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Isotope Labeling | Very Important Paper

# Nickel Catalyzed Carbonylative Cross Coupling for Direct Access to Isotopically Labeled Alkyl Aryl Ketones

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**Abstract:** Here we present an effective nickel-catalyzed carbonylative cross-coupling for direct access to alkyl aryl ketones from readily accessible redox-activated tetrachlorophthalimide esters and aryl boronic acids. The methodology, which is run employing only 2.5 equivalents of CO and simple Ni(II) salts as the metal source, exhibits a broad substrate scope under mild conditions. Furthermore, this carbonylation chemistry provides an easy switch between isotopologues for stable ($^{13}$CO) and radioactive ($^{14}$CO) isotope labeling, allowing its adaptation to the late-stage isotope labeling of pharmaceutically relevant compounds. Based on DFT calculations as well as experimental evidence, a catalytic cycle is proposed involving a carbon-centered radical formed via nickel(I)-induced outer-sphere decarboxylative fragmentation of the redox-active ester.

## Introduction

Isotopologues of pharmaceutical candidates enriched with $^{14}$C are important compounds necessary for modern drug development programs. They provide access to essential metabolism data of such candidates through in vivo studies in animals and humans, as well as providing an opportunity to explore their pharmacokinetic/pharmacodynamic properties and environmental fate.[1] Generally, carbon isotopes are preferred over other elements for isotope labeling because of the metabolic stability of the carbon skeleton, simplifying the interpretation of the generated data.[2] However, synthesis of $^{14}$C-isotopologues is generally more challenging than accessing the parent compound. Firstly, it is essential that the radiolabel is installed at a chemically and biologically stable position of the target molecule to track the fate of the drug candidate. Secondly, there is only a limited and expensive pool of radiolabeled starting materials available as a source for the radiolabeling. The corresponding stable $^{13}$C-isotopologues play important roles as internal standards for bioassays, as well as compounds for the assessment of a number of pharmacological properties.[3] Although the selection of $^{13}$C labeled precursors is significantly larger than those containing $^{14}$C, the synthetic challenges for installing the carbon isotope label in the correct position of the target candidate remains the same.

Carbonyl-containing functional groups, including carboxylic acids and esters, carboxamides and ketones constitute some of the most common motifs in pharmaceuticals and drug-like molecules.[4] Therefore, these groups represent ideal targets for late-stage carbon isotope incorporation, which has also been explored with various strategies, including dynamic exchange and low-pressure carbonylative cross-coupling methods.[5] One powerful strategy for the introduction of the desired carbon label relies on transition metal-mediated carbonylation chemistry applying stoichiometric $^{13/14}$C-isotopically labeled CO.[6] The CO itself may be generated from an appropriately labeled carbon monoxide

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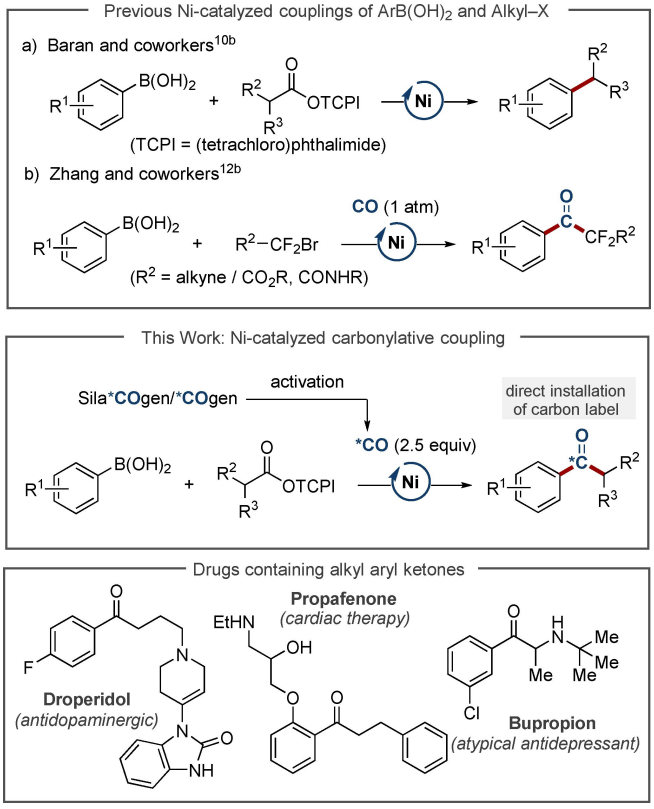
releasing molecule (CORM). We have earlier demonstrated the value of such a strategy for both alkoxy- and aminocarbonylations with aryl electrophiles,[7] but also for the installation of carbonyl groups onto $sp^3$ carbon centers.[8]

Suzuki cross couplings and amide bond forming reactions are some of the most abundantly employed chemical transformations in drug development research.[4,9] As a result, both alkyl carboxylic acids and aryl boronic acids are among the most widely used starting materials in organic synthesis. Therefore, the development of new cross-coupling reactions exploiting these inexpensive and abundant building blocks is highly attractive.[10] Carboxylic acids activated as redox-active esters can participate in single-electron transfer (SET) reactions providing access to open shell alkyl species via radical reductive decarboxylative fragmentation applying nickel catalysis.[11] Previously, the groups of Baran[10b,11a,b] and Zhang[12] demonstrated the use of commercially available homogeneous nickel-catalysts for the efficient cross-coupling of aryl boronic acids and alkyl electrophiles via alkyl radical intermediates (Scheme 1). Baran and co-workers reported the successful coupling of redox-active *N*-hydroxy (tetrachloro)phthalimide (TCNHPI) esters with aryl boronic acids applying a simple homogeneous nickel catalyst prepared from the commercially available bipyridine ligand 4,4'-di-*tert*-butyl-2,2'-bipyridyl (dtbbpy) and $NiCl_2 \cdot 6H_2O$.[10b] With a similar readily available nickel catalyst, Zhang and co-workers disclosed the carbonylative cross-coupling of difluoroalkyl bromides with aryl boronic acids under 1 atm of CO to form difluoroalkyl aryl ketones.[12b] Although successful, the reaction proved unrewarding for non-activated electrophiles, posing a challenge to develop general conditions for the synthesis of alkyl aryl ketones.

