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COMBINED BRØNSTED-BASE-MEDIATED DIRECT C-H CARBOXYLATION OF HETEROARENES WITH CO_2

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This paper is dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday.

Abstract – This review article summarizes that the combined Brønsted-base system comprising LiO-*t*-Bu, CsF, and 18-crown-6 efficiently proceeds the direct carboxylation of electron-rich heteroarenes, such as benzothiophene and benzofuran, with CO_2. Good functional group compatibility is displayed, allowing the use of Me, MeO, halogen, CN, ketone, and amide moieties. 3-Substituted indoles are also used for C-2 carboxylation, while double-carboxylation of 2-alkylheteroarenes is achieved by LiO-*t*-Bu and CsF.

CONTENTS

1. INTRODUCTION

Heteroaromatic carboxylic acid derivatives are the core structures of biologically active compounds.[1] For their synthesis, carboxylation of heteroaromatic substrates with CO_2 is of significant importance since CO_2 is a cheap, abundant, and non-toxic C1 source.[2] Particularly, the direct conversion of the heteroaromatic C(sp^2)–H bond is a powerful and straightforward protocol, compared to those of pre-functionalized chemical bonds (i.e., C–Li, C–Mg, C–B, C–Si, C–Zn, C–Al, and C–halogen), from both step and atom economy viewpoints.[3] During the last decade, such a methodology was demonstrated by transition metal catalysts, such as Au, Cu, Rh, and Ni complexes, with a base or reducing reagent[4] and by Lewis acids.[5] The former proceeds the reactions of both electron-rich and -poor substrates under relatively mild conditions (room temperature to 80 °C); however, it usually requires the use of a precious metal and/or ligand.[4] On the other hand, the latter is only effective for the conversion of electron-rich substrates, achieved through CO_2 electrophilicity enhancement.[5] High CO_2 pressure conditions (~30 atm) are also required.

The Brønsted-base system affords an alternative access for direct carboxylation, which involves the deprotonation of the heteroaromatic substrate followed by *in situ* trapping of the generated anionic species with CO_2 (Figure 1).[3a,6-11] The system is anticipated to broaden the substrate scope and functional group compatibility and to display different regioselectivity, based on a mechanistic process that differs from those of the above-mentioned reactions. To date, several Brønsted-base-mediated carboxylations have been achieved. Specifically, Kobayashi et al. reported that LiO-*t*-Bu proceeds the carboxylation of NH indoles (indole NH, pKa = 21) at the 3-position [Figure 1 (a)].[6a] They also applied the conditions to the carboxylation of NH pyrroles, whereby the pyrroles that possess an ester, imine, or phenyl functionality at the 2-position react with CO_2 at the 5-position.[6b] Hu et al. demonstrated that Cs_2CO_3 mediates the carboxylation of electron-poor azaarenes including multiple heteroatoms, such as benzoxazole, benzothiazole, oxazoles, and 1,3,4-oxadiazoles [Figure 1 (b)],[7] while Ackermann et al. showed that the reactions occur under 1 atm pressure using KO-*t*-Bu [Figure 1 (b)].[8] In these studies, the substrates contain relatively acidic protons (pKa $\leq$ 27) and are deprotonated smoothly to form nucleophilic anionic species. As an exception, Kanan et al. described that molten Cs_2CO_3 salt mediates the conversion of 2-furoic acid (C–H at the 5-position, pKa ~35) and benzene (pKa >40); however, harsh reaction conditions are needed and the detailed substrate scope was not noted [Figure 1 (c)].[9-11] Thus, we became interested in the development of such a system, which enables the carboxylation of a wide range of low-acidic substrates. The combined Brønsted-base system LiO-*t*-Bu/CsF/18-crown-6, which has been reported to be potent in the reactions of electron-rich heteroarenes such as benzothiophene (pKa = 32) and benzofuran [pKa = 33.2; Figure 1 (d, i)],[12-15] allowed the use of a variety of functional groups including Me, MeO, halogen, CN, ketone, and amide moieties. The system also achieved the double-carboxylation of 2-alkylheteroarenes [Figure 1 (d, ii)].[16] This article reviews the results of this system.

