Palladium-Catalyzed Addition of Pronucleophiles to Allenes

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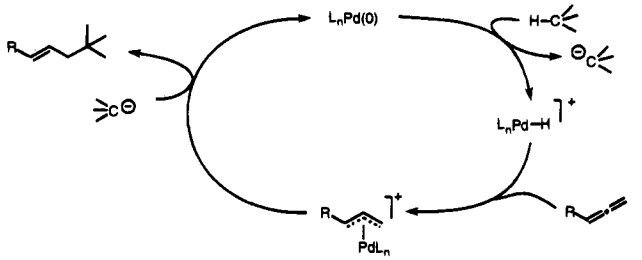
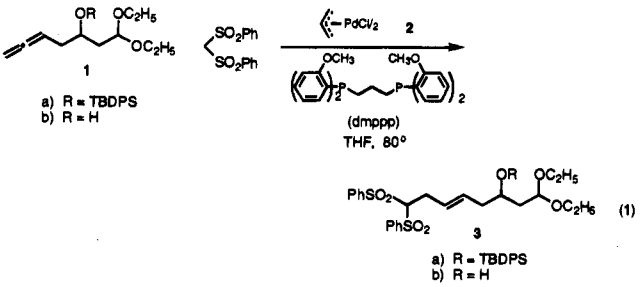
The Michael reaction constitutes one of the most useful C−C bond-forming reactions, wherein the C−H bond of an "active" methylene or methine adds across an alkene bearing an electron-withdrawing group in the presence of a base catalyst.[1] The requirement for an electron-deficient alkene as an acceptor may be obviated by use of a transition metal catalyst,[2,3] wherein a sequence as outlined in Scheme 1 for the case of an allene may be envisioned. While our previous studies involving additions of terminal alkynes to allenes involve C−C bond formation at the internal allenic carbon,[4−6] we anticipated a process initiated by hydrometalation would proceed as in Scheme 1. A problem that must be overcome is the high propensity of allenes to oligomerize in the presence of palladium catalysts.[7] In light of a recent Communication, wherein cyano-activated pronucleophiles added to simple allenes in yields ranging from 10 to 75%,[8] we wish to report our independent studies which resulted in a highly chemoselective addition of an apparently broader scope involving a different catalytic system and for which we propose a different mechanistic rationale.

Our studies were initiated by the addition of bis(benzenesulfonyl)methane to allene **1a**, as shown in eq 1. Using π-allylpalladium chloride dimer (**2**) as the palladium source and the bidentate ligand dmppp [1,3-bis(di-(2-methoxylphenyl)-phosphino)propane] (Pd/P = 1/2.5) in THF at reflux (3.5−5 mol %) in the presence of 3.5−5 mol % potassium *tert*-butoxide gave addition product **3a**[9] in 64% yield, exclusively as the *E* isomer.[10] Using the allene bearing a free alcohol **1b**, the identical reaction gave the corresponding adduct **3b**[9] in 71% yield as a 75:25 *E/Z* mixture.

Scheme 1. Proposed Addition of Pronucleophile to an Allene Catalyzed by Palladium

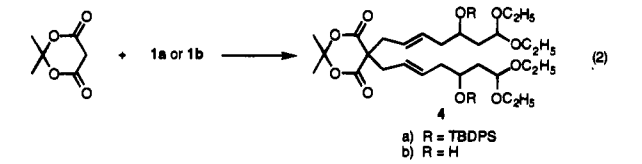


Employment of Meldrum's acid as the pronucleophile with **1a** and **1b** could not be stopped at the monoalkylation stage.



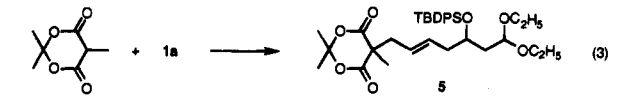
(1)

The dialkylation products **4a**[9] and **4b**,[9] both possessing only *E* olefin geometry, were isolated in 73% and 36% yields, respectively (eq 2). While **2** was invariably used as the



