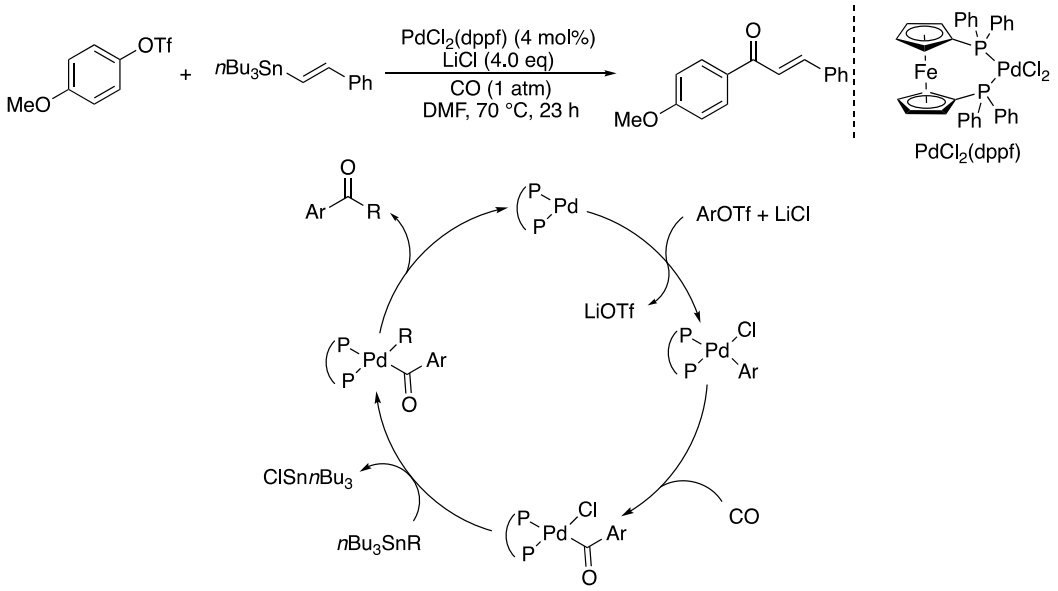


Figure 1.18 Pd-catalyzed carbonylative Stille reactions. dppf: 1,1'-ferrocenediyl-bis(diphenylphosphine)

Beller and coworkers developed an efficient route for the synthesis of diaryl ketones via carbonylative Suzuki reaction.[181,182] Starting with aryl or heteroaryl bromides and boronic acids, diaryl ketones were obtained in moderate to good yields.[183,184] The choice of sodium ethoxide as base extensively favored the chemoselectivity (94%) towards the formation of diary ketone over biarylation. Also, high carbon monoxide pressure helped the CO insertion, thus shifting the reaction to carbonylation (Figure 1.19). There are also some examples taking advantage of *N*-heterocyclic carbene ligands for this coupling reaction.[185,186]

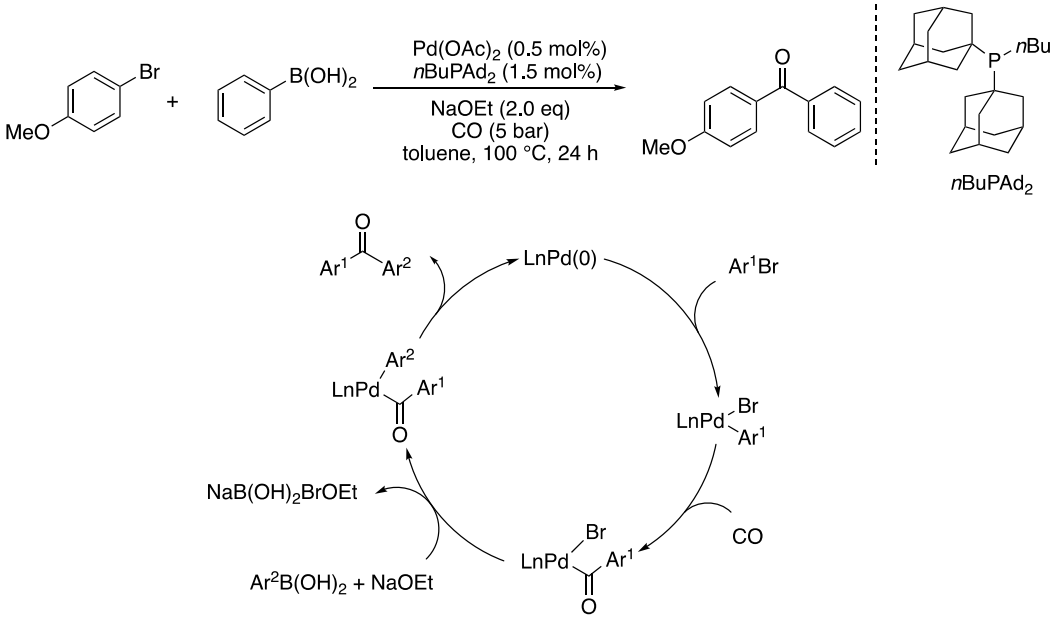
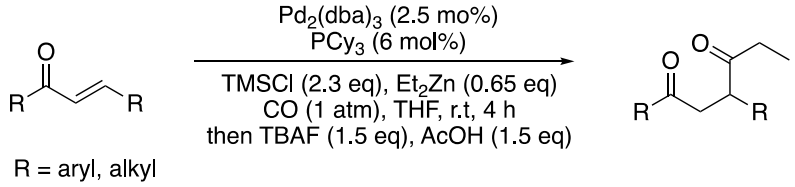


Figure 1.19 Pd-catalyzed Suzuki type carbonylation

It is comparably rare to perform carbonylations with organozinc reagents.[187,188] In 1983, Yoshida and coworkers first realized carbonylation with aryl iodides and alkyl iodides under 1 bar of CO.[189] Aryl alkyl ketones were achieved with stoichiometric addition of Zn-Cu. An interesting finding was made by Morken in 2010 as Negishi-type carbonylation took place in the presence of a carbonyl moiety in the substrate[190] (Scheme 1.26). This conjugate addition reaction accomplished variety of 1,4-diketones with dialkyl zinc reagent. Even the β-substituted enones provided the targeted diketone, which was not observed in a similar transformation.



Scheme 1.26 Pd-catalyzed carbonylative Negishi reaction with unsaturated carbonyls

1.2.3.3. Carbonylation of C-H bonds

Although the cross-coupling reaction is a powerful method for synthesis with multiple components, it requires the use of pre-functionalized substrates: electrophiles such as aryl halides pseudohalides, and nucleophiles such as organometallic reagents. From the perspective of atom economy, direct C-H carbonylation would require less reagents and enable shorter synthetic routes. With regard to dehydrogenative carbonylation, it mostly proceeds through an oxidative pathway. In 2008, Yu at el. presented a direct C(sp^2)-H carboxylation of benzoic acids or derivatives[191] (Figure 1.20). With the assistance of the carboxylic moiety as the directing group, dicarboxylic acids can be constituted in a selective manner. For the phenyl acetic acid substrates, the product was a mixture of dicarboxylic acids and anhydrides. This method worked well with variety of functional groups; nevertheless, substrates with electron-deficient substituents and the carboxylic acid group itself retarded the reaction, which was believed to undergo an electrophilic palladation. Subsequently, CO insertion and reductive elimination took place to yield the anhydride product **C**. Last, part of dicarboxylic acids were converted to anhydrides to yield mixed products.

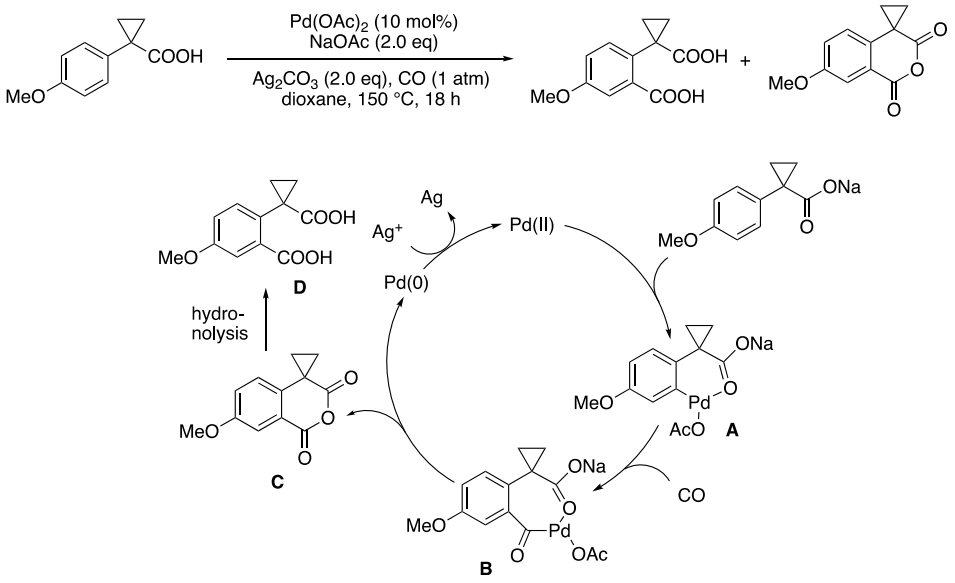
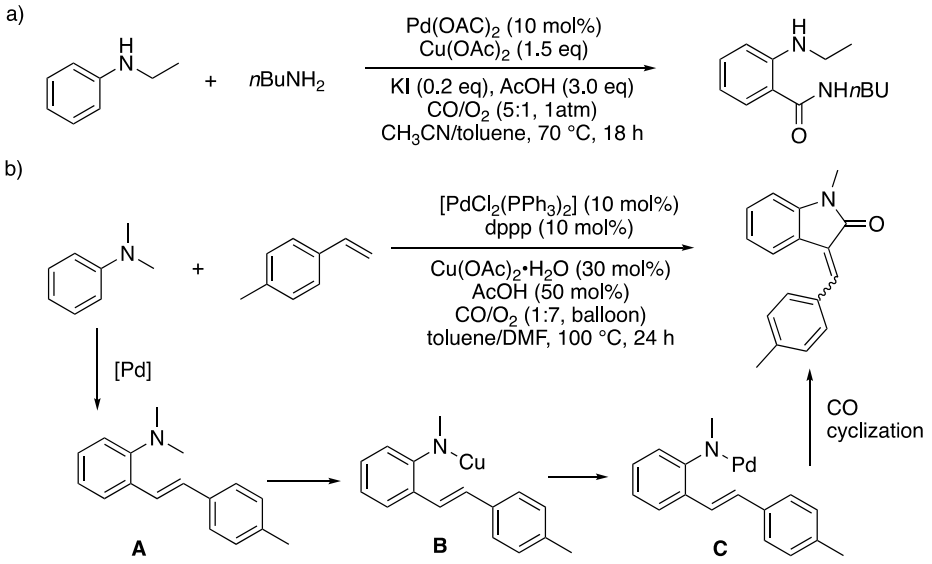


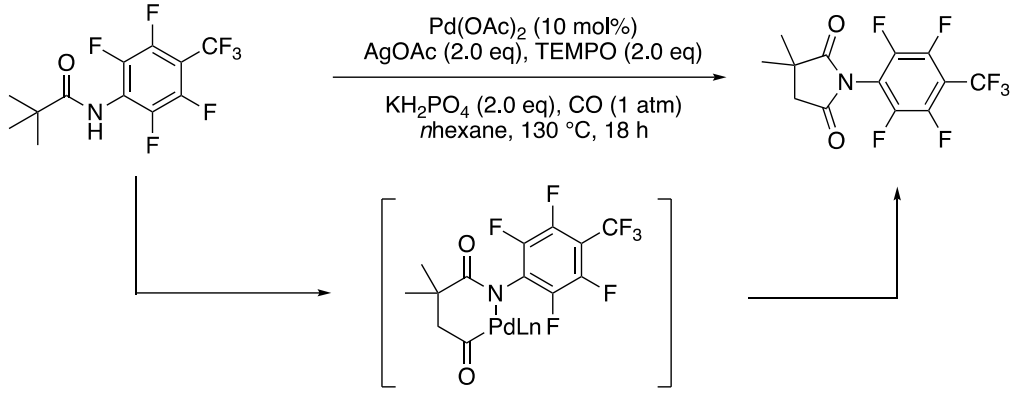
Figure 1.20 Pd-catalyzed carboxylation of aryl C-H bonds for the synthesis of 1,2 and 1,3-dicarboxylic acids

Direct aminocarbonylation of C(sp^2)-H bonds was also investigated. In 2016, Zhang group achieved the *ortho*-selective C-H carbonylation in the presence of an amine directing group.[192] Under mild conditions, many different *ortho*-aminobenzamides were synthesized from *N*-substituted anilines and primary amines in one-pot strategy (Scheme 1.27a). In terms of C(sp^2)-H activation, Lei and coworkers reported a beautiful cascade reaction co-catalyzed by palladium and copper.[193] Starting with the tertiary anilines, a palladium catalyzed *ortho*-C(sp^2)-H alkenylation occurred with the terminal olefins. The Heck-type coupling gave the formation of the alkenylated intermediate **A**. Thereafter, the C(sp^3)-N bond was activated by copper and transmetallated with palladium to finish the carbonylation and cyclization (Scheme 1.27b).



Scheme 1.27 a) Pa-catalyzed ortho-selective C-H carbonylation b) Pd/Cu-catalyzed cascade transformation: C-H alkenylation and N-dealkylative carbonylation

On the basis of carboxylation of *ortho*-C(sp^2)-H bonds, the group of Yu continuously explored new possibilities with C-H carbonylation.[194] Two years later, they demonstrated a β-C(sp^3)-H carbonylation in the presence of an acidic amide directing group. The succinimide products could be accessed in good to moderate yields, and then converted to valuable 1,4-dicarboxylic acids. The protocol required the addition of TEMPO reagents as the co-oxidant with silver acetates for the catalyst regeneration (Scheme 1.28). Meanwhile, there are also studies carried out on other C(sp^3)-H bonds,[195, 196] including allylic C-H bonds,[68] benzylic C-H bonds[197] or remote C-H bonds.[198]



Scheme 1.28 Pd-catalyzed carbonylation of C(sp^3)-H bonds; TEMPO: 2,2,6,6-tetramethylpiperidine 1-oxyl

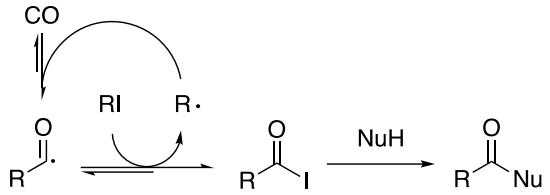
1.3. Metal-catalyzed radical carbonylation

In the context of carbonylation, the previous subchapter has mainly discussed transformations with precious metals that favor two-electron redox cycling. The substrates were constrained to unsaturated compounds, like olefins, alkynes or sp^2-carbon substrates. Even the well-established Monsanto and Cativa processes encounter limitations with substrates containing longer alkyl chains. Indeed, it is rare to see carbonylative transformations with alkyl substrates due to the slow oxidative addition of alkyl halides and potential isomerization from β-hydrogen elimination of metal-alkyl intermediates.[199] As a consequence, single electron chemistry provides a useful alternative and conceptually addresses the problems, since the alkyl radicals do not suffer from the isomerization in such conditions.

1.3.1. Radical chain carbonylation and photochemistry

After the pioneering study done by Coffman in 1952,[200] Ryu and coworkers extensively studied this topic with alkyl iodides.[17] Their development of carbonylation of alkyl substrates consists of reaction between alkyl radicals and CO, and an iodine atom transfer step to yield an important acyl iodide intermediate. Relying on this atom transfer

carbonylation (ATC) process, various compounds can be synthesized from alkyl iodide starting materials, such as esters, amides, lactams and lactones (Scheme 1.29).



Scheme 1.29 Atom transfer carbonylation

The example depicted in Figure 1.21 illustrates an intramolecular carbonylation to afford γ-lactones under photoirradiation and palladium catalyst.[201] They envisioned that alkyl radical underwent atom transfer carbonylation to yield the acylpalladium intermediate, then it was quenched with the alcohol to give the final product. The direct C(sp^3)-H carbonylation was also investigated by several researchers. In 1991, Crabtree and coworkers used metallic Hg as a photocatalyst under 254-nm irradiation to carbonylate cyclohexane under mild conditions.[202] However, relatively poor selectivity (<60%) for the cyclohexyl aldehyde was observed under all conditions examined, with the main byproducts being cyclohexyl dimer from radical homocoupling and dicyclohexyl ketone.

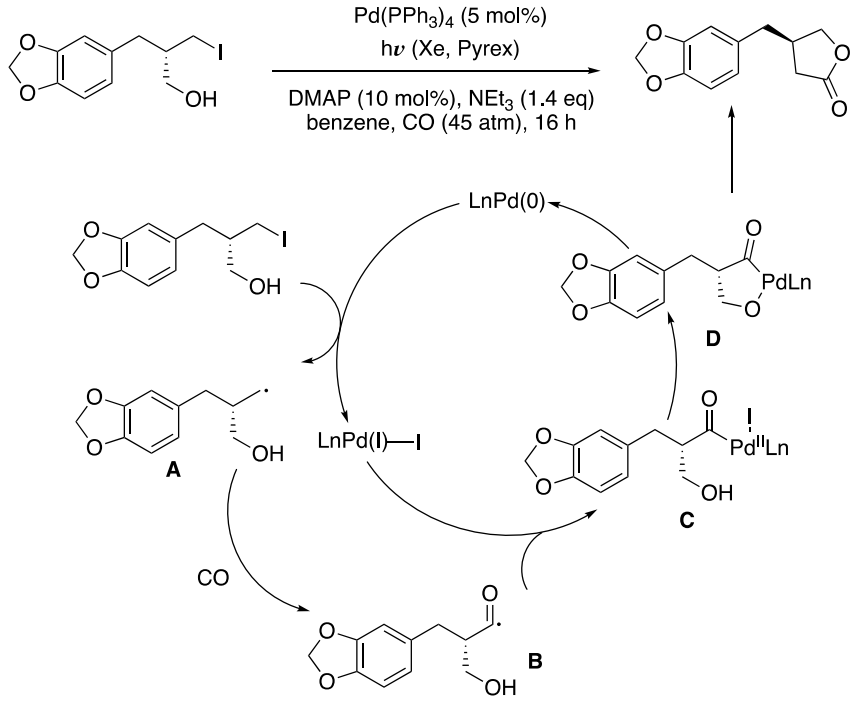


Figure 1.21 Pd/light-accelerated atom transfer carbonylation of alkyl iodides. DMAP: 4-methylaminopridine

Our group has also studied the atom transfer carbonylation under copper systems. It was found that group found that hydrocarbonylative coupling of alkynes with tertiary alkyl halides provided highly-substituted allylic

alcohol derivatives, presumably via *in situ* 1,2-reduction of the α,β-unsaturated ketone formed from the coupling reaction.[203] In this atom transfer carbonylation chain, the tertiary alkyl halide is carbonylated without metal mediation, producing an acyl iodide intermediate **B**. The acyl iodide then adds to the copper catalyst to form **D**, ultimately expelling the coupled product by reductive elimination (Figure 1.22).

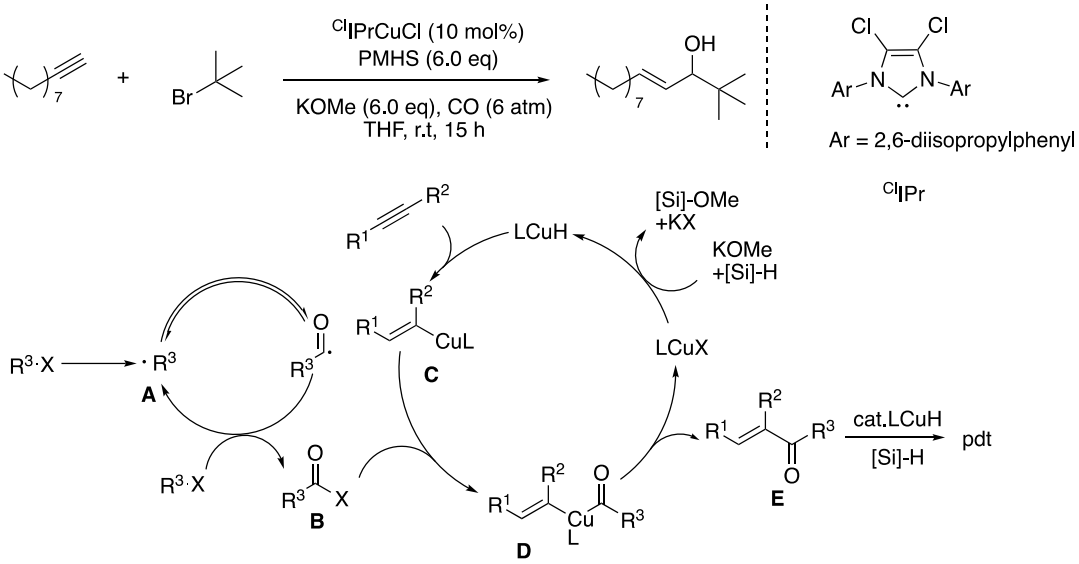


Figure 1.22 Cu-catalyzed Hydrocarbonylative carbonylation of alkynes and alkyl halides. PMHS: poly(methylhydrosiloxane)

1.3.2. Metal-induced radical carbonylation

Based on seminal work by Heck and Breslow in 1963 on alkoxycarbonylation and aminocarbonylation of alkyl iodides catalyzed by $[Co(CO)_4]^-$ and $[Mn(CO)_5]^-$, the Alexanian group developed a practical manganese-catalyzed carbonylation of alkenes to constitute diversified cyclic or bicyclic esters under very mild conditions (Figure 1.23).[204] In the proposed mechanism, homolysis of $Mn_2(CO)_{10}$ produces the active $[Mn(CO)_5]\cdot$ catalyst.[205] Therefore, iodine atom abstraction then forms a carbon-centered radical **A**, which cyclizes to provide intermediate **B**. After a sequence of carbonylation and nucleophilic substitution via intermediate **C**, the carbonylated and cyclized product is delivered. Recently, another manganese-catalyzed carbonylation of alkyl iodides or bromides was explored by Wu group.[206] To establish various imides from readily available amides, a Mn radical catalyst was similarly generated by thermolysis of $Mn_2(CO)_{10}$.

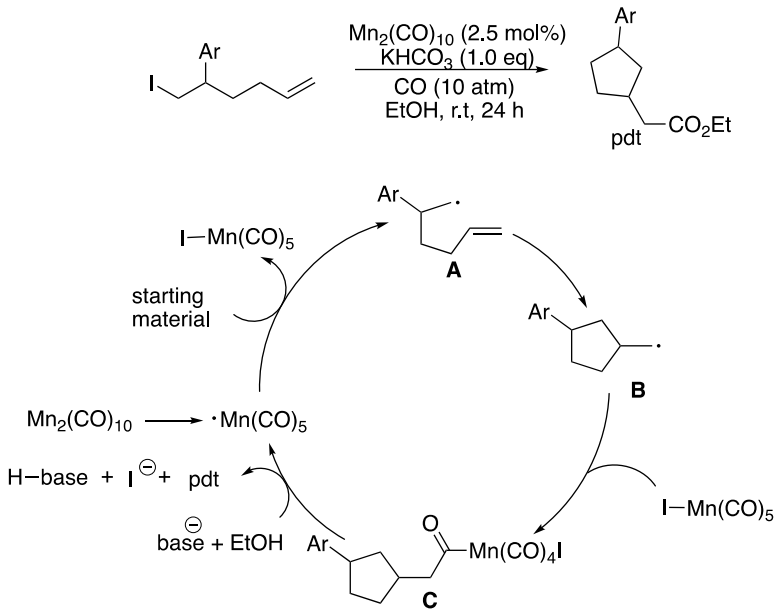


Figure 1.23 Mn-catalyzed carbonylative cyclization

Our group sought to replace the heteroatom nucleophiles in these Mn-catalyzed carbonylation reactions with carbon nucleophiles. In 2017, we reported a carbonylative Suzuki coupling reaction of alkyl halides with arylboronic ester derivatives Co-catalyzed by (NHC)CuCl and Na[$Mn(CO)_5$] (NHC = *N*-heterocyclic carbene).[207] In the proposed mechanism (Figure 1.24), alkylation of $[Mn(CO)_5]^-$ occurs by a radical rebound pathway. Subsequent carbonylation produces an electrophilic acylmanganese intermediate. Separately, transmetallation of the arylboronic ester nucleophile to the copper(I) catalyst produces a nucleophilic arylcopper(I) intermediate **A**. A bimetallic C-C coupling step, whose plausibility was verified in a stoichiometric experiment, releases the ketone product and regenerates both co-catalysts. A key aspect of this process is the mild nucleophilicity of organocopper species, which prevent further addition to the carbonyl group in the ketone product.

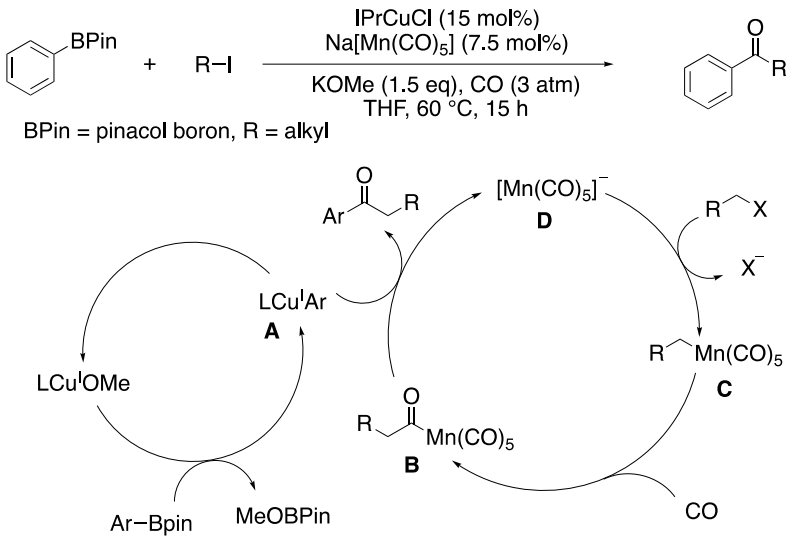


Figure 1.24 Cu/Mn co-catalyzed carbonylative Suzuki coupling

Skrydstrup et al. reported a nickel-catalyzed carbonylative coupling of benzyl bromides with alkylzinc reagents [208] (Figure 1.25). To suppress the formation of inactive Ni poly(carbonyl) species, a *NN_2*-type pincer ligand was used to prevent coordination of multiple CO equivalents to Ni. Furthermore, controlled CO release was achieved using a solid CO precursor via a two-chamber reaction apparatus. Transmetallation between Ni(II) complex **A** and the alkylzinc reagent was proposed to produce intermediate **B**, followed by CO insertion to produce an acylnickel(II) intermediate **C**. Then a bimetallic oxidative addition occurs with **C** and benzyl bromide, resulting in Ni(III) complexes **D** and **E**. Reductive elimination from **E** delivers the ketone product and a Ni(I) species **F**, which comproportionates with **D** to regenerate **A**. Reisman reported an asymmetric variant using a nickel(II) catalyst and a chiral bis(oxazoline) ligand, allowing for coupling of acid chlorides with racemic benzyl chlorides to provide enantioenriched α,α-disubstituted ketones.[209] Gong and Hu also reported a series of nickel-catalyzed reductive couplings of primary, secondary, and tertiary alkyl halides with different carboxylate derivatives[210,211] or ethyl chloroformates[212] to provide dialkyl ketone products.

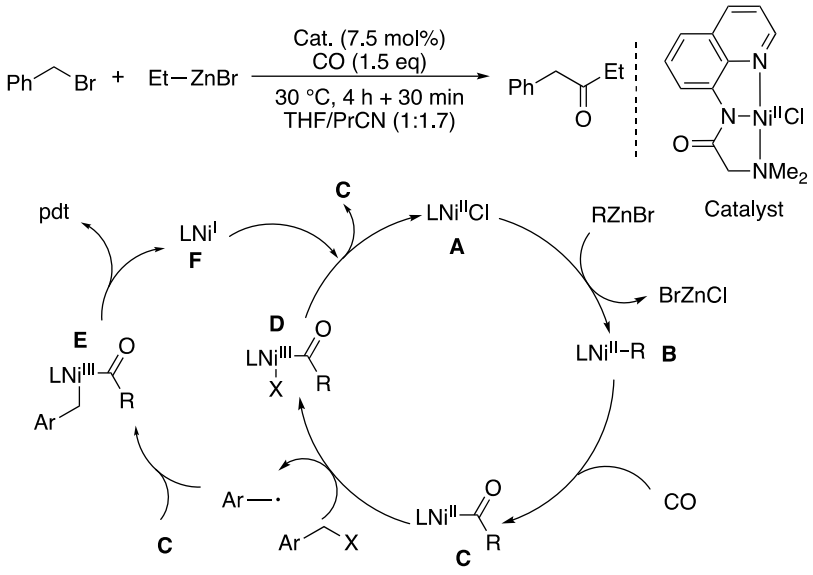


Figure 1.25 Ni-catalyzed carbonylative Negishi coupling

Our group developed a carbonylative coupling of commercially available alkynes, alkyl iodides or bromides, and B_2Pin_2 to acquire a largely unknown class of tetrasubstituted, β-borylated α,β-unsaturated ketones.[213] Moreover, the β-borylated enones obtained from this method were further transformed to other valuable organic substances through reduction, oxidation, halogenation and protodeboronation. The catalytic cycle starts with the addition of the *in situ* generated (NHC)CuBPin catalyst to an alkyne, producing β-borylated alkenylcopper(I) intermediate **A**. Alkyl iodide activation by SET forms a Cu(II) complex **B**. Meanwhile, alkyl radical carbonylation occurs to afford an acyl radical **C**. Subsequently, radical **C** rebounds to intermediate **B** to yield Cu(III) complex **D**. Reductive elimination then expels the β-borylated α,β-unsaturated ketone (Figure 1.26). When a silane reagent (PHMS) was using under similar conditions in place of B_2Pin_2, unsymmetrical dialkyl ketone were easily constructed from terminal alkynes and primary or secondary alkyl iodides via a tandem sequence of hydrocarbonylative coupling followed by in-situ 1,4-reduction.[214]

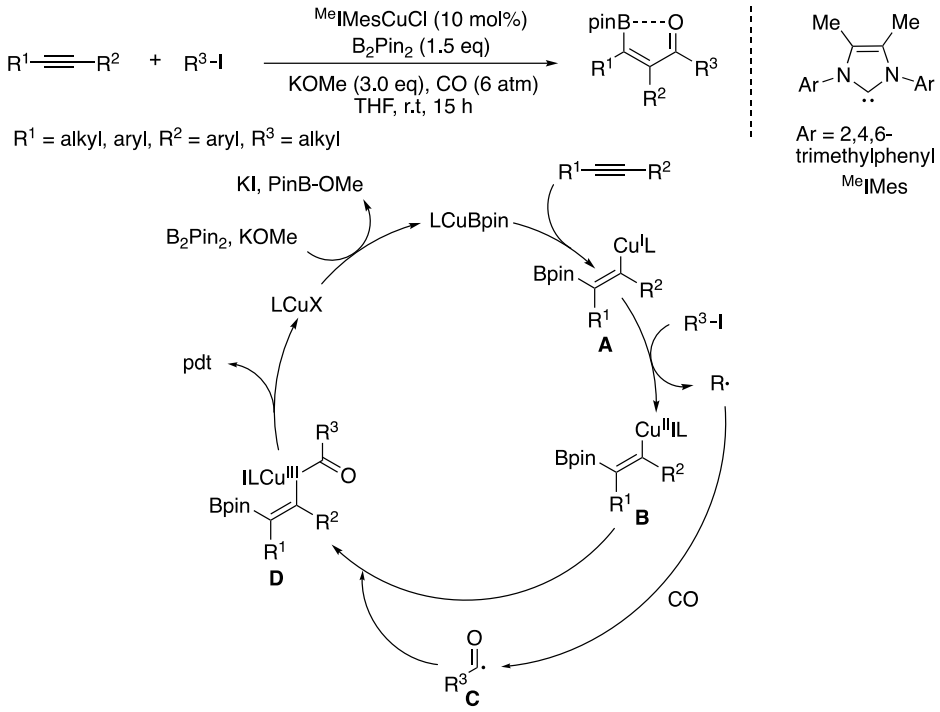


Figure 1.26 Borocarbonylative coupling reactions of alkynes with alkyl halides

Apart from Ryu's signature work on Pd-catalyzed radical carbonylation mentioned above, a couple of Pd-catalyzed thermal radical processes were reported by Skrydstrup[215] and Liang[216] with fluorinated substrates. Another set of Pd-catalyzed carbonylation reactions were developed by Alexanian and coworkers. In 2010, they disclosed a Pd-catalyzed carbonylative Heck reactions of alkyl iodides, focusing on intramolecular variants that provide valuable carbocycle products.[217] A related alkoxycarbonylation of unactivated secondary alkyl bromides was developed by the same group in 2016.[218] A hybrid organometallic-radical pathway was supported by mechanistic investigations (Figure 1.27). Upon the treatment of Pd(0) with an alkyl bromide, bromine-atom abstraction results in a carbon-centered radical and a Pd(I) intermediate. These two species then undergo either migratory CO insertion or radical addition to a bound CO ligand to afford an acylpalladium(II) intermediate. Finally, a nucleophilic displacement by alcohol releases the ester product.

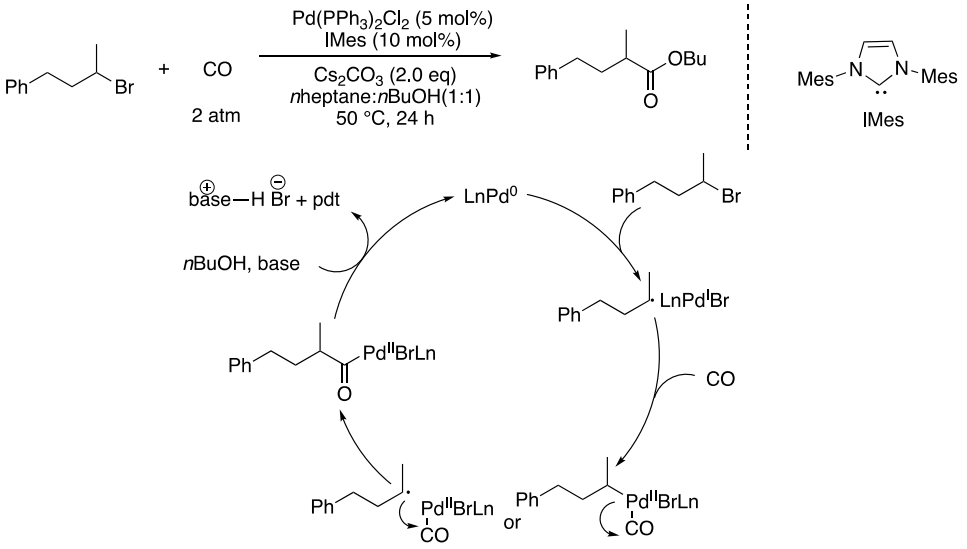


Figure 1.27 Pd-catalyzed alkoxycarbonylation of alkyl bromides

1.3.3. Oxidant-induced radical carbonylation

In 2012, Huang and coworkers reported a Pd-catalyzed oxidative alkoxycarbonylation of C(sp^3)-H bonds.[219] Di-*tert*-butyl peroxide (DTBP) was employed as the stoichiometric oxidant at 120 °C and 10 atm, and a variety of functionalized alkylarenes underwent alkoxycarbonylation without assistance of coordinating directing groups[197] (Figure 1.28). The proposed mechanism for this transformation involves the reaction of DTBP and alkylarene to produce *tert*-butoxy and benzyl radicals, both of which add to the palladium(0) catalyst to provide benzylpalladium(II) intermediate **A**. Carbonylation of **A** was reported to be slow due to steric hindrance, and so first alkoxide exchange with the ethanol nucleophile provides intermediate **B**, which then readily undergoes carbonylation, ultimately producing the product via reductive elimination of **C**.

