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Effect of High Pressure on a Transition-Metal-Catalyzed Cycloaddition

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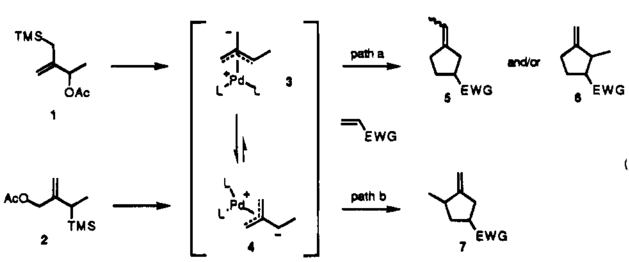
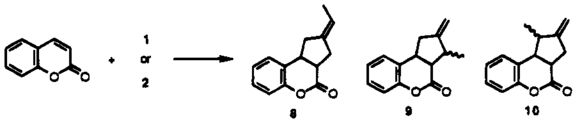
Reactions in solution that experience a change in volume upon reaching a transition state as a consequence either of bond breaking or making or of differential solvation will be affected by changes in pressure.[1,2] Cycloadditions represented by the Diels−Alder reaction serve as prime examples of the dramatic effects, notably in rates of reaction, that can be observed by applications of high pressures (>7.5 kbar).[3] On the other hand, effects on regioselectivity in the Diels−Alder reaction have been small but noticeable.[3] Outside of carbonylation chemistry, effects of high pressure on homogeneous transition-metal-catalyzed reactions have been relatively unexplored.[1,2,4] In a Heck arylation and Pd-catalyzed cross-coupling, rate accelerations have been observed qualitatively even in the presence of excess ligand.[4b] The large number of steps frequently involved in a catalytic cycle make it difficult to predict the net effect. We wish to report the effect of high pressure on the cycloadditions involving TMM−PdL$_2$, which dramatic affects regioselectivity and rate, the latter in contrast to the recently reported results on other Pd-catalyzed reactions.

Nevertheless, considering the extensive work on thermal cycloadditions, we were intrigued about the effects of high pressure on transition-metal-catalyzed cycloadditions—specifically the effect on regioselectivity with unsymmetrical donors in the palladium-catalyzed trimethylenemethane (TMM) cycloadditions.[5] Consider the case of a monomethyl-substituted TMM unit as illustrated in eq 1. Starting from bifunctional conjunctive reagents **1** or **2**, three regioisomeric products **5**, **6**, and **7** are possible but one, i.e., **7**, normally predominates.[6] Calculations[7] support the interpretation that, although **1** should initially produce **3** and **2** should produce **4**, equilibration of these species faster than cycloaddition should preferably involve the thermodynamically favored complex **4** via path b as observed experimentally. If this interpretation is correct, high pressure should enhance the bimolecular process (i.e., path a and/or b) at the expense of the unimolecular process, which simply interconverts **3** and **4**. In this event, the regioisomeric starting materials should now diverge, wherein **1** should begin to prefer formation of **5** and **6** via path a and **2** will prefer **7** via path b. We wish to record the effects of high pressure on this Pd-catalyzed TMM cycloaddition in terms of both rate and regioselectivity.

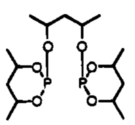


(1)

The reaction of coumarin with **1** and **2** was explored, with the results summarized in eq 2 and Table 1. As noted previously, the overwhelming product under standard conditions was cycloadduct **10**,[6] regardless of the regiochemistry of the starting material (entries 1 and 2). The regioselectivity of these reactions is independent of the solvent (toluene or THF) and the palladium source and has only a slight dependence on the ligand. For example, with **1** and **2**, no difference in regioselectivity was observed between triphenylphosphine and triisopropyl phospite as ligands in their cycloadditions.[6] Applying pressure inverts the regioselectivity in the cycloaddition starting from **1**, favoring cycloadduct **8**[6] (entry 3), although the conversion is significantly reduced. Thus, high pressure *decreased* the rate of this reaction. With triisopropyl phosphite as ligand, the reaction proceeded at ambient temperature and showed a dependence of conversion on ligand to palladium ratio. As this ratio decreased from 6:1 to 2:1, the yield increased from 12% to 71% (entries 4, 5, and 6). Using the latter conditions but increasing the pressure from 9.8 to 15 kbar increased the regioselectivity favoring **8** and **9** from 1.4:1 to 3.3:1 (entries 5, 6, and 7). Just as in the case of the ambient pressure reactions of **1**, the change of ligand from triphenylphosphine to triisopropyl phosphite had no effect (cf. entries 3 and 7). Utilizing the bidentate phosphite ligand tpdp (**11**)[8] increased the regioselectivity further (entry 8). Additionally, the isomeric bifunctional conjunctive reagent **2** showed enhanced selectivity for cycloadduct **10** at high pressure (entries 2 and 9).

