# Evidence for a Concerted Mechanism in a Palladium Trimethylenemethane Cycloaddition

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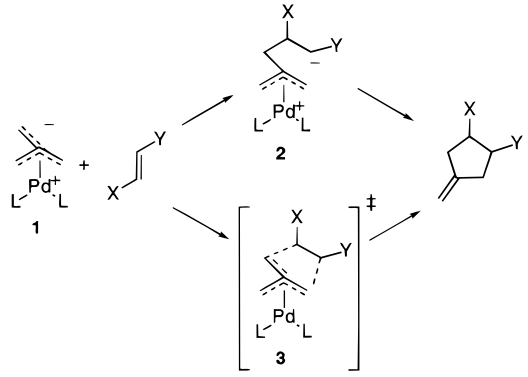
**Abstract:** Carbon kinetic isotope effects were determined at natural abundance for the palladium trimethylenemethane cycloaddition of ester−amide **5**. Substantial intermolecular $^{13}C$ KIEs were observed for both olefinic carbons of **5**. In contrast, a Michael addition to **5** exhibits a significant $^{13}C$ KIE only at the carbon $\beta$ to the ester group. Intramolecular KIEs determined for the product-determining step(s) for reaction of the Pd−TMM intermediate would require a surprising isotope-dependent selection between diastereomeric ring closures. These results cannot be reconciled with a stepwise cycloaddition mechanism but are readily interpreted in terms of a concerted cycloaddition.

## Introduction

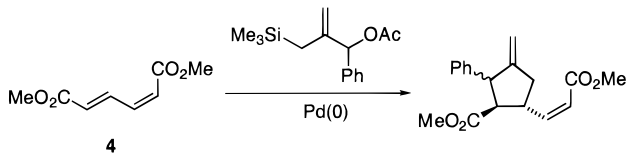
The development of palladium trimethylenemethane (TMM) cycloadditions has been a seminal advance in ring-construction methodology.[1] The generality and versatility of these reactions have been illustrated by their use in [3 + 2] cycloadditions to form both cyclopentanes[2] and heterocycles,[3] [3 + 4] and [3 + 6] cycloadditions,[4,5] and many applications in total synthesis.[6] Owing in part to analogy with concerted Diels−Alder reactions forming six-membered rings, there has been considerable interest in the mechanism of TMM cycloadditions. The palladium−TMM complex **1**, supported by many lines of evidence,[7,8] can conceivably react by either a stepwise mechanism involving the zwitterionic intermediate **2** or a direct, orbital-symmetry-allowed concerted cycloaddition (Scheme 1).

Much of the evidence bearing on the concerted versus stepwise mechanisms has been stereochemical. Early studies noted that trans alkenes tend to afford trans-substituted products, while cis alkenes usually afford mixtures of cis and trans adducts. This lack of stereospecificity would be considered indicative of a stepwise process. However, a number of these reactions do exhibit near or complete stereospecificity—at least one cis alkene affords purely cis product[9] and trisubstituted alkenes appear to generally react stereospecifically. Among alkenes that do not react stereospecifically there is a substantial memory effect—the cis adduct is usually the major product from cis alkenes, and cis and trans alkenes never afford the same mixture of products. This observation has been rationalized as resulting from ring closure in **2** being faster than scrambling of the stereochemistry through bond rotation. The intermediacy of **2** is consistent with a requirement for alkene activation by electron-withdrawing groups.

**Scheme 1**




Some other observations appear to favor a concerted mechanism. Trans alkenes react faster than cis, in line with Huisgen's general observation for concerted cycloadditions.[10] In the example of dimethyl *cis,trans*-muconate **4**, the adduct with the trans double bond is formed exclusively. Cis alkenes react faster




in established stepwise processes. $\beta$-Alkoxyenones afford adducts in a normal fashion, though the intermediate **2** (X = OR, Y = COR) would be expected to rapidly eliminate an alkoxy group.

