J. Am. Chem. Soc. **1993,** *115,* 7027-7028

Palladium-Catalyzed Iodine–Zinc Exchange Reactions. A New Palladium-Mediated Intramolecular Carbozincation of Alkenes

Heinz Stadtmüller, Ruth Lentz, Charles E. Tucker,
Thomas Stüdemann, Wolfgang Dörner, and Paul Knochel*[1]

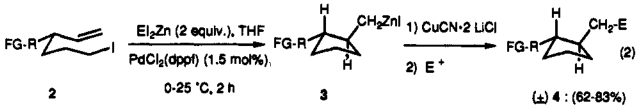
Fachbereich Chemie der Philipps-Universität Marburg
Hans-Meerwein-Strasse, W-35043 Marburg, Germany

Received April 5, 1993

The preparation of organolithiums from the corresponding iodides by an iodine–lithium exchange[2,3] is one of the most efficient preparations of these organometallics. Extensions of the iodine–metal exchange reaction to the preparation of RMgX or RZnX have been rarely used and are lacking of generality.[4] We have recently reported that primary organic iodides undergo an iodine–zinc exchange reaction when treated with an excess of Et_2Zn (5 equiv, neat, 50–55 °C, 10–40 h).[5] The resulting dialkylzincs proved to be excellent reagents for a catalytic enantioselective addition to aldehydes (62–95%, 60–97% ee).[5] Remarkably, several functional groups can be present in the organic iodides (CN, COOR, Cl, $B(OR)_2$); however, the need of a large excess of Et_2Zn and the long reaction time limit somewhat the synthetic utility of the reaction. We observed recently that the addition of small amounts of CuI (0.3 mol %) halves the reaction times and reduces the amount of Et_2Zn needed from 5 equiv to 1.5 equiv.[5,6] This observation led us to examine the effect of catalytic amounts of various transition-metal complexes on the rate of the iodine–zinc exchange reaction. We found little effect with $MnCl_2$, $CoCl_2$, and $FeCl_2$. However, the addition of small amounts of Pd(II) or Ni(II) complexes had a pronounced effect on the rate of the exchange reaction. Thus, the addition of Et_2Zn (2 equiv) to octyl iodide (1 equiv) and a catalytic amount of dichloro-(1,1′-bis(diphenylphosphino)ferrocene)palladium(II) (**1**; $PdCl_2$(dppf), 3 mol %)[7] in THF at –60 °C produces, after 1.5 h at 25 °C, octylzinc iodide (78%)[8] and ca. 8.5% of octene (*β*-hydride elimination). Interestingly, whereas the Cu(I) catalysis provides a dialkylzinc, the Pd(II) and Ni(II) catalysis leads to an alkylzinc iodide as shown by gravimetric analysis[9] (eq 1).

$$\mathrm{Oct_2Zn} \xleftarrow[\substack{\mathrm{CuI\ (0.3\ mol\%),\ 50\ ^\circ C} \\ \mathrm{-\ C_2H_5I}}]{\mathrm{Et_2Zn\ (1.5\ equiv.),\ neat}} \mathrm{OctI} \xrightarrow[\substack{\mathrm{PdCl_2(dppf)\ (1.5\ mol\%),\ 0\text{-}25\ ^\circ C} \\ \mathrm{-\ H_2C{=}CH_2,\ -CH_3CH_3}}]{\mathrm{Et_2Zn\ (2\ equiv.),\ THF}} \mathrm{OctZnI} \quad (1)$$

Functionalized iodides such as $EtO_2C(CH_2)_3I$ or $NC(CH_2)_3I$ react within 0.1–0.5 h at 25 °C (>90%) without the formation of any *β*-hydride elimination product. In the absence of $PdCl_2$(dppf), these exchange reactions with Et_2Zn require ca. 24 h at 25 °C. In order to get further insights into the reaction mechanism,[10] we used 5-hexenyl iodides **2** as precursors and were pleased to observe smooth ring closure leading to a cyclopentylmethylzinc iodide of type **3** (ca. 80% yield). In strong contrast to numerous radical cyclizations which provide a highly reactive cyclized intermediate radical,[11] we obtain an organozinc reagent which, after transmetalation with CuCN·2LiCl,[12] produces a copper derivative that reacts with a wide range of electrophiles in satisfactory yields (eq 2 and Table I).[13]