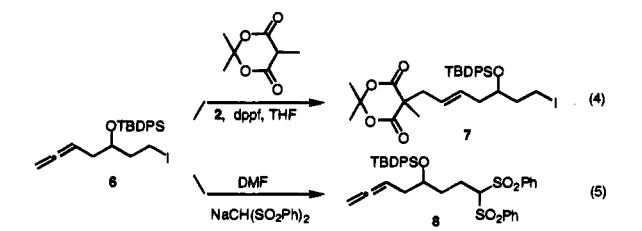
(2)

palladium source, the ligand was varied. For formation of **4a** and **4b**, 1,3-bis(diphenylphosphino)propane (dppp) and 1,1′-bis-(diphenylphosphino)ferrocene (dppf) were employed, respectively. On the other hand, use of a monosubstituted Meldrum's acid with dppp as ligand led to smooth monoalkylation to give adduct **5** (eq 3) in 77% yield as the *E* isomer.



(3)

The use of the iodoallene **6** highlights the chemoselectivity possible. Using methylated Meldrum's acid as the pronucleophile in the presence of a palladium catalyst with (dppf) as ligand gave the allene addition product **7**[9] in 72% yield (eq 4). In the



(4)

(5)

absence of the palladium catalyst and in DMF as solvent, nucleophiles effect normal displacement of the iodide, as illustrated in eq 5 for the sodium salt of bis(benzenesulfonyl)-methane, wherein **8**[9] was produced in 81% yield.

The latter set the stage for exploration of an intramolecular addition. Indeed, the same conditions effected smooth cycliza-

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.1, pp 1−67.

(2) For addition of active methylene compounds to alkynes in the presence of a cobalt catalyst, see: Stammler, R.; Malacria, M. *Synlett* **1994**, 92. Cruciani, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 6677.

(3) For addition of active methylene groups to 1,3-dienes, see: Trost, B. M.; Zhi, L. *Tetrahedron Lett.* **1992**, *33*, 1831. (b) Jolly, P. W.; Kokel, N. *Synthesis* **1990**, 771. (c) Mercier, C.; Mignani, G.; Aufrand, M.; Allmang, G. *Tetrahedron Lett.* **1991**, *32*, 1433. (d) Andell, O. S.; Bäckvall, J.-E.; Moberg, C. *Acta Chem. Scand. Ser. B* **1986**, *40*, 184.

(4) Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816.

(5) For some other examples of Pd-catalyzed additions involving C−C bond formation at the central carbon of allenes, see: Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233. Larock, R. C.; Veraprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274. Alper, H.; Hartstock, F. W.; Despeyroux, B. *Chem. Commun.* **1984**, 905. Ahmar, M.; Barieux, J. J.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, *43*, 513. Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615. Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88. Davies, I. W.; Scopes, D. I. C.; Gallagher, T. *Synlett* **1993**, 85.

(6) Also see: Trost, B. M.; Matsuda, K. *J. Am. Chem. Soc.* **1988**, *110*, 5233. Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 5231.

(7) Coulson, P. R. *J. Org. Chem.* **1972**, *37*, 1253; **1973**, *38*, 1483. Siegel, H.; Hopf, H.; Germer, A.; Binger, P. *Chem. Ber.* **1978**, *111*, 3112. Krymov, B. P.; Zhukovskii, S. S.; Taber, A. M.; Zel'dis, I. M.; Kalechits, I. V.; Vasserberg, V. E.; Chernykh, S. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 2111; *Chem. Abstr.* **1983**, *98*, 53798. Kunakova, R. V.; Sidorova, V. V.; Dzehemilev, U. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 2624; *Chem. Abstr.* **1986**, *105*, 1717802.

(8) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019.

(9) This compound has been satisfactorily characterized.

(10) The addition of potassium *tert*-butoxide promotes formation of the requisite Pd(0) catalyst.

