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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 aldehydes[2a)] provides a promising method, but its stereoselectivity is limited to 90-95% Other promising approaches include the reaction of enolates with enol ether-iron complexes[2b)] 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 ketone[5,6)] and ester[7)] 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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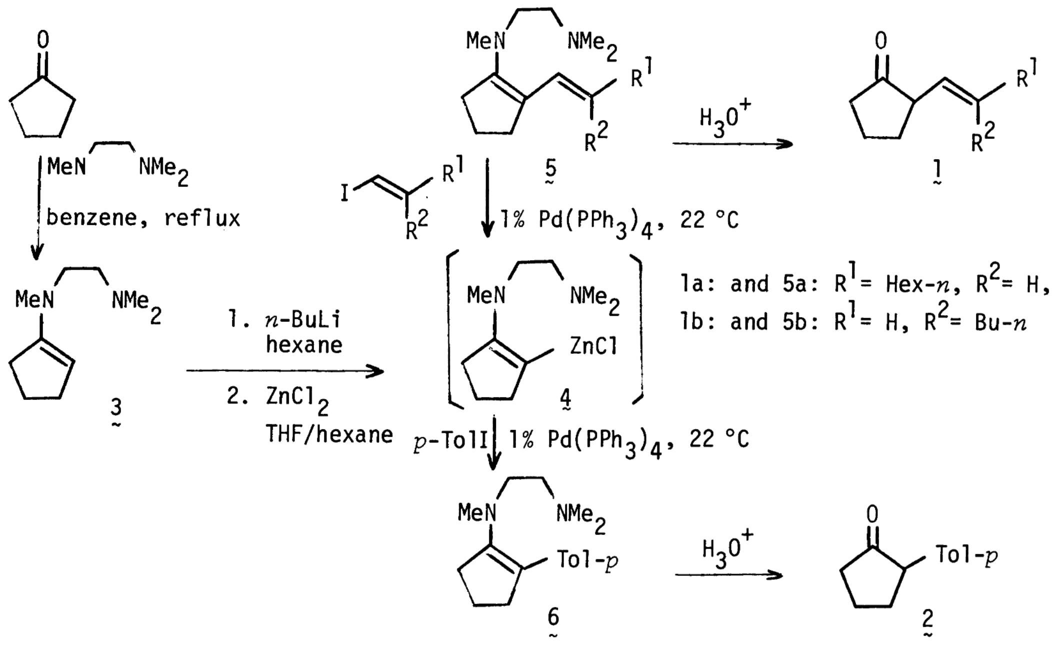
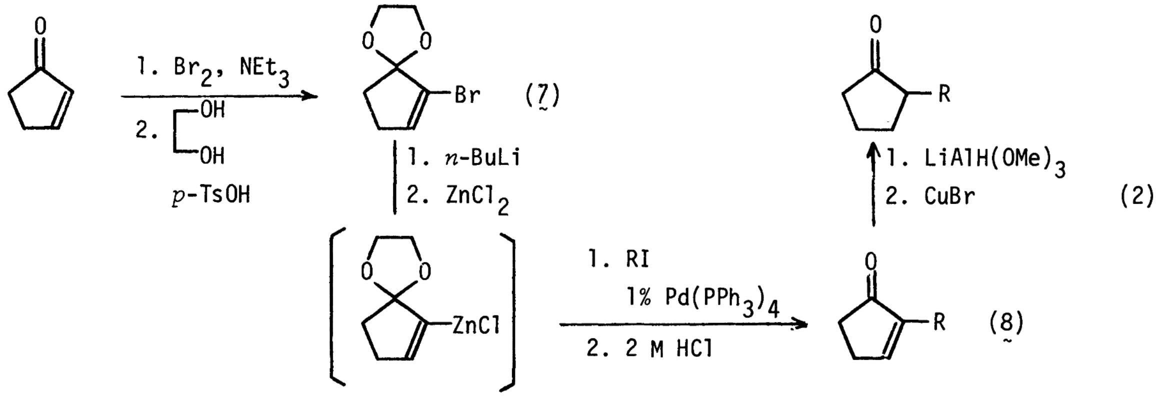
disappointing are the Pd- or Ni-catalyzed reaction of (E)-1-octenyl iodide with potassium cyclopentenoxytriethylborate or zinc cyclopentenolate, which has been highly effective in the Pd-catalyzed α-allylation,[8)] as well as the Pd- or Ni-catalyzed reaction of 2-bromocyclopentanone with (E)-1-octenylzinc chloride. In no case is the yield of 2-[(E)-1-octenyl]cyclopentanone >5-10%.

