On the Effect of the Nature of Ion Pairs as Nucleophiles in a Metal-Catalyzed Substitution Reaction

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Abstract: Two mechanistic features of the palladium-catalyzed allylic alkylation reaction of dienyl acetates—vinyl (π-allyl)palladium intermediate equilibration and palladium-catalyzed ionization of the bisallylic malonate products—account for the observed product ratios and nucleophile counterion effects. Three hexadienyl acetate substrates, isomeric with respect to the location of the leaving group to the dienyl system, were studied. The sodium, cesium, tetramethylammonium, and tetrahexylammonium salts of dimethyl malonate and dimethyl benzylmalonate were employed as nucleophiles, and both triphenylphosphine and tributylphosphine ligands were tested. The observed alkylation product ratios varied in a consistent way with the identity of the nucleophile counterion. The palladium-catalyzed ionization of bisallyl malonate products (i.e., the nucleophile serves as a leaving group for palladium ionization) was found to alter the observed product distribution only under certain circumstances such as extended reaction times or temperatures. Nucleophile crossover experiments demonstrated that the monoallylic products did not reionize or isomerize. These results are most consistent with a reaction mechanism where the vinyl (π-allyl)palladium(II) intermediate proximal to the leaving group is formed initially and nucleophilic addition occurs either competitive with or after complete thermodynamic equilibration of the two isomeric vinyl (π-allyl)palladium(II) intermediates. The observed product distribution primarily reflects the kinetic balance of these two processes—nucleophilic addition and intermediate equilibration. Thus, the cesium and tetrahexylammonium counterions slow down the rate of nucleophilic addition relative to intermediate equilibration and allow the vinyl (π-allyl)palladium isomerization process to completely equilibrate the intermediates prior to nucleophilic addition. This effect may relate to the ability of these counterions to affect higher levels of asymmetric induction than other counterions in enantioselective alkylation reactions.

The palladium-catalyzed allylic alkylation reaction is a powerful synthetic tool for the construction of carbon−carbon, carbon−hydrogen, and carbon−heteroatom bonds.[1] Its effective use makes it important to understand the mechanism of this complicated process in detail. Mechanistic features related to regioselectivity and stereochemistry have been investigated.[2] While such studies did take into account the effect of nucleophiles, they did so only in terms of the structure of the anion, which is the portion of the nucleophile that ultimately becomes bonded to the allyl unit. In conjunction with our studies of the asymmetric alkylation of 3-acetoxycyclopentene, the cation seemed to play a more significant role than the anion in helping to maximize the ee.[3] In trying to understand the nature of this phenomenon, we hypothesized that the cation had an effect on the rate of the reaction and, in turn, the ee. This idea led, however, to the surprising suggestion that tetrahexylammonium or cesium counterions led to *slower* rates of nucleophilic attack than tetramethylammonium or sodium counterions.

We decided to explore this question in the context of a competition-type experiment. In the absence of symmetry considerations, simple allyl substrates can give rise to two regioisomeric products (Scheme 1). Conjugated dienyl substrates can, in the general case, give rise to three regioisomeric products (Scheme 2). For convenience, the terms proximal and distal addition refer to attack at the carbon of the intermediate metal complexes with respect to the carbon to which the leaving group was attached in the starting material. The two products of nucleophilic addition proximal to the leaving group could arise from attack on the initially formed π-allyl intermediate at the primary (a) or bisallylic positions (b). The third or distal product must arise via some other process, and interconversion

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(1) (a) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 3.3. (b) Davies, J. A. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, U.K., 1995; Vol. 9, p 291. (c) Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis;* John Wiley: Chichester, 1995. (d) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (e) Trost, B. M. *Pure Appl. Chem.* **1996**, *68*, 779. (f) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

(2) (a) Trost, B. M.; Verhoven, T. R. *J. Am. Chem. Soc.* **1980**, 102, 4730. (b) Akermark, B.; Hansson, S.; Krakenberger, B.; Viragliano, A.; Zetterberg, K. *Organometallics* **1984**, *3*, 679. (c) Trost, B. M.; Hung, M. H. *J. Am. Chem. Soc.* **1984**, *106*, 6837. (d) Yamamoto, K.; Deguchi, R.; Ogimura, Y. Tsuji, J. *Chem. Lett.* **1984**, 1657. (e) Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921. (f) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723. (g) Fiaud, J. C.; Legros, J. Y. *J. Org. Chem.* **1987**, *52*, 1907. (h) Faller, J. W.; Linebarrier, D. *Organometallics* **1988**, *7*, 1670. (i) Keinan, E.; Roth, Z. *Isr. J. Chem.* **1990**, *30*, 305. (j) Backvall, J. E.; Granberg, K. L.; Heumann, A. *Isr. J. Chem.* **1991**, *31*, 17. (k) Stary, I.; Zajicek, J.; Kocovsky, P. *Tetrahedron* **1992**, *48*, 7229. (l) Granberg, K. L.; Backvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6858. (m) Kurosawa, H.; Kajimaru, H.; Ogoshi, S.; Yoneda, H.; Miki, K.; Kasai, N.; Murai, S.; Ikeda, I. *J. Am. Chem. Soc.* **1992**, *114*, 8417. (n) Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1. (o) Dvorak, D.; Stary, I.; Kcovsky, P. *J. Am. Chem. Soc.* **1995**, *117*, 6130. (p) Hayashi, T.; Yamane, M.; Ohno, A. *J. Org. Chem.* **1997**, *62*, 204.

(3) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. Also see: Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 99.

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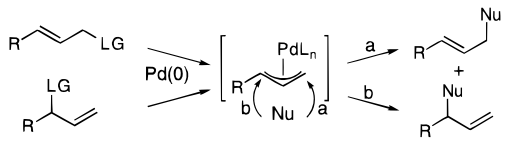
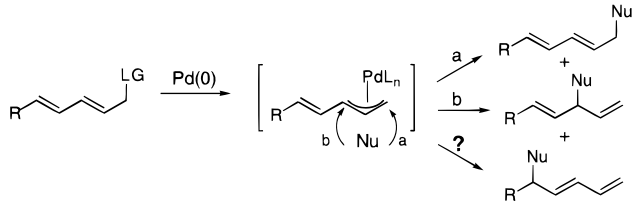
Scheme 1

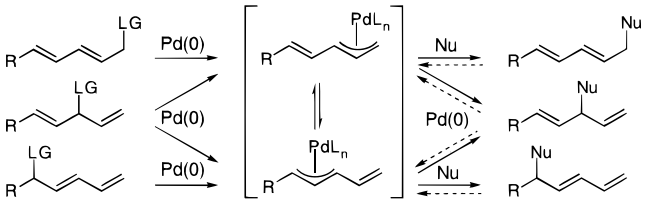


LG = Cl, Br, OPh, SO_2R, OCOR, OCO_2R, $OCONR^1R^2$, etc.

Scheme 2



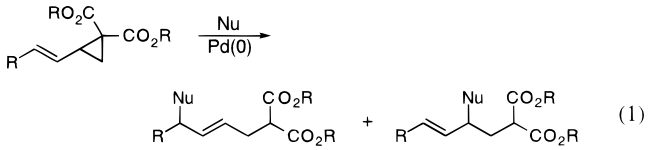
Scheme 3



of the vinyl (π-allyl)palladium intermediates[4] and product isomerization via palladium-catalyzed ionization[5] have been proposed as possible explanations. Various combinations of S_N2'-type ionizations or nucleophilic additions, though not previously documented for allylic alkylations, might also account for the observed results. This system could provide a reasonable testing ground for the effect of counterion on the rate of alkylation if the equilibration of the vinyl (π-allyl)palladium intermediates best accounted for the formation of the distal product isomer as depicted in Scheme 3. In this full account,[6] we provide support for this primary mechanism using additional counterions and catalyst systems, delineate the conditions under which palladium-catalyzed ionization of the bisallylic products can occur, and offer an explanation for the role of the counterion in affecting the observed product ratios. These results provide a consistent mechanistic picture of the reaction pathways for dienyl substrates and also suggest an explanation based on steric interactions for the effect of the nucleophile counterion in asymmetric allylic alkylation reactions.[3]