Considering the importance of alkyl aryl ketones as a common framework in a variety of active pharmaceutical ingredients (Scheme 1),[4,13] we wondered whether the previous methodology disclosed by Baran and his team[10b] could be adapted to carbonylation chemistry. If successful, such an approach would provide a rapid route to the corresponding isotopically labeled compounds through a nickel-catalyzed carbonylative cross-coupling between aryl boronic acids and alkyl carboxylic acids with stoichiometric amounts of CO released from an appropriate CORM.[14] Below, we describe the development and usefulness of this protocol as a platform for the late-stage synthesis and (radio)labeling of alkyl aryl ketones. Furthermore, mechanistic details of the catalytic cycle of the carbonylative cross coupling are revealed through DFT calculations, underlining the importance of alkyl radical intermediates generated from the redox-active ester, as well as a migratory insertion step of CO into a nickel aryl bond. The study also suggests that transmetallation of an aryl boronic acid onto a $Ni^I$ species is feasible, increasing the propensity of the nickel center to transfer a single electron to the redox-active ester.[8d,15]



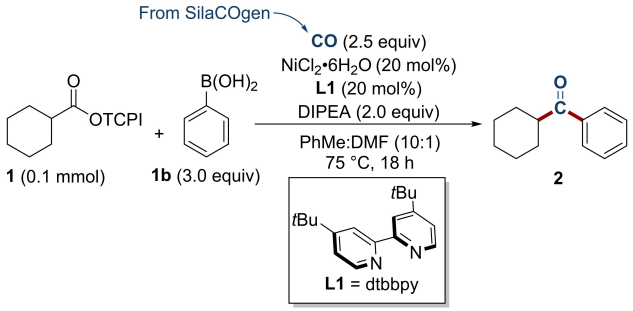

***Scheme 1.*** Ni-catalyzed cross-couplings of aryl boronic acids and alkyl electrophiles; Marketed drugs containing alkyl aryl ketones.

## *Results and Discussion*

Inspired by the previous reports from the groups of Baran[10b] and Zhang,[12] we were curious as to whether the Ni-catalyzed cross coupling of aryl boronic acids with activated alkyl esters could be readily adapted to carbonylation chemistry, thereby providing a general synthesis of alkyl aryl ketones. Furthermore, for its applicability to carbon isotope labeling, it is crucial that reaction conditions involving only stoichiometric quantities of carbon monoxide could be identified. As such, we initially investigated the carbonylative cross coupling of the activated ester of cyclohexane carboxylic acid (**1**) and phenylboronic acid (**1b**), applying the simple $NiCl_2 \cdot 6H_2O$ complex with the bipyridine ligand, dtbbpy, exactly as reported by Baran and co-workers.[10b] All reactions were run in the two chamber reactor, COware®. SilaCOgen was used as the CO releasing precursor in all cases except for the studies related to $^{14}C$-labeling, whereby COgen was employed because of its easier synthesis as a $^{14}CO$ precursor. The yields of the optimization reactions were obtained by GC analysis compared to an internal standard.[14b,d]

After an extensive initial optimization of this transformation, with some of the results revealed in Table 1, we were able to successfully obtain the phenyl cyclohexyl ketone **2** in a 60% yield (entry 1). The best yield was observed with 2.5 equivalents of SilaCOgen along with DIPEA as base and with a solvent mixture of toluene : DMF (10 : 1). Alternative conditions including exchange of toluene for other solvents (entries 2–4) or increasing the number of

***Table 1:*** Initial reaction optimization.



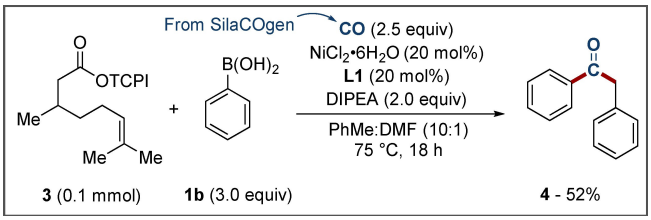

| Entry | Deviations from above conditions | Yield [%][a] |
|---|---|---|
| 1 | None | 60 |
| 2[b] | 1,4-dioxane instead of PhMe | 42 |
| 3[b] | THF instead of PhMe | 18 |
| 4[b] | DMF instead of PhMe | <5 |
| 5 | DIPEA (10.0 equiv) | 54 |
| 6 | without base | <5 |
| 7 | $Et_3N$ (5.0 equiv) | 39 |
| 8 | $K_2CO_3$ (10.0 equiv) | <5 |
| 9[c] | NHPI ester instead of **1** | <5 |
| 10[c] | PhBpin instead of **1b** | <5 |
| 11[c] | $NiCl_2$ instead of $NiCl_2 \cdot 6H_2O$ | 7, 41[d] |
| 12[c] | $NiCl_2$(dme) instead of $NiCl_2 \cdot 6H_2O$ | 18, 48[d] |
| 13 | 1.5 equiv. CO | 56[e] |
| 14 | PhH instead of PhMe | 63 (61)[f] |

[a] Yields were determined by GC-FID with *n*-tridecane as internal standard. [b] Using $Et_3N$ (10.0 equiv) instead of DIPEA. [c] Using 10.0 equiv. DIPEA instead of 2.0 equiv. [d] With $H_2O$ (1.2 equiv). The full optimization can be found in the Supporting Information. [e] An increase in the direct coupling product was observed by GC–MS analysis compared to that of 2.5 equiv. [f] Isolated yield in brackets.

