5-Bromo-norborn-2-en-7-one derivatives as a carbon monoxide source for palladium catalyzed carboxylation reactions†

China M. Payne, Kyulee Cho and David S. Larsen *

Norbornene (5b), obtained from the reaction of 2,5-dimethyl-3,4-diphenylcyclopentadienone dimer (3) with bromomalenic anhydride (4b), provides an excellent base-triggered source of carbon monoxide for palladium-catalysed carboxylation reactions. Aminocarbonylation, ketoamide synthesis, and Suzuki–Miyaura reactions of aryl iodides carried out in a two-chamber reaction vessel gave good to excellent yields of carboxylated products.

Introduction

In order to avoid the use of carbon monoxide (CO) gas as a reactant in small scale reactions in situ generation from many sources including carbon dioxide, aldehydes, formates, and formamides such as N-formyl saccharin developed by Manabe and coworkers has been utilized. This circumvents the need for equipping small-scale chemical laboratories with cylinders of this highly toxic, odourless and colourless gas. In early work, the most commonly used CO sources were metal carbonyl compounds such as Mo(CO)₆, which proved useful, among others, for palladium catalysed aminocarbonylations and carboxylative Stille reactions of aryl halides. Recently, we have reported the development of norbornene derivatives such as oCOm-21 as physiologically relevant carbon monoxide releasing molecules. This water soluble Carbon Monoxide Releasing Molecule (CORM) undergoes an E₁,ₐ elimination of HBr to a norbornadienone intermediate that spontaneously undergoes chelotropic release of CO in TRIS-sucrose buffer at pH 7.4 at 37 °C with a half-life of 19 minutes (Scheme 1). The rate of release is pH dependent and at higher pH the half-life is much reduced.

In parallel work to the development of these compounds, we viewed that simpler norborneneone constructs could provide readily accessible and bench stable CO sources for various palladium catalysed carboxylation reactions as originally described by Heck, Suzuki and coworkers and Yamamoto. These would be an alternative to compounds such as sila-carboxylic acids 1a-e and 9-methyl-fluorene-9-carbonyl chloride (2) for CO generation for use in two-chamber reaction system such as that developed, and comprehensively studied, by the Skrydstrup group. They have demonstrated the utility of this approach, using SilaCOgen 1b and COgen 2 (along with their ¹³C and ¹⁴C labelled counterparts) in a number of palladium catalysed carboxylations including, aminocarbonylation, double carbonylations, Heck, and Suzuki–Miyaura reactions of both aryl iodides and bromides. CO release from COgen 2 is triggered in one chamber upon heating with a trip-t-butylphosphine ligated palladium catalyst while that of silacarboxylic acids such as 1a produces CO at ambient temperature upon treatment with a fluoride source. The synthesis of both COgen (2) and SilaCOgen (1a) requires carbonylation with CO₂ to install the carboxyl group (Fig. 1). More recently, this group has developed a tablet form of 2 that contains tri-t-butylphosphonium tetrafluoroborate and Pd(OAc)₂ which allows convenient CO generation without the need for use of a glovebox for carboxylative transformations.

Herein, we report the development of readily accessible, stable norbornene derivatives as efficient base-triggered CO donors as alternatives to 1 and 2 for palladium catalysed carboxylation reactions of aryl iodides using a two-chamber reaction system without the need for glovebox equipment.

Results and discussion

Our initial investigations into the viability of norborneneone based CORMs as suitable CO donors for various palladium catalysed carboxylation utilized 5a as an ex situ CO surrogate.
2,5-Dimethyl-3,4-diphenylecyclopentadienone (3), readily available from the condensation of benzil and 3-pentanone,\(^2\) exists as a reversible dimer, which reacted smoothly with \(N\)-phenyl-3-bromomaleimide (4a) to give cycloadduct 5a in 71% yield as a bench stable solid (Scheme 2). The efficiency of 5a as a CO donor was tested with the aminocarbonylation of \(p\)-iodonaphthalene (6a) and butylamine (7), catalysed by \(\text{Pd}_2(\text{dba})_3\), and using triethylamine as a base. This reaction gave \(N\)-butyl \(p\)-methoxybenzamide (8a) in 97% yield using a two-chamber reaction system similar to that developed by Skrydstrup et al.\(^3\)

Given the success of this reaction, the more readily accessible norbornadiene derivative 5b was synthesized from commercially available bromomaleic anhydride (4b) and cyclopentadienone dimer 3 as an 8 : 1 mixture of the endo and exo-isomers in 96% yield, again as a bench stable solid. It was viewed that the anhydride moiety of 5b would better facilitate the base induced elimination of HBr due to the electron withdrawing property of the anhydride compared to that of imide 5a.

