Tetrahedron Letters, Vol.32, No.35, pp 4453-4456, 1991
Printed in Great Britain

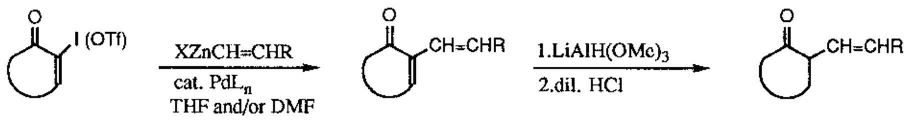
0040-4039/91 \$3.00 + .00
Pergamon Press plc

STRICTLY REGIO-CONTROLLED METHOD FOR α-ALKENYLATION OF CYCLIC KETONES VIA PALLADIUM-CATALYZED CROSS COUPLING

Ei-ichi Negishi,* Zbyslaw R. Owczarczyk, and Douglas R. Swanson
Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, USA

Summary: Cyclic α-iodoenones and α-triflyloxyenones, but not α-bromoenones, smoothly react with alkenylzinc and related derivatives in the presence of a catalytic amount of a palladium-phosphine complex, such as $Pd(PPh_3)_4$ or $Cl_2Pd(PPh_3)_2$ treated with *n*-BuLi (2 equiv), to give α-alkenylenones which can be conjugately reduced to the corresponding α-alkenyl ketones with complete retention of both enone regiochemistry and alkenyl stereochemistry.

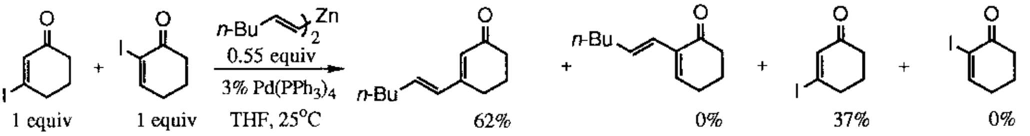
Methods of introducing an E- or Z-alkenyl group in an α-position of ketones with strict control of regiochemistry are highly desirable but rare.[1,2] We recently reported an indirect method requiring conversion of conjugated enones into α-bromoenones protected as their cyclic ketal derivatives.[1] Besides being somewhat cumbersome, the conversion of conjugated enones into their cyclic ketal derivatives has proved to be problematical in some cases even with a modified procedure using bis(trimethylsiloxy)ethane.[3] We now report that cyclic α-iodoenones and α-triflyloxyenones, but not α-bromoenones, directly react with alkenylmetal derivatives containing Zn, Al, or Sn in the presence of a catalytic amount of a palladium-phosphine complex, such as $Pd(PPh_3)_4$ or $Cl_2Pd(PPh_3)_2$ treated with 2 equiv of *n*-BuLi, to give α-alkenylenones which can be conjugately reduced to the corresponding α-alkenyl ketones (eq. 1).



(1)

X = halogen or alkenyl, $PdL_n = Pd(PPh_3)_4$, $Cl_2Pd(PPh_3)_2$ + 2 *n*-BuLi, etc.

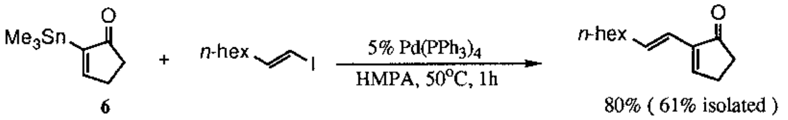
In trying to assess the relative reactivity of α- and β-haloenones, we compared the reactions of 0.55 equiv of (*E*)-$(n\text{-}BuCH{=}CH)_2Zn$ derivatives with α-bromo-2-cyclohexenone, β-bromo-2-cyclohexenone, and 1-bromocyclohexene in the presence of 3 mol% of $Pd(PPh_3)_4$ in DMF. The reaction of β-bromo-2-cyclohexenone was complete within 1 h at 25°C, producing 3-[(*E*)-1-hexenyl]-2-cyclohexenone in 77% yield. Although much more sluggish, the reaction of 1-bromocyclohexene also gave 1-[(*E*)-1-hexenyl]cyclohexene in 46% yield along with an 8% yield of bis(1-cyclohexenyl) in 24 h at 75°C. On the other hand, the reaction of α-bromo-2-cyclohexenone did not yield the cross coupling product, even though the starting α-bromoenone was totally consumed within 1 h at 25°C. The lower reactivity and higher instability of α-haloenones relative to the β-halo isomers[4,5] were also demonstrated by the results of a competitive experiment shown in eq. 2. These results mandate that the desired cross coupling reaction of α-haloenones be faster than their decomposition reaction.



