New Directions in Transition Metal Catalyzed Carboxylation Chemistry

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Abstract: Carbon monoxide (CO) represents an important C1-building block for the construction of some of the most fundamental chemical functionalities carrying a carbon–oxygen double bond. Transition metal catalysis plays a key role in promoting such transformations. We have earlier shown that the combination of palladium catalysis with CO releasing molecules and the two-chamber reactor, COware, provides a convenient and safe means for performing traditional Pd-catalyzed carboxylation reactions, as well as being a platform for the discovery of new carboxylation reactions. Furthermore, the method can be adapted to $^{13}$C- and $^{15}$C-isotope labeling, as well as providing for a suitable setting for developing efficient carboxylation reactions with $^{14}$CO. Herein, we provide a short overview of our latest findings in this area with emphasis on carboxylation reactions with fluorinated building blocks, but also discuss our efforts to develop viable Ni-catalyzed carboxylation reactions with aliphatic substrates, which can be performed efficiently under low CO partial pressures.

Keywords: Carboxylation · Catalysis · Fluorination · Isotope labeling · Nickel · Palladium

1. Introduction

Palladium-catalyzed carboxylation reactions have proven to be a robust and versatile method for installing carboxyl groups into a variety of compounds since the initial reports from Heck and co-workers.[1] Although CO is an excellent one-carbon building block, it is not without its drawbacks as the handling of the toxic gas is often a cause for concern. Many research groups have therefore explored the potential of employing CO-releasing molecules (CORMs) in order to eliminate the risks of exposure to CO.[2] In 2011, we reported on two different CORMs that could produce CO ex situ in a two-chamber system enabling a safe and efficient alternative for performing traditional CO-consuming reactions.[3] The application of this methodology in traditional Pd-catalyzed carboxylation transformations, such as amino- and alkoxycarbonylations and carboxylation analogs of named cross-coupling reactions (Suzuki-Miyaura and Sonogashira) was summarized in an account from 2016.[4] In this work, we wish to report on some recent discoveries developed in our laboratories. Focus will be directed towards Pd-catalyzed carboxylation transformations using fluorinated building blocks, and efforts on exploiting nickel as an effective catalyst for carboxylation chemistry.

2. Carboxylation Reactions using Fluorinated Reagents

Incorporation of fluorine atoms into bioactive compounds often leads to increased lipophilicity and metabolic stability. Fluorinated drugs have become more common,[5] and a recent table from the Njardarson group,[6] summarizing the top pharmaceutical products by retail sales in 2016, reveals that 12 out of the top 30 low molecular weight pharmaceutical drugs contained a fluorinated compound, some of which are depicted in Fig. 1. As can be seen in this Figure, different fluorination patterns (mono-, di- and trifluorination) and positioning (C(sp$^2$)-F and C(sp$^3$)-F) are utilized. Therefore, new and efficient methodologies for installing fluorine atoms into bioactive compounds are highly desirable. We have previously developed a carboxylation methodology transforming perfluorinated arenes into the corresponding diarylketone through C–H activation.[7] In order to access more diverse fluorinated scaffolds, α,α,α-bromodifluorocarbonyl compounds were selected as possible coupling partners. Hartwig, Zhang and others have previously demonstrated the potential of using these fluorinated molecules in a range of α-arylation procedures.[8,9] Given our prior experience with carboxylative α-arylation reactions for accessing 1,3-dicarbonyl structures,[10] these fluorinated molecules were chosen as the electrophile for forming α,α-difluoro analogs of these useful scaffolds. The optimized conditions and some representative examples are depicted in Scheme 1.[11,12] Starting from different aryl boronic acid derivatives (Ar-Bpin, Ar-Bnep, Ar-BF$_2$K), high yields could be obtained for the β-ketoamides such as 1 and 2 and the corresponding β-ketoester as for 3. This latter compound could be transformed to the corresponding α,α-difluorocetophenone 4 through an acid-mediated decarboxylation, or to pyrazalone 5 via a condensation-acyl...
substitution sequence. The β-ketoamide 6 was isolated using 13CO generated from 13COgen in a good yield (75%), and could further be isotopically-enriched by reduction using NaBD4 to the [M+4]-diol 7.

The developed methodology illustrated in Scheme 1 was limited to aryl boronic derivatives. The concept could nonetheless be extended to include aliphatic boron reagents[13] by lowering the temperature and increasing the CO pressure as shown in Scheme 2.[14] The nucleophilic boron reagents were obtained from the hydrobororation of the corresponding alkene in the presence of (9-BBN). Octyl-substituted α,α-difluoro-β-ketoamides 8 and 9 could be isolated in good yields and 13C-labeling was also possible using 13COgen as for compound 10. Hydroborated styrenes could also be utilized as nucleophiles for this carbonylative cross-coupling as exemplified by β-ketoamides 11 and 12. Notably, the C(sp2)-Br bond in 11 remained untouched under these mild conditions allowing for potential further manipulations. Furthermore, three additional fluorine atoms could be incorporated into the desired product 12 by having a CF3-group pre-installed on the electrophile. Finally, a mono-fluorinated β-ketoester 13 could be generated in a good yield by employing ethyl 2-bromo-2-fluorooacetate as the electrophile.

