Geminal Dicarboxylates as Carbonyl Surrogates for Asymmetric Synthesis. Part I. Asymmetric Addition of Malonate Nucleophiles

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Abstract: Asymmetric alkylations of allylic geminal dicarboxylates with dialkyl malonates have been investigated. The requisite allylic geminal dicarboxylates are prepared in good yields and high isomeric purities by two catalytic methods, ferric chloride-catalyzed addition of acid anhydrides to α,β-unsaturated aldehydes and palladium-catalyzed isomerization and addition reactions of propargylic acetates. The complex of palladium(0) and the chiral ligand derived from the diamide of *trans*-1,2-diaminocyclohexane and 2-diphenylphosphinobenzoic acid most efficiently catalyzed the asymmetric process to provide allylic carboxylate esters with high ee. By systematic optimization studies, factors affecting the enantioselectivity of the reaction have been probed. In general, higher ee's have been achieved with those conditions which facilitate kinetic capture of the incipient π-allylpalladium intermediate. These conditions also proved effective for achieving high regioselectivities. The minor regioisomeric product was formed when reactive substrates or achiral ligands were employed for the reaction, and could be minimized through the use of the chiral ligand. Under the established conditions, the alkylation of various *gem*-dicarboxylates afforded monoalkylated products in high yields with greater than 90% ee. The process constitutes the equivalent of an addition of a stabilized nucleophile to a carbonyl group with high asymmetric induction.

Introduction

The palladium-catalyzed allylic alkylation reaction is one of the most powerful tools for the controlled introduction of carbon−carbon and carbon−heteroatom bonds into organic compounds.[1−6] Recent employment of chiral ligands in this process has provided an opportunity to perform the reaction in an enantioselective fashion, thereby greatly increasing the utility of this method.[7−12] Unlike most transition metal-catalyzed processes, asymmetric allylic alkylations offer multiple mechanisms as a source of asymmetry because the enantio-discriminating event can arise in any one of many steps in the catalytic cycle. Thus, this unique feature of the asymmetric allylic alkylation (AAA) reaction allows for the conversion of starting materials of various types, such as racemic, *meso*-, and achiral compounds, into enantiomerically enriched material.[13] Strategies to effect such transformations derive from recognition of the stereochemical courses in each step of the catalytic cycle and analysis of symmetry elements imparted in the substrates or intermediates. The current strategies involve differentiation of (1) the enantiotopic leaving groups of *meso*-compounds,[14−16] (2) the allylic termini of symmetric intermediates,[17−20] (3) two interconverting intermediates,[21−24] (4) the enantioface of alkenes,[25−27] and (5) the enantiofaces of nucleophiles.[28−33]

Another strategy is represented by the desymmetrization transformation in eq 1 wherein the two enantiotopic leaving groups located on the same carbon atom of an achiral substrate are differentiated. The asymmetric induction of this system,

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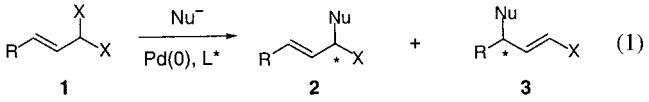
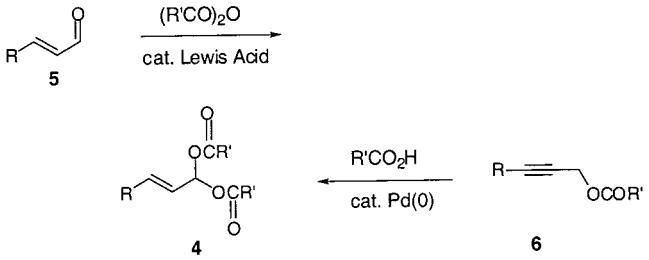
however, is complicated by the fact that there are two prochiral elements present in the substrate, the leaving groups and the π-faces of the alkene. Since both the complexation and the ionization steps are a potential source of enantioselectivity, the AAA reaction of this type presents a formidable control problem. In addition, due to the unsymmetric nature of the π-allylpalladium intermediate, there is a regioselectivity problem depicted in eq 1. Thus, differentiation of the two enantiotopic leaving groups by a substitution process constitutes a rare example in which asymmetric catalysis is achieved by chiral recognition between two geminal sp^3-sp^3 bonds.[34]



(1)

