Pergamon

Tetrahedron Letters 43 (2002) 7111–7114

TETRAHEDRON
LETTERS

# Palladium-catalyzed cross coupling of Grignard reagents with in situ-derived enol phosphates

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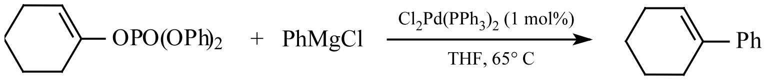
Received 20 June 2002; accepted 8 July 2002

**Abstract**—A useful, one-pot protocol has been developed for the conversion of enolizable ketones to alkylated or arylated olefins by Pd-catalyzed cross coupling of in situ-generated enol phosphate intermediates with Grignard reagents. © 2002 Elsevier Science Ltd. All rights reserved.

The Pd- and Ni-catalyzed cross coupling of enol triflates[1] and -phosphates[2] with organometallic reagents is becoming an increasingly important synthetic tool. When viable, coupling reactions utilizing enol phosphates are preferred relative to use of the corresponding triflates because the former are generally less expensive, easier to prepare, and more stable. While Pd-catalyzed coupling of enol phosphates with certain alkyl Grignard reagents (e.g. $Me_3SiCH_2MgCl$) is known in the literature,[2c] there have been no examples reported of this reaction using aryl Grignard reagents. With this in mind, we briefly screened reaction conditions for this coupling reaction and found that it can proceed readily. As shown in Eq. (1), coupling of the diphenyl enol phosphate derived from cyclohexanone with phenylmagnesium chloride in the presence of a palladium catalyst affords 1-phenylcyclohexene in 81% yield after 1 h at 65°C.[3] The process is indeed catalyzed by Pd; no 1-phenylcyclohexene is produced in the absence of the Pd catalyst.



(1)

The synthetic utility of this reaction could be markedly enhanced if the preparation of the enol phosphate and its subsequent Pd-catalyzed cross coupling could be carried out as a ‘one-pot process’ from the ketone substrate (i.e. ketone → enol phosphate → arylated olefin). In order to do this, the enol phosphate would need to be produced using a base (B:) whose conjugate acid (B:H) would not be acidic enough to protonate the Grignard reagent coupling partner. For this reason, we explored the deprotonation of various ketones utilizing sterically hindered Grignard reagents. As shown in Table 1, *i*-PrMgCl, *t*-BuMgCl, and 2-mesitylmagnesium bromide (MesMgBr) are all effective bases for conversion of β-tetralone to its enol phosphate. On the other hand, only MesMgBr proved to be effective for selective deprotonation of the α-tetralone substrate. Finally, the even more sterically bulky Grignard reagent 2,4,6-tri-*t*-butylphenylmagnesium bromide (TTBP–MgBr)[4] proved necessary to use for efficient conversion of a simple dialkyl ketone (i.e. cyclohexanone) to its enol phosphate derivative.

With viable conditions in hand for preparing enol phosphates in situ from the corresponding ketones using hindered Grignard reagents, we examined the possibility of a ‘one-pot process’ for converting ketones into alkylated/arylated olefins via their enol phosphate intermediates. As shown in Table 2 (entry 1), sequential treatment of a mixture of α-tetralone and $ClPO(OPh)_2$ with MesMgBr produced the corresponding enol phosphate. This solution was treated with the Pd catalyst and then PhMgCl was added at 65°C to give the 1-phenyl-3,4-dihydronaphthalene product in high yield (85% isolated).

Several features of this reaction sequence are noteworthy (Table 2). First, a broad scope with respect to ketone substrates and Grignard reagents used in the

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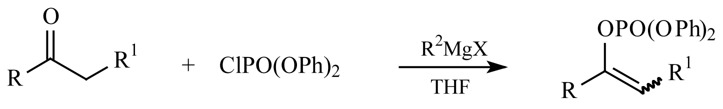
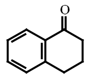
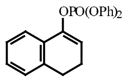
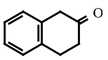
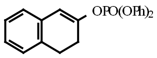
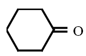
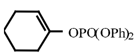
PII: S0040-4039(02)01600-3