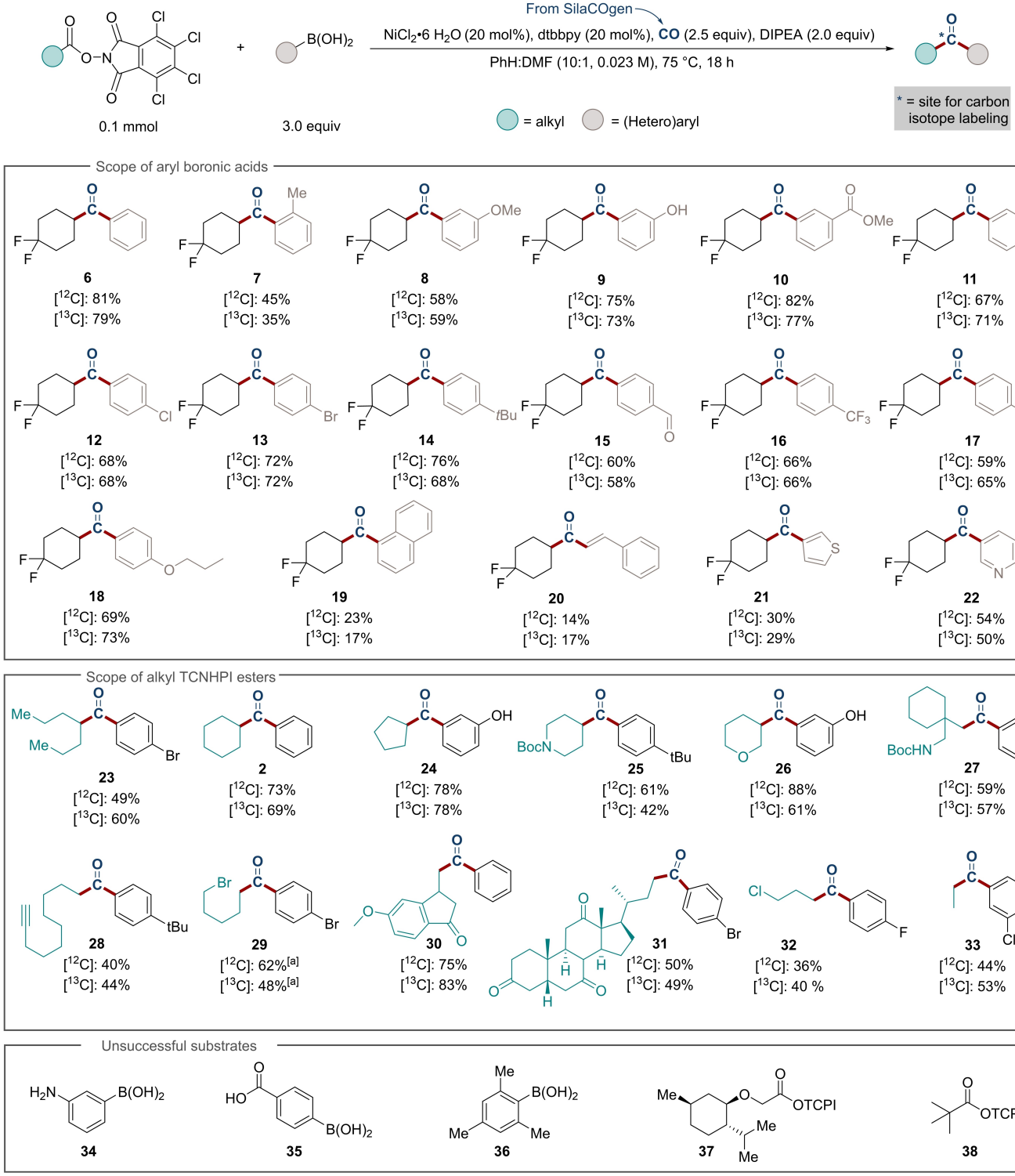
equivalents of DIPEA (entry 5) did not lead to an improved yield of ketone **2**. Leaving out the base or exchanging DIPEA for triethylamine or potassium carbonate (entries 6–8) were unrewarding. No product formation was observed when the reaction conditions were applied to the more electron-rich redox-active NHPI ester (entry 9). Similarly, substituting phenylboronic acid with its pinacol ester derivative yielded no ketone product (entry 10). Moreover, different $Ni^{II}$ sources were also evaluated in anhydrous forms as well as with the addition of water. While anhydrous $NiCl_2$ provided a low yield of 7%, the addition of $H_2O$ (1.2 equiv) almost restored reactivity (entry 11). The same effect was observed when $NiCl_2 \cdot$dme was applied (entry 12), highlighting the importance of water in the coupling reaction. Using only 1.5 equiv. CO lowered the yield of the carbonylated product compared to that with 2.5 equiv. (entry 13). When excluding CO from the reaction conditions, the direct cross-coupling product could be isolated (see Supporting Information Scheme S3).

During these initial screening experiments, using the TCNHPI ester of citronellic acid **3** we discovered that a significant amount of the toluene-coupled side-product **4** was formed when using toluene as solvent (Scheme 2). This undoubtedly originates from hydrogen abstraction of toluene by reactive radical intermediates formed under the reaction conditions (for more information, see Supporting Information). An analogous side-reaction was previously observed by the Fu and co-workers in the nickel-catalyzed Suzuki arylation of tertiary alkyl bromides using toluene rather than benzene as the solvent.[16] To avoid this parasitic reaction, we turned to the use of benzene, which slightly improved the GC yield of **2**, resulting in a 61% isolated yield of ketone **2** (Table 1, entry 14).