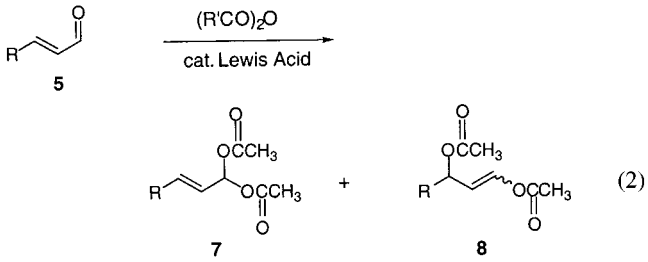
The geminal dicarboxylates (**4**, X = OCOR′ in **1**), also known as "acylals",[35,36] are a simple addition product of acid anhydrides and aldehydes and are well suited as a substrate for reaction as in eq 1. The seemingly labile *gem*-diester functionality has served as an interesting protective group for aldehydes due to its considerable stability to acid yet ease of removal under very mildly basic conditions, complementing the commonly used base stable acetal-protecting group.[37] A wide variety of Lewis and Brönsted acids can catalyze this process to produce the diesters of allylic 1,1-diols.[38] Thus, the requisite allylic *gem*-carboxylates are readily available from α,β-unsaturated aldehydes **5**. Alternatively, they can be prepared from the corresponding propargylic acetates **6** by a novel Pd-catalyzed redox-isomerization and intermolecular addition reaction.[39]



The Pd-catalyzed alkylation in eq 1 has been demonstrated in a nonchiral fashion through the utilization of allylic *gem*-diacetates (X = OAc).[40,41] In these studies, it was demonstrated that *gem*-diacetates could undergo an allylic substitution reaction with stabilized nucleophiles to afford products such as **2** and **3**. It is worth noting that the alkylation generated monoalkylated products in good yields despite the presence of two leaving groups in the starting *gem*-diacetate. Partial or complete control of the product distribution was achieved, depending on the nature of *gem*-diacetates and nucleophiles.

While employment of a chiral ligand could potentially induce asymmetry for this process, it is of interest to see whether the guidelines of chemo- and regioselectivities established within the context of nonchiral reactions can be applicable to the asymmetric process. In this regard, the AAA of the present system offers a good testing ground to examine the ability of a chiral ligand to control other types of selectivities beyond enantioselectivity. Herein, we report a full account of our efforts in the development of asymmetric alkylation of *gem*-dicarboxylates with malonate esters.[42]

Preparation of Allylic *gem*-Dicarboxylates. To evaluate the efficacy of various acid catalysts, *trans*-2-hexenal (**5a**, R = C_3H_7) was selected as a model substrate and reacted with acetic anhydride (eq 2). The mixture of **5a** and 2−5 equiv of acetic anhydride neat or in methylene chloride was treated with various Lewis acids (BF_3OEt_2,[43] PCl_3,[44] H_2SO_4,[45] I_2,[46] K-10 Clay,[47] $FeCl_3$,[48] etc.). In all cases, the reaction was complete within 2 h at 0 °C, providing the desired *trans*-1,1-diacetoxy-2-hexene (**7a**) as the major product in 60−95% yields. However, the formation of minor isomers **8** (5−15% by GC) was also detected before the complete consumption of the starting aldehyde. It appeared that the Lewis acid catalyzed not only the formation of allylic *gem*-diacetate **7** but also its rearrangement to vinyl acetates **8**. The allylic rearragement is particularly undesirable



(2)

and complicates the interpretation of the result because the stereochemical outcome of the asymmetric alkylation is inevitably affected by the presence of racemic chiral **8**. Thus, it was necessary to quench the reaction before a significant amount of the desired product underwent rearrangement in order to secure high isomeric purity at the expense of yield. Among the various acid catalysts tested, ferric chloride gave the best result, giving rise to desired *gem*-diacetate **7a** (R = C_3H_7) in 67% yield and greater than 95% isomeric purity. Table 1 summarizes the range of enals examined in the current study.

The *gem*-diesters possessing a carboxy moiety other than an acetoxy group could also be prepared.[48] Employing propionic and isobutyric anhydride in the same manner as acetic anhydride furnished the corresponding *gem*-dipropionates and *gem*-diisobutyrates (Table 2). The reaction of crotonaldehyde (**11**) with acetic anhydride generated a mixture of desired *gem*-diacetate **12a** as the major product and the isomeric vinyl acetates of type **8** as minor products (entry 4). Similarly, both the *gem*-dipropionate **12b** and the *gem*-diisobutyrate **12c** were prepared in good yields albeit with somewhat lowered isomeric purity of 89% (entries 5 and 6). Nevertheless, simple chromatographic purification increased their isomeric purity to 94%.[49]

While most of the *gem*-diesters were prepared from their corresponding α,β-unsaturated aldehydes, some were synthe-

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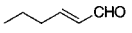
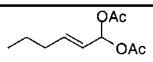
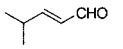
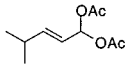
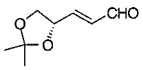
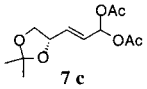
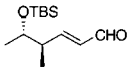
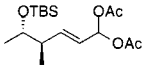
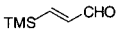
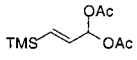
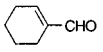
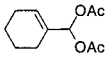
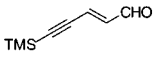
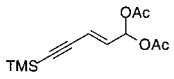
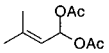
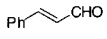
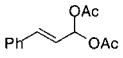
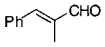
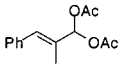
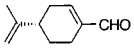
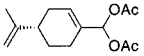
(49) Commercially available **12a** (Aldrich) was only 85% isomerically pure.