(1) For reviews, see: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.
(2) Trost, B. M; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315−25.
(3) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902−15. Trost, B. M.; Marrs, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 6636.
(4) Trost, B. M.; Schneider, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 213.
(5) Trost, B. M.; Seoane, P. R. *J. Am. Chem. Soc.* **1987**, *109*, 615−17.
(6) Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668−72. Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 284−91. Paquette, L. A.; Sauer, D. R.; Cleary, D. G.; Kinsella, M. A.; Blackwell, C. M.; Anderson, L. G. *J. Am. Chem. Soc.* **1992**, *114*, 7375−87. Cossy, J.; Belotti, D.; Pete, J. P. *Tetrahedron* **1990**, 46, 1859−70. Trost, B. M.; Acemoglu, M. *Tetrahedron Lett.* **1989**, *30*, 1495−8. Ishibashi, H.; Okano, M.; Tamaki, H.; Maruyama, K.; Yakura, T.; Ikeda, M. *Chem. Commun.* **1990**, 1436−7.
(7) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1980**, *102*, 6359−61.
(8) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2326−35.
(9) Trost, B. M.; Mignani, S. M. *Tetrahedron Lett.* **1986**, *27*, 4137−40.
(10) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.

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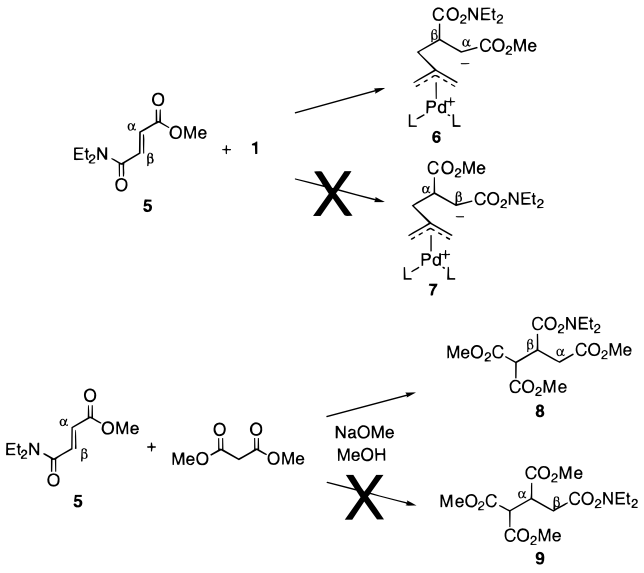
**Scheme 2**



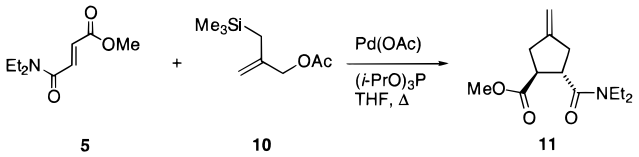

Overall, mechanistic opinion appears to be weighed most heavily by the lack of stereospecificity with some alkenes, and the zwitterionic character of **2** is credited with giving the reaction some of the characteristics of concerted cycloadditions.[11] After all, loss of alkene stereointegrity is, having excluded starting alkene isomerization, unambiguous evidence that at least some of the reaction proceeds by a stepwise process. In contrast, we report here compelling kinetic isotope effect evidence of a palladium trimethylenemethane cycloaddition that proceeds by a concerted mechanism. The results suggest a reinterpretation of some of the fascinating observations associated with these reactions.

## Results

Our plan was to follow the venerable mechanistic strategy of determining the carbon kinetic isotope effects for both carbons of an alkene undergoing a "cycloaddition".[12] The choice of alkene is critical. Symmetrical alkenes would show symmetrical KIEs whether the cycloaddition is stepwise or concerted due to averaging. However, a highly unsymmetrical alkene might unduly favor a stepwise mechanism or result in a highly asynchronous cycloaddition that would be difficult to distinguish from a stepwise process. The "nearly symmetrical" fumarate ester amide **5**[13] was chosen for study with the idea that a stepwise mechanism involving a conjugate addition as the first step would be expected to strongly favor formation of the ester enolate **6** over the amide enolate **7** (Scheme 2). This expected preference is supported by the observation that the Michael addition of dimethyl malonate to **5** afforded exclusively the adduct **8** with no observable formation of the alternative regioisomer **9**. Thus a stepwise cycloaddition with **5** would be expected to exhibit a significant $^{13}$C KIE at C$\beta$ but not C$\alpha$.