With these reaction conditions in hand, attention was turned towards the substrate scope of the carbonylative nickel-catalyzed cross-coupling reaction. First, the structural diversity of the aryl boronic acid coupling partner was investigated (Scheme 3, top). The TCNHPI ester of 4,4-difluorocyclohexanecarboxylic acid (**5**) was chosen as the coupling partner due to its ease in identification with $^{19}F$ NMR spectroscopy. Various boronic acids coupled successfully to **5**, providing the alkyl aryl ketones **6**–**22**. The coupling with the simplest aryl boronic acid, phenylboronic acid, provided the corresponding coupling product **6** in 81% yield. The introduction of an *ortho* substituent appeared




***Scheme 2.*** Unwanted side-reaction in toluene.



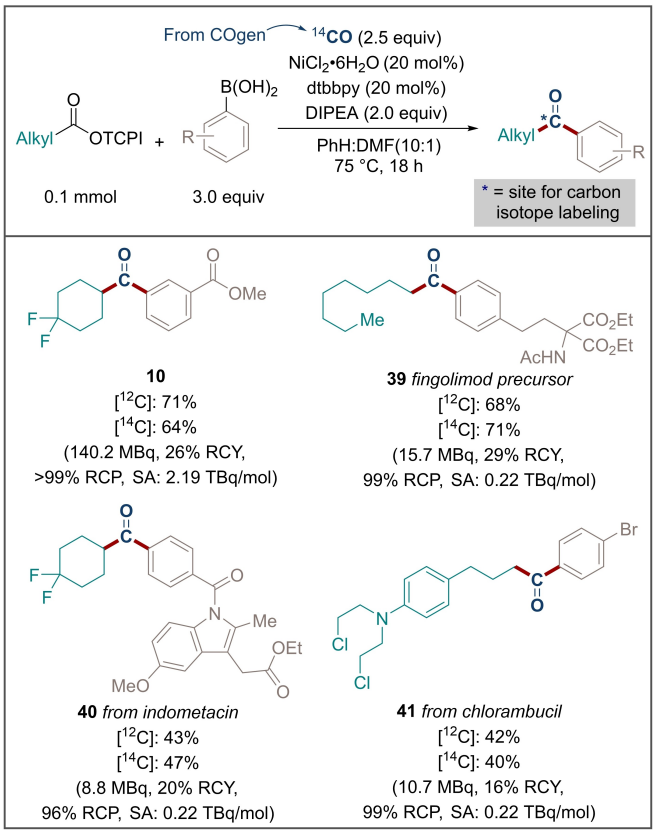

***Scheme 3.*** Reaction scope. [a] With $NiBr_2 \cdot 6H_2O$ (20 mol%) instead of $NiCl_2 \cdot 6H_2O$ (20 mol%). All experimental details can be found in the Supporting Information.

more sterically challenging as alkyl aryl ketone **7** was obtained in only 42% yield. Subsequently, *meta*-substituted aryl boronic acids were investigated. Interestingly, (3-methoxyphenyl)boronic acid was significantly more challenging to the method than (3-hydroxyphenyl)boronic acid, yielding **8** and **9** in 58% and 75%, respectively. The steric and electronic effects of hydroxyl and methoxy groups are similar, so this discrepancy suggests that the phenolic proton assists the reactivity and causes a higher yield compared to the phenolic ether. (3-(Methoxycarbonyl)phenyl)boronic

acid was also well tolerated, and the corresponding ketone **10** could be isolated in a good 82 % yield. Thus, both electron-donating and electron-withdrawing substituents in the *meta* position operate well in the reaction. Next, various *para* substituents were investigated. As demonstrated by substrates **11**–**13**, halides proved to be suitable substituents, providing the alkyl aryl ketones in 67 %, 68 %, and 72 % yields, respectively. Additionally, the bulky *tert*-butyl substituent had no considerable effect on the outcome of the reaction, resulting in a 76 % yield of **14**. Boronic acids bearing electron-withdrawing *para*-substituents afforded the corresponding alkyl aryl ketones in moderate yields, and compounds **15**–**17** were obtained in 60 %, 66 %, and 59 % yields, respectively. Additionally, 4-propoxyphenylboronic acid bearing an electron-donating *para* substituent afforded the corresponding alkyl aryl ketone **18** in a yield of 69 %. Accordingly, as for the *meta* substitution, both electron-donating and electron-withdrawing substituents were tolerated in the *para* position. Like *o*-tolylboronic acid the sterically demanding nature of naphthalen-1-ylboronic acid appeared to significantly affect the outcome of the coupling reaction, resulting in a relatively low yield of compound **19**. In addition to boronic acids based on benzene scaffolds, styryl and hetereoaromatic boronic acids were tolerated in the cross-coupling reaction although in modest yields. Thus, the coupling of (*E*)-styryl boronic acid provided **20** in a 14 % yield. Thiophene and pyridine based boronic acids could also be coupled, giving **21** and **22** in 30 % and 54 %, respectively.

