Organic Syntheses

Discussion Addendum for:

Pd-Catalyzed External-CO-Free Carbonylation: Preparation of 2,4,6-Trichlorophenyl 3,4-Dihydronaphthalene-2-Carboxylate

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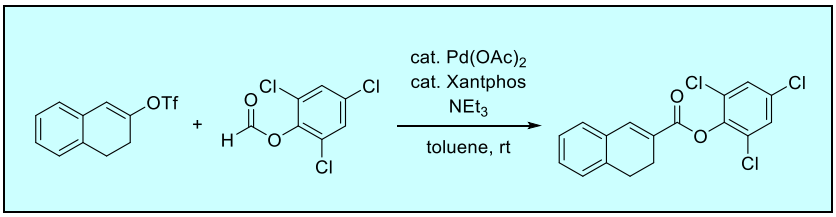

Transition-metal-catalyzed carbonylation using carbon monoxide (CO) has been recognized as a powerful tool for the installation of a carbonyl group.[2–4] While CO gas is industrially used as an inexpensive chemical feedstock, its use is inevitably accompanied by safety requirements for conducting reactions with special caution and handling techniques because of its gaseous and toxic nature. Such disadvantages limit the use of CO gas, often rendering the catalytic carbonylation reaction impractical, especially on laboratory scale.

One promising strategy to avoid the use of CO gas is the development of CO surrogates.[5–9] These are non-gaseous compounds that generate CO by chemical reactions or physical stimuli. Once CO is formed from CO surrogates inside a closed reaction vessel, it can be efficiently consumed by the carbonylation reactions. Thereby, exposure to CO gas can be avoided during the reactions. Since most CO surrogates are less toxic than CO gas, they are considered to be potentially safe and practical substitutes for CO gas for use in carbonylation reactions. It is also advantageous that CO surrogates

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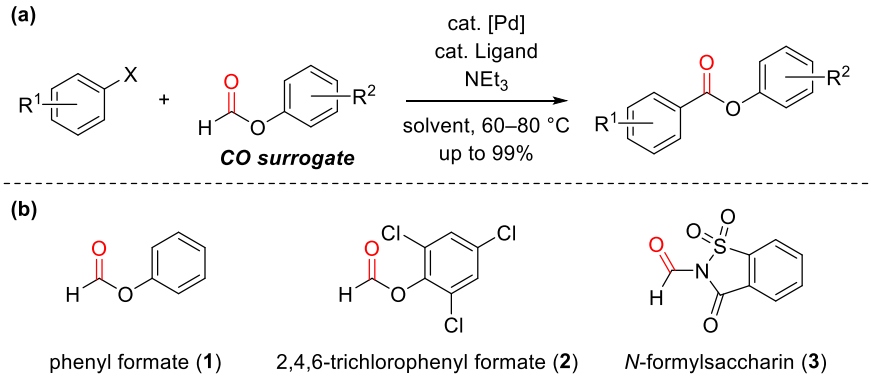
can be weighed easily, compared with CO gas; this enables the use of near-stoichiometric amounts of CO surrogates.

The groups of Manabe[10] and Tsuji[11] independently developed aryl formates like phenyl formate (**1**) as a new type of CO surrogate suitable for the Pd-catalyzed external-CO-free aryloxycarbonylation of haloarenes (Scheme 1(a)). In this reaction, aryl formates play dual roles as sources of CO and nucleophilic phenols, where both compounds are efficiently incorporated into aryl esters. Later, our group discovered that 2,4,6-trichlorophenyl formate (**2**) and *N*-formylsaccharin (**3**) are stable but more reactive CO surrogates (Scheme 1(b)) for aryloxycarbonylation,[12] reductive carbonylation,[13] and fluorocarbonylation.[14]



Scheme 1. (a) Pd-catalyzed aryloxycarbonylation of haloarenes and (b) aryl formates and *N*-formylsaccharin as CO surrogates

At the time our procedure was published in *Organic Syntheses* (2014) describing the Pd-catalyzed external-CO-free carbonylation using 2,4,6-trichlorophenyl formate,[15] aryl formates and *N*-formylsaccharin were increasingly applied as CO surrogates in various synthetic organic chemistry fields. In this Discussion Addendum, we describe the fundamental features of aryl formates and *N*-formylsaccharin, as well as the advances made in their chemistry as CO surrogates since our initial reports.[10,12,13]