Table 1. Preparation of Allylic *gem*-1,1-Diacetates Using Ferric Chloride

Entry	Reactant	Reagents	Temp., Time	Product	%Yield[a]
1	 **5a**	2 eq Ac_2O 0.2% $FeCl_3$	0 °C, 0.5 h	 **7a**	67
2	 **5b**	4 eq Ac_2O 0.1% $FeCl_3$	0 °C, 15 min	 **7b**	54
3	 **5c**	2 eq Ac_2O 1% $FeCl_3$	0 °C, 4 h	 **7c**	92
4	 **5d**	4 eq Ac_2O 2% $FeCl_3$	25 °C, 8 h	 **7d**	73
5	 **5e**	2 eq Ac_2O 0.1% $FeCl_3$	0 °C, 0.5 h	 **7e**	98
6	 **5f**	4 eq Ac_2O 1% $FeCl_3$	0 °C, 0.5 h	 **7f**	50
7	 **5g**[b]	4 eq Ac_2O 0.5% $FeCl_3$	0 °C, 0.5 h	 **7g**[c]	88 (90)[d]
8	 **5h**	2 eq Ac_2O 0.1% $FeCl_3$	25 °C, 2 h	 **7h**	72
9	 **5i**	5 eq Ac_2O 0.1% $FeCl_3$	0 °C, 0.5 h	 **7i**	85
10	 **5j**	5 eq Ac_2O 0.25% $FeCl_3$	0 °C, 1 h	 **7j**	97
11	 **5k**	3 eq Ac_2O 0.2% $FeCl_3$	25 °C, 4 h	 **7k**	86

[a] Isolated yield. [b] *E*:*Z* = 10:1 by GC. [c] *E*:*Z* = 8.3:1 by ^{1}H NMR. [d] Isomeric purity measured by GC.

sized from propargylic esters by the palladium-catalyzed reaction as summarized in Table 3. First, propargylic acetate **6a** was subjected to the previously developed conditions which typically employed 5% Pd_2dba_3·$CHCl_3$, 50% triphenylphosphine, and 5 equiv of acetic acid (entry 1).[39] When heated in toluene for 4 h, **6a** was cleanly converted to *gem*-diacetate **13a** as a single isomer in 87% yield. Performing the same reaction with Pd-$(PPh_3)_4$ as catalyst also proved effective, giving a yield of 89% (entry 2). It should be noted that only 0.5% catalyst and 1.5 equiv of acetic acid were required in this case. Propargylic acetates bearing a stereogenic center were reacted under these modified conditions to give *gem*-diacetates without affecting the stereochemical integrity (entries 3−5). While *gem*-diacetate **13b** was obtained in 51% yield from the TBDMS-protected ester **6b**, switching the ligand to the more electron-rich and sterically demanding tri(*o*-anisyl)phosphine gave a somewhat better yield of 61%. When the TBDMS protective group was replaced with the bulky and robust TBDPS group, more significant improvement was achieved as the yield of **13c** increased to 81%.

Initial Alkylation Results. With the requisite *gem*-diesters in hand, the investigation on their asymmetric alkylation commenced with *trans*-cinnamyl 1,1-diacetate (**7i**) as a substrate. The alkylation with sodium dimethyl alkylmalonates **14** and **15** was carried out with 2.5% π-allylpalladium chloride dimer (**16**), and 7.5% chiral ligand **17**[50,51] (P:Pd = 3:1) in THF at ambient temperatures. The nucleophile was generated from 2.0 equiv of sodium hydride and 2.5 equiv of dimethyl methyl- or benzylmalonate. The reactions proceeded to completion in 2 h to give the desired products **18** and **19** as single regioisomers in 92 and 75% yields, respectively (eq 3). The reaction using Pd_2dba_3·$CHCl_3$ as the palladium source gave rather capricious results, leading to inconsistent yields and ee's. The alkylation