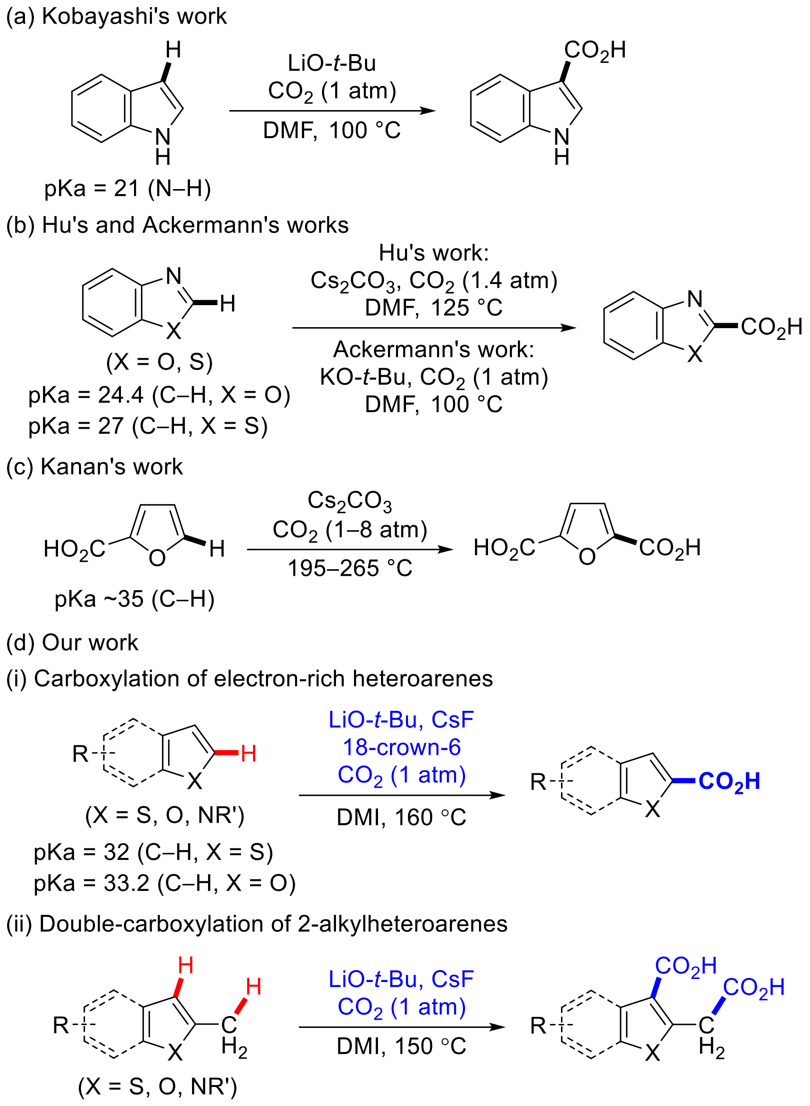
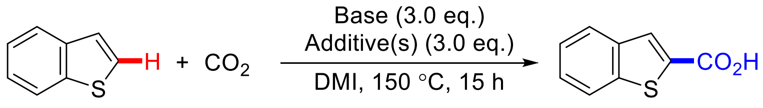


Figure 1. Brønsted-base-mediated direct C–H carboxylation of heteroarenes

2. CARBOXYLATION OF ELECTRON-RICH HETEROARENES[12]

At the beginning of our studies of electron-rich heteroaromatic carboxylation, we tested the hexamethyldisilazide (HMDS)–amide base system generated *in situ* for the reaction of benzothiophene **1a** [Figure 2 (1)];[17] however, no carboxylated product (**2a-H**) was obtained. The use of the carbonate bases K_2CO_3 and Cs_2CO_3 was also fruitless [Figure 2 (2)]. We next examined the use of the alkoxide base LiO-*t*-Bu [Figure 2 (3)], which afforded the target product in 11% yield. Addition of CsF afforded **2a-H** in 46% yield, and further addition of 18-crown-6 increased the yield to 86% (Entries 1–5). On the other hand, the cesium salts CsCl and CsI were ineffective (Entries 6 and 7). The use of 15-crown-5 instead of 18-crown-6 and NaO-*t*-Bu and KO-*t*-Bu instead of LiO-*t*-Bu slightly decreased the yield (Entries 8–10).

Finally, when the reaction was carried out at 160 °C, the carboxylated product, methyl ester **2a**, was isolated in 95% yield (Figure 3).



1a (1 atm) **2a-H**

(1) Amide base generated *in situ*:
CsF (30 mol%), N(TMS)$_3$ (3.0 eq.)
CsF (3.0 eq.), N(TMS)$_3$ (3.0 eq.)
Me$_4$NF (30 mol%), N(TMS)$_3$ (3.0 eq.)
Me$_4$NF (3.0 eq.), N(TMS)$_3$ (3.0 eq.)
(2) Carbonate base:
K$_2$CO$_3$, Cs$_2$CO$_3$

No **2a-H** formation

(3) Alkoxide base, additive(s):	Yield of **2a-H** (%)[b]
1. LiO-*t*-Bu	11
2. LiO-*t*-Bu, CsF	46
3. LiO-*t*-Bu, 18-crown-6	13
4. LiO-*t*-Bu, CsF, 18-crown-6	**86**
5. CsF, 18-crown-6	0
6. LiO-*t*-Bu, CsCl, 18-crown-6	28
7. LiO-*t*-Bu, CsI, 18-crown-6	15
8. LiO-*t*-Bu, CsF, 15-crown-5	76
9. NaO-*t*-Bu, CsF, 18-crown-6	71
10. KO-*t*-Bu, CsF, 18-crown-6	73

Figure 2. Optimization of the carboxylation of **1a**.[a] [a]Reactions conducted in 0.3 mmol scale. [b]Yields determined by ^{1}H-NMR using 1,1,2-trichloroethane as the internal standard.