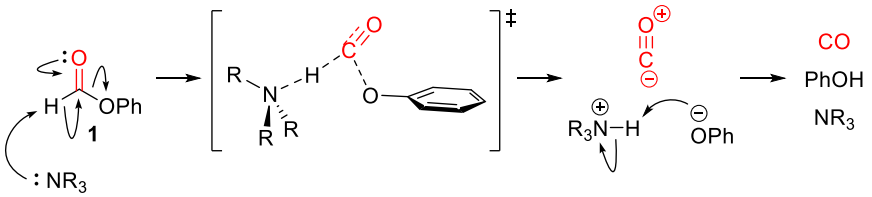
Merits of Aryl Formates and Mechanism of CO Generation

Some aryl formates are commercially available, although at high prices. The alternative is to consider their in-house preparation, especially for planning syntheses on larger scale. Aryl formates are easily synthesized by

the single-step formylation of the corresponding phenols. After mixing formic acid and acetic anhydride to form acetic formic anhydride at 60 °C, phenols and sodium acetate are added at room temperature to afford the desired aryl formates after aqueous work-up and recrystallization or distillation.[15] Metal-catalyzed preparation methods have also been reported.[16]

The most striking feature of 2,4,6-trichlorophenyl formate (**2**) and *N*-formylsaccharin (**3**) compared to other CO surrogates is the mild reaction conditions required for CO generation. While conventional CO surrogates require harsh conditions like high temperature, a transition metal catalyst, and a strong acid/base, our CO surrogates **2** and **3** generate CO in the presence of a weak base like triethylamine within 30 min at room temperature, despite their highly crystalline and stable nature.[12,13] Neither special apparatus nor the activation of the CO surrogates are required, providing a simple and convenient carbonylation setup. The mild reaction conditions contribute to the broadening of functional group compatibility and the suppression of undesired side reactions, which significantly increases the feasibility of the carbonylation process.

Our mechanistic study of CO generation from phenyl formate (**1**) revealed that abstraction of formyl proton by a weak base like trialkylamine triggers the simultaneous formation of CO and phenoxide in a concerted bimolecular α-elimination fashion (Scheme 2).[17] The base works catalytically, and the use of stronger bases or polar solvents accelerates the CO generation. The introduction of electron-withdrawing groups into phenyl formate also enhances its reactivity, which rationalizes the higher reactivity of 2,4,6-trichlorophenyl formate (**2**) compared to that of **1**. Importantly, the rate of CO generation can be actively controlled by adjusting the reaction conditions and changing the structure of the aryl formates. Indeed, we have succeeded in performing room-temperature carbonylation of iodoarenes using **1** that previously required a high temperature (80 °C) for CO generation.[17]

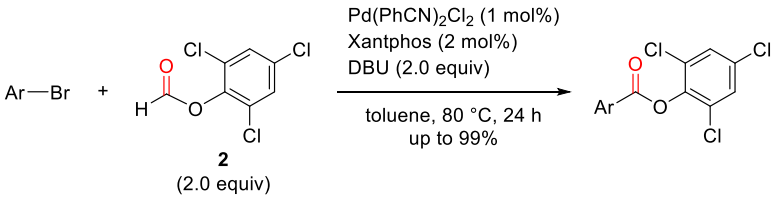


Scheme 2. Mechanism of CO generation from 1

It is noteworthy that a simple aqueous work-up is sufficient for removal of excess trichlorophenol in both the preparation and reaction of 2,4,6-trichlorophenyl formate (**2**). As mentioned in the original *Organic Syntheses* procedure,[15] alkali washing enables the easy separation of the desired aryl esters from trichlorophenol, and this also applies for most aryl formates and *N*-formylsaccharin (**3**).