**Table 1.** Preparation of enol phosphates from ketones using sterically hindered Grignard reagents[a]

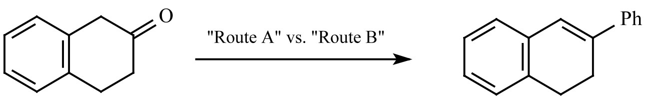


| Entry | Ketone | R$^2$MgX | Reaction Time | Enol Phosphate | Yield[b] | Recovered Ketone[b] |
|---|---|---|---|---|---|---|
| 1 |  | i-PrMgCl | 30 min |  | 28% | 35% |
| 2 | | t-BuMgCl | 30 min | | 14% | 18% |
| 3 | | MesMgBr | 30 min | | 93% | 0 |
| 4 |  | i-PrMgCl | 30 min |  | 97% | 0 |
| 5 | | t-BuMgCl | 30 min | | 98% | 2% |
| 6 | | MesMgBr | 30 min | | 97% | 0 |
| 7 |  | MesMgBr | 30 min |  | 32% | 17% |
| 8 | | TTBP-MgBr[c] | 24 h | | 78% | 7% |

[a] A solution of ketone (1.0 equiv) and ClPO(OPh)$_2$ (1.1 equiv) in THF was treated at 0° with R$^2$MgX (1.0 equiv), and then stirred at room temperature for the indicated period. [b] Yields are by GC analysis using an internal reference standard. [c] 1.4 equiv of TTBP-MgBr was used in this run.

Pd-catalyzed cross coupling portion of the process (aryl and alkyl) are tolerated. Second, the enol phosphate intermediate can be derived from diethyl- or diphenylchlorophosphate with similar results (compare entries 4 and 5). Third, organolithium reagents (e.g. PhLi; entry 2) also function efficiently in the cross coupling portion of this 'one-pot process'.

Finally, this new methodology can offer a useful alternative to 'classical' methodology (i.e. addition of a Grignard reagent to a carbonyl group, followed by acid catalyzed dehydration) for carrying out this same ketone → arylated/alkylated olefin transformation. For example, Scheme 1 compares these two methodologies for conversion of β-tetralone into 2-phenyl-3,4-dihydronapthalene. While this new enol phosphate based route ('Route B') affords the product in high yield (91% isolated), the 'classical' chemistry ('Route A') gives this same product in low yield (29%) along with a significant amount (47%) of starting material indicative of competing enolization of the ketone by the phenyl Grignard reagent.[3] At least in the case of readily enolized ketone substrates, the chemistry described herein can clearly be advantageous to 'classical' methods.



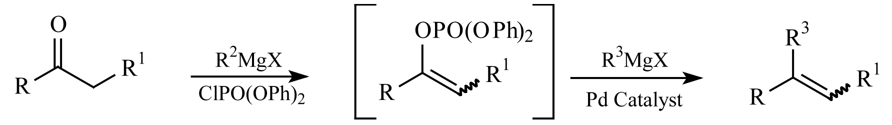
"Route A": 1. PhMgCl; 2. HCl (aq.); 29% yield/47% enolization
"Route B": 1. MesMgBr/ClPO(OPh)$_2$; 2. PhMgCl/Cl$_2$Pd(PPh$_3$)$_2$ cat.; 91% yield

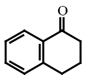
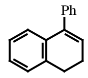
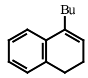
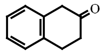
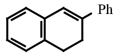
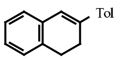
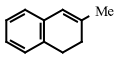
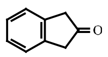
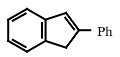
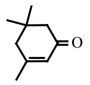
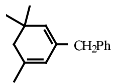
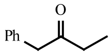
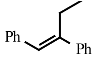
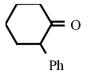
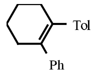
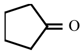
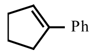
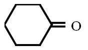
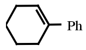
**Scheme 1.**

## Acknowledgements

We thank Professor B. M. Trost (Stanford University), Dr. Tamim Braish (Pfizer Inc.) and Dr. Frank Urban (Pfizer Inc.) for helpful discussions concerning this chemistry.

