Synthesis of Ketones from Iodoalkenes, Carbon Monoxide and 9-Alkyl-9-bora-bicyclo[3.3.1]nonane Derivatives via a Radical Cyclization and Palladium-Catalysed Carbonylative Cross-coupling Sequence

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Under irradiation (tungsten lamp), the palladium-catalysed three-component cross-coupling reaction between iodoalkenes such as 6-iodo-1-hexene or their derivatives, carbon monoxide (1 atm) and 9-alkyl- or 9-aryl-9-BBN derivatives (9-BBN = 9-borabicyclo[3.3.1]nonane) produces unsymmetrical ketones in moderate to high yields; the oxidative addition of iodoalkenes to a palladium(0) complex proceeds via a radical process, thus allowing cyclization of the iodoalkenes to five-membered rings prior to the couplings with carbon monoxide and boron reagents.

Carbonylative cross-coupling reactions of organic halides with organometallic reagents such as tin,[1] boron,[2] aluminium[3] and zinc[4] compounds have been extensively studied to provide a direct synthesis of unsymmetrical ketones. Although a wide variety of organic electrophiles, e.g. aryl, 1-alkenyl, benzyl and allyl halides, have been utilized for palladium-catalysed cross-coupling reactions, the reaction has not been extended to alkyl halides possessing an sp³ carbon with a β-hydrogen due to the slow rate of oxidative addition of palladium(0) complexes and the fast β-hydride elimination from σ-alkylpalladium(ii) intermediates. Thus, the use of alkyl halides for cross-coupling reactions is a challenging problem.[5] We have recently found that the palladium-catalysed carbonylative cross-coupling reaction of 9-alkyl-9-borabicyclo[3.3.1]nonanes (9-R-9-BBN) with iodoalkanes takes place readily under irradiation with a tungsten lamp, thus allowing the use of alkyl halides in the synthesis of ketones.[6] A particularly interesting feature in this transformation is that the oxidative addition of iodoalkanes to the palladium(0) complex proceeds through a radical process under this irradiation; presumably, it is initiated by an electron transfer from the palladium(0) complex to iodoalkanes to form a radical pair (Pd^{I}X + R·). Thus, the iodoalkenes 1 or their derivatives provided cyclized ketones via radical cyclization prior to the subsequent carbon monoxide insertion and coupling with 9-alkyl- or 9-aryl-9-BBN derivatives, as shown in Scheme 1.

The use of 9-BBN derivatives was essential both for alkyl and even for aryl couplings, whereas arylboronic acids or their esters have been successfully utilized for many direct cross-coupling reactions with organic halides.[7] Pd(PPh₃)₄ gave the best catalytic activity, in combination with K₃PO₄ as a base to accelerate the transmetallation from boron to the palladium(ii) intermediate. Irradiation using a tungsten lamp greatly accelerated the reaction rate, but UV irradiation resulted in only low yields of ketones.

In a typical procedure, Pd(PPh₃)₄ (0.06 mmol) and powdered anhydrous K₃PO₄ (6 mmol) were placed in a flask flushed with

1a X = CH₂, Y = H   2   3
1b X = O, Y = H
1c X = NTs, Y = Me
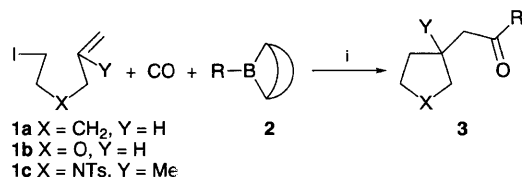
Scheme 1 *Reagents and conditions:* i, hv, Pd(PPh₃)₄, K₃PO₄, benzene, room temp.
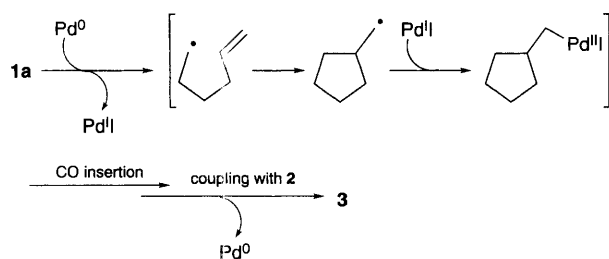
Scheme 2

nitrogen. Benzene (12 ml), a solution of 9-alkyl- † or 9-aryl-9-BBN[8] (1 mol dm⁻³ solution in THF, 2 mmol) and iodoalkene (3 mmol) were added successively. The flask was flushed with 1 atm carbon monoxide and then placed before a 100 W unsmoked tungsten lamp and the mixture stirred for 16–24 h at room temp.

The results obtained are summarized in Table 1. The representative iodoalkenes, which have been utilized for the radical cyclization reaction,[9] afforded the corresponding cyclized ketones in yields of 59–79%. The reaction of iodoalkyne also provided a five-membered unsaturated ketone (entry 6). Annulation of iodocycloalkenes resulted in cis-fused bicyclic alkanes, though the stereochemistry of the carbonyl side chains was not fixed (entries 8–10). The coupling with 9-phenyl-9-BBN shown in entry 10 gave the only product for which both isomers were purely separated by chromatography. The cis-cyclization (4 and 5)‡ starting from the trans-iodide was clearly evidenced by NOE (ca. 4%) between the two hydrogens at the bridgehead carbons.