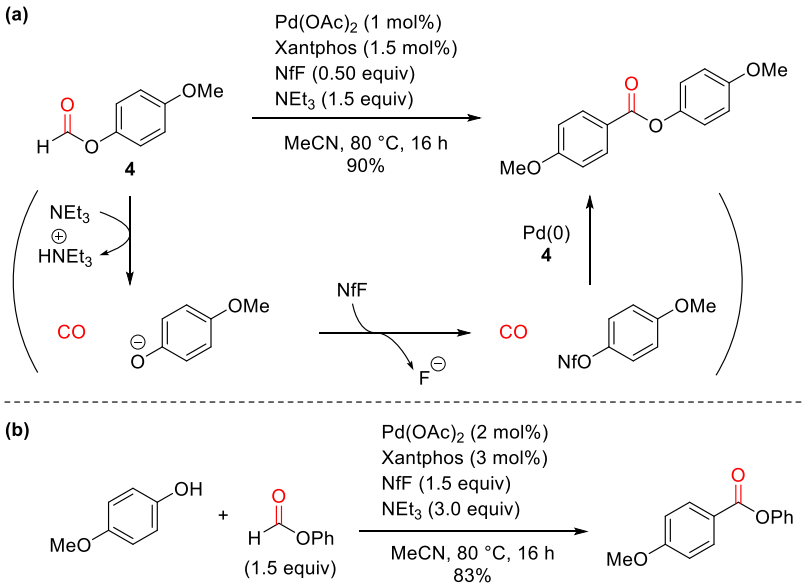
Synthesis of Aryl Esters and Their Use in Synthetic Organic Chemistry

In the initial study on the catalytic aryloxycarbonylation using 2,4,6-trichlorophenyl formate (**2**), the reaction of iodoarenes proceeded smoothly at room temperature. However, bromoarenes required both a higher temperature (100 °C) and the slow addition of the solution of **2** (3 h). Recently, we improved the reaction conditions by replacing the slow addition technique for the reaction of bromoarenes (Scheme 3). While a high temperature (80 °C) was still required, probably due to the slower oxidative addition of bromoarenes to Pd(0) compared to that of iodoarenes, the catalyst loading could be reduced to 1 mol% without any loss of reactivity.[18]



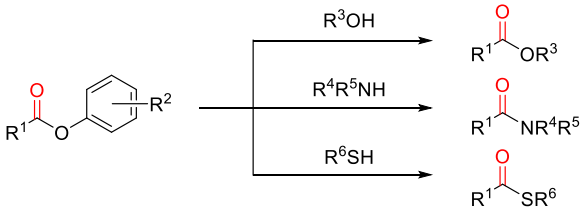
Scheme 3. Catalytic aryloxycarbonylation of bromoarenes using 2

Beller, Wu, and coworkers have reported that aryl formates act as both precursors of electrophiles and carbonylating agents (Scheme 4(a)).[19] The reaction of aryl formate and triethylamine generates CO and phenoxide, and the latter reacts with perfluorobutanesulfonyl fluoride (NfF) to form a sulfonate electrophile, a substrate for catalytic aryloxycarbonylation. Some phenols were also applied for *in-situ* formation of aryl sulfonates that were carbonylated to afford phenyl esters, obviating the preparation of the sulfonate electrophiles (Scheme 4(b)).

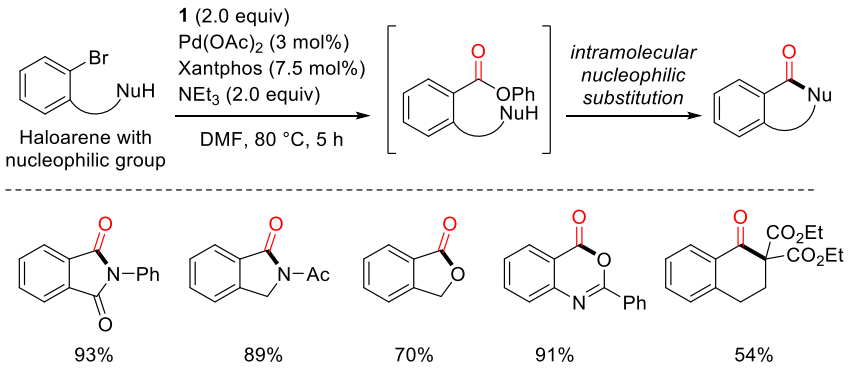


Scheme 4. (a) Catalytic aryloxycarbonylation using aryl formate and NfF and (b) aryloxycarbonylation of phenol

Since aryl esters, products of catalytic aryloxycarbonylation, are electronically activated toward a nucleophilic attack, various carbonyl compounds, such as esters, amides, and thioesters are obtained by the reaction with nucleophiles (Scheme 5). It is also feasible to perform the inter- or intramolecular nucleophilic substitution after the aryloxycarbonylation in a one-pot procedure. We demonstrated the latter synthetic strategy using phenyl formate (**1**) and haloarenes containing nucleophilic moieties to create cyclic carbonyl compounds (Scheme 6).[20] It was confirmed that the corresponding phenyl ester is actually a reaction intermediate by quenching the reaction before completion. Likewise, several (hetero)cyclic carbonyl compounds were synthesized via the formation of phenyl esters.[21–23]