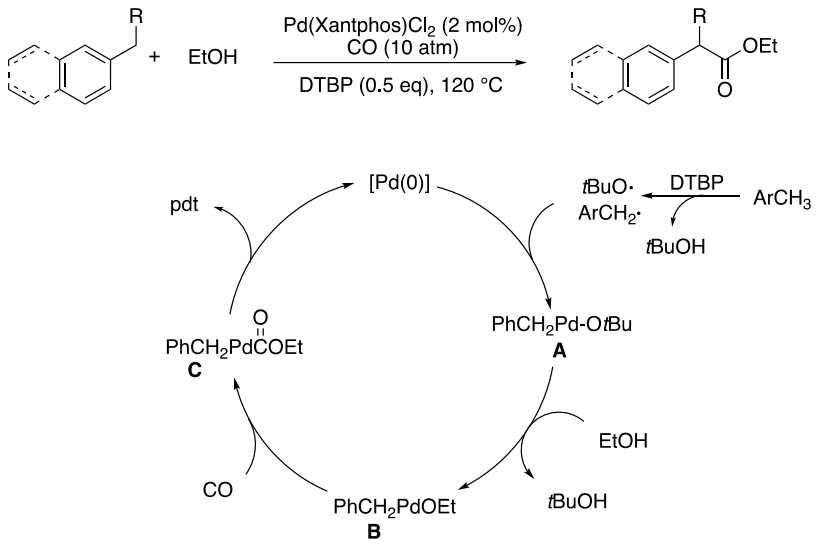


Figure 1.28 Oxidative alkoxycarbonylation of benzylic C-H bonds

The Wu group reported remarkable radical carbonylation reactions coupling alkanes with nucleophiles under copper-catalyzed conditions with di-*tert*-butyl peroxide (DTBP) as the stoichiometric oxidant[220,221] (Figure 1.29). The authors proposed that reactions initiate with homolytic cleavage of DTBP, followed by hydrogen atom abstraction from a substrate such as cyclohexane by the *tert*-butoxy radical. The resulting alkyl radical adds to the copper(II) catalyst **A** to yield a copper(III) complex **B**. This complex **B** then undergoes ligand exchange with the nucleophilic partner (alcohol or amine) to produce intermediate **C**. Subsequently, CO insertion affords intermediate **D** or **D'**, followed by a reductive elimination to release the carbonylated product (ester or amide). Paraformaldehyde could be directly applied to this transformation to yield corresponding esters from the *in situ* generated alcohol. A limitation of this noteworthy methodology is that site selectivity for C-H carbonylation was not well controlled for substrates such as *n*-pentane or *n*-hexane. Other peroxide oxidants were also studied by several groups for the carbonylation of alkyl substrates, such as dicumyl perioxides (DCP) by Wu,[222] and *tert*-butyl hydroperioxides (TBHP) by Li,[223] Reddy[224] and Ye[225] respectively.

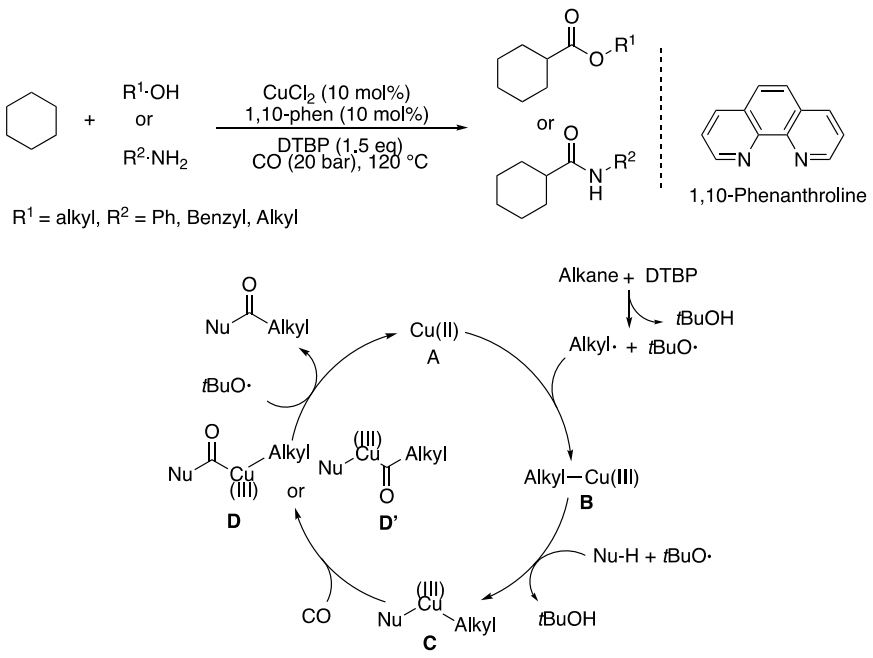


Figure 1.29 Cu-catalyzed oxidative C-H carbonylation

Azo compounds can act as both initiators and CO sources in carbonylation of C(sp^2)-H bonds. In 2016, Zhang et al. reported a cobalt-catalyzed and 8-aminoquinoline group-assisted carbonylation to construct phthalimides[226] (Figure 1.30). Based on mechanistic observations, they hypothesized that an esteric radical was generated through thermal decomposition of diisopropyl azodicarboxylate (DIAD). This radical then either attacked the Co intermediate **B** to furnish a Co(IV) intermediate **C** or underwent further decomposition to release CO, which subsequently inserted into complex **B**. Koley and coworkers investigated the same reaction but with a copper catalyst and 2,2'-azaobisisobutyronitrile (AIBN) as initiator.[227] Daugulis reported a related strategy for Co-catalyzed aminoquinoline-directed carbonylation of sulfonamide C(sp^2)-H bonds using DIAD as the oxidant.[228] Here, a CN radical is generated from AIBN and oxygen.[229] Then a C-H cyanation is followed by hydrolysis to afford carbonylated product. However, electron-deficient benzamides were not applicable under these conditions. Zhong group also conducted a similar cobalt-catalyzed, traceless directing group assisted, and regioselective C(sp^2)-H carbonylation with diethyl azodicarboxylate (DEAD).[230]

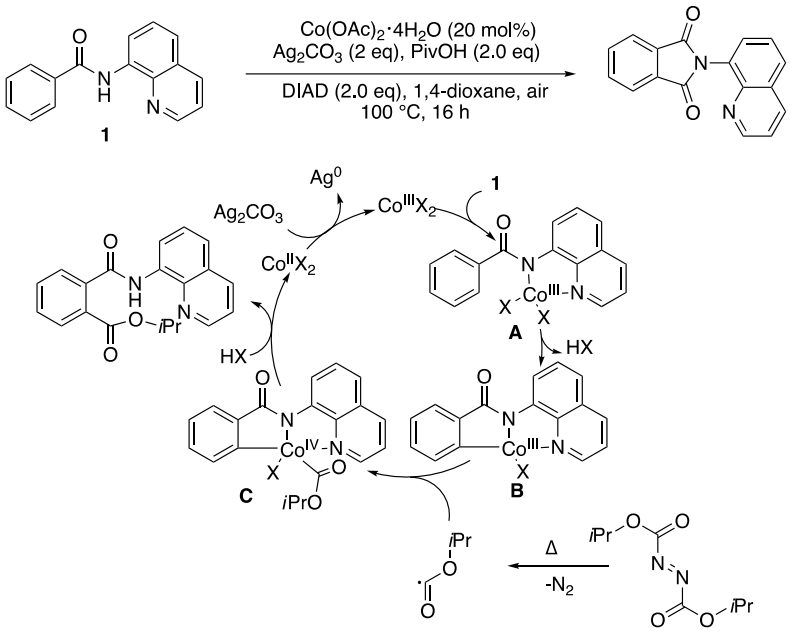


Figure 1.30 Co-catalyzed C(sp^2)-H carbonylation

1.4. Research goals

Most of the established carbonylation reactions are catalyzed by precious metal systems operating via the classic two-electron pathway, including the oxidative addition and reductive elimination. Such mechanism inherently favors chemistry with C(sp^2)-hybridized coupling partners that readily undergo the oxidative addition step. The activation of C(sp^3) substrates via such mechanism would suffer from possible β-hydride elimination. In contrast, the single-electron transfer (SET) approach could ideally avoid the problem as demonstrated by the excellent work shown in subchapter 1.3. The carbonylation could take place with alkyl radicals generated by different means, such as metal-induced SET, peroxide oxidants, or photoirradiation. Thus, SET paths would be ideal to realize the carbonylation of C(sp^3)-X reactants.

Precious metals (*e.g.* Rh and Pd) are reluctant to execute oxidative addition towards C(sp^3)-hybridized substrates using two-electron mechanisms. On the other hand, base metals such as copper and nickel favor SET mechanism and thus activate alkyl halides readily.[231, 232] The different chemical behavior of base metals opens up a new landscape in terms of reactivity that complements to classic precious metal catalysts. Furthermore, the use of base metals as catalysts features the lower cost and toxicity. The lower pricing of copper ($6.55/kg) and iron ($0.12/kg) is stemmed from the rich abundance of these metals in Earth's crust compared to palladium ($74493/kg) or rhodium ($69927/kg). In addition, base metals have a higher oral exposure limits in comparison to precious metals, which benefits the

purification process of active pharmaceutical ingredients when removing the trace metal residues in research and development.

In summary, activation of C(sp^3)-hybridized reactants via a SET approach is less developed in the field of carbonylation. In the continuing efforts to develop novel organic transformations in our lab, the goal of the research described in this thesis is to innovate radical carbonylations with alkyl substrates using base metal systems under mild conditions.

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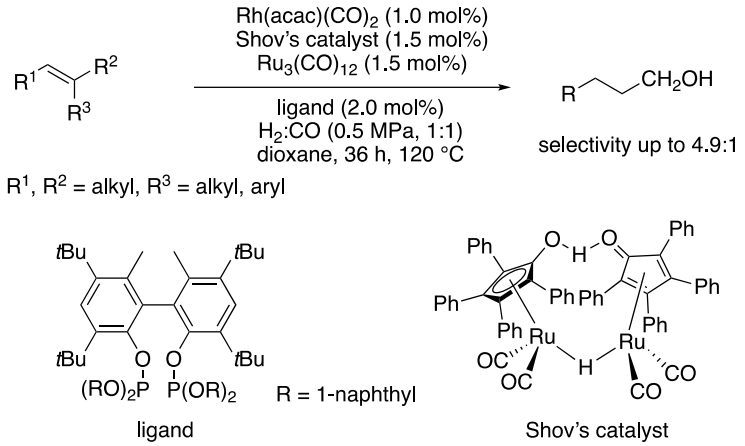
2. Copper-catalyzed hydroxymethylation of alkyl iodides with CO to construct one carbon extended alcohols

This chapter closely follows the content presented in Zhao, S.; Mankad, N. P., Cu-Catalyzed Hydroxymethylation of Unactivated Alkyl Iodides with CO To Provide One-Carbon-Extended Alcohols. *Angewandte Chemie International Edition* **2018,** *57* (20), 5867-5870.

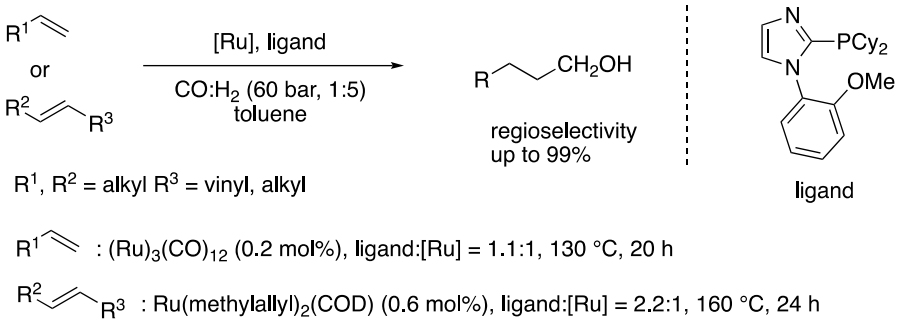
2.1. Introduction

The ubiquitous alcohol functional group is typically introduced onto organic substrates by stepwise installation and subsequent reduction of a carbonyl moiety. A comparatively efficient strategy for installing alcohol groups is hydroxymethylation. We have discussed plenty of hydroformylation reactions of either unsaturated compounds or aryl halides in Chapter 1. However, hydroxymethylation of such compounds is rarely reported. The first findings were observed by Alvila[1] and Pakkanen[2] through a $Ru_3(CO)_{12}$-catalyzed and Ir-catalyzed hydroformylation of olefins, respectively, in 1993. Under the reductive atmosphere of H_2 and CO, the formation of alcohol was detected with the yield of 19% as the side products demonstrated in Scheme 1.4. Later on, Nozaki et al. published hydroxymethylation of olefins only focusing on internal olefins[3] (Scheme 2.1). To the solve the issue of reactivity, Shov's catalyst was introduced, cooperating with a Rh catalyst ($Rh(acac)(CO)_2$) to promote the reaction performance by contributing to both isomerization and hydrogenation. Furthermore, the treatment of a third catalyst $Ru_3(CO)_{12}$ enhanced the regioselectivity with *n*:*i* ratio up to 4.9:1 via accelerating the isomerization.



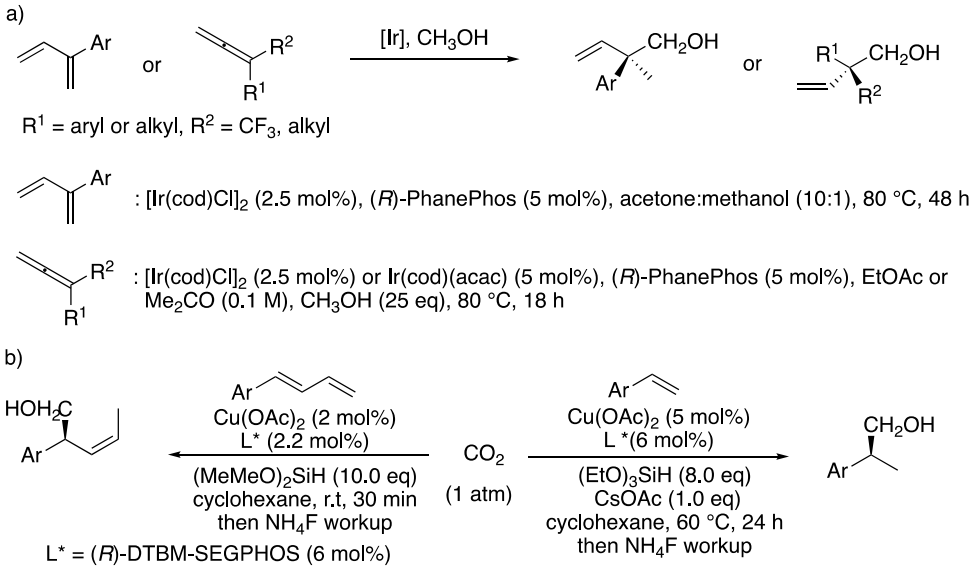
Scheme 2.1 Dual Ru/Ru-catalyzed hydroxymethylation of internal olefins. Selectivity of 9.3:1 was achieved with only one substrate, *Z*-6-nonen-1-ol.

During the same year, Beller and coworkers identified systems where alkenes could be hydroxymethylated by CO/H_2 mixtures using Ru catalysts[4,5] (Scheme 2.2). Beller developed the catalyst system of $Ru_3(CO)_{12}$ and 2-phosphino-substituted imidazole ligand to promote the hydroxymethylation of terminal alkenes to linear alcohols (selectivity up to 99%). A slightly different catalyst, $Ru(methylallyl)_2COD$, was used for the regioselective transformation of internal olefins to linear alcohols, and a different ligand to catalyst ratio was applied. However, the reaction proceeded with a high pressure of the syn gas at 50 bar and high temperature of more than 130 °C.



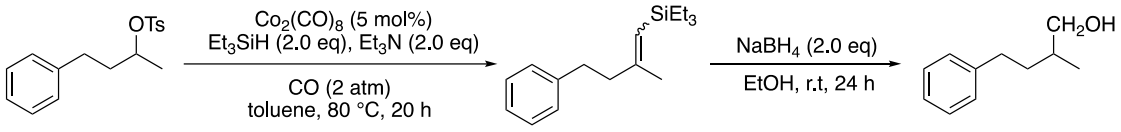
Scheme 2.2 Ru-catalyzed hydroformylation/reduction of olefins to alcohols

Recent advances by Krische have enabled enantioselective hydroxymethylations of allenes[6,7] and dienes[8] with Ir catalyst. Methanol was used directly as the C1 source and co-solvent for this C-functionalization (Scheme 2.3a). Almost the same time when we published this work, Yu and coworkers reported a related Cu-catalyzed hydroxymethylation method for alkenes using CO_2 and a silane reductant in place of CO/H_2.[9] With the choice of different silanes, styrenes or 1,3-dienes could be transformed enantio- and regioselectively to benzylic alcohols (Scheme 2.3b).



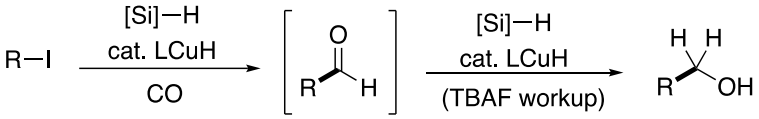
Scheme 2.3 a) Ir-catalyzed hydroxymethylation of dienes or allenes using methanol as C1 building block. b) Cu-catalyzed enantio- and regioselective reductive carbonylation of styrenes or 1,3-dienes using CO_2

A related research with alkyl substrates has also been reported by Alexanian group.[10] Starting with secondary alkyl tosylates, various of silyl enol ethers could be prepared through silylcarbonylation catalyzed by $Co_2(CO)_8$. Then the homologated products can be achieved after a second step of $NaBH_4$ treatment. However, this reaction is only applicable to secondary substrates. And to our knowledge, there has not been a report of reductive hydroxymethylation of C(sp^3)-X substrates.



Scheme 2.4 C-catalyzed silylcarbonylation of secondary alkyl tosylates

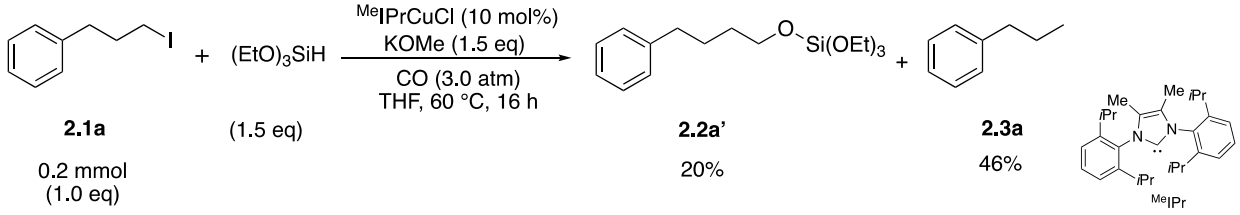
In this context, our group has been studying carbonylative C-C coupling reactions of alkyl halides catalyzed by Cu carbenes.[11, 12] In these reactions, *in situ* generated alkyl radicals are carbonylated and coupled with organocopper nucleophiles to generate ketones. We hypothesized that under reductive conditions, copper hydride nucleophiles could instead provide aldehydes, which would be expected to undergo further reduction under CuH-catalyzed conditions to provide hydroxymethylated products via a tandem carbonylation/reduction sequence as shown in Scheme 2.5.



Scheme 2.5 Proposed carbonylation/reduction of alkyl iodides

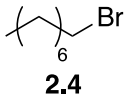
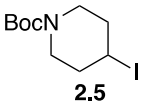
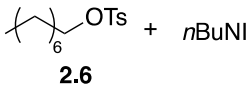
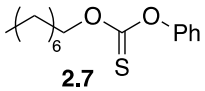
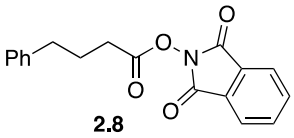
2.2. Reaction optimization

We began our study with 0.2 mmol of 1-iodo-3-phenylpropane (**2.1a**) as a model substrate under 3 atm of CO pressure. It was treated with 1.5 eq. $(EtO)_3SiH$ (0.3 mmol), 1.5 eq. KOMe (0.3 mmol) and ^{Me}IPrCuCl (10 mol%) in THF (2 ml) at 60 °C for 16 hours. The crude mixture was analyzed by ^{1}H NMR with 0.2 mmol 1,1,2,2-tertrachloroethane as internal standard. The targeted silyl ether (**2.2a'**) was observed in the yield of 20% as well as 1-phenylpropane (**2.3a**) in the yield of 46% (Scheme 2.6).



Scheme 2.6 Initial results with alkanes side products

To inhibit the formation of **2.3a**,[13] efforts have been made from different aspects. The alkyl bromide **2.4** was first treated to the reaction in place of 1-iodo-3-phenylpropane, the yields of both the silyl ether **2.2'** and side product **2.3** dropped (Table 2.1 entry 1). Then the use of a secondary Boc protected 4-iodopiperidine **2.5** increased the yield of **2.2** to 39% as well as with 40% alkane (Table 2.1 entry 2). Next, we modified the way to generate radical species by switching to 1-octyl tosylate **2.6** and tetra-*n*-butyl ammonium iodide (TBAI), thiocarbonate **2.7**, and *N*-phthalimide ester **2.8** (Table 2.1 entry 3-5). However, these modifications only diminished the reaction. Increasing the pressure of CO only facilitated the side reaction (Table 2.1 entry 6). Thus we decided to keep using the alkyl iodide **2.1a** as the starting material.

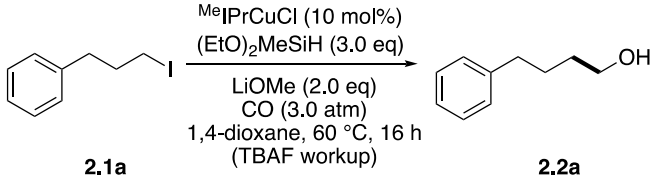
Entry	Modifications	Yield of **silyl ether** (%)	Yield of **2.3** (%)
1	 **2.4**	10	14
2	 **2.5**	39	42
3	 **2.6**	13	17
4	 **2.7**	6	14
5	 **2.8**	0	6
6	**2.1a** with 10 atm CO	21	59

Reaction conditions: **2.4**-**2.8** (0.2 mmol), $(EtO)_3SiH$ (0.2 mmol), ^{Me}IPrCuCl (10 mol%), KOMe (0.3 mmol), CO (3 atm), THF (2 ml), 60 °C, 16 h. Yields were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard.

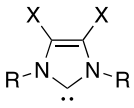
Table 2.1 Results with modifications to suppress the side reaction

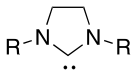
After we screened all various reaction parameters (see Experimental Section 2.5.2 and Tables 2.4-2.10), the ^{Me}IPrCuCl catalyst with addition of 3.0 eq of diethoxymethylsilane and 2.0 eq of LiOMe were found to be critical to achieve good yield of desired alcohol product (Table 2.2, entry 1). The presence of copper catalyst was necessary for

successful reaction (Table 2.2 entry 2). Although other NHC ligands such as IPr, SIPr, ^{Cl}IPr and IMes can be used in this transformation, they only provided moderate yields (Table 2.2 entries 3-6). Activation of the alkyl iodide was significantly affected by the choice of hydrosilane. Only trace conversion was observed with Et_3SiH, while other more frequently used hydrosilanes in copper hydride chemistry provided slightly higher conversions (Table 2.2 entries 7-9). Use of CsF as the base afforded moderate yield, and use of NaO*t*Bu as the base or toluene as solvent favored reduction of the alkyl iodide over carbonylation (Table 2.2 entries 10-12). Decreasing the amount of catalyst to 5 mol% diminished the yield measurably (Table 2.2 entry 13). Conducting the reaction at 60°C and at 3 atm of CO pressure also were found to be required (Table 2.2 entries 14-15).



2.1a **2.2a**





SIPr R = 2,6-(diisopropyl)phenyl

IPr R = 2,6-(diisopropyl)phenyl X = H
IMes R = 2,4,6-(trimethyl)phenyl X = H
^{Me}IPr R = 2,6-(diisopropyl)phenyl X = Me
^{Cl}IPr R = 2,6-(diisopropyl)phenyl X = Cl

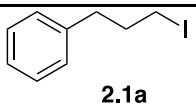
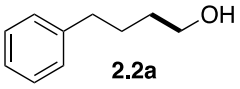
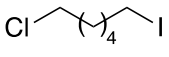
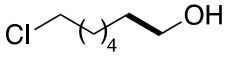
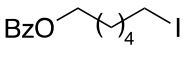
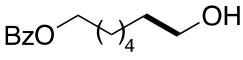
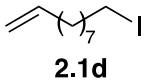
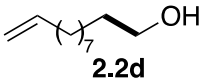
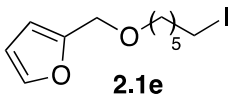
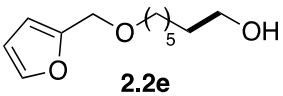
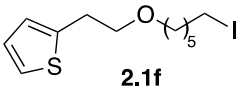
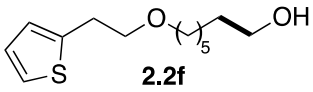
Entry	Modifications from the optimized conditions	Yield of **2.2a** (%)	Conversion of **2.1a** (%)
1	None	85	100
2	No catalyst	7	30
3	IPrCuCl catalyst	58	100
4	SIPrCuCl catalyst	60	100
5	^{Cl}IPrCuCl catalyst	50	100
6	IMesCuCl catalyst	42	100
7	Et_3SiH as the hydrosilane	0	1
8	PMHS as the hydrosilane	13	50
9	TMDSO as the hydrosilane	15	18
10	CsF base	53	72
11	NaO*t*Bu base	16	100
12	Toluene solvent	13	96
13	5 mol% catalyst	64	100
14	r.t	0	0
15	1 atm CO	58	100

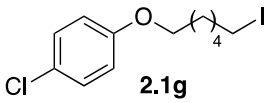
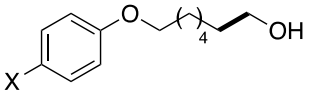
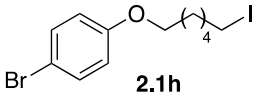
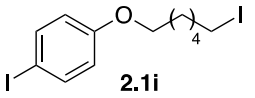
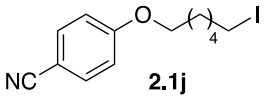
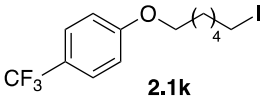
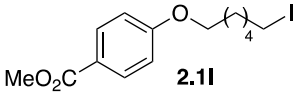
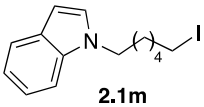
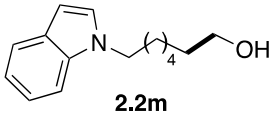
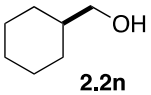
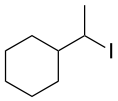
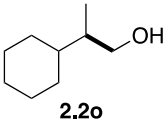
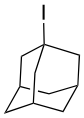
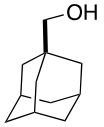
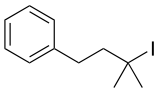
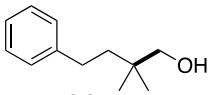
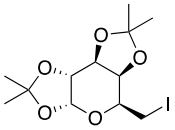
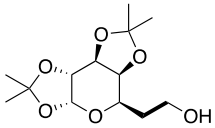
Reactions performed on a 0.2mmol scale. Yields and conversions are were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard. PMHS = polymethoxylhydrosiloxane, TMDSO = 1,1,3,3-tetramethyldisioxane.

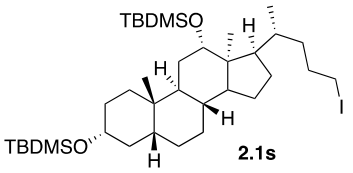
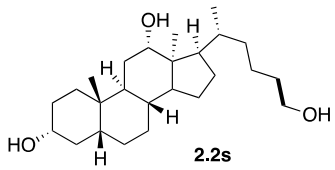
Table 2.2 Selected optimization table for hydroxymethylation of alkyl iodides

2.3. Substrate scope screening

Having identified the optimal conditions, we examined the substrate scope of alkyl iodides. As shown in Table 2.3, the method shows good generality, and a variety of synthetically valuable functional groups are compatible in this transformation. Primary (**2.2a**), secondary (**2.2n**, **2.2o**) and tertiary alkyl iodides (**2.2p**, **2.2q**) were efficiently converted into the targeted alcohols. Substrates containing aryl halides (**2.2g**, **2.2h**,and **2.2i**) underwent this transformation very smoothly, thus implying that this reaction is orthogonal to classical Pd-catalyzed cross-couplings. Other synthetically relevant functional groups, such as terminal alkene (**2.2d**), ether (**2.2c**) and trifluoromethyl (**2.2k**), posed no problem during the process. It is worth noting that some base-sensitive functional groups such as ester (**2.2l**) and cyano group (**2.2j**) also survived but provided only modest yields. Heterocycles such as furan (**2.2e**), thiophene (**2.2f**) and indole (**2.2m**) were well tolerated. Furthermore, the method was also applied to provide complex carbohydrate (**2.2r**), and steroid (**2.2s**) hydroxymethylated products. To our delight, formation of **2.2b** revealed the high chemoselectivity for activating alkyl iodides over alkyl chlorides, providing opportunities for subsequent transformations at the alkyl chloride site.

Entry	Alkyl iodides	Alcohol products	Yields of alcohols (%)[a]
1	 **2.1a**	 **2.2a**	75
2	 **2.1b**	 **2.2b**	80
3	 **2.1c**	 **2.2c**	82
4	 **2.1d**	 **2.2d**	48
5	 **2.1e**	 **2.2e**	80
6	 **2.1f**	 **2.2f**	84

7	 **2.1g**		X= Cl **2.2g**	74
8	 **2.1h**		X= Br **2.2h**	70
9	 **2.1i**		X= I **2.2i**	87[b]
10	 **2.1j**		X= CN **2.2j**	60[c]
11	 **2.1k**		X= CF_3 **2.2k**	84
12	 **2.1l**		X=CO_2Me **2.2l**	47
13	 **2.1m**	 **2.2m**		72
14	 **2.1n**	 **2.2n**		89
15	 **2.1o**	 **2.2o**		58
16	 **2.1p**	 **2.2p**		99
17	 **2.1q**	 **2.2q**		62[d]
18	 **2.1r**	 **2.2r**		41[d]

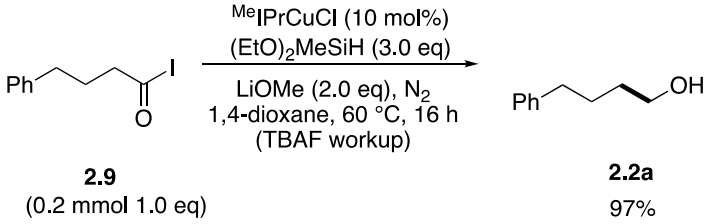
19	 **2.1s**	 **2.2s**	50[d]

[a] Alkyl iodides 0.5 mmol. 10 mol% ^{Me}IPPrCuCl, 3.0 eq $(EtO)_2MeSiH$, 2.0 eq LiOMe, 3 atm CO, 4 ml dioxane solvent, 60 °C, 16 h, followed with TBAF workup. All yields are isolated yields. [b] Product was isolated with 21% inseparable 7-phenoxyheptan-1-ol. [c] 10 mol% IPrCuCl was used as catalyst. [d] Reaction was conducted on a 0.2 mmol scale.

Table 2.3 Substrate scope of alkyl iodides for hydroxymethylation

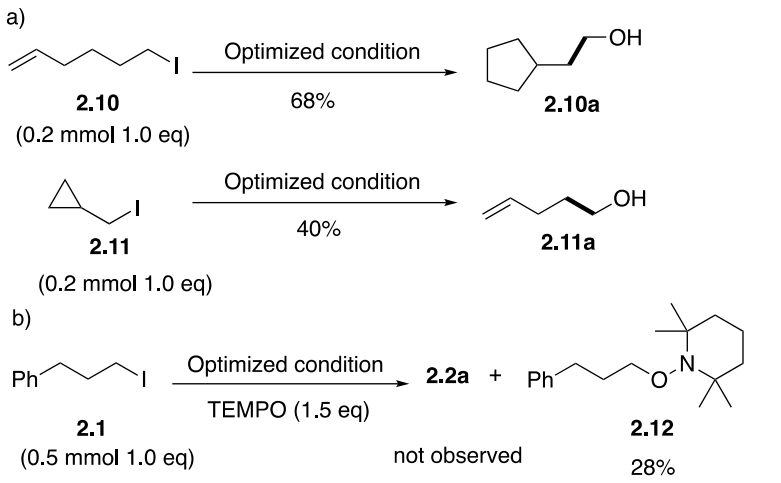
2.4. Mechanistic study

To examine the mechanism of Cu-catalyzed hydroxymethylation of alkyl iodides, acyl iodide **2.9** was subjected to the optimized conditions under N_2 atmosphere (Scheme 2a). The desired alcohol **2.2a** was observed in 97% yield, which implies that the acyl iodide can serve as an intermediate in the catalytic transformation.



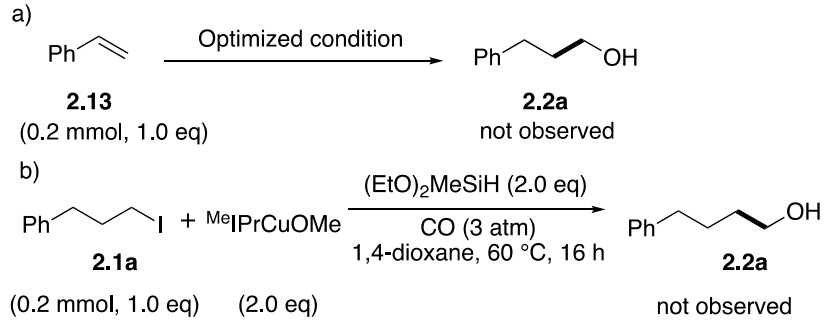
Scheme 2.7 Stoichiometric reduction of acyl iodide under inert atmosphere

Radical clock experiments were conducted with iodoalkanes **2.10** and **2.11** under the optimized conditions (Scheme 2.8a). The corresponding alcohols **2.10a** and **2.11a** derived from radical ring closing and opening, respectively, were obtained in 68% and 40% yield. In addition, when the radical trapping reagent TEMPO was added to the standard reaction, **2.2a** was not detected; 28% of the radical trapped product **2.12** was isolated while 71% starting **2.1a** was recovered (Scheme 2.8b). Collectively, these observations are indicative of alkyl radical intermediates during catalysis.



Scheme 2.8 a) Radical clock experiments. Yields were determined by ^{1}H NMR with dibromomethane as internal standards. b) Radical trapping experiment with TEMPO reagent. Yield is isolated yield. TEMPO: 2,2,6,6-tetramethyl-1-piperidine 1-oxyl.

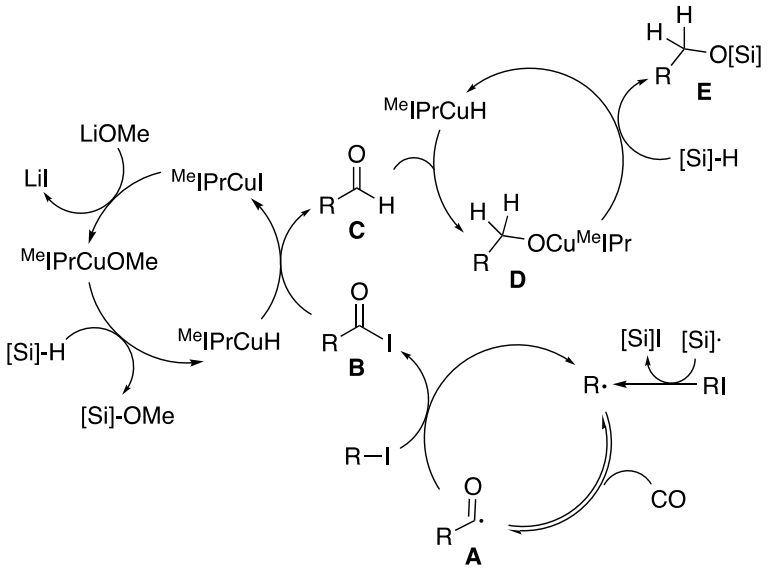
Conducting the reaction with styrene under optimized condition resulted in no targeted alcohol. (Scheme 2.9a) This observation allows us to exclude a possible pathway involving base-mediated HI elimination followed by hydrocupration/formylation. In addition, a stoichiometric reaction between **2.1a** and *in situ* generated ^{Me}IPrCuH gave no product (Scheme 2.9b), which argues against potential Cu-mediated alkyl radical generation as we have proposed previously.[14] Furthermore, conducting the reaction without copper catalyst yielded some alcohol product and small amounts of the corresponding methyl ester, indicating that the carbonylation portion of the tandem sequence doesn't require involvement of the catalyst (Table 2.1, entry 2).



Scheme 2.9 a) Probe experiment with styrene. b) Control experiment with ^{Me}IPrCuH. Reaction was performed on a 0.05 mmol scale. Yields were determined by ^{1}H NMR with dibromomethane as internal standard for both a) and b).