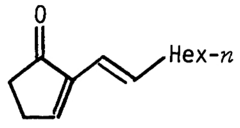
Turning our attention to indirect routes via the Pd- or Ni-catalyzed alkenyl-alkenyl coupling,[4)] an enamine **3** was prepared in 86% yield and converted into its lithio derivative by a recently reported procedure.[9)] The corresponding zinc derivative **4** was generated by treatment of the lithio 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**.



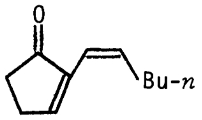
(1)

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]cyclohexanone[10)] and 2-(p-tolyl)cyclohexanone[10)] 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 CuBr14) 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.

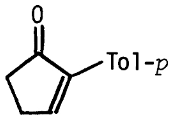




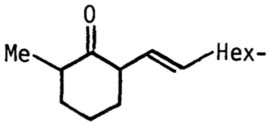
8a



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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References

1) Nickel- or Palladium-catalyzed Cross Coupling. 30. Part 29. E. Negishi, K. Akiyoshi, and T. Takahashi, J. Organomet. Chem., in press.

2) a) P. F. Hudrlik and A. K. Kulkarni, J. Am. Chem. Soc., 103, 6251 (1981) and pertinent references cited therein; b) T. C. T. Chang, M. Rosenblum, and S. B. Samuels, ibid., 102, 5931 (1980).

3) P. A. Wender, D. A. Holt, and S. M. Sieburth, J. Am. Chem. Soc. 105, 3348 (1983).

4) For a review of Pd- or Ni-catalyzed alkenyl-alkenyl coupling, see E. Negishi, Acc. Chem. Res., 15, 340 (1982).

5) For papers reporting α-arylation, see M. F. Semmelhack, R. D. Stauffer, and T. D. Rogerson, Tetrahedron Lett., 1973, 4519; I. Kuwajima and H. Urabe, J. Am. Chem. Soc., 104 6831 (1982); M. Kosugi, I. Hagiwara, and T. Migita, Chem. Lett., 1982, 939.

6) For a paper reporting α-alkenylation, see M. Kosugi, I. Hagiwara, and T. Migita, Chem. Lett., 1983, 839.

7) A. A. Millard and M. W. Rathke, J. Am. Chem. Soc., 99, 4833 (1977); J. F. Fauvargue, and A. Jutand, J. Organomet. Chem., 177, 273 (1979); J. F. Fauvarque and A. Jutand, ibid., 209, 109 (1981).

8) E. Negishi, H. Matsushita, S. Chatterjee, and R. J. John, J. Org. Chem., 47, 3188 (1982); E. Negishi, F. T. Luo, A. J. Pecora, and A. Silveira, Jr., ibid., 48, 2427 (1983); E. Negishi and R. A. John, ibid., 48, 4098 (1983).

9) G. Stork, C. S. Shiner, C. W. Cheng, and R. L. Polt, J. Am. Chem. Soc. 108, 304 (1986).

10) Satisfactory spectral and analytical data have been obtained.

11) F. A. Cotton, O. D. Faut, and D. M. Goodgame, J. Am. Chem. Soc., 83, 344 (1961).

12) A. B. Smith,III, S. J. Branca, M. A. Guaciaro, P. M. Wovkulich, and A. Korn, Org. Synth., 61, 57 (1983). The yield we have observed for bromination was 88% which was considerably higher than that reported by these authors.

13) J. M. Fortunato and B. Ganem, J. Org. Chem., 41, 2194 (1976).

14) M. F. Semmelhack, R. D. Stauffer, and A. Yamashita, J. Org. Chem., 42, 3180 (1977).

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