# Palladium-Catalyzed Cross Coupling Reactions of $\beta$-Iodo $\beta,\gamma$-Enones with Organozinc Chlorides

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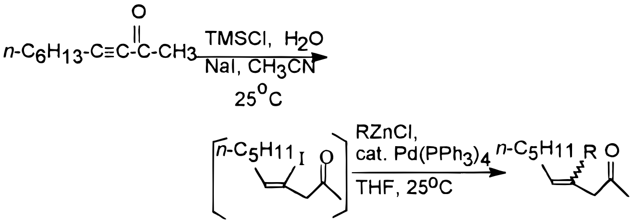
The synthesis of $\beta$-substituted $\beta,\gamma$-enones poses a synthetic challenge. We have reported recently that the one-pot reaction of terminal alkynes with *in situ* generated hydrogen iodide, from sodium iodide/trimethylsilyl chloride/water, and organozinc compounds in the presence of palladium catalyst provides a simple and useful method for the preparation of *gem*-disubstituted alkenes.[1] Under these reaction conditions acetylenic ketones give ($Z$)-$\beta$-iodo $\beta,\gamma$-enones with isomeric purity $\geq$95% as the hydroiodination product.[2,3] These undergo cross coupling reactions to give various $\beta$-substituted-$\beta,\gamma$-enones in high yield but with *low* stereoselectivities.

Representative alkyl, phenyl, 2-furyl, and silylated alkynylzinc chlorides were chosen for the cross coupling reaction. The results obtained in the hydroiodination of 3-decyn-2-one followed by cross coupling with these organozinc chlorides are shown in Table 1. The yields of products from the cross coupling reaction are high. Mechanistically, the first step in this reaction would be the 1,4-addition of iodide anion to the trimethylsilyl activated ynone to give the iodo allenylsilyl ether which undergoes stereoselective 1,3-hydrogen shift and kinetic protonation to give ($Z$)-4-iodo-4-decen-2-one.

Surprisingly, we found that the cross coupling reaction occurred with loss of stereoselectivity.[4] We also observed that there was no change in the stereochemistry of the carbon−carbon double bond after the intermediate ($Z$)-4-iodo-4-decen-2-one was stirred with 5 mol % of Pd(PPh$_3$)$_4$ in THF at room temperature for 12 h as judged by $^1$H-NMR spectral analysis. Once phenylzinc chloride was added to the reaction mixture, a 1:1 mixture of the *E* and *Z* stereoisomers of the product 4-phenyl-4-decen-2-one was formed after 0.5 h at room temperature, as determined by $^1$H-NMR spectral analysis. This confirmed that the basic organozinc compound causes the loss in the stereoselectivity of the cross coupling step. This loss may result from coordination of the zinc cation with the carbonyl oxygen after transmetalation. This coordination effect will accelerate the $\beta$-elimination process to form an alleneone intermediate, as shown in Figure 1. After nonstereoselective rehydropalladation and reductive elimination, an ($E$)/($Z$) mixture will be produced with low stereoselectivity. In the case of furylzinc chloride, we observed mainly retention of the stereochemistry of the carbon−carbon double bond in the cross coupling process. This result may be due to coordination of the oxygen atom in the furan ring with the zinc cation, which in the same way decreases the rate of the $\beta$-elimination relative to reductive elimination.

**Table 1. One-Pot Conversion of 3-Decyn-2-one into 4-Substituted-4-decen-2-one**



($E$) or ($Z$) **1a-f**

| entry | R | yield, % | ($Z$):($E$)[a,b] |
|---|---|---|---|
| 1 | Me | 72 (**1a**) | 1:1 |
| 2 | Bu | 67 (**1b**) | 1:1 |
| 3 | Ph | 83 (**1c**) | 1:1 |
| 4 | 2−furyl | 79 (**1d**) | 20:1 |
| 5 | PhC≡C− | 76 (**1e**) | 1:3 |
| 6 | Me$_3$SiC≡C− | 74 (**1f**) | 1:1 |

[a] The ratio was determined by $^1$H-NMR spectral analysis of the crude reaction mixture. [b] The stereochemistry was determined by 2D-NOESY $^1$H-NMR spectral analysis.

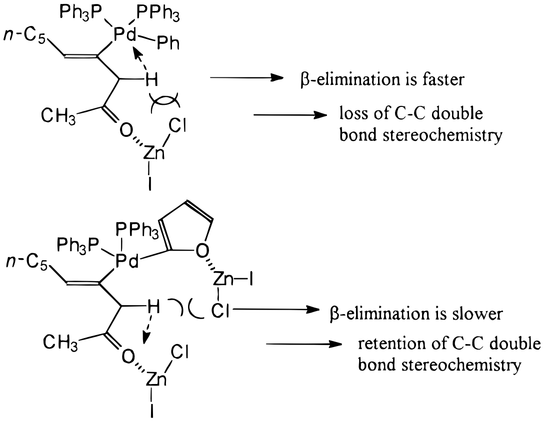


**Figure 1.**

## Conclusion

The one-pot reaction of ($Z$)-4-iodo-4-decen-2-one with *in situ* generated hydrogen iodide followed by cross coupling with organozinc chlorides in the presence of Pd(PPh$_3$)$_4$ provides a simple method for the preparation of 4-substituted-4-decen-2-ones in high yield. The coordination effect between zinc and oxygen is an important factor to be considered in the palladium-catalyzed cross coupling reactions.