Subsequently, the substrate scope with respect to the TCNHPI esters was investigated (Scheme 3, middle). Simple acyclic and cyclic secondary ester substrates performed well in the carbonylation reaction and provided the corresponding coupling products **23**, **2**, and **24** in yields of 49 %, 73 %, and 78 %, respectively. Moreover, the reaction is largely unaffected by various functional groups, including Boc-carbamates and ethers, as shown by the formation of alkyl aryl ketones **25** and **26** in yields of 61 % and 88 %. Esters of primary carboxylic acids were also well tolerated. Indicatively, compound **27** bearing a Boc-carbamate was obtained in 59 % yield. In addition, the reaction is also orthogonal to alkynes, as demonstrated by the isolation of substrate **28** in a 40 % yield, opening up for possible sequential radical cross-coupling and click reactions. In order to probe the chemoselectivity of the coupling reaction, a substrate containing both a TCNHPI-ester and an alkyl bromide was synthesized. $NiBr_2$ with the addition of $H_2O$ was used instead of $NiCl_2 \cdot 6H_2O$ as the nickel source to avoid halogen exchange between the catalyst and the substrate. Complete chemoselectivity was observed for the TCNHPI ester, and **29** was isolated in 62 % yield, demonstrating the orthogonality to other cross-couplings, and highlighting the prospect of sequential couplings. Additionally, the methodology was successful for more complex redox-active esters. Thus, **30** was isolated in 75 % yield, and the ester of dehydrocholic acid could also be successfully coupled, giving ketone **31** in a 50 % yield. Furthermore, the ketones **32** and **33** were prepared in 36 % and 44 % yield in preparation for the synthesis of the active pharmaceutical ingredients bupropion and droperidol.

Some substrates were unsuccessful in the coupling reaction (Scheme 3, bottom). Boronic acids of aniline **34** and carboxylic acids **35** as well as sterically encumbered aryl boronic acid **36** failed. α-Oxy and tertiary TCNHPI esters **37** and **38** also showed no or severely diminished reactivity. A full overview of substrates that proved unfruitful is presented in the Supporting Information. Next, the potential of the methodology for late-stage radiolabeling of drug-like molecules and pharmaceuticals was investigated (Scheme 4). To incorporate a $^{14}C$ label, $^{14}$COgen (for its synthesis, see Supporting Information) was used instead of SilaCOgen and the labeled alkyl aryl ketone products were purified by HPLC instead of automated flash column chromatography. The simple substrate **10** together with COgen was first chosen to ensure that both procedure modifications would not significantly affect the yield before moving to the radiolabeling with $^{14}$COgen. Fortunately, these modifications only decreased the coupling yield from 82 % (Scheme 3) to 71 %. Motivated by this result, $^{12}$COgen was replaced by $^{14}$COgen, and **[$^{14}$C]-10** was isolated in a satisfactory yield of 64 % (140.2 MBq, 26 % RCY, >99 % RCP, SA: 2.19 TBq/mol). To reduce the radioactive waste, $^{14}$COgen was diluted with unlabeled $^{12}$COgen. Thereafter 10 % $^{14}$COgen in $^{12}$COgen was used with a specific activity of 0.220 TBq/mol for the subsequent reactions. As a viable candidate for our



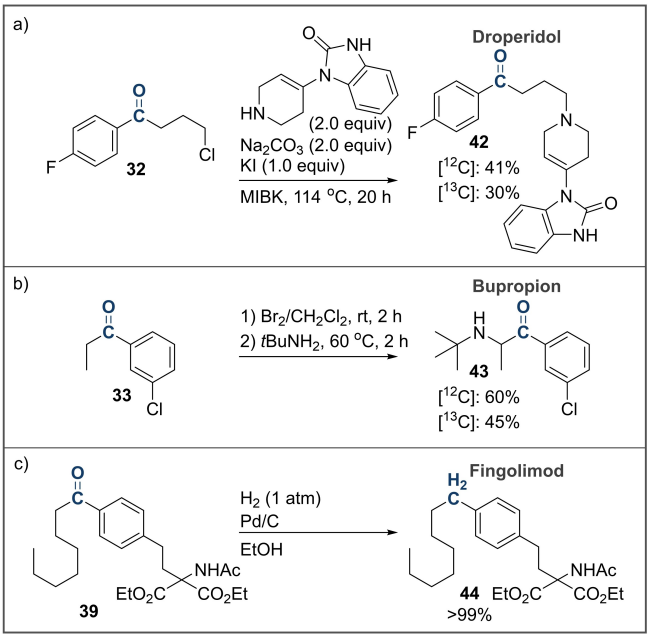

***Scheme 4.*** Radiolabeling of pharmacologically relevant compounds. Diluted $^{14}$COgen ($^{14}C/^{12}C$: 10:90) was used to reduce radioactive waste.

$^{14}$C labeling cross-coupling, we identified **39** (Scheme 4), which is a precursor of the immunomodulatory drug fingolimod.[17] Applying diluted $^{14}$COgen provided access to **[$^{14}$C]-39** isolated in 71 % yield (15.7 MBq, 29 % RCY, 99 % RCP, SA: 0.22 TBq/mol) with the expected specific activity within the error margin. Derivatives of two other FDA-approved drugs were also prepared as their $^{14}$C-isotopologues via this late-stage isotope incorporation. First, the nonsteroidal anti-inflammatory drug indometacin was borylated and then used as a coupling partner in the carbonylative cross-coupling reaction. The reaction yielded the coupled product **[$^{14}$C]-40** in 40 % yield (8.8 MBq, 20 % RCY, 96 % RCP, SA: 0.22 TBq/mol).