With the synthesis of cycloadduct 5b complete, we investigated the scope of this compound as a CO source for palladium-catalysed carboxylation reactions. Initially, aminocarbonylations using a range of aryl iodides as the limiting reagent with both butylamine and morpholine as coupling partners were investigated (Scheme 3). In general, 1.5 equivalents of CO donor 5b were dissolved in 1,4-dioxane and 2.0 equivalents of base were used to liberate CO in Chamber A. In all cases, complete conversion of 5b into 9 was observed. Furthermore, in Chamber B high conversions of aryl iodide substrates into amides 8a–e and 10a–e were observed with isolated yields after column chromatography ranging from 72–99%, as detailed in Tables 1 and 2.

In addition to cycloadduct 5b, a second CO source was investigated which produces a norbornadiene intermediate that spontaneously undergoes chelotropic loss of CO. A Diels–Alder reaction was carried out between cyclopentadienone dimer 3 and diethyl acetylenedicarboxylate in the CO producing chamber (Scheme 4). On heating both chambers in 1,4-dioxane substituted benzene 12 (ref. 25) was produced in Chamber A in 91% yield. The aminocarbonylation reaction in Chamber B (see Table 1; Entries 1 and 2, note c) gave \(N\)-butyl-4-iodo- and \(N\)-butyl-4-nitro-benzamides (8a and 8b) in 95 and 82% yields, respectively.

![Scheme 2](image-url)  
**Scheme 2** Reaction of 3 and 4a or 4b to give corresponding cycloadduct 5a or 5b.

![Table 1](image-url)  
**Table 1** Palladium-catalysed aminocarbonylation reactions carried out with aryl iodides and \(n\)-butylamine. All reactions were carried out at 80 °C for 20 hours in a sealed two-chamber apparatus.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl iodide</th>
<th>Product</th>
<th>Conversion(^a) (%)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a, (R = p)-MeO</td>
<td>8a</td>
<td>100</td>
<td>88 (93)</td>
</tr>
<tr>
<td>2</td>
<td>6b, (R = p)-NO(_2)</td>
<td>8b</td>
<td>100</td>
<td>99 (82)</td>
</tr>
<tr>
<td>3</td>
<td>6c, (R = p)-Br</td>
<td>8c</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>6d, (R = H)</td>
<td>8d</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>6e(^d)</td>
<td>8e</td>
<td>90</td>
<td>88</td>
</tr>
</tbody>
</table>

\(^a\) Measured from \(^1\)H NMR spectra of the crude reaction mixture as compared to the limiting reactant. An example is provided in Fig. SI1 (ESI). \(^b\) Isolated yields after column chromatography. \(^c\) Yield in brackets have been obtained from reactions using the alternative source of CO in Chamber A as shown in Scheme 4. \(^d\) \(6e\) = 1-iodonaphthalene.
Table 2  Palladium-catalysed aminocarbonylation reactions carried out with aryl iodides 6a–e and morpholine (9). All reactions were carried out at 100 °C for 20 hours in a sealed two-chamber apparatus.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl iodide</th>
<th>Product</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a, R = p-MeO</td>
<td>10a</td>
<td>100 (80)</td>
<td>75 (39)</td>
</tr>
<tr>
<td>2</td>
<td>6b, R = p-NO2</td>
<td>10b</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>6c, R = p-Br</td>
<td>10c</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>6d, R = H</td>
<td>10d</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>6e</td>
<td>10e</td>
<td>80</td>
<td>75</td>
</tr>
</tbody>
</table>

* Measured from 1H NMR spectra of the crude reaction mixture as compared to the limiting reactant. An example is provided in Fig. S1 (ESI). b Isolated yields after column chromatography. c Reaction carried out at 80 °C for 20 h. d 6e = 1-iodonaphthalene.

In order to show the scope of cycloadduct 5b as a CO donor, other palladium catalysed carbonylation reactions were investigated. Following a 2006 report by Kondo et al. on room temperature double carbonylations,26 the Skrydstrup group have successfully utilized both COgen and SilaCOgen as an *ex situ* CO sources for double carbonylation reactions.13,27 The reaction of iodoanisole (6a) and butylamine (7) with CO generated from three equivalents of 5b in Chamber A gave doubly carbonylated z-ketoamide product 13 in 64% yield. This result demonstrated that cycloadduct 5b could liberate CO at room temperature (Scheme 5).

Scheme 4 Reaction of 3 and diethyl acetylenedicarboxylate to give 12 and CO.

Another example of widely utilized palladium catalysed carbonylation reactions is the well-known Suzuki–Miyaura carbonylation. This was first reported in 1998 following development of the cross coupling reaction of the same name.28 A brief investigation into the optimization of reaction conditions for our system showed a ligand-free system could be used and a higher CO/Pd(0) ratio was necessary when compared to the aminocarbonylation reaction. This was achieved by using three equivalents of CO donor in the CO releasing chamber (Scheme 6). With optimized reaction conditions in hand, a series of Suzuki–Miyaura carbonylation reactions were carried out with the goal of synthesizing fenofibrate – a biologically relevant example of an unsymmetrical biaryl ketone. Entry 4, Table 3 shows the synthesis of a model system that involved the synthesis of simpler aryl iodide component 6f reacting with 4-chlorophenylboronic acid (14b) to give the corresponding biaryl ketone 15d in 75% yield. In a similar

Scheme 5 The double carbonylation of p-iodoanisole (6a) and butylamine (7) using cycloadduct 5b as a CO source. Chamber A: toluene, rt. (a) DBU (3.0 eq.), Chamber B: Pd2(dba)2 (5 mol%), [tBu3PH]BF4 (10 mol%), DBU (2.0 eq.), 64%.