Table 2. Preparation of *Gem*-Dicarboxylates

Entry	Aldehyde	Anhydride	Conditions	Product	%Yield[a]
1	TBDPSO⟋⟍CHO **9**	$(CH_3CO)_2O$ 4 eq	0.5% $FeCl_3$ 0 °C, 0.5 h	TBDPSO⟋⟍(OCOCH$_3$)OCOCH$_3$ **10a**	98
2		$(C_2H_5CO)_2O$ 2 eq	0.5% $FeCl_3$ 0 °C, 2 h	TBDPSO⟋⟍(OCOC$_2$H$_5$)OCOC$_2$H$_5$ **10b**	88
3		$(i\text{-}C_3H_7CO)_2O$ 2 eq	2% $FeCl_3$ 0 °C, 0.5 h	TBDPSO⟋⟍(OCO*i*-Pr)OCO*i*-Pr **10c**	78
4	⟋⟍CHO **11**	$(CH_3CO)_2O$ 2 eq	0.1% $FeCl_3$ –20 °C, 0.5 h	⟋⟍(OCOCH$_3$)OCOCH$_3$ **12a**	80 (93)[b]
5		$(C_2H_5CO)_2O$ 2 eq	0.5% $FeCl_3$ 0 °C, 0.5 h	⟋⟍(OCOC$_2$H$_5$)OCOC$_2$H$_5$ **12b**	85 (89)[b]
6		$(i\text{-}C_3H_7CO)_2O$ 2 eq	1% $FeCl_3$ 25 °C, 3 h	⟋⟍(OCO*i*-Pr)OCO*i*-Pr **12c**	81 (89)[b]

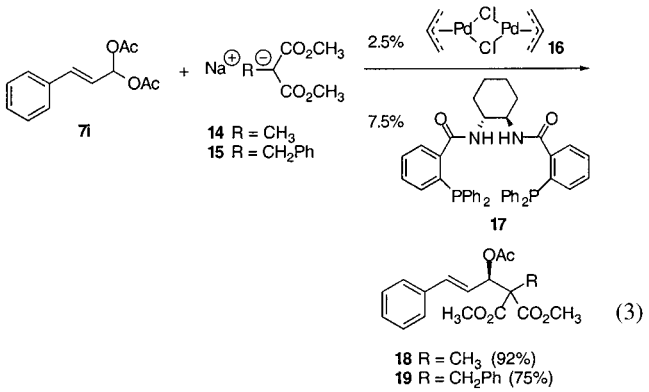
[a] Isolated yields. [b] Isomeric purity of the crude product measured by GC.

Table 3. Preparation of *gem*-Diacetates from Propargylic Acetates[a]

Entry	Propargylic Acetate	Catalyst / Ligand	AcOH (equiv.)	Time (h)	Product	%Yield[b]
1	CH$_3$O(OAc) **6a**	5% Pd_2dba_3•$CHCl_3$ 50% PPh_3	5.0	4	CH$_3$O(OAc)OAc **13a**	87
2		0.5% $Pd(PPh_3)_4$	1.5	12		89
3	TBDMSO(OAc) **6b**	1% $Pd(PPh_3)_4$	2.0	3	TBDMSO(OAc)OAc **13b**	51
4		1% Pd_2dba_3•$CHCl_3$ 8% P(*o*-$MeOC_6H_4$)$_3$	2.0	2		61
5	TBDPSO(OAc) **6c**	1% $Pd(PPh_3)_4$	1.2	1	TBDPSO(OAc)OAc **13c**	81

[a] All reactions were run in toluene at 110 °C. [b] Isolated yields.

products could be readily isolated in analytically pure forms by typical flash chromatography on a silica gel column.

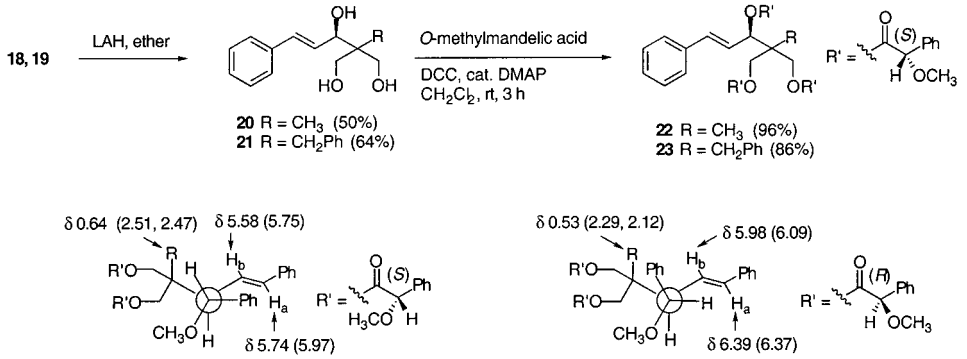


(3)

