Rhodium-Catalyzed Intramolecular Aminocarbonylation of Aryl Halides Using Aldehydes as a Source of Carbon Monoxide

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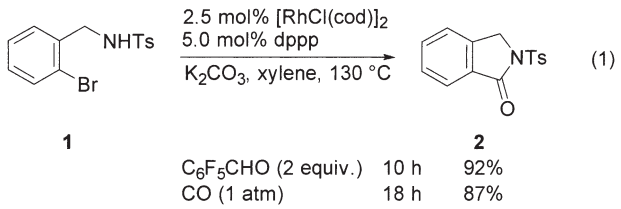
The reaction of *N*-Ts-(2-bromophenyl)alkylamines with aldehydes in the presence of a catalytic amount of a rhodium complex results in the intramolecular aminocarbonylation of the aryl halides to give five-, six-, and seven-membered benzolactams.

Catalytic carbonylation reactions using carbon monoxide have found widespread use in many areas of organic synthesis.[1] The use of highly poisonous carbon monoxide, however, is essential for the carbonylation reaction to proceed. Recently, carbonylation processes, in which gaseous carbon monoxide is not required, have been developed, to solve this drawback. It has been reported that palladium-catalyzed carbonylative coupling reactions of aryl halides with alcohols and amines can be carried out using carbon monoxide generated in situ by the treatment of formate[2] or formamide[3] with strong bases. Alper has also reported on the palladium-catalyzed carbonylation of organic halides using chloroform and aqueous alkali.[4] A palladium carbonyl complex formed from its noncarbonyl precursor and the dichlorocarbene, generated in situ from the reaction of chloroform and aqueous alkali, plays a key role in this carbonylation. Owing to the requirement of a strong base, these methods are limited to applications of carbonylations which permit or require the presence of a base.[2–4] Larhed reported that the in situ liberation of carbon monoxide from $Mo(CO)_6$ under neutral conditions could be applied to the catalytic aminocarbonylation of aryl halides with amines, but the reaction required a stoichiometric amount of $Mo(CO)_6$.[5] Simonato utilized carbon monoxide, generated by the thermolysis of formic acid, which requires a high temperature (190 °C), to achieve the hydrocarboxylation of cyclohexene.[6]

We previously reported on the first use of aldehydes as a source of carbon monoxide in carbonylation reactions,[7] in the catalytic Pauson–Khand-type reaction of enynes, in which aldehydes were used as a source of carbon monoxide.[8] This development of a CO gas-free carbonylation method under neutral and mild conditions prompted us to explore its general use. We wish to describe herein a novel carbonylation system, in which aldehydes are used as a source of carbon monoxide, which is applicable to the intramolecular animocarbonylation of aryl halides leading to the production of benzolactams.[9]

The reaction of *N*-Ts-2-bromobenzylamine (**1**, 0.25 mmol) with pentafluorobenzaldehyde (0.50 mmol) and K_2CO_3 (0.50 mmol) in xylene (2 cm^3) at 130 °C in the presence of $[RhCl(cod)]_2$ (0.00625 mmol) and 1,3-bis(diphenylphosphino)-propane (dppp, 0.0125 mmol) afforded the benzolactam **2** in 92% yield (Eq 1).[10] This demonstrates that the carbonylation system, which consists of the rhodium catalyst and an aldehyde, is applicable, not only to the carbonylative cyclization of enynes,[7] but to the aminocarbonylation of aryl halides as well, which involves the oxidative addition of an aryl halide to the rhodium metal.[11]

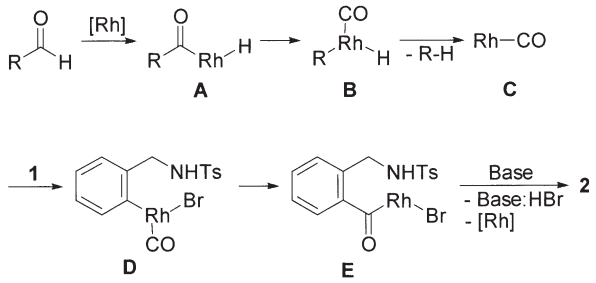


(1)

When the reaction of **1** was carried out under the same conditions using 1 atm of carbon monoxide instead of C_6F_5CHO, 87% of **2** was obtained, although a longer reaction time (18 h) was required for the complete consumption of **1** (Eq 1). These results show that the presence of excess carbon monoxide appears to inhibit the catalysis.