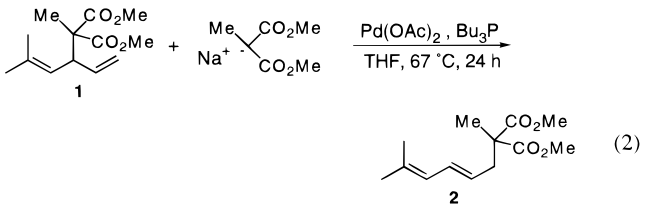
The effects of counterions and ion pair structure are well documented in classical substitution reactions[7] and enolate chemistry;[8] however, the effects of the counterion of the nucleophile are generally assumed to be negligible in palladium-catalyzed allylic alkylation reactions.[9] Typically, nucleophiles such as malonate esters are deprotonated with a convenient base, such as sodium hydride, without examining other counterions, despite the fact that the stabilized nucleophiles employed in these reactions can form a variety of ion pair structures.[10]

An approach for the successful interpretation of counterion effects may be derived from an understanding of the reaction mechanism for dienyl acetates. The pathway by which the distal product isomer forms is of particular importance to understanding the counterion effects, and some uncertainty remains about this issue.[5] With carbon nucleophiles, the addition step to the (π-allyl)palladium intermediate was generally considered to be irreversible. This was shown not to be the case with certain substituted vinyl cyclopropanes[11] (eq 1) and some bisallylic

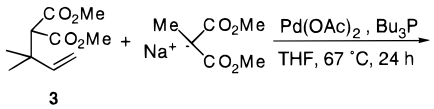


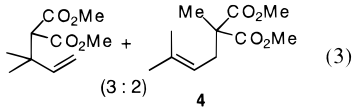
(1)

malonate type products[5] (eq 2). Recently, nucleophile crossover experiments have demonstrated that even in simple allylic systems stabilized carbanions can function as leaving groups for palladium-catalyzed allylic ionizations (eqs 3 and 4) under certain conditions.[5b,12]

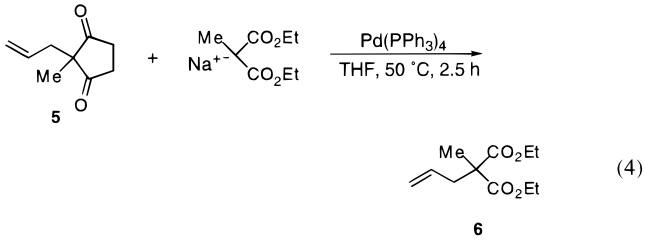


(2)





(3)



(4)

The reversibility of the nucleophilic addition step would obviously affect the product ratios obtained from dienyl substrates and obscure the role of the counterion. In principle, complete thermodynamic equilibration of the products could result if all three products reionize, and thus isomerize, under the reaction conditions. Therefore, this investigation has two interrelated objectives: (1) elucidation of the reaction mechanism for the alkylation of dienyl substrates with particular attention to the possibility of reversible steps in the reaction

(4) Trost, B. M.; Urch, C. J.; Hung, M. H. *Tetrahedron Lett.* **1986**, *27*, 4949.

(5) (a) Andersson, P. G.; Backvall, J. E. *J. Org. Chem.* **1991**, *56*, 5349. (b) Nilsson, Y. I. M.; Andersson, P. G.; Backvall, J. E. *J. Am. Chem. Soc.* **1993**, *115*, 6609.

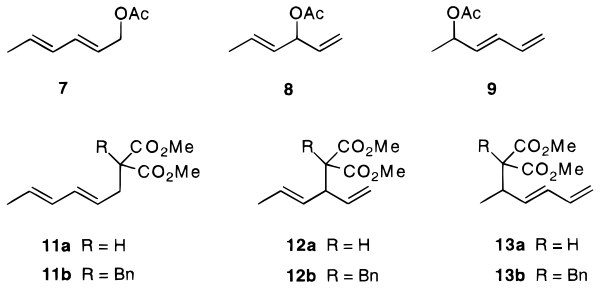
(6) For a preliminary report of a portion of this work, see: Trost, B. M.; Bunt, R. C. *Tetrahedron Lett.* **1993**, *34*, 7513.

(7) (a) Szwarc, M. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; John Wiley & Sons: New York, 1972; Vol. 1, Chapter 1. (b) Raber, D. J.; Harris, J. M.; Schleyer, P. v. R.; In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; John Wiley & Sons: New York, 1974; Vol. 2, Chapter 3. (c) Arnett, E. A.; Maroldo, S. G.; Schriver, G. W.; Schilling, S. L.; Troughton, E. B. *J. Am. Chem. Soc.* **1985**, *107*, 2091. (d) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (e) Cacciapaglia, R.; Mandolini, L. *J. Org. Chem.* **1988**, *53*, 2579. (f) Ciula, J. C.; Streitwieser, A. *J. Org. Chem.* **1992**, *57*, 431.

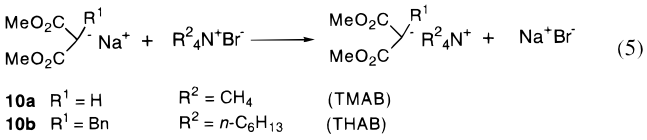
(8) (a) Heathcock, C. H. In *Modern Synthetic Methods*; Scheffold, R., Ed.; VCH Publishers: New York, 1988; Vol. 6, Chapter 1. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (c) Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.4. (d) For a contrasting example, see: Lambert, C.; Wu, Y. D.; Schleyer, P. v. R. *J. Chem. Soc., Chem. Commun.* **1993**, 255.

and (2) exploration of the role that nucleophile counterion plays in allylic alkylation reactions. These objectives have been achieved by examining the product ratios obtained under a variety of alkylation reaction conditions (nucleophile, counterion, ligand, and time dependence), as well as nucleophile crossover control experiments.

Experimental Design. Three isomeric dienyl acetate substrates were employed: acetate **7** is commercially available and acetates **8** and **9** are readily available via known methods.[5a,13] The palladium-catalyzed alkylation of each dienyl acetate (**7**−**9**) in separate reactions with a nucleophile derived from either dimethyl malonate (**10a**) or dimethyl benzylmalonate (**10b**) gives a mixture of all three products (**11**−**13**). The sodium



malonate salts were generated directly with sodium hydride, and the cesium salts were generated with cesium carbonate. A salt metathesis reaction between the sodium salt of either nucleophile (**10a** or **10b**) and either tetra-n-hexylammonium bromide (THAB) or tetramethylammonium bromide (TMAB) was used to generate the ammonium salts of the malonate nucleophiles *in situ* (eq 5).



(5)

The single methyl group in each isomer differentiates the two termini of the dienyl system and, thus, distinguishes the product of proximal attack (e.g., **11** from the alkylation of **7** or **13** from **9**) from the product of distal attack (e.g., **13** from the alkylation of **7** or **11** from **9**). The product ratios (**11**:**12**:**13**) obtained from alkylation of each of the substrates provide information about the mechanism of the reaction. Comparisons are made both between the individual product ratios for each substrate under specific reaction conditions (a set of ratios) and between the sets of product ratios obtained for different reaction conditions. In particular, the similarity or difference of the product ratios within each set of conditions is used to probe for a common intermediate or common intermediates in the reaction pathway. Observation of the same product ratio for each of the three substrates under particular reaction conditions would suggest a common intermediate or pathway for the three reactions. This consideration applies most directly to the question of intermediate equilibration or product isomerization. Separate product crossover experiments and time dependence studies serve to distinguish these two pathways. The question of S_N2'-type ionization processes occurring in the reaction pathway is addressed with the bisallylic starting material (**8**) which can only undergo a direct ionization. Results with this substrate that are similar to the other substrates (**7** and **9**) would suggest that S_N2'-type ionizations do not play a role in the reaction mechanism. Likewise, the bisallylic products (**12a** or **12b**) can only arise from direct nucleophilic addition to a (π-allyl)palladium intermediate. Similar appearance of these products from all three substrates would suggest that S_N2'-type nucleophilic additions do not play a role in the reaction mechanism.

Product Identification and Ratio. The individual dimethyl benzylmalonate product isomers (**11b**, **12b**, and **13b**) were separated by preparative HPLC from an alkylation reaction of **9**. The identity of each of the three isomers was established from their ^{1}H NMR spectra. Comparison of the GC retention times (Table 6, Supporting Information) of the authentic samples with those of the product mixtures from the alkylation reactions allowed routine assignment of the product ratios from the mixture of isomers.

