Tetrahedron Letters, Vol. 33, No. 7, pp. 919-922, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

Modified Stille Coupling Utilizing α-Iodoenones

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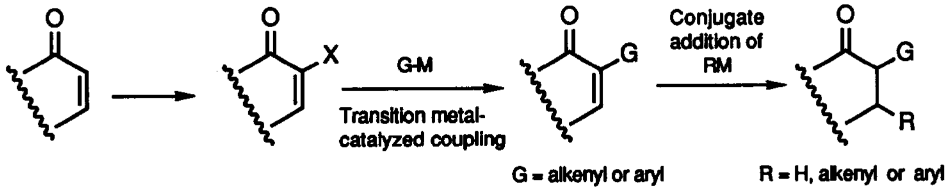
Summary: *α-Iodoenones undergo Pd-catalyzed coupling with alkenyl- and aryltributylstannanes providing an efficient route to the corresponding α-substituted enones.*

A procedure for the facile introduction of carbon functionality at the α-position of α,β-enones would have significant utility in synthesis. Such α-substitution of enones has been accomplished by several divergent techniques. The method of Kim involving treatment of enones with the combination of a dimethyl acetal, pyridine and trimethylsilyl triflate results in α-(1-methoxyalkyl)enones.[1] The metallation of α-bromo-α,β-enones masked as ketals for α-functionalization has been used by several groups, including Smith's.[2] Recently there have been published several related procedures for the coupling of α-trifluoromethanesulphonyloxy-α,β-enones with vinyl or aryl tin reagents.[3,4] The drawback of this procedure is that the enones are available only from the corresponding 1,2-diketones and regiochemical problems may be encounted.

Scheme 1



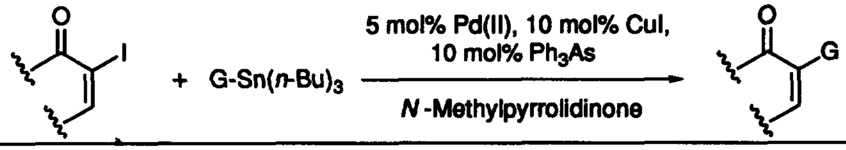
α-Substituted enones could of themselves be of importance but, perhaps, of more general interest would be the utilization of these as intermediates for the production of α-substituted alkanones or α,β-disubstituted alkanones through the aegis of conjugate addition procedures (Scheme 1). Such a strategy, involving first the introduction of the alpha substitutent followed by the beta, would be a reversal of the usual technique involving conjugate addition followed by trapping of the resulting enolate with a carbon electrophile. The inverse process would avoid many of the limitations and pitfalls attendant to the trapping of enolates with carbon electrophiles. As this strategy has the potential of meeting several needs in our current research programs we began to investigate the possibility of utilizing readily available α-bromoenones in classical Stille coupling procedures.[5] With model systems such as the Pd-catalyzed coupling of 2-bromocyclohexenone with tributylvinylstannane we were unable to obtain yields greater than 20%.[6] It became apparent to us that the related α-iodoenones might serve as superior coupling partners. A direct method, involving treatment of enones with iodine/pyridine, developed in conjuction with researchers at Hoffmann-La Roche, provided the desired α-iodoenones.[7] This breakthrough in starting material production along with Liebeskind's[8] observation that copper(I) iodide co-catalyses Stille couplings and Farina's[9] work involving the effects of highly polar solvents and soft ligands, brought all the necessary elements together for our sought goal of a general, mild and high yielding procedure for the syntheses of the desired α-substituted enones.

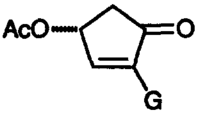
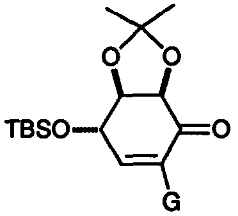
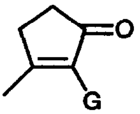
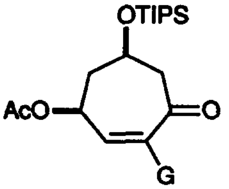
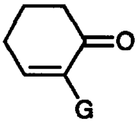
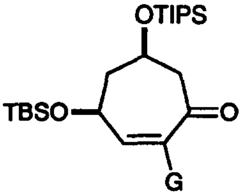
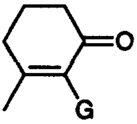
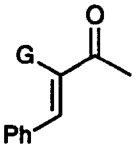
The reaction conditions which we favor utilize *N*-methylpyrrolidinone as solvent, a 5 mol% palladium(II) catalyst (for ease of preparation and air stability *bis*(benzonitrile)-palladium(II) chloride is used), 10 mol% copper(I) iodide, and 10 mol% triphenylarsine in the presence of the α-iodo-α,β-enones and a slight excess of an alkenyl- or aryltributyltin reagent. The results are listed the Table.