The ee of the products was determined by chiral shift studies using (+)-Eu(hfc)$_3$ in $CDCl_3$.[52] Only a single set of signals was observed in both cases, suggesting that the ee's of these products were greater than 95%. To confirm this conclusion, the alkylation products were derivatized to the *O*-methylmandelate esters.[53] Due to a facile retro-aldol process upon hydrolysis of the acetyl group, **18** and **19** were first reduced with LAH to triols **20** and **21** and subsequently condensed with both (*R*)- and (*S*)-*O*-methylmandelic acid using DCC independently to provide the corresponding esters **22** and **23** in good yields (Scheme 1). The signals for the two vinylic protons and quaternary alkyl groups were completely resolved in the ^{1}H NMR spectra of the two diastereomers from (*R*)- and (*S*)-*O*-methylmandelic acid. The appearance of only one set of signals from **22** and **23** clearly indicated that the de was >95%, and thus the ee of **18** and **19** was >95%.

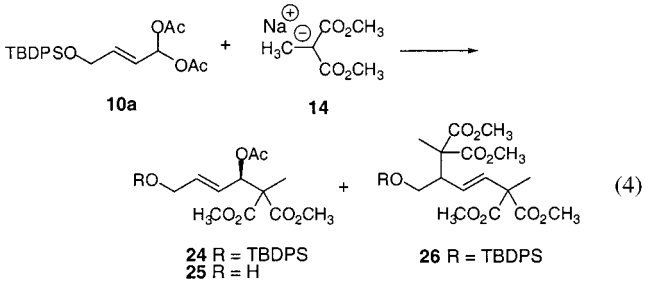
(50) Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228.
(51) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
(52) Sullivan, G. E. *Top. Stereochem.* **1978**, *10*, 287.
(53) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

Scheme 1. Derivatization to *O*-Methylmandelate and Absolute Configuration



The *O*-methylmandelate method to obtain diastereomers also allows for assignment of the absolute stereochemistry of the alkylation reaction using *R,R*-ligand **17**.[53] The ^{1}H NMR signals of the two vinylic protons H_a and H_b in (*S*)-mandelate **22** appeared at δ 5.74 and 5.58, whereas δ 6.39 and 5.98 were observed for the corresponding chemical shifts in the (*R*)-mandelate. The methyl group on the quaternary carbon also followed the well-established pattern of change in chemical shifts: δ 0.64 for the (*S*)-mandelate and δ 0.53 for the (*R*)-mandelate. This shielding−deshielding pattern was equally pronounced for the chemical shift (shown in parentheses) of benzyl series **23**. On the basis of these ^{1}H NMR correlation results, the absolute configuration of the carbinol chiral centers could be assigned to be "*R*" as depicted.

Ligand Comparison. With the excellent regio- and enantioselectivities obtained from the alkylation of the cinnamyl system, the investigation was then extended to other substrates. The straight-chain derivative **10a** was subjected to the standard alkylation conditions (eq 4). The reaction with **14** proceeded smoothly to generate acetate **24** as a single product in 68% yield. An ee of 89% was obtained from chiral shift experiments on desilylated alcohol **25** which was prepared in a quantitative yield by treatment of **24** with TBAF. Performing the alkylation reaction at 0 °C increased the yield to 85% and the ee to 91%. Through a number of repeated runs, it was found that the amount of the catalyst could be lowered to 0.5% of **16** and 1.5% of **17** with no detrimental effect on the yield or enantioselectivity.



Having established a protocol for ee measurement, the reaction of eq 4 was carried out with various achiral and chiral ligands as summarized in Table 4. The alkylation was first run with achiral ligands. The use of triphenylphosphine as the ligand generated monoalkylated product (*rac*)-**24** in 80% yield (entry 1). In contrast, the reaction employing dppp went to completion in only 0.5 h to give a mixture of mono- and dialkylated products (entry 2). In the presence of excess nucleophile, the same reaction produced only the dialkylated product (*rac*)-**26** as a single regioisomer in 86% yield (entry 3). A variety of chiral ligands synthesized by a modular method (Figure 1) were tested for the reaction (entries 4−14).[51] The chiral pocket provided by various ligands was expected to exert differential chiral recognition in the enantio-discriminating ionization step due to the different steric and electronic properties of each chiral ligand. Thus, the analysis of the outcome in terms of similarities and dissimilarities of these ligands would provide a basis for evaluating the structural and electronic aspects of the ligand effect. The ligands **27a**−**27e** share the same chiral scaffold, while they differ in the structure of linkers and metal binding sites. Other ligands containing anthracenyl (**27f** and **27g**), diphenyl (**27h**), tartrate- (**27i**), or sugar-derived (**27j**) chiral scaffolds were also tested for the alkylation. The C_2-symmetry present in the standard ligand **17** no longer exists in ligands **27b** and **27d**.