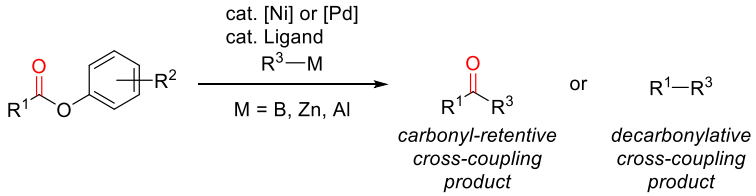


Scheme 5. Nucleophilic substitution of aryl esters



Scheme 6. Aryloxycarbonylation/intramolecular nucleophilic substitution for the synthesis of cyclic carbonyl compounds

Another important application of aryl esters involves their use as unconventional electrophiles in catalytic cross-coupling with organometallic partners (Scheme 7). More recently, the development of novel catalyst-ligand systems has advanced the capabilities of Pd- or Ni-catalyzed cross-coupling of aryl esters to enable the oxidative addition of an aryl ester to a metal center. Both carbonyl-retentive coupling[24–29] and decarbonylative coupling[30–34] were reported, and some catalyst systems exhibited a switchable selectivity by choosing appropriate ligands.[35,36] Therefore, two types of products, ketones and alkyl/aryl arenes, are directly accessible by cross-coupling of aryl esters.



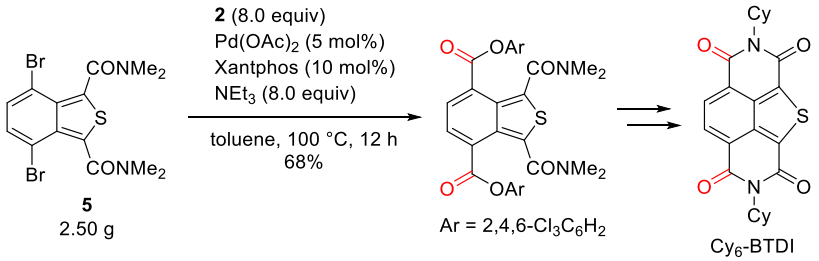
Scheme 7. Catalytic cross-coupling of aryl esters

Selected Applications of Aryl Formates and *N*-Formylsaccharin

The suitability of aryl esters for various syntheses and the favorable attributes of aryl formates and *N*-formylsaccharin have been corroborated by an increasing number of applications using them as CO surrogates. Installation of a one-carbon functional group using a CO surrogate is an

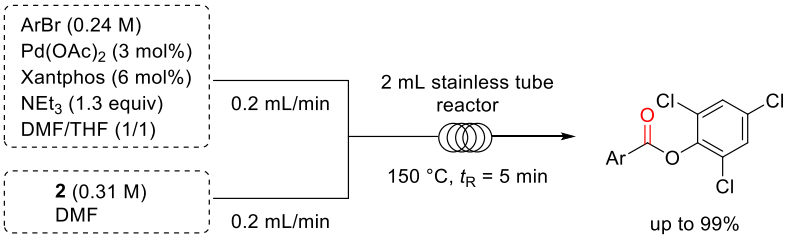
attractive method by which to form activated aryl esters and acyl fluorides and subsequently to generate other carboxylic acid derivatives by nucleophilic substitution. Most examples shown below were successfully performed in reactions at hundreds of milligram to gram-scale, indicating the robustness and reliability of this carbonylation.

Okamoto and coworkers used 2,4,6-trichlorophenyl formate (**2**) to synthesize functional molecules (Scheme 8).[37] Two carbonyl moieties were introduced into dibromo compound **5** by carbonylation, which was further converted into an *N*-substituted benzo[*c*]thiophene diimide (Cy_6-BTDI) that serves as an air-stable organic field-effect transistor.



Scheme 8. Synthesis of Cy_6-BTDI utilizing CO surrogate 2

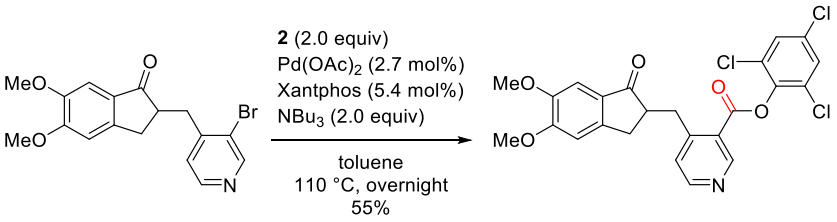
De Borggraeve, Alcázar, and coworkers applied CO surrogates in continuous-flow carbonylation reactions (Scheme 9).[38] Compound **2** was an optimal CO surrogate with respect to appropriate reactivity and solubility in organic solvents. This continuous-flow system could reduce the amount of **2** required for the reaction (from 2.0 to 1.3 equivalent) and was scaled up to synthesize 3 g of trichlorophenyl ester.



