

PALLADIUM-CATALYZED CYCLIZATION OF ALKENYL AND ARYL HALIDES CONTAINING
 α, β -UNSATURATED CARBONYL GROUPS VIA INTRAMOLECULAR CARBOPALLADATION¹

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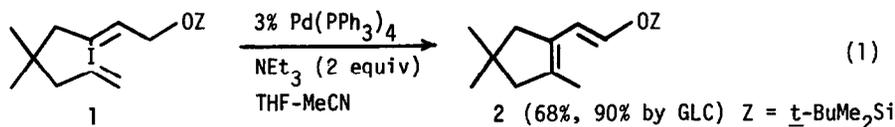
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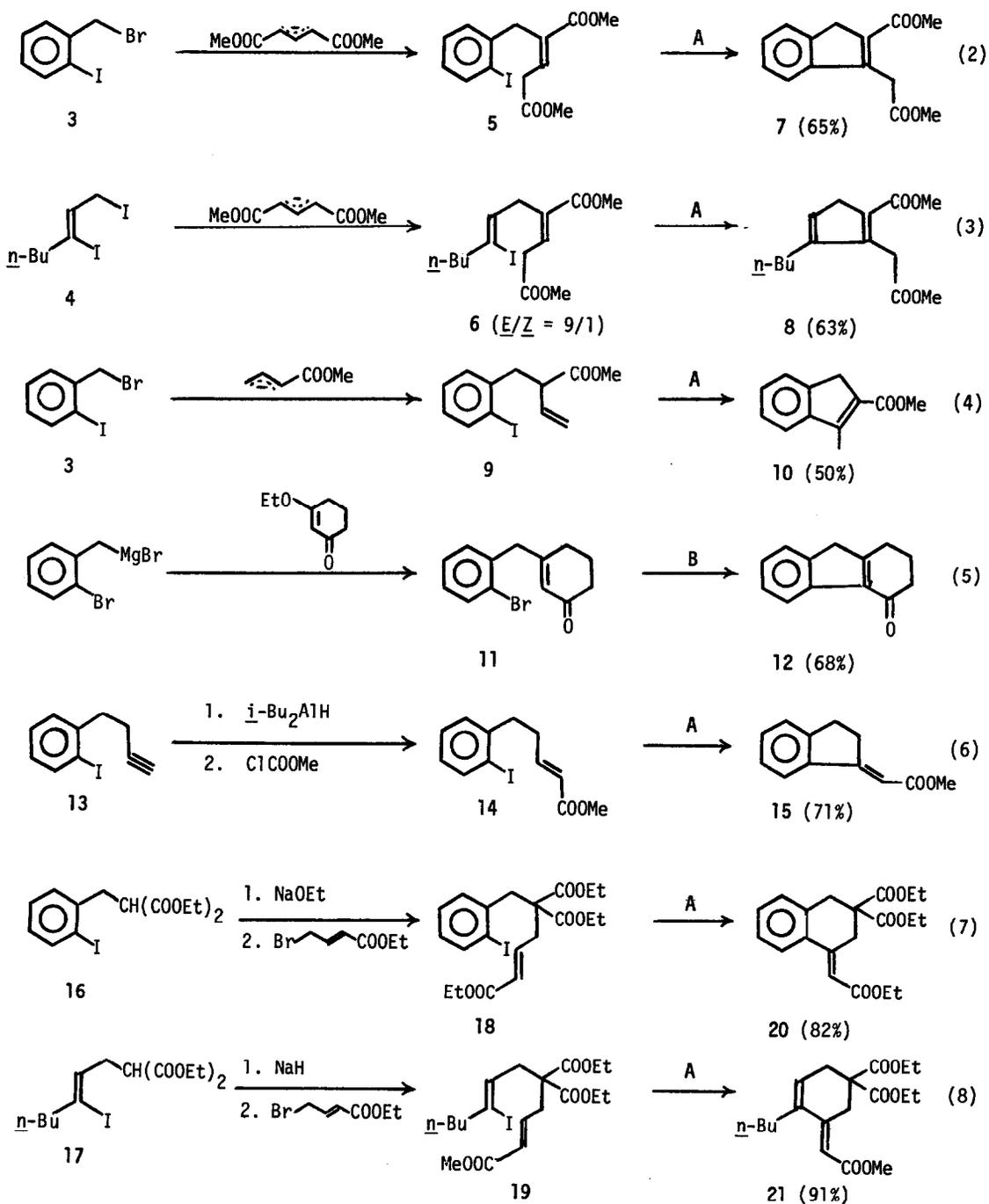
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SUMMARY: Treatment of alkenyl and aryl iodides and bromides containing an appropriate α, β -unsaturated carbonyl group with a catalytic amount (3-5 mol %) of either a Pd(0) or a Pd(II) complex, e.g., Pd(PPh₃)₄, and a base, e.g., NEt₃, can induce highly regioselective cyclization via intramolecular carbopalladation; formation of exocyclic alkenes can also be highly stereoselective.