For the alkylation reactions with dimethyl malonate as the nucleophile, the individual product isomers were not separated chromatographically. Rather, the product isomers were identified from the ^{1}H NMR spectra of the product mixtures by comparison with the established spectra of the dimethyl benzylmalonate products and with the literature spectral data.[5] To obtain the product ratios, the relative ^{1}H NMR integration ratios of the products were correlated with the relative peak areas of the GC data (i.e., the major product by NMR was assigned to the major GC peak).

The regioisomeric products should have identical or nearly identical response factors with a flame ionization detector. Therefore, the GC peak areas accurately reflect the true product ratios within a reasonably small experimental error. The product ratio for each reaction was determined by GC analysis both before and after flash chromatographic purification. The crude and purified product ratios were identical within experimental error (±1−2%). The purified product ratios and isolated yields are reported throughout.

Results

Alkylation Reactions. The palladium-catalyzed allylic alkylations of **7**−**9** were performed under a variety of conditions to test the effects of counterions and catalyst systems of the product ratios. To facilitate these comparisons, several experimental conditions were held constant. These reactions were carried out on 0.2 mmol of substrate with 5% palladium catalyst and 2 equiv of the nucleophile in THF except where noted. TLC analysis indicated complete consumption of the starting material in equal times for all three substrates.

The alkylations of **7**−**9** were initially carried out with the sodium and tetra-*n*-hexylammonium (THA) salts of dimethyl malonate (**10a**) employing triphenylphosphine as the ligand

(9) For some asymmetric examples where the counterion was varied, see: (a) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586. (b) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (c) Frost, C. G.; Williams, J. M. J. *Synlett* **1994**, 551. (d) Tanner, D.; Andersson, P. G.; Harden, A.; Somfai, P. *Tetrahedron Lett.* **1994**, *35*, 4631. (e) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493. (f) Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595. (g) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1995**, *36*, 461. (h) von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Rugger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265. (i) Knuhl, G.; Sennhenn, P.; Helmchen, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1845.

(10) (a) DePalma, V. M.; Arnett, E. M. *J. Am. Chem. Soc.* **1978**, *100*, 3514. (b) Arnett, E. A.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759. (c) Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.*, **1991**, *113*, 7288. (d) Reetz, M. T.; Hutte, S.; Goddard, R. *J. Am. Chem. Soc.* **1993**, *115*, 9339.

(11) (a) Burgess, K. *J. Org. Chem.* **1987**, *52*, 2046. (b) Backvall, J. E.; Vagberg, J. O.; Zercher, C.; Genet, J. P.; Denis, A. *J. Org. Chem.* **1987**, *52*, 5430.

(12) Vicart, N.; Gore, J.; Cazes, B. *Synlett* **1996**, 850.

(13) Shackelford, J. M.; Schwartzman, L. H. *J. Org. Chem.* **1962**, *27*, 1047.

Table 1. Alkylations of **7**−**9** with Dimethyl Malonate Nucleophiles (**10a**) and Triphenylphosphine Ligands for Palladium

entry	substr[a]	counterion[b]	reactn time,[c] h	yield (%)	product ratio (%) **11a**	**12a**	**13a**
1	**7**	Na^+	1.5	81	66	33	1
2	**8**	Na^+	1.5	78	51	48	1
3	**9**	Na^+	1.5	86	37	49	14
4	**7**	THA^+	4	64	57	34	9
5	**8**	THA^+	4	71	55	39	6
6	**9**	THA^+	4	84	58	33	9

[a] Reaction conditions: 5% $(Ph_3P)_4Pd$, THF, 67 °C. [b] THA, tetrahexylammonium.

Table 2. Alkylations of **7**−**9** with Dimethyl Benzylmalonate Nucleophiles (**10b**) and Triphenylphosphine Ligands for Palladium

entry	substr[a]	counterion[b]	reactn time, h	yield (%)	product ratio (%) **11b**	**12b**	**13b**
1	**7**	Na^+	1.5	81	78	20	2
2	**8**	Na^+	1.5	79	70	28	2
3	**9**	Na^+	1.5	87	57	33	10
4	**7**	TMA^+	4	75	80	18	2
5	**8**	TMA^+	4	80	60	38	2
6	**9**	TMA^+	4	96	56	36	8
7	**7**	THA^+	4	89	76	21	3
8	**8**	THA^+	4	99	72	25	3
9	**9**	THA^+	4	94	77	20	3
10	**7**	Cs^+	4	82	52	45	3
11	**8**	Cs^+	4	85	53	44	3
12	**9**	Cs^+	4	84	53	43	4

[a] Reaction conditions: 5% $(Ph_3P)_4Pd$, THF, 67 °C. [b] TMA, tetramethylammonium; THA, tetrahexylammonium.

(Table 1). With sodium as the counterion the reactions were complete in 1.5 h at 67 °C, and a different product ratio was obtained for each substrate. For example, the alkylation of **9** (entry 3) gives more of product **13a** than the alkylation of either **7** or **8** (entries 1 and 2) gives. With the THA counterion, the reactions took 4 h to go to completion at 67 °C, and in this case essentially the same product ratio was obtained for each substrate within a reasonable level of experimental error.

An expanded range of counterions was tested with dimethyl benzylmalonate as the nucleophile (Table 2). Under the otherwise identical alkylation reactions, the sodium counterion again gave rise to different product ratios for each substrate (entries 1−3). In contrast, with THA as the counterion, each substrate gave essentially the same ratio of products (entries 7−9). In both cases, the product ratios were somewhat shifted in favor of the primary alkylation product (**11b**) with the more sterically demanding nucleophile (**10b**) (i.e., with the same counterion nucleophile, **10b** gave more of the product arising from attack at the primary terminus (**11b**) than nucleophile **10a** gave of **11a** for all three substrates). Nevertheless, within each set of reactions the product ratios were different for sodium and the same for THA.

The product ratios arising from the reactions with the two additional counterions employed, tetramethylammonium (TMA) and cesium, exhibited behavior similar to that of sodium and THA, respectively. Under identical conditions to those employed for the THA reactions, the TMA alkylation reactions gave significantly different product ratios (entries 4−6). Each substrate gave a different product ratio, and with the possible exception of substrate **8**, the ratios match those obtained with sodium. When cesium was used as the counterion, each substrate gave the same ratio of products (entries 10−12). Quantitatively, these results differ from those using THA in that less of the product derived from attack at the primary terminus (**11b**) resulted, while more of the bisallylic product (**12b**) formed. Qualitatively, within each set of reaction conditions, THA or cesium, the same ratio of products was obtained. Overall, these results differ from the sodium and TMA results.

Table 3. Alkylations of **7**−**9** with Dimethyl Malonate Nucleophiles (**10a**) and Tributylphosphine Ligands for Palladium

entry	substr[a]	counterion	conditions	yield (%)	product ratio (%) **11a**	**12a**	**13a**
1	**7**	Na^+	25 °C, 45 min	80	74	24	2
2	**8**	Na^+	25 °C, 45 min	96	57	41	2
3	**9**	Na^+	25 °C, 45 min	98	46	32	22
4	**7**	Na^+	67 °C, 4 h	78	97	0	3
5	**8**	Na^+	67 °C, 4 h	89	90	6	4
6	**9**	Na^+	67 °C, 4 h	94	90	0	10

[a] Reaction conditions: 5% $Pd(OAc)_2$, Bu_3P, THF.

Table 4. Time Dependence of the Product Ratio from the Alkylation of **9** with the Sodium Salt of **10b**

time (h)[a]	**11b** (%)	**12b** (%)	**13b** (%)
0.5	59	28	12
1.5[b]	64	24	12
3	77	10	13
24	86	2	13

[a] $(Ph_3P)_4Pd$, THF, 67 °C. [b] Standard reaction time.

Two of the previously reported product ionization examples (eqs 2 and 3) employed tributylphosphine as the ligand. As the more electron rich tributylphosphine may favor product isomerization, this ligand was examined in the alkylation reactions of **7**−**9** with the sodium salt of **10a** (Table 3). At 25 °C the reactions went to completion in 45 min and gave rather different product ratios for each substrate (entries 1−3). For comparison, the identical reactions were allowed to proceed for 4 h at 67 °C, the same conditions typically employed in the other reactions. At this extended reaction time and higher temperature, quite an altered set of product ratios was obtained (entries 4−6). The ratios were similar to each other. Each substrate gave predominantly **11a** and little or no **12a**. In the case of substrate **9** (entry 6), a significant amount of **13a** was obtained, though less than was obtained at the milder, less forcing conditions (entry 3).