Scheme 6 Synthesis of aromatic ketones using 5b (3.0 eq.) and Et3N (3.5 eq.) in 1,4-dioxane as the CO source from Chamber A for palladium-catalysed carbonylative Suzuki–Miyaura reactions. Reagents and conditions: 80 °C; Chamber A: 5b (3.0 eq.), NEt3 (3.5 eq.), dioxane. Chamber B: aryl iodides 6 (1 eq.), Pd2(dba)2 (2 mol%), K2CO3 (3.0 eq.), anisole.

Table 3 Suzuki–Miyaura carbonylation reactions carried out with selected aryl iodides and boronic acids. All reactions were carried out at 80 °C for 25 hours in a sealed two-chamber apparatus.

<table>
<thead>
<tr>
<th>Entry (%)</th>
<th>Aryl iodide</th>
<th>Boronic acid</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>14a</td>
<td>15a</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>6d</td>
<td>14a</td>
<td>15b</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>6a</td>
<td>14b</td>
<td>15c</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>6f</td>
<td>14b</td>
<td>15d</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>6g</td>
<td>14b</td>
<td>15e</td>
<td>80</td>
</tr>
</tbody>
</table>

* Isolated yields after column chromatography.
Conclusions

In conclusion, we have shown that readily synthesized norbornones 5a and 5b are excellent alternatives to using CO gas for small scale carbonylation reactions using a two-chamber reaction system. CO release is triggered by organic bases such as triethylamine and DBU. With the latter base release is rapid even at room temperature which is essential for forming ω-ketoamides via a double carbonylation reaction. Alternatively, CO gas can be generated by the thermally promoted Diels–Alder reaction of cyclopentadienone 4 and diethyl acetylenedicarboxylate which was also effective for aminocarbonylation reactions.

Experimental

Aminocarbonylation reactions

General procedure A: synthesis of secondary amides from aryl halides and primary amine (n-butylamine) using diethyl acetylenedicarboxylate as CO source. The two-chamber system, equipped with Teflon® coated magnetic stirrer bars, was loaded with all solid reagents. In Chamber A; diene dimer 3 (0.75 eq.). In Chamber B; Pd₂(dba)₃ (0.025 eq.) and PPh₃ (0.1 eq.). Then, all liquid reagents were added via syringe: to Chamber A; 1,4-dioxane (5 mL) and diethyl acetylenedicarboxylate (1.5 eq.); to Chamber B; 1,4-dioxane (4 mL), aryl halide 6 (1 eq.; aryl halides that were solids at room temperature were added with the catalyst and ligands), n-butylamine (7) (2.3 eq.) and Et₃N (2.3 eq.). The system was sealed with screwcaps fitted with silicon seal inserts. The two chamber system was heated in an oil bath at 80 °C with stirring, for 20 h. The reaction mixture was cooled to rt then the solvents in Chamber A and B were individually concentrated in vacuo. The crude material obtained was purified by silica gel column chromatography.

General procedure B: synthesis of secondary and tertiary amides from aryl halides and primary amine (n-butylamine) using cycloadduct 6b as the CO source. The two-chamber system, equipped with Teflon® coated magnetic stirrer bars, was loaded with all solid reagents. In Chamber A; cycloadduct 5b (1.5 eq.). In Chamber B; Pd₂(dba)₃ (0.025 eq.) and PPh₃ (0.1 eq.), the aryl halide (1 eq.), if solid. Then, all liquid reagents were added to Chamber B via syringe: aryl halide 6 (1 eq.) (if liquid), n-butylamine (2.3 eq.) and 1,4-dioxane (Chamber A: 5 mL, Chamber B: 4 mL). The system was cooled in an ice bath (with sodium chloride) and flushed with argon. Et₃N (2.3 eq.) was added to Chamber B via syringe, and the cap (fitted with a silicon seal insert) screwed in place. Et₃N (2.3 eq.) was also added to Chamber A via syringe, and the system was sealed. The two chamber system was heated in an oil bath at either 80 or 100 °C with stirring, for 20 h. The reaction mixture was cooled to rt then the solvent in Chamber B was concentrated in vacuo. The crude material obtained was purified by silica gel column chromatography.

Suzuki–Miyaura carbonylation

General procedure C: synthesis of unsymmetrical biaryl ketones using cycloadduct 6b as the CO source. The two-
The two chamber system was heated in an oil bath at 80 °C for 1 h. The reaction mixture was cooled to rt, and the solvent in Chamber B was concentrated in vacuo. The crude material obtained was purified by silica gel column chromatography.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Notes and references