Based on these observations, we propose the mechanism depicted in Scheme 2.10. The reaction is initiated by the formation of an alkyl radical, which may result from a radical initiator generated from the hydrosilane and metal alkoxide.[15,16] Atom transfer carbonylation to afford acyl iodide **B** then proceeds through acyl radical intermediate **A**.[17,18] Subsequently, nucleophilic substitution takes place between **B** and a concomitantly-formed copper

hydride to yield aldehyde **C**. To furnish the final silyl-protected alcohol **E**, aldehyde **C** undergoes reduction by established copper hydride catalysis.[19] A similar ATC mechanism has been proposed for selected Cu-catalyzed carbonylative coupling reactions with tertiary alkyl halides. Based on this hypothetical mechanism, β-hydride elimination is avoided because of a lack of any metal-alkyl intermediates. However, we cannot definitively rule out a copper-mediated radical pathway as observed in related carbonylative coupling reactions for primary and secondary alkyl iodides.[14]



Scheme 2.10 Proposed catalytic cycles

2.5. Experimental Section

2.5.1. General information

General Procedures. Reactions requiring anhydrous conditions were conducted in a N_2-filled glovebox or using standard Schlenk line techniques. Reactions at greater than atmospheric pressure were conducted in a Parr 4621 General Purpose Pressure Reactor. A fitted, aluminum rack was customized for the Parr reactor that could hold up to nine 22 mL scintillation vials for running reactions in parallel. Thin layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by UV light (254 nm) or $KMnO_4$ stain. Purification of compounds was achieved by column chromatography using Merck Flash Silica Gel 60 (230-400 mesh). Organic solutions were concentrated under reduced pressure using a rotary evaporator.

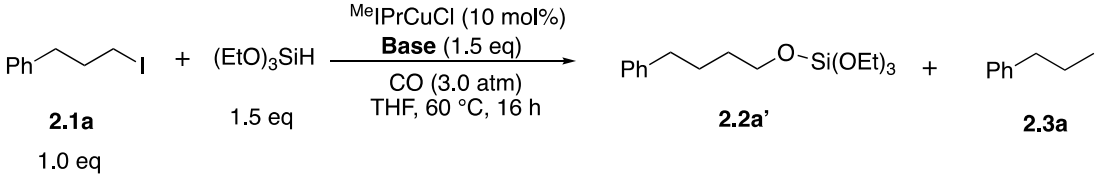
Materials. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Common commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific or VWR International Co. without further purification

unless otherwise noted. Solvents were dried using a Glass Contour Solvent System built by Pure Process Technology, LLC. CO gas was purchased from Praxair at a purity of 99.99% (4.0RS research grade) and used directly from the cylinder. Diethoxymethylsilane was purchased from Fisher Scientific. IMesCuCl, IPrCuCl,[20] SIPrCuCl, SIMesCuCl,[21] ^{Me}IPrCuCl, and ^{Cl}IPrCuCl[22] were prepared according to literature procedures.

Instrumentation. Nuclear Magnetic Resonance (NMR) spectra were recorded on BRUKER AV (400 MHz) or BRUKER AV (500 MHz) at 298 K. Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard (chloroform at 7.26 and 77.00 ppm for ^{1}H and ^{13}C NMR spectroscopy, respectively). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet; br., broad. Coupling constants were taken from the spectra directly and are uncorrected. ^{1}H and ^{13}C NMR provided are taken directly using material for which the yield is quoted, without further purification, and are representative of purity. FT-IR spectra were recorded on a Thermo Nicolet iS5 FT-IR. Absorptions are given in wavenumbers (cm^{-1}). HRMS (ESI) were measured with a Shimadzu LCMS-IT-TOF Mass Spectrometer.

2.5.2. Reaction optimization

In a glovebox, base, copper catalyst, 3-iodo-1-phenylpropane (0.2 mmol, 1.0 eq) and THF (4.0 mL) were added to a 20-mL vial charged with a 1.5cm stir bar. Then hydrosilane was added to the mixture. The vial was then placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas and released after 5 min. This procedure was repeated three times, after which the reaction was heated and stirred vigorously. After 16 h, the reaction was cooled to room temperature and the CO gas was released. The solvent was removed under reduced pressure. The residue was diluted with Et_2O and then filtered through a pad of silica gel (a pipette with about 3 cm silica gel). The filtrate was concentrated under reduced pressure. The residue was dissolved in $CDCl_3$ and $(CHCl_2)_2$ (0.2 mmol) was added as internal standard for ^{1}H NMR analysis. After the investigation, the optimal base, silane, ligand, CO pressure and solvent were identified for the targeting hydroxymethylation.



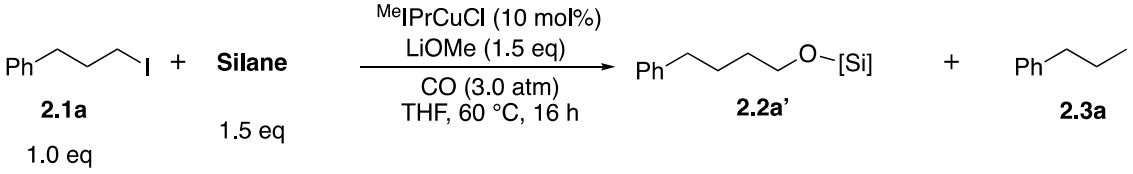
2.1a 1.0 eq | 1.5 eq | **2.2a'** | **2.3a**

Entry	**Base**	Yield of **2.2a'** (%)	Yield of **2.3a** (%)	Recovered **2.1a** (%)

1	KO*t*Bu	0	10	0
2	NaO*t*Amyl	0	64	0
3	KOMe	20	46	4
4	NaOMe	0	75	0
5	LiOMe	37	39	17

NaO*t*Amyl = sodium *tert*-pentoxide

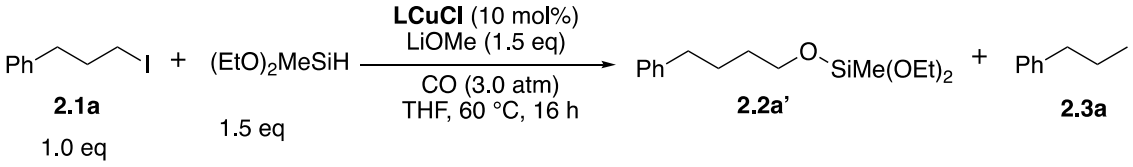
Table 2.4 Base investigation



Entry	**Silane**	Yield of **2.2a'** (%)	Yield of **2.3a** (%)	Recovered **2.1a** (%)
1	$(EtO)_3SiH$	40	36	14
2	$(EtO)_2MeSiH$	50	24	22
3	$(OEt)Me_2SiH$	47	25	23
4	$PhSiH_3$	0	36	14
5	Ph_2SiH_2	0	36	14
6	Et_3SiH	0	0	100
7	PMHS	24	24	52
8	TMDSO	50	20	30

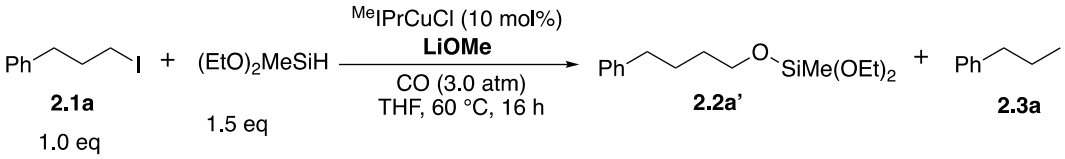
TMDSO = 1,1,3,3-tetramethylsiloxane

Table 2.5 Silane investigation



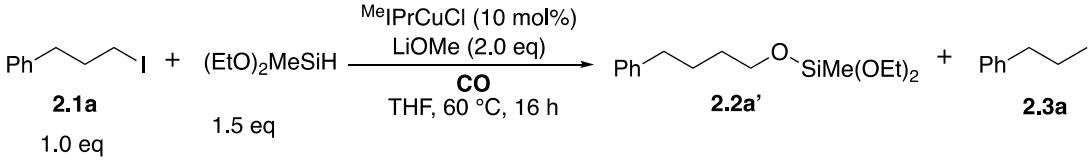
Entry	**LCuCl**	Yield of **2.2a'** (%)	Yield of **2.3a** (%)	Recovered **2.1a** (%)
1	I*i*PrCuCl	43	31	0
2	IPrCuCl	45	24	20
3	SIPrCu	33	28	13
4	^{Me}IPrCuCl	52	29	29
5	^{Cl}IPrCuCl	35	39	9
6	IMeCuCl	33	28	20

Table 2.6 Ligand investigation



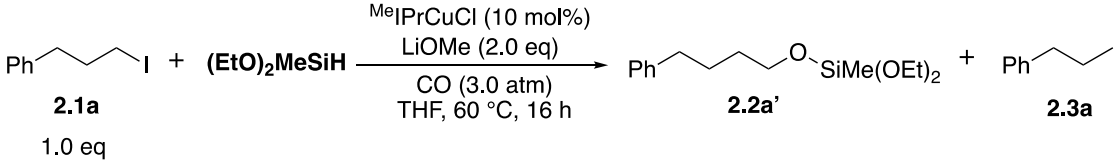
Entry	**LiOMe(eq)**	Yield of **2.2a'** (%)	Yield of **2.3a** (%)	Recovered **2.1a** (%)
1	1.0	56	18	12
2	1.5	41	28	23
3	2.0	37	25	0
4	2.5	47	34	0

Table 2.7 Amount of LiOMe investigation



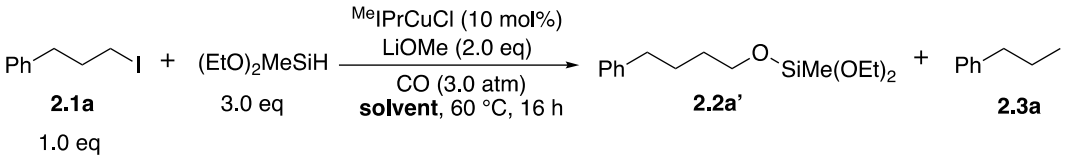
Entry	**CO (atm)**	Yield of **2.2a'** (%)	Yield of **2.3a** (%)	Recovered **2.1a** (%)
1	1.3	43	34	17
2	3	50	24	22
3	6	41	27	25
4	10	21	59	4

Table 2.8 CO pressure investigation



Entry	**$(EtO)_2MeSiH$(eq)**	Yield of **2.1a** (%)	Yield of **2.2a' (%)**	Recovered **2.3a** (%)
1	1.5	33	32	0
2	2.0	64	35	0
3	3.0	70	30	0

Table 2.9 Amount of silane investigation

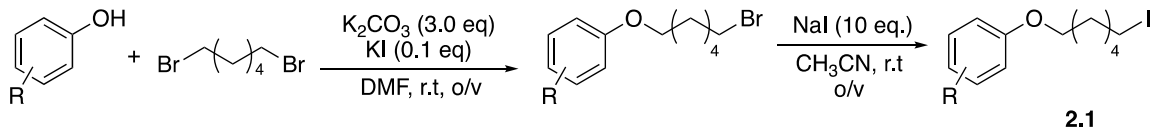


Entry	**Solvent**	Yield of **2.2a'** (%)	Yield of **2.3a** (%)	Recovered **2.1a** (%)
1	Toluene	13	29	4
2	THF	70	30	0
3	1,4-dioxane	85	15	0
4	THF/1,4-dioxane (1:1)	79	20	0

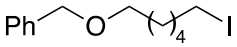
Table 2.10 Solvent investigation

2.5.3. Synthesis and characterization of alkyl iodides

Phenol or alcohol (1.0 eq) was dissolved with 100 mL dimethylformamide (DMF) in 250 mL round bottom charged with stir bar. Then K_2CO_3 (3.0 eq) was added to the mixture, stirring for half an hour at room temperature. 1,6-dibromohexane (5.0 eq) and KI (0.1 eq) were added. The mixture was left stirring overnight at room temperature. Workup the reaction by adding 50 mL DI water and 50 mL EtOAc to the reaction mixture. The organic layer was washed with DI water (5 × 50 mL) in a separatory funnel then collected, dried over $MgSO_4$. Solvent was removed by a rotatory evaporator. For iodination step, NaI (10.0 eq) was dissolved in 100 mL acetonitrile, and the crude mixture obtained from last step was added to the solution slowly. The round bottom was wrapped with tin foil, left stirring at room temperature overnight. The reaction mixture was dried under reduced pressure, then diluted with hexane. The solution was filtered through a Buchner funnel, and filtrate was dried by rotatory evaporator. The crude residue was purified by silica gel chromatography (hexane/ethyl acetate) to afford the desired primary iodides. For the heterocycle substrates (thiophene, furan, indole), sodium hydride was used as base instead of K_2CO_3. NaH was quenched with saturated NaS_2O_3 solution.

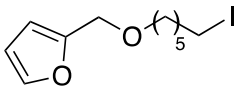


Scheme 2.11 General reaction scheme for the synthesis of alkyl iodides



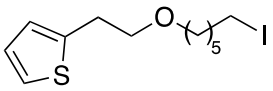
2.1c

(((6-iodohexyl)oxy)methyl)benzene (2.1c) Prepared according to literature procedure[23] using (chloromethyl)benzene (1.9 mL, 16.5 mmol, 1.1 eq) and hexane-1,6-diol (1.77 g, 15 mmol, 1.0 eq). The crude material was purified by silica gel chromatography (hexane/ethyl acetate = 80 : 20, Rf = 0.19) to afford the title compound as a colorless oil (1.1 g, 37%). Then collected 6-(benzyloxy)hexan-1-ol (0.5 g, 2.6 mmol, 1.0 eq) reacted with I_2 (0.86 g, 3.38 mmol, 1.3 eq) according to literature procedure. The crude material was purified by silica gel chromatography (hexane/ethyl acetate = 80 : 20, Rf = 0.52) to afford the title compound as a colorless oil (0.46 g, 56%). The characterization has been reported by literature.[24]



2.1e

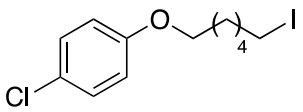
2-(((6-iodohexyl)oxy)methyl)furan (2.1e) Prepared according to general procedure using furan-2-ylmethanol (1.2 g, 12.20 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate = 95 : 5, Rf = 0.30) to afford the title compound as a yellow liquid (0.78 g, 22%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (m, 2H), 6.44 – 6.37 (m, 1H), 4.36 (s, 2H), 3.44 (t, *J* = 6.5 Hz, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 1.82 (p, *J* = 6.9 Hz, 2H), 1.60 (p, *J* = 6.6 Hz, 2H), 1.39 (ddq, *J* = 15.0, 9.3, 5.7, 3.4 Hz, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.25, 140.48, 122.50, 110.34, 69.94, 64.08, 33.43, 30.28, 29.48, 25.16, 7.08. **IR (neat)** 2931.25, 2854.72, 1500.88, 1204.65, 1159.09, 1099.00, 1019.09, 873.43, 785.01, 726.64, 599.50 cm^{-1}.



2.1f

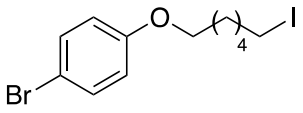
2-(2-((6-iodohexyl)oxy)ethyl)thiophene (2.1f) Prepared according to general procedure using 2-(thiophen-2-yl)ethan-1-ol (1.5 g, 11.70 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate = 85 : 15, Rf = 0.22) to afford the title compound as an orange oil (1.17 g, 29%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.85 (dt, *J* = 3.6, 1.2 Hz, 1H), 3.65 (t, *J* = 6.8 Hz, 2H), 3.46

(t, *J* = 6.5 Hz, 2H), 3.19 (t, *J* = 7.0 Hz, 2H), 3.10 (t, *J* = 5.0 Hz, 2H), 1.83 (p, *J* = 7.1 Hz, 2H), 1.67 – 1.53 (m, 2H), 1.40 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.41, 126.59, 125.01, 123.56, 71.38, 70.80, 33.44, 30.50, 30.27, 29.45, 25.13, 7.11. **HRMS** (ESI) Calcd. for $C_{12}H_{20}IOS$ ($[M+H]^+$): 339.0279; Found: 339.0254. **IR (neat)** 2930.61, 2854.55, 1205.26, 1109.62, 849.70, 822.62, 792.3 cm^{-1}.



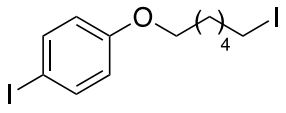
2.1g

1-chloro-4-((6-iodohexyl)oxy)benzene (2.1g) Prepared according to general procedure using 4-chlorophenol(0.8 g, 6.22 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate = 95 : 5, Rf = 0.30) to afford the title compound as a white powder (1.40 g, 67%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 10.0 H, 2H), 6.81 (d, *J* = 10.0 Hz, 2H), 3.92 (t, *J* = 6.4 Hz, 2H), 3.20 (t, *J* = 7.0 Hz, 2H), 1.86 (t, *J* = 6.9 Hz, 2H), 1.78 (t, *J* = 6.9 Hz, 2H), 1.51 – 1.43 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.63, 129.26, 125.36, 115.72, 68.02, 33.34, 30.20, 28.98, 25.02, 6.92. **IR (neat)** 2941.08, 1490.51, 1467.99, 1254.64, 1233.83, 822.32 cm^{-1}.



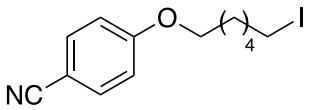
2.1h

1-bromo-4-((6-iodohexyl)oxy)benzene (2.1h) Prepared according to general procedure using 4-bromophenol(1.73 g, 10.0 mmol) to afford the title compound as a colorless liquid (2.0 g, 52%). Characterization has been reported by previous literature.[25]



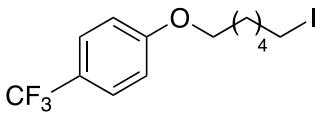
2.1i

1-iodo-4-((6-iodohexyl)oxy)benzene (2.1i) Prepared according to general procedure using 4-iodophenol(1.0 g, 4.5 mmol) to afford the title compound as a white powder (1.59 g, 82%). Characterization has been reported by previous literature.[13]



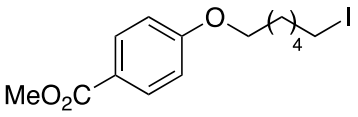
2.1j

4-((6-iodohexyl)oxy)benzonitrile (2.1j) Prepared according to general procedure using 4-cyanophenol(1.0 g, 8.4 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate = 95 : 5, Rf = 0.20) to afford the title compound as a white powder (2.34 g, 81%). Characterization has been reported by previous literature.[13]



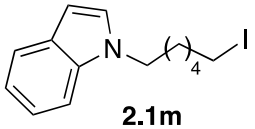
2.1k

1-((6-iodohexyl)oxy)-4-(trifluoromethyl)benzene (2.1k) Prepared according to general procedure using 4-trifluoromethylphenol. The crude material was purified by silica gel chromatography (hexane, Rf = 0.17) to afford the title compound as colorless oil (1.11 g, 60%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.53 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.21 (t, *J* = 7.0 Hz, 2H), 1.84 (m, 4H), 1.60 – 1.41 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 157.63, 129.25, 125.36, 115.72, 109.57, 77.20, 68.01, 33.34, 30.20, 28.98, 25.02, 6.93. **IR (neat)** 2936.17, 1615.01, 1588.95, 1518.75, 1323.63, 1309.18, 1205.29, 1157.89, 1107.11, 1066.16, 833.57 cm^{-1}.



2.1l

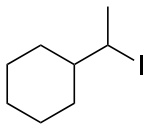
Methyl 4-((6-iodohexyl)oxy)benzoate (2.1l) Prepared according to general procedure using methyl 4-hydroxybenzoate (0.8 g, 5.26 mmol). The crude material was purified by silica gel chromatography (petroleum ether/ethyl acetate = 90 : 10, Rf = 0.55) to afford the title compound as white powder (1.48 g, 75%). Characterization has been reported by previous literature.[13]



2.1m

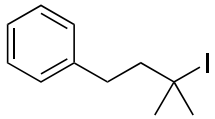
1-(6-iodohexyl)-1*H*-indole (2.1m) Prepared according to general procedure using 1*H*-indole (1.0 g, 8.5 mmol). The

crude material was purified by silica gel chromatography (hexane/ethyl acetate = 97 : 3) to afford the title compound as a yellow oil (1.14 g, 41%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.14 – 7.07 (m, 2H), 6.50 (d, *J* = 3.2 Hz, 1H), 4.13 (t, *J* = 7.0 Hz, 2H), 3.16 (t, *J* = 6.9 Hz, 2H), 1.87 (m, 2H), 1.79 (m, 2H), 1.48 – 1.29 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.90, 128.55, 127.72, 121.34, 120.95, 119.19, 109.30, 100.96, 46.19, 33.23, 30.06, 30.03, 25.92, 6.85. **HRMS** (ESI) Calcd. for $C_{14}H_{19}IN$ ($[M+H]^+$): 328.0562; Found: 328.0546. **IR (neat)** 2929.33, 2853.75, 1509.87, 1462.33, 1313.61, 883.49 cm^{-1}.



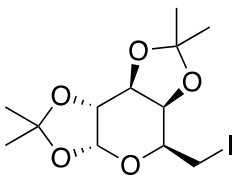
2.1o

(1-iodoethyl)cyclohexane (2.1o) Prepared according to literature procedure[26] using 1-cyclohexylethan-1-ol (1.0 g, 7.8 mmol), a colorless liquid obtained (0.76 g, 40%).



2.1q

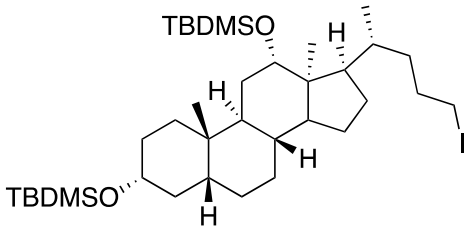
(3-iodo-3-methylbutyl)benzene (3.1q) Prepared according to literature procedure[27] using 2-methyl-4-phenylbutan-2-ol (1.0 g, 6.1 mmol), a light yellow liquid was obtained without further purification. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.30 (d, *J* = 7.2 Hz, 2H), 7.25 – 7.16 (m, 3H), 2.89 – 2.80 (m, 2H), 2.00 (d, *J* = 1.4 Hz, 6H), 1.95 – 1.88 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 141.40, 128.45, 125.98, 52.40, 51.37, 38.04, 35.15.



2.1r

1,2:3,4-di-O-isopropylidene-6-iodo-D-galactopyranse (2.1r) Prepared according to literature procedure9 using 1,2:3,4-di-O-isopropylidene-D-galactopyranose. A colorless oil was obtained after column chromatography (hexane/ethyl acetate = 90 : 10). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.54 (d, J = 5.1 Hz, 1H), 4.61 (dd, J = 7.9, 2.5 Hz,

1H), 4.40 (dt, J = 7.9, 1.8 Hz, 1H), 4.30 (dt, J = 4.2, 2.1 Hz, 1H), 3.95 (td, J = 7.0, 1.9 Hz, 1H), 3.32 (ddd, J = 8.5, 6.8, 1.6 Hz, 1H), 3.21 (ddd, J = 8.9, 7.2, 1.6 Hz, 1H), 1.54 (s, 3H), 1.44 (s, 3H), 1.34 (d, J = 9.5 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 71.59, 71.13, 70.58, 68.96, 26.04, 25.96, 24.89, 24.45, 2.32. **HRMS** (EI) Calcd. for C12H20IO5 ([M]+): 370.0277; Found: 370.0316. Mass was determined on JEOL GCmate.



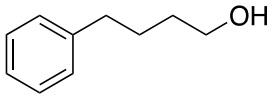
2.1s

24-iodo-5β-cholane-3α,12α-diol (2.1s) Prepared according to literature procedure[26] using corresponding alcohol (4.0 g, 6.56 mmol). The compound was purifies by column chromatography (hexane/ ethyl acetate = 95 : 5), a colorless oil was obtained (2.9 g, 62%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 3.96 (d, *J* = 4.4 Hz, 1H), 3.56 (dq, *J* = 10.6, 5.4, 4.6 Hz, 1H), 3.24 – 3.07 (m, 2H), 1.91 – 1.22 (m, 25H), 0.97 (d, *J* = 6.6 Hz, 4H), 0.92 – 0.83 (m, 21H), 0.67 (s, 3H), 0.05 (d, *J* = 1.4 Hz, 6H), 0.01 (s, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 73.20, 72.77, 48.23, 47.43, 46.48, 42.28, 36.88, 36.73, 36.09, 35.41, 34.84, 34.18, 33.68, 30.94, 30.38, 28.72, 27.57, 27.26, 26.12, 25.96, 25.70, 23.67, 23.25, 18.32, 17.72, 12.73, 7.82.

2.5.4. Synthesis and characterization of alcohols

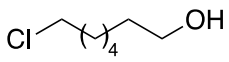
In a glovebox, LiOMe (0.037 g, 1.0 mmol, 2.0 eq), ^{Me}IPrCuCl (0.027 g, 0.05 mmol, 10 mol%), and 1,4-dioxane (8.0 mL) were added to a 20-mL vial charged with a 1.5 cm stir bar. 3-iodo-1-phenylpropane (80 μL, 0.5 mmol, 1.0 eq) and diethoxymethylsilane (240 μL, 1.5 mmol, 3.0 eq) were added to the mixture. Then the vial was placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas and released after 5 min. This procedure was repeated three times, after which the reaction was heated to 60 ℃ and stirred vigorously. After 16 h, the reaction was cooled to room temperature and the CO gas was released. The solvent was removed under reduced pressure. The residue was dissolved with Et_2O, then filtered through a pad of silica gel (a pipette with about 5 cm silica gel). The filtrate was concentrated under reduced pressure, then diluted with 4 mL THF.

The mixture was subjected to tetrabutylammonium fluoride solution (4 mL, 4 mmol, 4.0 eq) (1M in THF), stirring at room temperature for 2 hours. Then the mixture was washed with water (3 × 10 mL) in separatory funnel. The organic layer was collected and dried over $MgSO_4$. Solvent was removed by a rotatory evaporator. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to afford the corresponding alcohols.



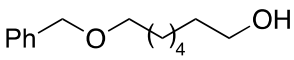
2.2a

4-phenylbutan-1-ol (2.2a) Prepared according to general procedure using **1a** (80 μL, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.25) to afford the title compound as colorless liquid (0.06 g, 75%). Characterization has been reported by previous literature.[28] **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.28 (t, *J* = 7.5 Hz, 3H), 7.19 (d, *J* = 6.7 Hz, 2H), 3.66 (t, *J* = 6.5 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.74 – 1.67 (m, 2H), 1.64 – 1.58 (m, 2H), 1.25 (bs, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ142.30, 128.39, 128.29, 125.74, 62.84, 35.63, 32.34, 27.54.



2.2b

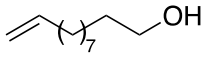
7-chloroheptan-1-ol (2.2b) Prepared according to general procedure using 1-chloro-6-iodohexane (0.13 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.19) to afford the title compound as colorless liquid (0.06 g, 80%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 3.64 (t, *J* = 6.6 Hz, 2H), 3.53 (t, *J* = 6.7 Hz, 2H), 1.77 (q, *J* = 6.9 Hz, 2H), 1.64 – 1.52 (m, 2H), 1.44 (q, *J* = 7.0, 6.4 Hz, 2H), 1.37 (m, 4H), 1.27 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 62.94, 45.09, 32.64, 32.53, 28.67, 26.82, 25.59. **IR (neat)** 3334.06, 2930.75, 2857.01, 2359.70, 1463.53, 1290.85, 1055.39, 724.93, 667.99, 650.01 cm^{-1}.



2.2c

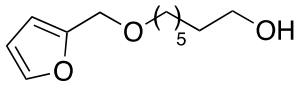
7-(benzyloxy)heptan-1-ol (2.2c) Prepared according to general procedure using **2.1c** (0.16 g, 0.5 mmol). The crude material was purified by silica gel chromatography to afford the title compound as colorless liquid (0.96 g, 82%).

Characterization has been reported by previous literature.[29] **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.33 (d, J = 3.8 Hz, 3H), 7.30 – 7.24 (m, 2H), 4.50 (s, 2H), 3.62 (t, J = 6.6 Hz, 2H), 3.46 (t, J = 6.6 Hz, 2H), 1.59 (ddq, J = 29.2, 7.9, 6.5 Hz, 4H), 1.43 – 1.29 (m, 6H), 1.27 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 138.66, 128.32, 127.60, 127.46, 72.85, 70.41, 63.01, 32.71, 29.68, 29.23, 26.16, 25.68.



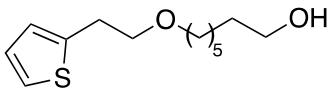
2.2d

Undec-10-en-1-ol (2.2d) Prepared according to general procedure using (**2.1d)** (0.13 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =70: 30, Rf = 0.13) to afford the title compound as colorless liquid (0.04 g, 48%). Characterization has been reported by previous literature.[30] **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.81 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.03 − 4.86 (m, 2H), 3.63 (t, J = 6.7 Hz, 2H), 2.03 (q, J = 7.1 Hz, 2H), 1.56 (p, J = 6.7 Hz, 2H), 1.39 – 1.22 (m, 13H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 139.20, 114.09, 63.06, 33.79, 32.79, 29.54, 29.40, 29.10, 28.91, 25.72.



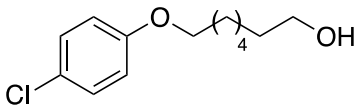
2.2e

7-(furan-2-ylmethoxy)heptan-1-ol (2.2e) Prepared according to general procedure using 2-(((6-iodohexyl)oxy)methyl)furan (0.15 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.12) to afford the title compound as colorless liquid (0.08 g, 80%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.44 – 7.32 (m, 2H), 6.40 (m, 1H), 4.35 (s, 2H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.43 (t, *J* = 6.6 Hz, 2H), 1.64 – 1.49 (m, 4H), 1.46 (s, 1H), 1.41 – 1.26 (m, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.20, 140.45, 122.52, 110.32, 70.14, 64.01, 62.92, 32.67, 29.57, 29.19, 26.11, 25.65. **HRMS** (ESI) Calcd. for $C_{12}H_{21}O_3$ ($[M+H]^+$): 213.1490; Found: 213.1485. **IR (neat)** 3280.49, 2930.54, 2856.36, 2359.68, 2221.11, 1605.04, 1508.50, 1257.09, 1060.65, 1020.36 cm^{-1}.



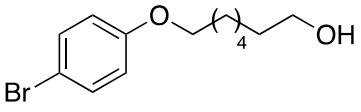
2.2f

7-(2-(thiophen-2-yl)ethoxy)heptan-1-ol (2.2f) Prepared according to general procedure using 2-(2-((6-iodohexyl)oxy)ethyl)thiophene (0.17 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.23) to afford the title compound as light yellow oil (0.10 g, 84%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 6.92 (dd, *J* = 5.2, 3.4 Hz, 1H), 6.84 (d, *J* = 3.4 Hz, 1H), 3.64 (dt, *J* = 8.6, 6.8 Hz, 4H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.09 (t, *J* = 6.9 Hz, 2H), 1.58 (tq, *J* = 13.9, 6.4 Hz, 4H), 1.43 (s, 1H), 1.41 – 1.28 (m, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 141.39, 126.57, 124.98, 123.52, 71.35, 71.03, 62.94, 32.68, 30.47, 29.59, 29.19, 26.10, 25.65. **HRMS** (ESI) Calcd. for $C_{13}H_{23}O_2S$ ($[M+H]^+$): 243.1419; Found: 243.1408. **IR (neat)** 3352.19, 2928.95, 2854.94, 2359.58, 1109.11, 1055.49, 691.21 cm^{-1}.



2.2g

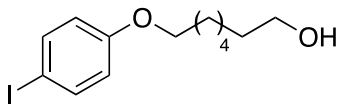
7-(4-chlorophenoxy)heptan-1-ol (2.2g) Prepared according to general procedure using 1-chloro-4-((6-iodohexyl)oxy)benzene (0.17 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.21) to afford the title compound as colorless liquid (0.09 g, 74%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.25 – 7.16 (m, 2H), 6.87 – 6.74 (m, 2H), 3.91 (t, *J* = 6.5 Hz, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 1.85 – 1.69 (m, 2H), 1.58 (td, *J* = 10.0, 8.5, 5.3 Hz, 2H), 1.52 – 1.42 (m, 2H), 1.39 (p, *J* = 3.5 Hz, 5H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 157.69, 129.23, 125.28, 115.72, 68.21, 62.96, 32.67, 29.13, 29.10, 25.97, 25.66. **HRMS** (ESI) Calcd. for $C_{13}H_{20}ClO_2$ ($[M+H]^+$): 243.1152; Found: 243.1162. **IR (neat)** 3290.12, 2936.10, 2856.92, 1596.87, 1492.83, 1472.79, 1200.87, 1074.78, 996.55 cm^{-1}.



2.2h

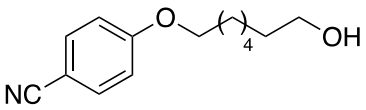
7-(4-bromophenoxy)heptan-1-ol (2.2h) Prepared according to general procedure using 1-bromo-4-((6-iodohexyl)oxy)benzene (0.19 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =75: 25, Rf = 0.30) to afford the title compound as colorless liquid (0.10 g, 70%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.38 – 7.32 (m, 2H), 6.80 – 6.71 (m, 2H), 3.91 (t, *J* = 6.5 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 1.83 –

1.71 (m, 2H), 1.64 – 1.52 (m, 2H), 1.51 – 1.42 (m, 2H), 1.39 (p, *J* = 3.6 Hz, 4H), 1.30 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.19, 132.16, 116.26, 112.56, 68.14, 62.95, 32.67, 29.13, 29.08, 25.96, 25.65. **HRMS** (ESI) Calcd. for $C_{13}H_{20}BrO_2$ ($[M+H]^+$): 287.0646; Found: 287.0637. **IR (neat)** 3292.66, 2935.09, 2855.30, 1591.02, 1490.30, 1471.96, 1200.63, 1173.93, 1073.14, 996.69, 829.83 cm^{-1}.



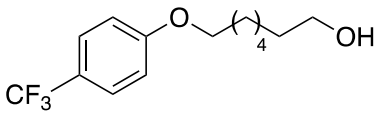
2.2i

7-(4-iodophenoxy)heptan-1-ol (2.2i) Prepared according to general procedure using 1-iodo-4-((6-iodohexyl)oxy)benzene (0.19 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.30) to afford the title compound as colorless liquid (0.14 g, 87%). However, it contained with 21% inseparable 7-phenoxyheptan-1-ol. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 5.0 Hz, 2H), 3.91 (t, *J* = 6.5 Hz, 2H), 3.64 (t, *J* = 6.9 Hz, 2H), 1.77 (p, *J* = 6.9 Hz, 2H), 1.57 (q, *J* = 8.0, 7.3 Hz, 2H), 1.52 – 1.29 (m, 6H), 1.21 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 138.40, 117.16, 114.73, 109.85, 68.27, 63.24, 32.94, 29.32, 26.23, 25.92.



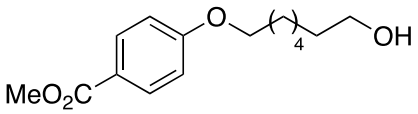
2.2j

4-((7-hydroxyheptyl)oxy)benzonitrile (2.2j) Prepared according to general procedure using 4-((6-iodohexyl)oxy)benzonitrile (0.16 g, 0.5 mmol) but 10 mol% IPrCuCl was used as catalyst instead of ^{Me}IPrCuCl. The crude material was purified by silica gel chromatography (hexane/ethyl acetate =75: 25, Rf = 0.15) to afford the title compound as colorless liquid (0.07 g, 60%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.61 – 7.48 (m, 2H), 6.95 – 6.85 (m, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.65 (q, *J* = 6.1 Hz, 2H), 1.81 (p, *J* = 6.7 Hz, 2H), 1.64 – 1.53 (m, 2H), 1.48 (s, 2H), 1.40 (q, *J* = 4.4 Hz, 4H), 1.21 (t, *J* = 5.2 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 133.95, 115.15, 68.31, 62.94, 32.65, 29.10, 28.91, 25.92, 25.66. **IR (neat)** 3274.60, 2931.15, 2856.64, 2220.46, 1605.23, 1509.62, 1302.56, 1263.27, 1175.55, 1056.30, 1023.54, 995.53, 838.75 cm^{-1}.



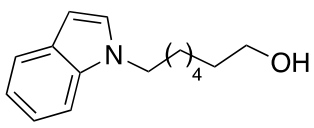
2.2k

7-(4-(trifluoromethyl)phenoxy)heptan-1-ol (2.2k) Prepared according to general procedure using 1-((6-iodohexyl)oxy)-4-(trifluoromethyl)benzene (0.19 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.18) to afford the title compound as colorless liquid (0.12 g, 84%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.53 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 1.80 (p, *J* = 6.7 Hz, 2H), 1.58 (td, *J* = 9.1, 8.0, 5.0 Hz, 2H), 1.53 – 1.44 (m, 2H), 1.44 – 1.34 (m, 4H), 1.26 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 161.55, 126.84, 126.81, 114.39, 68.14, 62.97, 32.67, 29.12, 29.02, 25.96, 25.67. **HRMS** (ESI) Calcd. for $C_{14}H_{19}F_2O_2$ ($[M-F]^+$): 257.1353; Found: 257.1293. **IR (neat)** 3331.36, 2932.40, 2858.75, 2359.82, 1615.20, 1519.09, 1330.12, 1324.67, 1255.98, 1100.58, 1066.58, 1008.52 cm^{-1}.