Product Equilibration. In light of the previously mentioned examples of product isomerization and the results of the alkylations with tributylphosphine as the ligand, it seemed that some process was possible that could alter or possibly equilibrate the alkylation products. To determine if product isomerization was occurring either during or after the reaction with triphenylphosphine as the ligand, the product ratio was measured as a function of reaction time. Under the same alkylation conditions employed previously, reactions were carried out with **9** using the sodium and THA salts of **10b**. Small aliquots were removed from each reaction at various time intervals and rapidly worked up (aqueous quench and diethyl ether extraction). The product ratio at each time point was then determined. With the sodium salt of **10b**, the product ratio changed very little up to the standard reaction time of 1.5 h (Table 4). After this time, the relative amount of **12b** dropped significantly and the amount of **11b** increased. During the course of this reaction up to 24 h, the amount of **13b** did not change significantly. A similar time dependence experiment was performed with **9** and the THA salt of **10b** (Table 5). At the normal reaction time of 4 h, the product ratio had changed very little. After 24 h, the amount of **12b** had diminished, though a higher percentage remained than in the case with the sodium salt, and the percentage of **11b** had increased by a corresponding amount. As in the previous case, the amount of **13b** was unchanged from the initial

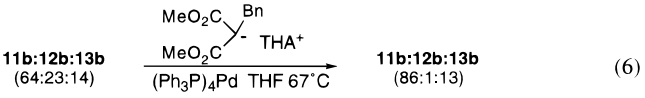
Table 5. Time Dependence of the Product Ratio from the Alkylation of **9** with the THA Salt of **10b**

time (h)[a]	**11b** (%)	**12b** (%)	**13b** (%)
0.5	72	25	3
1	73	24	3
4[b]	73	24	3
8	77	20	3
24	86	10	4

[a] $(Ph_3P)_4Pd$, THF, 67 °C. [b] Standard reaction time.

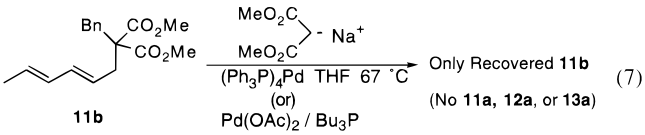
time point. However, the product ratio, a relative comparison, could change as a result of loss of one or more products in an absolute sense.

An additional isomerization experiment demonstrates that product decomposition does not account for the loss of **12b** with time. Substrate **9** was reacted with the sodium salt of **10b** under standard reaction conditions and a 64:23:14 ratio of **11b**:**12b**:**13b** was isolated and purified by flash chromatography. This mixture was resubjected to the reaction conditions for 24 h (eq 6). After workup, an 86:1:13 ratio of **11b**:**12b**:**13b** was obtained in 81% yield from the initial alkylation reaction of **9**. The 81% yield for both reactions is comparable to the isolated yields typically obtained in the normal reaction runs. The product ratio obtained in this experiment was essentially the same as was obtained previously after 24 h (Table 4).



(6)

Nucleophile Crossover. The results from the time dependent product ratio, as well as the direct alkylation reactions with tributylphosphine as the ligand, suggest that a product isomerization process of some sort affects the product ratios under certain conditions. As the reionization of bisallylic malonate products (e.g., **12**) has been previously demonstrated[5] (eq 2), one of the monoallylic products (**11b**) was tested for similar behavior with both the triphenylphosphine and tributylphosphine ligand conditions (eq 7). When isolated **11b**, a dimethyl benzylmalonate product was subjected to either catalyst system ($(Ph_3P)_4Pd$ or $Pd(OAc)_2/Bu_3P$) in THF at 67 °C for 24 h with the sodium salt of **10a**, neither reaction showed any amount of dimethyl malonate incorporated products (**11a**, **12a**, or **13a**); only recovered **11b** was observed.



(7)

Discussion

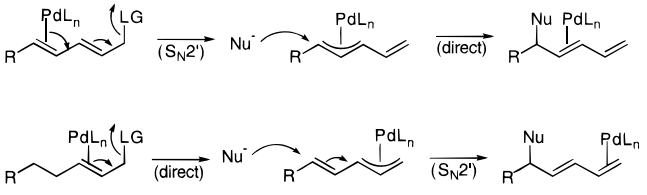
Product Isomerization. Several lines of evidence indicate that product isomerization alone cannot account for the observed product ratios or for the formation of the distal products. The nucleophile crossover experiments with **11b** show that the terminal monoallylic product does not isomerize under the reaction conditions with either catalyst system employed. Likewise, the time course studies of the product ratios from the alkylation of **9** (Tables 4 and 5) demonstrate that the internal monoallylic product (**13b**) does not isomerize under the reaction conditions. The separate product isomerization experiment establishes that product decomposition does not account for the change in product ratio. Only the bisallylic products **12b**, and by analogy **12a** as well, isomerize at all upon prolonged reaction times under the present reaction conditions. Furthermore, the rate of this isomerization is ligand dependent—being significantly faster with tri-*n*-butylphosphine compared to the more commonly used triphenylphosphine.

These results contrast with, but do not contradict, the carbanion (product) ionization results obtained with vinylcyclopropanes (eq 1)[11] and monoallylic alkylation products, such as **3** or **5** (eqs 3 and 4).[5b,12] In those cases, either the increased acidity of the carbanion leaving group or the increased stability of the metal-complexed allyl cation type intermediate facilitates the palladium-catalyzed ionization of allylic carbon−carbon bonds. The propensity for palladium to catalyze the ionization of carbanion leaving groups (e.g., malonates) is related to the strength of the carbon−carbon bond involved in the ionization. Relief of ring strain in the cyclopropyl substrates, steric compression of the quaternary center (**3** and **5**), formation of tertiary allyl cation (**3**), and acidity of the cyclic diketone (approximately 3 pK_a units vs dimethyl malonate) can all provide additional driving force not present in the monoallylic dienyl products in these studies (i.e., **11a/b** and **13a/b**). Although the borderline for ionization of carbanions is perhaps closer than previously thought, it seems not to have been crossed in these experiments except for the bisallylic products.

The product ratio versus time experiments provide five additional key results. First, under the alkylation conditions for these counterion studies ($(PPh_3)_4Pd$, THF, 67 °C), the product ratio changes very little up to the time that the reactions are normally complete (90 min for sodium and 240 min for THA). Second, the distal product (**13b**) forms before significant isomerization of **12b** occurs, particularly with the sodium counterion. Therefore, product isomerization from **12b** cannot account for the formation of **13b**. Third, the amount of **13b** does not increase as **12b** disappears, indicating a preference for formation of the terminal monoallylic product (**11b**) from isomerization of **12b**. Thus, isomerization of **12b** cannot account for the formation of **13b** from substrate **7** (a distal process) either. In contrast, isomerization of **12b** leads to some formation of **11b** from substrate **9** (the other distal process). Fourth, the THA counterion conditions lead to slower isomerization than the sodium counterion conditions. This conflicts with the hypothesis that the similar product ratios obtained with THA reflect increased isomerization, and hence thermodynamic equilibration, of the products compared to the different ratios obtained with sodium. Fifth, the final product ratios observed after 24 h from the alkylation of **9** with either sodium (Table 4) or THA (Table 5) as the counterion differ from the product ratios obtained under the previous alkylation conditions with cesium or THA (Table 2, entries 7−12) which each gave rise to identical sets of product ratios. Product isomerization of any kind is insufficient to explain these results. A single set of identical product ratios obtained under a given set of conditions could be explained by equilibration to a truly thermodynamic mixture provided that the alkylation step is reversible for all three products—which it is not. However, the cesium and THA counterions give rise to different sets of internally similar product ratios. To account for these two different sets of product ratios, the counterions would have to affect the position of the thermodynamic equilibrium which seems unlikely. Thus, the similar product ratios obtained with cesium and THA counterions do not reflect thermodynamic product ratios.

The use of tributylphosphine as the ligand increases the overall rate of the reaction and the rate of isomerization of the bisallylic product (**9a**) but does not cause complete equilibration of the products. At 25 °C the reactions of **7**−**9** with the sodium

Scheme 4



salt of **10a** are complete in 45 min and give rise to different product ratios for each starting material (Table 3, entries 1−3). The ratios are qualitatively similar to the results obtained for the reactions with triphenylphosphine as the ligand (Table 1, entries 1−3). Under more forcing reaction conditions (67 °C for 4 h), the bisallylic product **12a** isomerizes to **11a,** but product **13a** remains (Table 3, entries 4−6). The anomalous persistence of **12a** in entry 5 may be due to premature inactivation of the catalyst in that particular instance before complete isomerization could occur. The observation of different amounts of **13a** from the alkylation of **9** (entries 3 vs 6) does not necessarily imply that **13a** can isomerize. Equilibration of the vinyl (π-allyl)-palladium intermediates (the preferred mechanism, *vide infra*) at 67 °C is most likely faster relative to nucleophilic addition than the rate of equilibration relative to nucleophilic addition at 25 °C. Thus, more of the initially formed proximal vinyl (π-allyl)palladium intermediate (which can lead to **13a**) can isomerize prior to nucleophilic addition.

