Evidence that Palladium(0)-Promoted Cyclizations of Unsaturated α-Iodocarbonyls Occur by an Atom Transfer Mechanism

Dennis P. Curran*¹ and Chi-Tai Chang Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

Summary: The isomerization of several unsaturated α -iodocarbonyls to cyclic γ -iodocarbonyls gave identical product mixtures by using catalytic quantities of either hexalkylditin or palladium (0). This indicates that palladium does not serve as a catalyst in an organometallic reaction, but as a promoter of a free radical chain involving atom transfer. In contrast, an allylic iodide showed no tendency to produce radical chain products when treated with Pd(0).

Over the past several years, Mori, Ban, and coworkers have developed palladium(0)-promoted isomerization reactions of unsaturated α -iodocarbonyls into a powerful synthetic method.² The basic transformation, which was termed ene-halogenocyclization, is outlined in eq 1. Treatment of an α -iodocarbonyl 1 with 1-10% *tetrakis* triphenylphosphinepalladium(0) in HMPA gave isomerized products 2 and 3 in modest to excellent yields. A proposed mechanism involving 1) generation an α -palladiocarbonyl 4, and 2) insertion of the C-Pd bond across the double bond to give 5 was supported by several observations: 1) a common side product 6 could arise by well-precedented metal hydride elimination from 5, 2) the reaction did not occur in the absence of palladium(0), and 3) presumed authentic intermediates 4 generated by the method of Saegusa³ also gave 6 (but not 2/3), albeit in much lower yields, with other types of products predominating. A major problem with this mechanism, which was recognized by Mori, Ban, *et al.*, was that the direct reductive elimination of an alkylpalladium iodide complex like 5 to form an alkyl iodide is not a well precedented reaction. Instead, they proposed that 2 might arise by a substitution reaction of iodide on complex 5. However, given the known chemistry of σ -alkylpalladium complexes,⁴ it is difficult to believe that either of these reactions of 5 could compete with metal hydride elimination to form 6.



As the work of Mori, Ban, *et al.* unfolded, we were studying radical cyclizations of α -iodocarbonyls by the atom transfer method.⁵ We initially believed that our reactions provided the same types of products (γ -iodocarbonyls) as the above "ene-halogenocyclization," but through a different mechanism. However, we began to doubt this belief as our studies revealed that the kinetic regio- and stereoselectivities of carbonyl-substituted radicals were similar to the product ratios observed by Mori and Ban. They reported other observations that were also consistent with an atom transfer chain: 1) iodides are much more reactive than bromides, 2) in substrates that were expected to undergo slow radical cyclizations, coupled dimers^{2c} and hydrogen transfer products^{2f} were found, and 3) in at least one example,^{2c} the reaction showed a concentration dependence characteristic of a radical cyclization. We have recently conducted a series of experiments to compare the two different reaction conditions. These experiments provide overwhelming circumstantial evidence that the palladium-promoted isomerization of α -iodocarbonyls involves free radical rather than organometallic intermediates.

We have previously shown that photolytic isomerization of iodo ester 7 in the presence of 10% hexabutylditin provided a mixture of 8-cis/trans and 9-cis/trans in excellent overall yield (eq 2).⁵ Mechanistic studies, including detailed rate measurements,⁶ established that these products were formed by radical cyclizations under strict kinetic control. When 7 was exposed to Pd(0) under conditions typical to those used by Mori and Ban (10% Pd(dppe)₂, 50 °C, benzene, 15 min), cyclization smoothly occurred, and the ¹H NMR spectrum of the crude reaction mixture was virtually identical to that of the ditin reaction. The same products were produced in the same ratio and yield. Next the iodomalonate 10 was smoothly isomerized to 11 and 12. Again, the ratio of products was identical (within experimental error) whether the isomerization was conducted by irradiation with ditin or by stirring with Pd(0) at 25 °C.