Scheme 9. Continuous-flow carbonylation using CO surrogate 2

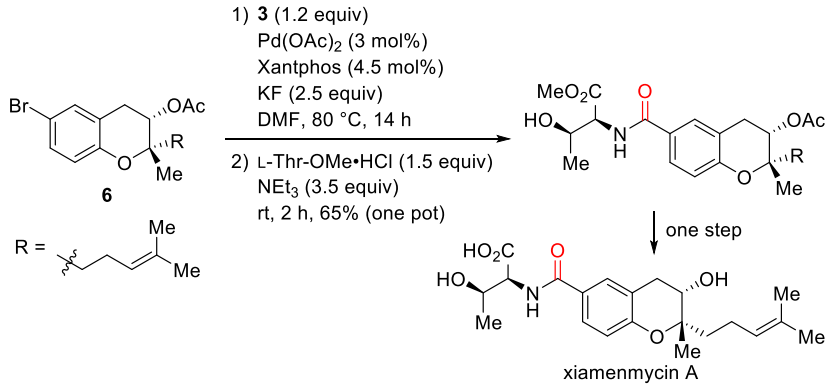
Levacher and coworkers applied **2** for medicinal chemistry studies to develop acetylcholinesterase inhibitors (Scheme 10).[39] The resulting

trichlorophenyl ester was utilized as a platform to access various esters and amides to further investigate structure-activity relationships.



Scheme 10. CO surrogate 2 applied for medicinal chemistry studies.

Xu, Xie, and coworkers employed *N*-formylsaccharin (**3**) for the asymmetric total synthesis of xiamenmycin A (Scheme 11).[40] To introduce an amide functional group, bromoarene **6** was converted into an acyl fluoride using **3** and potassium fluoride, which then reacted with a protected amino acid in a one-pot procedure to complete the synthesis of the xiamenmycin A structure.

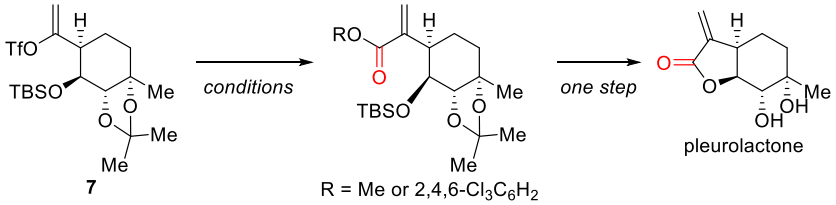


Scheme 11. Utilization of CO surrogate 3 for the total synthesis of xiamenmycin A

It is important to note that the use of CO surrogates sometimes results in better product yields than using CO gas. This might be ascribed to the effective equilibrium shift of the carbonyl-ligated metal to form an oxidative addition intermediate due to the suppression of the excessive coordination of CO to a metal center.[41] Since the CO amount used in chemical reactions can be strictly controlled by applying CO surrogates, several total synthesis

benefited from their use. Ito and coworkers utilized 2,4,6-trichlorophenyl formate (**2**) in the synthesis of pleurolactone (Table 1).[42] Compound **2** outperformed CO gas in the carbonylation of enol triflate **7**, affording the desired aryl ester in a gram-scale transformation.

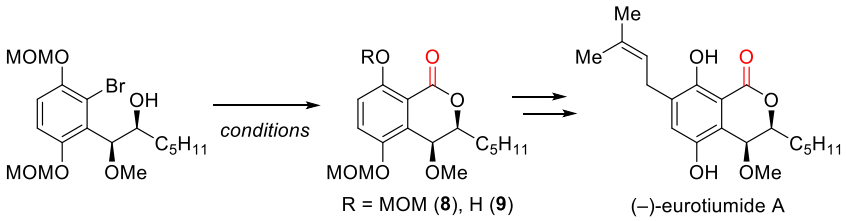
Table 1. Employing CO surrogate 2 for the total synthesis of pleurolactone



entry	conditions	yield (%)
1	CO gas (1 atm), $Pd(PPh_3)_4$ (10 mol%), NEt_3 (3.1 equiv) MeOH (31 equiv), DMF, 80 °C, 2 h [100 mg scale]	67
2	**2** (2.0 equiv), $Pd(OAc)_2$ (4 mol%), Xantphos (8 mol%), NEt_3 (2.0 equiv) toluene, rt, 5 h [1.0 g scale]	90