S_N2'-Type Processes. The additional vinyl substituent on the starting material and the (π-allyl)palladium intermediate opens the possibility of reaction pathways not possible in simple allylic alkylations. Oxidative addition of palladium (substrate ionization) or nucleophilic attack could occur in an S_N2'-type fashion. Conceivably, either process could lead to distal product formation (Scheme 4). These processes would have to supplement the direct ionization and nucleophilic addition processes as substrate **8** cannot ionize in an S_N2' fashion and products **12a/b** cannot be formed in an S_N2' fashion. For example, among other combinations for substrate **7**, nucleophilic attack on the initially formed vinyl (π-allyl)palladium intermediate in an S_N2' fashion could generate the distal product (**13a/b**) while the two proximal products (**11a/b** and **12a/b**) could arise from direct nucleophilic attack on the π-allyl intermediate. Conversely, the ionization could occur in both a direct and an S_N2' type fashion to generate both (π-allyl)palladium intermediates. Nucleophilic attack in a direct fashion on either intermediate would then generate all three products. A plethora of combinations or hybrids of these mechanisms, such as S_N2' ionization, followed by vinyl π-allyl equilibration, etc., could be proposed to account for the observed product distributions. The combination of rates of the individual processes would have to be extraordinarily well balanced to account for the cases where identical product ratios are observed for each substrate (cesium and THA counterions). Furthermore, this finely balanced combination of direct and S_N2'-type processes would have to change in step with the counterion and nucleophile (**10a/b**) to account for differences between the three such sets of internally similar yet externally different product ratios. Mechanisms involving S_N2' ionizations or nucleophilic additions, which are thus far unprecedented, add unnecessary complexity to a system that can more easily be explained by a process with direct experimental support, namely, the vinyl (π-allyl)palladium interconversion mechanism. Therefore, S_N2' mechanisms need not be considered further unless additional future evidence warrants their inclusion.

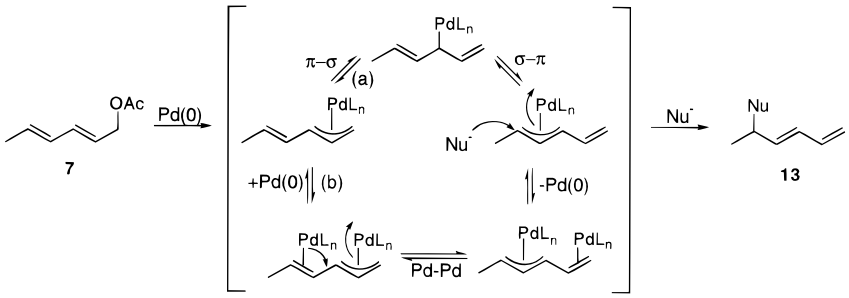
Vinyl π-Allylpalladium Equilibration. The gross observation of similar product ratios from a series of substrates suggests a common pathway or mechanism proceeding through identical intermediates. Conversely, different product ratios from the same series of substrates suggest different intermediates or different amounts of the same intermediates in the pathway. The alkylation results of dienyl acetates **7**−**9** fall distinctly into two such groups. The alkylations with cesium and THA counterions give rise to the same sets of product ratios indicating common intermediates, while the alkylations with sodium and TMA counterions give rise to a divergent product spectrum indicating different intermediates or ratios of intermediates (Tables 1−3). Interconversion of two vinyl (π-allyl)palladium intermediates via either the σ-bis(allyl)palladium intermediate[14] (path a) or the displacement by a second palladium(0) species coordinating to the remaining double bond[21] (path b) is sufficient to explain these observed similarities and differences in the sets of product ratios, as well as the formation of the distal product (shown for the case of **7** to **13** in Scheme 5). The specific pathway for vinyl (π-allyl)palladium interconverion ($\pi-\sigma-\pi$ or Pd−Pd, i.e., bimolecular substitution of one palladium by a second one) does not affect any of the following mechanistic arguments as they relate to the effect of the ion pair on the rate of alkylation. Unlike a product isomerization mechanism, a vinyl (π-allyl)palladium interconversion mechanism allows the distal product to form at the very beginning of the reaction as is observed in the time dependence studies (Tables 4 and 5).

The key factor determining the product ratio is the extent of interconversion or equilibration of the two vinyl (π-allyl)-palladium intermediates (**A** and **B**) prior to nucleophilic addition (Scheme 6). Substrate **8** initially ionizes to give a mixture of the two vinyl (π-allyl)palladium intermediates (**A** and **B**), and substrates **7** and **9** initially ionize to give only the respective proximal intermediates—**7** to **A** and **9** to **B**. If the rate of equilibration between **A** and **B** is slower than or comparable to the rate of nucleophilic addition, then each substrate with its own unique initial ratio of intermediates (**7** only **A**, **8** both **A** and **B**, **9** only **B**) will give rise to a different set of product ratios; the regiochemical bias of the substrate is reflected in the product ratio. Such is the case with the sodium salts of **10a** (Table 1, entries 1−3) and **10b** (Table 2, entries 1−3) and the TMA salts of **10b** (Table 2, entries 4−6). Since at least some, though sometimes a quite large amount, of the distal product is observed in every reaction, the initially formed intermediate(s) must equilibrate to at least some extent prior to nucleophilic addition in all cases. Analysis of the product ratios shows that full equilibration of intermediates **A** and **B** is not reached in the three cases just mentioned.

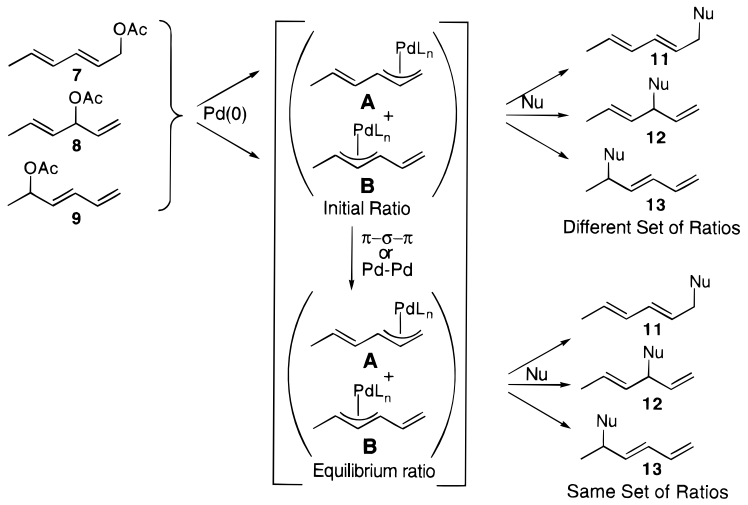
The two conjugated products (**11** and **13**) can only form from one of the two intermediates—**11** from **A** and **13** from **B**. Thus, they can provide information about the relative amounts of the intermediates at the time alkylation occurs. More of product **11** is formed from substrate **7**, which initially ionizes to **A**, in each of these cases. Conversely, more of product **13** is formed in all three of these cases from substrate **9**, which initially ionizes to **B**, than either of the other substrates. Thus, more **A** is present in the first case and more **B** is present in the latter. The ionization of **8** to a mixture of **A** and **B** is also evident from the product ratios. Less **11** and more **12** are formed than with **7**, and more **11** is formed than with **9**. The general steric bias for alkylation at the primary terminus of the dienyl system, which favors formation of product **11**, skews the results in this direction

(14) (a) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642. (b) Sakaki, S.; Satoh, H.; Shono, H.; Ujino, Y. *Organometallics* **1996**, *15*, 1713.

Scheme 5



Scheme 6



in all three cases without totally overwhelming the kinetic bias for addition to the initially formed intermediate (**A** from **7** or **B** from **9**). Note that this pattern of behavior is also true for the sodium salts in the reactions with tributylphosphine as the ligand (Table 3). The apparent similarity of the product ratios at longer reaction times (Table 3 entries 4−6) is due to secondary ionization (*vide supra*) not equilibration of the intermediates, as the different amounts of **13a** plainly demonstrate.

