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Palladium-Catalyzed Carbonylative Cross-Coupling Reaction of Iodoalkanes with 9-Alkyl-9-BBN Derivatives. A Direct and Selective Synthesis of Ketones

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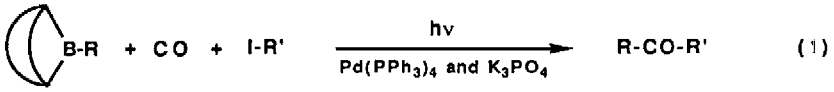
Summary: The synthesis of unsymmetrical ketones by means of the palladium-catalyzed carbonylative cross-coupling reaction of 9-alkyl-9-BBN derivatives with iodoalkanes under a carbon monoxide atmosphere is described.

The cross-coupling reaction[1] of organic electrophiles with organometallic reagents in the presence of transition metals provides a synthetic challenge to the method of forming carbon-carbon bonds. Although the methodology with a variety of organometallic reagents has been currently developed, such reactions are limitedly applicable to 1-alkenyl, 1-alkynyl, aryl, allyl, and benzyl halides, but not being extended to alkyl halides with sp^3 carbon containing β-hydrogen.[2] In a course of our study[3] on the cross-coupling reaction of organoboron compounds, we have discovered that 9-alkyl-9-borabicyclo[3.3.1]nonane derivatives (9-R-9-BBN) react with iodoalkanes under a carbon monoxide atmosphere in the presence of K_3PO_4 and a catalytic amount of $Pd(PPh_3)_4$ yielding unsymmetrical ketones[4,5] in good yields. The reaction was extremely accelerated by irradiation of light (Eq. 1).



R=primary, R'= primary, secondary, and tertiary

Although the reaction takes place slowly under dark, the irradiation of light accelerates the rate of coupling as shown in Table 1. The irradiation of UV or a higher carbon monoxide pressure gives no satisfactory results. Tetrakis(triphenylphosphine)palladium(0) gives the best catalytic activity among the catalysts we examined such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd(CO)(PPh_3)_3$, $PdCl_2(dppe)$, $PdCl_2(dppf)$, and $Pt(PPh_3)_4$.

As shown in Table 2, various iodoalkanes including primary, secondary, and tertiary iodides are carbonylated and coupled with 9-alkyl-9-BBN under mild conditions to afford the corresponding ketones. The reaction can be extended readily to the relatively large alkenes such as a side chain of steroid. The cross-coupling reaction with alkyl groups having β-hydrogen often affords competitive side reactions: the formation of alkenes caused by β-hydride elimination and the isomerization of alkyl groups.[4,5] In the present reaction, however, such side reactions are not serious, less than 10%, as revealed in the experimental section and the entry 6 in Table 2. As a variety of functional groups in both iodoalkanes and 9-alkyl-9-BBN are tolerated in the coupling reaction, the synthesis of several functionalized ketones having acetal, nitrile, and carbomethoxy

Table 1. Reaction Conditions[a]

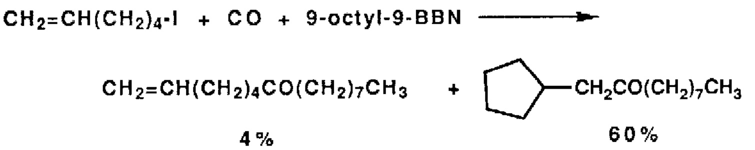
entry	iodide (equiv)	CO (atm)	time (h)	light	yield (%)[b]
1	1.1	1	52	dark	18
2	1.1	1	24	dark	27[c]
3	1.1	1	24	UV	40
4	1.1	1	5	visible	44
5	1.1	1	24	visible	50
6	1.5	1	24	visible	67
7	1.5	3	24	visible	32

[a] All reactions were carried out at room temperature in 6 mL of dioxane (entries 1-4) or benzene (entries 5-7) using 9-octyl-9-BBN (1 mmol), 1-iodohexane (1-1.5 mmol), $Pd(PPh_3)_4$ (3 mole%) and K_3PO_4 (3 mmol). [b] GLC yields based on 9-octyl-9-BBN. [c] The reaction was conducted at 60 °C.

groups is feasible by this reaction.