Late in the course of development of this chemistry, a communication appeared from the Negishi group reporting that "cyclic α-iodoenones and α-triflyloxyenones, but not α-bromoenones, directly react with alkenyl metal derivatives containing Zn, Al, or Sn in the presence of a palladium phosphine complex. . . . to give α-alkenyl enones . . .".[4] The increased range of coupling partners and the reactions conditions herein described complement the earlier Negishi report and serve to emphasize the remarkable synthetic potential of this variant of Stille chemistry.

Example Procedure. 3-Methyl-2-*p*-tolyl-2-cyclopentenone. In an argon flushed flask, 2-iodo-3-methyl-2-cyclopentenone[7] (222 mg, 1 mmol), copper (I) iodide (19 mg, 0.1 mmol), triphenylarsine (31 mg, 0.1 mmol) and *bis*(benzonitrile)palladium(II) chloride (19 mg, 0.05 mmol) were placed and *N*-methylpyrrolidinone (1 mL) was added. The flask and its black colored solution were immediately lowered into an oil-bath maintained at 100 °C and *p*-tolyl-tributylstannane (0.37 mL, 1.2 mmol) was added. After 30 min the flask and contents were allowed to cool to room temperature and the reaction mixture was dissolved into ethyl acetate (100 mL) and washed successively with aqueous potassium fluoride solution (0.67 satd, 3 x 30 mL) and water (2 x 30 mL). The aqueous layers were combined and then back-extracted with ethyl acetate (60 mL). The combined organic layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a dark oily residue which was purified by column chromatography [silica gel (Kieselgel 60), gradient elution from 2% ethyl acetate / 98% petroleum ether to 10% ethyl acetate / 90% petroleum ether] to give the title enone (165 mg, 89%) as a colorless solid: mp 102-103 °C (EtOAc-petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (4H, d, J = 2.7 Hz), 2.61 (2H, m), 2.51 (2H, m), 2.35 (3H, s), 2.15 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 171.2, 140.1, 137.2, 128.9, 34.7, 31.7, 21.2, 18.2. IR ν_{max} ($CHCl_3$) 1685 cm^{-1}; HRMS for $C_{13}H_{14}O$ (M^+) calcd 186.1044, found *m/z* 186.1040. Anal. Calcd for $C_{13}H_{14}O$: C, 83.87; H, 7.54. Found C, 84.06; H, 7.42.

Table. α-Alkenylation and α-Arylation of α-Iodoenones



Product (isolated yield, reaction temperature, reaction time)[a]	
 G = Vinyl (80%, RT, 12 h) G = 2-Methylpropenyl (76%, 80°C, 1 h) G = p-Tolyl (66%, 50°C, 18 h)	 G = Vinyl (91%, RT, 16 h) G = 2-Methylpropenyl (85%, 80°C, 0.5 h) G = p-Tolyl (60%, 50°C, 18 h)
 G = Vinyl (81%, 90°C, 20 min) G = 2-Methylpropenyl (93%, 100°C, 0.5 h) G = p-Tolyl (89%, 100°C, 30 min)	 G = Vinyl (93%, RT, 4 h) G = 2-Methylpropenyl (55%, 80°C, 2 h) G = p-Tolyl (56%, 80°C, 18 h)
 G = Vinyl (60%, RT, 18 h) G = 2-Methylpropenyl (75%, 80°C, 40 min) G = p-Tolyl (86%, 80°C, 4 h)	 G = Vinyl (95%, RT, 4 h) G = 2-Methylpropenyl (80%, 80°C, 2 h) G = p-Tolyl (95%, 60°C, 24 h)
 G = Vinyl (95%, 80 °C, 30 min) G = 2-Methylpropenyl (83%, 110°C, 5 h) G = p-Tolyl (89%, 110°C, 7 h)	 G = Vinyl (65%, 35°C, 43 h) G = 2-Methylpropenyl (82%, 70°C, 16 h) G = p-Tolyl (87%, 85°C, 16 h)

[a] TBS = t-Bu(Me)$_2$Si; TIPS = (iPr)$_3$Si. All coupled products were characterized by ^{1}H and ^{13}C NMR, IR, microanalysis and/or HRMS.

Acknowledgment. This work was supported by grant CHE 8922955 from the National Science Foundation.

References and Notes

1. Kim, S.; Kim, Y. G.; Park, J. H. *Tetrahedron Lett.* **1991**, *32*, 2043.
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6. Negishi and co-workers have also noted the poor reactively of this substrate in their coupling procedure (ref. 4); they report that this substrate and (*E*)-(*n*-BuCH=CH)$_2$Zn did not yield the cross coupled product.
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8. Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293. These workers report that bromo- and chloro-substituted cyclobutenediones undergo palladium-catalyzed cross coupling with aryl-, alkenyl- and alkynylstannanes. See also Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.
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(Received in USA 13 November 1991)