**Table 2.** Examples of Pd-catalyzed cross coupling of Grignard reagents with in situ-derived enol phosphates[a]



| Entry | Ketone | $R^2MgX$ | $R^3MgX$ | Pd Catalyst | Product | Yield[b] (Isolated) |
|---|---|---|---|---|---|---|
| 1 |  | MesMgBr | PhMgCl | $Cl_2Pd(PPh_3)_2$ |  | (85%) |
| 2 | | MesMgBr | (c) | $Cl_2Pd(PPh_3)_2$ | | 65% |
| 3 | | MesMgBr | n-BuMgCl | $Cl_2Pd(dppf)$ |  | 79% |
| 4 |  | MesMgBr | PhMgCl | $Cl_2Pd(PPh_3)_2$ |  | (91%) |
| 5 | | MesMgBr[d] | PhMgCl | $Cl_2Pd(PPh_3)_2$ | | 76% |
| 6 | | i-PrMgCl | PhMgCl | $Cl_2Pd(PPh_3)_2$ | | 81% |
| 7 | | MesMgBr | p-TolMgBr | $Cl_2Pd(PPh_3)_2$ |  | 82% |
| 8 | | MesMgBr | MeMgCl | $Cl_2Pd(PPh_3)_2$ |  | 82% |
| 9 |  | MesMgBr | PhMgCl | $Cl_2Pd(PPh_3)_2$ |  | (61%) |
| 10 |  | MesMgBr | $PhCH_2MgCl$ | $Pd(PPh_3)_4$ |  | 65% |
| 11 |  | MesMgBr | PhMgCl | $Cl_2Pd(PPh_3)_2$ |  | 65% |
| 12 |  | MesMgBr | p-TolMgBr | $Cl_2Pd(PPh_3)_2$ |  | 58% |
| 13 |  | MesMgBr | PhMgCl | $Cl_2Pd(PPh_3)_2$ |  | 58% |
| 14 |  | TTBP-MgBr | PhMgCl | $Cl_2Pd(PPh_3)_2$ |  | 60% |

[a] All reactions were carried out with stoichiometries, catalyst loadings, temperatures, reaction times, etc., as illustrated in the representative procedure[5]. [b] Unless indicated, yields are by GC analysis using an internal reference standard. [c] Phenyllithium was used in the coupling reaction. [d] The enol phoshate was prepared in situ using $ClPO(OEt)_2$.

## References

1. (a) For Ni-catalyzed cross coupling of an enol triflate with an aryl Grignard reagent, see: Busacca, C. A.; Eriksson, M. C.; Fiaschi, R. *Tetrahedron Lett.* **1999**, *40*, 3101; (b) For a review of enol triflate chemistry, including Ni- and Pd-catalyzed cross coupling reactions, see: Ritter, K. *Synthesis* **1993**, 735.
2. See the following representative references for Ni- or Pd-catalyzed cross coupling of enol phosphates with organometallic reagents: (a) Pd/$R_3Al$: Takai, K.; Sato, M.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 108; (b) Ni/$R_3Al$: Fukamiya, N.; Oki, M.; Aratani, T. *Chem. Ind. (London)* **1981**, 606; (c) Ni- or Pd/$Me_3SiCH_2MgCl$: Hayashi, T.; Fujiwa, T.; Okamoto, Y.; Katsuro, Y.; Kumada, M. *Synthesis* **1981**, 1001; (d) Ni/RMgX: Sofia, A.; Karlstrom, E.; Itami, K.; Backvall, J. *J. Org. Chem.* **1999**, *64*, 1745; (e) Ni/RZnX: Wu, J.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 7875; (f) Pd/$R_nMn$: Fugami, K.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, 2203.

3. These results were obtained by GC analysis of a reaction sample (containing tridecane as an internal standard) quenched in a mixture of 1 M sodium citrate (aq.) and ether.
4. Stuermann, M.; Weidenbruch, M.; Klinkhammer, K. W.; Lissner, F.; Marsmann, H. *Organometallics* **1998**, *17*, 4425.
5. *Representative procedure* (1-phenyl-3,4-dihydronaphthalene; Table 2, entry 1): A solution of 2-mesitylmagnesium bromide in THF (20.0 mL of 1.02 M solution; 20.4 mmol; Aldrich) was added over 10–15 min to a solution containing a mixture of 1-tetralone (2.66 mL; 20.0 mmol) and diphenyl chlorophosphate (4.56 mL; 22.0 mmol). The resultant solution was stirred at 0°C for 30 min, allowed to warm to room temperature, and then stirred for an additional 30 min. The reaction mixture was then treated with dichlorobis(triphenylphosphine)palladium (0.140 g; 1 mol%) and warmed to 65°C. Phenylmagnesium chloride (11.5 mL; 24.0 mmol; 2.08 M in THF) was added over 5–10 min to the reaction mixture, resulting in a gentle reflux of the solvent. After stirring at 65°C for 30 min, the mixture was cooled to room temperature and poured into a mixture of 3N HCl (30 mL) and pentane (30 mL). The phases were separated, and the aqueous portion was extracted with pentane (25 mL). The combined organic phase was washed sequentially with 3N HCl (15 mL), 3N NaOH (twice, using 15 mL each extraction), and brine (20 mL). The resulting organic phase was dried ($MgSO_4$), concentrated, and then distilled using a Kugelrohr apparatus (oven temp. = 120–150°C; 0.1 torr) to provide 3.51 g of 1-phenyl-3,4-dihydronaphthalene (85% yield based on 1-tetralone).