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# Highly Selective Methods for α-Alkenylation and α-Arylation of Ketones via Palladium- or Nickel-Catalyzed Cross Coupling(1)

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Two procedures for α-alkenylation and α-arylation of ketones, that permit, for the first time, introduction of a stereo-defined alkenyl group (E or Z) in the α-position of cyclic ketones in high yields with essentially complete retention (>98%) of the alkenyl stereochemistry are reported. Furthermore, the one that is represented by Eq.2 permits complete control of regiochemistry as well.

One of the highly desirable but underdeveloped synthetic transformations is α-alkenylation of ketones. Critically needed are those methods that permit introduction of an E- or Z-alkenyl group in the α position of cyclic or acyclic ketones with essentially complete regio- and stereo-control. Although some methods for α-alkenylation have been reported,2,3) those that satisfy the above requirements are extremely rare. The reaction of ketone enolates with α-silyl aldehydes2a) provides a promising method, but its stereoselectivity is limited to 90-95% Other promising approaches include the reaction of enolates with enol ether-iron complexes2b) and a reductive rearrangement of alkenyl halohydrins followed by oxidation.3) Their application has, however, been limited to the preparation of the E isomers. We report here two highly selective and high-yielding procedures involving Pd- or Ni-catalyzed alkenyl-alkenyl coupling.4)

Our current attempts at the synthesis of cyclopentanoids have made it desirable to be able to introduce an alkenyl group in an α-position of a cyclopentanone derivative with essentially 100% control of regio- and stereochemistry. We have therefore examined the applicability of various reported methods for the Ni- or Pd-catalyzed α-arylation or α-alkenylation of methyl ketone5,6) and ester7) enolates to the desired α-alkenylation as well as α-arylation of cyclopentenolates using (E)-1-octenyl iodide and p-tolyl iodide as electrophiles, respectively. To our disappointment, none of the above-cited methods gives either 2-[(E)-1-octenyl]-cyclopentanone(**1**) or 2-(p-tolyl)cyclopentanone(**2**) in more than ca. 30% yields, typical yields being <10%. Indeed, a major difference between methyl ketones and other ketones including cycloalkanones has been observed previously.5,6) Also

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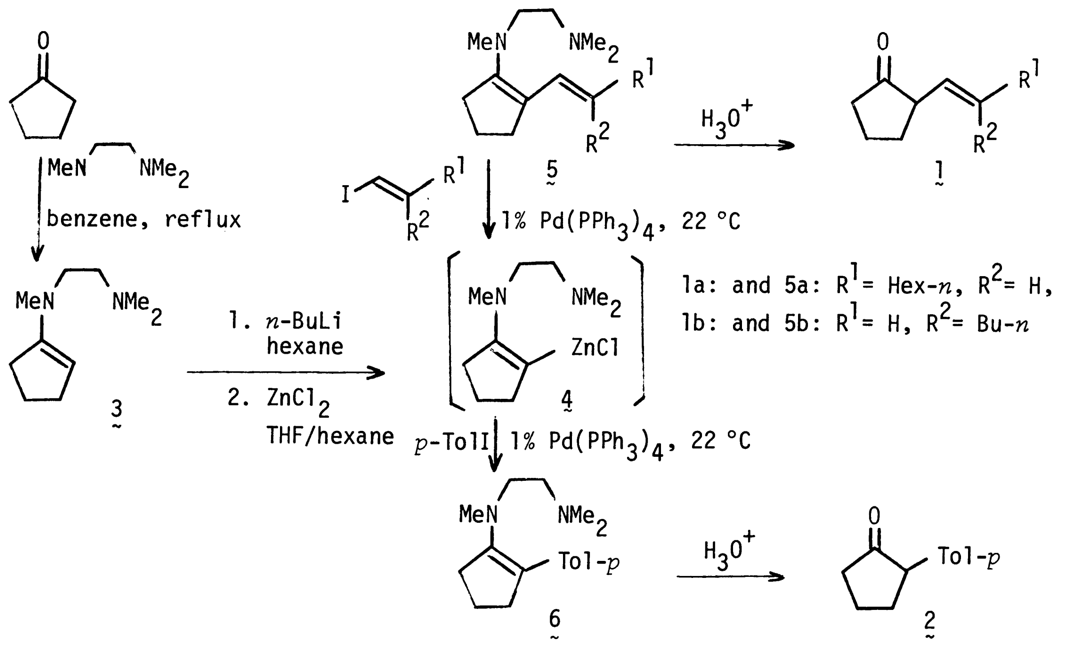
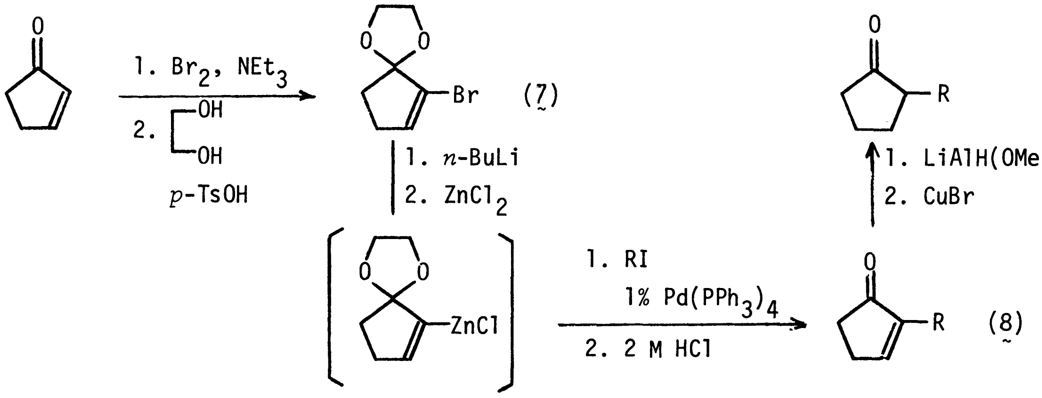
disappointing are the Pd- or Ni-catalyzed reaction of (E)-1-octenyl iodide with potassium cyclopentenoxytriethylborate or zinc cyclopentenolate, which has been highly effective in the Pd-catalyzed α-allylation,8) as well as the Pd- or Ni-catalyzed reaction of 2-bromocyclopentanone with (E)-1-octenylzinc chloride. In no case is the yield of 2-[(E)-1-octenyl]cyclopentanone >5-10%.