We discovered that the optimized reaction conditions are applicable to the carboxylation of a variety of heteroaromatic substrates (Figure 3). Indeed, benzothiophenes **1b**–**1g**, respectively equipped with the functionalities Me, OMe, F, Cl, Br, and CN at the 5-position, afforded the carboxylated products in high yields (87–99%). Moreover, the compatibility of the C(sp^2)–Br bond in **2f** provided some insight into the reaction mechanism (vide infra). Sterically hindered 3-methyl- and 3-bromobenzothiophene afforded **2h** and **2i** in 88 and 93% yields, respectively. 2-Phenylthiophene **2j** and its derivatives **2k**–**2m**, having the respective substituents OMe, Cl, and Br, were also suitable substrates, while 2-bromothiophene **2n** afforded the product in 83% yield. Electrophilic keto and amide moieties in the respective substrates **2o** and **2p** were well compatible, while furan derivative **2q** and benzofuran **2r** were carboxylated in respective yields of 53 and 86%.

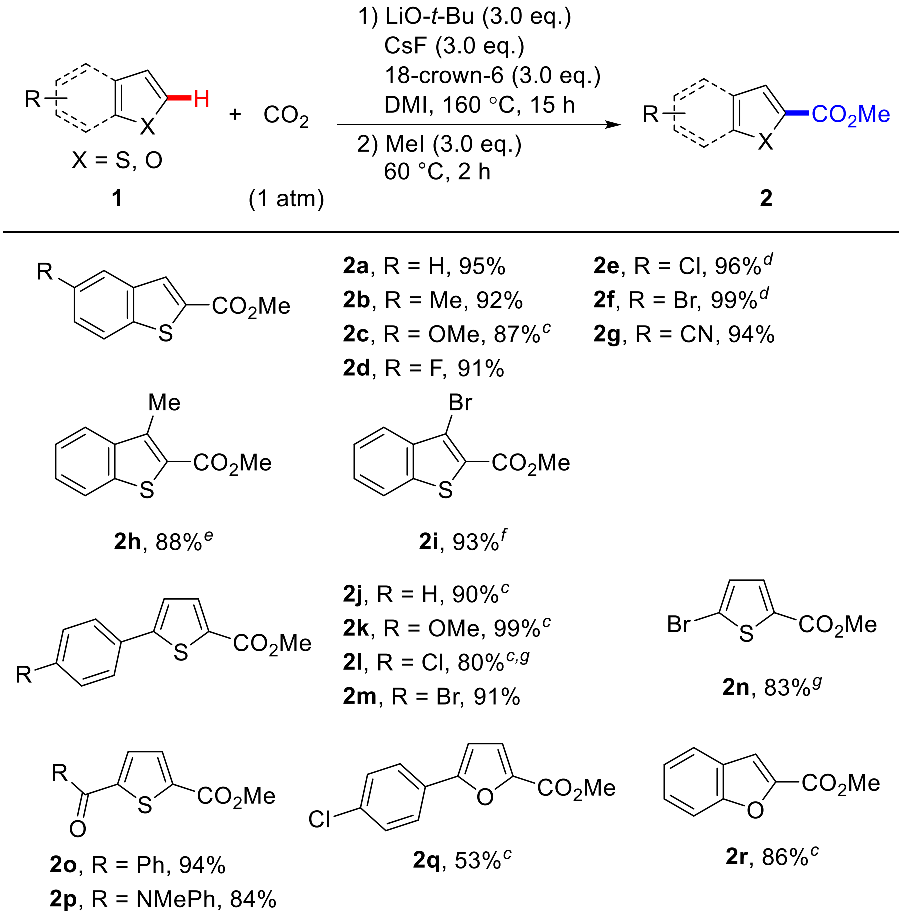
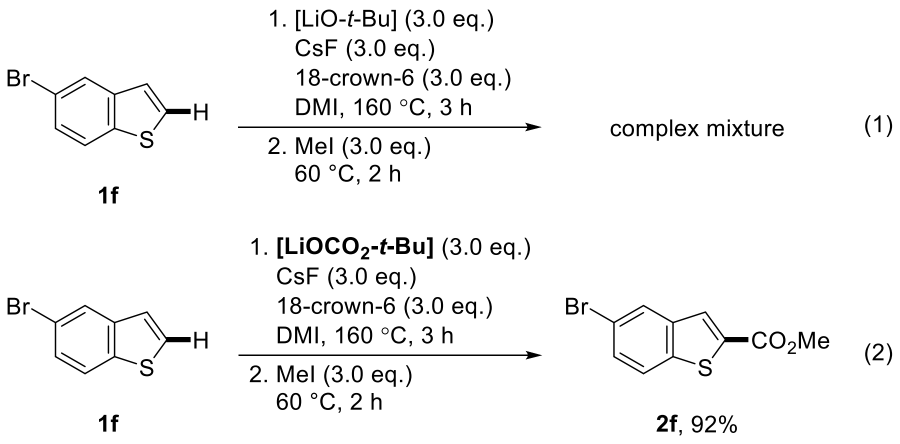