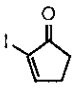
(2)

The experimental results of α-alkenylation of cyclic α-iodoenones and α-triflyloxyenones are summarized in **Table I**. The required α-iodoenones, such as **1** and **2**, can be prepared in 50-60% yields by treating the corresponding enones with NaN_3 and ICl in MeCN.[6] The preparation of **3** was achieved via Zr-promoted bicyclization-iodination of 7-(trimethylstannyl)-1,6-heptenyne.[7] Commercially available 2-hydroxy-3-methyl-2-cyclopenten-1-one was treated with $(CF_3SO_2)_2O$ and NEt_3[8] to give **4** in 53% yield. The relative efficiency of several metals widely used in Pd-catalyzed cross coupling was determined using **1** as a test α-iodoenone. The alkenylmetal derivatives were prepared from the parent alkenyllithium via transmetallation, except in cases where hydrometallation provides directly the required reagents. As indicated in **Table I**, alkenyl derivatives containing Zn[9,10] and Al[9,11] yielded very satisfactory results. (*E*)-1-Hexenyltri(*n*-butyl)stannane[12] did not react with **1** at 25°C, but the reaction proceeded at 65°C to give, after 13 h, **5** in 64% yield. The other (*E*)-1-hexenylmetal derivatives containing $ZrCp_2Cl$[4,10a] (27%), Cu•$MgBr_2$[13] (<2%), $BO_2C_6H_4$[14] (<2%), MgBr[15] (<2%), and Li[16] (<2%) were unsatisfactory in our hands, producing **5** in yields indicated in parentheses. We also successfully achieved coupling between **6** and (*E*)-*n*-HexCH=CHI in 80% (61% isolated) yield[17] (eq. 3), but failed to achieve cross coupling in a related reaction with **7**. The present method appears to be satisfactory for α-arylation as well. On the other hand, preliminary results indicate that the corresponding reactions of *n*-Bu_2Zn and $(n\text{-BuC}{\equiv}\text{C})_2Zn$ may not produce the desired coupling products in significant yields.[18] In most cases, a Pd catalyst generated in situ by treating $Cl_2Pd(PPh_3)_2$ with 2 equiv of *n*-BuLi is used. This *n*-BuLi procedure has proved to be a convenient way of generating an active Pd catalyst from thermally stable $Cl_2Pd(PPh_3)_2$. For the conversion of **3** into **8**, however, it was necessary to use a catalyst generated in situ by treating $Cl_2Pd[P(2\text{-furyl})_3]_2$[19] with 2 equiv of *n*-BuLi. Tetrahydrofuran (THF), which is satisfactory for many cases of Pd-catalyzed alkenyl-alkenyl cross coupling,[4,9-11] is unsatisfactory for the desired α-alkenylation. The use of DMF, DMSO, and N-methylpyrrolidone (NMP) has proved to be essential. In favorable cases, the dimers of enones have not been detected in more than trace quantities. The use of a 10% excess of the alkenylmetal reagents has usually led to the formation of the corresponding conjugated dienes in roughly 5-15% yields.