Table 4. Comparison of Ligands in Alkylations of **10a**[a]

entry	ligand	time (h)	%yield[b] of **24**	%yield[b] of **26**	% ee[c] of **24**
1[d]	PPh_3	2	80	0	−
2	dppp	0.5	33	57	−
3[e]	dppp	18	0	86	−
4	**17**	2	68	0	89
5	**27a**	4	86	0	68
6	**27b**	2	54	0	77
7	**27c**	12	68	5	∼0
8	**27d**	24	no reaction	−	−
9	**27e**	24	no reaction	−	−
10	**27f**	1	70	0	(−)13[f]
11	**27g**	4	82	0	(−)10[f]
12	**27h**	9	no reaction	−	−
13	**27i**	4	88	0	70
14	**27j**	5	55	0	(−)19[f]

[a] All reactions were performed in THF (0.2 M in substrate) with 1.5 equiv of nucleophile in the presence of 2.5% of **16** and 7.5% of the ligand unless otherwise noted. [b] Isolated yields. [c] Enantiomeric excess determined by chiral shift studies on the desilylated alcohol **25**. [d] 20% of the ligand was used. [e] 3.0 equiv of nucleophile were employed. [f] The ee of the opposite enantiomer, (*ent*)-**24**.

Although many ligands did generate the alkylation product **24**, none of these ligands gave a better result than the standard ligand **17**. A modest level of ee's was still obtained with naphthyl ligand **27a**[54] and non-C_2-symmetric ligand **27b**. On the other hand, despite the identity of the chiral scaffold, ligand **27c** possessing a sulfonamide linker generated a mixture of monoalkylated **24** and dialkylated **26** in which the monoalkylated product was almost racemic (entry 7). Changing the metal binding site from a phosphine to a nitrogen(s) resulted in no reaction (entries 8 and 9). Ligands **27f** and **27g**, based on an anthracenyl scaffold, gave results inferior to those seen with the standard conditions. The "invertomer" ligand **27g** in which the amide linkage was inverted gave a similar result as the "normal" ligand **27f**.[55] Surprisingly, diphenyl derivative **27h**,

(54) Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 99.

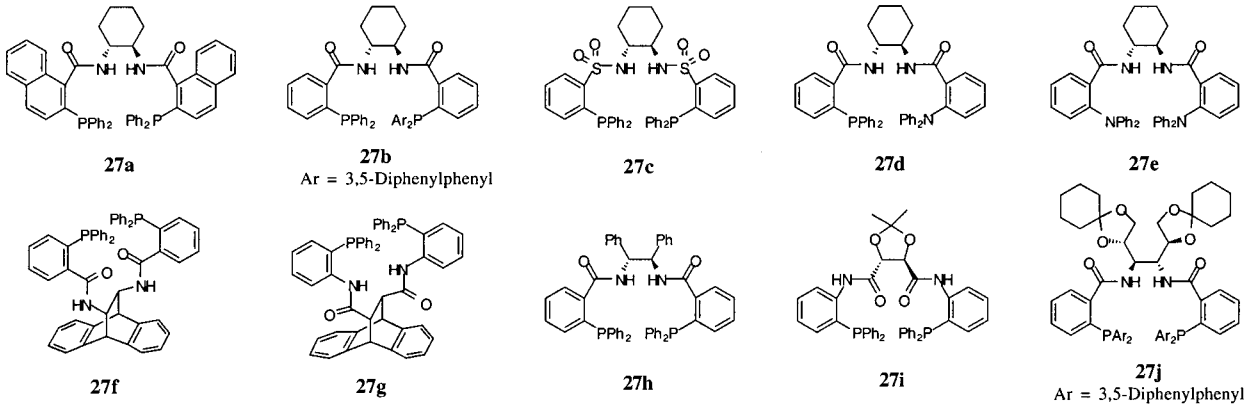


Figure 1. Chiral ligands synthesized by a modular method.