Some other rhodium complexes, such as $RhCl(CO)(PPh_3)_2$ (86%), $[RhCl(cod)]_2$/dppe (51%), and $[RhCl(cod)]_2$/dppb (32%), also showed catalytic activity. Among other aldehydes examined as a source of carbon monoxide, the use of cinnamaldehyde (5 equiv.) and paraformaldehyde (10 equiv.) resulted in the formation of **2** in 93% and 69% yields, respectively, although only a trace amount of **2** was obtained in the case of benzaldehyde, *p*-anisaldehyde, *p*-trifluoromethylbenzaldehyde, and decanal. When the substituent on the nitrogen atom was changed to Boc, the corresponding benzolactam was obtained in 22% yield along with 63% of unreacted substrate (54 h), while no lactams were obtained from the reaction of the substrates having other substituents, such as H, Ac, Bn, and *p*-$MeOC_6H_4$. A high temperature is not essential for the reaction to proceed; 59% of **2** was obtained at 110 °C for a 19 h reaction.

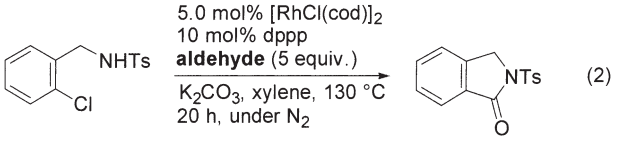
Although the mechanism for the intramolecular aminocarbonylation of an aryl halide is currently unclear, a possible mechanism is shown in Scheme 1. This mechanism includes (a) decarbonylation of the aldehyde by the rhodium(I) complex to form the rhodium(I) carbonyl **C**, (b) oxidative addition of the aryl halide to rhodium(I) to give arylrhodium(III) halide **D**,[12] (c) insertion of CO into the rhodium–carbon bond to give acylrho-



Scheme 1. Possible mechanism.

dium(III) complex **E**, and (d) reductive cleavage of the acylrhodium bond to produce benzolactam **2** and regeneration the rhodium(I) complex. In the reaction using C_6F_5CHO, cinnamaldehyde, and paraformaldehyde, decarbonylation of the acylrhodium(III) **A** to R-rhodium(III) **B** would readily occur due to thermodynamic stability of **B** (R = C_6F_5, Ph–CH=CH, and H), and therefore, optimal carbonylation catalysis would result.

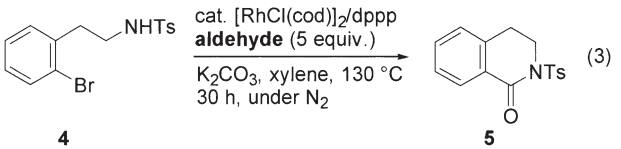
Replacement of the Br atom in **1** by a Cl atom also resulted in the formation of **2** in high yields both with pentafluorobenzaldehyde and with cinnamaldehyde as the source of carbon monoxide (Eq 2).