A more striking effect of a CO surrogate has been demonstrated by Namba, Nakayama, and coworkers, who utilized *N*-formylsaccharin (**3**) for a carbonylation/lactonization cascade to create the bicyclic (–)-eurotiumide A structure (Table 2).[43] While atmospheric CO gas generated the desired lactone **8** and **9** in only 8% yield, the use of **3** dramatically improved the yield to 65% and finally 95% at a slightly higher temperature. They finally succeeded in a 9.8 g-scale reaction of the starting bromide to provide **9** (5.7 g) through the removal of one methoxymethyl (MOM) group by a one-pot treatment with $MgBr_2$ after the carbonylation.

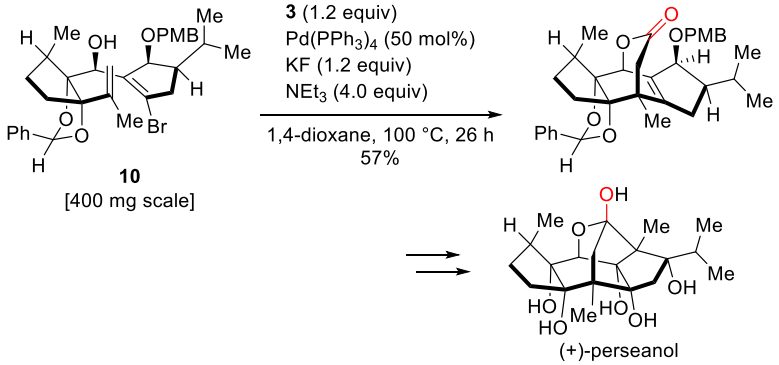
Table 2. Application of CO surrogate 3 for the total synthesis of (–)-eurotiumide A.



entry	conditions	yield (%)[a]
1	CO gas (1 atm), $Pd(OAc)_2$ (20 mol%), Xantphos (30 mol%) DMF, 80 °C, 36 h	8
2	**3** (1.5 equiv), $Pd(OAc)_2$ (20 mol%), Xantphos (30 mol%), KF (5.0 equiv) DMF, 80 °C, 36 h	65
3	**3** (1.5 equiv), $Pd(OAc)_2$ (20 mol%), Xantphos (30 mol%), KF (5.0 equiv) DMF, 115 °C, 36 h	95

[a] Combined yield of **8** and **9**.

Furthermore, Reisman and coworkers have elegantly demonstrated a carbopalladation/carbonylation/lactonization sequence as a key transformation for the asymmetric total synthesis of (+)-perseanol (Scheme 12).[44] While this transformation was promoted by a stoichiometric amount of a Pd complex and CO gas, the application of **3** as a CO surrogate enabled the catalytic conversion of bromoalkene **10** into the desired lactone as a single diastereomer, thereby creating the tetracyclic core.



Scheme 12. Use of CO surrogate 3 for the total synthesis of (+)-perseanol

In summary, aryl formates or *N*-formylsaccharin have witnessed a wide range of synthetic applications as CO surrogates. Due to the beneficial features of these CO surrogates regarding stability, safety, practicality, and commercial availability, the catalytic external-CO-free carbonylation is used as a reliable and standard strategy to generate a variety of carboxylic acid derivatives. Some applications of CO surrogates, especially in the total synthesis of biologically active compounds, clearly indicate the excellent functional group compatibility and potential scalability of this type of carbonylation.

References

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Hideyuki Konishi was born in Takamatsu, Japan in 1979. He obtained his Ph.D. degree in pharmaceutical sciences at the University of Tokyo in 2008 under the direction of Professor Shū Kobayashi. He carried out his postdoctoral research in Professor Viresh H. Rawal's laboratory at the University of Chicago. In 2009, he became a Research Assistant Professor in the group of Professor Kei Manabe at the University of Shizuoka and promoted to Assistant Professor in 2017. His research interests include the development of practical and efficient catalytic reactions for the synthesis of pharmaceutically and synthetically important compounds.

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