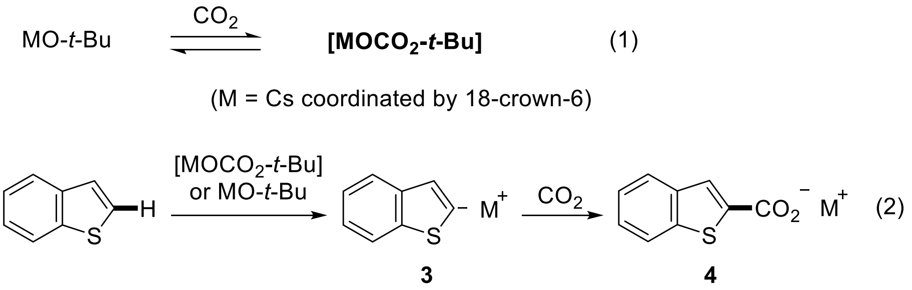
Figure 3. Scope of heteroarenes.[a, b] [a]Carboxylation conditions: **1** (0.30 mmol), CO_2 (1 atm), LiO-*t*-Bu (0.90 mmol), CsF (0.90 mmol), 18-crown-6 (0.90 mmol), DMI (1.5 mL), 160 °C, 15 h. [b]Isolated yields. [c]180 °C. [d]3 h. [e]LiO-*t*-Bu (1.20 mmol), CsF (1.20 mmol), and 18-crown-6 (1.20 mmol). [f]1 h. [g]24 h.

(Hetero)aromatic C(sp^2)–Br bonds are well compatible, as demonstrated by the reactions of **1f**, **1i**, **1m**, and **1n**. The results were somewhat unexpected, since *tert*-butoxides were previously reported to achieve one-electron transfer reactions and form aryl radical species from haloarenes.[18] The reactivity was used for the biaryl coupling of haloarenes and C–H arenes. Indeed, the reaction of **1f** conducted under Ar atmosphere, instead of CO_2, afforded a complex mixture (Scheme 1, Eq. 1), while the reaction of **1f** with the pre-prepared carbonate base [$LiOCO_2$-*t*-Bu], CsF, and 18-crown-6 under Ar afforded the carboxylated product **2f** (Scheme 1, Eq. 2). Based on these results, under the specified reaction conditions, MO-*t*-Bu (M = Cs coordinated by 18-crown-6) reacts with CO_2 and forms the weaker carbonate base [$MOCO_2$-*t*-Bu] (Scheme 2, Eq. 1). Here, the equilibrium shifts toward the carbonate side, and the concentration of MO-*t*-Bu remains low,[4k] resulting in the inhibition of C(sp^2)–Br bond side reactions.[19]



Scheme 1. Reactions of **1f** with [LiO-*t*-Bu], CsF, and 18-crown-6 (Eq. 1) and [LiOCO$_2$-*t*-Bu], CsF, and 18-crown-6 (Eq. 2) under Ar

The proposed mechanism is depicted in Scheme 2: Deprotonation of the substrate occurs either by the *tert*-butoxide base MO-*t*-Bu or the carbonate [MOCO$_2$-*t*-Bu]. The formed carbanion species **3** reacts with CO$_2$ and furnishes carboxylated product **4**. The increased reactivity obtained by the combined Brønsted-base system was attributed to the formation of a cesium base by cation exchange, forming a stable LiF salt,[20] and the complexation of cesium cations with 18-crown-6.[21]



Scheme 2. Proposed mechanism

3. CARBOXYLATION OF 3-SUBSTITUTED INDOLES[13]

We next applied this protocol to the C-2 carboxylation of indole derivatives bearing an electron-withdrawing substituent at the 3-position (Figure 4). Indole 2-carboxylic acid derivatives are also present in a variety of natural compounds and biologically active compounds.[22] In our system, the carboxylation of 3-cyanoindole **5a** and its derivatives **5b**–**5h** possessing various functionalities at the 5-position smoothly proceeded in high yields (85–99%). The 6- and 7-chloro-substituted indoles **5i** and **5j** provided the products in 94 and 93% yields, respectively, and benzyl, methoxymethyl, phenyl, and 2-pyridyl substitutions were allowed on the indole nitrogen atom. Electrophilic functionalities other than the cyano group were next examined. The formyl substituent, which is susceptible to nucleophilic addition, was tolerated and a series of substrates (**5o**–**5u**) could be used. Benzoyl-, phenylsulfonyl-, phenylsulfinyl-, and chloride-substituted indoles also reacted to form the target products (**6v**–**6y**, respectively) in good yields (66–91%).

