

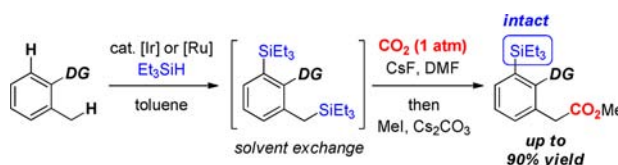
Sequential Protocol for C(sp³)–H Carboxylation with CO₂: Transition-Metal-Catalyzed Benzylic C–H Silylation and Fluoride-Mediated Carboxylation

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ABSTRACT



One of the most challenging transformations in current organic chemistry is the catalytic carboxylation of a C(sp³)–H bond using CO₂ gas, an inexpensive and ubiquitous C1 source. A sequential protocol for C(sp³)–H carboxylation by employing a nitrogen-directed, metal-assisted, C–H activation/catalytic silylation reaction in conjunction with fluoride-mediated carboxylation with CO₂ was established. The carboxylation proceeded only at the benzylic C(sp³)–Si bond, not at the aromatic C(sp²)–Si, which is advantageous for further manipulations of the products.

Carbon dioxide (CO₂) is a very attractive C1 feedstock that should be used more diversely for organic synthesis in view of the diminishing supplies of conventional petroleum products starting to become problematic within several decades. Therefore, considerable efforts have recently been made for the development of effective CO₂ incorporation reactions.¹ Among these technologies, catalytic carboxylations with CO₂ via aromatic C(sp²)–H bond activation have recently been achieved. Nolan² and Hou³ independently reported pK_a-dependent carboxylations of electron-deficient aromatic compounds catalyzed by Au(I) or Cu(I) complexes, while Iwasawa reported a chelation-assisted carboxylation of 2-aryl pyridine and 1-aryl pyrazole derivatives

catalyzed by Rh(I) complexes.^{4,5} Although those protocols are obviously landmarks in catalytic CO₂ incorporation into C–H bonds, there is still room for the development of catalytic carboxylation of a C(sp³)–H bond with CO₂, which should provide a new entry to CO₂ incorporation chemistry.

We recently reported that *N*-Boc- α -amido benzyl stannanes, which can be prepared from imines or imine equivalents,⁶ can be easily carboxylated in the presence of CsF and CO₂ gas to afford the corresponding arylglycine

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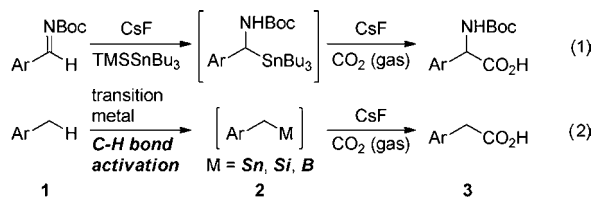
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derivatives (Scheme 1, eq 1).^{7,8} If a similar benzylic metalloid species **2** (M = Sn, Si, or B) could be prepared by a C–H metalation reaction, catalyzed by a transition metal complex,^{9,10} the corresponding acid **3** could also become available following activation of metalloid species **2** with a fluoride anion under a CO₂ atmosphere (eq 2). Ideally, these two steps could be carried out in one pot¹¹ without isolation of the benzylic metalloid intermediates **2**, which is deemed to be a formal C(sp³)–H carboxylation with CO₂.

Scheme 1. Synthetic Strategies for α -Aryl Acetic Acids Using CO₂ Gas



First, simple benzyl stannane, silane, and boron compounds **2aa** to **2ac** were synthesized to evaluate their reactivities toward carboxylations with CO₂ using 3 equiv of CsF under 1 atm of CO₂ (balloon) (Table 1). Benzyl stannane **2aa** was completely consumed at 140 °C, but after methyl esterification, only 20% of methyl α -phenyl acetate (**3a**) was obtained, probably due to the generation of a large amount of toluene by the undesired protodestannylation. To our delight, benzyl silane **2ab** was a suitable substrate, affording **3a** in 86% yield within 1 h at 100 °C.¹² In contrast, the reaction became sluggish when using benzyl pinacolboron **2ac** at 140 °C, giving **3a** only in 21% yield.