## Experimental Section

Reactions involving organometallic compounds were carried out in oven- and/or flame-dried glassware equipped with a side arm, gas outlet adapter, and mercury bubbler for the purpose of maintaining an inert atmosphere. Tetrakis(triphenylphosphine)palladium was prepared by published procedures.[5] Zinc chloride was dried before use at >50 °C and at <1 mmHg for 2 h. Organozinc reagent was prepared by treating the corresponding organolithium with 1 equiv of dry zinc chloride. All other materials were obtained from commercial suppliers and used without further purification unless otherwise stated.

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[3] Luo, F. T.; Hsieh, L. C. *Tetrahedron Lett.* **1994**, *35*, 9585.

[4] For highly stereoselective cross coupling reactions of alkenyl iodide and organozinc compounds via palladium catalyst, see: (a) Negishi, E. I.; Matsushita, H.; Okukado, N. *Tetrahedron Lett.* **1981**, *22*, 2715. (b) Negishi, E. I.; Luo, F. T. *J. Org. Chem.* **1983**, *48*, 1560 and references cited therein.

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**General Procedure for the Preparation of 4-Substituted-4-decen-2-ones.** To anhydrous sodium iodide (0.75 g, 5 mmol) in $CH_3CN$ (5 mL) in a dry flask under a nitrogen atmosphere were added sequentially TMSCl (0.55 g, 5 mmol), water (0.09 g, 5 mmol), and 3-decyn-2-one (0.76 g, 5 mmol). The mixture was stirred at rt for 30 min and then allowed to react with 1.1 equiv of the organozinc chloride, prepared from the corresponding organolithium compound and zinc chloride in THF, in the presence of tetrakis(triphenylphosphine)palladium(0) (0.29 g, 0.25 mmol). The reaction was stirred for another 6 h at rt, quenched with water, and extracted with ether. The ether layer was concentrated *in vacuo* and the respective $\beta$-substituted $\beta,\gamma$-unsaturated ketone was purified by column chromatography (silica gel, hexane/ether = 4/1).

***(E)-4-Methyl-4-decen-2-one, (E)*-1a:** colorless oil; IR ($CHCl_3$) $\nu$ 2960, 2930, 1700 cm$^{-1}$; $^1$H-NMR ($CDCl_3$, TMS) $\delta$ 0.89 (t, $J$ = 7.0 Hz, 3 H), 1.27−1.43 (m, 6 H), 1.62 (s, 3 H), 1.9−2.1 (m, 2 H), 2.14 (s, 3 H), 3.12 (s, 2 H), 5.27 (tq, $J$ = 7.2, 1.1 Hz, 1 H) ppm; $^{13}$C-NMR ($CDCl_3$, TMS) $\delta$ 16.15, 23.94, 27.90, 28.65, 29.16, 31.39, 47.32, 54.87, 128.03, 129.35, 207.89 ppm; MS *m/z* 168 ($M^+$), 153, 125, 110; HRMS calcd for $C_{11}H_{20}O$ 168.1514, found 168.1519. Anal. Calcd for $C_{11}H_{20}O$: C, 78.50; H, 11.99. Found: C, 78.65; H, 11.85.

***(Z)-4-decen-2-one, (Z)*-1a:** colorless oil; IR ($CHCl_3$) $\nu$ 2959, 2928, 1703 cm$^{-1}$; $^1$H-NMR ($CDCl_3$, TMS) $\delta$ 0.89 (t, J = 6.8 Hz, 3 H), 1.27−1.43 (m, 6 H), 1.71 (s, 3 H), 1.9−2.1 (m, 2 H), 2.13 (s, 3 H), 3.05 (s, 2 H), 5.39 (t, J = 6.8 Hz, 1 H) ppm; $^{13}$C-NMR ($CDCl_3$, TMS) $\delta$ 13.91, 22.42, 27.94, 28.20, 29.05, 31.39, 47.32, 54.87, 128.54, 130.22, 206.93 ppm; MS *m/z* 268 ($M^+$), 153, 125, 110; HRMS calcd for $C_{11}H_{20}O$ 168.1514, found 168.1517.

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**Supporting Information Available:** Physical constants for enones (*Z*)- and (*E*)-**1b**−**f** are available (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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