Because of the exceptional functional group compatibility of organozinc species, this cyclization provides a unique construction of polyfunctional cyclopentanes. This is demonstrated by the alkyl iodides **2d** (FG-R = *p*-NCPh), **2e** (FG-R = *p*-*t*-$BuCO_2Ph$), and **2f** (see Table I) which cyclize smoothly, leading, after quenching with ethyl 2-(bromomethyl)acrylate,[14] to the (±)-*trans*-cyclopentanes (>98% *trans*) **4h** (83%) and **4i** (62%) and to the triester **4j** (73%). A trisubstituted double bond undergoes

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(1) Alfred P. Sloan Foundation Fellow, 1992–1993.

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(8) This yield of RZnX was determined by capillary GC analysis using an internal standard. By assuming this conversion and adding CuCN·2LiCl (1 equiv) and ethyl *α*-(bromomethyl)acrylate (1.5 equiv), ethyl 2-nonylacrylate was isolated in 87% yield. When $Ni(acac)_2$ (1.5 mol %) was used instead of $PdCl_2$(dppf), a shorter reaction time was observed (25 °C, 0.5 h) and ethyl 2-nonylacrylate was isolated in 85%.

(9) After the completion of the exchange reaction, the excess of Et_2Zn was removed under vacuum and the residue was hydrolyzed with diluted aqueous HNO_3. A known volume of this solution was treated with an excess of aqueous $AgNO_3$, leading to AgI (ca. 90% of the theoretical value).

(10) The Pd-catalyzed exchange reaction exhibits some of the following features: (i) it is inhibited by small amounts of nitrobenzene; (ii) it does not occur with alkyl tosylates or mesylates or if Me_2Zn is used; (iii) it is a very slow reaction in ether, suggesting a radical character for the Pd-catalyzed iodine–zinc exchange.

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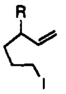
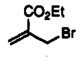
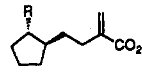
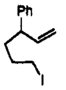
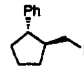
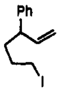
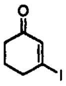
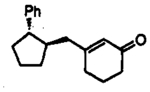
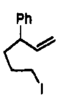
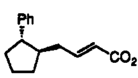
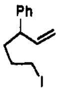
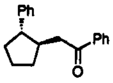
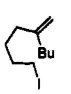
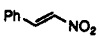
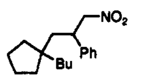
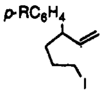
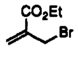
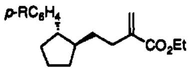
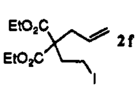
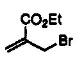
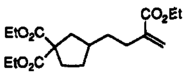
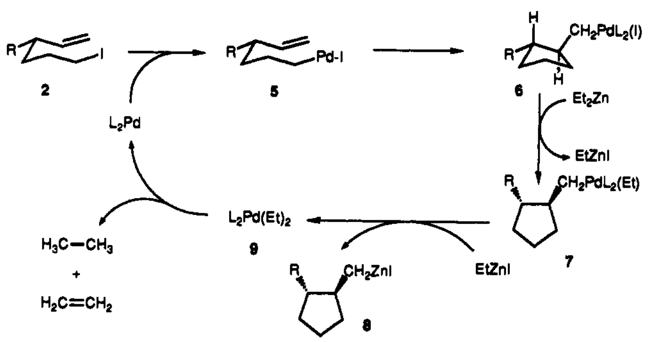
Table I. Cyclization Products **4** Obtained by the Palladium-Catalyzed Carbozincation of Alkyl Iodides **2** Followed by Their Copper-Mediated Trapping with an Electrophile

iodide		electrophile	product		yield (%)[a]
	**2a**: R = H **2b**: R = Ph			**4a**: R = H **4b**: R = Ph	80 73
	**2b**	I_2		**4c**	77
	**2b**			**4d**	80
	**2b**	HC≡C–CO$_2$Et		**4e**	64
	**2b**	PhCOCl		**4f**	76
	**2c**			**4g**	81
	**2d**: R = CN **2e**: R = OPiv			**4h**: R = CN **4i**: R = OPiv	83 62
	**2f**			**4j**	73