Isotope effects for the methylenecyclopentane annulation of **5** with 3-acetoxy-2-trimethylsilylmethyl-1-propene (**10**) catalyzed by $Pd(OAc)_2$/triisopropyl phosphite were determined at natural abundance by novel methodology. We have previously used analysis of starting material reisolated from reactions taken to high conversion to attain high-precision KIEs from lower precision NMR integrations.[14] Unfortunately, this methodology suffered from two problems in the reactions of **5**. First, assuming that formation of a Pd−TMM complex from **10** is irreversible, starting material analysis cannot provide information about TMM isotope effects for cycloaddition. Second, the process of taking reactions of **5** to high conversion and reisolation of highly pure **5** proved difficult on a scale large enough for the NMR analysis. For these reasons, the KIEs here were determined by analysis of the product isolated from reactions taken to low conversion. Product analysis limits the precision of the KIEs obtained, but the NMR results proved sufficiently precise for chemical interpretation.

The reaction of **5** with **10** proceeds cleanly in refluxing THF with no detectable byproducts derived from **5**.[15] Reactions of **5** with limiting **10** were taken to ≈20% conversion on a 0.1 mol scale, and product **11** was isolated by direct column chromatography of the complete reaction mixture. An NMR-standard sample of **11** was formed by taking **5** from the same starting lot to 100% conversion. The two samples of **11** were compared




by $^{13}$C NMR, and the relative changes in $^{13}$C composition were calculated directly from the changes in integrations relative to one of the methylene carbons of the amide as internal standard.[16]

The results from eight analyses (involving six spectra for each sample and each standard) of three reactions are summarized in Figure 1. These results represent KIEs for C1−C9 (uncorrected for the % conversion of the reactions).[17] However, because **10** was used as a limiting reagent in the partial-conversion reactions and added in limiting portions in the 100% conversion reactions, both are equivalent with respect to **10**. Thus, the isotopic composition for the carbons in **11** that are derived from **10** (C10−C13 in Figure 1) should be the same at

(11) Trost, B. M.; Miller, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 3687−9.

(12) Benjamin, B. M.; Collins, C. J. *J. Am. Chem. Soc.* **1973**, *95*, 6145. Kupczyk-Subotkowska, L.; Shine, H. J. *J. Am. Chem. Soc.* **1993**, *115*, 5296−7.

(13) Bienaymé, H.; Longeau, A. *Tetrahedron* **1997**, *28*, 9637. Compound **5** may also be prepared by treating maleic anhydride with 2 equiv of diethylamine, isomerization of the resulting acid amide in refluxing toluene, and Fischer esterification.

(14) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357−9358.

(15) No cis isomer of **5** or **11** was observed. The stereochemistry of reactions of diethyl or dimethyl maleate and fumarate was investigated in more detail. Only the trans cycloadducts were observed in reactions with diethyl and dimethyl fumarate, while reactions of dimethyl maleate afforded varying ratios of cis and trans cycloadducts, depending on the reaction conditions. The largest amount of cis cycloadduct from dimethyl maleate was observed in a reaction employing excess **10** and 20 mol % $Pd(OAc)_2$, with the catalyst preactivated in a reaction of diethyl fumarate. In this case the cis:trans ratio varied from 0.7:1 to 1.4:1 as the reaction progressed. In a reaction of a 1:1 mixture of di*ethyl* maleate and di*methyl* fumarate taken to ≈90% conversion of the dimethyl fumarate, ≈3% of a mixture of trans and cis diethyl maleate-derived cycloadducts was formed. From this observation, the $k_{trans}/k_{cis}$ rate ratio was at least 30:1. (Dimethyl maleate and diethyl maleate were found to react at about the same rate in a competition reaction.) Under these reaction conditions, maleate to fumarate isomerization was observed when the cycloaddition was precluded by a lack of **10**. Owing to the high $k_{trans}/k_{cis}$ rate ratio and the potential cis−trans isomerization, we have not been able to conclude whether the formation of trans cycloadduct from maleates is the result of a nonstereospecific cycloaddition or prior isomerization of the maleate.

(16) (a) The $^{13}$C peaks for the quaternary carbons in **11** were very narrow, and the standard deviations on their integrations were unusually large (up to 12%). For this reason, no meaningful KIE could be determined for the quaternary carbons. (b) The stereochemistries of the separate ethyl group $^{13}$C peaks for the diethylamide of **11** were not assigned, and the results for these carbons are shown arbitrarily in Figure 1.