Turning our attention to indirect routes via the Pd- or Ni-catalyzed alkenyl-alkenyl coupling,4) an enamine **3** was prepared in 86% yield and converted into its lithio derivative by a recently reported procedure.9) The corresponding zinc derivative **4** was generated by treatment of the lithio derivative with dry $ZnCl_2$ and reacted with (E)-1-octenyl iodide, (Z)-1-hexenyl iodide, and p-tolyl iodide in the presence of 1 mol% of $Pd(PPh_3)_4$ to cleanly produce **5a** (95%), **5b** (95%), and **6** (90%), respectively. On the other hand, the use of the corresponding alkenyllithium compound does not give **5** or **6** in more than 5% yield. Protonolysis of **5a, 5b,** and **6** with 2 M HCl gave **1a**10) (78%), **1b**10) (80%), and **2**10) (76%), respectively. The yields shown in parentheses are based on **3**.

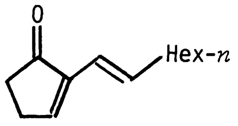


(1)

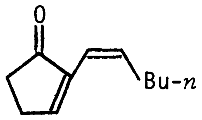
Both **1** and **5** were formed as stereoisomerically >98% pure species essentially uncontaminated by any isomers. It should be noted that the success in developing this α-alkenylation procedure critically hinges on our finding that protonation at the α-alkenyl carbon atom of **5** is unaccompanied by that at the α-alkenyl carbon atom. In an analogous manner, 2-[(E)-1-octenyl]cyclohexanone10) and 2-(p-tolyl)cyclohexanone10) were obtained in 67 and 74% yields, respectively, based on cyclohexanone. The use of a Ni catalyst generated in situ by treating $Cl_2Ni(PPh_3)_2$11) with 2 equiv. of n-BuLi in place of $Pd(PPh_3)_4$ in the preparation of **5a** and **6** led to comparable results, although the reaction of p-tolyl iodide produced bis(p-tolyl) in 10% yield as a byproduct. Despite the very favorable results presented above, this method is not readily amenable to α-alkenylation of ketones with complete regio-control. Since α,β-unsaturated ketones not only serve as precursors to saturated ketones but also provide a simple means of differentiating the two sides of ketones, we considered the Pd- or Ni-catalyzed α-alkenylation of α,β-unsaturated ketones. 2-Cyclopentenone was converted into **7** in 78% yield by a literature procedure.[12)] Its sequential treatment with n-BuLi (-78 °C, THF), dry $ZnCl_2$ in THF (-78 to 0 °C, 1 h), (E)-1-octenyl iodide in the presence of 1 mol% of $Pd(PPh_3)_4$ (22 °C, 2 h), and 2 M HCl (room temp , 0.5 h) gave **8a**[10)] (>98% E) in 92% yield (Eq. 2). Here again, the use of the corresponding alkenyllithium fails to give **8** in >5% yield. Although treatment of **8a** with $LiBH(Bu\text{-}s)_3$[13)] in THF (-78 to 0 °C) gave at least three apparently isomeric products, its reaction with $LiAlH(OMe)_3$ and CuBr[14)] in THF (-78°C to room temperature) cleanly provided **1a** in excellent yield with no sign of double bond migration. The presumed dienolate intermediates must have undergone protonation exclusively at the α position also in this case. Similarly, **8b**[10)] and **8c**[10)] were prepared in 85 and 80% yields, respectively. The stereoisomeric purity of **8b** was >98%. On the other hand, the Pd-catalyzed reaction of 2-bromo- and 2-iodo-2-cyclopentenones as well as **7** and its iodo analogue with (E)-1-octenylzinc chloride failed to give **8a** in more than 5-10% yields.



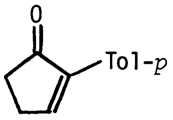
(2)



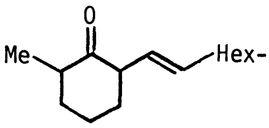
8a



8b



8c



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Since both the preparation of **8** and its conjugate reduction proceed with 100% retention of the regiochemistry, the overall process should be 100% regiospecific. To unequivocally demonstrate this point, however, **9**[10)] was prepared in 55% yield as an isomerically >98% pure compound from 6-methyl-2-cyclohexenone.

In summary, the synthetic chemists have now at their disposal high-yielding and selective procedures for α-alkenylation and α-arylation of ketones with essentially complete regio- and stereo-control. Their application to the selective synthesis of cyclopentanoids is underway in our laboratories.

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