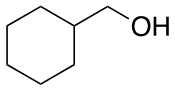
2.2l

Methyl 4-((7-hydroxyheptyl)oxy)benzoate (2.2l) Prepared according to general procedure using methyl 4-((6-iodohexyl)oxy)benzoate (0.18 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane, Rf = 0.10) to afford the title compound as white solid (0.06 g, 47%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.03 – 7.91 (m, 2H), 6.95 – 6.83 (m, 2H), 4.00 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 3H), 3.65 (t, *J* = 6.6 Hz, 2H), 1.80 (p, *J* = 6.7 Hz, 2H), 1.66 – 1.53 (m, 2H), 1.48 (m, 2H), 1.39 (m, 4H), 1.25 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 131.56, 114.04, 68.09, 62.97, 51.83, 32.68, 29.13, 29.04, 25.97, 25.67. **HRMS** (ESI) Calcd. for $C_{15}H_{23}O_4$ ($[M+H]^+$): 267.1596; Found: 267.1587. **IR (neat)** 3334.06, 2930.75, 2857.01, 2359.70, 1463.53, 1431.86, 1290.85, 1055.39, 724.93, 667.99, 667.99, 650.07 cm^{-1}.



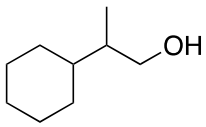
2.2m

7-(1*H*-indol-1-yl)heptan-1-ol (2.2m) Prepared according to general procedure using 1-(6-iodohexyl)-1*H*-indole (0.16 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.13) to afford the title compound as colorless liquid (0.08 g, 72%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.21 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.13 – 7.07 (m, 2H), 6.49 (d, *J* = 3.1 Hz, 1H), 4.12 (t, *J* = 7.1 Hz, 2H), 3.61 (t, *J* = 6.6 Hz, 2H), 1.85 (q, *J* = 7.0 Hz, 2H), 1.53 (m, 2H), 1.33 (m, 6H), 1.21 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.92, 128.55, 127.75, 121.27, 120.92, 119.13, 109.34, 100.84, 62.90, 46.36, 32.61, 30.15, 29.01, 26.95, 25.59. **HRMS** (ESI) Calcd. for $C_{15}H_{22}NO$ ($[M+H]^+$): 232.1701; Found: 232.1686. **IR (neat)** 3335.06, 2928.38, 2854.78, 2359.79, 1510.13, 1462.79, 1314.15, 737.14 cm^{-1}.



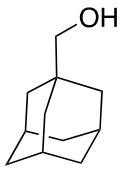
2.2n

Cyclohexylmethanol (2.2n) Prepared according to general procedure using **2.1n** (65 μL, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.35) to afford the title compound as colorless liquid (0.05 g, 89%). Characterization has been reported by previous literature.[31] **^{1}H NMR (500 MHz, $CDCl_3$)** δ 3.44 (t, *J* = 5.9 Hz, 2H), 1.76 (m, 4H), 1.69 (m, 1H), 1.48 (m, 1H), 1.30 – 1.19 (m, 4H), 0.95 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 69.07, 40.76, 29.81, 26.85, 26.10.



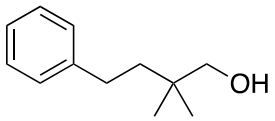
2.2o

2-cyclohexylpropan-1-ol (2o) Prepared according to general procedure using **2.1o** (0.12 g, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =85: 25, Rf = 0.31) to afford the title compound as colorless liquid (0.04 g, 58%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 3.65 – 3.56 (m, 1H), 3.46 (ddd, *J* = 10.5, 6.9, 5.7 Hz, 1H), 1.77 – 1.68 (m, 2H), 1.68 – 1.59 (m, 3H), 1.49 (dq, *J* = 7.2, 5.6 Hz, 1H), 1.38 – 0.92 (m, 7H), 0.88 (dd, *J* = 7.0, 2.2 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 66.32, 40.92, 39.36, 30.96, 28.78, 26.78, 26.68, 26.61, 13.37.



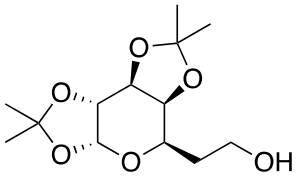
2.2p

1-Adamantane methanol (2.2p) Prepared according to general procedure using adamantine iodide **2.1p** (76 μL, 0.5 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.19) to afford the title compound as colorless liquid (0.08g g, 99%). Characterization has been reported by previous literature. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 3.20 (d, *J* = 5.9 Hz, 2H), 1.99 (p, *J* = 3.0 Hz, 3H), 1.78 – 1.69 (m, 3H) 1.69 – 1.60 (m, 2H), 1.51 (d, *J* = 2.9 Hz, 6H), 1.22 (q, *J* = 6.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 73.90, 39.04, 37.18, 28.19.



2.2q

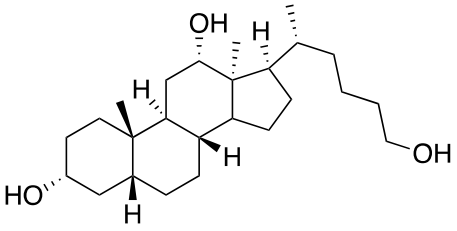
2,2-dimethyl-4-phenylbutan-1-ol (2.2q) Prepared according to general procedure using **2.1q** (0.055 g, 0.2 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =85: 15, Rf = 0.31) to afford the title compound as colorless liquid (0.022 g, 62%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.28 (t, *J* = 7.7 Hz, 2H), 7.22 – 7.14 (m, 3H), 3.39 (d, *J* = 6.0 Hz, 2H), 2.63 – 2.54 (m, 2H), 1.61 – 1.52 (m, 2H), 1.32 (t, *J* = 6.0 Hz, 1H), 0.97 (s, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.14, 128.34, 128.28, 125.63, 71.85, 40.89, 35.32, 30.52, 23.82.



2.2r

(-)-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galacto-heptopyranose (2.2r) Prepared according to general procedure using **2.1r** (0.074 g, 0.2 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =65: 35, Rf = 0.06) to afford the title compound as colorless liquid (0.022 g, 41%). **^{1}H NMR (500 MHz, $CDCl_3$)** *δ* 5.53 (d, *J* = 5.1 Hz, 1H), 4.61 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.31 (dd, *J* = 5.1, 2.4 Hz, 1H), 4.14 (dd, *J* = 7.9, 1.8

Hz, 1H), 4.01 (ddd, *J* = 9.7, 3.9, 1.8 Hz, 1H), 3.79 (h, *J* = 7.1, 6.4 Hz, 2H), 1.97 (m, 2H), 1.76 (dq, *J* = 11.1, 4.1 Hz, 1H), 1.54 (s, 3H), 1.46 (s, 3H), 1.34 (d, *J* = 9.3 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 96.47, 73.08, 70.91, 70.53, 65.76, 59.91, 32.50, 26.02, 24.97, 24.41. **HRMS** (ESI) Calcd. for $C_{13}H_{23}O_6$ ($[M+H]^+$): 275.1416; Found: 275.1483.

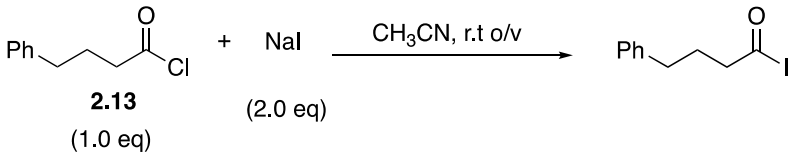


2.2s

Deoxycholic alcohol (2.2s) Prepared according to general procedure using **2.1s** (0.14 g, 0.2 mmol). The crude material was purified by silica gel chromatography (hexane/ethyl acetate =60: 40, Rf = 0.06) to afford the title compound as colorless liquid (0.043 g, 50%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 3.99 (s, 1H), 3.69 – 3.53 (m, 3H), 1.86 – 1.38 (m, 22H), 1.30 – 1.17 (m, 5H), 1.16 – 1.03 (m, 3H), 0.97 (d, *J* = 6.6 Hz, 4H), 0.91 (s, 3H), 0.68 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 73.25, 71.85, 63.09, 48.29, 47.67, 46.49, 42.11, 36.47, 36.07, 35.58, 35.44, 35.23, 34.13, 33.70, 33.25, 30.55, 28.57, 27.59, 27.15, 26.14, 23.65, 23.16, 22.28, 17.68, 12.74. **HRMS** (ESI) Calcd. for $C_{25}H_{41}O$ ($[M-2H_2O+H]^+$): 357.3079; Found: 357.3156.

2.5.5. Mechanistic experiments

A. Synthesis of acyl iodides

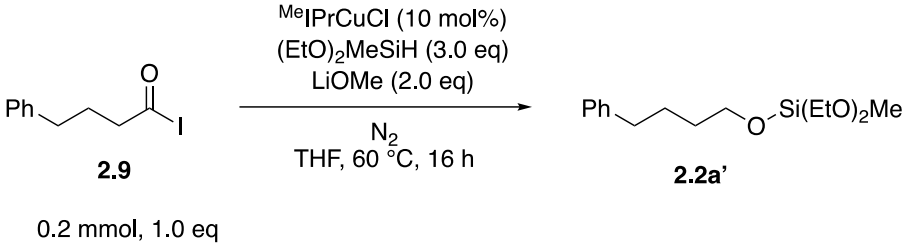


Scheme 2.12 Synthesis of 4-phenylbutanoyl iodide

In glovebox, NaI (0.082 g, 0.55 mmol, 2.0 eq) was dissolved with 2 mL acetonitrile in a vial charged with stir bar. Then 4-phenylbutanoyl chloride (0.05 g, 0.27 mmol, 1.0 eq) was added to the above mixture dropwise. The mixture was left stirring overnight at room temperature. The formation of white precipitate was observed. Then the reaction mixture was left under reduced pressure to remove all the solvent. The residue was dissolved with about 5

mL pentane, then filtered through a frit. The filtrate was left under vacuum until it was completely dry. A light yellow oil was obtained, and stored in freezer. It was characterized by NMR. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.31 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 1.98 (p, *J* = 7.3 Hz, 2H).

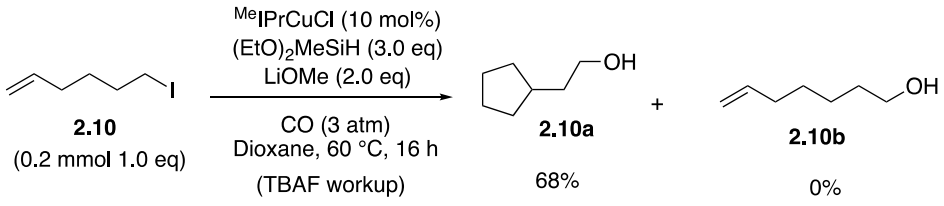
B. Stoichiometric reduction of acyl iodide by CuH



Scheme 2.13 Stoichiometric reaction with acyl iodide

In glovebox, the previous obtained 4-phenylbutanoyl iodide (0.05 g, 0.2 mmol) was subjected to a vial containing LiOMe (0.015 g, 0.4 mmol, 2.0 eq), ^{Me}IPrCuCl (0.01 g, 0.02 mmol, 10 mol%), and 1,4-dioxane (2.0 mL) and diethoxymethylsilane (96 μL, 0.6 mmol, 3.0 eq) with a 1.5 cm stir bar. The vial was left at 60 ℃ for 16 hours. Then removed the solvent under vacuum. The crude mixture was taken ^{1}H NMR in $CDCl_3$ with dibromomethane as internal standard. The result shows the formation of **2.2a'** in 97%.

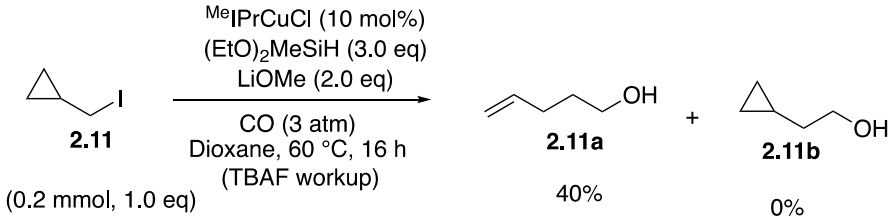
C. Radical clock experiments



Scheme 2.14 Radical clock experiment with 6-iodohex-1-ene

In glovebox, 6-iodohex-1-ene **2.10** (27 μL, 0.2 mmol) was subjected to a vial containing LiOMe (0.015 g, 0.4 mmol, 2.0 eq), ^{Me}IPrCuCl (0.01 g, 0.02 mmol, 10 mol%), and 1,4-dioxane (2.0 mL) and diethoxymethylsilane (96 μL, 0.6 mmol, 3.0 eq) with a 1.5 cm stir bar. Then it was capped and sit in the pressure reaction. The proceeded as described in the general procedure and worked up with TBAF. The crude oil mixture was taken for NMR analysis in $CDCl_3$ with dibromomethane as internal standard. According to the ^{1}H NMR, the yield of **2.10a** was identified as 68%

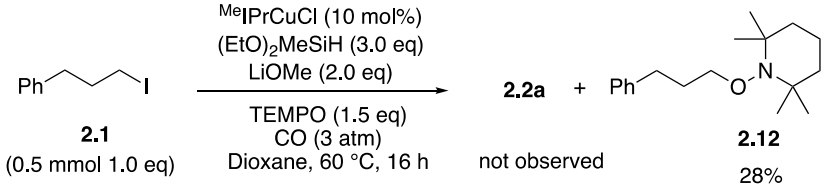
and no formation of **2.10b** while dibromomethane as internal standard (Characterization of **2.10a**[32] and **2.10b**[33] was reported in previous literatures).



Scheme 2.15 Radical clock experiment with (iodomethyl)cyclopropane

In glovebox, (iodomethyl)cyclopropane **2.11** (0.036 g, 0.2 mmol) was subjected vial containing LiOMe (0.015 g, 0.4 mmol, 2.0 eq), ^{Me}IPrCuCl (0.01 g, 0.02 mmol, 10 mol%), and 1,4-dioxane (2.0 mL) and diethoxymethylsilane (96 μL, 0.6 mmol, 3.0 eq) with a 1.5 cm stir bar. Then it was capped and sit in the pressure reactor and proceeded as described in the general procedure and worked up with TBAF. The crude oil mixture was taken for NMR analysis in $CDCl_3$ with dibromomethane as internal standard. According to the ^{1}H NMR, the yield of **2.11a** was identified as 40% and no formation of **2.11b** while 1,1,2,2-tetrachloroethane was used as internal standard (Characterization of **2.11a**[34] and **2.11b**[35] were reported in previous literatures).

2.5.6. Radical trapping experiment



Scheme 2.16 Reaction with radical scavenger TEMPO

In glovebox, 3-iodo-1-phenylpropane **2.1** (80 μL, 0.5 mmol) was subjected to the optimized conditions of the catalytic reaction with TEMPO (0.12 g, 0.75 mmol). After TBAF workup, the crude mixture was characterized by ^{1}H NMR. It was found there was no formation of **2.2a**, but the TEMPO adduct **2.12** was isolated as a colorless liquid (0.04 g, 28%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.28 (d, *J* = 7.8 Hz, 1H), 7.23 – 7.14 (m, 2H), 3.77 (t, *J* = 6.5 Hz, 2H), 2.71 (dd, *J* = 9.1, 6.9 Hz, 2H), 1.92 – 1.79 (m, 2H), 1.55 (s, 1H), 1.44 (dd, *J* = 8.5, 4.3 Hz, 4H), 1.31 (d, *J* = 12.7 Hz,

1H), 1.12 (d, *J* = 13.7 Hz, 13H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 142.43, 128.35, 128.25, 125.65, 76.11, 59.66, 39.62, 33.08, 32.75, 30.52, 20.11, 17.16. **HRMS** (ESI) Calcd. for $C_{18}H_{30}NO$ ($[M+H]^+$) : 276.2327; Found : 276.2319.

2.6. Conclusion

In summary, we have developed a Cu-catalyzed hydroxymethylation reaction of alkyl iodides to construct one carbon-extended alcohols under mild conditions.[36] This protocol is compatible with a broad range of functional groups and heterocycles. Mechanistic experiments are consistent with a metal-free radical atom transfer carbonylation of the alkyl iodide followed in tandem by a CuH-mediated reduction sequence.

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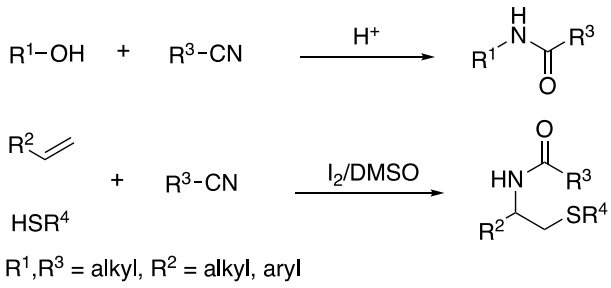
3. Synergistic copper-catalyzed reductive aminocarbonylation of alkyl iodides with nitroarenes

This chapter comes from the content presented in Zhao, S.; Mankad, N. P., Synergistic Copper-Catalyzed Reductive Aminocarbonylation of Alkyl Iodides with Nitroarenes. *Organic Letters* **2019,** *21* (24), 10106-10110.

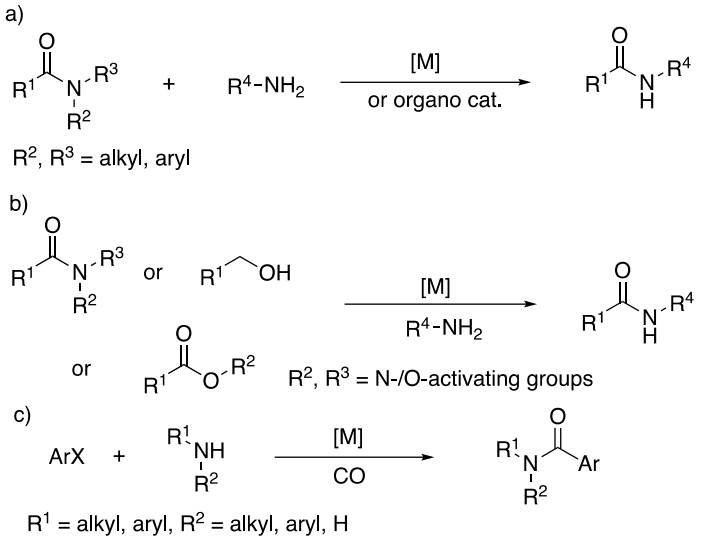
3.1. Introduction

The development of methodology that teases new transformations out of our established reductive carbonylation system continues to spur us on to explore synthesis routes for more interesting compounds. Amides are among of the most important chemical units in all of organic and biology chemistry,[1] and so the synthetic community has maintained an interest in developing different, complementary synthetic methods to target diverse amide compounds. For example, the classic Ritter reaction[2] involves protonation of an alcohol or alkene and *in situ* trapping of the resulting carbocation with a nitrile nucleophile;[3] thus, only *N*-alkyl amides are accessible[4] (Scheme 3.1).



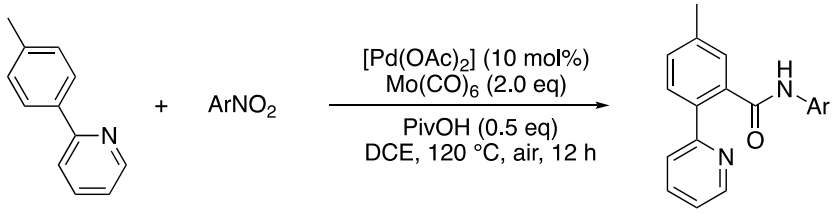
Scheme 3.1 Ritter reaction and its recent modification

Similarly, transamidation between amides and amines typically produce *N*-alkyl amides, and it is challenging for secondary amide reactants and non-nucleophilic amines[5] (Scheme 3.2a). Meanwhile, cross coupling between amines/alcohols and amides/esters also serves as a powerful manifold for the construction of new amide bonds[6] (Scheme 3.2b). Another efficient method for *N*-aryl amide synthesis is aminocarbonylation of aryl halides with anilines under CO atmosphere (Scheme 3.2 c); here use of alkyl electrophiles has proven challenging and limits the scope of accessible products to arylamides.



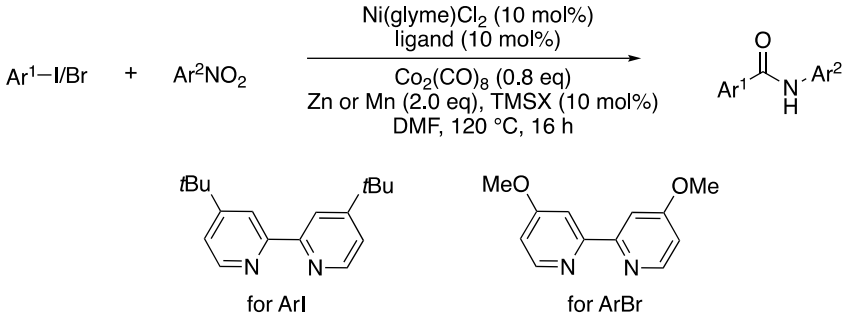
Scheme 3.2 Traditional transamidation between amides and amines. b) Cross-coupling reaction amines and amides, alcohols, or esters

Nitroarenes can act as surrogates for anilines under reductive conditions, in some cases exhibiting orthogonal functional group tolerance to classical amine nucleophiles in various coupling reactions.[7-9] However, there are only a few reports of successful reductive aminocarbonylation using nitroarenes as the nitrogen source, none of which involve C(sp^3)-hybridized electrophiles. Driver reported a Pd-catalyzed reductive aminocarbonylation of aromatic C-H bonds with $Mo(CO)_6$ serving as both reducing agent and CO source, producing *N*-aryl arylamides as long as the substrate contained an *ortho*-pyridyl directing group[10] (Scheme 3.3). Mechanistic investigation revealed that reduction of nitroarenes occurred to form nitrosoarenes as intermediates for the next aminocarbonylation step.



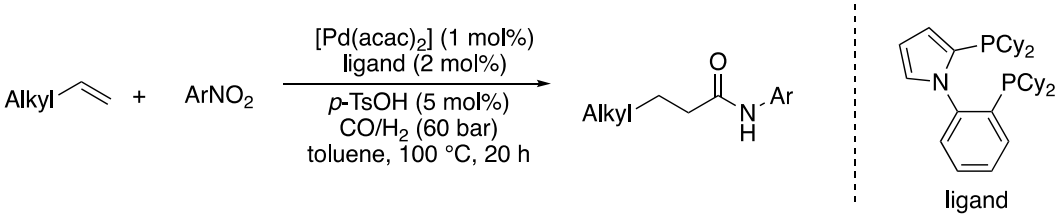
Scheme 3.3 Pd-catalyzed C-H aminocarbonylation of *N*-heteroarenes

Additionally, recent advances by Hu have enabled Ni-catalyzed reductive aminocarbonylation of aryl halides. With the presence of $Co_2(CO)_8$ and Zn or Mn reducing reagents, a modular synthesis for a wide range of arylamides was established under mild conditions[11] (Scheme 3.4). The same group also achieved such transformations with aryl or alkyl esters and $Mo(CO)_6$ without external reductant.[12] Meanwhile, empowering the aminocarbonylation with coupling partners, such as aryl boronic acids,[13, 14] alkynes,[15] and allenes[16] were also documented.



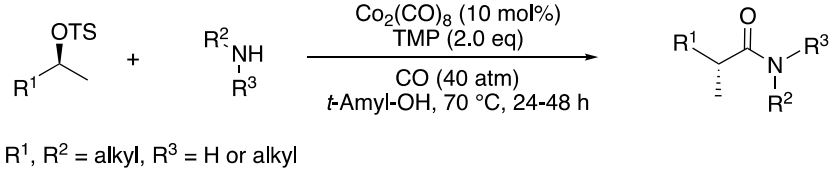
Scheme 3.4 Ni-catalyzed aminocarbonylation of aryl halides and nitroarenes

The only example of *N*-aryl alkylamide synthesis by reductive aminocarbonylation was reported by Beller, who disclosed a Pd-catalyzed coupling of terminal alkenes with nitroarenes under syn-gas pressure to provide *N*-aryl alkylamides.[17] It was suggested the aniline was generated in situ, then proceeded to functionalization. Nevertheless, the range of accessible products was limited by the fact that only monosubstituted alkenes were amenable to coupling. Recently, Hu also furnished alkylamides through reductive transamidation between nitroarenes and amides.[18, 19]



Scheme 3.5 Pd-catalyzed aminocarbonylation with olefins and nitroarenes

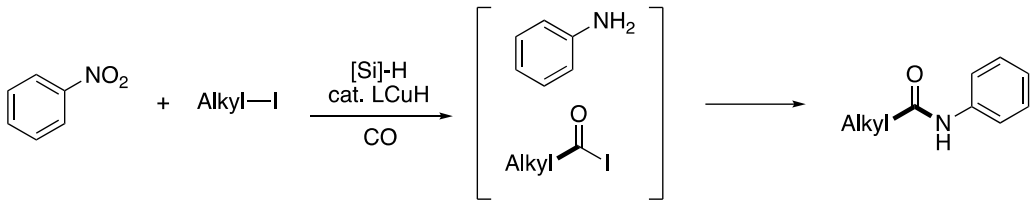
Although C(sp^3)-X electrophiles have not been investigated in reductive aminocarbonylation, they have been used in aminocarbonylation with amine nucleophiles,[20, 21] including a recent report by Alexanian of stereospecific aminocarbonylation with alkyl tosylates with primary and secondary amines (Scheme 3.6). The absolute stereochemistry of the secondary alkyl substrates was retained during the transformation, yielding a new range of alkyl alkyl amides in good yields and excellent enantioselectivities.



Scheme 3.6 Co-catalyzed stereospecific aminocarbonylation of alkyl tosylates. TMP: 2,2,6,6-tetramethylpiperidine.

Our group has reported several examples of carbonylative coupling reactions involving single-electron transfer activation of alkyl halides mediated by *N*-heterocyclic carbene (NHC) copper catalysts in the presence of

reducing agents such as hydrosilanes.[22-24] Thus, we wondered whether this methodology could be extended to reductive aminocarbonylation with nitroarenes as pro-nucleophiles, providing anilines as intermediates, with the copper catalyst playing dual roles of synergistically mediating nitroarene reduction and alkyl halide carbonylation (Scheme 3.7). To our knowledge, copper catalysts have not been explored previously for reductive aminocarbonylation.[25, 26] Nonetheless, Beller and Thomas have successfully reduced nitroarenes to anilines using iron hydrides,[9, 27, 28] and Yin recently showed that copper catalysis is appropriate for reductive C-N coupling with nitroarenes using hydrosilane reductants.[29]



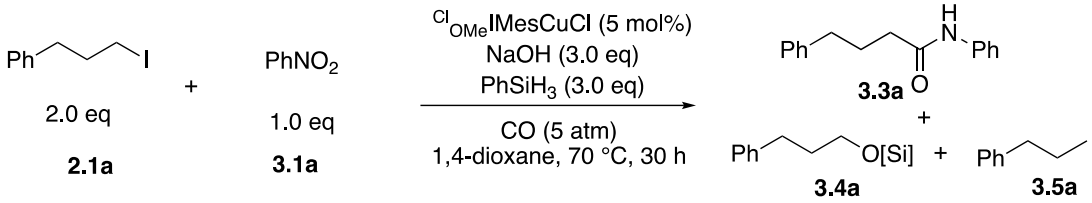
Scheme 3.7 Proposed reductive aminocarbonylation of alkyl iodides with nitroarenes

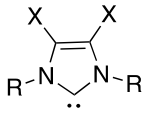
However, to realize our goal that involves controlling a complex sequence of reduction, radical carbonylation, and amidation steps, we have envisioned possible side reactions such as the competing reduction of alkyl halides by the copper hydride catalyst,[30] the competing hydroxymethylation via reduction of carbonylated intermediates by the copper hydride rather than by the nitrogen nucleophile as described in the chapter 2 and the potential multiple CO insertion.[31, 32]

3.2. Reaction optimization

We began our study with nitrobenzene (**3.1a**) and 1-iodo-3-phenylpropane (**2.1a**) as substrates, targeting amide compound **3.3a**. (Table 3.1) After screening with different NHC ligands, we found that while direct reduction of alkyl iodides (**3.5a**) can be avoided by the choice of ligands (Table 3.1, entry 5), hydroxymethylation (**3.4a**) cannot be avoided completely. In order to compensate the loss of iodide substrate consumed by hydroxymethylation, we employed 2.0 equivalents of **2.1a** in the. Based on further investigation, we noticed that the electronegativity of ligand is crucial to improve the yield of **3.3a**. For example, while IMes and ^{Cl}IMes provided almost the same yields (Table 3.1, entries 4-5), ^{Br}IMes decreased yield (Table 3.1, entry 6) and $^{Cl}_{OMe}$IMes boosted the yield up to 78%. (Table 3.1, entry 1) The choice of NaOH as the base and $PhSiH_3$ as the hydrosilane are necessary for the successful transformation (Table 3.1, entries 7-9). It is worth noting that the use of LiOMe favored the hydroxymethylation side reactions described above, which is in agreement with the previous work in chapter 2 (Table 3.1, entry 8). Reducing the amount

of hydrosilane or raising catalyst loading both diminished the desired reaction (Table 3.1, entries 10-11). Finally, we observed moderate yields at lower temperature and pressure (Table 3.1, entries 12-13).





IPr	R = 2,6-(diisopropyl)phenyl	X = H
IMes	R = 2,4,6-trimethylphenyl	X = H
ClIMes	R = 2,4,6-trimethylphenyl	X = Cl
BrIMes	R = 2,4,6-trimethylphenyl	X = Br
ClOMeIMes	R = 4-methoxy-2,6-dimethylphenyl	X= Cl

Entry	Change from optimized conditions	Yields of **3.3a** (%)	Yields of **3.4a** (%)	Yields of **3.5a** (%)
1	None	78	40	12
2	No catalyst	0	0	0
3	IPrCuCl catalyst	38	50	24
4	IMesCuCl catalyst	61	34	14
5	^{Cl}IMesCuCl catalyst	59	32	0
6	^{Br}IMesCuCl catalyst	38	39	23
7	LiOH base	18	22	18
8	LiOMe base	13	25	22
9	Ph_2SiH_2 as silane	0	0	0
10	2.0 eq. $PhSiH_3$	28	18	3
11	10 mol% catalyst	62	64	12
12	60 °C	51	39	10
13	3 atm CO	30	31	6

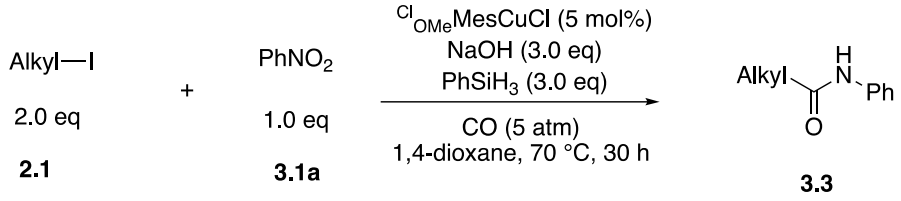
Reactions were done on a 0.1 mmol scale. And all yields relative to **3.1a** were determined by ^{1}H NMR with 1,1,2,2, tetrachloroethane as internal standard.

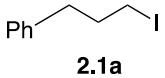
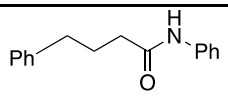
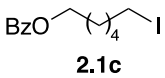
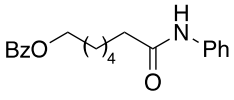
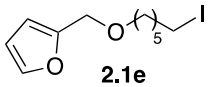
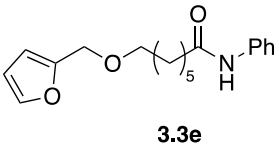
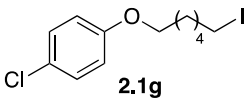
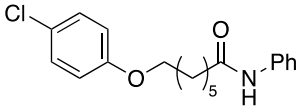
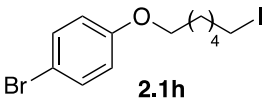
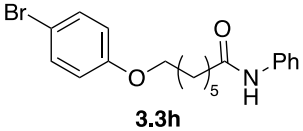
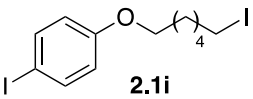
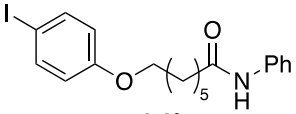
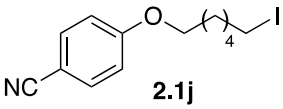
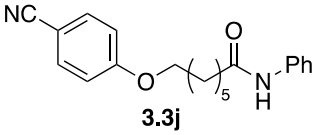
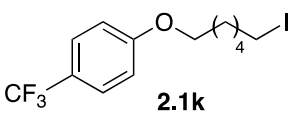
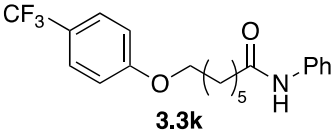
Table 3.1 Reaction optimization for reductive aminocarbonylation of alkyl iodides and nitrobenzenes

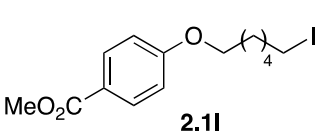
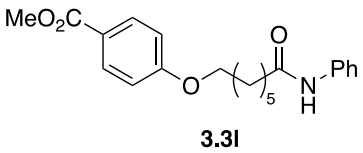
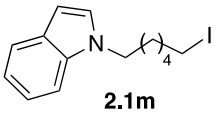
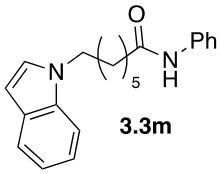
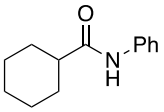
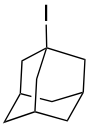
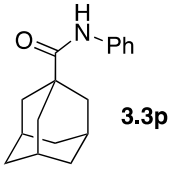
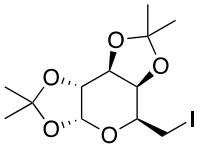
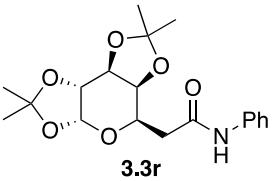
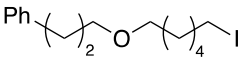
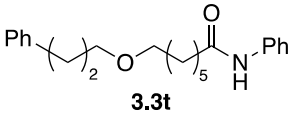
3.3. Substrate scope in alkyl iodides and nitroarenes

With the optimized conditions in hand, we started to test the scope of alkyl iodides (Table 3.2). Simple primary (**2.1a**), secondary (**2.1n**), and tertiary (**2.1p**) alkyl iodides underwent the transformation smoothly. Substrates containing aryl halides were efficiently converted to target amides (**2.1g**-**2.1l**), implying that this methodology is orthogonal to classical Pd-catalyzed couplings. Synthetically important moieties, such as ether (**2.1t**), cyano (**2.1j**) and

trifluoromethyl (**2.1k**) are all compatible. To our delight, some base-sensitive groups including benzyl ether (**2.1c**) and methyl ester (**2.1l**) survived under these conditions. Heterocyclic groups such as furan (**2.1e**) and indole (**2.1m**) gave modest yields and required use of ^{Cl}IMes in place of $^{Cl}{}_{OMe}$IMes. This method can also be applied to complex carbohydrate substrates (**2.1r**).



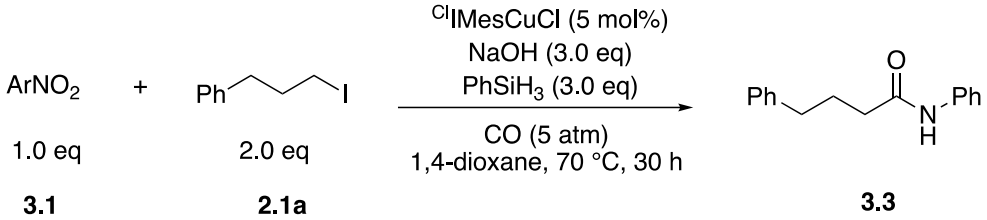
Entry	Alkyl iodides **2.1**	Amide products	Yields of amides **3.3** (%)[a]
1	 **2.1a**	 **3.3a**	78(54[b])
2	 **2.1c**	 **3.3c**	74
3	 **2.1e**	 **3.3e**	55[c]
4	 **2.1g**	 **3.3g**	70
5	 **2.1h**	 **3.3h**	72
6	 **2.1i**	 **3.3i**	58
7	 **2.1j**	 **3.3j**	47
8	 **2.1k**	 **3.3k**	51

9	 **2.1l**	 **3.3l**	51
10	 **2.1m**	 **3.3m**	47
11	 **2.1n**	 **3.3n**	80
12	 **2.1p**	 **3.3p**	86
13	 **2.1r**	 **3.3r**	51[c]
14	 **2.1t**	 **3.3t**	75

[a] Reactions were done on a 0.1 mmol scale. All yields are isolated yields relative to **3.1a** and average two parallel experiments. [b] Reactions were done on a 1 mmol scale. Reported as average isolated yield relative to **3.1a** from two parallel experiments. [c] ^{Cl}IMesCuCl catalyst was used instead of $^{Cl}_{OMe}$CuCl.