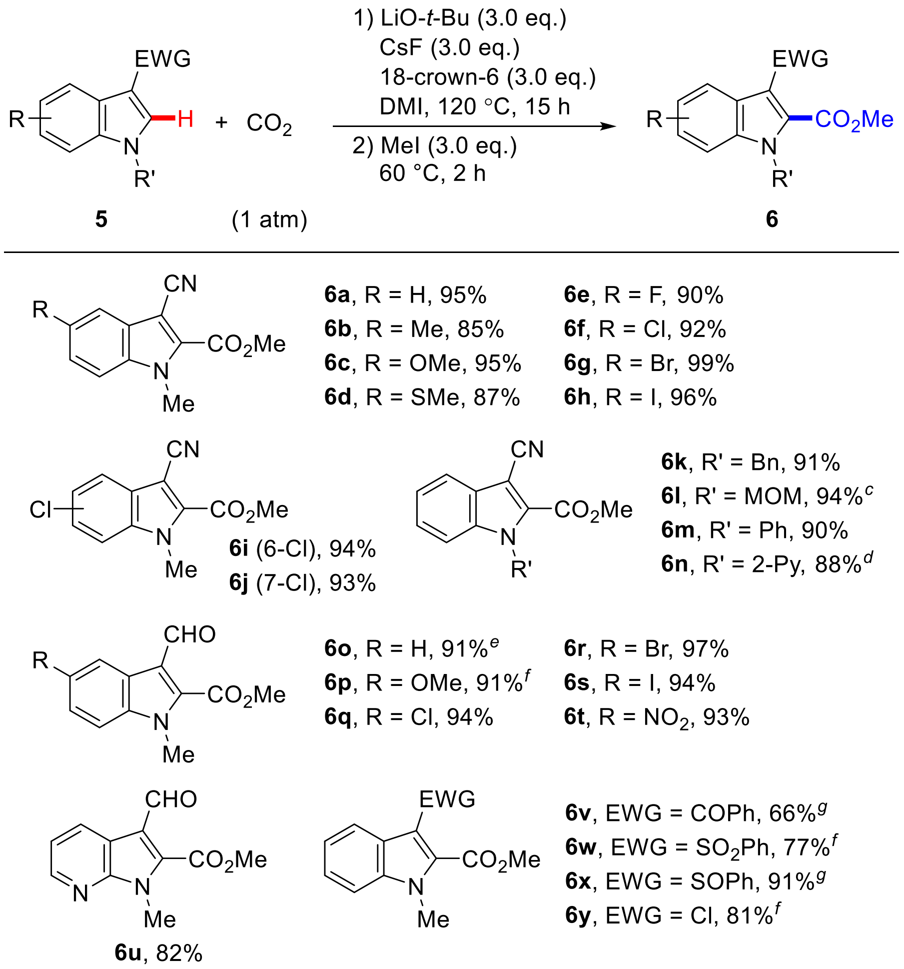
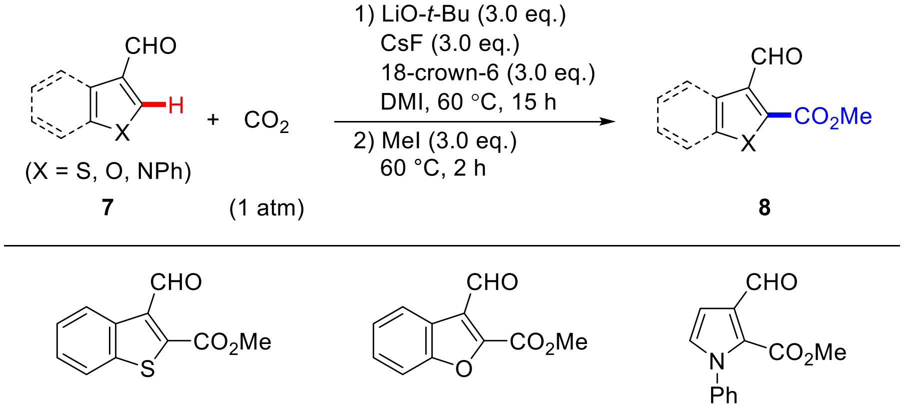


Figure 4. Scope of 3-substituted indoles.[a, b] [a]Carboxylation conditions: **5** (0.30 mmol), CO_2 (1 atm), LiO-*t*-Bu (0.90 mmol), CsF (0.90 mmol), 18-crown-6 (0.90 mmol), DMI (1.5 mL), 120 °C, 15 h. [b]Isolated yields. [c]140 °C. [d]130 °C. [e]150 °C. [f]160 °C. [g]180 °C.

The tolerance of the formyl group displayed by **5o**–**5u** intrigued us to examine the applicability of other formyl substituted heteroarenes (Figure 5). Notably, the reactions achieved with the respective benzothiophene, benzofuran, and pyrrole substrates **7a**–**7c** retained the formyl moiety. In these reactions, the self-condensation product was not observed. The compatibility of the formyl group was attributed to the lower reactivity (electrophilicity) of the formyl moiety attached to the electron-rich heteroaryl ring, over that of CO_2, and/or *in situ* protection by the hemiacetal alkoxide base.[23]



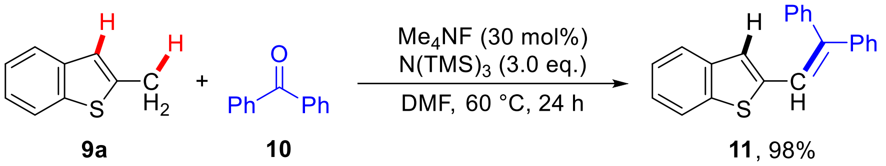
8a, 93% **8b**, 86%[c] **8c**, 52%[d]

Figure 5. Scope of 3-formyl-substituted heteroarenes other than the indoles.[a, b] [a]Carboxylation conditions: **7** (0.30 mmol), CO_2 (1 atm), LiO-*t*-Bu (0.90 mmol), CsF (0.90 mmol), 18-crown-6 (0.90 mmol), DMI (1.5 mL), 60 °C, 15 h. [b]Isolated yields. [c]80 °C. [d]130 °C.