Table 5. Solvent Effect in Alkylations of **10a** with Dimethyl Methylmalonate[a]

entry	solvent	base	time (h)	% yield[b]	% ee[c]
1	THF	NaH	2	68	89
2	benzene	NaH	4	61	66
3	CH_2Cl_2	NaH	3.5	65	65
4	1,4-dioxane	NaH	2	65	81
5	DME	NaH	2	93	88
6[d]	DMF	NaH	1	91	6
7[d]	DMSO	NaH	1	89	(−)5[e]
8	THF	Cs_2CO_3	10	92	39
9	CH_2Cl_2	Cs_2CO_3	12	80	12
10	CH_3CN	Cs_2CO_3	10	68	(−)12[e]
11	DMF	Cs_2CO_3	5	81	(−)13[e]

[a] All reactions were performed with 2.0 equiv of base and 2.5 equiv of nucleophile at room temperature in the presence of 1.0% **16** and 3.0% of ligand **17** unless otherwise noted. [b] Isolated yields. [c] Determined by chiral shift studies on the desilylated alcohol **25**. [d] The reactions were run at 0 °C. [e] ee of the opposite enantiomer, (*ent*)-**25**.

which showed the same efficacy as **17** in a number of cases,[51,56] was found to be absolutely ineffective for the reaction. While tartrate derived ligand **27i** gave a moderate ee, mannitol derived ligand **27j** containing a sterically demanding metal binding site proved much less effective. It is noteworthy that the configuration of the major enantiomer can be predicted by a sterochemical mnemonic which provides a structural and physical link between the ligand chirality and the mode of enantioselection.[13,42,51] On the basis of this ligand screening result, the standard ligand, **17**, was used for all of the following studies.

Solvent Effect. The solvent has an effect on both the ionization and nucleophilic addition steps in the catalytic cycle, thereby potentially influencing the ee.[57] As summarized in Table 5, the use of solvents other than THF for the reaction of eq 4 provided inferior results relative to the standard reaction. In the cases of benzene and methylene chloride, the low solubility of the nucleophile in these solvents led to the formation of a heterogeneous reaction mixture and a longer reaction time. While a modest range of ee's was observed for these nonpolar solvents (entries 2 and 3), ethereal solvents gave significantly better results (entries 4 and 5). In particular, the alkylation using DME afforded an almost identical ee as the standard reaction. Surprisingly, the use of polar solvents resulted in a dramatic drop of the ee despite the rapid conversion and good yields

(55) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386.
(56) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1996**, *118*, 3039.
(57) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, Germany, 1988.

Table 6. Effect of Base and Additive in Alkylations of **10a** with Dimethyl Methylmalonate[a]

entry	base	solvent	additive	time (h)	% yield[b]	% ee[c]
1	*n*-BuLi	THF−hexane	−	4	90	69
2	NaH	THF	−	2	68	89
3	KH	THF	−	5	57	73
4[d]	KH	THF	−	6	64	86
5	*t*-BuOK	THF	−	6	58	48
6	Cs_2CO_3	THF	−	10	92	39
7	TMG[e]	THF	−	10	no reaction[f]	−
8	NaH	THF	Me_4NBr	2	86	83
9	NaH	THF	20% 18-C-6	3	88	87
10	NaH	CH_2Cl_2	−	3	65	65
11	NaH	CH_2Cl_2	Me_4NBr	3	79	60
12	NaH	CH_2Cl_2	Hex_4NBr	3	83	28
13	DBU	CH_2Cl_2	−	12	no reaction[f]	−

[a] All reactions were run with 2.0 equiv of base and 2.5 equiv of nucleophile at room temperature in the presence of 1.0% **16** and 3.0% of ligand **17** unless otherwise noted. [b] Isolated yields. [c] Determined by chiral shift studies on alcohol **25**. [d] The reaction was run with 3.8% **16** and 11% **17** at 0 °C. [e] 1,1,3,3-Tetramethylguanidine. [f] Unreacted starting material **10a** and aldehyde **9** were recovered.

(entries 6 and 7). When cesium carbonate was used instead of sodium hydride, the effect of solvent polarity was more striking (entries 8−11). The major enantiomer from polar solvents had the opposite stereochemistry although the ee's in this series were much lower.

Counterion Effect. The dependence of the ee on the solvent leads to speculation that counterions may also have an effect since their role in the nucleophilic addition step should be different in a given solvent due to the differential solvation energy. Thus, a series of alkali metal hydride and carbonate bases were tested for the alkylation (Table 6). Due to the kinetic inefficiency of lithium hydride as base, the lithium enolate was generated by the addition of a hexane solution of *n*-BuLi to a THF solution of dimethyl methylmalonate at −78 °C. Indeed, different bases had a strong effect on the enantioselectivity of the reaction. Interestingly, the relationship between the ee and the size of cations exhibited a nonlinear behavior wherein sodium proved to be most effective in contrast to our earlier work involving nucleophilic attack on the π-allyl intermediate as the enantiodiscriminating event.[17] The use of sodium hydride provided a homogeneous reaction mixture and the fastest reaction. In the case of lithium, an aggregated insoluble reaction mixture, which remained as a heterogeneous suspension throughout the course of the reaction, gave an ee of 69% (entry 1). Large differences in the ee were noted within a category of the same cation (entries 3−5). Whereas the ee and yield were