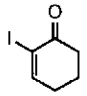
We have previously demonstrated[1] that α-alkenylenones can be conjugately reduced with freshly prepared $LiAlH(OMe)_3$ (4 equiv) and CuBr (4 equiv).[20] Workup with 2N HCl is satisfactory in most cases, leading to exclusive α-protonation without causing regio- and/or stereo-scrambling of the *E* or *Z* alkenyl side chain. In the case of **9**, the use of methanolic NH_4Cl led to the formation of **10** in 90% yield. On the other hand, workup with HOAc-THF at -20°C immediately followed by quenching with saturated $NaHCO_3$ at -20°C cleanly provided **11** in 80% yield. Unfortunately, we have thus far been unsuccessful in conjugately reducing either **8** or **12**, even though the reaction of **12** with $LiCuMe_2$ (3 equiv) afforded **13** in 85% yield.



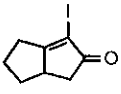
(3)



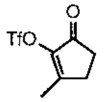
1



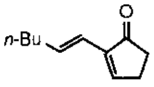
2



3

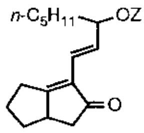


4

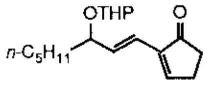


5

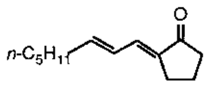
7



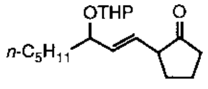
8 a: Z = THP, b: Z = MOM



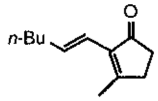
9



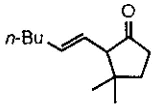
10



11



12



13

Table I. Palladium-Catalyzed α-Alkenylation of α-Iodo- and α-Triflyloxyenones[a]

$(RCH{=}CH)_nM^b$							
R	M	*n*	Enone	Catalyst[c]	Solvent	Cross-coupled product, %[d]	RCH=CH-)$_2$ %[e]
(*E*)-*n*-Bu	Zn	2	**1**	I	THF	31	12
(*E*)-*n*-Bu	Zn	2	**1**	I	THF-DMF (1:1)	87	6
(*E*)-*n*-Bu	Zn	2	**1**	I	DMF	100(86)	10
(*E*)-*n*-Bu	Zn	2	**1**	II	DMF	88	5
(*E*)-*n*-Bu	Zn	2	**1**	I	NMP	74	24
(*E*)-*n*-Bu	Zn	2	**1**	I	DMSO	80	4
(*E*)-*n*-Bu	$AlMe_2$	1	**1**	I	DMF	71	7
(*E*)-*n*-Bu	$Al(Bu\text{-}i)_2$	1	**1**	I	DMF	89	3
(*E*)-*n*-Bu	$Al(Bu\text{-}i)_2$[f]	1	**1**	I	DMF	44	2
(*E*)-*n*-Bu	$SnBu_3$	1	**1**	I	DMF	trace	trace
(*E*)-*n*-Bu	$SnBu_3$	1	**1**	I	DMF	64[g]	6[g]
(*E*)-*n*-Bu	$ZrCp_2Cl$[f]	1	**1**	I	DMF	27	6[h]
(*Z*)-*n*-Bu	Zn	2	**1**	I	DMF	99(89)	8
(*E*)-*n*-Bu	Zn	2	**2**	I	DMF	81(75)	12
(*E*)-*n*-Bu	Zn	2	*i*	I	DMF	83	6
k	ZnBr	1	**1**	I	DMF	89	8
(*E*)-*n*-Bu	Zn	2	**4**	I	DMF	58(45)	10
(*E*)-*n*-Bu	Zn	2	**3**	I	DMF	82(66)	18
j	ZnBr	1	**3**	I	DMF	13	32
j	ZnBr	1	**3**	III	DMF	51	18
k	ZnBr	1	**3**	I	DMF	52	28
k	ZnBr	1	**3**	III	DMF	81(63)	20
m-Tolyl	Zn	2	**1**	I	DMF	92	11