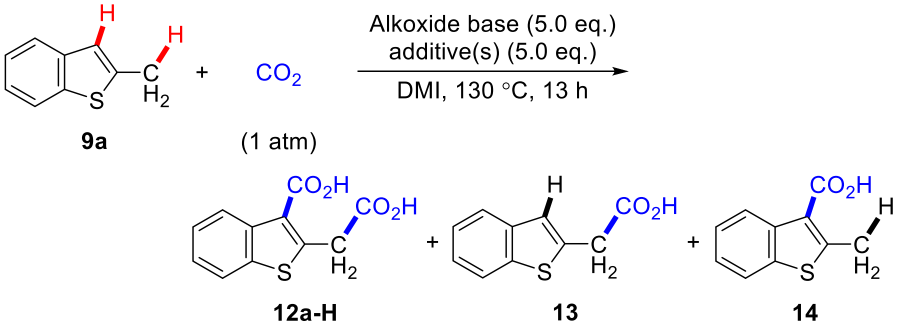
4. DOUBLE-CARBOXYLATION OF 2-ALKYLHETEROARENES[16]

Next, we became interested in developing the carboxylation of 2-alkylheteroarenes. Before starting the project, we observed that the *in situ* generated amide base underwent deprotonative coupling of 2-methylbenzothiophene **9a** with benzophenone **10**, yielding the stilbene derivative **11** [Figure 6 (a)].[17b] Thus, we predicted the formation of monocarboxylated product **13** [Figure 6 (b)]. However, contrary to this assumption, **12a-H**, which was double-carboxylated at the benzylic and β-positions, was the major product during the course of the Brønsted base evaluation [Figure 6 (b)]. Such a direct double-carboxylation of two C−H bonds has been regarded as difficult to develop. This is because the initial carboxylation imposes steric hindrance and lowers the nucleophilicity of the molecule, rendering the second carboxylation insufficient.[24-27] Thus, the examples were limited to specific substrates.[24] We therefore decided to establish the reaction conditions and investigate the scope of the substrates.

(a) Amide base generated *in situ* promoted stilbene formation



(b) Combined Brønsted base mediated double-carboxylation[a]



Alkoxide base, additive(s):	Yield of **12a-H** (%)[b]	Yield of **13** (%)[b]	Yield of **14** (%)[b]
1. LiO-*t*-Bu	12	0	0
2. LiO-*t*-Bu, CsF	**83**	**2**	**0**
3. LiO-*t*-Bu, CsF, 18-crown-6	77	6	10
4. LiO-*t*-Bu, RbF	24	5	0
5. LiO-*t*-Bu, CsCl	14	0	0
6. LiO-*t*-Bu, CsI	5	1	0
7. NaO-*t*-Bu, CsF	77	3	3
8. KO-*t*-Bu, CsF	57	7	2
9. LiO-*t*-Bu, CsF[c]	**94**	**1**	**3**

Figure 6. (a) Stilbene formation of 2-methylbenzothiophene **9a** with benzophenone **10** by an *in situ* generated amide base and (b) double-carboxylation of **9a** with CO_2 by a combined Brønsted base. [a]Reactions conducted in 0.3 mmol scale. [b]Yields determined by ^{1}H-NMR using 1,1,2-trichloroethane as an internal standard. [c]Reaction conducted at 150 °C.

A survey of the reaction conditions revealed that the combination of LiO-*t*-Bu and CsF was the most productive [Figure 6 (b)], and the reaction of **9a** provided **12a-H** in a high yield of 83% with a small amount of **13** (2% yield; Entry 2). In this reaction, the addition of 18-crown-6 decreased the yield of **12a-H** (Entry 3). The use of other alkali metal salts and alkoxides was not very effective (Entries 4–8). On the other hand, when the reaction with LiO-*t*-Bu and CsF was carried out at 150 °C, **12a-H** was furnished in 94% yield (Entry 9). The product was converted to a dimethyl ester (**12a**) and isolated in 83% yield (Figure 7).

With the optimized conditions in hand, we proceeded to survey the substrate scope, wherein the product was isolated in dimethyl ester form (Figure 7). Substrates **9b**, **9c**, **9i**, and **9j**, containing electron-donating methyl and methoxy groups, reacted smoothly. Halogens (F, Cl, and Br), cyano, and *tert*-butyl ester afforded products **12d**–**12h**, respectively, in good yields (74–87%). The reactions of 2-ethylbenzothiophene (**9k**) and 2-propylbenzothiophene (**9l**) were also sufficient and afforded the target products in 81 and 76% yields, respectively. Substrate **9m**, which carries two benzothiophene units, afforded the triple-carboxylated product **12m** in 31% yield and the double-carboxylated product **12m’** in 26% yield. Heteroaromatic substrates other than benzothiophene were subsequently used. The thiophene derivatives possessing aryl moieties (**9n** and **9o**) and those equipped with benzoyl and *N*-methyl-*N*-phenylamide functionalities (**9p** and **9q**, respectively) afforded satisfactory results. Moreover, 2-methylbenzofuran **9r** and 2-methyl-5-phenylfuran **9s** reacted efficiently and furnished the desired products in 92 and 77% yields, respectively. 2-Methylindoles **9t**–**9v** were also employed successfully.