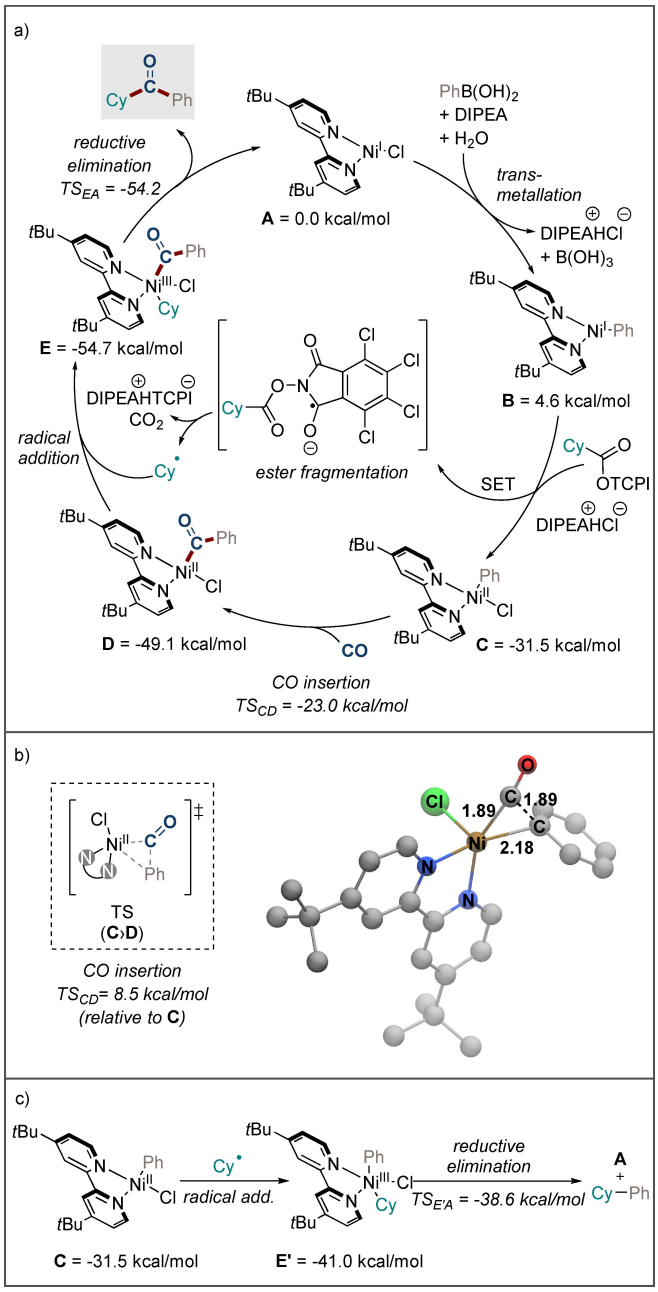
In addition, the TCNHPI ester of the anticancer agent chlorambucil was applied to the reaction conditions, resulting in the successful labeling and isolation of **[$^{14}$C]-41** in 40 % yield (10.7 MBq, 16 % RCY, 99 % RCP, SA: 0.22 TBq/mol).

The ketones **32**, **33** and **39** were employed to form pharmaceuticals droperidol and bupropion, as well as fingolimod with standard protecting groups (Scheme 5). Thus, ketone **32** was transformed into droperidol (**42**) in a 41 % yield by a substitution reaction (Scheme 5a). **33** was subjected to a one-pot $\alpha$-bromination and subsequent substitution with *t*-BuNH$_2$ to form bupropion (**43**) in a 60 % overall yield (Scheme 5b). Ketone **39** could be subjected to catalytic hydrogenation, affording the protected fingolimod (**44**) in >99 % yield (Scheme 5c). This high-yielding hydrogenation under mild conditions highlights the option for using our carbonylative cross-coupling method for isotope labeling of alkylbenzenes in addition to alkyl-aryl ketones.

To obtain a better understanding of the underlying mechanistic details, we performed state-of-the-art DFT calculations (PBE0-D3(BJ)[IEFPCM]), specifically probing the reaction between phenylboronic acid **1b** and cyclohexyl TCNHPI ester **1** as the model system. Four alternative mechanisms (I–IV) were evaluated, with the most plausible catalytic cycle (mechanism I) presented in Scheme 6a (see Supporting Information for alternative pathways).




***Scheme 5.*** Synthesis of pharmaceuticals via alkyl-aryl ketones.




***Scheme 6.*** Proposed catalytic cycle based on DFT calculations (mechanism I). a) Proposed catalytic cycle for the Ni-catalyzed cross-coupling in the presence of CO leading to cyclohexyl phenyl ketone. The energy reference state is A, which comprises Ni(I)-Cl, TCNHPI, phenylboronic acid, and CO. b) The optimized TS geometry for CO insertion. The C–C bond forming atoms are connected by a black dotted line. Distances are given in Å and hydrogen atoms are omitted for clarity. c) Formation of phenylcyclohexane product in the absence of CO. Free energies are at 298 K (kcal/mol, PBE0-D3(BJ)/pc-2,SDD[Ni](PCM)//PBE0-D3(BJ)/pc-1,SDD[Ni](PCM)).

The proposed catalytic cycle is initiated from the $Ni^{I}Cl$ species **A**. This may be generated in situ by double transmetallation of $Ni^{II}Cl_2$ and boronic acid with subsequent reductive elimination and comproportionation of the resulting $Ni^0$ species with another $Ni^{II}Cl_2$ species.[18] Subsequently, transmetallation of the aryl boronic acid onto the nickel center occurs, assisted by $H_2O$ and the base. The generated nickel-phenyl species **B** has a relative energy of 4.6 kcal/mol. Subsequent SET from **B** to the TCNHPI ester and recoordination of the chloride ion forms the $Ni^{II}$ species **C** with a relative energy of −31.5 kcal/mol. The reduced TCNHPI ester is proposed to undergo radical fragmentation releasing $CO_2$, tetrachlorophthalimide anion ($TCPI^-$) and a cyclohexyl radical, making the overall reaction to **C** irreversible. Radical trapping experiments (see below) support the presence of a free cyclohexyl radical in the reaction mixture. Meanwhile, species **C** can undergo feasible CO insertion with a computed barrier of 8.5 kcal/mol relative to **C**, producing $Ni^{II}$(acyl) intermediate **D**.The corresponding TS geometry for CO insertion is shown in Scheme 6b.