The work of Mori and Ban has focused on methods to prepare heterocycles, and they have not reported cyclizations of 7 or 10. To exclude the possibility that these substrates behave differently from hetero-substituted counterparts, we prepared the known α -iodoester 13^{2a} (eq 3). Cyclization of 13 occurred when it was irradiated with 10% hexabutylditin (50 °C, benzene), or when it was heated with 8% Pd(PPh₃)₄ (50 °C, HMPA) with or without Proton Sponge.⁷ Despite the differences in solvent, the crude ¹H NMR spectra of all three reactions were virtually identical. Although the structures and amounts of the products 14-16 could not be completely determined at this juncture (four products, each with two carbamate rotamers⁸), the complexity of the spectrum served as a nice

fingerprint of the reaction. That each reaction gave an identical fingerprint is evidence that the same mechanism operates. To analyze the reaction, the crude mixture from the ditin isomerization was reduced with tributyltin hydride. After chromatography, 17 (6-exo trans product), 18 (6-exo cis product) and 19 (7-endo product) were isolated in a ratio of about 1/1/2 in 76% combined yield.^{9,10} The structures of 17-19 were readily assigned by comparison with their carbocyclic analogs.¹¹



Although the comparison of ratios of reaction products under different conditions does not provide definitive mechanistic evidence, it is very unlikely that the three substrates tested would provide the same ratio of products unless the same mechanism is operative. The mechanism of the ditin-promoted radical isomerization is well understood, and is shown in Scheme 1. We have suggested that the ditin serves a dual role as an initiator and as a trap for iodine (a chain suppressant).¹² We now propose that the low valent palladium compound serves the same roles,^{13,14} and that "ene-halogeno-cyclization" should be classed as a radical chain reaction that proceeds by an atom transfer mechanism. Indeed, the use of low valent metals to promote radical cyclization and addition reactions of polyhalo-alkanes (Kharasch reactions) is a common technique.¹⁵ Palladium(0) and related low valent metals may be useful substitutes for ditin in conducting other iodine atom transfer reactions.



It is well known that the reactions of allylic substrates (halides, carbonates, acetates, etc) with Pd(0) proceed through π -allylpalladium intermediates.^{4b,16} To address the question of whether radical chains could ever intervene in these organometallic reactions, we prepared allylic iodides 20 and 21 (eq 4). While 20 gave mainly allylic dimers under standard ditin conditions, 21 gave a 50% yield of 22, accompanied by allylic dimers and a trace of 23.¹⁷ In contrast to the reactions of iodocarbonyls, when 21 was treated with Pd(dppe)₂ in benzene, none of the radical products indicated in eq 4 were formed.¹⁸ We conclude that allylic iodides react with Pd(0) by normal pathways (presumably by formation of π -allyl Pd complexes) more rapidly than radical chains can initiate and propagate.¹⁹