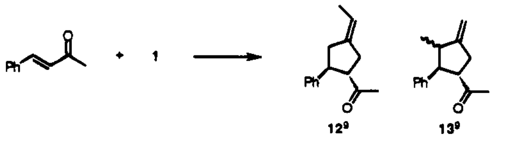


(2)



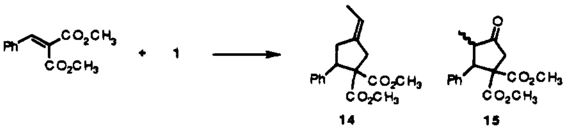
11 ≡ tpdp

A similar reversal of regioselectivity was observed in the cases of benzylideneacetone (eq 3) and dimethyl benzylidenemalonate (eq 4) with **1**. The latter example is particularly noteworthy in that only the cycloadduct **14**[6] was obtained at high pressure.



(3)

	12[9]		**13**[9]
1 atm, Pd(OAc)$_2$, (i-C$_3$H$_7$O)$_3$P, PhCH$_3$, 38%	1	:	3
15 kbar, (η^3-C$_3$H$_7$PdCl$_2$), tpdp, PhCh$_3$-PhH, 90%	3.6	:	1



(4)

	14		**15**
1 atm, (Ph$_3$P)$_4$Pd, THF, 82%	1	:	3.3
10 kbar, Pd(OAc)$_2$,(i-C$_3$H$_7$O)$_3$P, PhCH$_3$, 71%	only		–

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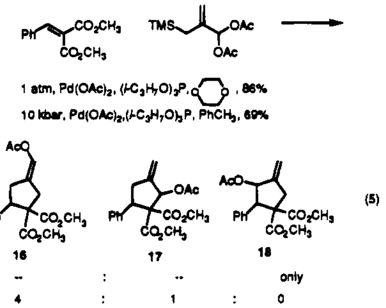
Table 1. Regioselectivity of Addition of $CH_3-TMM-PdL_2$ to Coumarin

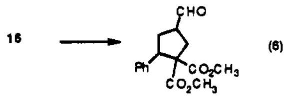
entry	TMM precursor	Pd source (mol %)	added ligand (mol %)	solvent (ratio)	pressure (temp °C)	ratio **8+9:10**	ratio **8:9**	yield[a] (%)
1[b]	**1**	$(Ph_3P)_4Pd$ (5)	Ph_3P (5)	THF	1 atm (65)	1:8.9	1:0	63
2[b]	**2**	$(Ph_3P)_4Pd$ (5)	Ph_3P (5)	THF	1 atm (65)	1:10.1	1:0	63
3	**1**	$(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5)	Ph_3P (10)	$PhCH_3$:PhH (7:3)	15 kbar (70)	3.2:1	2.2:1	38
4	**1**	$Pd(OAc)_2$ (5)	$(i\text{-}C_3H_7O)_3P$ (30)	$PhCH_3$	9.8 kbar (25)	3.7:1	1:0	12
5	**1**	$Pd(OAc)_2$ (5)	$(i\text{-}C_3H_7O)_3P$ (25)	$PhCH_3$	9.8 kbar (25)	1.4:1	1:0	30
6	**1**	$(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5)	$(i\text{-}C_3H_7O)_3P$ (10)	$PhCH_3$	9.8 kbar (25)	1.4:1	1:0	71
7	**1**	$(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5)	$(i\text{-}C_3H_7O)_3P$ (10)	$PhCH_3$:PhH(7:3)	15 kbar (25)	3.3:1	2.9:1	64
8	**1**	$(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5)	tpdp (5)	$PhCH_3$:PhH(7:3)	15 kbar (70)	3.8:1	3.1:1	77
9	**2**	$(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5)	$(i\text{-}C_3H_7O)_3P$ (10)	$PhCH_3$:PhH (7:3)	15 kbar (25)	1:14	1:0	67

[a] Isolated yields. [b] Taken from ref 6.

Bifunctional conjunctive reagents bearing substituents other than methyl show similar behavior. Particularly intriguing is the acetoxy-substituted TMM precursor,[10] where the regioselectivity completely inverted in its reaction with dimethyl benzylidenemalonate at high pressure (eq 5). The vinyl acetate **16**[9] is a useful derivative since it converts to an aldehyde upon acidic hydrolysis (eq 6) and is an enolate equivalent.