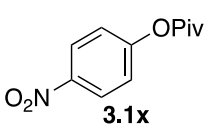
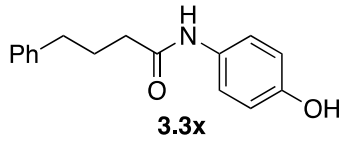
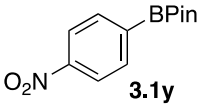
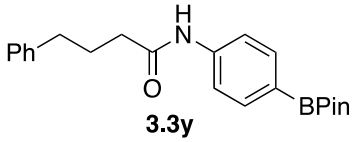
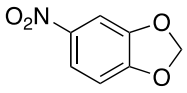
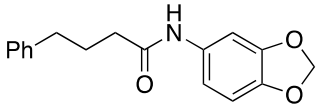
Table 3.2 Substrate scope regarding to alkyl iodides

Next, we investigated the substrate scope with respect to nitroarenes. We found ^{Cl}IMes performed better than $^{Cl}_{OMe}$IMes in this transformation with substituted nitroarenes (Table 3.3). Aryl halide (**3.1f**-**3.1u**) and thioether (**3.1w**) substituents posed no problem in the transformation, whereas protected phenols (**3.1x**) and heterocyclic groups (**3.1z**) gave moderate yields. Use of IPr as ligand allowed for smooth conversion with nitroarenes containing boronic esters (**3.1y**) and anisole (**3.1u**), while $^{Cl}_{OMe}$IMes was required for trifluoromethoxyl substituted nitroarenes (**3.1v**) to give good yield.



1.0 eq **3.1** 2.0 eq **2.1a** **3.3**

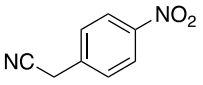
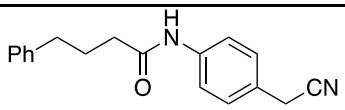
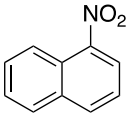
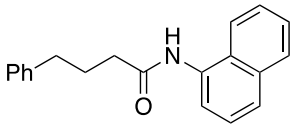
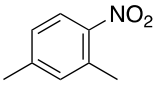
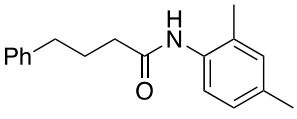
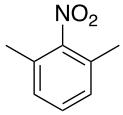
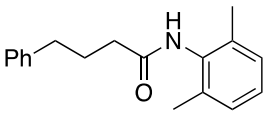
Entry	Nitroarene **3.1**	Amide products **3.3**	Yields of **3.3** (%)
1	$PhNO_2$ **3.1b**	**3.3b**	82[a]
2	**3.1d**	**3.3d**	92
3	**3.1f**	**3.3f**	77
4	**3.1o**	**3.3o**	64
5	**3.1q**	**3.3q**	54
6	**3.1s**	**3.3s**	57[b]
7	**3.1u**	**3.3u**	47[c]
8	**3.1v**	**3.3v**	75[d]
9	**3.1w**	**3.3w**	73

10	 **3.1x**	 **3.3x**	51[e]
11	 **3.1y**	 **3.3y**	70[c]
12	 **3.1z**	 **3.3z**	52

Reaction were done a 0.1 mmol scale. All yields are isolated yields relative to **3.1** average of two parallel experiments. [a] 1-iodoocatane was used instead of **2.1a**. [b] Product was isolated with 10% inseparable impurities. [c] IPr ligand was used instead of ^{Cl}IMes. [d] The $^{Cl}_{OMe}$IMes ligand was used instead of ^{Cl}IMes. [e] The phenolic group underwent deprotection during the reaction without any further treatment.

Table 3.3 Substrate scope of aminocarbonylation with respect to nitroarenes

However, cyanide groups on the nitroarene (**3.6a**) inhibited the reaction, and a polyaromatic nitroarene (**3.6b**) performed poorly in this reaction. We also found this method is highly sensitive to steric environment on the nitrobenzene partner (**3.6c** and **3.6d**). (Table 3.4)

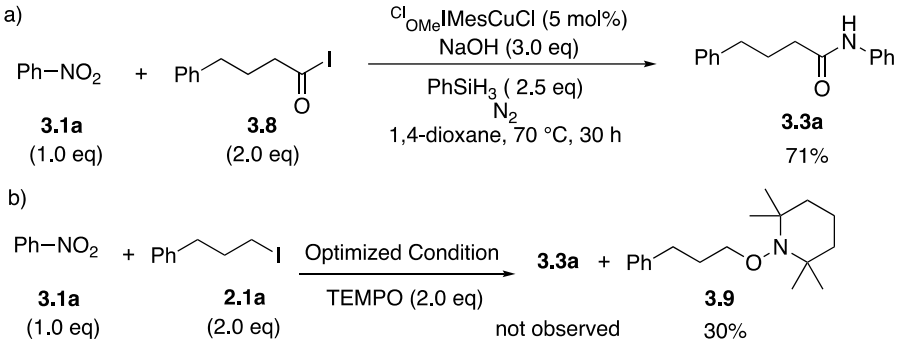
Entry	Nitroarene	Amide product	Yield of Amides (%)
1	 **3.6a**	 **3.7a**	0
2	 **3.6b**	 **3.7b**	34
3	 **3.6c**	 **3.7c**	17
4	 **3.6d**	 **3.7d**	0

Reactions were conducted on a 0.1 mmol scale under the optimized conditions in Table 3.3. Yields were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard.

Table 3.4 Failed nitroarene substrates for reductive aminocarbonylation

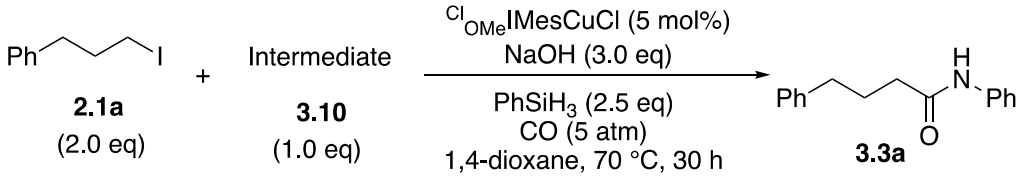
3.4. Mechanistic Investigation

To examine the mechanism of this reductive aminocarbonylation, a stoichiometric reaction was carried out by subjecting acyl iodide **3.8** to the standard reaction in place of **2.1a** under N_2 atmosphere (Scheme 3.8 a). The expected amide **3.3a** was obtained in 71% yield, implying that acyl iodide might serve as the carbonylated intermediate during catalysis. Then the radical nature of this transformation was confirmed by the addition of radical scavenger TEMPO to the standard reaction. The target amide **3.3a** was not observed; instead the TEMPO adduct compound **3.9** was isolated in 30% yield (Scheme 3.8 b).

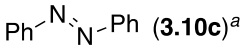
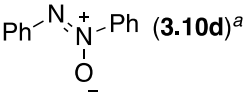


Scheme 3.8 a) Stoichiometric reaction with acyl iodide under inert atmosphere. b) Reaction with TEMPO reagent. Yield is isolated yield. For both a) and b) reactions were done on a 0.1mmol scale, and yields were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard.

To gain insight into the reactive nitrogen nucleophile during catalysis, several possible intermediates resulting from nitroarene reduction were tested under catalytic conditions (Table 3.5). No amide product was detected with azobenzene (**3.10c**), and nitrosobenzene (**3.10a**), *N*-phenyl hydroxyamine (**3.10b**) and azoxybenzene (**3.10d**) gave low yields. Only aniline (**3.10e**) gave quantitative yield (94%) under the standard reaction conditions. Thus, we propose that aniline might be the major reactive intermediate for C-N bond formation. However, we cannot rule out a potential role of other intermediates such as hydroxylamine serving as nitrogen sources by minor pathways.



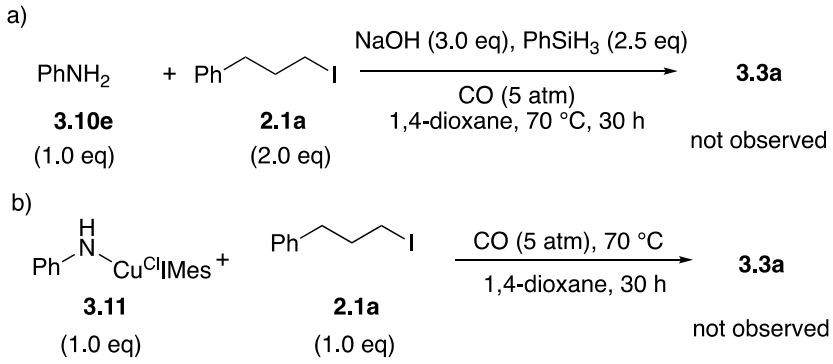
Entry	Intermediate **3.10**	Yield of **3.3a** (%)
1	PhNO (**3.10a**)	26
2	PhNHOH (**3.10b**)	14

3	 (**3.10c**)[a]	0
4	 (**3.10d**)[a]	32
5	$PhNH_2$ (**3.10e**)	94

Reactions were done on a 0.1 mmol scale and yields were determined by determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard. [a] 0.05 mmol intermediates were used instead of 0.1 mmol.

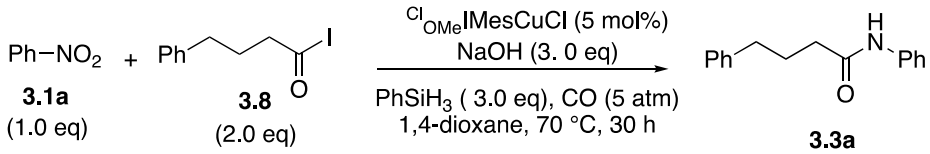
Table 3.5 Reactions with possible intermediates from nitrobenzene

Then the aniline intermediate (**3.10e**) was subjected to condition shown in Scheme 3.9 a without the presence of copper catalyst. Surprisingly, amide **3.3a** or other carbonylated compounds were not detected. This indicates that the carbonylation is a copper-mediated radical process rather than a radical chain-type atom transfer carbonylation.[33] Another potential copper amide intermediate **3.11** was also tested under optimized conditions shown in Scheme 3.9 b. The absence of targeted **3.3a** help to eliminate the possible route of a copper amide intermediate mediating radical carbonylation.



Scheme 3.9 a) Control experiments without Cu catalyst. b) Control experiment with potential copper amide intermediate. For both a) and b), reactions were done on a 0.1 mmol scale, and yields were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard.

To probe the reducing reagent responsible for nitroarene reduction, several control experiments were conducted. Since carbon monoxide, hydrosilanes, and metal hydrides have all been shown to reduce nitroarenes,[8, 34] each of them was eliminated individually. According to the results shown in Table 3.6, we can conclude that only (NHC)CuH intermediates are competent to reduce nitroarenes under these conditions.



Entry	CO	$PhSiH_3$	Catalyst	Yield of **3.3a** (%)
1	✗	✓	✗	0
2	✓	✗	✓	0
3	✗	✓	✓	71

Reactions were done on a 0.1mmol scale, and yields were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard.

Table 3.6 Control experiments with potential reducing agents

Currently, there is definitive evidence that the copper catalyst plays a dual role of synergistically mediating both alkyl iodide carbonylation and nitroarene reduction. While the detailed mechanism of each step requires more study, we propose that the dual roles of the copper catalyst produce the two reactive intermediates, acyl iodide and aniline, which then engage in C-N coupling via a rapid, uncatalyzed step.

3.5. Experimental section

3.5.1. General information

Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Common commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific or VWR International Co. and used without further purification unless otherwise noted. Solvents were dried using a Glass Contour Solvent System built by Pure Process Technology, LLC. CO gas was purchased from Praxair at a purity of 99.99% (4.0RS research grade) and used directly from the cylinder. IPrCuCl , SIPrCuCl,[35] IMesCuCl, SIMesCuCl,[36] ^{Me}IPrCuCl, ^{Br}IMesCuCl, ^{Cl}IPrCuCl, and $^{Cl}_{OMe}$IMesCuCl[37] were prepared according to literature procedures. Alkyl iodides were prepared according to literatures in previous chapter.

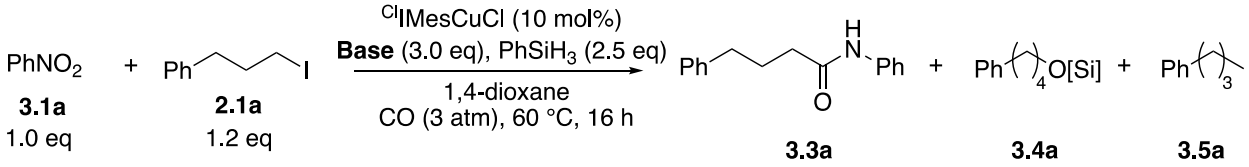
Nuclear Magnetic Resonance (NMR) spectra were recorded on BRUKER AV (400 MHz) or BRUKER AV (500 MHz) spectrometers at 298 K. Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard (chloroform at 7.26 and 77.16 ppm for ^{1}H and ^{13}C NMR spectroscopy, respectively). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet; br., broad. Coupling constants were taken from the spectra directly and are uncorrected. ^{1}H and ^{13}C NMR data provided are taken directly using material for which the yield is quoted, without further purification, and are representative of purity. FT-IR

spectra were recorded on a Bruker Platinum ATR spectrometer. Absorptions are given in wavenumbers (cm^{-1}). HRMS (ESI) were measured with a Waters Q-TOF Ultima ESI Mass Spectrometer.

Reactions requiring anhydrous conditions were conducted in a N2-filled glovebox or using standard Schlenk line techniques. Reactions at greater than atmospheric pressure were conducted in a Parr 4621 General Purpose Pressure Reactor. A fitted, aluminum insert was custom-made for the Parr reactor that could hold up to nine 22-mL scintillation vials for running reactions in parallel. Thin layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by UV light (254 nm) or KMnO4 stain. Purification of compounds was achieved by column chromatography using Merck Flash Silica Gel 60 (230-400 mesh). Organic solutions were concentrated under reduced pressure using a rotary evaporator.

3.5.2. Reaction optimization

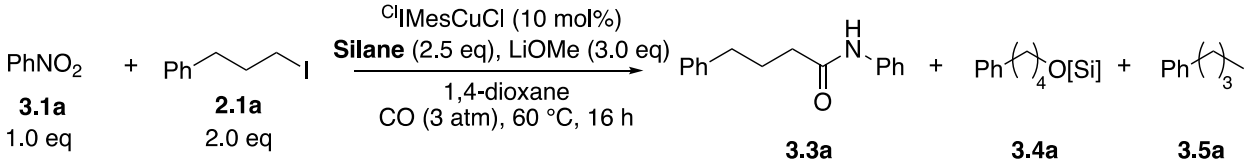
In a glovebox, base, copper catalyst, and. 1,4-dioxane (2.0 mL) were added to a 20-mL vial charged with a 1.5-cm stir bar. Then nitrobenzene (0.1 mmol, 1.0 eq), 3-iodo-1-phenylpropane (0.2 mmol, 2.0 eq) and hydrosilane were added to the mixture. The vial was then placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas and released after 5 min. This procedure was repeated three times, after which the reaction was heated on heating mantle and stirred vigorously. After desired reaction time, the reaction was cooled to room temperature and the CO gas was released. The solvent was removed under reduced pressure. The residue was diluted with Et_2O and then filtered through a pad of silica gel (a pipette with about 2 cm silica gel). The filtrate was concentrated under reduced pressure. The residue was dissolved in $CDCl_3$, and $CHCl_2CHCl_2$ (0.1 mmol) was added as internal standard for ^1H NMR analysis.



Entry	**Base**	Yield of **3.3a** (%)	Yield of **3.4a** (%)	Yield of **3.5a** (%)
1	KF	0	0	0
2	KOH	0	20	0
3	NaOH	28	30	0

4	LiOMe	24	22	11
5	KOMe	0	19	0
6	CsF	16	20	0
7	CsOAc	21	22	0

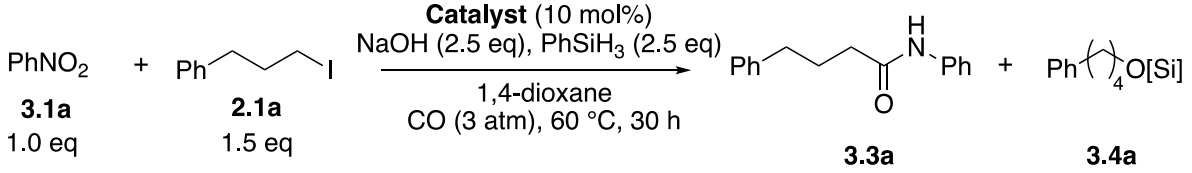
Table 3.7 Base investigation



Entry	**Silane**	Yield of **3.3a** (%)	Yield of **3.4a** (%)	Yield of **3.5a** (%)
1	$PhSiH_3$	10	0	0
2	Et_3SiH	0	0	0
3	$(EtO)_3SiH$	0	0	0
4	PMHS	0	0	0

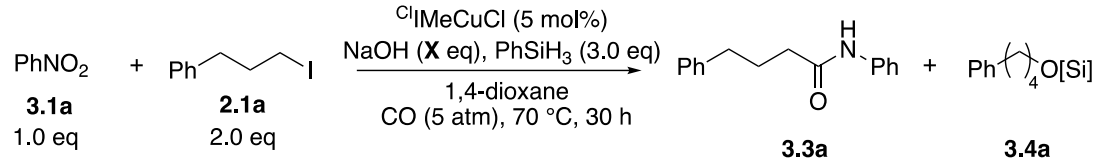
PMHS = (Poly)methylyhydrosiloxane

Table 3.8 Silane investigation



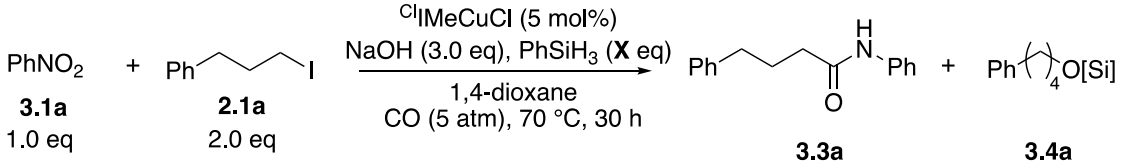
Entry	**Catalyst**	Yield of **3.3a** (%)	Yield of **3.4a** (%)
1	^{Cl}IMesCuCl	31	0
2	IMesCuCl	32	20
3	SIMesCuCl	20	0
4	^{Me}IMesCuCl	22	14
5	^{Cl}IPrCuCl	10	26
6	IPrCuCl	5	22
7	SIPrCuCl	13	26
8	^{Me}IPrCuCl	8	36

Table 3.9 Catalyst investigation



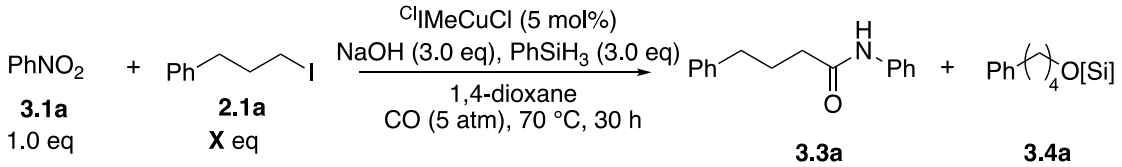
Entry	NaOH (**X eq**)	Yield of **3.3a** (%)	Yield of **3.4a** (%)
1	2.5	52	20
2	3.0	59	38
3	3.5	52	42

Table 3.10 Amount of base investigation



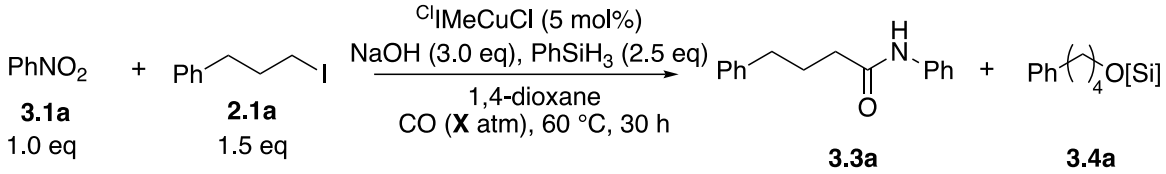
Entry	$PhSiH_3$ (**X eq**)	Yield of **3.3a** (%)	Yield of **3.4a** (%)
1	2.5	54	30
2	3.0	59	38
3	3.5	53	45

Table 3.11 Amount of silane investigation



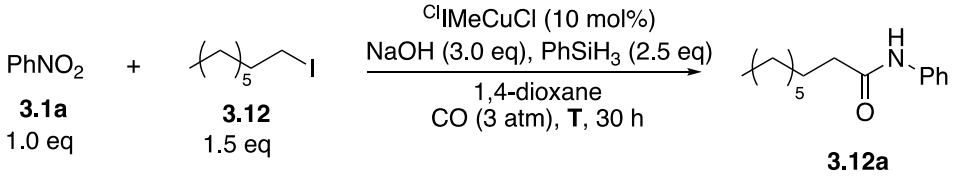
Entry	**2.1a** (**X** eq)	Yield of **3.3a** (%)	Yield of **3.4a** (%)
1	0.67	0	0
2	1.2	28	30
3	1.5	49	41
4	2.0	59	32

Table 3.12 Amount of alkyl iodides investigation



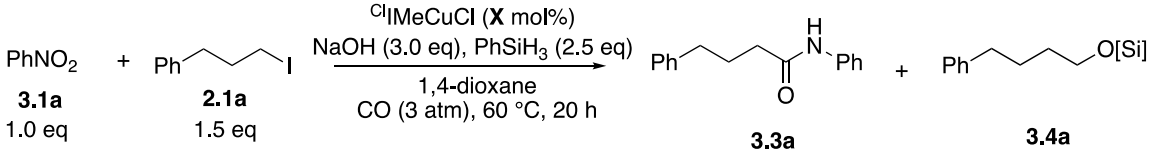
Entry	CO (**X** atm)	Yield of **3.3a** (%)	Yield of **3.4a** (%)
1	3	30	18
2	5	50	44
3	6	42	40

Table 3.13 Pressure investigation



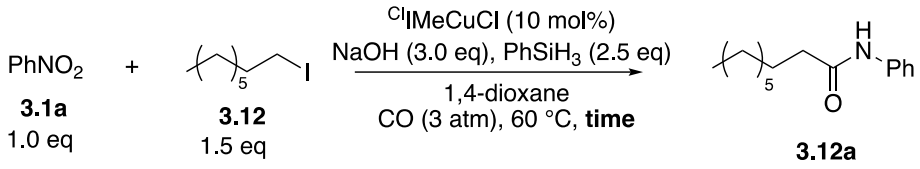
Entry	**T** (℃)	Yield of **3.12a** (%)
1	50	0
2	60	48
3	70	62
4	80	54

Table 3.14 Reaction time investigation



Entry	**Catalyst loading** (mol%)	Yield of **3.3a** (%)	Yield of **3.4a** (%)
1	5	47	26
2	8	26	20
3	10	23	20
4	12	15	18

Table 3.15 Catalyst loading amount investigation

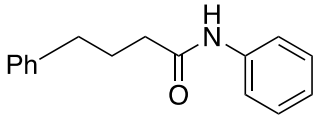


Entry	**time** (h)	Yield of **3.12a** (%)
1	16	26
2	20	35
3	24	48
4	30	52

Table 3.16 Reaction time investigation

3.5.3. Procedure for synthesis and characterization of amide products

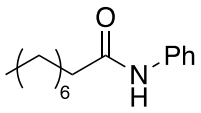
In a glovebox, NaOH (0.012 g, 0.3 mmol, 3.0 eq), catalyst (0.005 mmol, 5 mol%), and 1,4-dioxane (2.0 mL) were added to a 20-mL vial charged with a 1.5-cm stir bar. Then nitroarene (0.1 mmol, 1.0 eq), alkyl iodide (0.2 mmol, 2.0 eq) and phenylsilane (37 μL, 0.3 mmol, 3.0 eq) were added to the mixture. Then the vial was placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas and released after 5 min. This procedure was repeated three times, after which the reaction was heated to 70 ℃ and stirred vigorously. After 30 h, the reaction was cooled to room temperature and the CO gas was released. The solvent was removed under reduced pressure. The residue was dissolved with Et_2O, then filtered through a pad of silica gel (a pipette with about 2 cm silica gel). The filtrate was concentrated under reduced pressure for silica column chromatography.



3.3a

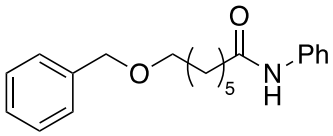
***N*,4-diphenylbutanamide** (**3.3a**) Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =90: 10, Rf = 0.18) to afford the title compound as a white solid (0.037 g, 78%). Characterization has been reported by previous literature.[17] 1mmol scale reaction was done according to the above

general procedure and separated using the same elute on silica gel chromatography. 0.26 g white solid was obtained from two parallel experiments in the yield of 54%. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 (d, J = 7.9 Hz, 2H), 7.33-7.28 (4H), 7.21-7.20 (m, 3H), 7.12-7.08 (m, 1H), 7.10 (s, 1H), 2.73 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.11-2.05 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.0, 129.2, 128.7, 128.6, 126.2, 124.4, 119.9, 36.9, 35.2, 27.0. **HRMS** (ESI) Calcd. for $C_{15}H_{23}NO$ ([M+H]+): 234.1858; Found: 234.1864. **IR** (neat) 3267, 3024, 2922, 1663, 1598, 1520, 1443, 1376, 1331, 1250, 1193, 731, 686, 497 cm-1.



3.3b

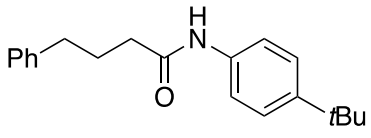
***N*-phenylnonanamide (3.3b)** Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and 1-iodoocatane (36 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =90: 10, Rf = 0.19) to afford the title compound as a white solid (0.038 g, 82%).[38] **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.11-7.08 (m, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.76-1.70 (m, 2H), 1.38-1.27 (m, 10H), 0.88 (t, *J* = 6.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 129.2, 124.3, 119.9, 38.1, 32.0, 29.5, 29.4, 29.3, 25.8, 22.8, 14.2. **HRMS** (ESI) Calcd. for $C_{15}H_{24}NO$ ($[M+H]^+$): 234.1858; Found: 234.1864. **IR (neat)** 3303, 2916, 2849, 1655, 1599, 1536, 1443, 754, 600, 503 cm^{-1}.



3.3c

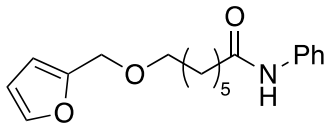
7-(benzyloxy)-*N*-phenylheptanamide (3.3c) Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1c** (0.064g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.20) to afford the title compound as a light yellow solid (0.046 g, 74%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (s, 2H), 7.34-7.26 (m, 6H), 7.18 (s, 1H), 7.11-7.08 (t, *J* = 7.5 Hz, 1H), 4.50 (s, 2H), 3.47 (t, *J* = 6.2 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.73 (q, , *J* = 7.0 Hz, 2H), 1.62 (q, *J* = 10.0 Hz, 2H), 1.41 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.4, 138.8, 138.1, 129.1, 128.5, 127.8, 127.6, 124.3, 120.0,

73.0, 70.4, 37.8, 29.7, 29.2, 26.1, 25.7**. HRMS** (ESI) Calcd. for $C_{20}H_{26}NO_2$ ($[M+H]^+$): 312.1964; Found: 312.1958. **IR (neat)** 3305, 3037, 2935, 2852, 1657, 1596, 1530, 1497, 1442, 1362, 1296, 1099, 737, 695, 499 cm^{-1}.



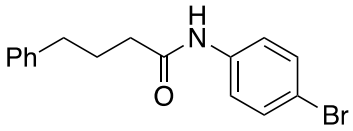
3.3d

***N*-(4-(tert-butyl)phenyl)-4-phenylbutanamide (3.3d)** Prepared according to general procedure using **3.1d** (0.018 g, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =90: 10, Rf = 0.09) to afford the title compound as a brown solid (0.054 g, 92%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.32 (d, *J* = 8.6 Hz, 2H), 7.24-7.18 (m, 4H), 7.12- (m, 3H), 7.01 (s, 1H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.23 (t, *J* = 7.4 Hz, 2H), 1.97 (quintet, *J* = 7.4 Hz, 2H), 1.207.09 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 170.9, 147.3, 141.5, 135.4, 128.7, 128.6, 126.2, 125.9, 119.8, 36.9, 35.2, 31.5, 27.1. **HRMS** (ESI) Calcd. for $C_{20}H_{26}NO$ ($[M+H]^+$): 296.2014; Found: 296.2013. **IR (neat)** 3294, 2957, 1653, 1598, 1538, 1404, 1256, 834, 695, 472 cm^{-1}.



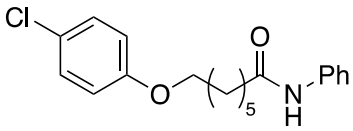
3.3e

7-(furan-2-ylmethoxy)-*N*-phenylheptanamide (3.3e) Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1e** (0.052g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.10) to afford the title compound as a light yellow oil (0.033 g, 55%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 7.8 Hz, 2H), 7.39-7.39 (m, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.10 (m, 2H), 6.41 (m, 1H), 4.36 (s, 2H), 3.44 (t, *J* = 6.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.73 (quintet, *J* = 7.2 Hz, 2H), 1.60 (quintet, *J* = 6.6 Hz, 2H), 1.40 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.3, 143.4, 140.7, 138.1, 129.2, 124.3, 122.7, 119.9, 110.5, 70.2, 64.2, 37.9, 29.7, 29.2, 26.1, 25.7. **HRMS** (ESI) Calcd. for $C_{18}H_{24}NO_3$ ($[M+H]^+$): 302.1756; Found: 302.1751. **IR (neat)** 3304, 2928, 2856, 1664, 1597, 1535, 1442, 1094, 693, 498 cm^{-1}.



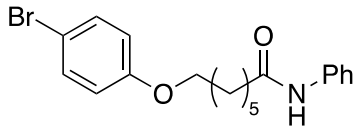
3.3f

***N*-(4-bromophenyl)-4-phenylbutanamide (3.3f)** Prepared according to general procedure using **3.1f** (0.02 g, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =85: 15, Rf = 0.17) to afford the title compound as a yellow solid (0.049 g, 77%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.43-7.39 (m, 4H), 7.32-7.27 (m, 2H), 7.21 (dd, *J* = 13.4, 7.2 Hz, 4H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.06 (quintet, *J* = 7.4 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.1, 141.3, 132.1, 128.6, 128.6, 128.6, 126.2, 121.4, 116.9, 77.2, 36.8, 35.2, 26.8. **HRMS** (ESI) Calcd. for $C_{16}H_{17}NOBr$ ($[M+H]^+$): 318.0494; Found: 318.0497. **IR (neat)** 3289, 3060, 2866, 1657, 1587, 1516, 1485, 1392, 1283, 1130, 1007, 813, 740, 695, 695, 497 cm^{-1}.



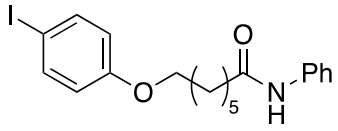
3.3g

7-(4-chlorophenoxy)-*N*-phenylheptanamide (3.3g) Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1g** (0.067g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.21) to afford the title compound as a white solid (0.046 g, 70%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.22-7.20 (m, 2H), 7.17 (s, 1H), 7.11-7.08 (t, *J* = 7.5 Hz, 1H,), 6.82-6.79 (d, *J* = 9.0 Hz, 2H), 3.91 (t, *J* = 6.4 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.77 (sextet, *J* = 7.2 Hz, 4H), 1.52-1.43 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.3, 157.8, 138.0, 129.4, 129.2, 125.5, 124.4, 119.9, 115.9, 77.2, 68.2, 37.8, 29.2, 29.1, 26.0, 25.6**. HRMS** (ESI) Calcd. for $C_{19}H_{23}NO_2Cl$ ($[M+H]^+$): 332.1417; Found: 332.1420. **IR (neat)** 3292.66, 2935.09, 2855.30, 1591.02, 1490.30, 1471.96, 1200.63, 1173.93, 1073.14, 996.69, 829.83 cm^{-1}.



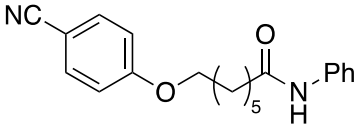
3.3h

7-(4-bromophenoxy)-*N*-phenylheptanamide (3.3h) Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1h** (0.076g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.22) to afford the title compound as a white solid (0.054 g, 72%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 7.9 Hz, 2H), 7.36-7.34 (m, 2H), 7.33-7.30 (m, 2H), 7.14-7.09 (m, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 3.91 (t, *J* = 6.4 Hz, 2H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.81-1.74 (m, 4H), 1.53-1.42 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.2, 158.3, 138.0, 132.3, 129.2, 124.4, 119.9, 116.4, 112.8, 68.2, 37.8, 29.13, 29.07, 26.0, 25.6. **HRMS** (ESI) Calcd. for $C_{19}H_{23}BrNO_2$ ($[M+H]^+$): 376.0912; Found: 376.0908. **IR (neat)** 3300, 2940, 2881, 1660, 1597, 1531, 1488, 1442, 1214, 818, 691, 500 cm^{-1}.



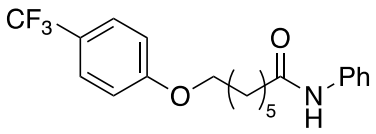
3.3i

7-(4-iodophenoxy)-*N*-phenylheptanamide (3.3i) Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1i** (0.086g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.20) to afford the title compound as a white solid (0.049 g, 58%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.56-7.48 (m, 4H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.13-7.07 (m, 2H), 6.66 (d, *J* = 8.9 Hz, 2H), 3.91 (t, *J* = 6.4 Hz, 2H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.81-1.74 (m, 4H), 1.52-1.42 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.2, 159.0, 138.3, 129.2, 119.9, 117.1, 82.6, 68.0, 37.8, 29.1, 29.1, 26.0, 25.6. **HRMS** (ESI) Calcd. for $C_{19}H_{23}INO_2$ ($[M+H]^+$): 424.0774; Found: 424.0768. **IR (neat)** 3307, 2939, 2854, 1651, 1589, 1531, 1486, 1435, 1283, 1247, 1176, 753, 500 cm^{-1}.



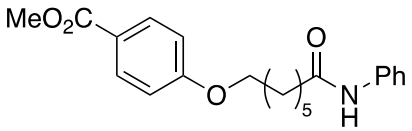
3.3j

7-(4-cyanophenoxy)-*N*-phenylheptanamide (3.3j) Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1j** (0.065g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.07) to afford the title compound as a white solid (0.030 g, 47%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.56 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.15 (bs, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.99 (t, *J* = 6.4 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 1.80 (dquintet, *J* = 15.0, 5.4 Hz, 4H), 1.53-1.44 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.2, 169.1, 162.5, 138.0, 134.1, 129.2, 124.4, 119.8, 119.5, 115.3, 68.3, 37.7, 29.0, 28.9, 25.9, 25.5. **HRMS** (ESI) Calcd. for $C_{20}H_{23}N_2O_2$ ($[M+H]^+$): 323.1760; Found: 323.1762. **IR (neat)** 3310, 2939, 2850, 2216, 1663, 1597, 1526, 1506, 1438, 1301, 1259, 1170, 838, 501 cm^{-1}.