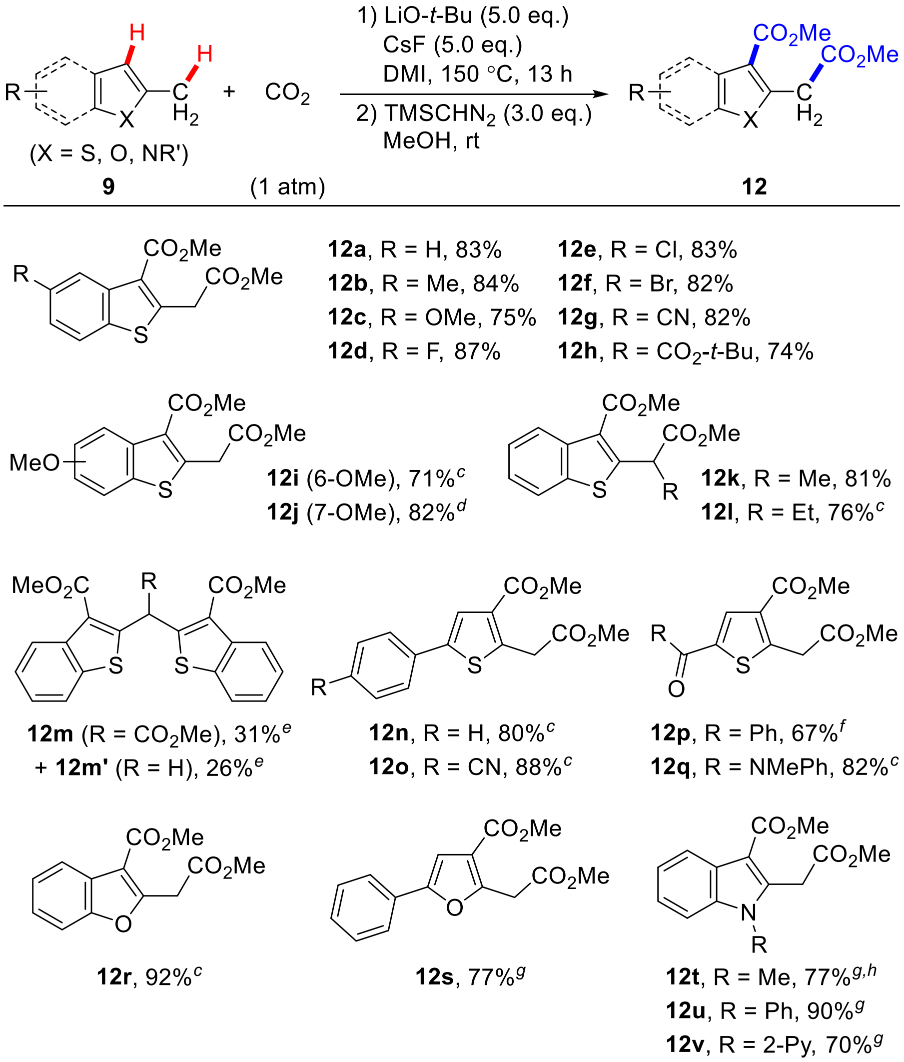


Figure 7. Scope of 2-alkylheteroarenes.[a, b] [a]Carboxylation conditions: **9** (0.30 mmol), CO_2 (1 atm), LiO-*t*-Bu (1.50 mmol), CsF (1.50 mmol), DMI (1.5 mL), 150 °C, 13 h. [b]Isolated yields. [c]160 °C. [d]140 °C. [e]100 °C. [f]130 °C. [g]180 °C. [h]DMI (2.0 mL).

Mechanistically, two different pathways, A and B, are presumed to be involved (Figure 8). In both cases, the benzylic C(sp^3)–H bond is initially deprotonated by the cesium base and forms benzyl anion **15**. In pathway A, **15** undergoes the first carboxylation at the benzylic position, followed by deprotonation, and the second carboxylation at the β-position to form product **19**. Alternatively, pathway B comprises carboxylation first at the β-position and subsequently at the benzylic position.