The catalytic cycle of the present reaction is analogous to the related carbonylative coupling reactions,[10] except that radical cyclization takes place during the oxidative addition of iodoalkenes to the palladium(0) complex (Scheme 2). The evidence of radical chain process for oxidative addition of alkyl halides with M(PEt₃)₃ (M = Pt, Pd) was first offered by Osborn.[11] Although this unique process has not been appreciably used for the catalytic reaction with palladium,[12] the present reaction exhibits a selectivity characteristic of a radical process: the predominance of five-membered over six-membered cyclization;§ the formation of cis-fused bicyclic alkanes from the trans-iodides (entries 9 and 10); and the distortion of the carbonyl side chain stereochemistry (entries 6, 8–10). Thus, the results do not reflect the alternative cyclization process taking place, the first oxidative addition of the C–I bond to palladium(0) complex, followed by insertion into an intramolecular double bond.[13]

The radical-mediated cyclization process developed by Stork[9] has proven a valuable synthetic tool for creation of the carbon–carbon bond for the construction of polycyclic compounds involving a five-membered ring. Although this technique is very general for a hydrogen or iodine atom transfer termination, combination with the palladium-catalysed process may allow further extension of a carbonyl side chain after the cyclization.
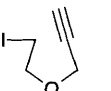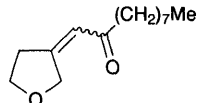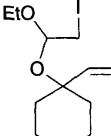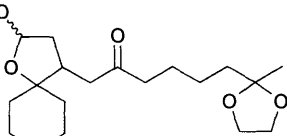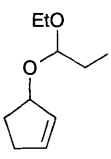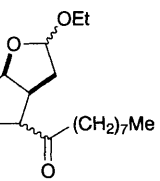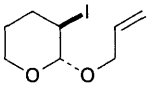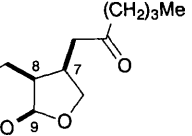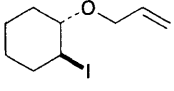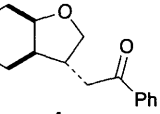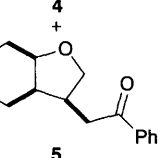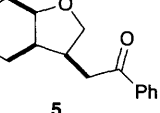
Footnotes

† The borane solutions obtained by hydroboration of alkenes with 9-BBN (Aldrich) were used directly.

‡ Both isomers were separated by chromatography over silica gel with CH₂Cl₂–ether = 40:1. *Spectroscopic data for* **4**: ¹H NMR (400 MHz, CDCl₃) δ 1.2–1.9 (m, 9 H), 2.5–2.7 (m, 1 H), 3.02 (dd, 1 H, *J* = 8.3, 17.5 Hz), 3.20 (dd, 1 H, *J* = 6.1, 17.5 Hz), 3.46 (dd, 1 H, *J* = 5.0, 9.0 Hz), 3.97 (dt, 1 H, *J* = 4.4, 4.7 Hz), 4.34 (dd, 1 H, *J* = 7.7, 9.0 Hz), 7.47 (dd, 2 H, *J* = 7.1, 7.5 Hz), 7.56 (d, 1 H, *J* = 7.5 Hz), 7.95 (d, 2 H, *J* = 7.1 Hz).

Table 1 Synthesis of ketones (Scheme 1)

Entry	Iodoalkene	2, R =	Product	Yield (%)[a]
1	**1a**	octyl	**3** (X = CH_2, Y = H, R = octyl)	60
2	**1b**	octyl	**3** (X = O, Y = H, R = octyl)	73
3	**1b**	2-MeC$_6$H$_4$	**3** (X = O, Y = H, R = 2-MeC$_6$H$_4$)	70
4	**1c**	octyl	**3** (X = NTs, Y = Me, R = octyl)	59
5	**1c**	2-thienyl	**3** (X = NTs, Y = Me, R = 2-thienyl)	60
6		octyl		74[b]
7				68[c]
8		octyl		62[d]
9		butyl		77[c]
10		phenyl		79 (4 : 5 = 3 : 2)

[a] Isolated yields by column chromatography, based on **2**. [b] A 1 : 1 mixture of (E)- and (Z)-isomers. [c] Inseparable mixture of 2 : 1. [d] A mixture of at least 4 stereoisomers. [e] The major product was tentatively assigned by NOE between hydrogens at C-7, 8 and 9. However, the product contained less than 10% of α-carbony group isomer at C-7.

For **5**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.1–2.1 (m, 9 H), 2.9–3.0 (m, 2 H), 3.19 (dd, 1 H, J = 9.4, 19.5 Hz), 3.59 (dd, 1 H, J = 8.2, 9.3 Hz), 4.02 (q, 1 H, J = 3.0 Hz), 4.14 (t, 1 H, J = 8.2 Hz), 7.47 (dd, 2 H, J = 7.1, 7.5 Hz), 7.56 (d, 1 H, J = 7.5 Hz), 7.96 (d, 1 H, J = 7.1 Hz).

§ Under similar conditions, the reaction of allyl 3-iodopropyl ether with 9-octyl-9-BBN gave a mixture of cyclized and uncyclized ketones; 3-(2-oxodecanyl)tetrahydropyran (13%) and 1-allyloxy-4-dodecanone (12%).

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