[a] Overall isolated yields of analytically pure products.

cyclization; thus **2c** (Table I) provides, after addition to nitrostyrene in the presence of CuCN·2LiCl, the expected nitro derivative **4g** in 81% yield.[15] Although only fragmentary mechanistic information is available, we propose the following tentative mechanism (Scheme I): the *in situ* generated L$_2$Pd (L$_2$ = dppf) oxidatively adds to the alkyl iodide **2**, leading to a Pd(II) intermediate (**5**) which undergoes a carbopalladation reaction,[16] affording the cyclized complex **6**. Reaction with Et$_2$Zn provides the mixed dialkylpalladium **7**, which does not reductively eliminate (a slow process if both organic groups attached to Pd are saturated).[17] The complex **7** prefers to further exchange its ligands[18] with remaining EtZnX, providing the alkylzinc iodide **8** and Et$_2$PdL$_2$ (**9**), which rapidly decomposes,[19,20] leading to ethylene and ethane and regenerating the Pd(0) catalyst.

Scheme I



Further extensions of this new palladium-catalyzed intramolecular carbozincation reaction are currently underway in our laboratories.[21]

Acknowledgment. We thank the DFG (SFB 260), the Fonds der Chemischen Industrie, the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous support, and the Schering AG (Bergkamen) for the generous gift of chemicals.

Supplementary Material Available: Analytical data for all products (3 pages). Ordering information is given on any current masthead page.

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(15) Typical procedure for preparation of 1-butyl-1-(3-nitro-2-phenylpropyl)cyclopentane (**4g**): a 3-necked flask equipped with a magnetic stirring bar, a thermometer, and a gas inlet and charged with PdCl$_2$(dppf) (**1**) (0.07 g, 2 mol %) in THF (5 mL) was cooled to –78 °C. The iodide (**2c**) (1.33 g, 5 mmol) and Et$_2$Zn (1.0 mL, 1.23 g, 10 mmol) were added. After the mixture was warmed to 25 °C and stirred for 4 h, the solvent and excess Et$_2$Zn were removed (0.1 mm Hg, 25 °C, 1 h). After addition of THF (5 mL) and cooling of the mixture to –40 °C, CuCN·2LiCl (5 mmol) in THF (5 mL) was added, and the reaction mixture was warmed to 0 °C (5 min) and cooled to –78 °C. Nitrostyrene (1.12 g, 7.5 mmol) in THF (3 mL) was added, and the reaction mixture was slowly warmed to 0 °C and stirred for 2 h. After the usual workup, the residual oil was purified by flash column chromatography (ether: hexanes 1:9) to yield **4g** as a clear oil (1.16 g; 81%).

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(18) Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313.

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(20) Ethylene has been characterized as being a product of this reaction.

(21) The reaction can be extended to benzylic halides. Benzyl bromide is converted to benzylzinc bromide (Et$_2$Zn (2.5 equiv), 1.5 mol % Pd(dba)$_2$, 6 mol % PPh$_3$, DMF, 25 °C, 1 h). After transmetalation with CuCN·2LiCl and reaction with ethyl α-(bromomethyl)acrylate, the desired product (ethyl 2-(2-phenylethyl)acrylate) is obtained in 74% yield. Under our reaction conditions, less than 5% of reduction product and less than 2% of Wurtz-coupling product is observed. Compare with: (a) Agrios, C.; O'Dowd, H.; Srebnik, M. *Abstracts of Papers*, 205th National Meeting of the American Chemical Society, Denver, CO, March 28–April 2, 1993; American Chemical Society: Washington, DC, 1993; ORGN 158. (b) Wu, G.; Shimoyama, I.; Negishi, E. *J. Org. Chem.* **1991**, *56*, 6506.