In the other kinetic extreme, if equilibration is much faster than nucleophilic addition, then for each substrate the initial ratio will fully equilibrate to the intrinsic thermodynamic ratio of intermediates **A** and **B**. Since this ratio of **A** and **B** depends only on the structure of the intermediates, all three substrates will give the same equilibrium ratio and therefore the same set of product ratios (lower half of Scheme 6). This behavior is observed with the THA salts of **10a** (Table 1, entries 4−6) and **10b** (Table 2, entries 7−9) and the cesium salts of **10b** (Table 2, entries 10−12). The specific ratio of products obtained from nucleophilic attack on the equilibrium ratio of **A** and **B** will, of course, depend on the particular nucleophile. Hence, the differences between the internally similar sets of product ratios for THA with **10a** and **10b** and cesium with **10b** reflect the inherent preferences of the nucleophile system for attack at the two positions in **A** and the two positions in **B**. This preference is a function of both the nucleophile **10a** or **10b** (cf. Table 1, entries 4−6, and Table 2, entries 7−9) and the counterion THA or cesium (cf. Table 2, entries 7−9, and Table 2, entries 10−12). Qualitatively, the more sterically demanding nucleophile (**10b**) and the larger cation (THA vs cesium) show the stronger preferences for attack at the least sterically demanding position of the dienyl system to give product **11**. The comparison of cation sizes is obviously more complicated than simple ionic radii as TMA is clearly larger than cesium and yet it exhibits completely opposite behavior; the kinetics based on product ratios are similar to sodium. The mechanistic conclusion based on the product ratios observed with the various nucleophile counterions, namely, the partial or complete equilibration of intermediates **A** and **B** prior to nucleophilic addition, is reached independent of the specific effects of each counterion and the origins of these effects. These last two issues are discussed further in the next section.

Mechanistically, the palladium-catalyzed alkylations of hexadienyl acetates provide an interesting opportunity to observe reactions as they cross the boundary between Curtin−Hammett and non-Curtin−Hammett reaction conditions.[15] Under the alkylation conditions with sodium or TMA counterions, nucleophilic attack occurs under non-Curtin−Hammet conditions. The ratio of vinyl (π-allyl)palladium intermediates is skewed toward the initially formed intermediate, proximal to the leaving group. The product ratio then reflects, to some extent, the ratio of the reactive intermediates rather than solely the ratio of the differences in transition state energies for nucleophilic attack on the intermediates. Under the alkylation conditions with cesium or THA counterions, product formation occurs under Curtin−Hammett control. The ratio of products reflects the relative rate of nucleophilic attack (i.e., differences in transition state energies) at either terminus of the two interconverting vinyl (π-allyl)palladium intermediates and not the ratio of the reactive intermediates either as generated initially or at equilibrium.

Role of the Counterion. Several experimental controls show that these changes in product ratios and kinetic behavior relate specifically to the counterion rather than some other experi-

(15) (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 2719. (c) Seeman, J. I.; Farone, W. A. *J. Org. Chem.* **1978**, *43*, 1854.

mental factor that changes concomitantly. First, the similarity of the product ratio behavior for a specific counterion with both **10a** and **10b** suggests that the primary effect is due to the counterion. Although other carbanions might show different behavior, such as the increased propensity for more acidic carbanions to undergo palladium-catalyzed ionization (eq 4), there is no reason to suppose that the counterion effects change. In such cases, the final product ratios might appear quite different due to the secondary ionization and resulting product isomerization. Second, increasing the catalyst nucleophilicity by employing tributylphosphine as the ligand alters the outcome but does not change the counterion trends. For the cases with the alkylammonium counterions, a specific effect due to bromide or added salt is ruled out by the divergent behavior of the TMA and THA nucleophile systems which are both generated from the bromide salts. Finally, generation of the cesium nucleophiles from cesium carbonate rather than sodium hydride is likely not a factor on the basis of other results with asymmetric alkylation reactions. The direct comparison between sodium carbonate and cesium carbonate cannot be made because the reactions fail to go to completion with sodium carbonate as the base due to its lower solubility and basicity. However, the enantiomeric excess of alkylation products for reactions employing sodium hydride, sodium carbonate, potassium hydride, potassium carbonate, and cesium carbonate correlates with the cation rather than the identity of the base despite the lower yields with sodium and potassium carbonate.[1f,16] Thus, in the cases where the experimental conditions vary in order to introduce a different counterion, the effects relate specifically to the identity of the counterion.

Although the new carbon−carbon bond in the product forms directly between the (π-allyl)palladium intermediate and the carbanion nucleophile, the nucleophile counterion affects the rate of this process. The involvement of ion pairs, though typically not considered in metal-catalyzed allylic alkylation reactions, seems apparent.[9] THF has a very limited ability to specifically solvate cations and almost no ability to specifically solvate anions.[17] The formation of tight or some degree of solvent-separated ion pairs seems assured under these conditions.[18] Formation of higher order aggregates, as is seen with lithium enolates, is not generally observed for more acidic anions like malonates in solvents such as THF.[7,10,19] A dimeric structure has been reported for the tetrabutylammonium salt of diethyl malonate in the solid state, though the stability of such a complex in tetrahydrofuran solution seems doubtful.[10d] Therefore, to a first approximation, the nucleophilic species might be viewed as simply the anion plus the cation in some minimum state of solvation. In this way, larger counterions might be expected to slow down the rate of nucleophilic addition simply due to increased steric interactions with the (π-allyl)-palladium intermediate. Cesium has a larger ionic radius than sodium (1.67 vs 0.97 Å),[20] and nucleophilic addition is slowed down (relative to intermediate equilibration) with cesium as the counterion. One could alternately suggest that the rate of equilibration is increased with cesium (or THA), though how such an effect would originate is unclear. Added bromide from the alkylammonium salts seems a more logical candidate to increase the rate of equilibration through an associative mechanism with the palladium intermediate. A specific effect of bromide has already been ruled out by comparison of TMAB and THAB (*vide supra*). Thus, the decreased rate of nucleophilic addition remains the most likely conclusion.

For the ammonium counterions, tetrahexylammonium is obviously larger than tetramethylammonium, and nucleophilic addition is slowed down (again relative to intermediate equilibration with the same caveats) with THA as the counterion. The simple steric interpretation breaks down when trying to compare the alkali metal salts with the alkylammonium salts. The smallest tetraalkylammonium salt, TMA, is clearly larger than either sodium or cesium. This apparent contradiction can be reconciled if the effects of solvation on the nature of the ion pair are considered. The alkylammonium salts show greater tendencies toward solvent separated ion pair formation; that is, they are more effectively solvated by solvents, such as THF, than metal cations.[7] This solvation may pull the counterion away from the reacting anion during carbon−carbon bond formation and thereby lessen its steric effect. In other words, the tightness of the ion pair may determine the effective steric bulk of the nucleophile. This interpretation suggests that the alkylammonium cations have a much smaller "effective" size as counterions for malonate nucleophiles in THF. The much larger THA counterion may be necessary to have the same steric effect as cesium. The specific correspondence between THA and cesium is also seen in asymmetric alkylation reactions—smaller alkylammonium counterions, such as tetrabutylammonium, do not give as high levels of enantiomeric excess as cesium and THA.[3,16] The similarity in sets of product ratios between sodium and tetramethylammonium counterions and between cesium and tetrahexylammonium counterions, despite their obvious differences in actual size, may be a reflection of their effective solvated sizes, which affects the relative rate of nucleophilic addition through simple steric interactions.