Since we found that benzyl silane was a suitable substrate for promoting the carboxylation at ambient pressure

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Table 1. Carboxylations of Benzylic Metalloids

entry	M		temp (°C)	time (h)	3a (%) ^a
1	SnBu ₃	(2aa)	140	6	20
2	SiEt ₃	(2ab)	100	1	86
3	B(pin)	(2ac)	140	0.5	21

^aYields were determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

of CO₂, the synthesis of benzylic silanes was envisioned via a benzylic C(sp³)–H activation protocol; Kakiuchi and co-workers have already reported Ru₃(CO)₁₂-catalyzed benzylic C(sp³)–H silylation in the presence of Et₃SiH and norbornene as a hydrogen trapping agent.⁹ However, Ir(I)-catalyzed intermolecular C–H silylation reactions¹³ are less developed even though iridium catalysts are well-known to promote thermal C–H borylation reactions.^{10d} Therefore, we first employed an Ir(I) catalyst to unveil its reactivity toward C(sp³)–H silylation; 8-methylquinoline **1b** was used as a substrate with a combination of [Ir(cod)Cl]₂ and Et₃SiH (Scheme 2, method A1). As a result, the C(sp³)–H silylation reaction proceeded smoothly and catalytically even in the absence of norbornene,¹⁴ affording **2b** in 98% yield.¹⁵ The reaction should not be conducted in a closed system (e.g., sealed tube) in order to release generated hydrogen gas. We also investigated Ru₃(CO)₁₂-catalyzed C(sp³)–H silylation according to Kakiuchi's protocol⁹ with some modifications (reactions conducted in a sealed tube), and **2b** was also obtained in 93% yield in the presence of norbornene (the reported yield: 78%) (method B1). The chelation mode between **1b** and Ir or Ru is expected to be a stable five-membered one. Subsequently, substrate **1c** possessing pyridine as a directing group was selected for C(sp³)–H silylation. Both Ir(I) and Ru(0) catalysts were active. However, product distribution largely depended on the catalyst employed. The Ir(I) catalyst induced aromatic C(sp²)–H silylation selectively even when an excess amount

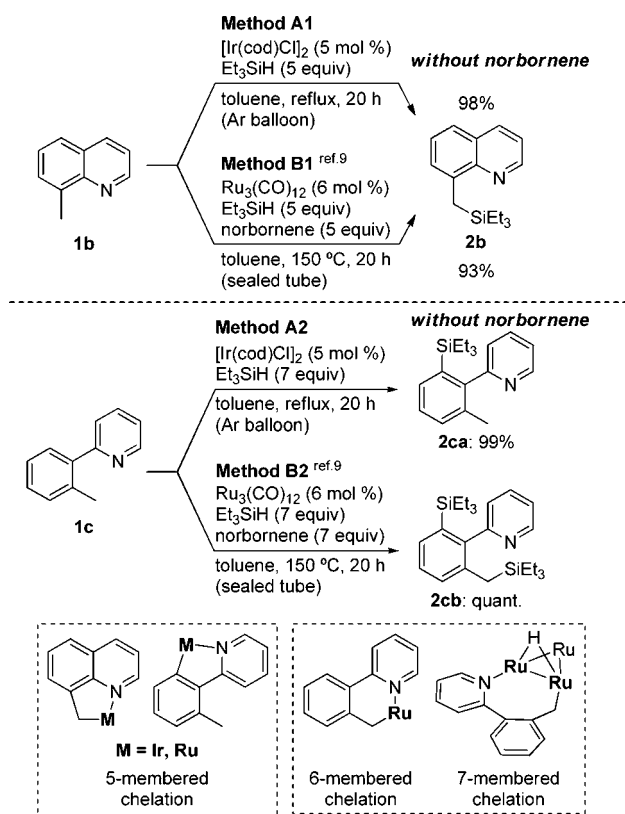
(13) For iridium-catalyzed C–H silylations using hydrosilanes and disilanes, see: (a) Gustavson, W. A.; Epstein, P. S.; Curtis, M. D. *Organometallics* **1982**, *1*, 884. (b) Ishiyama, T.; Sato, K.; Nishio, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5346. (c) Ishiyama, T.; Sato, K.; Nishio, Y.; Saiki, T.; Miyaura, N. *Chem. Commun.* **2005**, 5065. (d) Saiki, T.; Nishio, Y.; Ishiyama, T.; Miyaura, N. *Organometallics* **2006**, *25*, 6068. (e) Lu, B.; Falck, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 7508. (f) Simmons, E. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 17092. (g) Simmons, E. M.; Hartwig, J. F. *Nature* **2012**, *483*, 70.

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of Et₃SiH was used (method A2: 7 equiv of Et₃SiH used), while the Ru(0) catalyst induced both C(sp²)-H and C(sp³)-H silylations (method B2: 7 equiv of Et₃SiH and norbornene used). We considered that this regioselective silylation was due to the different modes of metal coordination, Ir prefers a stable five-membered mode of coordination, while Ru forms not only a five-membered but also a six-membered metallacycle. In addition, a seven-membered metallacycle containing two ruthenium atoms¹⁶ derived from trinuclear Ru₃(CO)₁₂ might also be expected as a possible intermediate.