Over the past few years the Pd-catalyzed cyclization of alkenyl and aryl halides via intramolecular carbometallation² has emerged as a potentially attractive method for the synthesis of carbocycles.³ Unfortunately, however, the lack of complete regio-control has been a difficulty encountered in virtually all of the reported cases. This difficulty, in fact, aborted our attempts to apply the methodology to the development of stereodefined exocyclic alkenes (eq 1), although the results do represent a rare case of essentially 100% regioselectivity.



To avoid the regiochemical complications in the intramolecular carbopalladation, we turned our attention to the reaction of α, β -unsaturated carbonyl compounds and have found that the use of α, β -unsaturated carbonyl compounds can indeed lead to clean formation of single regio- and/or stereoisomers.⁵ The experimental results are shown in the equations 2-8. The following procedure for converting 19 into 21 is representative. A mixture of 19 (0.48 g, 1 mmol), Pd(PPh₃)₄ (57 mg, 0.05 mmol), and NEt₃ (0.20 g, 0.28 mL, 2 mmol) in 5 mL of MeCN was refluxed under nitrogen for 90 min, quenched with 3 M HCl, extracted with ether, washed with NaHCO₃ and brine, dried over MgSO₄, concentrated, filtered through a plug of silica gel with a 10:1 pentane-ether mixture, and evaporated to give 0.32 g (91%) of 21: IR (neat) 1740 (s), 1725 (s), 1610 (s), 1250 (s), 1230 (s), 1170 (s), 1060 (s), 1015 (s), 870 (m) cm⁻¹; ¹H NMR (CDCl₃, Me₄Si) δ 0.89 (t, J = 7 Hz, 3 H), 1.21 (t, J = 7 Hz, 6 H), 1.1-1.3 (m, 4 H), 2.18 (t, J = 7 Hz, 2 H), 2.78 (d, J = 3 Hz, 2 H), 3.52 (s, 2 H), 3.72 (s, 3 H), 4.0-4.2 (m, 4 H), 5.89 (s, 1 H), 5.96 (bs, 1 H); ¹³C NMR (CDCl₃) δ 13.52, 13.59, 22.11, 30.26, 31.05, 31.77, 32.00, 50.64, 53.48, 61.13, 112.89, 130.33, 136.62, 149.18, 166.82, 170.27.



A: $\text{Pd}(\text{PPh}_3)_4$, (5%), NEt_3 (1-2 equiv), MeCN, 50-100°C. B: $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$ (10%), NaHCO_3 (2 equiv), DMF, 80°C.

In all cases we have so far examined (eqs 2-8), single cyclization products of $\geq 98\%$ isomeric purity were obtained. All of these compounds yielded satisfactory spectral and analytical data. All α, β -unsaturated carbonyl compounds reacted with essentially complete retention of regiochemistry. The reaction of **3** and **4**⁶ with the lithium salt of dimethyl (E)-2-pentendioate⁷ directly gave **5** and **6**, respectively, in good yields. Although **5** was essentially homogeneous, **6** was a ca. 9:1 mixture of the E and Z isomers. No detectable amounts of the other two possible regioisomers were present. Treatment of **5** and **6** with Pd(PPh₃)₄ (5%) and NEt₃ (1.5 equiv) in MeCN at 100°C for 16 h produced **7** and **8** in 65 and 67% yields, respectively, as the only cyclization products. Unlike **5**, **9** was produced as a β, γ -unsaturated species. Its treatment with Pd(PPh₃)₄ under the same conditions as above gave **10** in 50% yield. The regiocontrolling effect of the ester group is apparent, if one compares the results shown in eq 4 with those of the corresponding reaction of o-(3-butenyl)iodobenzene reported earlier by us.^{3b}

Cyclization of **11** using Pd(OAc)₂(PPh₃)₂ (5%) and NaHCO₃ (2 equiv) in DMF⁸ at 80°C for 36 h gave **12** in 68% yield (76% by GLC) along with a 10% yield of the debrominated but uncyclized product and the starting compound (15%). The use of NEt₃ as a base under otherwise the same conditions did not induce cyclization.