Conclusions

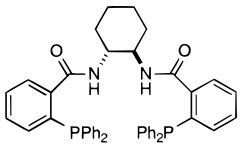
In summary, all the alkylation results with dienyl acetates can be understood in terms of a single unified mechanism. Dienyl acetates all initially ionize to form the vinyl (π-allyl)-palladium intermediate proximal with respect to the leaving group (**A** from **7** and **B** from **9**, but **A** and **B** from **8**). This initial π-allyl intermediate can then either be trapped by the nucleophile or it can begin to equilibrate to some mixture of vinyl π-allyl intermediates. If nucleophilic addition occurs before this mixture of intermediates has a chance to fully equilibrate, the product ratio is different for each substrate. If the mixture of π-allyl intermediates reaches equilibrium (i.e., the same distribution of intermediates from all three isomeric starting materials) prior to nucleophilic addition, then the product ratio is the same for each substrate. This does not imply that the final product ratio necessarily reflects the ratio of intermediates; the typical Curtin−Hammett considerations apply. In addition, the bisallylic malonate products ionize under certain conditions and thus can isomerize to one of the other products. This process does not significantly alter the product ratios at typical reaction times, but it can totally consume the bisallylic product at long reaction times. These two phenomena: (1) varying degrees of equilibration between vinyl (π-allyl)-palladium intermediates and (2) ionization of the bisallylic products resulting in isomerization, are sufficient to explain all the observed product ratios and the formation of the distal products. The identity of the nucleophile counterion and the nature of the ion pair has a profound effect on the relative rates

(16) Trost, B. M.; Bunt, R. C. Manuscript in preparation.
(17) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.
(18) Winstein, S.; Clippinger, E.; Fainberg, A. H.; Heck, R.; Robinson, G. C. *J. Am. Chem. Soc.* **1956**, *78*, 328.
(19) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Ekwall, P. J. *Colloid Interfac. Sci.* **1969**, *29*, 16. (c) Peri, J. B. *Colloid Interfac. Sci.* **1969**, *29*, 6.
(20) *CRC Handbook of Chemistry and Physics*, 68th ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1987; p F-159.

of intermediate equilibration and nucleophilic addition. The tetrahexylammonium and cesium counterions slow down the relative rate of nucleophilic addition to the (π-allyl)palladium intermediates compared to sodium and tetramethylammonium counterions on the basis of their effective steric size, which is a function of the tightness of the ion pair. The alkylammonium counterions (TMA and THA) form looser ion pairs due to increased solvation and therefore must have larger absolute sizes to have the same effect on the rate of nucleophilic addition as the more tightly ion paired alkali metal counterions (sodium and cesium). This change in relative rates allows the equilibration of the intermediates to become the dominant mechanistic feature leading to identical product ratios for each substrate.

Normally, cesium and tetraalkylammonium salts are employed to speed up the rate of alkylations. With (π-allyl)palladium cations as the substrates, the results are clearly counterintuitive—these two counterions slow the rate of alkylation.

There is an excellent correlation of the results reported herein with the effect of counterion on the ee in the palladium-catalyzed asymmetric alkylation of 3-acetoxycyclopentene with the chiral pocket ligand **14**.[3]



14

Sodium and tetramethylammonium salts gave modest ee's, whereas excellent ee's (>95%) were obtained with cesium and tetrahexylammonium salts. A consistent picture emerges by attributing the effects of counterion on regioselectivity (the present study) and on enantioselectivity to rate differences as discussed herein—a fact that lends further credence to this interpretation.

Experimental Section

All experiments were performed under an atmosphere of dry nitrogen unless otherwise indicated. THF was distilled from sodium/benzophenone ketyl prior to use. Dichloromethane was distilled from calcium hydride. Tetrakis(triphenylphosphine)palladium(0) was prepared by the method of Coulson.[21] Hexadienyl substrate **7** is commercially available; **8** and **9** were prepared via known methods.[6] All other reagents were of commercial grade and were either distilled or recrystallized prior to use.[22] NMR chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. GC analyses were performed using a Heliflex AT-1 (0.2 μm) fused silica capillary column (temperature program: 50 °C 2 min, 20 °C/min, 250 °C 10 min). Preparative HPLC was performed with a Microsorb column (5 μm SiO_2, 100 Å pore size, 10 mm × 250 mm) eluted with 4% ethyl acetate in hexane at 3.5 mL/min, using a Waters 490 detector operating at 254 nm with a Waters 745B data module.

Alkylation of Hexadienyl Acetates with Sodium Malonates. General Procedure. To a preformed solution of the catalyst (0.05 equiv) in THF was added a solution of the sodium malonate (prepared from sodium hydride (2.0 equiv) and the malonate ester (2.25 equiv) in THF) followed by addition of the hexadienyl acetate (1.0 equiv). All reaction were done with a final substrate concentration of 0.1 M and a final nucleophile concentration of 0.2 M (based on NaH or other base; 0.45 M based on total malonate ester). To get to the final concentrations, a 0.40 M nucleophile solution was added to an equal volume of a 0.2 M substrate solution (typically 1 mL of each). The reaction was heated at reflux for 1.5 h (TLC indicated that starting material was consumed) and then quenched with water. The aqueous phase was extracted three times with diethyl ether, and the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The product mixture was purified by flash chromatography and then analyzed by GC to determine the product ratio (analysis of the crude product mixture gave identical results).

Alkylation of (*E*,*E*)-2,4-hexadienyl Acetate with Sodium Dimethyl Malonate. To a 5 mL test tube were added 11.6 mg (0.01 mmol) of tetrakis(triphenylphosphine)palladium(0) (via glovebox) and 1 mL of THF. A solution of sodium dimethyl malonate (prepared from 16 mg (0.40 mmol) of 60% sodium hydride and 60 mg (0.45 mmol) of dimethyl malonate in 1 mL of THF) was added followed by 28.0 mg (0.20 mmol) of (*E*,*E*)-2,4-hexadienyl acetate. The reaction was heated at reflux for 1.5 h. The reaction was then quenched with 5 mL of water and extracted with 3 × 10 mL of diethyl ether. The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The product mixture was purified by flash chromatography on silica gel (2 cm × 14 cm, 5% ethyl acetate in hexanes) to give 34.3 mg (81%) of a 66:33:1 ratio (by GC) of **11a**:**12a**:**13a**[4] as a clear oil.

Dimethyl Benzyl-(*E*,*E*)-2,4-hexadienylmalonate (11b). R_f 0.49 (20% ethyl acetate in hexanes). IR (film from $CDCl_3$): 3030, 2953, 1738, 1600, 1436, 1279, 1203, 1084 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.2−7.3 (m, 3H), 7.1 (m, 2H), 6.0−6.1 (m, 2H), 5.6 (dq, J = 13.5, 6.6 Hz, 1H), 5.4 (dt, J = 13.5, 7.4 Hz, 1H), 3.7 (s, 6H), 3.2 (s, 2H), 2.5 (d, J = 7.4 Hz, 2H), 1.7 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 136.0, 134.7, 131.3, 130.0, 128.6, 128.2, 127.0, 124.5, 59.5, 52.2, 38.5, 35.6, 17.9. HRMS: calcd for $C_{18}H_{22}O_4$ 302.15181. Found: 302.15225.

Dimethyl Benzyl-(*E*)-1,4-hexadien-3-ylmalonate (12b). R_f 0.49 (20% ethyl acetate in hexanes). IR (film from $CDCl_3$): 3032, 2953, 1732, 1497, 1436, 1257, 1211, 1179, 1084 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.1−7.3 (m, 5H), 5.9 (ddd, J = 17.8, 10.4, 7.5 Hz, 1H), 5.5−5.6 (dq, J = 15.3, 6.0 Hz, 1H), 5.4−5.5 (ddq, J = 15.2, 7.8, 1.3 Hz, 1H), 5.1 (m 2H), 3.64 (s, 3H), 3.61 (s, 3H), 3.4 (t, J = 7.6 Hz, 1H), 3.24 (d, J = 13.8 Hz, 1H), 3.17 (d, J = 13.9 Hz, 1H), 1.7 (dd, J = 5.7, 1.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 137.2, 136.9, 130.3, 129.1, 128.6, 127.9, 126.8, 117.0, 63.3, 51.9, 51.7, 40.3, 18.0, 15.3. HRMS: calcd for $C_{18}H_{22}O_4$ 302.15181. Found: 302.15253.

Dimethyl Benzyl-(*E*)-3,5-hexadien-2-ylmalonate (13b). R_f 0.49 (20% ethyl acetate in hexanes). IR (film from $CDCl_3$): 3031, 2952, 1731, 1604, 1261, 1212, 1091, 1006 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.1−7.3 (m, 5H), 6.3 (dt, J = 16.8, 10.1 Hz, 1H), 6.1 (dd, J = 15.3, 10.3 Hz, 1H), 5.7 (dd, J = 15.1, 8.8 Hz, 1H), 5.15 (d, J = 16.6 Hz, 1H), 5.05 (dd, J = 10.1, 1.4 Hz, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.27 (d, J = 13.9 Hz, 1H), 3.17 (d, J = 13.9 Hz, 1H), 2.95 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.65, 170.55, 136.9, 136.5, 138, 132.7, 130.0, 128.0, 126.9, 116.3, 63.3, 51.9, 41.4, 40.3, 29.7, 17.2. Anal. Calcd for $C_{18}H_{22}O_4$: 302.15181. Found: 302.15223.