3.3k

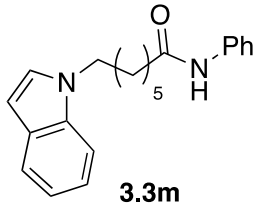
***N*-phenyl-7-(4-(trifluoromethyl)phenoxy)heptanamide (3.3k)** Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1k** (0.074g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.18) to afford the title compound as a white solid (0.037 g, 51%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.52 (t, *J* = 7.7 Hz, 4H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.16 (s, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 3.99 (t, *J* = 6.4 Hz, 2H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.79 (td, *J* = 13.6, 6.5 Hz, 4H), 1.52-1.46 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.2, 161.7, 138.0, 129.2, 127.8, 127.0, 126.9, 125.7, 124.4, 123.6, 123.2, 122.9, 122.7, 122.4, 121.6, 119.9, 114.5, 68.1, 37.8, 29.1, 26.0, 25.6. **HRMS** (ESI) Calcd. for $C_{20}H_{23}NO_2F_3$ ($[M+H]^+$): 366.1681; Found: 366.1685. **IR (neat)** 3319, 2940, 2880, 1658, 1518, 1441, 1225, 1177, 694, 637 cm^{-1}.



3.3l

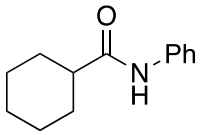
Methyl 4-((7-oxo-7-(phenylamino)heptyl)oxy)benzoate (3.3l) Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1l** (0.072g, 0.2 mmol). The crude materials were combined from two parallel experiments

and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.11) to afford the title compound as a white solid (0.037 g, 51%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.98-7.96 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.14-7.10 (m, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.88 (s, 3H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.79 (dquintet, *J* = 20.8, 7.0 Hz, 4H), 1.49 (dq, *J* = 24.5, 7.7 Hz, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.2, 167.1, 163.0, 138.0, 131.7, 129.2, 124.4, 122.5, 119.8, 114.2, 68.1, 52.0, 37.8, 29.1, 26.0, 25.6. **HRMS** (ESI) Calcd. for $C_{21}H_{26}NO_4$ ([M+H]$^+$): 356.1862; Found: 356.1858. **IR (neat)** 3325, 2944, 2864, 1711, 1668, 1605, 1527, 1439, 1259, 1170, 1107, 693, 501 cm^{-1}.



3.3m

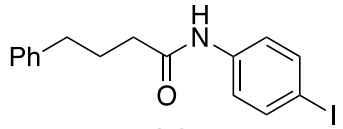
7-(1*H*-indol-1-yl)-*N*-phenylheptanamide (3.3m) Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1m** (0.065g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.16) to afford the title compound as a white solid (0.030 g, 47%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.64 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.32 (dt, *J* = 13.5, 7.2 Hz, 3H), 7.21 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.12-7.09 (m, 3H), 6.49 (dd, *J* = 3.1, 0.8 Hz, 1H), 4.12 (t, *J* = 7.0 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 1.85 (quintet, *J* = 7.2 Hz, 2H), 1.69 (quintet, *J* = 7.4 Hz, 2H), 1.39-1.33 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.2, 138.0, 136.1, 129.1, 128.7, 128.0, 124.3, 121.5, 121.1, 119.9, 119.3, 109.5, 101.0, 46.4, 37.6, 30.1, 28.9, 26.8, 25.4. **HRMS** (ESI) Calcd. for $C_{21}H_{25}N_2O$ ([M+H]$^+$): 321.1964; Found: 321.1967. **IR (neat)** 3254, 2930, 2855, 1663, 1595, 1439, 1310, 1131, 747, 502 cm^{-1}.



3.3n

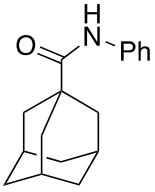
***N*-phenylcyclohexanecarboxamide (3.3n)** Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1n** (129 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.26) to afford the title compound as a white solid

(0.032 g, 80%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.53 (d, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.21 (s, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 2.23 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.97-1.94 (m, 2H), 1.86-1.82 (m, 2H), 1.70 (ddt, *J* = 9.0, 3.2, 1.6 Hz, 1H), 1.59-1.51 (m, 2H), 1.35-1.23 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.5, 138.2, 129.1, 124.2, 119.9, 46.7, 29.8, 25.8. **HRMS** (ESI) Calcd. for $C_{13}H_{18}NO$ ($[M+H]^+$): 204.1388; Found: 204.1389. **IR (neat)** 3310, 2922, 2850, 1660, 1598, 1528, 1500, 1497, 1296, 1251, 1177, 1133, 731, 689, 585, 507, 439 cm^{-1}.



3.3o

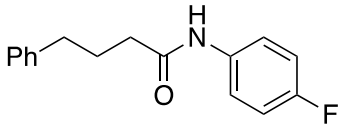
***N*-(4-iodophenyl)-4-phenylbutanamide (3.3o)** Prepared according to general procedure using **3.1o** (0.025 g, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =90: 10, Rf = 0.19) to afford the title compound as a yellow solid (0.047 g, 64%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.60 (d, *J* = 8.6 Hz, 2H), 7.31-7.26 (m, 5H), 7.23-7.18 (m 3H), 2.70 (t, *J* = 7.3 Hz, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 2.06 (q, *J* = 7.2 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.1, 141.3, 132.1, 128.6, 128.6, 128.6, 126.2, 121.4, 116.9, 77.2, 36.8, 35.2, 26.8. **HRMS** (ESI) Calcd. for $C_{16}H_{17}NOI$ ($[M+H]^+$): 366.0355, 366.0344; Found: 366.0353. **IR (neat)** 3292, 3024, 2942, 2352, 1660, 1581, 1513, 1389, 1280, 1129, 1003, 812, 748, 695, 489 cm^{-1}.



3.3p

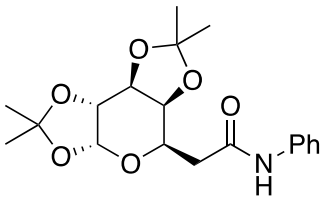
(3r,5r,7r)-N-phenyladamantane-1-carboxamide (3.3p) Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1p** (0.26 g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.24) to afford the title compound as a white solid (0.044 g, 86%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.54 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.33-7.29 (m, 3H), 7.11-7.07 (m, 1H), 2.10 (s, 3H), 1.97 (d, *J* = 2.6 Hz, 6H), 1.76 (q, *J* = 11.1 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.2, 138.2,

129.1, 124.2, 120.0, 41.6, 39.4, 36.6, 28.3. **HRMS** (ESI) Calcd. for $C_{17}H_{22}NO$ ($[M+H]^+$): 256.1701; Found: 256.1703. **IR (neat)** 3274, 2896, 2849, 1643, 1596, 1536, 1489, 1435, 1327, 1307, 1252, 754, 694, 512 cm^{-1}.



3.3q

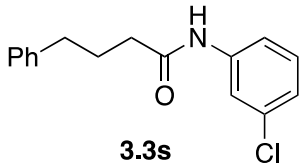
***N*-(4-fluorophenyl)-4-phenylbutanamide (3.3q)** Prepared according to general procedure using **3.1q** (21 μL, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =85: 15, Rf = 0.16) to afford the title compound as a colorless oil (0.028 g, 54%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.46-7.43 (m, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.10 (bs, 1H), 7.00 (t, *J* = 8.6 Hz, 2H), 6.95-6.91 (m, 1H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 2.10-2.04 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.0, 160.4, 158.5, 141.4, 134.0, 128.7, 128.6, 126.2, 121.8, 121.7, 115.8, 115.7, 36.7, 35.2, 26.9. **HRMS** (ESI) Calcd. for $C_{16}H_{17}NOF$ ($[M+H]^+$): 258.1294; Found: 258.1292. **IR (neat)** 3287, 3063, 3027, 1658, 1508, 1407, 1152, 831, 740, 696, 492 cm^{-1}.



3.3r

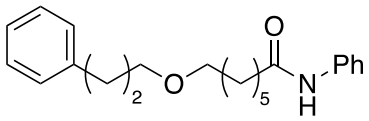
***N*-phenyl-2-((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-5-yl)acetamide (3.3r)** Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1r** (0.074 g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.19) to afford the title compound as a white solid (0.037 g, 51%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.32 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.62 (d, *J* = 4.9 Hz, 1H), 4.65 (dd, *J* = 7.9, 2.5 Hz, 1H), 4.38 (t, *J* = 2.5 Hz, 1H), 4.26 (d, *J* = 9.8 Hz, 1H), 4.19 (dd, *J* = 7.9, 1.7 Hz, 1H), 2.84 (dd, *J* = 16.4, 9.9 Hz, 1H), 2.54 (dd, *J* = 16.4, 2.8 Hz, 1H), 1.52 (s, 3H), 1.47 (s, 3H),

1.36 (d, *J* = 3.8 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.1, 138.4, 129.0, 124.1, 119.9, 109.8, 109.7, 109.5, 96.7, 72.8, 70.8, 70.6, 65.1, 38.7, 26.1, 25.1, 24.5.



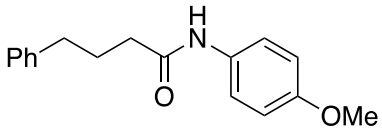
3.3s

***N*-(3-chlorophenyl)-4-phenylbutanamide (3.3s)** Prepared according to general procedure using **3.1s** (0.16 g, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =90: 10, Rf = 0.08) to afford the title compound as a yellow oil (0.031 g, 57%) with around 10% inseparable impurities. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.63 (s, 1H), 7.33-7.28 (m, 3H), 7.33-7.27 (m, *J* = 9.5, 6.2 Hz, 4H), 7.17-7.13 (m, 2H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.07 (quintet, *J* = 7.5 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.1, 141.3, 130.1, 128.7, 128.6, 128.6, 126.3, 124.4, 120.0, 117.8, 35.1, 33.2, 26.8. **HRMS** (ESI) Calcd. for $C_{16}H_{17}NOCl$ ($[M+H]^+$): 274.0999; Found: 274.1005.



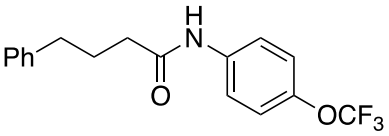
3.3t

***N*-phenyl-7-(3-phenylpropoxy)heptanamide (3.3t)** Prepared according to general procedure using **3.1a** (10 μL, 0.1 mmol) and **2.1t** (0.069g, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.18) to afford the title compound as a colorless liquid (0.051 g, 75%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 7.9 Hz, 2H), 7.30 (m, 5H), 7.19 (d, *J* = 7.5 Hz, 3H), 7.10 (t, *J* = 9.5 Hz, 1H), 3.41 (td, *J* = 6.5, 3.8 Hz, 4H), 2.69 (t, *J* = 7.7 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.92-1.88 (m, 2H), 1.76-1.72 (m, 2H), 1.60 (t, *J* = 6.5 Hz, 2H), 1.42 (d, *J* = 6.8 Hz, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.4, 142.2, 138.1, 129.1, 128.6, 128.4, 125.9, 124.3, 119.9, 70.9, 70.1, 37.9, 32.5, 31.5, 29.7, 29.2, 26.1, 25.7. **HRMS** (ESI) Calcd. for $C_{22}H_{30}NO_2$ ($[M+H]^+$): 340.2277; Found: 340.2283. **IR (neat)** 2919, 2850, 1585, 1487, 1316, 1199, 1152, 1066, 841, 492 cm^{-1}.



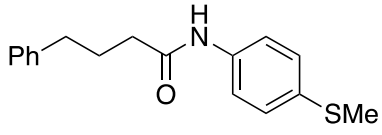
3.3u

***N*-(4-methoxyphenyl)-4-phenylbutanamide (3.3u)** Prepared according to general procedure using **3.1u** (0.015 g, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 10, Rf = 0.20) to afford the title compound as a brown solid (0.026 g, 47%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.39 (d, *J* = 8.9 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 6.1 Hz, 3H), 7.10 (s, 1H), 6.86-6.84 (m, 2H), 3.78 (s, 3H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.07 (quintet, *J* = 7.4 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 170.9, 141.5, 131.1, 128.7, 128.6, 126.6, 126.2, 121.9, 114.3, 55.6, 36.7, 35.2, 27.1. **HRMS** (ESI) Calcd. for $C_{17}H_{20}NO_2$ ($[M+H]^+$): 270.1494; Found: 270.1496. **IR (neat)** 3274, 3050, 2928, 1650, 1510, 1430, 1244, 1026, 824, 728, 695, 499 cm^{-1}.



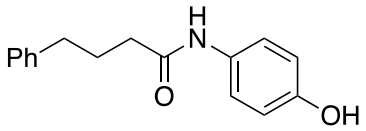
3.3v

4-phenyl-*N*-(4-(trifluoromethoxy)phenyl)butanamide (3.3v) Prepared according to general procedure using **3.1v** (0.021 g, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =85: 15, Rf = 0.19) to afford the title compound as a yellow solid (0.048 g, 75%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.52 (d, *J* = 8.9 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.21-7.15 (m, 6H), 2.72 (t, *J* = 7.4 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.07 (quintet, *J* = 7.4 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.4, 145.6, 141.6, 136.9, 128.9, 126.5, 123.0, 122.1, 121.9, 121.2, 119.8, 37.0, 35.4, 27.1. **HRMS** (ESI) Calcd. for $C_{17}H_{17}NO_2F_3$ ($[M+H]^+$): 324.1211; Found: 324.1219.



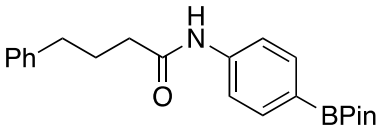
3.3w

***N*-(4-(methylthio)phenyl)-4-phenylbutanamide (3.3w)** Prepared according to general procedure using **3.1w** (0.017 g, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 10, Rf = 0.20) to afford the title compound as a light pink solid (0.042 g, 73%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.43 (d, *J* = 8.6 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.23-7-16 (m, 5H), 7.16 (s, 1H), 2.71 (d, *J* = 7.4 Hz, 2H), 2.46 (s, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 2.06 (quintet, *J* = 7.5 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.0, 141.4, 135.7, 133.6, 128.7, 128.6, 128.2, 126.2, 120.6, 36.8, 35.2, 26.9, 16.9. **HRMS** (ESI) Calcd. for $C_{17}H_{20}NOS$ ($[M+H]^+$): 286.1266; Found: 286.1273. **IR (neat)** 3284, 3176, 2918, 1650, 1592, 1528, 1492, 1396, 1349, 1308, 1092, 821, 741, 696, 481 cm^{-1}.



3.3x

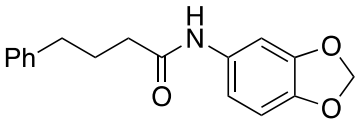
***N*-(4-hydroxyphenyl)-4-phenylbutanamide (3.3x)** Prepared according to general procedure using pivalic acid protected **3.1x** (0.017 g, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =70: 30, Rf = 0.08) to afford the title compound as a reddish solid (0.042 g, 51%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.30 (t, *J* = 7.8 Hz, 3H), 7.22-7.19 (m, 3H), 6.96 (s, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.02 (s, 1H), 2.72 (t, *J* = 7.4 Hz, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 2.10-2.04 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.0, 141.5, 131.0, 128.7, 128.6, 126.2, 115.8, 36.7, 35.2, 27.1. **HRMS** (ESI) Calcd. for $C_{16}H_{18}NO_2$ ($[M+H]^+$): 256.1338; Found: 256.1246.



3.3y

4-phenyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butanamide (3.3y) Prepared according to general procedure using **3.1y** (0.025 g, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =85: 15, Rf = 0.16) to afford the title compound as a brown solid (0.051 g, 70%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 8.1

Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.31-7.28 (m, 2H), 7.20-7.17 (m, 4H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.10-2.03 (m, 2H), 1.34 (s, 12H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.3, 141.5, 140.7, 136.0, 134.2, 128.7, 128.6, 126.2, 118.6, 83.9, 37.0, 35.2, 26.9, 25.0.

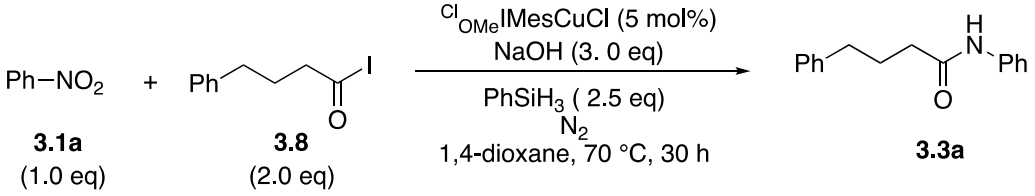


3.3z

***N*-(benzo[*d*][1,3]dioxol-5-yl)-4-phenylbutanamide (3.3z)** Prepared according to general procedure **3.1z** (0.017 g, 0.1 mmol) and **2.1a** (32 μL, 0.2 mmol). The crude materials were combined from two parallel experiments and were purified by silica gel chromatography (hexane/ethyl acetate =80: 20, Rf = 0.17) to afford the title compound as a reddish solid (0.024 g, 52%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.22-7.19 (m, 4H), 7.05 (s, 1H), 6.76-6.71 (m, 2H), 5.93 (s, 2H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.06 (quintet, *J* = 7.4 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 170.9, 141.5, 132.2, 128.7, 128.6, 128.5, 126.2, 113.1, 108.2, 103.0, 101.4, 36.8, 35.2, 27.0. **HRMS** (ESI) Calcd. for $C_{17}H_{18}NO_3$ ($[M+H]^+$): 284.1287; Found: 284.1292. **IR (neat)** 3273, 3060, 3025, 2919, 1650, 1502, 1487, 1447, 1209, 1130, 1097, 1035, 924, 695, 487 cm^{-1}.

3.5.4. Mechanistic Study

A. Stoichiometric reaction with acyl iodide

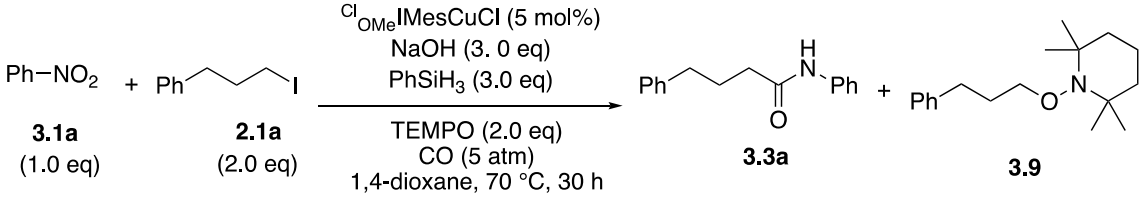


Scheme 3.10 Stoichiometric reaction with acyl iodide

In a glovebox, NaOH (0.012 g, 0.3 mmol, 3.0 eq), $^{Cl}_{OMe}$IMeCuCl (0.003 g, 0.005 mmol, 5 mol%), nitrobenzene **3.1a** (10 μL, 0.1 mmol, 1.0 eq) and 1,4-dioxane (2.0 mL) were added to a 20-mL vial charged with a 1.5-cm stir bar. Then, phenylsilane (30 μL, 0.25 mmol, 2.5 eq) and acyl iodide **3.8** (0.055g, 0.2 mmol, 2.0 eq) were added to the mixture. Then the vial was placed in an aluminum rack within a Parr pressure reactor. Next, the reactor

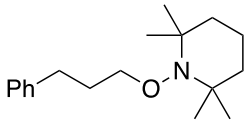
was closed and taken out of the glovebox. The reaction was heated to 70 ℃ and stirred vigorously. After 30 h, the reaction was cooled to room temperature, and then dissembled the reactor. The solvent was removed under reduced pressure. The residue was dissolved with Et_2O, then filtered through a pad of silica gel (a pipette with about 2 cm silica gel). The filtrate was concentrated under reduced pressure for ^1H NMR analysis in $CDCl_3$. The corresponding amide **3.3a** was observed in 71% .

B. TEMPO experiment



Scheme 3.11 Standard reaction with TEMPO addition

In a glovebox, NaOH (0.012 g, 0.3 mmol, 3.0 eq), $^{Cl}_{OMe}$IMesCuCl (0.003 g, 0.005 mmol, 5 mol%), TEMPO (0.03 g, 0.2 mmol, 2.0 eq) and 1,4-dioxane (2.0 mL) were added to a 20-mL vial charged with a 1.5-cm stir bar. Then nitrobenzene (0.1 mmol, 1.0 eq), alkyl iodide (0.2 mmol, 2.0 eq) and phenylsilane (37 μL, 0.3 mmol, 3.0 eq) were added to the mixture. Then the vial was placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas and released after 5 min. This procedure was repeated three times, after which the reaction was heated to 70 ℃ and stirred vigorously. After 30 h, the reaction was cooled to room temperature and the CO gas was released. The solvent was removed under reduced pressure. The residue was dissolved with Et_2O, then filtered through a pad of silica gel (a pipette with about 2 cm silica gel). The filtrate was concentrated under reduced pressure for ^1H NMR analysis. The was no formation of any amide **3.3a** but with **3.9**. And 0.008 g **3.9** was obtained in 30% as a colorless oil after silica column chromatography.

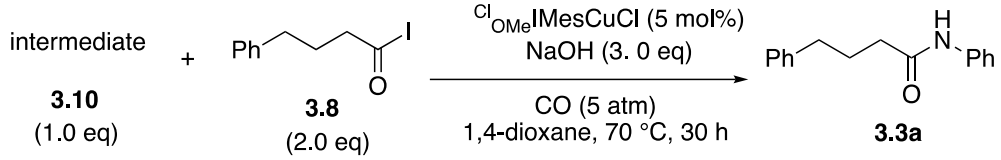


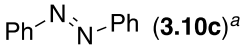
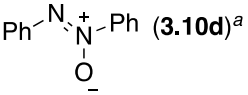
3.9

^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 7.22-7.20 (m, 2H), 7.19-7.16 (m, 1H), 3.77 (t, *J* = 6.5 Hz, 2H), 2.71 (t, *J* = 8.0 Hz, 2H), 1.89-1.83 (m, 2H), 1.55 (m, 1H), 1.44 (d, *J* = 5.1 Hz, 4H), 1.32 (m, 1H), 1.12 (d, *J* = 14.1 Hz,

12H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 128.51, 128.41, 125.8, 59.8, 39.8, 33.2, 32.9, 30.7, 20.3, 17.3 **HRMS** (ESI) Calcd. for $C_{18}H_{30}NO$ ($[M+H]^+$): 276.2327; Found: 276.2321.

C. Possible intermediates from nitroarene reduction



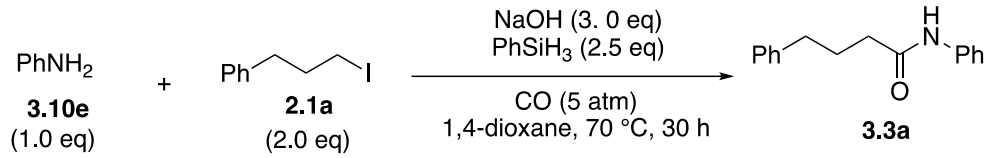
Entry	Intermediate **3.10**	Yield of **3.3a** (%)
1	PhNO (**3.10a**)	21
2	PhNHOH (**3.10b**)	72
3	 (**3.10c**)[a]	39
4	 (**3.10d**)[a]	0
5	$PhNH_2$ (**3.10e**)	100

Reactions were done a 0.1 mmol scale and yields were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard.
[a] 0.05 mmol intermediate was used instead of 0.1 mmol.

Table 3.17 Reactions with possible reduction intermediates and acyl iodides

In addition to the experiments shown in Table 3.5, more control experiments with possible intermediates were carried out with 2.0 eq acyl iodide (0.055g, 0.2 mmol, 2.0 eq) in the absence of hydrosilanes. Azoxybenzene provide none of the target compound. The rest of them performed the aminocarbonylation to some extent, although nitrosobenzene and azobenzene gave poor yields. Combining the results in Table 3.5, we cannot exclude other intermediates being relevant to amide formation by minor pathways. However, we still conclude aniline serve as the major intermediate in this reductive aminocarbonylation.

D. Control experiment without catalyst



Scheme 3.12 Control experiment with aniline and without copper catalyst

In a glovebox, NaOH (0.012 g, 0.3 mmol, 3.0 eq), phenylsilane (30 μL, 0.25 mmol, 2.5 eq), alkyl iodide **2.1a** (32 μL, 0.2 mmol, 2.0 eq) and 1,4-dioxane (2.0 mL) were added to a 20-mL vial charged with a 1.5-cm stir bar. Then aniline (9 μL, 0.1 mmol, 1.0 eq) were added to the mixture. Then the vial was placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas and released after 5 min. This procedure was repeated three times, after which the reaction was heated to 70 ℃ and stirred vigorously. After 30 h, the reaction was cooled to room temperature and the CO gas was released. The solvent was removed under reduced pressure. The residue was dissolved with Et_2O, then filtered through a pad of silica gel (a pipette with about 2 cm silica gel). The filtrate was concentrated under reduced pressure for ^{1}H NMR analysis in $CDCl_3$ with $ClCH_2CH_2Cl$ as internal standard. There was no formation of **3.3a**.

3.6. Conclusion

In conclusion, we have developed a copper-catalyzed reductive aminocarbonylation from simple nitroarenes and alkyl iodides.[39] This methodology has shown good tolerance with variety of functional groups and serves as the only reductive aminocarbonylation method for C(sp^3)-hybridized electrophiles. Mechanistic studies suggested that NHC copper catalyst serves a dual function in the tandem process: a copper catalyzed carbonylation of alkyl iodides followed by amidation with *in-situ* generated anilines resulting from nitroarenes reduction catalyzed by the same copper catalyst.

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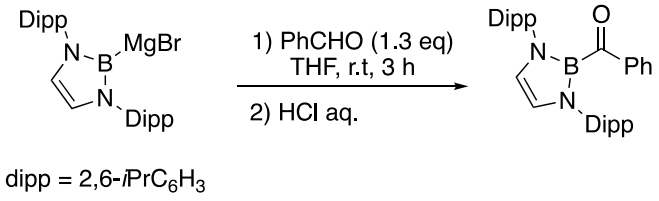
4. One-Step Synthesis of Acylboron Compounds via Cu-Catalyzed Carbonylative Borylation of Alkyl Halides

This chapter comes from the content presented in Cheng, L.-J.; Zhao, S.; Mankad, N. P., One-Step Synthesis of Acylboron Compounds via Cu-Catalyzed Carbonylative Borylation of Alkyl Halides. *Angewandte Chemie International Edition.* Accepted Manuscript. doi:10.1002/anie.202012373.

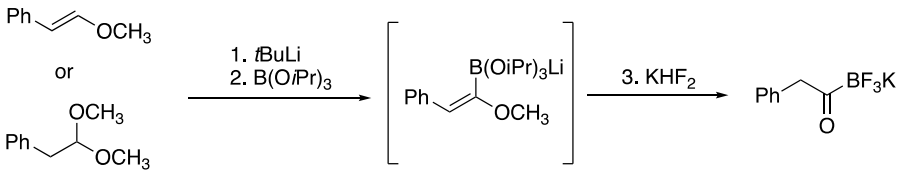
4.1. Introduction

Organoboron compounds are important building blocks and widely used in various organic transformations.[1] Therefore, the development of efficient protocols for the synthesis of organoborons has been extensively investigated during the past decades. However, as a rare class of organoborons, acylboron compounds have received much less attention.[2-4] While they were proposed as reactive intermediates in several transformations long ago,[5-7] it was not until 2007 that Nozaki and co-workers first reported the isolation and characterization of amino-stabilized acylborons by reacting boryl nucleophiles with benzoyl chloride or benzaldehyde[8] (Scheme 4.1).



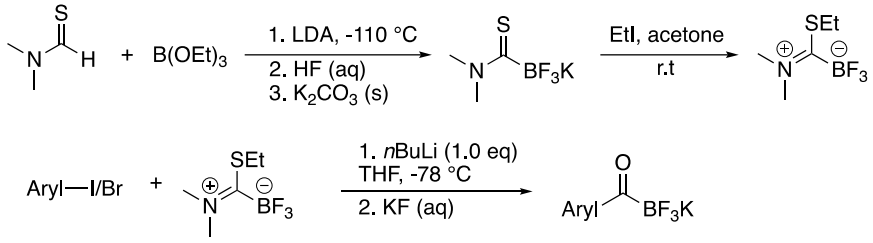
Scheme 4.1 Synthesis of acylborons from benzaldehyde

The recent observation of unique acylboron reactivity, especially the fast and chemoselective amide-bond-forming reaction between potassium acyl trifluoroborates and amines derivatives (KAT ligation) in functionalization of proteins and peptides,[9, 10] has sparked growing interest in their synthesis, and several elegant synthetic routes have been reported. Molander reported the method of deprotonation of vinyl ether followed by the treatment of $B(OiPr)_3$ and KHF_2 or a metalation of the acetal[11] (Scheme 4.2). The Bode group also enabled a similar route with *N*,*O*-acetals.[12]



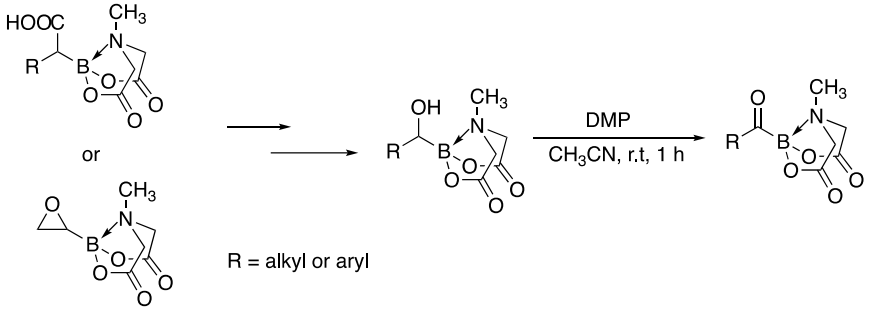
Scheme 4.2 Synthesis of KATs from vinyl ethers or acetals

Few years later, Bode and coworkers synthesized a zwitterion which was produced from the lithiation of *N*,*N*-dimethyl thioformamide and trapped by $B(OEt)_3$ in gram scale. By taking advantage of the zwitterion as an acylboron transfer reagent, a broad range of aryl KATs could be constructed in one single step[13] (Scheme 4.3). Aliphatic KATs were also achieved by the use of alkyllithium or alkylmagnesium and copper (I) salt.[14]



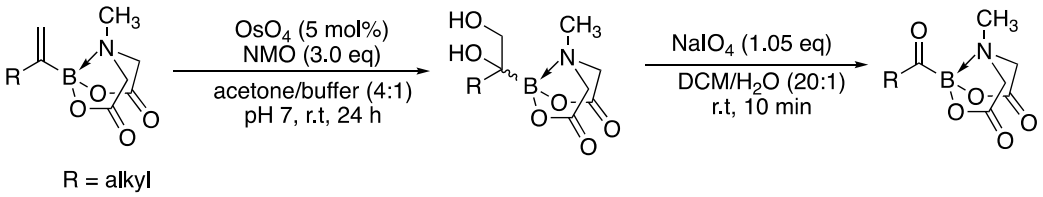
Scheme 4.3 Synthesis of KATs from aryl halides and zwitterions. LDA: lithium diisopropylamide

In addition, oxidative protocols to approach *N*-methyliminodiacetyl (MIDA)-protected acylboronates or KATs have been developed by several groups. Yudin has enabled the formation of MIDA-supported KATs via the oxidation of α-hydroxy alkylboronates by Dess-Martin reagent.[15, 16] However, the access to α-hydroxy alkylboronates requires multistep synthesis from α-carboxylic boronates or α-MIDA boryl epoxides (Scheme 4.4). More recently, Wang reported the nucleophilic ring opening of α-chloroepoxyboronates to synthesize α-functionalized acylborons.[17]



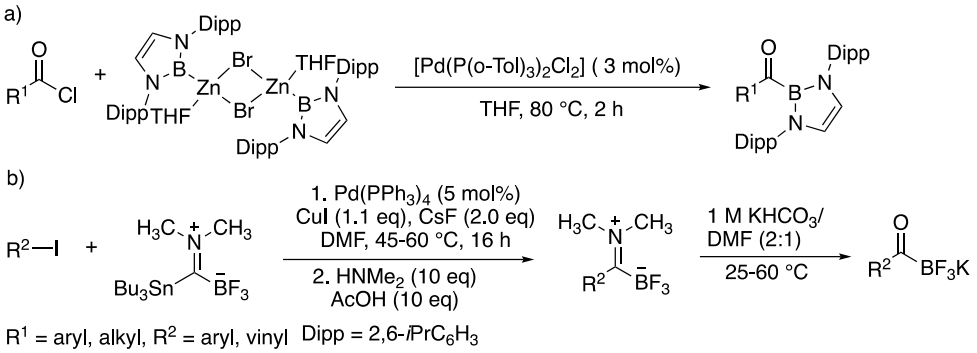
Scheme 4.4 Synthesis of MIDA-boronates through oxidation of α-hydroxy boronates

An alternative route to approach such KATs or MIDA-supported acylboronates is from vinylborons. Perrin developed a facile preparation method with alkenyl-2-boronate ester via a sequence of dihydroxylation of the double bond and oxidative diol cleavage. This work provides a concise route to α-amino acylboronates, which are not accessible by previous methods[18] (Scheme 4.5). A similar approach was reported by Ito via the ozonolysis of olefins.[19]



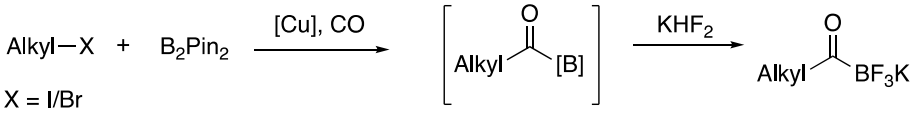
Scheme 4.5 Synthesis of MIDA-supported acylboronates from vinylboronates. NMO: *N*-methylmorpholine *N*-oxide. Buffer: aqueous monobasic phosphate buffer

On the other hand, transition metal-catalyzed borylation has been recognized as one of the most efficient methods for synthesis of organoborons. Surprisingly, catalytic methods for synthesis of acylborons are very rare, with only two reported examples that both use Pd catalysts. In 2015, Campos and Aldridge reported a boron version of the Negishi C-C coupling of acyl chlorides with a bis(boryl)zinc reagent[20] (Scheme 4.6a). Recently, a Stille-type coupling of aryl or vinyl halides with a stannyl iminium trifluoroborate was developed by the Bode group.[21] These stannyl immium trifluoroborates play roles both as cross-coupling reagents and as acylboronate transfer reagents (Scheme 4.6b). Both methods involve the use of boryl coupling reagents that themselves require multistep syntheses.



Scheme 4.6 a) Pd-catalyzed synthesis of acylboronates with acyl chlorides. b) Pd-catalyzed cross-coupling of aryl or vinyl iodides and a bifuncitonal reagent.

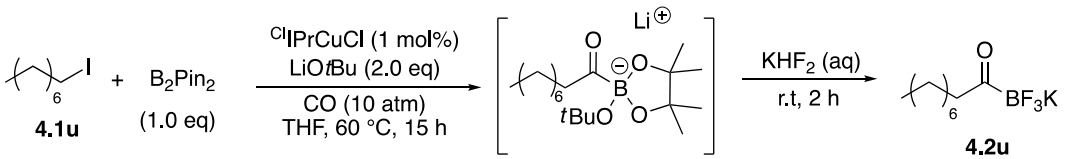
Compared to these methods, carbonylative coupling of organohalides and commercially-available boron reagents would provide a more convenient route to acylboronate products. Although the carbonylation of organoboranes has been explored to generate acylborons, the isolation of acylborons remains a challenge due to their notorious instability and susceptibility to rearrangement.[5, 22-24] On the basis of developing a series of Cu-catalyzed carbonylative coupling reactions of unactivated alkyl halides with NHC-Cu catalysts (NHC = *N*-heterocyclic carbene) and the key acyl intermediate,[25-28] we envisioned that this strategy could be amendable for the synthesis of acylborons by trapping the acyl radical using a nucleophilic borylcopper species generated from the copper catalysts and commercially available bis(pinacolato)diboron, B_2Pin_2 (Scheme 4.7).