As part of a long-range project,⁴ we examined the feasibility of developing a stereoselective method for synthesizing exocyclic alkenes via intramolecular carbopalladation. The preparation of **13** was achieved in modest yield by the reaction of **3** with 1,3-dilithiopropyne. Hydroalumination of **13** followed by treatment with ClCOOMe⁹ gave **14** in 81% yield. Its cyclization using 5% of Pd(PPh₃)₄ and 1.5 equiv of NEt₃ in MeCN-benzene at 60°C for 24 h afforded **15** in 71% yield. Similarly, **16** and **17** were converted into **18** and **19** in high yields by the reaction of their sodium salts with esters of γ -bromocrotonic acid, and the latter were subjected to the standard cyclization conditions using 5% of Pd(PPh₃)₄ and 1-1.5 equiv of NEt₃ to give **20** and **21** in 82 and 91% yields, respectively. All three exocyclic alkenes are isomerically $\geq 98\%$ pure by ¹³C NMR and GLC. The 2D-NOESY ¹H NMR data for **20** and **21** support the assigned E geometry. The E isomers are the predicted products on the basis of both the presumed syn addition-syn elimination mechanism² and the known tendency for β -aryl or β -alkenyl α, β -unsaturated carbonyl compounds to favor the E geometry. At this time, however, it remains to be clarified whether or not the formation of exocyclic alkenes via cyclic carbopalladation is stereospecific and capable of selectively producing the Z isomers as well.

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REFERENCES AND NOTES

- (1) Metal-Promoted Cyclization. 20. Part 19. Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. Submitted for publication.
- (2) For reviews of the Heck-type carbopalladation-dehydropalladation reaction including many references on the synthesis of heterocycles, see (a) Heck, R. F. Org. React. **1982**, 27, 345. (b) Heck, R. F. "Palladium Reagents in Organic Syntheses," Academic Press, New York, 1985.
- (3) (a) Grigg, R.; Stevenson, P.; Worakun, T. J. Chem. Soc., Chem. Commun. **1984**, 1073. (b) Tour, J. M.; Negishi, E. J. Am. Chem. Soc. **1985**, 107, 8289. (c) Abelman, M. M.; Oh, T.; Overman, L. E. J. Org. Chem. **1987**, 52, 4133. (d) Abelman, M. M.; Overman, L. E. J. Am. Chem. Soc. **1988**, 110, 2328. (e) Negishi, E.; Zhang, Y.; O'Connor, B. Tetrahedron Lett. **1988**, 29, 0000. (f) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. Tetrahedron Lett. **1988**, 29, 0000.
- (4) For our previous papers in this area, see (a) Luo, F. T.; Negishi, E. J. Org. Chem. **1983**, 48, 5144. (b) Miller, J. A.; Negishi, E. Israel J. Chem. **1984**, 24, 76. (c) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. J. Am. Chem. Soc. **1985**, 107, 2568. (d) Negishi, E.; Zhang, Y.; Cederbaum, F. C.; Webb, M. B. J. Org. Chem. **1986**, 51, 4080. (e) Negishi, E.; Zhang, Y.; Bagheri, V. Tetrahedron Lett. **1987**, 28, 5793. (f) Negishi, E. Advan. Metal-Org. Chem. **1977**, 1, 0000.
- (5) After completion of this work, we noted that Grigg had recently reported the use of one α,β -unsaturated carbonyl derivative, which unfortunately gave two regioisomers in comparable yields [Grigg, R.; Stevenson, P.; Worakun, T. Tetrahedron **1988**, 44, 2033]. In light of our results herein presented, we find the reported results somewhat puzzling.
- (6) The reagent **4** was prepared from 2-heptyn-1-ol via reduction with LiAlH_4 , iodolysis (Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. J. Am. Chem. Soc. **1967**, 89, 4245) and iodination of the iodoalcohol (Olah, G.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. J. Org. Chem. **1979**, 44, 1247).
- (7) Kaneko, C.; Fujii, H.; Kato, K. Heterocycles **1982**, 17, 395.
- (8) Iida, H.; Yuasa, Y.; Kibayashi, C. J. Org. Chem. **1980**, 45, 2938.
- (9) Zweifel, G.; Miller, J. A. Org. React. **1984**, 32, 375.

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