Scheme 2. Catalytic Benzylic C(sp³)-H Silylations



Given the establishment of high-yielding C(sp³)-H silylation at a benzylic position, prepared benzyl silanes **2b** and **2cb** were subjected to fluoride-mediated carboxylation (Scheme 3: 3 equiv of CsF under 1 atm of CO₂).¹² Since the desired amino carboxylic acids are water-soluble, the reaction mixture was directly treated with MeI and Cs₂CO₃, affording methyl ester **3b** in 91% yield together with the protodesilylation product **1b** in 9% yield. Notably, 1 atm of CO₂ was sufficient for selective carboxylation in contrast to our previous reports.^{7,8} Substrate **2cb** was

also a good substrate for carboxylation; under the fluoride-mediated conditions, the aromatic C(sp²)-Si bond was intact and **3c** was obtained in 82% yield along with **2ca** in 11% yield.

By concatenating Ir(I) or Ru(0)-catalyzed C(sp³)-H silylation and fluoride-mediated carboxylation,¹⁷ we have established a sequential protocol¹¹ for a formal C(sp³)-H carboxylation with CO₂ (Figure 1). Since C-H silylation did not proceed at all in DMF, the best solvent for the following carboxylation, solvent exchange was necessary after the silylation. By installation of a simple solvent exchange via evaporation of toluene and other volatile materials (Et₃SiH and norbornene if used) followed by the introduction of DMF, sequential reactions for various substrates possessing a nitrogen atom at an appropriate position proceeded smoothly. Aiming at the five-membered chelation system, [Ir(cod)Cl]₂ was employed for 8-methylquinoline derivatives to afford the corresponding carboxylic acid derivatives **3b**, **3d**, and **3e** in high yields without affecting other methyl groups at nonchelating positions. Although **1** was consumed completely in the silylation step, **1** was regenerated by the undesired protodesilylation under the fluoride-mediated conditions, which can be reused as a substrate for this sequential process. 5-Methylquinoxaline (**1f**) was also applicable for the sequential carboxylation, affording **3f** in moderate yield. Next, various substrates having a pyridine directing group were examined in the presence of Ru₃(CO)₁₂ and norbornene. When **1c** was used, monocarboxylate **3c** attached to the TES group on the aromatic ring was obtained in 81% yield. Again, the aromatic C(sp²)-Si bond was intact during the fluoride-mediated carboxylation. In addition, double carboxylations at two benzylic positions were achieved for **1g**, and a primary C(sp³)-H bond was selectively silylated for **1h**. The reaction of methyl naphthalene **1i** proceeded only at the benzylic position to afford the product in 90% yield. Furthermore, a pyrimidine as well as a quinoline directing group was also effective in this sequential protocol, giving the corresponding methyl esters in moderate yields. Benzoxazole **1j** was also compatible for Ru-catalyzed reaction (72%) but not for Ir-catalyzed reaction (8%) even though a favorable five-membered chelation would be expected for both catalysts.

Considering the utility of the remaining silyl group of **3c**, we demonstrated further manipulation of **3c**, in which the C(sp²)-Si moiety could be iodinated quantitatively in the presence of ICl. The Pd(0)-catalyzed coupling reaction of **4c** (e.g., Suzuki-Miyaura cross-coupling with phenyl boronic acid) resulted in C-C bond formation without affecting the acidic methylene carbonyl moiety, affording **5c** in 83% yield (Scheme 4).

(17) The reaction of **1b** and **1c** by using 1.2 equiv of *sec*-BuLi or LDA (lateral lithiation) in THF at -78 °C under CO₂ (1 atm) did not give any carboxylated products; either a *sec*-butyl group was introduced on the 2-position or no reaction occurred. These observations suggested that this one-pot process has synthetic utility as well, even though an excess amount of Et₃SiH should be employed. For a review on lateral lithiation, see: Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1.