Besides α,α,β-bromodifluoroamines and esters described above, perfluorinated alkyl iodides have also been examined as electrophiles in transition-metal catalyzed reactions. Nevado and Chajadaj reported on the exploitation of such compounds in three-component Pd-catalyzed reaction with boronic acids and alkenes to access tri- and tetra-substituted perfluorinated olefins.[15] Furthermore, a four-component methodology based on these reports incorporating CO as the fourth reactant for making α,β-unsaturated esters and amides was recently reported by Liang and co-workers.[16] Inspired by these results, we recently developed a Pd-catalyzed four component methodology for accessing perfluorinated enones and indolin-2-ones.[17,18] Representative examples are illustrated in Scheme 3.

Using perfluorinated iodobutane as the electrophile combined with (hetero)aromatic boronic acids and phenylacetylene or pentynediol allowed for the isolation of enones 14–16 in good yields. Alkyl iodides containing longer perfluorinated chains could also be utilized as exemplified by compounds 17 and 18. Furthermore, applying ethyl α,α,α-bromodifluoroacetate, similar to the work shown in Schemes 1 and 2, generated the desired 1,5-ketoester 19 in a reasonable yield (55%). Interestingly, when 2-ethylhenanlines were investigated in the presence of a catalytic amount of boronic acid (for catalyst activation), the formation of the indolin-2-ones could be achieved as exemplified with the products 20 and 21.

The developed methodologies presented vide supra all relied on fluorinated electrophiles. The most popular fluorinated nucleophile is arguably the Ruppert-Prakash reagent (TMSCF3), which has been widely used for introducing a CF3 group into a plethora of organic compounds.[19] Given our interest in carbonylation and fluorination chemistry we sought to utilize this useful reagent in a carbonylative transformation. Notably, there are no examples of using TMSCF3 in carbonylation chemistry in the literature. This can most likely be ascribed to the instability of the trifluoromethyl anion formed in situ. A solution to this challenge is to form copper-ligated CF3 complexes, which have been studied by the groups of Hartwig and Grushin.[20] Wu and co-workers have recently published a carbonylative transformation of aryl iodides using stoichiometric ‘CuC3F7’ for accessing trifluoromethyl ketones.[21] Similar to this, the Grushin group have studied the formation of fluorinated ketones from acid chlorides and stoichiometric ‘CuC3F7 CF3’.[22] Since the free CF3 anion is not present in the above-mentioned strategies, addition to the electrophilic fluorinated ketone forming the corresponding hexafluoroisopropanol (HFIP) or decafluoroisopropanol derivatives was avoided. Nevertheless, a carbonylative approach relying on the double addition of TMSCF3 for accessing the HFIP motif would be interesting as compounds containing this motif display interesting inhibitory activity for the enzyme malonyl-CoA decarboxylase.[23] This goal was realized by applying a Pd-catalyzed carbonylative transformation of aryl bromides to the corresponding acid fluorides, developed by Manabe.[24]
followed by addition of two equivalents TMSCF₂, as shown in Scheme 4.[25]

5-Bromopyrimidine or 3,5-dibromopyrimidine could effectively be transformed to incorporate one or two HFIP groups, respectively, as shown with compounds 22 and 23. Fluorosulfates have recently emerged as reactive coupling partners for transition metal cross couplings including their use in the presence of a disilane which was a suitable electrophile for the ROMP polymerization process.[24] Considering the availability and cost of palladium, the development of similar carbonylations relying on catalysts prepared from less expensive Earth-abundant metals would be noticeably more desirable. In this respect, nickel is interesting being a masked aldehyde, an ethyl carboxylate, an olefin or a cyclopentyl ring could all form the corresponding ketones 35–37, respectively, as shown being as its carbon-13 labeled version when ¹³CQgen was applied. Ketones 31–37 were all prepared using a propyl organozinc reagent, however, other aliphatic Negishi reagents carrying a masked aldehyde, an ethyl carboxylate, an olefin or a cyclopentyl ring could all form the corresponding ketones 38–41 in high yields from 1-(bromomethyl)-4-(tert-butyl) benzene. The mechanism for the transformation is proposed to go through a catalytic cycle involving a bimetallic oxidative addition sequence as earlier demonstrated by Hu in his work on the use of Ni(ii)-pincer complexes for obtaining a better understanding of their reaction mechanisms.[34,35]

4. Conclusion

In this short account, we have presented some of our most recent findings in the pursuit of novel carbonylative transformations. Aromatic and aliphatic organoboron reagents could be coupled to α,α,α-trifluorinated aryl halides forming a range of α,α,α-trifluorinated β-ketoamides and esters. Furthermore, perfluorinated alky iodides could effectively be combined with CO, aryl boronic acids and alkynes in a four-component reaction providing access to perfluorinated enones and indolin-2-ones. Additionally, the Ruppert-Prakash reagent was demonstrated to participate in a carbonylative transformation forming aryl hexafluorooisopropanol derivatives in good yields from aryl bromides and fluorosulfates. Finally, a rare example of a Ni-catalyzed carbonylative cross-coupling for the construction of C(sp³)–C(sp³) ketones was demonstrated enabled by a new pincer ligand. Future work will focus on expanding both the methodologies and in particular for obtaining a better understanding of the operating mechanisms.

Scheme 3. Four-component reactions affording perfluorinated enones and indolin-2-ones.

Scheme 4. Pd-catalyzed carbonylative approach towards hexafluorooisopropanol-containing arenes.
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Conflicts of Interest

Troels Skrydstrup is co-owner of SyTracks a/s, which commercializes the two-chamber technology and COgen.

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Scheme 5. Ni-catalyzed carbonative Negishi cross-coupling for the synthesis of benzyl alkyl ketones.