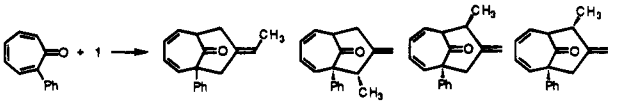


(5)



(6)

These trends extend to (6 + 4) cycloadditions.[11] Using a phenyl substituent as a marker to discern kinetic versus thermodynamic regioselectivity, the thermodynamic products **21** and **22** derive from the methyl-substituted carbon of the intermediate TMM complex attacking the sterically less hindered 7 position of the tropone. Under normal conditions [1 atm, $Pd(OAc)_2$, $(i\text{-}C_3H_7O)_3P$, $PhCH_3$, reflux], a 54% yield of the 1:6.3 ratio of kinetic (**19**+**20**)[9,12a]: thermodynamic (**21**+**22**)[9,12a] products are obtained (eq 7). This ratio inverted when the same ligand was used at high pressure [15 kbar, $(\eta^3\text{-}C_3H_5PdCl)_2$, $(i\text{-}C_3H_7O)_3P$, $PhCH_3$–PhH, 50 °C] to give a 58% yield favoring the kinetic products (**19**+**20**:**21**+**22** 2.3:1).[12b] The bidentate phosphite ligand **11** increased this ratio to 6.6:1[12c] and the yield to 84%.



(7)

High pressure clearly plays a significant role in this transition-metal-catalyzed reaction. Unlike thermal processes and the other reported Pd-catalyzed reactions,[4b,c] the major effect is not a rate enhancement.[13] In fact, depending upon the ligand to palladium ratio, a rate retardation was experienced. This can be readily understood by the effect of pressure on ligand dissociation. Since exchange of a phosphorus ligand for the olefin of the TMM precursor is required for reaction, inhibiting this process at high pressure may now make this step rate determining, whereas at ambient pressure it may be fast relative to subsequent reactions. When the Pd–P ratio is the minimum required for an active catalyst (i.e., 1:2), this effect disappears and the reaction proceeds even at ambient temperature in many cases.

The dramatic effect of high pressure is on regioselectivity.[13] In reactions of substrates like **1**, the regioselectivity inverts at high pressure compared to ambient pressure. One explanation would be that the ΔV values for reactions of **3** are smaller than those of **4**. If this explanation were correct, then the regioselectivity would be independent of $CH_3-TMM-PdL_2$ precursor, which is not the case. The simplest explanation that fully accounts for all of the current results returns to our original working hypothesis that we can now increase the rate of the bimolecular addition to the acceptor compared to the unimolecular interconversion of TMM complexes **3** and **4** so that we can effectively trap the kinetic complex. This explanation also predicts enhanced regioselectivity for the cycloadducts of type **7** (eq 1, path b) starting from **2**, as observed experimentally. To our knowledge, this represents the first example of such an effect at high pressure. Further, it provides strong support for the unsymmetrical nature of the $TMM-PdL_2$ complexes[14] in contrast to virtually all other metal complexes of this fragment[15] and for a dynamic process in which the palladium whirls around the perimeter of the TMM fragment. Synthetically, the utilization of high pressure extends the nature of the regioselectivity available in the palladium-catalyzed cycloadditions with substituted trimethylenemethane units.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. J.R.P. was a recipient of an ACS Organic Division Fellowship sponsored by ICI Americas. Mass spectra were provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources. Special thanks go to Professor William G. Dauben for his aid in assisting our acquisition of a high-pressure apparatus according to his design and Dr. Osman Achmatowicz, who performed some of the first experiments at high pressure (6.9 kbar).

Supplementary Material Available: Characterization data for **12**, **13**, **16**, **17**, **19**, **21**, and **22** (2 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 Internet access instructions.

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(9) This compound has been satisfactorily characterized spectroscopically and elemental composition established by high-resolution mass spectrometry and/or combustion analysis.

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(12) (a) Ratio of **19**:**20**, 1.0:0, and **21**:**22**, 1:3.5. (b) Ratio of **19**:**20**, 4.4:1.0, and **21**:**22**, 1.0:2.3. (c) Ratio of **19**:**20**, 3.5, and **21**:**22**, 1.2:1.0.

(13) In the case of a Heck arylation, the regioselectivity of the C-C bond formation was not affected by pressure, whereas the position of the double bond in the product which arises by metal-catalyzed double bond migration in the kinetic product was—a type of selectivity effect very different than that recorded herein. See ref 4c.

(14) For an X-ray structure of a $TMM-PdL_2$ bearing strong electron-withdrawing groups, see: Su, C.-C.; Chen, J.-T.; Lee, G.-H.; Wang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4999. While this structure corresponds to η^3 coordination of palladium, as proposed herein, its distortion toward this structure by virtue of the electron-withdrawing substituents cannot be excluded.

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