Typically, 9-nonadecanone was prepared by the following procedure. To a solution of 9-octyl-9-BBN (2 mmol) in THF, obtained by hydroboration of 1-octene with 9-BBN, were added benzene (12 mL), $Pd(PPh_3)_4$ (0.06 mmol), powdered K_3PO_4 (6 mmol), and 1-iodododecane (2 mmol). The flask was flushed with 1 atm of carbon monoxide, and the reaction mixture was stirred for 24 h at room temperature under irradiation of 100W unsmoked tungsten light. After the usual work up, analysis revealed the formation of 9-nonadecanone (63%), 1-decene (8%), and undecenoic acid (10%). When, 1.5 equiv of 1-iododecane was used, the yield of 9-nonadecanone was improved to 71%.

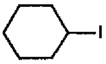
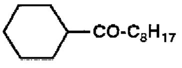
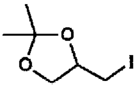
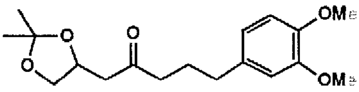
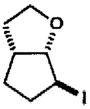
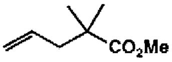
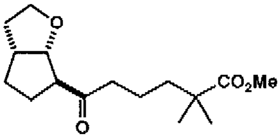
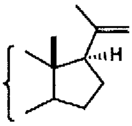
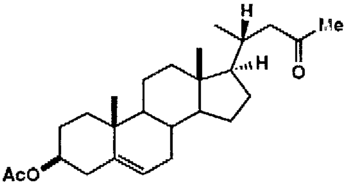
A particularly interesting transformation is observed in the case of reaction with 1-iodo-5-hexene (Eq. 2). The reaction with 9-octyl-9-BBN under the standard carbonylative coupling conditions does not furnish the expected ketone as the major product, instead, 1-cyclopentyl-2-dodecanone is obtained in a 60% yield. The transformation may be presumed by the mechanism involving a free radical process[6,4c] at the oxidative addition of iodoalkenes to palladium(0) complex.



(2)

Under an atmosphere of carbon monoxide, $Pd(PPh_3)_4$ may be converted to carbonyl(triphenylphosphine)palladium[7] which is a coordinatively saturated and relatively unreactive species decreasing the electron density on the palladium(0) complex. The complex can undergo dissociation[8] of ligands by irradiation of light to form unsaturated palladium complexes which facilitate an electron transfer to alkyl halides to form a radical pair ($Pd^IX + R\cdot$). This pair can be collapsed to the oxidative adduct (RPdX). Migration of alkyl group to a coordinated carbon monoxide to give RCOPdX, transfer of alkyl group from 9-

Table 2. Synthesis of Ketone (Eq. 1)[a]

entry	iodide	alkene	product	yield (%)[b]
1	$C_6H_{13}I$	1-octene	C_6H_{13}-CO-C_8H_{17}	67
2	MeI	$CH_2{=}CH(CH_2)_8CO_2Me$	Me-CO-$(CH_2)_{10}CO_2Me$	(76)
3		1-octene		65
4	t-C_4H_9I	1-octene	t-C_4H_9-CO-C_8H_{17}	69
5		4-allylveratrole		(73)
6				(65)[c]
7	$NC(CH_2)_3I$	$CH_2{=}CH(CH_2)_2OCH_2Ph$	$NC(CH_2)_3$-CO-$(CH_2)_4OCH_2Ph$	(70)
8	$MeO_2C(CH_2)_3I$	$CH_2{=}CH(CH_2)_8CN$	$MeO_2C(CH_2)_3$-CO-$(CH_2)_{10}CN$	(65)
9	MeI			(50)

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[a] A solution of 9-alkyl-9-BBN in THF obtained by hydroboration of alkene (1 mmol) with 9-BBN (1.05 mmol) was directly used for the next coupling reaction. The couplings was coducted in benzene (6 ml) at room temperature for 24 h using iodoalkane (1.5 mmol), CO (1 atm), $Pd(PPh_3)_4$ (0.03 mmol), K_3PO_4 (3 mmol) under irradiation of 100W tungsten light.

[b] GLC yields based on alkenes employed and isolated yields are in parentheses.

[c] The product was contaminated by the cis isomer in 11%.

R-9-BBN in an aid of base,[3] and reductive elimination of ketone complete a catalytic cycle of the carbonylative coupling.

Use of alkyl halides for the palladium-catalyzed cross-coupling reaction has been hampered by the slow rate of oxidative addition and the β-elimination from oxidative adducts. The present study could make it possible for alkyl halides to be used as organic electrophiles. Indeed, our preliminary results[9] indicated that 1-iodohexane couples with 9-octyl-9-BBN under similar conditions to give tetradecane in a yield of 60 %. Further studies of the alkyl-alkyl coupling are now in progress.

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