[a] Unless otherwise mentioned, the reaction was carried out at 25°C for 1 h using a 10% excess of the alkenylmetal reagent. [b] Unless otherwise mentioned, the reagent was prepared by treatment of the corresponding alkenyllithium with an appropriate metal halide. [c] I = $Cl_2Pd(PPh_3)_2$ + 2 *n*-BuLi. II = $Pd(PPh_3)_4$. III = $Cl_2Pd[P(2\text{-furyl})_3]_2$ + 2 *n*-BuLi. The amount of a catalyst was 3-5 mol%. [d] By ^1H NMR and/or GLC. The number in parentheses is an isolated yield. [e] Unless otherwise mentioned, the yield of the enone dimer and the amount of the starting enone remaining unreacted are both <2-3%. [f] Prepared by hydrometallation of alkynes. [g] The reaction was run at 60-65°C for 13 h. [h] The starting enone **1** remained unreacted to the extent of 18%. [i] 2-Triflyloxy-2-cyclohexenone. [j] (*E*)-*n*-C_5H_{11}CH(OTHP)CH=CH-. [k] (*E*)-*n*-C_5H_{11}CH(OMOM)CH=CH-.

Acknowledgments. We thank the National Institutes of Health (GM 36792) for support of this research and Johnson Mathey for a loan of $PdCl_2$.

REFERENCES AND NOTES

(1) For our earlier paper, see Negishi, E.; Akiyoshi, K. *Chem. Lett.* **1987**, 1007.

(2) For regio-controlled α-alkenylation of ketones with selective introduction of a stereo-defined alkenyl group, see (a) Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251. The regiochemical aspect of the method is unclear. (b) Kosugi, M.; Hagiwara, I.; Migita, T. *Chem. Lett.* **1983**, 839. This method appears to be satisfactory only for α-alkenylation of methyl ketones. (c) Wender, P. A.; Holt, D. A.; Sieburth, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 3348. The stereochemistry of the alkenyl group is limited to that which is accessible via LiAlH reduction of propargyl alcohols. (d) Moloney, M. G.; Pinhey, J. T. *J. Chem. Soc., Chem. Comm.* **1984**, 965; *J. Chem. Soc., Perkin Trans.* **1988**, 2847. (e) Hashimoto, S.; Miyazaki, Y.; Shinoda, T.; Ikegami, S. *Tetrahedron Lett.* **1989**, 1100.

(3) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(4) For an early example of Pd-catalyzed cross coupling of β-bromoenones, see Okukado, N.; Van Horn, D. E.; Klima, W. L.; Negishi, E. *Tetrahedron Lett.* **1978**, 1027.

(5) For related reactions that can be viewed as either α- or β-alkenylation, see (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. (b) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293.

(6) McIntosh, J. M. *Can. J. Chem.* **1971**, *49*, 3045.

(7) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

(8) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.

(9) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393.

(10) (a) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254. (b) Negishi, E.; Luo, F. T. *J. Org. Chem.* **1983**, *48*, 1560.

(11) (a) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729. (b) Negishi, E.; Takahashi, T.; Baba, S. *Org. Synth.* **1987**, *66*, 60.

(12) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (c) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.

(13) Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 959.

(14) (a) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178. (b) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

(15) Dang, H. P.; Linstumelle, G. *Tetrahedron Lett.* **1978**, 191.

(16) Murahashi, S. I.; Yamamura, M.; Yanagisawe, K.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408.

(17) We acknowledge that this experiment was performed by Dr. K. Akiyoshi.

(18) We have previously noted that alkyl- and alkynylmetals can be considerably less reactive than their alkenyl and aryl counterparts. See, for example, Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Organomet. Chem.* **1987**, *334*, 181.

(19) Farina, V.; Baker, S. R.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, *29*, 6043. We thank Drs. V. Farina, W. J. Scott, and L. S. Liebeskind for useful information regarding $P(2\text{-furyl})_3$.

(20) Semelhack, M. F.; Stauffer, R.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180.

(Received in USA 13 May 1991)