(17) After correction for ≈20% conversion, the actual KIEs would be ≈10% further from 1.000 than the values in Figure 1. This correction is small compared to the uncertainty in these values.

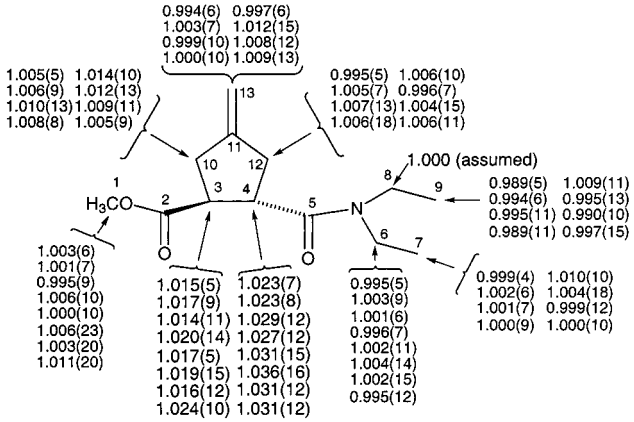
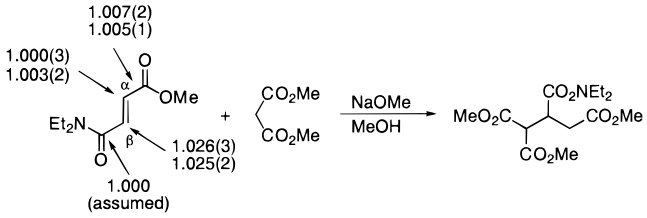



**Figure 1.** Relative changes in $^{13}C$ isotope composition between **11** isolated from reactions taken to completion versus reactions taken to ≈20% conversion. These numbers represent KIEs ($k^{12}_C/k^{13}_C$) for C1−C9 but not for C10−C13 (see text). Standard deviations ($n = 6$) are shown in parentheses.

**Scheme 3**

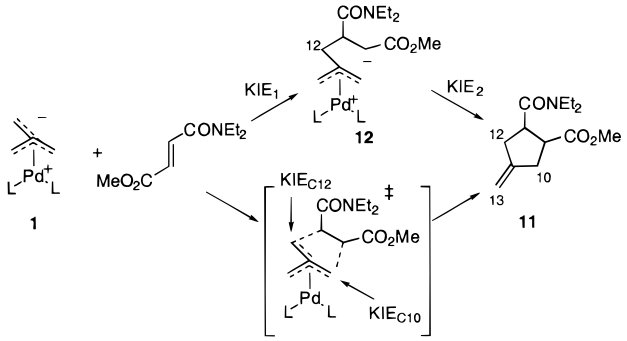



20% and complete conversion. In addition, little or no KIE would be expected at the carbons in **5** not at reactive centers (C1 and C6−C9 in Figure 1). The results are in accord with these expectations—only 2 out of 56 measurements are over a standard deviation away from 1.000.[16] In contrast, all of the KIE measurements for both olefinic carbons in **5** (C3 and C4 in Figure 1) are over a standard deviation greater than 1.000. Despite the large standard deviation on each individual measurement, these results taken in toto strongly support a substantial $^{13}C$ KIE at both olefinic carbons of **5**.

To compare these results with the KIEs for a normal Michael addition, the KIEs for reaction of **5** with dimethyl malonate were measured using our standard natural-abundance methodology.[14] Reactions of **5** on an ≈0.25 mol scale with dimethyl malonate in refluxing methanol catalyzed by ≈10 mol % sodium methoxide were taken to 76(±2)% and 82.2(±1.4)% conversion, and unreacted **5** was isolated after removal of the methanol under vacuum by flash chromatography and analyzed by NMR compared to standard samples of **5** from the same synthetic lot. The relative changes in $^{13}C$ composition for **5** were calculated using the amide carbonyl carbon as an "internal standard" with the assumption that its isotopic composition does not change.[18] From the changes in isotopic composition, the KIEs were calculated as previously described.[14] The resulting KIEs are summarized in Scheme 3. A small KIE is observed at the ester carbonyl carbon, and a substantial KIE is observed at the carbon undergoing attack in the Michael addition, but $k^{12}_C/k^{13}_C$ for the other olefinic carbon is very close to unity.