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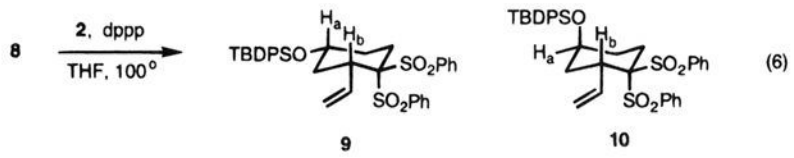
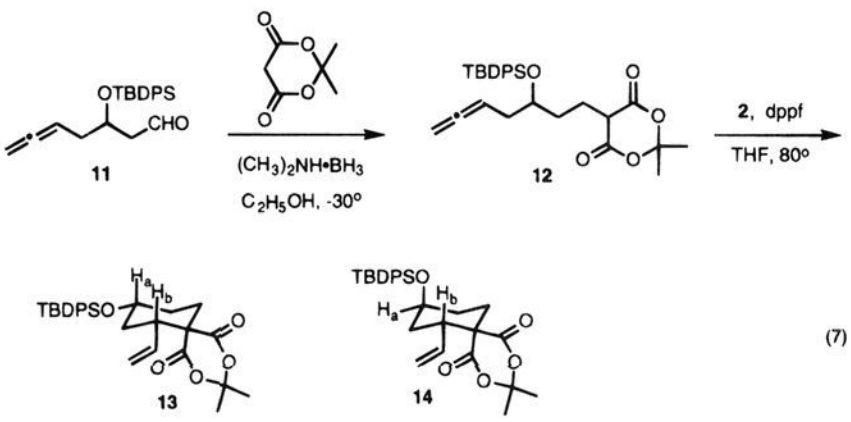
tion of **8** to give exclusively the six-membered rings **9**[9] (75%) and **10** (25%) in 68% yield (eq 6). The stereochemistry was



(6)

assigned on the basis of the ^{1}H NMR spectra. The absorptions for H_b for **9** and **10** appear as dd's when decoupled from the vinyl proton with axial−axial and axial−equatorial couplings, consistent with this proton being axial in both isomers (**9**, δ 2.95, dd, J = 12.4, 4.1 Hz; **10**, δ 3.45, dd, J = 11.8, 3.9 Hz). While the exact coupling constants for H_a could not be discerned, the $W_{1/2}$ values for the signals at 3.64 and 4.08 of 20.8 and 7.2 Hz for **9** and **10**, respectively, indicate an axial and an equatorial proton, respectively. Analogy to the subsequent cyclization products reinforces this conclusion.

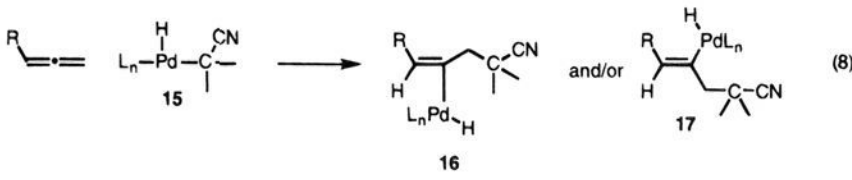
The advantage of such methodology is illustrated in the sequence depicted in eq 7. Reductive alkylation of Meldrum's



(7)

acid[11] with an allenic aldehyde **11** generated the cyclization substrate **12** in 58% yield. Cyclization proceeded at 80° C to give a 53:47 diastereomeric mixture of **13** and **14** in 85% yield. The stereochemistry of **13** and **14** was established by ^{1}H NMR as above [**13**, H_a δ 3.72, $W_{1/2}$ = 23.4 Hz, H_b (irradiating vinyl proton) δ 2.80, dd, J = 12.9, 4.0 Hz; **14**, H_a δ 4.21, $W_{1/2}$ = 7.2 Hz, H_b (irradiating vinyl proton) δ 3.60, dd, J = 12.8, 4.0 Hz]. These assignments were further supported by the observation of a 9% NOE between H_a and H_b in **13** but no NOE between these protons in **14**.

While the previous workers proposed a carbametalation pathway for the key step depicted in eq 8, proceeding via **16** and/or **17** under their conditions, we favor an alternative



(8)