References and Notes

- 1. Dreyfus Teacher-Scholar, 1985-89; National Institutes of Health Research Career Development Awardee, 1987-92.
- (a) Mori, M.; Kubo, Y.; Ban, Y. Tetrahedron 1988, 44, 4321. (b) Mori, M.; Kanda, N.; Ban, Y.; Aoe, K. J. Chem. Soc., Chem. Commun. 1988, 12. (c) Mori, M.; Kanda, N.; Ban, Y. Ibid. 1986, 1375. (d) Mori, M.; Kanda, N.; Oda, I.; Ban, Y. Tetrahedron 1985, 41, 5465. (e) Mori, M.; Kubo, Y.; Ban, Y. Tetrahedron Lett. 1985, 26, 1519. (f) Mori, M.; Oda, I.; Ban, Y. Tetrahedron Lett. 1982, 23, 5315.
- (a) Ito, Y.; Aoyama, H.; Saegusa, T. J. Am. Chem. Soc. 1980, 102, 4519.
 (b) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. J. Am. Chem. Soc. 1979, 101, 494.
- (a) Heck, R. F. "Palladium Reagents in Organic Synthesis" Academic Press Inc. (London) LTD. 1985. (b) Trost, B. M.; Voerhoeven, T. in "Comprehensive Organometallic Chemistry", Wilkinson, G.; Stone, F. G. A., Eds.; Pergamon: Oxford, 1982, Vol. 8, pp 799-938.
- (a) Curran, D. P.; Chang, C.-T. Tetrahedron Lett. 1987, 28, 2477.
 (b) Curran, D. P.; Chang, C.-T. J. Org. Chem. 1989, 54, 3140.
- 6. Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. J. Org. Chem. 1989, 54, 1826.
- 7. We initially chose this iodide because Mori, et. al. reported the exclusive formation of 14 (57%) (ref 2a). This seemed completely inconsistent with a radical mechanism. However, inspection of the reported NMR data leads us to conclude that the other products were present in their reaction, and that we have duplicated their conditions.
- 8. Simplification of the NMR spectra by heating the iodides to increase the rate of C-N bond rotation is not feasible because lactonization begins to occur (see ref. 5) at temperatures required for coalescence (>100 °C).
- 9. 17: ¹H NMR (DMSO, 120 °C): δ 7.36 (2H, t, J = 7.7 Hz), 7.18 (1H, t, J = 7.7 Hz), 7.13 (2H, m), 4.15 (2H, q, J = 7.1 Hz), 4.09-3.98 (2H, m), 3.05 (1H, m), 2.76 (1H, dd, J = 10.8, 13.3 Hz), 2.28 (1H, td, J = 10.8, 4.0 Hz), 1.95-1.61 (3H, m), 1.23 (3H, t, J = 7.1 Hz), 0.94 (3H, d, J = 6.6 Hz); IR (thin film): 1716, 1653, 1600, 1496 cm⁻¹; MS (m/z): 291, 246, 218, 198, 170, 142, 124, 109, 98, 81; HRMS: Calcd for C19H21NO4: 291.1470; Found: 291.1476; 18: ¹H NMR (DMSO, 120 °C): δ 7.35 (2H, t, J = 7.5 Hz), 7.18 (1H, m), 7.13 (2H, m), 4.13 (2H, q, J = 7.1 Hz), 3.94 (1H, m), 3.77 (1H, dd, J = 5.0, 13.2 Hz), 3.35 (1H, dd, J = 3.4, 13.2 Hz), 3.12 (1H, dd, J = 4.0, 9.7, 13.2 Hz), 2.76 (1H, td, J = 4.5, 9.5 Hz), 2.24 (1H, m), 1.86-1.74 (2H, m), 1.23 (3H, t, J = 7.1 Hz), 0.94 (3H, d, J = 6.6 Hz); IR (thin film): 1718, 1496 cm⁻¹; MS (m/z): 291, 246, 218, 198, 170, 150, 142, 124, 105, 98, 81; HRMS: Calcd for C19H21NO4: 291.1470; Found: 291.1464; 19: ¹H NMR (DMSO, 120 °C): δ 7.36 (2H, t, J = 7.6 Hz), 7.18 (1H, m), 7.13 (2H, m), 4.14 (2H, q, J = 6.9 Hz), 3.75-3.45 (4H, m), 2.61 (1H, m), 2.12 (6H, m), 1.23 (3H, t, J = 6.9 Hz); IR (thin film): 1722, 1595, 1495 cm⁻¹; MS (m/z): 291, 273, 246, 218, 198, 170, 150, 142, 124, 105, 98, 81; HRMS: Calcd for C19H21NO4: 291.1470; Found: 291.1450.
- 10. In this analysis, cis/trans stereochemical information on the 7-endo product 16 is lost.
- 11. Carbocyclic analogs of 14, 15, 16 are formed in a ratio of 5/3/2 (6-exo cis/6-exo trans/7-endo). See reference 5b.
- 12. Curran, D. P.; Chen, M.-H.; Kim, D. J. Am. Chem. Soc. 1989, 111, 6265.
- 13. Any low valent metal like Pd(0) will trap molecular iodine by oxidative addition.
- The actual initiation event is unknown. Electron transfer from low valent palladium and platinum complexes is precedented. See (a) Kramer, A. V.; Labinger, J. A.; Bradley, J. S.; Osborn, J. A. J. Am. Chem. Soc. 1974, 96, 7145. (b) Kramer, A. V.; Osborn, J. A. J. Am. Chem. Soc. 1974, 96, 7833. Photolytic cleavage of C-1 bonds by ambient light is also possible. See reference 12.
- See, for example: Bellus, D. Pure & Appl. Chem. 1985, 57, 1827. Hayes, T. K.; Villani, R.; Weinreb, S. M. J. Am. Chem. Soc. 1988, 110, 5533. In such reactions, the metal may play a role as initiator or source of halogen (via a metal halide), or it may promote formation of organometallic intermediates or metal-complexed radicals.
- Related organometallic transformations: Trost, B. M.; Luengo, J. I. J. Am. Chem. Soc. 1988, 110, 8239. Oppolzer, W. Angew. Chem., Int. Ed. Engl. 1989, 28 38. Negishi, E.; Iyer, S.; Rousset, C. J. Tetrahedron Lett. 1989, 30, 291.
- 17. The tin hydride cyclization (0.005M) of 21 (I = Br) gave the reduced 5-exo cis, 5-exo trans, and 6-endo products in a ratio of 59/32/9. Stork, G.; Reynolds, M. J. Am. Chem. Soc. 1988, 110, 6911. Our conditions appear to give less 6-endo product. Possibly, a small amount of equilibration occured during the tin hydride experiment?
- 18. Iodide 21 slowly disappeared over several hours. We did not characterize the products.
- 19. We thank the National Institutes of Health for financial support.