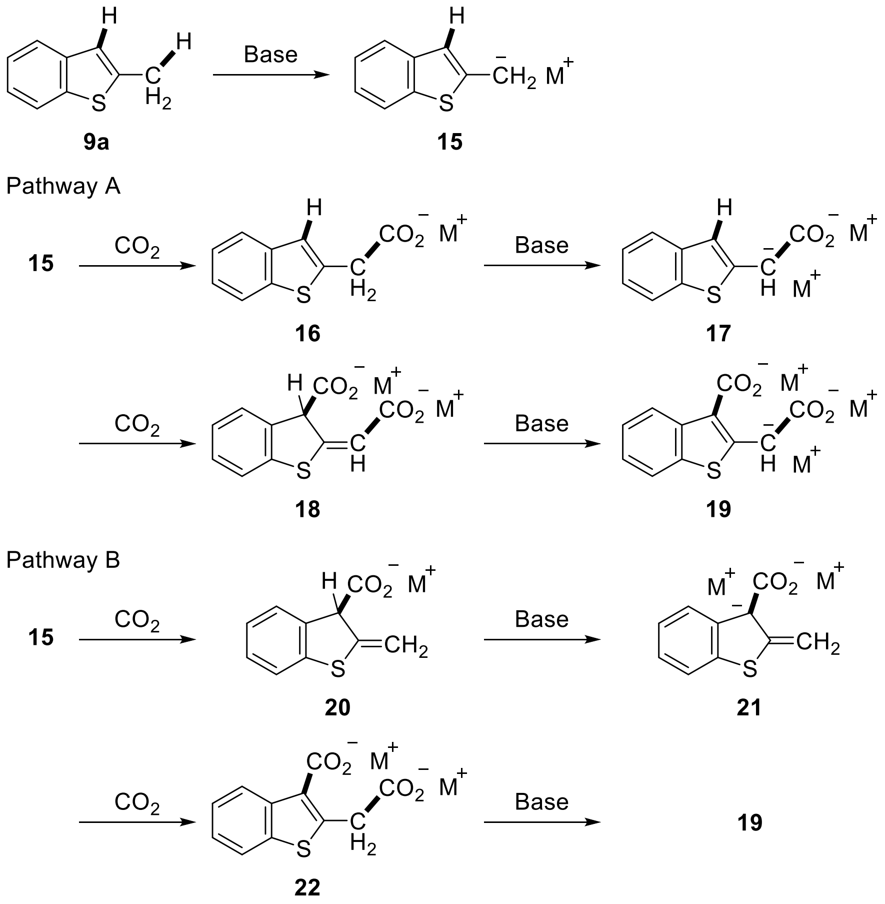
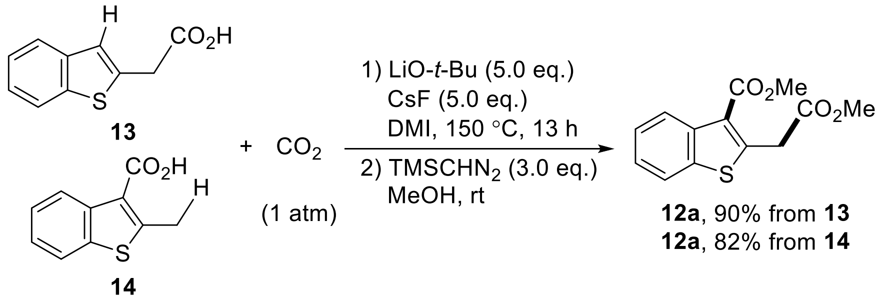
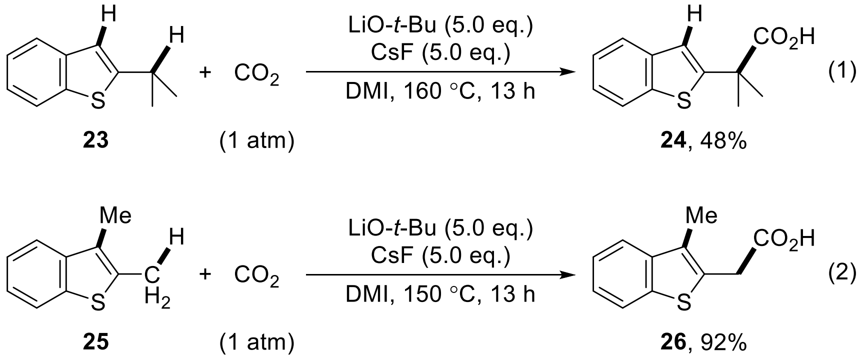


Figure 8. Proposed mechanisms

Experiments were next conducted to obtain insight into the reaction mechanism (Schemes 3 and 4). Both substrates **13** and **14**, which are carboxylated at the benzylic and β-positions, respectively, reacted with CO_2 under the established reaction conditions to afford **12a**. The results did not distinguish between pathways A and B. Next, 2-isopropylbenzothiophene **23** and 2,3-dimethylbenzothiophene **25** were subjected to the reactions, affording mono-carboxylated products **24** and **26**, respectively, at the benzylic position. These results favor pathway A over pathway B.



Scheme 3. Reactions of mono-carboxylated substrates **13** and **14**.[a, b] [a]Reactions were conducted in 0.3 mmol scale. [b]Isolated yields.



Scheme 4. Reactions of **23** and **25** at the benzylic position.[a, b] [a]Reactions were conducted in 0.3 mmol scale. [b]Isolated yields.

5. CONCLUSION

In summary, we revealed the unique reactivity of the combined Brønsted-base system for the direct carboxylation of heteroaromatic compounds, covering the carboxylation of electron-rich heteroarenes and 3-substituted indoles and the double-carboxylation of 2-alkylheteroarenes. Various functional groups, such as Me, MeO, MeS, halogen, CN, ketone, amide, and NO_2 moieties, are also allowed.

ACKNOWLEDGEMENTS

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