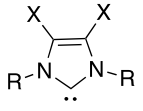


Scheme 4.7 Proposed Cu-catalyzed carbonylative borylation of alkyl halides

4.2. Reaction optimization

We began our work by studying the reaction of 1-iodooctane (**4.1u**) with bis(pinacolato)diboron (B_2Pin_2) under CO atmosphere. Being aware that the expected tricoordinated acylboron is likely not stable, we initially attempted to convert it into the corresponding KAT by working up the product mixture with aqueous KHF_2. After intensive investigation, we found that the desired potassium acyltrifluoroborate **4.2u** could be selectively generated in 73% yield when ^{Cl}IPrCuCl was used as catalyst in the presence of LiO*t*Bu as the base and THF as solvent (Table 4.1, entry 1). Without adding KHF_2, ^{11}B NMR spectroscopy of the crude mixture from the carbonylative coupling showed a new peak at 2.32 ppm, which is in the chemical shift range of tetracoordinated acylboron species.[29, 30] Although isolation and purification of this intermediate was unsuccessful, we speculated that the formed tricoordinated acylboron was further coordinated by one equivalent of LiO*t*Bu to form a more stable tetracoordinated acylboron compound. A control experiment showed the product was obtained in only 8% yield without the copper catalyst, clearly demonstrating that copper played a vital role in accelerating the reaction (Table 4.1, entry 2). The structure of the NHC ligand had a significant effect on the reaction: while IPr and ^{Me}IPr gave slightly lower yield (Table 4.1, entry 3-4), the less sterically bulky ^{Cl}IMes dramatically decreased the yield (Table 4.1, entry 5). The use of a less reactive electrophile, 1-bromooctane, provided the product in only 25% yield (Table 4.1, entry 6). Only trace amount of product was observed when more Lewis-acidic B_2cat_2 was employed as the diboron reagent (Table 4.1, entry 7). Low yield of product was obtained when other bases such as NaO*t*Bu, LiOMe, or LiO*i*Pr were used (Table 4.1, entry 8-10). We also found that the amount of the base is crucial for the success of this reaction: either increasing or decreasing the amount of LiO*t*Bu caused negative effect on the reaction (Table 4.1, entry 12-13). Changing the solvent to DME gave the product in lower yield, and trace product was obtained with 1,4-dioxane as solvent (Table 4.1, entry 14-15). Performing the reaction at room temperature or under 6 atm CO pressure afforded the product in 63% and 60% yield, respectively (Table 4.1, 16-17). It is noteworthy that although we typically performed reactions using 1.0 mol% copper catalyst, lowering the catalyst loading to 0.1 mol% gave a comparable result (Table 4.1, entry 18).





IPr R = 2,6-(diisopropyl)phenyl X = H
^{Cl}IMes R = 2,4,6-(trimethyl)phenyl X = Cl
^{Me}IPr R = 2,6-(diisopropyl)phenyl X = Me
^{Cl}IPr R = 2,6-(diisopropyl)phenyl X = Cl

Entry	Modifications from the optimized condition	Conversion of **4.1c** (%)	Yield of **4.2c** (%)
1	None	100	73
2	No catalyst	10	8
3	IPrCuCl catalyst	100	67
4	^{Me}IPrCuCl catalyst	100	66
5	^{Cl}IMesCuCl catalyst	100	30
6	Octyl-Br instead of **4.1u**	53	25
7	B_2cat_2 boron reagent	46	6
8	NaO*t*Bu base	100	34
9	LiOMe base	43	36
10	LiO*i*Pr base	46	32
11	1.5 eq B_2pin_2	100	48
12	1.0 eq LiO*t*Bu	84	24
13	3.0 eq LiO*t*Bu	100	53
14	DME solvent	100	36
15	1,4-dioxane sovlent	100	<5
16	r.t	82	63
17	6 atm CO	100	60
18	0.1 mol% ^{Cl}IPrCuCl	100	70

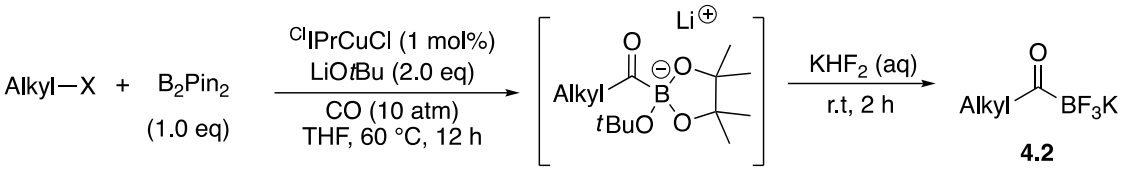
Reactions were performed on a 0.1 mmol scale, and all yields were determined by ^{1}H NMR with dibromomethane as internal standard. B_2cat_2: bis(catecholato)diboron. DME: dimethoxyethane.

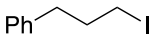
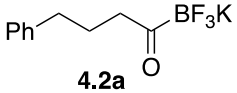
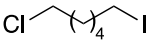
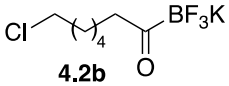
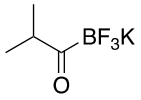
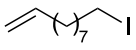
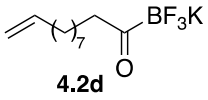
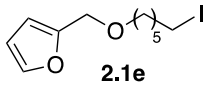
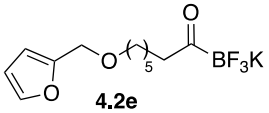
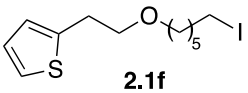
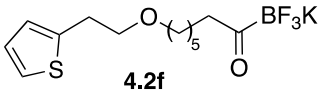
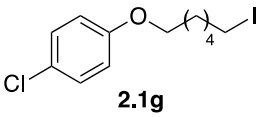
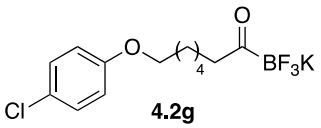
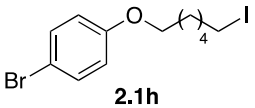
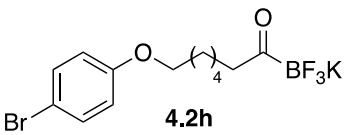
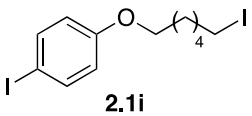
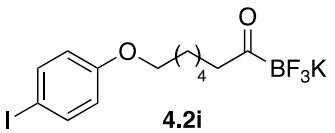
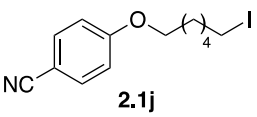
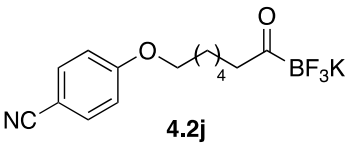
Table 4.1 Reaction investigation for carbonylative borylation of alkyl halides

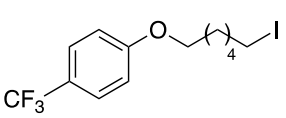
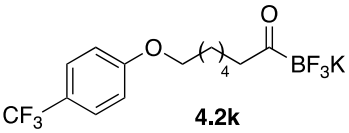
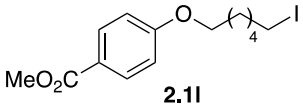
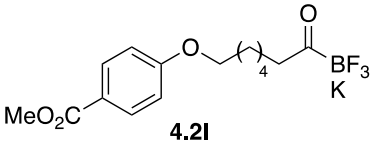
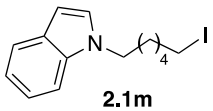
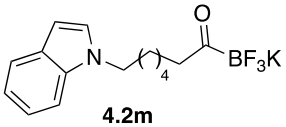
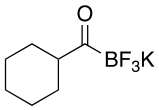
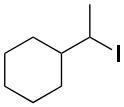
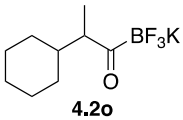
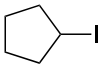
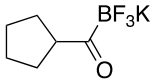
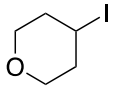
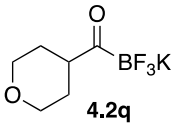
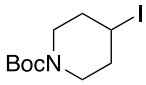
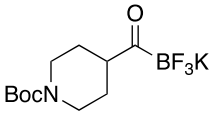
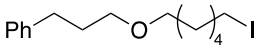
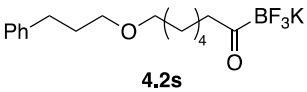
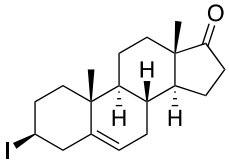
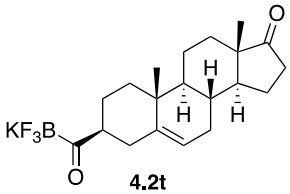
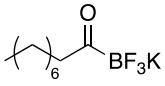
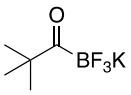
4.3. Substrate scope and further development

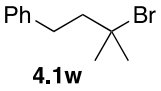
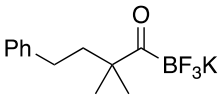
With the optimal conditions in hand, we next investigated the substrate scope in the presence of 1 mol% catalyst (Table 4.2). The mild reaction conditions allow the use of a variety of alkyl iodides containing different remote functional groups, including ether (**2.1s**), chloroalkyl (**2.1b**) and terminal alkene (**2.1d**). Heterocycles such as furan (**2.1e**), thiophene (**2.1f**) and indolyl (**2.1m**) were also compatible. The chloro, bromo, iodo, cyano, and trifluoromethyl groups on a remote phenyl ring (**2.1g-2.1j**) also survived during the reaction. However, lower yield was observed with an ester-substituted substrate (**2.1l**). Under the same reaction conditions, the alkyl electrophile scope could be extended from primary alkyl iodides to secondary alkyl iodides. Both acylic and cyclic secondary alkyl iodides gave the desired products in good yield. Increasing the steric hindrance of the secondary alkyl iodide (**2.1n**, **2.1o**, **4.1c, 4.1p**) had no effect on the yield. Ether (**4.1q**) and *N*-Boc (**4.1r**) functional groups within the cyclic electrophile were both tolerated.

In addition, the mild reaction conditions provide the opportunity for late-stage carbonylative borylation of an estrone derivative, providing acylboron **4.2t** diastereoselectively. Moreover, we were delighted to find this method was also applicable to synthesis of the more challenging tertiary acylborons (**4.2v**, **4.2w**) with tertiary alkyl bromides.



Entry	Alkyl halide	Acylboronate **4.2**	Yield of **4.2** (%)[a]
1	 **2.1a**	 **4.2a**	81
2	 **2.1b**	 **4.2b**	70[b]
3	 **4.1c**	 **4.2c**	84
4	 **2.1d**	 **4.2d**	48
5	 **2.1e**	 **4.2e**	84
6	 **2.1f**	 **4.2f**	61
7	 **2.1g**	 **4.2g**	90
8	 **2.1h**	 **4.2h**	60
9	 **2.1i**	 **4.2i**	61
10	 **2.1j**	 **4.2j**	98

11		 **4.2k**	89
12	 **2.1l**	 **4.2l**	43
13	 **2.1m**	 **4.2m**	61
14	 **2.1n**	 **4.2n**	85
15	 **2.1o**	 **4.2o**	65
16	 **4.1p**	 **4.2p**	76
17	 **4.1q**	 **4.2q**	64
18	 **4.1r**	 **4.2r**	48
19	 **2.1s**	 **4.2s**	74
20	 **4.1t**	 **4.2t**	62 (*dr* = 4:1)
21	 **4.1u**	 **4.2u**	81
22	 **4.1v**	 **4.2v**	49[c]

23	 **4.1w**	 **4.2w**	28[c] (54[d])

[a] Reactions were performed on 0.5 mmol scale, and yields are isolated yields. [b] Cyclized product 4.2n was formed in 12%. [c] I*t*BuCuCl was used as catalyst and the reaction was conducted at room temperature. [d] The yield was determined by ^{1}H NMR with dibromomethane as internal standard.

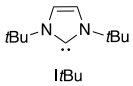
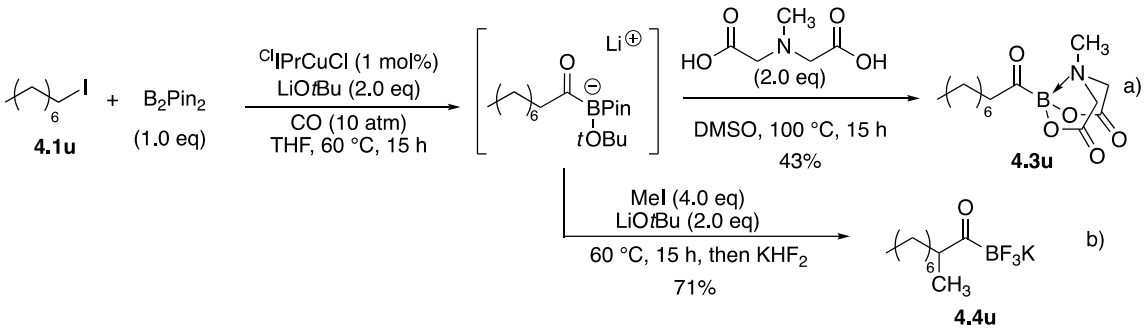


Table 4.2 Substrate scope for carbonylative borylation

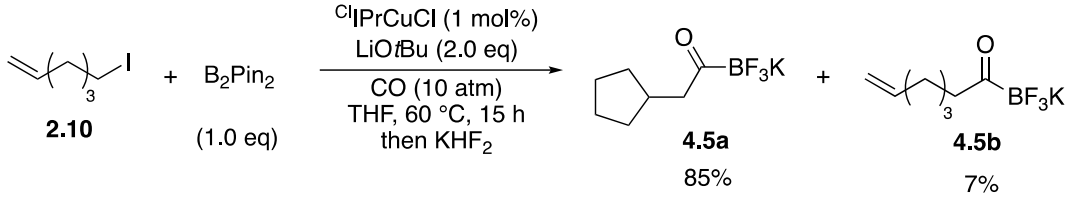
The formation of the novel tetracoordinated acylboron intermediates motivated us to further investigate their utility. (Scheme 4.8) First, we attempted the conversion of BPin into B(MIDA) by heating the reaction mixture from **4.1u** with *N*-methyliminodiacetic acid in DMSO at 100 ℃ for 15 h. Encouragingly, the acyl MIDA boronate **4.3u** was obtained in 43% yield. Next, we treated the same reaction mixture with iodomethane and α-methylated product **4.4u** was obtained in yield in good yield. In contrast, subjecting the potassium acyltrifluoroborate **4.2u** to the same reaction condition gave no product at all, probably due to B-F bond solvolysis under the basic conditions.[31] The current method is likely to find potential application in synthesis of other α-functionalized acylborons compounds.



Scheme 4.8 Application of the acylboron intermediate. Yields are isolated yields. a) was conducted on 0.1 mmol scale, b) was conducted on 0.5 mmol scale.

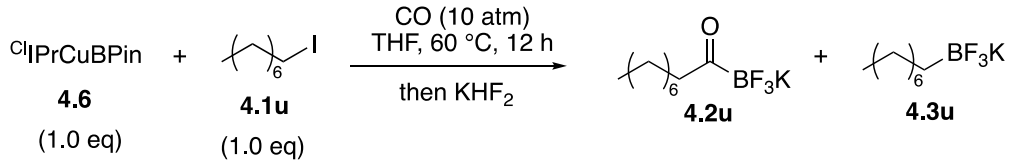
4.4. Mechanistic study

To explore the mechanism, several control experiments were conducted. First, a radical clock experiment was performed with 6-iodohexene **2.10**, and the cyclization product 6 was isolated in 85% yield (Scheme 4.9). This result revealed that the carbonylative borylation proceeds via alkyl radical intermediate, which is consistent with our previous work.[25-28]



Scheme 4.9 Radical clock experiment

We also prepared borylcopper species ^{Cl}IPrCuBPin (**4.6**) and performed stoichiometric reactions of **4.6** with primary alkyl iodide (**4.1u**) under CO atmosphere (Table 4.3). The reactions afforded no product, and significant amount of alkyl borane **4.3u** was observed as byproduct.[32-35] Considering the coordination of LiO*t*Bu to ^{Cl}IPrCuBPin might promote the single electron transfer process with alkyl halide, we also ran the same reaction with LiO*t*Bu. however, similar results were obtained.

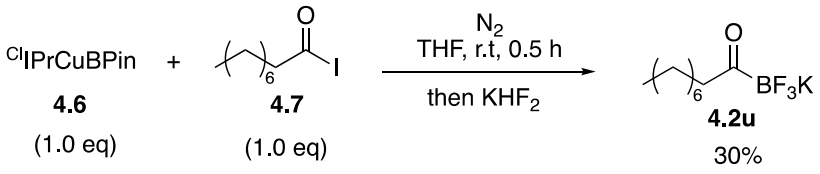


Additive	Yield of **4.2u** (%)	Yield of **4.3u** (%)
Without LiO*t*Bu	0	37
With 1.0 eq LiO*t*Bu	0	15

Reactions were done in 0.05 mmol scale. Yields were determined by 1H NMR with dibromomethane as internal standard.

Table 4.3 Stoichiometric reaction with alkyl iodide

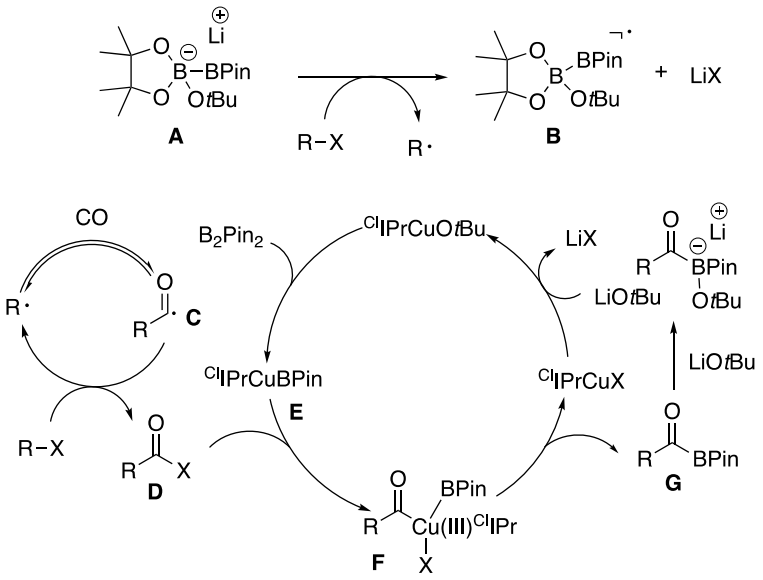
We next conducted the stoichiometric coupling of ^{Cl}IPrCuBpin (**4.6**) with nonanoyl iodide (**4.7**) under N_2, and **4.2u** was obtained in 30% yield (Scheme 4.10). These results exclude single electron transfer process between borylcopper and alkyl halide and supports the intermediacy of an acyl halide generated through an atom transfer carbonylation (ATC) pathway.[36, 37]



Scheme 4.10 Stoichiometric reaction with acyl iodide

Based on these results and our previous work on carbonylation of alkyl halides,[25-27] we propose the following catalytic mechanism (Scheme 4.11). First, LiO*t*Bu reacts with B_2Pin_2 to produce the tetra-alkoxy diboron compound

A.[29, 30] This activated B(sp^2)-B(sp^3) complex is able to reduce the alkyl halide through a single-electron transfer (SET) event, affording alkyl radical intermediate and initiating a radical chain. The alkyl radical then undergoes carbonylation with CO to give an acyl radical **C**, which reacts with alkyl halide to afford acyl halide **D** and propagate the radical chain. Then, the oxidative addition of acyl halide C to the borylcopper **E** forms the copper(III) complex **F**. Finally, reductive elimination affords the tri-coordinated acylboron **G** and regenerates the copper(I) catalyst. The acylboron **G** is further combined with LiO*t*Bu to form the more stable tetra-coordinated boron complex. As we could obtain a small amount of the product in the absence of copper catalyst (table 4.1, entry 2), we assumed acyl radical **C** also reacts with the boron radical **B** but in a relatively slow rate compared to its reaction with borylcopper **E**. An alternative to oxidative addition complex **F** would be addition of complex **E** to the carbonyl group of acyl halide **D** to provide acylboron species **G** directly, as has recently been modeled computationally for a hydrocarbonylative coupling reaction.[28]



Scheme 4.11 Proposed catalytical cycle for carbonylative borylation

4.5. Experimental section

4.5.1. General information

Reactions requiring anhydrous conditions were conducted in a N_2-filled glovebox or using standard Schlenk line techniques. Reactions at greater than atmospheric pressure were conducted in a Parr 4621 General Purpose Pressure Reactor. A fitted, aluminum rack was customized for the Parr reactor that could hold up to nine 20-mL scintillation vials for running reactions in parallel. Thin layer chromatography (TLC) was conducted with E. Merck silica gel 60

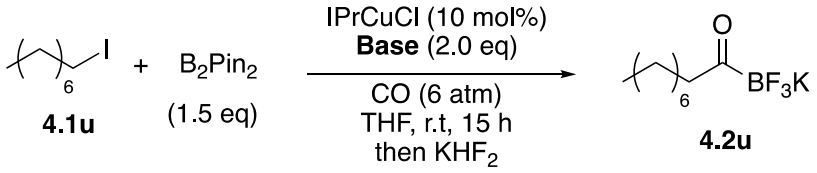
F254 pre-coated plates (0.25 mm) and visualized by UV light (254 nm). Purification of compounds was achieved by column chromatography using Merck Flash Silica Gel 60 (230-400 mesh). Organic solutions were concentrated under reduced pressure using a rotary evaporator.

Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Common commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific or VWR International Co. without further purification unless otherwise noted. Solvents were dried using a Glass Contour Solvent System built by Pure Process Technology, LLC. CO gas was purchased from Praxair at a purity of 99.99% (4.0RS research grade) and used directly from the cylinder. LiO*t*Bu was purchased from Alfa Aesar. B_2Pin_2 was purchased from TCI. IPrCuCl, SIPrCuCl,[38] IMesCuCl, SIMesCuCl,[39] ^{Me}IPrCuCl, ^{Cl}IPrCuCl,[40] ICyCuCl, and I*t*BuCuCl[39] were prepared according to literature procedures.

Nuclear Magnetic Resonance (NMR) spectra were recorded on BRUKER AV (400 MHz) or BRUKER AV (500 MHz) at 298 K. Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard (acetone-d_6 at 2.05 ppm and 29.84 ppm for ^{1}H and ^{13}C NMR spectroscopy; DMSO-d_6 at 2.50 ppm and 39.52 ppm for ^{1}H and ^{13}C NMR spectroscopy). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet; br., broad. Coupling constants were taken from the spectra directly and are uncorrected. ^{1}H and ^{13}C NMR provided are taken directly using material for which the yield is quoted, without further purification, and are representative of purity. FT-IR spectra were recorded on a Thermo Nicolet iS5 FT-IR. Absorptions are given in wavenumbers (cm–1). HRMS (ESI) were measured with a Shimadzu LCMS-IT-TOF Mass Spectrometer.

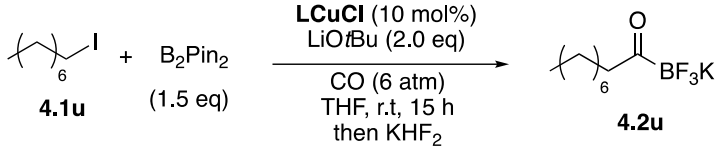
4.5.2. Reaction optimization

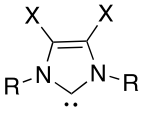
In a glovebox, base and solvent (4.0 mL) were added to a 20-mL vial with a 1.5 cm stir bar. The copper catalyst was dissolved in solvent (0.5 mL) and transferred to the above mixture. The mixture was stirred at room temperature for 2 min before B_2Pin_2 and 1-iodooctane (0.1 mmol) were added sequentially. The vial was then placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas and released after 2 min. This procedure was repeated three times, after which the reaction was stirred for 15 h. Then CO gas was released. The reaction mixture was added with aqueous KHF_2 solution (4.5 M in H_2O, 200μL, 0.9 mmol) and stirred at room temperature for 2 h. Then the solvent was removed under reduced pressure. The residue was dissolved in acetone-d_6 and dibromomethane (0.1 mmol) was added as internal standard for ^{1}H NMR analysis.



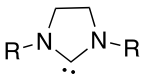
Entry	**Base**	Conversion of **4.1u** (%)	Yield of **4.2u** (%)
1	KOMe	100	<5
2	NaOMe	98	37
3	LiOMe	73	5
4	KO*t*Bu	100	16
5	NaO*t*Bu	100	9
6	LiO*t*Bu	78	51
7	NaOPh	77	24

Table 4.4 Base investigation





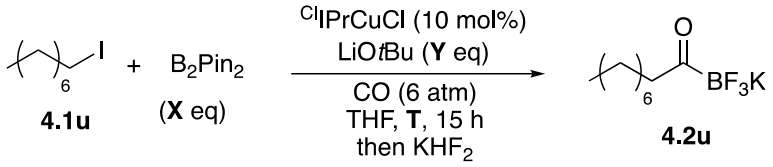
IPr R = 2,6-(diisopropyl)phenyl X = H
^{Cl}IMes R = 2,4,6-(trimethyl)phenyl X = Cl
^{Me}IPr R = 2,6-(diisopropyl)phenyl X = Me
^{Cl}IPr R = 2,6-(diisopropyl)phenyl X = Cl
ICy R = cyclohexyl X = H
I*t*Bu R = *tert*-butyl X = H



SIPr R = 2,5-diisopropylphenyl
SIMes R = 2,4,6-trimethylphenyl

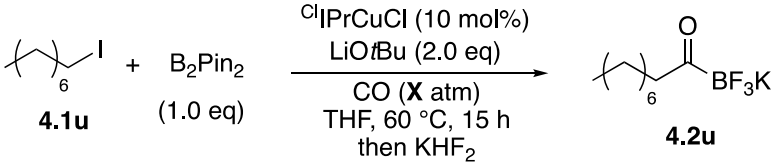
Entry	**LCuCl**	Conversion of **4.1u** (%)	Yield of **4.2u** (%)
1	IPrCuCl	78	51
2	SIPrCuCl	62	26
3	^{Me}IPrCuCl	76	56
4	^{Cl}IPrCuCl	98	58
5	IMesCuCl	100	28
6	SIMesCuCl	100	28
7	ICyCuCl	100	44
8	I*t*Bu	100	50

Table 4.5 Catalyst investigation



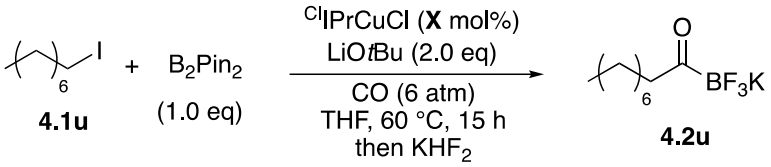
Entry	**T** (°C)	**X** (eq)	**Y** (eq)	Conversion of **4.1u** (%)	Yield of **4.2u** (%)
1	r.t	1.5	2.0	98	58
2	r.t	2.0	2.0	100	38
3	r.t	1.5	3.0	100	20
4	r.t	1.2	2.0	100	45
5	r.t	1.5	1.5	100	46
6	60	1.5	2.0	100	59
7	60	1.2	2.0	100	60
8	60	1.0	2.0	100	63
9	60	1.0	1.5	96	45

Table 4.6 Investigation of the amount of B_2Pin_2 and base at variable temperatures



Entry	CO (**X** atm)	Conversion of **4.1u** (%)	Yield of **4.2u** (%)
1	6	100	63
2	10	100	70
3	20	100	69

Table 4.7 Investigation of CO pressure

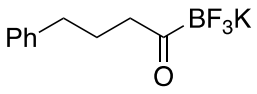


Entry	**X** (mol%)	Conversion of **4.1u** (%)	Yield of **4.2u** (%)
1	0	10	8
2	10	100	73
3	1	100	73
4	0.1	100	70
5	0.01	40	30

Table 4.8 Catalyst loading investigation

4.5.3. Synthesis and characterization of potassium acyltrifluoroborates

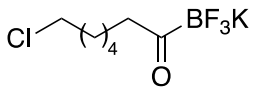
In a glovebox, LiO*t*Bu (80 mg, 1.0 mmol, 2.0 eq), ^{Cl}IPrCuCl (2.78 mg, 0.005 mmol, 1.0 mol%) and THF (30.0 mL) were added to a 80-mL vial with a 2.0 cm stir bar. The mixture was stirred at room temperature for 2 min before B_2Pin_2 (127 mg, 0.5 mmol, 1.0 eq) and alkyl halide (0.5 mmol, 1.0 eq) were added sequentially at room temperature. The vial was then placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas to 10 atm and released after 5 min. This procedure was repeated three times, after which the reaction was stirred at 60 ℃ for 15 h. Then, the reaction was cooled to room temperature and the CO gas was released. The reaction mixture was added with aqueous KHF_2 solution (4.5 M in H_2O, 1.0 mL, 4.5 mmol, 9.0 eq) and stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The resultant solid was dissolved in acetone and filtered through a pad of celite. The filtrate was concentrated and the resultant solid was washed with Et_2O to afford the corresponding potassium acyltrifluoroborates.



4.2a

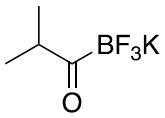
Potassium 3-phenylpropanoyltrifluoroborate (4.2a) The title compound was obtained as a white solid (103 mg, 81% yield) from1-iodo-3-phenylpropane (123 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz,**

acetone-d_6) δ 7.24 (t, J = 7.5 Hz, 2H), 7.18 (d, J = 7.0 Hz, 2H), 7.13 (t, J = 7.3 Hz, 2H), 2.57 – 2.49 (t, J = 7.8 Hz 2H), 2.44 (t, J = 7.3 Hz, 2H), 1.82 – 1.69 (m, 2H). **^{13}C NMR (126 MHz, acetone-d_6)** δ 143.8, 129.2, 128.9, 126.3, 44.5, 36.4, 25.2. The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. **^{11}B NMR (128 MHz, acetone-d_6)** δ -1.89 (q, J = 52.9 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -151.3 (q, J = 50.3 Hz). **HRMS** (ESI) Calcd. for C10H11BF3O ([M-K]-): 215.0860; Found: 215.0860. **IR** (neat) 2932, 1659, 1026, 967, 931, 743, 698, 632 cm^{-1}.



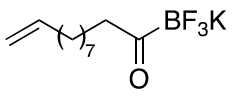
4.2b

Potassium 6-chloroheptanoyltrifluoroborate (4.2b) A mixture of the title compound and the cyclization product **2r** were obtained as a white solid (105 mg) from 1-chloro-6-iodohexane (123 mg, 0.5 mmol) according to general procedure. The ratio of the title compound and **2r** was determined to be 5.6:1 by ^{1}H NMR analysis of the isolated compound. **^{1}H NMR (500 MHz, acetone-d_6)** δ 3.59 (t, *J* = 6.8 Hz, 2H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.78 – 1.71 (m, 2H), 1.50 – 1.38 (m, 4H), 1.28 – 1.23 (m, 2H). **^{13}C NMR (126 MHz, acetone-d_6)** δ 45.7, 44.9, 33.3, 27.9, 27.5, 27.2, 26.8, 22.9. **^{11}B NMR (128 MHz, acetone-d_6)** δ -1.88 (q, *J* = 50.4 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -151.3 (q, *J* = 46.5 Hz). **HRMS** (ESI) Calcd. for $C_7H_{12}BClF_3O$ ([M-K]$^-$): 215.0627; Found: 215.0624. **IR** (neat) 2930, 2856, 2223, 1658, 978, 939, 724, 632 cm^{-1}.



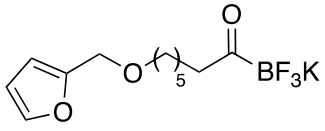
4.2c

Potassium isobutanoyltrifluoroborate (4.2c) The title compound was obtained as a white solid (75 mg, 84% yield) from 2-iodopropane (85 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-d_6)** δ 2.77-2.72 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (126 MHz, acetone-d_6)** δ 41.5, 17.4. **^{11}B NMR (128 MHz, acetone-d_6)** δ -2.34 (*J* = 54.6 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -149.2 (q, *J* = 54.0 Hz). **HRMS** (ESI) Calcd. for $C_4H_7BF_3O$ ([M-K]$^-$): 139.0547; Found: 139.0546. **IR** (neat) 2973, 2837, 2223, 1657, 1012, 939, 851, 713, 621 cm^{-1}.



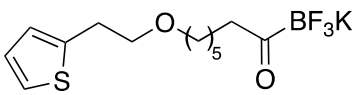
4.2d

Potassium trifluoro(undec-10-enoyl)borate (4.2d) The title compound was obtained as a white solid (62 mg, 48% yield) from 10-iodo-1-decene (133 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.85-5.77 (m, 1H), 4.99 (d, *J* = 17.0 Hz, 1H), 4.91 (d, *J* = 9.9 Hz, 1H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.47 – 1.26 (m, 14H). **^{13}C NMR (126 MHz, acetone-*d*$_6$)** δ 139.8, 114.6, 45.2, 34.5, 30.5, 30.4, 30.2, 23.2. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.90 (q, *J* = 53.76 Hz). **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -151.3 (q, *J* = 51.52 Hz). **HRMS** (ESI) Calcd. for $C_{11}H_{19}BF_3O$ ([M-K]$^-$): 235.1486; Found: 235.1487. **IR** (neat) 2923, 2852, 1661, 967, 908, 633 cm^{-1}.



4.2e

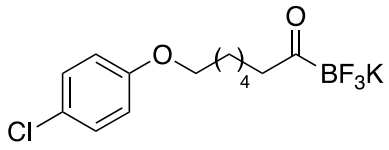
Potassium 7-(furan-2-ylmethoxy)heptanoyltrifluoroborate (4.2e) The title compound was obtained as a white solid (130 mg, 82%) from 3-(((6-iodohexyl)oxy)methyl)furan (154 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, aceton-*d*$_6$)** δ 7.64 – 7.37 (m, 2H), 6.43 (s, 1H), 3.40 (t, *J* = 6.6 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 1.57 – 1.49 (m, 2H), 1.47 – 1.40 (m, 2H), 1.35 – 1.29 (m, 2H), 1.27 – 1.20 (m, 2H). **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 143.5, 140.7, 122.5, 110.6, 69.3, 63.1, 44.1, 29.1, 29.1, 25.7, 22.2. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.89 (q, *J* = 52.9 Hz). **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -151.3 (q, *J* = 46.5 Hz). **HRMS** (ESI) Calcd. for $C_{12}H_{17}BF_3O_3$ ([M-K]$^-$): 277.1223; Found: 277.1224. **IR** (neat) 2931, 2857, 1660, 1158, 1094, 1017, 927, 873 cm^{-1}.



4.2f

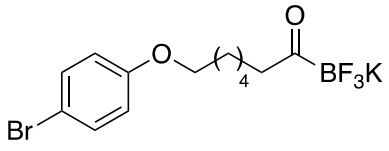
Potassium 7-(2-(thiophen-2-yl)ethoxy)heptanoyltrifluoroborate (4.2f) The title compound was obtained as a white solid (106 mg, 61%) from 2-(2-((6-iodohexyl)oxy)ethyl)thiophene (169 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-*d*$_6$)** δ 7.22 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.91 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.89 – 6.86 (m, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 3.42 (t, *J* = 6.5 Hz, 2H), 3.04 (t, *J* = 6.6 Hz, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 1.56 – 1.50 (m, 2H),

1.49 – 1.40 (m, 2H), 1.37 – 1.29 (m, 2H), 1.27 – 1.20 (m, 2H). **^{13}C NMR (126 MHz, DMSO-d_6)** δ 141.4, 126.6, 125.2, 124.0, 70.6, 70.1, 44.1, 29.8, 29.2, 29.1, 25.8, 25.2, 22.2. **^{11}B NMR (128 MHz, acetone-d_6)** δ -1.89 (q, *J* = 51.6 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -151.3 (q, *J* = 50.3 Hz).



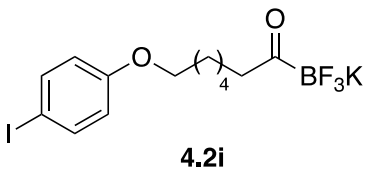
4.2g

Potassium 7-(4-chlorophenoxy)heptanoyltrifluoroborate (4.2g) The title compound was obtained as a white solid (157 mg, 90%) from 1-chloro-4-((6-iodohexyl)oxy)benzene (170 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-d_6)** δ 7.30 – 7.22 (m, 2H), 6.98 – 6.90 (m, 2H), 3.98 (t, *J* = 6.6 Hz, 2H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.78 – 1.69 (m, 2H), 1.51 – 1.39 (m, 4H), 1.34 – 1.26 (m, 2H). **^{13}C NMR (126 MHz, acetone-d_6)** δ 157.5, 129.2, 123.9, 116.2, 67.8, 44.1, 29.0, 28.5, 25.5, 22.1. **^{11}B NMR (128 MHz, acetone-d_6)** δ -1.89 (q, *J* = 51.6 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -151.26 (q, *J* = 44.0 Hz). **HRMS** (ESI) Calcd. for $C_{13}H_{16}BClF_3O_2$ ([M-K]$^-$): 307.0884; Found: 307.0885. **IR** (neat) 2937, 2864, 1664, 1492, 1242, 1008, 975, 919, 828 cm^{-1} .



