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A REACTIVITY CONTROL SUBSTITUENT IN THE PD CATALYZED CYCLOISOMERIZATION OF 1,7-ENYNES

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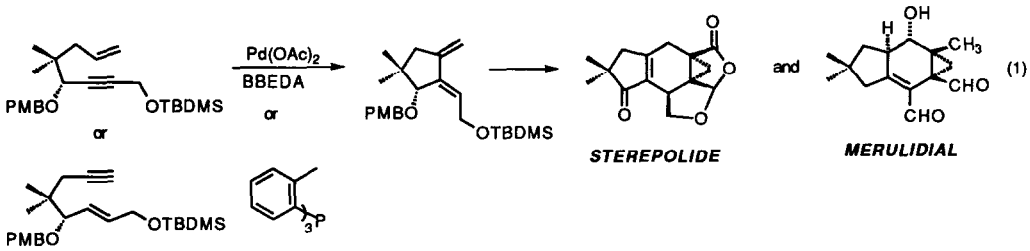
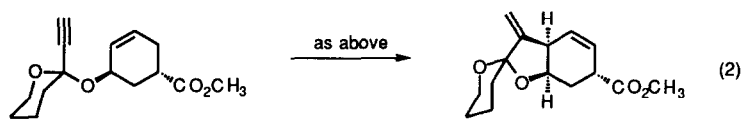
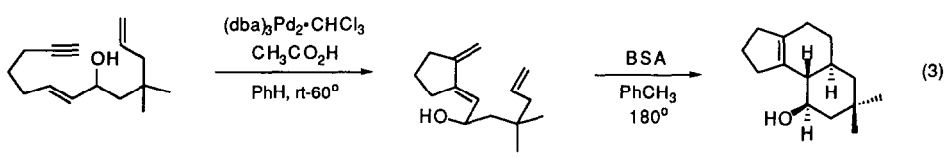
Summary: A free carboxylic acid substituent facilitates the Pd catalyzed cycloisomerization of enynes.

Atom economical reactions are simple additions in intermolecular cases and cycloisomerizations in intramolecular ones.[1] The palladium catalyzed cycloisomerizations of enynes[2] have proven to be very effective for the syntheses of five membered carbo- (eq. 1)[3] and heterocycles (eq. 2)[4] generating either 1,3- or 1,4-dienes as products. Since these reactions appear more limited in scope when applied to the creation of six membered

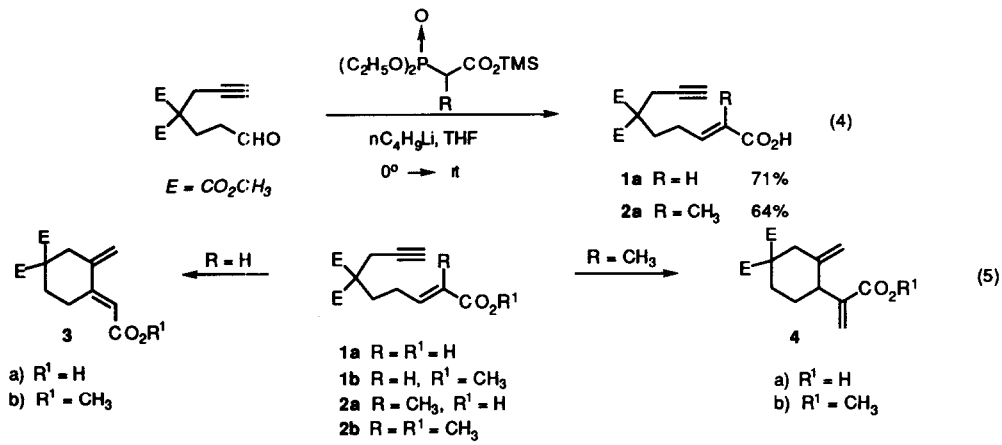




or larger rings, we considered ways to improve the generality. Our development of an effective catalytic system based upon the interaction of a Pd(0) complex with a carboxylic acid (eq. 3)[5] induced us to consider the effect of a free carboxylic acid group as a facilitator. These studies are reported herein.

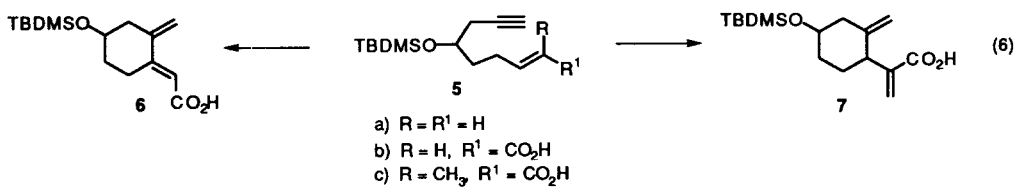


Initial studies examined the cycloisomerizations of 1,7-enynes **1** and **2** wherein the free acids were directly available by the Emmons-Wadsworth-Horner procedure using a trimethylsilyl ester[6] (eq. 4). Exposing **1a** to 3 mol% $(dba)_3Pd_2•CHCl_3$ and 6 mol% Ph_3P in benzene at room temperature gave a 63% yield of the 1,3-diene **3a**.[7] Using similar conditions but replacing the Ph_3P ligand with N,N'-bis (benzylidene)ethylenediamine[8] (BBEDA) at a temperature of 60°, acid **2a** produced a 79% yield of the crystalline 1,4-diene **4a**[7], mp 128-