Species **D** has a lower energy than **C**, making it a relevant candidate for the catalyst resting state, in agreement with earlier studies indicating a $Ni^{II}$ species as the predominant resting state in a nickel-catalyzed arylation reaction.[15c] As **D** is more abundant compared to other intermediate species, it is sensible that the cyclohexyl radical attacks **D** in a diffusion-controlled process to produce the $Ni^{III}$ species **E**. The subsequent reductive elimination is proposed to be rapid, with a computed barrier of only 0.5 kcal/mol (relative to **E**), producing the alkyl aryl ketone product and concluding the catalytic cycle by reforming the active Ni(I) species **A**. Since **D** may have a relatively large concentration, it is not likely that exactly the same metal center first undergoes SET as species **B** and later recombines with the formed radical as species **D**. Rather, two distinct metal centers may be involved in these steps for one radical species.[10b,15c,19]

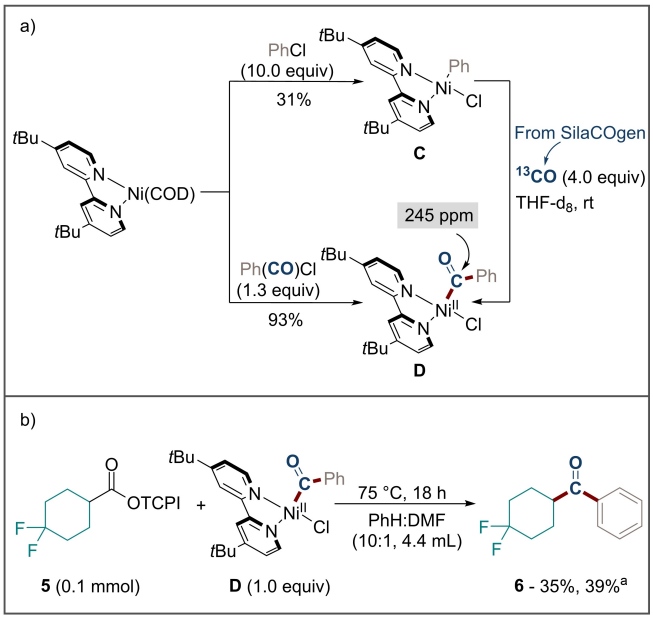
It has previously been shown that at low concentrations or in absence of CO, the non-carbonylated phenylcyclohexane product can be formed (Scheme S3).[10b] To elucidate this computationally, the binding of the cyclohexyl radical to **C**, forming $Ni^{III}$ phenyl species **E′** was computed (Scheme 6c). A subsequent reductive elimination generates the phenylcyclohexane product and **A** with a barrier of 2.4 kcal/mol relative to **E'**. Our computational results indicate that in absence of CO, formation of phenylcyclohexane is feasible, which concurs with our experimental evidence. However, in presence of sufficient concentrations of CO, **C** will be transformed into **D**, which will combine with the radical to generate the thermodynamically preferred **E**, thereby suppressing the formation of phenylcyclohexane.

To gain additional mechanistic insights and to support key steps in the proposed catalytic cycle, several experiments were conducted. First, the aryl nickel complex **C** and acyl nickel complex **D** were prepared via oxidative addition of $Ni(COD)_2$ into the corresponding electrophiles. Migratory insertion of CO into **C** to form **D** proceeded at room temperature and a CO pressure of ca. 0.5 bar, as evidenced by the appearance of a signal at 245 ppm in the $^{13}C$ NMR spectrum (Scheme 7a). Two additional $^{13}C$ NMR signals, resulting from benzophenone and benzoyl chloride at 197.0 and 164.9 ppm respectively appeared under these reaction conditions (see Figure S1).

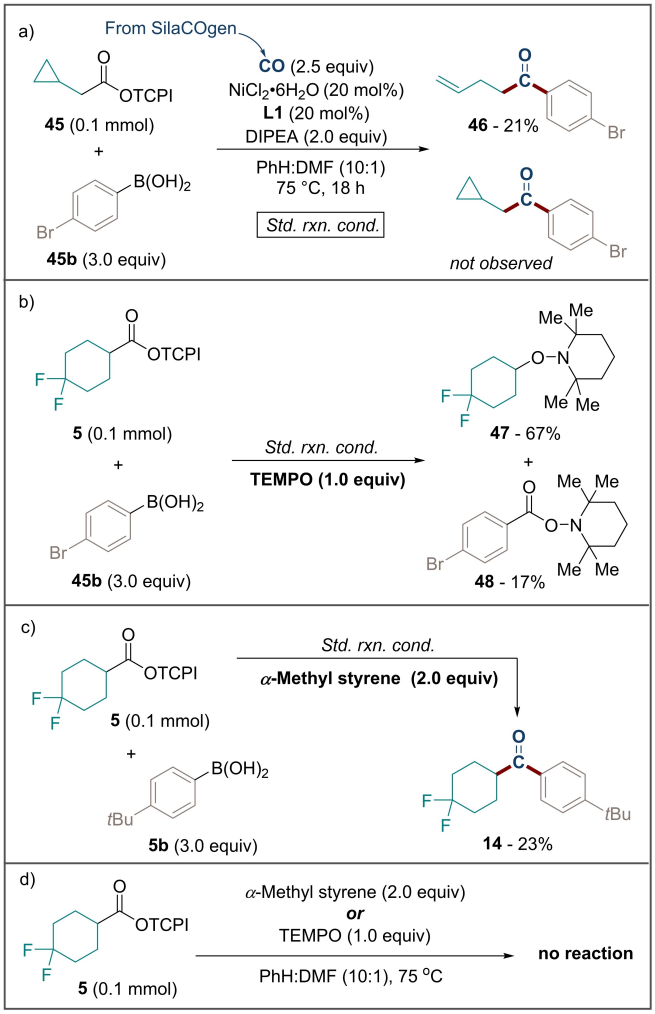
Next, a stoichiometric amount of complex **D** was combined with difluorocyclohexyl TCNHPI ester **5** in the absence and presence of $H_2O$ (5.6 equiv), forming the desired product **6** in 35 % and 39 % yields, respectively (Scheme 7b). These yields correspond to approximately half the yield of a standard reaction, which can be explained by the fact that SET occurs from $Ni^{I}$ (see Supporting Information for discussion and plausible mechanistic pathway, Scheme S2). The results presented in Scheme 7 are consistent with the DFT calculations, indicating a reaction sequence where alkyl aryl ketone **6** is formed from the acyl nickel species **D**, which in turn is generated by carbonylation of the aryl nickel species **C**.