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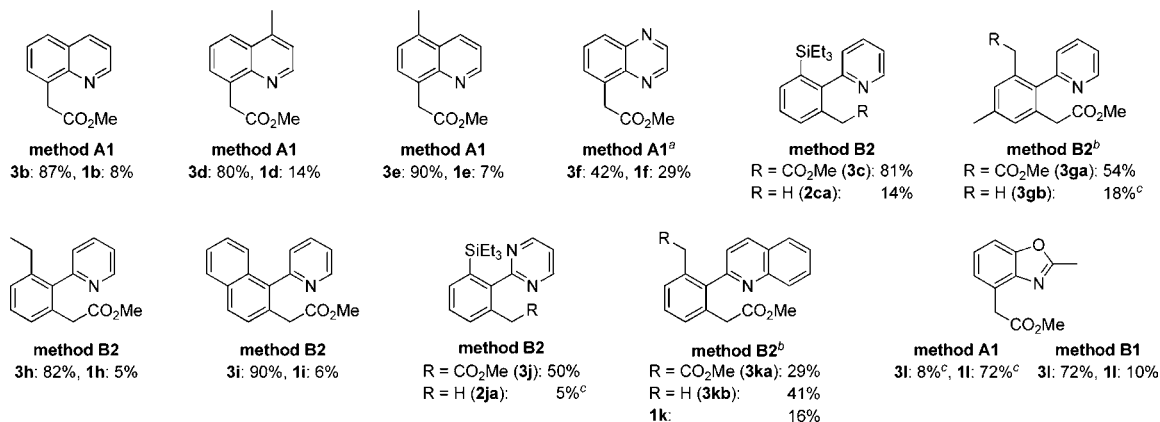
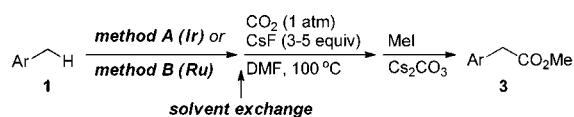
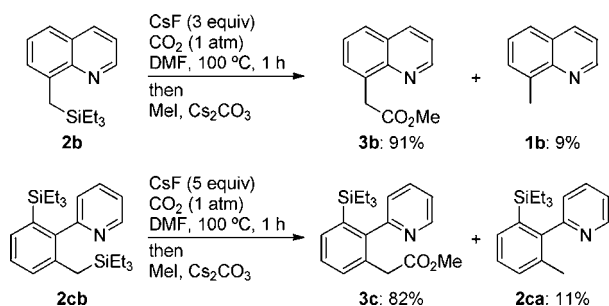
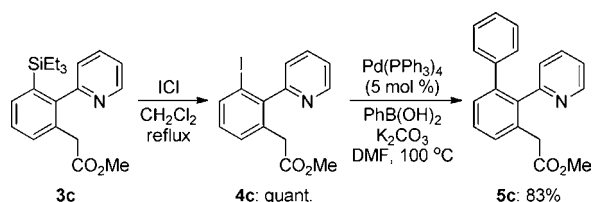


Figure 1. Reaction conditions: **method A:** a substrate (0.4 mmol), [Ir(cod)Cl]₂ (5 mol %), Et₃SiH (**A1:** 5 equiv, **A2:** 7 equiv), toluene (2.0 M), reflux, 20 h, then CsF (3 equiv), DMF (0.1 M), 100 °C, 2 h, then MeI (2 equiv), Cs₂CO₃ (2 equiv), rt, 30 min; **method B:** a substrate (0.3 mmol), Ru₃(CO)₁₂ (6 mol %), Et₃SiH (**B1:** 5 equiv, **B2:** 7 equiv), norbornene (**B1:** 5 equiv, **B2:** 7 equiv), toluene (2.0 M), 150 °C (closed), 20 h, then CsF (3 equiv), DMF (0.1 M), 100 °C, 2 h, then MeI (2 equiv), Cs₂CO₃ (2 equiv), rt, 30 min. Isolated yields are shown unless otherwise noted. ^a1.0 equiv of Cs₂CO₃ was used. ^b3.0 equiv of Cs₂CO₃ and 5.0 equiv of MeI were used. ^cYields were determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

Scheme 3. Carboxylations of Benzyl Silanes



Scheme 4. Functionalization of Aromatic C–Si Bond



In conclusion, we have developed a novel sequential protocol for C(sp³)–H carboxylation with CO₂ gas. This

reaction consists of a nitrogen-directed silylation catalyzed by either an Ir(I) or Ru(0) complex and a fluoride-mediated carboxylation, which could be operated in a single flask just by changing the reaction solvent. In this sequential reaction, the C(sp³)–Si bond was selectively activated by a fluoride anion to promote the following carboxylation with CO₂, affording the desired carboxylic acid derivatives in moderate to high yields. Further substrate scope studies including different directing groups on the aromatic ring as well as the development of a direct catalytic carboxylation of C(sp³)–H are now actively ongoing.

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Supporting Information Available. Details of experimental procedures and physical properties of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.