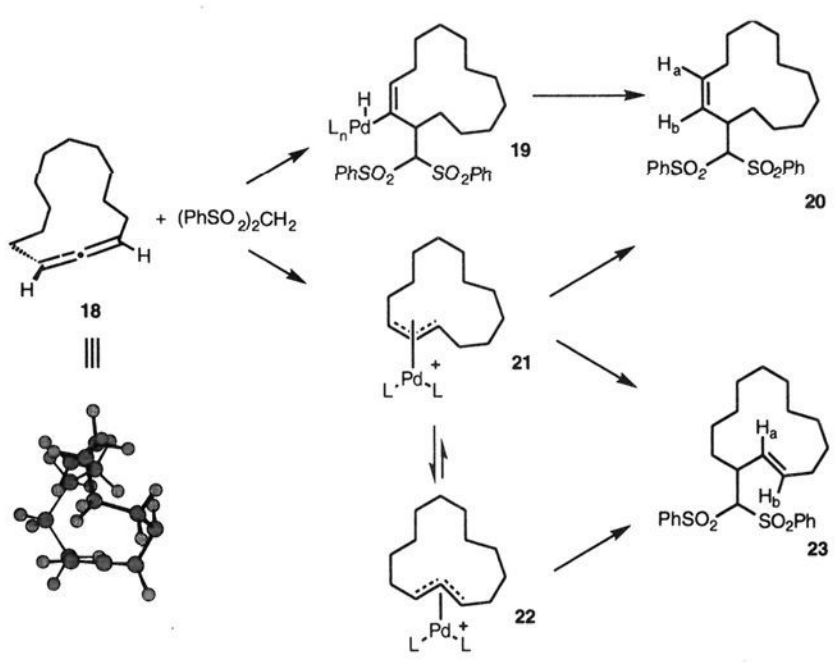
hydropalladation pathway which constituted our working hypothesis as illustrated in Scheme 1 for our catalytic system. Several literature observations support our proposal. A pathway as outlined in eq 8 with **15** as the reactive species would normally be expected to favor hydropalladation over carbapalladation.[12] Further, carbapalladation of allenes generally favors C−C bond formation at the central carbon of allenes, not at the terminal one.[4−6]

Olefin geometry may provide some insight into this question. In principle, carbametalation can generate two geometrical isomers, **16** and **17**, which could lead to Z and E olefinic products, respectively. The disubstituted allene **18** has one face of each double bond blocked by the ring methylene groups.

(11) Hrubowchak, D. M.; Smith, F. X. *Tetrahedron Lett.* **1983**, *24*, 4951. Also see Huang, X.; Xie, L. *Synth. Commun.* **1986**, *16*, 1701.

(12) Brookhart, M.; Hauptman, E.; Lincoln, D. M. *J. Am. Chem. Soc.* **1992**, *114*, 10394.

Thus, the carbapalladation route would initially form **19**, which should produce adduct **20**. On the other hand, the preference



for formation of a syn π-allyl complex suggests that **21** will be the initial product of hydropalladation which may alkylate to form **20** and/or **23** or equilibrate to the syn,syn complex **22**, which can form only **23**. In the event, addition of bis(benzenesulfonyl)methane to allene **18** produced a single crystalline adduct, mp 189 °C, whose ^{1}H NMR spectrum identified it as the E isomer **23**[9] (H_a δ 5.72, H_b δ 5.26, J_{ab} = 15 Hz) in 59% yield. This result is consistent with the hydrometalation but not the carbametalation mechanism.

This addition of active methylenes provides a highly selective and effective approach for C−C bond formation across a nonpolarized π-unsaturation. The ability to effect such an alkylation even in the presence of a reactive alkylating agent like an alkyl iodide highlights the chemoselectivity of the process. The compatibility of the allene functionality toward many types of reactions allows this "proelectrophile" to be carried through many transformations that a typical functionality that participates in alkylations would not survive, as we have illustrated in the syntheses of the cyclization substrates. The conditions described herein require only 4−5 h rather than 48 h and result in yields as good as if not better than those in the prior report. A typical experimental procedure follows.

A solution of allene **12** (115 mg, 0.233 mmol) in 2 mL of THF followed immediately by 8 μL (0.008 mmol) of a 1 M solution of potassium *tert*-butoxide in THF is added to a mixture of $(\eta^3$-$C_3H_5PdCl)_2$ (1.46 mg, 0.004 mmol) and dppf (5.54 mg, 0.01 mmol) in a pressure vial. After being heated at 80 °C for 5 h, the reaction mixture was concentrated *in vacuo* and the residue chromatographed directly (silica gel, 95:5 hexane/ethyl acetate) to give 98 mg (85% yield) of product.

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Supplementary Material Available: Characterization data for 3-5, 7-10, 12-14, and 23 (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Intermet access instructions.

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