Using a new technique recently developed in this laboratory for the determination of $^{13}C$ KIEs from absolute $^{13}C$ NMR integrations,[19] it was possible to measure *intramolecular* $^{13}C$ KIEs on the product-determining step(s) for reaction of the Pd−TMM intermediate. The nature of this intramolecular $^{13}C$ KIE can be understood by considering Scheme 1 with one of the methylene carbons of **1** containing a $^{13}C$. Because the methylene groups in **1** are either equivalent or rapidly interconverting (based on isotopic labeling studies[7,8]), the first step in the reaction of a $^{13}C$-containing **1** can exhibit a KIE on where $^{13}C$ ends up in the product. For the stepwise mechanism, a second intramolecular KIE is possible for the ring closure of **2**.

**Scheme 4**




Samples of **11** were analyzed by $^{13}C$ NMR under the more demanding requirements for accurate relative integrations within spectra. This includes high digital resolution (256K points over ≈31 000 Hz), long delays (100 s, $>5 \times T_1$), an expanded filter bandwidth, centering of the peaks of interest within the spectral window, and integration ranges that are a constant 10× multiple of the peak width at half-height. Under these conditions, the ratio of the integrations for the interchanging carbons C6 and C9 of the diethylamide were within experimental error of 1.00. A total of 24 measurements of the relative integrations of C12, C10, and C13 were carried out on samples from four different reactions. The resulting average integrations relative to C12 (assigned 1.000) were 1.000 for C10 and 1.029 for C13, with 95% confidence limits on these numbers of ±0.004 and ±0.006, respectively.

The interpretation of these results in terms of isotope effects depends on a choice of mechanistic model for the reaction (Scheme 4). If the cycloaddition proceeds by a stepwise mechanism, then the incorporation of $^{13}C$ into the C12 position of **11** for Pd−TMM complexes **1** containing a single $^{13}C$ will be determined by $KIE_1$, which is the statistically corrected relative rate of nucleophilic attack by a $^{12}C$ versus a $^{13}C$.[20] The relative incorporation of $^{13}C$ into C10 and C13 would then be directly related to $KIE_2$, the relative rate of nucleophilic attack at a $^{12}C$ versus a $^{13}C$ in the ring closure of **12**. The relative incorporation of $^{13}C$ into C12, C10, and C13 would be 1, $2 \times KIE_1/(1 + KIE_2)$, and $2 \times KIE_1 \times KIE_2/(1 + KIE_2)$, respectively. From the NMR data in the previous paragraph, $KIE_1$ would be 1.015(±0.005) and $KIE_2$ would be 1.029(±0.007).

If the cycloaddition proceeds by a concerted mechanism, then it is subject in a single step to different KIEs for the C12 and C10 positions (referred to as $KIE_{C12}$ and $KIE_{C10}$). The relative incorporation of $^{13}C$ into C12, C10, and C13 would be 1, $KIE_{C12}/KIE_{C10}$, and $KIE_{C12}$, respectively. From the NMR data, $KIE_{C12}$ would be 1.029(±0.006) and $KIE_{C10}$ would be 1.029(±0.007).

(18) Due to broadening by exchange, the ethyl group carbons could not be integrated accurately. The methoxy group is subject to exchange with solvent under the reaction conditions, so no KIE could be determined for the methoxy carbon.

(19) Singleton, D. A.; Szymanski, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9307−9312.

(20) The KIEs discussed here are relative values for the absolute KIEs at reactive versus nonreactive methylene carbons of the Pd−TMM. The absolute KIEs for the nonreactive methylene carbons in each step are assumed to be near 1.000.

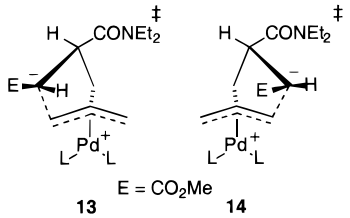
## Discussion

The observed KIEs will be readily interpretable in terms of a concerted cycloaddition mechanism. However, careful consideration must be given as to whether the results can also be reconciled with a stepwise mechanism.