3 **2** (2)

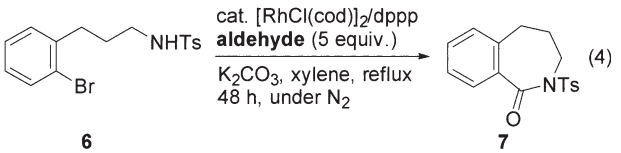
C_6F_5CHO	82%
PhCH=CHCHO	91%

The carbonylation reaction described here could be applied to the syntheses of six- and seven-membered benzolactams. Under conditions similar to Eq 2, the reactions of *N*-Ts-2-(2-bromophenyl)ethylamine (**4**) with pentafluorobenzaldehyde and cinnamaldehyde gave the six-membered benzolactam **5**[13] in 84% and 93% yields, respectively (Eq 3). In the case of *N*-Ts-3-(2-bromophenyl)propylamine (**6**), pentafluorobenzaldehyde served as a more efficient source of carbon monoxide than cinnamaldehyde, in contrast to the above reactions; the reaction of **6** with pentafluorobenzaldehyde for 48 h afforded 66% of the seven-membered benzolactam **7**[14] along with 16% of recovered **6**, while, with cinnamaldehyde, 17% of **7** was obtained and 77% of **6** was recovered (Eq 4).



4 **5** (3)

C_6F_5CHO	84%
PhCH=CHCHO	93%



6 **7** (4)

C_6F_5CHO	66% (16% of **6**)
PhCH=CHCHO	17% (77% of **6**)

In conclusion, we describe here the first catalytic intramolecular aminocarbonylation of an aryl halide using aldehydes as the source of carbon monoxide. The CO gas-free carbonylation system, consisting of the rhodium(I) complex and an aldehyde as a source of carbon monoxide, has also proven to be effective for carbonylation reactions under basic conditions. Thus, this carbonylation system has a wider scope of application than other CO gas-free carbonylations reported to date, and has the potential to become a new, powerful tool for carbonylation. The present reaction affords a new protocol for the synthesis of benzolactams.

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References and Notes

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9 For a representative report of the catalytic intramolecular aminocarbonylation of aryl halides, see: M. Mori, K. Chiba, and Y. Ban, *J. Org. Chem.*, **43**, 1684 (1978).
10 (**2**). White solid; mp 216–218 °C; R_f 0.29 (hexane/AcOEt = 2/1); ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 4.91 (s, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.62, 49.80, 123.30, 124.98, 128.09, 128.77, 129.71, 130.16, 133.82, 135.35, 140.97, 145.19, 166.06; IR (KBr, cm^{-1}) 1724, 1363, 1174, 1088; MS m/z (relative intensity, %) 223 (M^+–SO_2, 100); HRMS-FAB (m/z): $[M+H]^+$ calcd for $C_{15}H_{14}NO_3S$, 288.0694; found, 288.0693.
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13 (**5**). White solid; mp 132–133 °C; R_f 0.24 (hexane/AcOEt = 2/1); ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.13 (t, J = 6.0 Hz, 2H), 4.23 (t, J = 6.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.99 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.61, 28.89, 44.68, 127.33, 127.39, 128.14, 128.52, 129.12, 129.38, 133.45, 136.10, 139.21, 144.70, 163.39; IR (KBr, cm^{-1}) 1686, 1598, 1351, 1243, 1088; MS m/z (relative intensity, %) 237 (M^+–SO_2, 65), 118 (100); HRMS-FAB (m/z): $[M+H]^+$ calcd for $C_{16}H_{16}NO_3S$, 302.0851; found, 302.0850.
14 (**7**). White solid; mp 117–118 °C; R_f 0.28 (hexane/ether = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.17 (quint, J = 6.5 Hz, 2H), 2.43 (s, 3H), 2.84 (t, J = 6.5 Hz, 2H), 3.82 (t, J = 6.5 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 8.01 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.55, 29.19, 29.61, 44.77, 127.11, 128,64, 128.82, 129.32, 129.38, 132.57, 133.88, 136.04, 137.93, 144.67, 170.12; IR (KBr, cm^{-1}) 1692, 1354, 1167, 1001; MS m/z (relative intensity, %) 251 (M^+–SO_2, 52), 144 (100); HRMS-FAB (m/z): $[M+H]^+$ calcd for $C_{17}H_{18}NO_3S$, 316.1007; found, 316.1000.