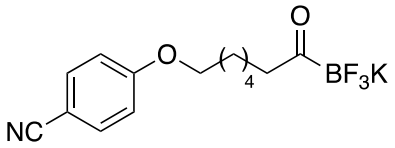
4.2h

Potassium 7-(4-bromophenoxy)heptanoyltrifluoroborate (4.2h) The title compound was obtained as a white solid (116 mg, 60%) from 1-bromo-4-((6-iodohexyl)oxy)benzene (192 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-d_6)** δ 7.46 – 7.36 (m, 2H), 7.00 – 6.83 (m, 2H), 3.97 (t, *J* = 6.6 Hz, 2H), 2.40 (t, *J* = 7.3 Hz, 2H), 1.77 – 1.71 (m, 2H), 1.50 – 1.40 (m, 4H), 1.32 – 1.28 (m, 2H). **^{13}C NMR (126 MHz, DMSO-d_6)** δ 158.0, 132.0, 116.7, 111.6, 67.7, 44.0, 28.9, 28.5, 25.5, 22.1. **^{11}B NMR (128 MHz, acetone-d_6)** δ -1.89 (q, *J* = 52.1 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -151.3 (q, *J* = 47.8 Hz). **HRMS** (ESI) Calcd. for $C_{13}H_{16}BBrF_3O_2$ ([M-K]$^-$): 351.0379; Found: 351.0376. **IR** (neat) 2937, 2864, 1666, 1489, 1474, 1243, 1009, 921 cm^{-1}.



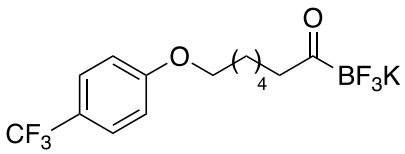
4.2i

Potassium 7-(4-iodophenoxy)heptanoyltrifluoroborate (4.2j) A mixture of the title compound and the deiodonized acylboron were obtained as a white solid (153 mg) from 1-iodo-4-((6-iodohexyl)oxy)benzene (215 mg, 0.5 mmol) according to general procedure. The ratio of the title compound and the deiodonized acylboron was determined to be 5:1 by ^{1}H NMR analysis of the isolated compound. **^{1}H NMR (500 MHz, acetone-d_6)** δ 7.62 – 7.53 (m, 2H), 6.84 – 6.74 (m, 2H), 3.97 (t, *J* = 6.6 Hz, 2H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.78 – 1.70 (m, 2H), 1.51 – 1.39 (m, 4H), 1.32 – 1.27 (m, 2H). **^{13}C NMR (126 MHz, acetone-d_6)** δ 160.1, 139.0, 130.2, 121.1, 118.0, 115.2, 82.5, 68.7, 45.1, 29.8, 26.7, 23.1. **^{11}B NMR (128 MHz, acetone-d_6)** δ -1.89 (q, *J* = 52.6 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -151.3 (q, *J* = 45.2 Hz). **HRMS** (ESI) Calcd. for $C_{13}H_{16}BIF_3O_2$ ([M-K]$^-$): 399.0240; Found: 399.0236. **IR** (neat) 2934, 2861, 1669, 1486, 1243, 999, 921 cm^{-1}.



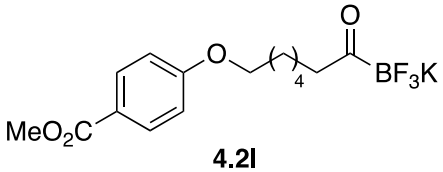
4.2j

Potassium 7-(4-cyanophenoxy)heptanoyltrifluoroborate (4.2j) The title compound was obtained as a white solid (164 mg, 98%) from 4-((6-iodohexyl)oxy)benzonitrile (164 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-d_6)** δ 7.71 – 7.64 (m, 2H), 7.13 – 7.08 (m, 2H), 4.10 (t, J = 6.6 Hz, 2H), 2.40 (t, *J* = 7.3 Hz, 2H), 1.82 – 1.75 (m, 2H), 1.49 – 1.41 (m, 4H), 1.34 – 1.28 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 162.2, 134.1, 119.2, 115.5, 102.5, 68.1, 44.0, 28.9, 28.3, 25.4, 22.1. **^{11}B NMR (128 MHz, acetone-d_6)** δ -1.89 (q, *J* = 51.6 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -151.25 (q, *J* = 46.5 Hz). **HRMS** (ESI) Calcd. for $C_{14}H_{16}NBF_3O_2$ ([M-K]$^-$): 298.1226; Found: 298.1227. **IR** (neat) 2941, 2862, 2226, 1603, 1508, 1260, 993, 919, 838 cm^{-1}.



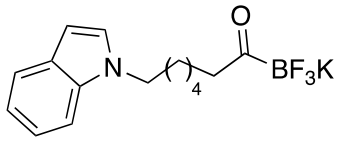
4.2k

Potassium 7-(4-(trifluoromethyl)phenoxy)heptanoyltrifluoroborate (4.2k) The title compound was obtained as a white solid (170 mg, 89%) from 1-((6-iodohexyl)oxy)-4-(trifluoromethyl)benzene (186 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-*d*$_6$)** δ 7.61 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 4.08 (t, *J* = 6.6 Hz, 2H), 2.40 (t, *J* = 7.3 Hz, 2H), 1.83 – 1.71 (m, 2H), 1.51 – 1.42 (m, 4H), 1.34 – 1.27 (m, 2H). **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 161.6, 126.9 (*J* = 3.8 Hz), 120.8 (*J* = 32.67 Hz), 114.9, 67.9, 44.1, 28.9, 28.4, 25.5, 22.1. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.89 (q, J = 52.1 Hz). **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -62.3, -151.3 (q, *J* = 46.5 Hz). **HRMS** (ESI) Calcd. for $C_{14}H_{16}BF_6O_2$ ([M-K]$^-$): 341.1148; Found: 341.1154. **IR** (neat) 2939, 2850, 1665, 1617, 1334, 1250, 1107, 1008, 918 cm^{-1}.



4.2l

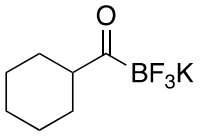
Potassium 7-(4-(methoxycarbonyl)phenoxy)heptanoyltrifluoroborate (4.2l) The title compound was obtained as a white solid (80 mg, 43%) from methyl 4-((6-iodohexyl)oxy)benzoate (180 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-*d*$_6$)** δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.08 (t, *J* = 6.7 Hz, 2H), 3.83 (s, 3H), 2.40 (t, *J* = 7.4 Hz, 2H), 1.81 – 1.75 (m, 2H), 1.52 – 1.41 (m, 4H), 1.35 – 1.26 (m, 2H). **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 165.9, 162.6, 131.2, 121.6, 114.4, 67.9, 51.8, 44.0, 28.9, 28.4, 25.5, 22.0. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.91 (q, *J* = 54.6 Hz). **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -151.3 (q, *J* = 49.0 Hz). **HRMS** (ESI) Calcd. for $C_{15}H_{19}BF_3O_4$ ([M-K]$^-$): 331.1328; Found: 331.1328. **IR** (neat) 2939, 2901, 2862, 1714, 1663, 1607, 1291, 1254, 1105, 1074, 930 cm^{-1}.



4.2m

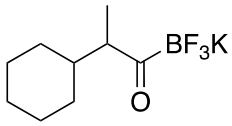
Potassium 7-(1H-indol-1-yl)heptanoyltrifluoroborate (4.2m) The title compound was obtained as a yellow solid (103 mg, 61%) from 1-(6-iodohexyl)-1*H*-indole (164 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-*d*$_6$)** δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 3.1 Hz, 1H), 7.13 (t, *J* = 7.6 Hz,

1H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.42 (d, *J* = 2.9 Hz, 1H), 4.19 (t, *J* = 7.1 Hz, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 1.84 – 1.78 (m, 2H), 1.45 – 1.39 (m, 2H), 1.32 – 1.25 (m, 4H). **^{13}C NMR (126 MHz, acetone-*d*$_6$)** δ 137.0, 129.7, 129.0, 121.8, 121.4, 119.7, 110.4, 101.3, 46.7, 31.0, 30.3, 29.4, 27.6, 23.1. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.89. **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -151.2. **HRMS** (ESI) Calcd. for $C_{15}H_{18}BNF_3O$ ([M-K]$^-$): 296.1434; Found: 296.1438.



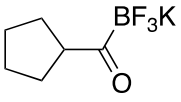
4.2n

Potassium cyclohexanecarbonyl trifluoroborate (4.2n) The title compound was obtained as a white solid (93 mg, 85% yield) from iodocyclohexane (105 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (400 MHz, acetone-*d*$_6$)** δ 2.54 (tt, *J* = 11.1, 3.2 Hz, 1H), 1.80 – 1.77 (m, 2H), 1.75 – 1.65 (m, 2H), 1.63 – 1.59 (m, 1H), 1.30 – 1.20 (m, 2H), 1.18 – 1.06 (m, 3H). **^{13}C NMR (126 MHz, acetone-*d*$_6$)** δ 52.3, 28.0, 27.3, 26.9. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.81 (q, *J* = 54.6 Hz). **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -149.3 (q, *J* = 50.5 Hz).



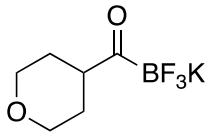
4.2o

Potassium 2-cyclohexylpropanoyltrifluoroborate (4.2p) The title compound was obtained as a white solid (80 mg, 65% yield) from 1-cyclohexyliodoethane (119 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-*d*$_6$)** δ 2.56 (p, *J* = 7.0 Hz, 1H), 1.85 – 1.74 (m, 1H), 1.67-1.54 (m, 5H), 1.25 – 1.05 (m, 3H), 0.96 (qd, *J* = 12.5, 3.1 Hz, 1H), 0.87 – 0.78 (m, 4H). **^{13}C NMR (126 MHz, acetone-*d*$_6$)** δ 206.3, 52.8, 38.7, 32.9, 27.3, 27.2, 11.6. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.89 (q, *J* = 52.3 Hz). **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -149.7 (q, *J* = 46.5 Hz). **HRMS** (ESI) Calcd. for $C_9H_{15}BF_3KO$ ([M-K]$^-$): 207.1171; Found: 207.1172. **IR** (neat) 2921, 2851, 1645, 974, 929, 904 cm^{-1}.



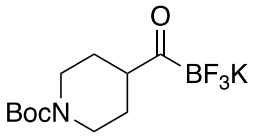
4.2p

Potassium cyclopentylmethanoyltrifluoroborate (4.2p) The title compound was obtained as a white solid (78 mg, 76% yield) from iodocyclopentane (98 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-d_6)** δ 3.11 – 3.00 (m, 1H), 1.77 – 1.70 (m, 2H), 1.61 – 1.54 (m, 2H), 1.49 – 1.40 (m, 4H). **^{13}C NMR (126 MHz, acetone-d_6)** δ 52.9, 27.6, 26.8. **^{11}B NMR (128 MHz, acetone-d_6)** δ -1.74 (q, *J* = 54.6 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -149.4 (q, *J* = 54.0 Hz). **HRMS** (ESI) Calcd. for $C_6H_9BF_3O$ ($[M\text{-}K]^-$): 165.0704; Found: 165.0706. **IR** (neat) 2961, 2872, 1654, 1014, 979, 964, 940, 859, 627 cm^{-1}.



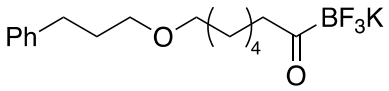
4.2q

Potassium tetrahydro-2H-pyran-4-ylmethanoyltrifluoroborate (4.2q) The title compound was obtained as a white solid (70 mg, 64% yield) from 4-iodo-tetrahydropyran (106 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (400 MHz, acetone-d_6)** δ 3.89 – 3.75 (m, 2H), 3.33 (td, *J* = 11.5, 2.3 Hz, 2H), 2.70 (tt, *J* = 11.2, 3.8 Hz, 1H), 1.68 – 1.65 (m, 2H), 1.47 – 1.36 (m, 2H). **^{13}C NMR (101 MHz, acetone-d_6)** δ 68.3, 28.2.



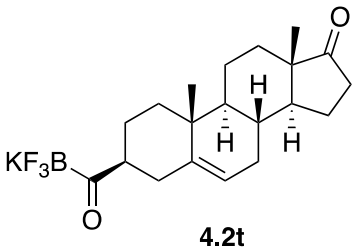
4.2r

Potassium *N*-[(tert-butoxy)carbonyl]piperidine-4-carbonyltrifluoroborate (4.2r) The title compound was obtained as a white solid (76 mg, 48% yield) from *N*-Boc-4-iodopiperidine (156 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-d_6)** δ 3.96 (brs, 2H), 2.76 (brs, 2H), 2.65 (tt, *J* = 11.2, 3.7 Hz, 1H), 1.74 – 1.72 (m, *2*H), 1.41 (s, 9H), 1.34 – 1.23 (m, 2H). **^{13}C NMR (126 MHz, acetone-d_6)** δ 155.0, 79.0, 49.9, 44.8, 44.0, 43.8, 28.5, 27.1. **^{11}B NMR (128 MHz, acetone-d_6)** δ -1.83 (q, *J* = 49.9 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -149.43 (q, *J* = 47.8 Hz). **HRMS** (ESI) Calcd. for $C_{11}H_{18}BF_3NO_3$ ($[M\text{-}K]^-$): 280.1337; Found: 280.1334. **IR** (neat) 2975, 2859, 1656, 1426, 1164, 996, 928 cm^{-1}.



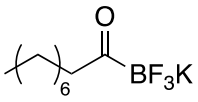
4.2s

Potassium 7-(3-phenylpropoxy)heptanoyltrifluoroborate (4.2s) The title compound was obtained as a white solid (132 mg, 74%) from methyl (3-((6-iodohexyl)oxy)propyl)benzene (170 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-*d*$_6$)** δ 7.26 (t, *J* = 7.5 Hz, 2H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 3.37 (td, *J* = 6.4, 3.9 Hz, 4H), 2.67 (t, *J* = 7.5 Hz , 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 1.86-1.80 (m, 2H), 1.56 – 1.49 (m, 2H), 1.49 – 1.42 (m, 2H), 1.38 – 1.30 (m, 2H), 1.28-1.23 (m, 2H). **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 141.8, 128.3, 128.2, 125.6, 70.0, 69.0, 44.1, 31.7, 31.0, 29.2, 29.1, 25.8, 22.1. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.89 (q, *J* = 52.1 Hz). **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -151.3 (q, *J* = 45.2 Hz). **HRMS** (ESI) Calcd. for $C_{16}H_{23}BF_3O_2$ ([M-K]$^-$): 315.1743; Found: 315.1748. **IR** (neat) 2930, 2855, 1660, 1157, 1111, 992, 925, 697 cm^{-1}.



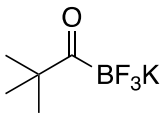
4.2t

Compound 4.2u The title compound was obtained as a white solid (126 mg, 62% yield) from 3*β*-iododandrost-5-en-17-one (199 mg, 0.5 mmol) according to general procedure. The *dr* was determined to be 4:1 by ^{1}H NMR. The assignment of 3*β* configuration in the major isomer was based on the large coupling constant at 2.56 ppm, typical of an axial proton in a cyclohexane chair system. **^{1}H NMR (400 MHz, acetone-*d*$_6$)** 5.29 – 5.30 (m, 1H), 2.56 (tt, J = 12.4, 3.4 Hz, 1H), 2.42 – 2.36 (m, 1H), 2.19 (t, J = 13.3 Hz, 1H), 1.98 – 1.87 (m, 3H), 1.77 – 1.47 (m, 7H), 1.37 – 1.15 (m, 4H), 1.13 – 0.91 (m, 6H), 0.85 (s, 3H). **^{13}C NMR (126 MHz, acetone-*d*$_6$)** δ 219.7, 144.3, 119.4, 53.7, 52.5, 51.7, 47.9, 40.4, 38.0, 36.0, 34.1, 32.5, 32.3, 31.5, 25.3, 24.2, 22.4, 20.9, 19.8, 13.8. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.81. **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -149.4 (major), 147.9 (minor).



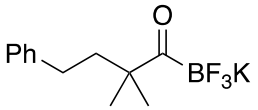
4.2u

Potassium nonanoyltrifluoroborate (4.2u) The title compound was obtained as a white solid (100 mg, 81% yield) from 1-iodooctane (120 mg, 0.5 mmol) according to general procedure. **^{1}H NMR (500 MHz, acetone-*d*$_6$)** δ 2.38 (t, *J* = 7.4 Hz, 2H), 1.47 – 1.37 (m, 2H), 1.31 – 1.19 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (126 MHz, acetone-*d*$_6$)** δ 45.1, 32.6, 30.5, 30.4, 23.3, 23.2, 14.3. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.90 (q, *J* = 53.8 Hz). **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -151.3 (q, *J* = 49.0 Hz). **HRMS** (ESI) Calcd. for $C_9H_{17}BF_3O$ ([M-K]$^-$): 209.1330; Found: 209.1331. **IR** (neat) 2957, 2923, 2853, 1661, 1016, 976, 926, 633 cm^{-1}.



4.2v

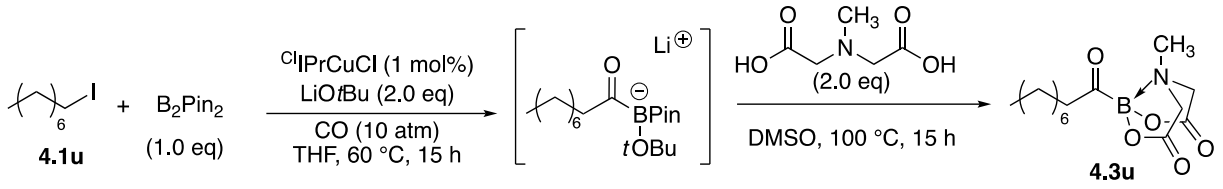
Potassium trifluoro(pivaloyl)borate (4.2v) The title compound was obtained as a white solid (47 mg, 49% yield) from *t*-butyl bromide (68 mg, 0.5 mmol) according to general procedure. I^{t}BuCuCl instead of ^{Cl}IPrCuCl was used as catalyst and the reaction was performed at room temperature. **^{1}H NMR (500 MHz, acetone-*d*$_6$)** δ 1.00 (s, 9H). **^{13}C NMR (126 MHz, acetone-*d*$_6$)** δ 45.2, 25.8. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.60 (q, *J* = 55.04 Hz). **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -144.6 (q, *J* = 54.0 Hz). **HRMS** (ESI) Calcd. for $C_5H_9BF_3O$ ([M-K]$^-$): 153.0704; Found: 153.0706. **IR** (neat) 2959, 1636, 1024, 978, 899, 804, 722 cm^{-1}.



4.2w

2,2-dimethyl-4-phenyl-butanoyltrifluoroborate (4.2w) The title compound was obtained as a white solid (40 mg, 28% yield) from (3-bromo-3-methylbutyl)benzene (113 mg, 0.5 mmol) according to general procedure. I^{t}BuCuCl instead of ^{Cl}IPrCuCl was used as catalyst and the reaction was performed at room temperature. The ^{1}H NMR analysis of the crude mixture using CH_2Br_2 (0.1 mmol) as internal standard showed that the compound **4.2w** was formed in 54% yield. **^{1}H NMR (500 MHz, acetone-*d*$_6$)** δ 7.29 – 7.17 (m, 4H), 7.11 (t, *J* = 7.0 Hz, 1H), 2.50 – 2.31 (m, 2H), 1.96 – 1.84 (m, 2H), 1.06 (s, 6H). **^{13}C NMR (126 MHz, acetone-*d*$_6$)** δ 144.9, 129.2, 128.9, 126.1, 48.9, 42.2, 32.3, 23.7. **^{11}B NMR (128 MHz, acetone-*d*$_6$)** δ -1.63 (q, *J* = 53.76 Hz). **^{19}F NMR (377 MHz, acetone-*d*$_6$)** δ -144.8 (q, *J* = 51.5

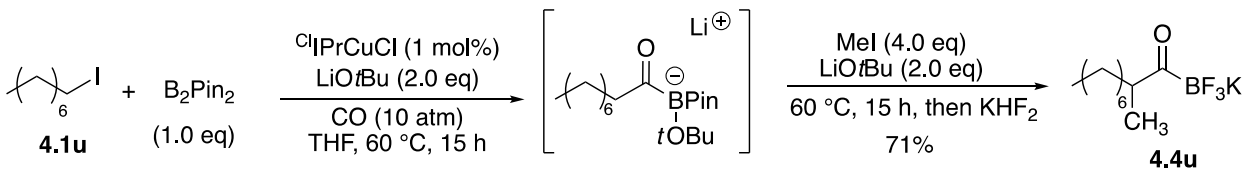
Hz). **HRMS** (ESI) Calcd. for $C_{12}H_{15}BF_3O$ ([M-K]$^-$): 243.1173; Found: 243.1171. **IR** (neat) 2962, 1632, 984, 964, 897, 721 cm^{-1}.



Scheme 4.12 Synthesis of MIDA-acylboronates from carbonylative borylation

In a glovebox, LiO*t*Bu (16 mg, 0.2 mmol, 2.0 eq), ^{Cl}IPrCuCl (0.56 mg, 0.001 mmol, 1.0 mol%) and THF (4.0 mL) were added to a 20-mL vial with a 1.5 cm stir bar. The mixture was stirred at room temperature for 2 min before B_2Pin_2 (25.4 mg, 0.1 mmol, 1.0 eq) and 1-iodooctane (24.0 mg, 0.1 mmol, 1.0 eq) were added sequentially at room temperature. The vial was then placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas to 10 atm and released after 2 min. This procedure was repeated three times, after which the reaction was stirred at 60 ℃ for 15 h. Then, the reactor was cooled to room temperature and the CO gas was released. The reactor was brought into the glovebox. *N*-Methyliminodiacetic acid (29.4 mg, 0.2 mmol, 2.0 eq) and DMSO (4.0 mL) were added to the reaction mixture at room temperature. The reaction was further stirred at 100 ℃ for 15 h before it was diluted with H_2O (20 mL) and Et_2O (20 mL). The organic phase was separated, and the aqueous layer was extracted twice with Et_2O (2 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated on a rotary evaporator. The crude material was purified by silica gel chromatography (ethyl acetate as eluent) to afford the title compound as a white solid (13 mg, 43% yield).

^{1}H NMR (500 MHz, CD_3CN) δ 4.02 (d, *J* = 16.9 Hz, 2H), 3.88 (d, *J* = 16.9 Hz, 2H), 2.80 (s, 3H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.54 – 1.44 (m, 2H), 1.27 (s, 10H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (126 MHz, CD_3CN)** δ 169.0, 62.9, 47.4, 47.3, 32.5, 30.2, 30.0, 29.9, 23.3, 22.7, 14.3. **^{11}B NMR (128 MHz, CD_3CN)** δ 4.01. **IR** (neat) 2920, 2852, 1767,1659, 1467, 1291, 1051 cm^{-1}.

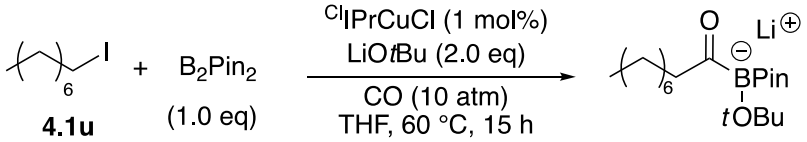


Scheme 4.13 Synthesis of α-methylated KATs from carbonylative borylation

In a glovebox, LiO*t*Bu (80 mg, 1.0 mmol, 2.0 eq), ^{Cl}IPrCuCl (2.78 mg, 0.005 mmol, 1.0 mol%) and THF (30.0 mL) were added to a 80-mL vial with a 2.0 cm stir bar. The mixture was stirred at room temperature for 2 min before B_2pin_2 (127 mg, 0.5 mmol, 1.0 eq) and 1-iodooctane (120 mg, 0.5 mmol, 1.0 eq) were added sequentially at room temperature. The vial was then placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas to 10 atm and released after 2 min. This procedure was repeated three times, after which the reaction was stirred at 60 ℃ for 15 h. Then, the reaction was cooled to room temperature and the CO gas was released. The reactor was brought into the glovebox. LiO*t*Bu (80 mg, 1.0 mmol) and MeI (284 mg, 2.0 mmol, 4.0 eq) were added to the reaction mixture at room temperature. The reaction was further stirred at 60 ℃ for 15 h before aqueous KHF_2 solution (4.5 M in H_2O, 1.0 mL, 4.5 mmol, 9.0 eq) was added at room temperature and the reaction was continued to stir at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The resultant solid was dissolved in acetone and filtered through a pad of celite. The filtrate was concentrated and the resultant solid was washed with Et_2O to afford a white solid (120 mg). The ^{1}H NMR and ^{19}F NMR showed a mixture of **4.4u** and **4.2u** were formed. The ratio of **4.4u** and **4.2u** was determined to be 3.3:1 by ^{1}H NMR analysis of the isolate mixture.

4.5.4. Mechanistic study

A. Formation of the tetra-coordinated acylboron species

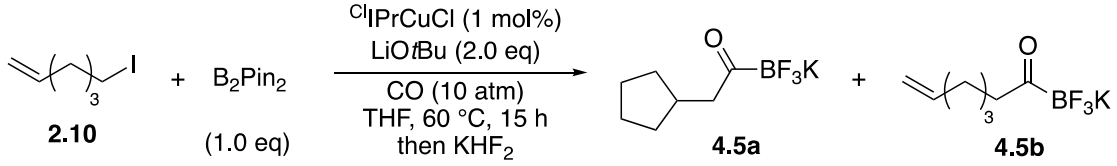


Scheme 4.14 Reaction for the detection of the tetra-coordinated acylboronates

In a glovebox, LiO*t*Bu (16 mg, 0.2 mmol, 2.0 eq), ^{Cl}IPrCuCl (0.56 mg, 0.001 mmol, 1.0 mol%) and THF (4.0 mL) were added to a 20-mL vial with a 1.5 cm stir bar. The mixture was stirred at room temperature for 2 min before B_2Pin_2 (25.4 mg, 0.1 mmol, 1.0 eq) and 1-iodooctane (24.0 mg, 0.1 mmol, 1.0 eq) were added sequentially at room temperature. The vial was then placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas to 10 atm and released after 2 min. This procedure was repeated three times, after which the reaction was stirred at 60 ℃ for 15 h. Then, the reactor was cooled to room temperature and the CO gas was

released. The reactor was brought into the glovebox. Then the solvent was removed under reduced pressure. The residue was dissolved in acetone-d_6 for NMR analysis. Although the ^{1}H NMR analysis was not clear, the ^{11}B NMR showed a new peak at 2.32 ppm, which is in the chemical shift range of tetracoordinated acylboron species.

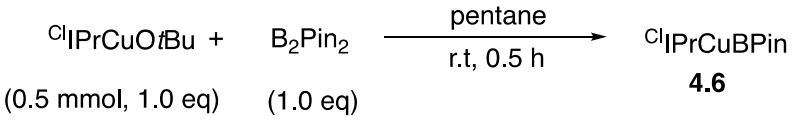
B. Radical clock experiment



Scheme 4.15 Radical clock experiment with 6-iodohexene

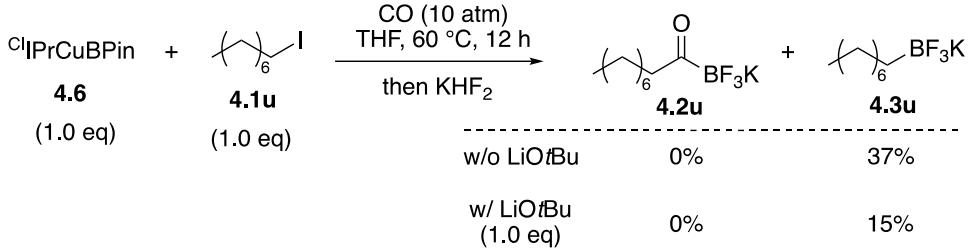
The reaction was performed according to the general procedure for synthesis of acylboron compounds using 6-iodohexene **2.10** (105 mg, 0.5 mmol) as a starting material. A white solid (100 mg, 92% yield) containing a mixture of cyclization product **4.5a** and the compound **4.5b** was obtained. The ratio of **4.5a** and **4.5b** was determined to be 12:1 by the ^{1}HNMR analysis of the isolated mixture. **^{1}H NMR (400 MHz, acetone-d_6)** δ 2.42 (d, *J* = 7.0 Hz, 2H), 2.28 – 2.20 (m, 1H), 1.77 – 1.65 (m, 2H), 1.61 – 1.41 (m, 4H), 1.06 – 0.94 (m, 2H). **^{13}C NMR (101 MHz, acetone-d_6)** δ 51.9, 35.0, 33.6, 25.6. **^{11}B NMR (128 MHz, acetone-d_6)** δ -1.94 (q, *J* = 53.8 Hz). **^{19}F NMR (377 MHz, acetone-d_6)** δ -151.3 (q, *J* = 50.3 Hz).

C. Stoichiometric reactions with ^{Cl}IPrCuBpin



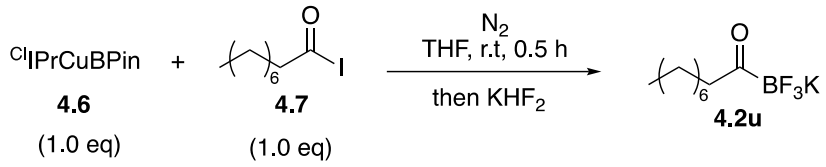
Scheme 4.16 Synthesis of ^{Cl}IPrCuBPin **4.6**

^{Cl}IPrCu-Bpin was prepared according to the previous literature.[41] In a glovebox, ^{Cl}IPrCuO*t*Bu (298 mg, 0.5 mmol, 1.0 eq), B_2pin_2 (127 mg, 0.5 mmol, 1.0 eq) and pentane (5 mL) were added to a 20-mL vial with a 1.5 cm stir bar. The reaction was stirred at room temperature for 0.5 h. Then the reaction mixture was filtered and washed with pentane to afford an off-white solid (240 mg, 74% yield). **^{1}H NMR (500 MHz, toluene-d_8)** δ 7.15 (t, *J* = 7.7 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 4H), 2.62 (sep, *J* = 6.9 Hz, 4H), 1.45 (d, *J* = 6.9 Hz, 12H),1.13 (d, *J* = 6.9 Hz, 12H), 1.01 (s, 12H).



Scheme 4.17 Stoichiometric reaction with alkyl iodide

In a glovebox, ^{Cl}IPrCuBPin (33 mg, 0.05 mmol) and THF (4 mL) were added to a 20-mL vial with a 1.5 cm stir bar. Then 1-iodooctane (12 mg, 0.05 mmol, 1.0 eq) was dissolved in THF (1.0 mL) and added to the above solution at room temperature. The vial was placed in an aluminum rack within a Parr pressure reactor. Next, the reactor was closed and taken out of the glovebox. A CO gas cylinder with a pressure regulator was connected to the reactor. The reactor was pressurized with CO gas to 10 atm and released after 2 min. This procedure was repeated three times, after which the reaction heated to 60 ℃ for 15 h. Then, the reaction was cooled to room temperature and the CO gas was released. The resulting mixture was quenched with aqueous KHF_2 solution (4.5 M in H_2O, 100 μL, 0.45 mmol, 9.0 eq) and stirred at room temperature for 2 h. Then the solvent was removed under reduced pressure. The residue was dissolved in acetone-d_6 and CH_2Br_2 (0.1 mmol) was added as internal standard for ^{1}H NMR analysis. The ^{1}H NMR analysis showed that the compound **4.2u** was not observed and alkyl borane **4.3u** was formed in 37% yield. Performing the above procedure in the presence of Li*O*t*Bu gave similar results with alkyl borane **4.3u** was formed in 15% yield.



Scheme 4.18 Stoichiometric reaction with acyl iodide

In a glovebox, ^{Cl}IPrCuBPin (65 mg, 0.10 mmol) and THF (4.0 mL) were added to a 20-mL vial with a 1.5 cm stir bar. Nonanoyl iodide **4.7** (27 mg, 0.1 mmol, 1.0 eq) was dissolved in THF (1 mL) and added to the above solution at room temperature. After that, the reaction was stirred at room temperature for 0.5 h. Next the resulting mixture was quenched with aqueous KHF_2 solution (4.5 M in H_2O, 200μL, 0.9 mmol, 9.0 eq) and stirred at room temperature for 2 h. Then the solvent was removed under reduced pressure. The residue was dissolved in acetone-d_6 and CH_2Br_2 (0.1 mmol) was added as internal standard for ^{1}H NMR analysis. The ^{1}H NMR analysis showed that the compound **4.2u** was obtained in 30% yield.

4.6. Conclusion

In summary, we have developed an efficient method to synthesize acylborons from unactivated alkyl halides and a commercially available boron reagent (B_2Pin_2) via a Cu-catalyzed carbonylative borylation.[42] A variety of aliphatic potassium acyltrifluoroborates (KATs) which previously required multi-step synthesis can now be approached in one step by sequentially adding aqueous KHF_2 to the reaction mixture. Primary, secondary, and tertiary alkyl halides are all suitable substrates. In addition, this method also provides facile access to *N*-methyliminodiacetyl (MIDA) acylboronate and can be potentially applied for synthesis of α-functionalized KATs. Mechanistic studies support a radical atom transfer carbonylation (ATC) mechanism to form acyl halide as a key intermediate that undergoes Cu-mediated borylation.

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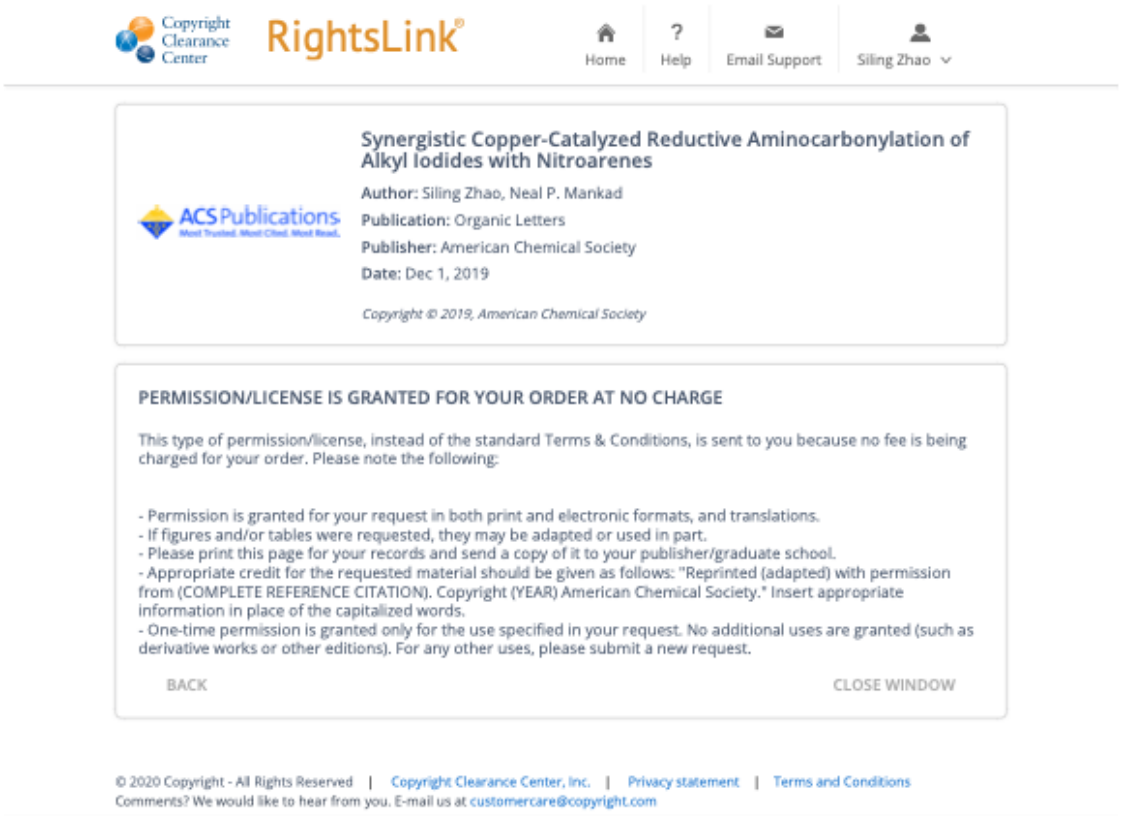

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BACK CLOSE WINDOW

VITA

NAME Siling Zhao

EDUCATION Ph.D. University of Illinois at Chicago, USA, 2020

M.A. University of Virginia, USA, 2015

B.S. Sichuan University, China, 2014

PUBLICATIONS Cheng, L.-J.; **Zhao, S**.; Mankad, N., One-Step Synthesis of Acylboron Compounds via Cu-Catalyzed Carbonylative Borylation of Alkyl Halides. *Angewandte Chemie International Edition.* Accepted Manuscript. doi:10.1002/anie.202012373

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PRESENTATIONS ACS Spring 2020 National Meeting & Expo, Philadelphia, PA, Oral presentation, 2020 (Accepted abstract, Conference cancelled due to COVID-19)

ACS Great Lakes Regional Meeting, Lisle, IL, Oral presentation, 2019