The qualitative interpretation of $^{13}$C KIEs is complicated by some question of when a primary KIE may be expected. Primary hydrogen KIEs are expected under the simple condition of hydrogen transfer in the rate-limiting step. However, primary carbon KIEs need not involve discreet carbon transfer (as in, for example, an $S_N2$ reaction) but rather may involve other significant bonding changes, such as bond formation or bond breaking to a carbon (as in, for example, a Diels−Alder reaction[14]). Therefore, whether conjugate addition to **5** at C$\beta$ could result in a substantial KIE at C$\alpha$ was not completely clear.[21] The lack of a significant $^{13}$C KIE at C$\alpha$ in the addition of dimethyl malonate to **5** (Scheme 3) strongly suggests that a stepwise cycloaddition with rate-limiting formation of **12** cannot account for the observed KIEs at C3 and C4 of **11**.[22] Notably, the substantial $^{13}$C KIE at C$\beta$ of **5** in the addition of dimethyl malonate establishes that carbon−carbon bond formation is the rate-limiting step in this Michael reaction.[23]

A stepwise mechanism with the second step, ring closure of **12**, being rate limiting would clearly not account for the large $^{13}$C KIE at C4 of **11**.[23] However, the complex possibility that the formation of **12** and its ring closure are each partially rate limiting requires more detailed attention. This scenario would require reversibility of the carbon−carbon bond formation in the first step as well as approximately equal barriers for the two steps of the cycloaddition. Each requirement might be considered unlikely, though reversible formation of **12** would be one way of explaining the alkene isomerization sometimes observed Pd−TMM reactions.[15] However, an additional difficulty with this possibility is that partially rate-limiting steps do not express the full intrinsic KIE for each step. If, for example, the formation of **12** were 60% rate-limiting and ring closure were 40% rate-limiting, intrinsic KIEs of ≈1.048 and ≈1.045 for the first and second steps would be required to account for the observed KIEs.[24] These intrinsic KIEs would be unreasonably large, as can be seen from comparison with the C$\beta$ KIE in the Michael addition of dimethyl malonate to **5**.

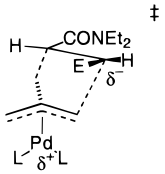
The conclusion that a stepwise mechanism cannot account for the C3 and C4 KIEs in **11** is supported by the intramolecular $^{13}$C KIEs for reaction of the palladium−TMM intermediate. The analysis here is more complex. The $KIE_2$ in Scheme 4, if the mechanism were stepwise, would result from an isotopic influence on the selection between the two transition states **13** and **14**. Although both **13** and **14** produce the same product,




**13** **14**

they are diastereomeric! Any difference in their energy would result in a decrease of the observed $KIE_2$ compared to the intrinsic isotope effect, and if **13** and **14** differ significantly in energy, no KIE for this step would be observed. The large observed $KIE_2$ (1.029(7)) would thus be surprising for the stepwise mechanism. A second issue is that a selection between **13** and **14** requires that the intermediate have sufficient lifetime to equilibrate between rotamers leading to the two transition states. This is not easily reconciled with the requirement of very rapid ring closure in order to explain the general observation of differing stereochemical results when starting from stereoisomeric alkenes.

It should be noted that the KIE results do not exclude a small portion of the reaction occurring by a stepwise mechanism, as the experimental KIEs reflect a weighted average of a reaction's mechanistic pathways. However, a concerted mechanism provides a consistent explanation for both the intermolecular KIEs in Figure 1 and the intramolecular KIEs observed for the Pd−TMM. The observation of substantial $^{13}$C KIEs at both C4 and C3 of **11** (C$\beta$ and C$\alpha$ of **5**) is the expected result when bonds are being formed to both carbons in the rate-limiting step as in a concerted cycloaddition. The magnitude of the effects is comparable to that observed in other cycloadditions,[12,14,25] and the greater KIE at C4 of **11** compared to C3 is suggestive of an asynchronous transition state with greater bond formation to C$\beta$ of **5** than C$\alpha$, as in **15**. The direction of this asynchroneity




**15** (E = $CO_2Me$)

would be reasonable, considering the nucleophilic character of the Pd−TMM intermediate **1** (clear from alkene reactivity observations) and the expectation that a partial negative charge generated at the transition state for a concerted asynchronous cycloaddition would preferably be adjacent to the more stabilizing ester group. It would perhaps be surprising for the intramolecular isotope effects $KIE_{C12}$ and $KIE_{C10}$ to be equal at 1.029(±0.006) and 1.029(±0.007), respectively, for an asynchronous transition state. However, the uncertainty in these values makes it readily possible that the "true" KIEs are not so equal.