Alkylation of Hexadienyl Acetates with Tetraalkylammonium Malonates. General Procedure. To a preformed solution of the catalyst (0.05 equiv) in THF was added a solution of the tetraalkylammonium malonate (prepared from sodium hydride (2.0 equiv), the malonate ester (2.25 equiv), and the tetraalkylammonium halide salt (2.25 equiv) in THF) followed by addition of the hexadienyl acetate (1.0 equiv). The reaction was heated at reflux for 4 h (TLC indicated that starting material was consumed) and then quenched with water. The aqueous phase was extracted three times with diethyl ether, and the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The product mixture was purified by flash chromatography and then analyzed by GC to determine the product ratio (analysis of the crude product mixture gave essentially identical results).

Alkylation of (*E*)-3,5-Hexadien-2-yl Acetate with Tetrahexylammonium Dimethyl Benzylmalonate. To an 8 mL test tube were added 11.6 mg (0.01 mmol) of tetrakis(triphenylphosphine)palladium(0) (via glovebox) and 1 mL of THF. A solution of tetrahexylammonium dimethyl benzylmalonate (prepared from 16 mg (0.40 mmol) of 60% sodium hydride, 100 mg (0.45 mmol) of dimethyl benzylmalonate, and 196 mg (0.45 mmol) of tetrahexylammonium bromide in 1 mL of THF)

(21) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.

(22) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: New York, 1988.

was added followed by 28.0 mg (0.20 mmol) of (*E*)-3,5-hexadien-2-yl acetate. The reaction was heated at reflux for 4 h. The reaction was then quenched with 5 mL of water and was extracted with 3 × 10 mL of diethyl ether. The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The product mixture was purified by flash chromatography on silica gel (2 cm × 12 cm, 5% ethyl acetate in hexanes) to give 56.9 mg (94%) of a 77:20:3 ratio (by GC) of **11b**:**12b**:**13b** as a clear oil.

Alkylation of Hexadienyl Acetates with Cesium Malonates. General Procedure. The malonate ester (2.25 equiv) was added to a preformed solution of the catalyst (0.05 equiv) and cesium carbonate (2.0 equiv) in THF followed by addition of the hexadienyl acetate (1.0 equiv). The reaction was heated at reflux for 4 h (TLC indicated that starting material was consumed) and then quenched with water. The aqueous phase was extracted three times with diethyl ether, and the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The product mixture was purified by flash chromatography and then analyzed by GC to determine the product ratio (analysis of the crude product mixture gave identical results).

Alkylation of (*E*)-1,4-Hexadienyl Acetate (8) with Cesium Dimethyl Benzylmalonate. To an 8 mL test tube were added 11.6 mg (0.01 mmol) of tetrakis(triphenylphosphine)palladium(0), 130 mg (0.40 mmol) of cesium carbonate (via glovebox), 1 mL of THF, and 100 mg (0.45 mmol) of dimethyl benzylmalonate. Following addition of 28.0 mg (0.20 mmol) of (*E*,*E*)-2,4-hexadienyl acetate (**8**), the reaction was heated at reflux for 4 h. The reaction was then quenched with 5 mL of water and extracted with 3 × 10 mL diethyl ether. The combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. The product mixture was purified by flash chromatography on silica gel (2 cm × 12 cm, 5% ethyl acetate in hexanes) to give 51.2 mg (85%) of a 53:44:3 ratio (by GC) of **11b**:**12b**:**13b** as a clear oil.

Hexadienylmalonate Product Isomerization. To an 8 mL test tube containing 11.6 mg (0.01 mmol) of tetrakis(triphenylphosphine)palladium(0) (via glovebox) was added a crude alkylation product mixture consisting of a 64:23:14 ratio of **11b**:**12b**:**13b** (0.20 mmol starting material from the initial alkylation reaction) in 1 mL of THF. A solution of tetrahexylammonium dimethyl benzylmalonate (prepared from 16 mg (0.40 mmol) of 60% sodium hydride, 100 mg (0.45 mmol) of dimethyl benzylmalonate, and 196 mg (0.45 mmol) of tetrahexylammonium bromide in 1 mL of THF) was added. The reaction was heated at reflux for 24 h. The reaction was then quenched with 5 mL of water and extracted with 3 × 10 mL of diethyl ether. The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The product mixture was purified by flash chromatography on silica gel (2 cm × 12 cm, 5% ethyl acetate in hexanes) to give 48.9 mg (81% from initial alkylation reaction) of a 86:1:13 ratio (by GC) of **11b**:**12b**:**13b** as a clear oil.

Crossover Experiment for Dimethyl Benzyl-(*E*,*E*)-2,4-hexadienylmalonate (11b) with $(Ph_3P)_4Pd$. To an 8 mL test tube containing 22 mg (0.07 mmol) of **11b** were added 5.8 mg (0.005 mmol) of tetrakis(triphenylphosphine)palladium(0) (via glovebox) and a solution of sodium dimethyl malonate (prepared from 8 mg (0.20 mmol) of 60% sodium hydride and 30 mg (0.22 mmol) of dimethyl malonate) in 1 mL of THF. The reaction was heated at reflux for 24 h. The reaction was then quenched with 3 mL of water and extracted with 3 × 5 mL of diethyl ether. The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. GC analysis showed only the presence of starting material (**11b**) and no detectable amounts of any dimethyl malonate incorporated products (**11a**, **11a**, or **13a**).

Crossover Experiment for Dimethyl Benzyl-(*E*,*E*)-2,4-hexadienylmalonate (11b) with $Pd(OAc)_2/Bu_3P$. To an 8 mL test tube containing 22 mg (0.07 mmol) of **11b** were added 5.8 mg (0.005 mmol) of palladium acetate, 4.0 mg (0.20 mmol) of tributylphosphine, and a solution of sodium dimethyl malonate (prepared from 8 mg (0.20 mmol) of 60% sodium hydride and 30 mg (0.22 mmol) of dimethyl malonate) in 1 mL of THF. The reaction was heated at reflux for 24 h. The reaction was then quenched with 3 mL of water and extracted with 3 × 5 mL diethyl ether. The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. GC analysis showed only the presence of starting material (**11b**) and no detectable amounts of any dimethyl malonate incorporated products (**11a**, **12a**, or **13a**).

Alkylation of Hexadienyl Acetates with Sodium Malonates and Tributylphosphine. General Procedure. To a preformed solution of palladium acetate (0.05 equiv) and tributylphosphine (0.20 equiv) in THF was added a solution of sodium dimethyl malonate (prepared from sodium hydride (2.0 equiv) and the malonate ester (2.25 equiv) in THF) followed by addition of the hexadienyl acetate (1.0 equiv). The reaction was performed at 25 or 67 °C for 1.5 or 4 h, respectively, and then quenched with water. The aqueous phase was extracted three times with diethyl ether, and the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The product mixture was purified by flash chromatography and then analyzed by GC to determine the product ratio (analysis of the crude product mixture gave identical results).

Alkylation of (*E*,*E*)-2,4-Hexadienyl Acetate with Sodium Dimethyl Malonate and Tributylphosphine. To an 8 mL test tube were added 2.3 mg (0.01 mmol) of palladium acetate, 1 mL of THF, and 8.1 mg (0.04 mmol) of tributylphosphine. A solution of sodium dimethyl malonate (prepared from 16 mg (0.40 mmol) of 60% sodium hydride and 60 mg (0.45 mmol) of dimethyl malonate in 1 mL of THF) was added followed by 28.0 mg (0.20 mmol) of (*E*,*E*)-2,4-hexadienyl acetate. The reaction was heated at reflux for 4 h. The reaction was then quenched with 5 mL of water and extracted with 3 × 10 mL diethyl ether. The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The product mixture was purified by flash chromatography on silica gel (2 cm × 14 cm, 20% diethyl ether in pentane) to give 32.9 mg (78%) of a 97:0:3 ratio (by GC) of **11a**:**12a**:**13a** as a clear oil.

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Supporting Information Available: Chromatographic retention times for the alkylation products, ^1H NMR spectra of **11b**, **12b**, and **13b,** and experimental data and yields for the remaining reactions (5 pages). See any current masthead page for ordering information and Internet access instructions.

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