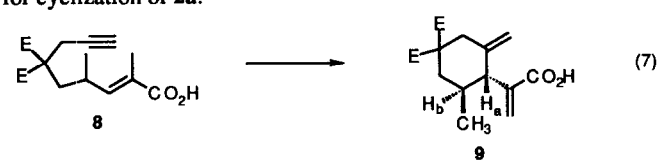


9°. While the cycloisomerization of the methyl ester (**1b**) corresponding to **1** showed only a diminishment in yield to 45% (producing **3b**), a much more dramatic effect was observed with the methyl ester corresponding to **2**. When **2b** was subjected to the catalytic conditions of eq. 5 but with the addition of an external carboxylic acid (5% HOAc), only a low yield of cycloisomer **4b** was obtained with a significant amount of dimer arising by acetylene coupling.[9] Increasing the amount of external acid up to 400 mol% showed increased conversion and production of cycloisomer **4b** but still large amounts of by-products. Clearly, incorporation of a free carboxylic acid into the substrate creates a dramatic improvement in the cyclization.

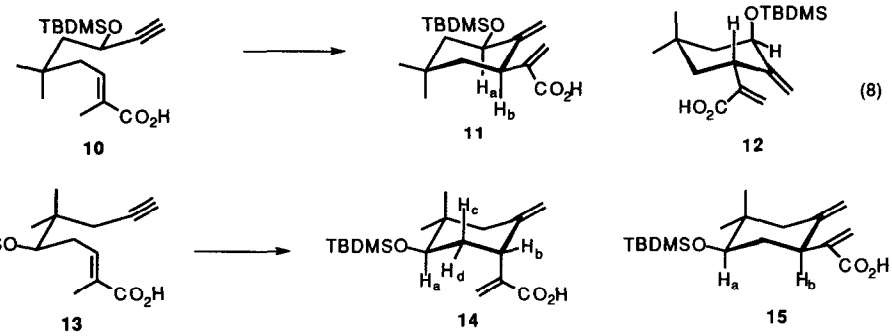
A similar dramatic effect was observed with enyne **5**. Whereas, substrate **5a** produced no cycloisomer, the corresponding carboxylic acid **5b** using the same conditions as for substrate **1a** gave the cycloisomer **6**[7] in



43% yield. A 1:1 mixture of diastereomeric cycloisomers **7**[7] was produced by cyclizing **5c** using the same conditions employed for cyclization of **2a**.

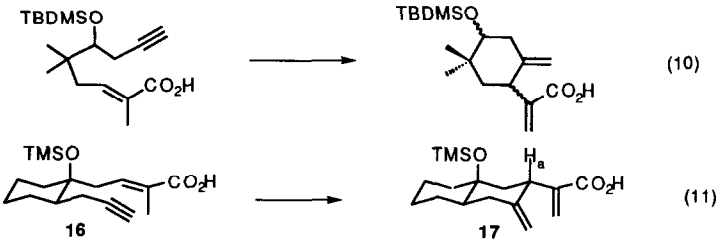


The diastereoselectivity of the cyclization as a function of the orientation of the substituents was examined using as a standard protocol 3% $(dba)_3Pd_2{\cdot}CHCl_3$ and 6% BBEDA in benzene or dichloroethane at 60°. Creating vicinal stereogenic centers from substrate **8** gave a single product **9**[7], mp 137-8° (63% yield) (eq. 7). The *E* stereochemistry derives from the 13.5 Hz coupling of H_a (δ 3.01) and H_b (δ 1.98). 1,3-Stereogenic centers were also created with good diastereoselectivity (eqs. 8 and 9). In the case of **10**, the ratio of