## Conclusions

The results here strongly support a concerted mechanism for the Pd−TMM cycloaddition with **5**. As a substrate for these

(21) The bonding changes occurring at C$\alpha$ are similar to those occurring at the central carbons of a diene in the Diels−Alder reaction. The $^{13}$C KIEs observed in these positions for Diels−Alder reactions are very small.[14]

(22) It might be argued that a stepwise Pd−TMM cycloaddition would differ from a Michael addition based on the possibility for a close association of the resulting enolate and Pd−$\pi$-allyl cation. Some evidence that such an association should not lead to a significant KIE at C3 (C$\alpha$) comes from isotope effects for the Lewis acid-catalyzed Diels−Alder reactions of isoprene with acrolein, ethyl acrylate, and methyl vinyl ketone (Singleton, D. A.; Merrigan, S. R.; Beno, B. R.; Houk, K. N *Tetrahedron Lett.* **1999**, *40*, 5817). In these cases, the $^2$H KIEs are indicative of a concerted process but the $^{13}$C KIEs at the carbons associated with the less-formed bond at the transition state are near unity. Thus, the relatively strong but distant interaction of two carbons in a concerted cycloaddition need not result in a significant KIE, so the much weaker interaction in a stepwise cycloaddition seems very unlikely to produce a substantial KIE.

(23) The equilibrium isotope effect for addition of a carbon nucleophile to an alkene would be expected to be slightly inverse ($k^{12}_C/k^{13}_C$ <1). See discussion in Yamataka, H.; Nagareda, K.; Takatsuka, T.; Ando, K.; Hanafusa, T.; Nagase, S. *J. Am. Chem. Soc.* **1993**, *115*, 8570. See also: Baddenbaum, W. E.; Shiner, V. J., Jr. In *Isotope Effects on Enzyme-Catalyzed Reactions*; Cleland, W. W., O'Leary, M. H., Northrop, D. B., Eds.; University Park Press: Baltimore, 1977; Chapter 1.

(24) This discussion assumes that the equilibrium isotope effect at C4 for the first step is near 1.000. If the equilibrium isotope effect for the first step is in fact slightly inverse, as expected (see ref 23), the intrinsic isotope effects would have to be even larger.

(25) DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907−8.

reactions, **5** might be expected to particularly favor a concerted mechanism. The concerted process would take advantage of the faster reaction of trans alkenes and the possibility for simultaneous delocalization of a partial negative charge (built up in the alkene at the transition state) into both carbonyls. There is thus no assurance that the results here are general—more unsymmetrical alkenes may favor a stepwise mechanism. It also seems unlikely that [3 + 2], [3 + 4], and [3 + 6] Pd−TMM cycloadditions can all occur through concerted mechanisms. Excluding starting alkene isomerization, partial loss of stereospecificity indeed indicates that a stepwise mechanism is operative in the formation of some of the product in some reactions. However, the observation of a concerted mechanism with **5** suggests that a concerted mechanism is the most plausible explanation of the observed cases of stereospecificity in these reactions.

## Experimental Section

All reactions were carried out in dried glassware and freshly purified solvent under a positive pressure of nitrogen using standard airless techniques. Triisopropyl phosphite was distilled under vacuum from sodium. 3-Acetoxy-2-trimethylsilylmethyl-1-propene (**10**) was prepared as previously described.[2]

**Pd−TMM Cycloaddition with 5. Methyl *trans*-2-(*N*,*N*-Diethylaminocarbonyl)-4-methylenecyclopentanecarboxylate (11). Example Procedure.** A mixture of 90 mg (0.4 mmol) of $Pd(OAc)_2$, 170 mg (0.8 mmol) of triisopropyl phosphite, 17.4 g (94 mmol) of **5**,[13] 3.5 g (18.8 mmol) of **10**, and 1.5 mL of THF was heated to 65 °C in an oil bath and monitored periodically by NMR of aliquots. An additional 3.1 g (16.7 mmol) of **10** was added in portions at ≈24 h intervals. After 142 h the conversion of **5** into **11** was 23 ± 2%. The reaction mixture was then directly subjected to chromatography on a 52 mm × 10 in. flash silica gel column using 15% EtOAc/hexanes as eluent, followed by a second column of the partially purified **11** on a 52 mm × 8 in. column. Kugelrohr distillation of the column isolate afforded 1.5 g of **11**: $^1$H NMR ($CDCl_3$) $\delta$ 4.84 (br s, 2 H), 3.62 (s, 3 H), 3.46−3.18 (m, 6 H), 2.79 (m, 1 H), 2.60 (m, 1 H), 2.44 (m, 2 H), 1.17 (t, 3 H), 1.06 (t, 3 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.9, 172.4, 147.9, 106.8, 51.7, 47.1, 44.1, 41.9, 40.5, 37.7, 35.9, 14.7, 13.0; MS, *m*/*e* 239.15332 (calcd for $C_{15}H_{24}O_5$, 239.15223).