Radical inhibition experiments confirmed the presence of a carbon-centered radical formed from the TCNHPI ester (Scheme 8). The reaction of cyclopropyl methyl TCNHPI ester **45** with (*p*-bromophenyl)boronic acid **45b** resulted in the formation of the ring-opened product **46** in 21 % yield with no observed cyclopropyl-containing product, demonstrating radical formation upon decarboxylative fragmentation of the redox-active ester, concurrent with the general consensus in the literature and the early work by Oda and Okada (Scheme 8a).[10b,20] The lower yield is in agreement with radical ring-opening experiments performed on similar systems.[10b,12b] When 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was added to the reaction of TCNHPI ester **5** and **45b**, no formation of the desired product was observed.

However, two TEMPO-intercepted products, **47** and **48**, derived from an alkyl and an aryl acyl radical, were isolated in 67 % and 17 % yields respectively (Scheme 8b). The




***Scheme 7.*** Experimental control experiments of intermediates involved in the carbonylation reaction. [a] With $H_2O$ (5.6 equiv).




***Scheme 8.*** Experiments probing radical intermediates. a) Radical cyclopropane ring-opening. b) Radical trapping with TEMPO. c) Radical trapping with α-methyl styrene. d) No fragmentation in the absence of nickel.

addition of α-methyl styrene to the reaction mixture of **5** and **5b** dramatically decreased the yield of the reaction (Scheme 8c).[12a] Next, the fragmentation of the TCNHPI ester was investigated in the absence of a nickel catalyst. In this case, no decarboxylative fragmentation of **5** to a carbon-centered radical was observed, suggesting that formation of an open-shell carbon species via thermal bond homolysis is not a reasonable mechanism (Scheme 8d). GC–MS analysis of the crude reaction mixture showed only the radical trap ( $\alpha$-methyl styrene or TEMPO, respectively), the TCNHPI ester, and tetrachlorophthalimide. Tetrachlorophthalimide presumably forms through thermal decomposition in the GC inlet (300 °C) since no intercepted radical was observed. These experiments substantiate the claim of a nickel-induced radical formation from the redox-active esters by a SET pathway. The observation of lowered reactivity with radical traps present in solution indicates that the carbon-centered radicals formed upon reductive decarboxylation are free in solution to some extent, making an outer-sphere mechanism functional. This agrees with the proposed mechanism (Scheme 6a) where radical fragmentation is independent of the metal center.[19a,b]

## Conclusions

In conclusion, a commercially available nickel bipyridine catalyst performed well in the decarboxylative-carbonylative cross-coupling reaction between aryl boronic acids and redox-activated alkyl carboxylic acids. The methodology is easily tuned to incorporate carbon isotope labels into the formed alkyl aryl ketones. Computational DFT and experimental investigations revealed the mechanistic involvement of carbon-centered radicals formed via nickel-induced outer-sphere decarboxylative fragmentation of TCNHPI esters. The CO insertion into an intermediate complex was feasible, leading to selectivity for the ketone product even at low CO pressures. This mechanistic insight contributes important knowledge to Ni-catalyzed cross-coupling reactions employing redox-active esters as coupling partners.

The investigation of the substrate scope revealed the compatibility of several aryl boronic acids and TCNHPI esters as coupling partners. A wide range of aryl boronic acids, with electron-donating or electron-withdrawing substituents exhibited moderate to good yields of the corresponding coupled product. The impact of steric hindrance in the *ortho* position was observed, with bulky substituents significantly affecting the outcome of the coupling reaction. Primary and secondary TCNHPI esters performed well, and the reaction exhibited compatibility with a wide range of functional groups and complex redox-active esters. In addition, a $^{14}C$ label was successfully incorporated into pharmaceutically relevant compounds using $^{14}CO$gen, demonstrating the compatibility of the reaction with radiolabeling strategies.

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## Conflict of Interest

Troels Skrydstrup is co-owner of SyTracks A/S, which commercializes the two-chamber system (COware), SilaCOgen and COgen.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Carbonylation · Carbon isotope labeling · Ketones · Nickel · Catalysis


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# Research Article

*Isotope Labeling*

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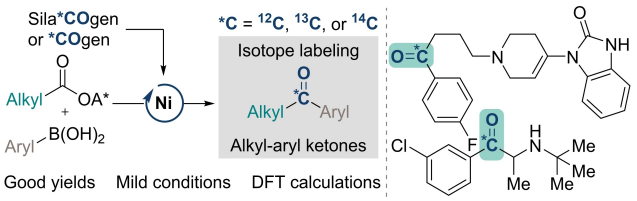
Nickel Catalyzed Carbonylative Cross Coupling for Direct Access to Isotopically Labeled Alkyl Aryl Ketones




The development of an effective nickel-catalyzed carbonylative cross coupling of redox-activated alkyl carboxylic acids and aryl boronic acids is presented. A wide variety of alkyl aryl ketones is obtained in good yields, and the chemistry is easily applicable to stable and radiocarbon isotope labeling. The mechanism of the transformation has been investigated applying experimental and DFT methods.