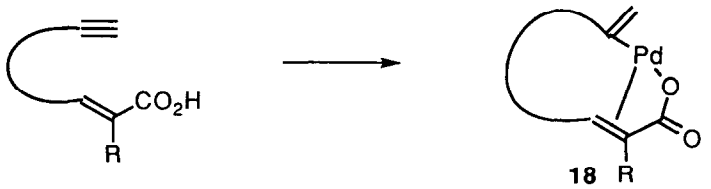


cycloisomers **11** and **12** varied with solvent increasing from 4:1 to 10:1 by switching from benzene to 1,2-dichloroethane allowing **11**[7] to be isolated in 56% yield. Observation of H_a (δ 4.23) as a dd, J = 11.5, 4.9 Hz, and H_b (δ 3.34) as a dd, J = 12.1, 4.1 Hz, indicate both of these hydrogens are axial -- thereby supporting the stereochemistry depicted in **11** rather than **12**. Cycloisomerization of **13** in benzene also produced a 4:1 ratio of cyclohexanes **14**[7] and **15**.[7] Surprisingly, the major isomer, mp 126-7°C, reveals H_a (δ 3.63) as a bd, J = 11.6 Hz, and H_b (δ 3.52) as a bs in addition to H_c (δ 1.92) as a btd, J = 12.2, 1.3 Hz and H_d (δ 1.58) as a dt, J = 13.2, 4.3 Hz which is in accord with the E stereochemistry depicted in **14**.[10] The minor isomer shows H_a (δ 3.52) as a dd, J = 8.7, 6.7 Hz and H_b (δ 3.21) as a dd, J = 10.4, 6.6 Hz which supports a slightly distorted chair of ***Z*** stereochemistry as depicted in **15**.

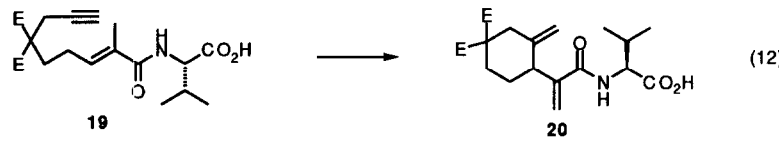
On the other hand, creation of 1,4-stereogenic centers (see eqs. 6 and 10) proceeds with no diastereoselectivity. Bicyclic systems (**16**→**17**) also form with excellent diastereoselectivity (eq. 11, >20:1). The stereochemistry of **17**[7] again derives from the observed coupling of H_a (δ 3.63) as a bd, J = 12.1 Hz.



The results clearly indicate that a free carboxylic acid facilitates cycloisomerizations of 1,7-enynes to form six membered rings. Since we believe a carboxylate is coordinated to palladium in the catalytic cycle[5], the enoic acid may then function as a bidentate ligand to palladium as in **18** to account for the



current success. The prospect that carboxylic acids coordinate raised the question of using amino acids as chiral auxilaries in these cycloisomerizations. The observation of a 50% de in the cycloisomerization of amide **19** derived from valine (eq. 12) provides strong support for this strategy for asymmetric induction in palladium catalyzed enyne cyclizations.



(12)

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References:

1. Trost, B.M. *Science* **1991**, *254*, 1471.
2. Trost, B.M. *Accounts Chem. Res.* **1990**, *23*, 34. For Co catalyzed cycloisomerizations, see Malaska, M.J.; Vollhardt, K.P.C. in "Advances in Natural Product Chemistry," Atta-ur-Rahman, ed. Harwood Academic Publishers: 1992, pp 53-63. For related cyclizations based upon the Heck reaction, see Gaudin, J.M. *Tetrahedron Lett.* **1991**, *32*, 6113; Grigg, R.; Coulter, T. *Tetrahedron Lett.* **1991**, *32*, 1359; Owczarczyk, Z.; Lamaty, F.; Vawter, E.J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091. Grigg, R.; Stevenson, P.; Worakun, T. *Chem. Commun.* **1984**, 1073; Grigg, R.; Worakun, T. *Tetrahedron* **1988**, *44*, 2033; Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *Chem. Commun.* **1986**, 1697; Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4329. Abelman, M.M.; Overman, L.E. *J. Am. Chem. Soc.* **1988**, *110*, 2328; Carpenter, N.E.; Kucera, D.J.; Overman, L.E. *J. Org. Chem.* **1989**, *54*, 5864; Overman, L.E.; Ricca, D.J.; Tran, V.D. *J. Am. Chem.Soc.* **1993**, *115*, 2042.
3. a) Trost, B.M.; Chung, J.Y.L. *J. Am. Chem. Soc.* **1985**, *107*, 4586; b) Trost, B.M.; Hipskind, P.A.; Chung, J.Y.L.; Chan, C. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1502; c) Trost, B.M.; Hipskind, P.A. *Tetrahedron Lett.* B1992, *33*, 4541.
4. Trost, B.M.; Edstrom, E.; Carter-Petillo, M.B. *J. Org. Chem.* **1989**, *54*, 4489.
5. Trost, B.M.; Lee, D.C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651; Trost, B.M.; Lee, D.C. *J. Org. Chem.* **1989**, *54*, 2271.
6. Lombardo, M.; Taylor, R.J.K. *Synthesis* **1978**, 131.
7. This compound has been satisfactorily characterized spectroscopically and elemental composition established by combustion analysis and/or high resolution mass spectrometry.
8. Trost, B.M.; Jebaratnam, D.J. *Tetrahedron Lett.* **1987**, *28*, 1611.
9. Trost, B.M.; Chan, C.; Rüther, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486.
10. Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

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