Two similar reactions were taken to 21 ± 2% conversion, with the modified procedure that the mixture of $Pd(OAc)_2$ and triisopropyl phosphite in THF was treated with 0.8 mmol of 2.56 M *n*-butyllithium in hexanes and stirred for 5 min at 25 °C before adding the **5** and **10**. An analogous reaction was taken to 100% conversion using an initial load of 1 equiv of **10** (relative to **5**) and with additional portions of **10** added periodically until **5** could not be detected by NMR.

**Michael Addition to 5.** A mixture of 45.1 g (243 mmol) of **5**, 26.15 g (198 mmol) of dimethylmalonate, 15.9 g (153 mmol) of *p*-xylene (internal standard), 55 mL of methanol, and 1.05 g (19.4 mmol) of sodium methoxide was heated to reflux, and the conversion into **8** was monitored periodically by NMR analysis of an aliquot. When the reaction had reached 76(±2)% reaction of the starting **5** (based on the remaining **5** versus the internal standard), the reaction was cooled and most of the methanol was removed on a rotary evaporator. The mixture was then filtered, and the solids were rinsed with three 50-mL portions of petroleum ether. The combined filtrates were concentrated on a rotary evaporator, and the residue was chromatographed on a 9.5 in. × 70 mm flash silica gel column using 35% EtOAc/petroleum ether as eluent, followed by a second column of the partially purified **5** on a 45 mm × 9 in. column. Kugelrohr distillation of the column isolate afforded 2.28 g of recovered **5**.

**NMR Measurements.** NMR samples were generally prepared using a 70:30 or 80:20 mixture of **11** or **5** and $CDCl_3$ in a 10 mm NMR tube with a sample height of 5.0 cm. In all cases the NMR samples for material isolated from partial-conversion reactions and their corresponding standard samples were prepared identically. The $^{13}$C spectra were obtained at 100.577 MHz on a Varian XL400 broadband NMR spectrometer, with inverse gated decoupling, calibrated 45° pulses, and $>5 \times T_1$ delays (for the slowest-decaying peak of interest) between pulses (100 s for **11**, 40 s for **5**). Integrations were determined numerically using a constant integration region for each peak. A zeroth order baseline correction was generally applied, but in no case was a first order (tilt) correction applied.

For the measurement of intramolecular isotope effects, each of the samples of **11**, including the standard from the reaction taken to 100% conversion, were reanalyzed by $^{13}$C NMR as described above, except collecting 256K points over ≈31 600 Hz with an expanded filter bandwidth of 19 100 Hz on each side of the center of the spectrum, centering the peaks for C10 and C12 versus C13 within the spectral window, and using integration ranges that were a constant 10× multiple of each peak's width at half-height. A blind trial by a different researcher on a different NMR spectrometer obtained results which were within experimental error. The average integrations relative to C12 for C10 and C13 were 1.000 and 1.029, respectively. The 95% confidence limits were calculated from the standard deviation on the relative integrations with $n = 24$ in a standard fashion.

The eight sets of results for **11** arose from three groups of spectra taken over the course of 2 months employing differing spectrometer parameters for each group (see Supporting Information for details). The integrations for the relevant peaks in **11** were set relative to integrations of 1000 for C9,[16b] and the averaged results from six spectra for each sample are shown in Supporting Information. The relative differences in isotopic composition at each position in **11**, summarized in Figure 1, were calculated as the ratio of the average integrations in 100% conversion reference samples compared to each sample from reactions taken to ≈20% conversion, and the standard errors were propagated in a normal fashion (see Supporting Information).

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**Supporting Information Available:** All integration results and details of isotope effect calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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