Table 7. Concentration and Temperature Effects in the Alkylation of **10a**

entry	**16** (mol %)	**17** (mol %)	temp (°C)	equiv of Nu	concn (M)	time (h)	% yield[a]	% ee[b]
1	2.5	8.0	25	1.6	0.50	1.5	68	89
2	2.5	7.0	0	1.2	0.29	2	76	91
3	2.0	6.0	0	1.5	0.14	2	85	91
4	1.0	3.0	0 to rt	1.5	0.55	6	87	90
5	2.5	7.5	−40	1.8	0.35	8	99	90
6[c,d]	1.0	3.0	0	2.5	0.20	3	94	(−)93[e]
7[d]	0.5	1.5	−5	2.0	0.16	3	87	93

[a] Isolated yields of **24**. [b] Determined by chiral shift studies on the desilylated alcohol **25**. [c] (*S,S*)-**17** was employed. [d] Slow addition procedure. [e] Opposite enantiomer, (*ent*)-**24**.

improved with higher catalyst loading and lower reaction temperatures, the enolate generated by potassium *tert*-butoxide resulted in a significantly lower ee. A much lower ee and a longer reaction time resulted when cesium carbonate was employed (entry 6). An attempted reaction with a nonmetal organic base such as TMG and DBU failed to produce the desired product (entries 7 and 13).

The notion that the low solubility of the nucleophile might be responsible for low ee's led to the exchange of the counterion for a more soluble alkylammonium or crown ether complexed cation. The addition of tetramethylammonium bromide caused a slight lowering in ee; whereas, the ee obtained with a crown ether was indistinguishable with that of the standard reaction (entries 8 and 9). The deterioration of ee by addition of alkylammonium salts was equally observed when methylene chloride was used as a solvent (entries 10−13). In particular, as the size of the cation increased from tetramethyl- to tetrahexylammonium, the ee further decreased—opposite to the case wherein nucleophilic attack on a π-allyl constitutes the enantiodiscriminating event.[17]

Temperature and Concentration Effect. The large change in the enantioselectivity with different solvents and counterions clearly indicates the strong influence of the reaction parameters. Other factors of kinetic importance are the temperature and concentration. In early studies, there was a small but discernible effect of the temperature on the ee. Furthermore, the observed reaction rate, though not rigorously measured, indicated that faster reactions generally gave better ee's. On the basis of these observations, it was anticipated that the ee could be improved by performing the reaction at higher concentrations or by using excess nucleophile. However, attempts to carry out the alkylation at high concentrations (>1.0 M) in THF met with difficulty due to the limited solubility of the nucleophile. The use of a large excess of nucleophile was not desirable because subsequent isolation and analysis of the alkylation products became problematic. To avoid these experimental difficulties, high concentration of nucleophile was achieved by a slow addition procedure in which substrates were slowly added to a mixture of the nucleophile and the catalyst.

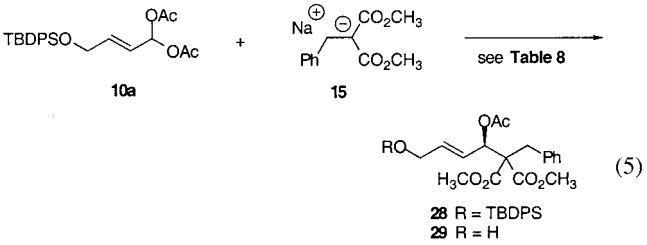
The results of alkylations of **10a** at various temperatures and concentrations are summarized in Table 7. As described before, an ee of 89% obtained from the reaction at ambient temperature was increased to 91% when the same reaction was performed at 0 °C (entries 1−4). Further lowering of the reaction temperature to −40 °C did not improve the ee (entry 5). No reaction occurred when the alkylation was attempted at −78 °C. Interestingly, the ee was rather insensitive to the amount of the catalyst and the final concentration. On the other hand, the ee was increased to 93% by the slow addition protocol (entries 6 and 7). It should be noted that using this slow addition protocol, the same ee could still be obtained when the catalyst loading was reduced to 0.5% **16** and 1.5% **17**.

Table 8. Alkylation of **10a** with Dimethyl Benzylmalonate

entry	**16** (mol %)	**17** (mol %)	temp (°C)	equiv of Nu	concn (M)	time (h)	% yield[a]	% ee[b]
1	2.5	7.5	25	1.2	0.20	2.5	58	80
2	2.5	7.0	0	2.0	0.24	2	86	90
3	2.0	6.0	0	4.0	0.20	2	98	90
4	0.5	1.5	0	1.2	0.35	3	76	90

[a] Isolated yields. [b] Chiral shift studies on the desilylated alcohol **29** using (+)-Eu(hfc)$_3$ in $CDCl_3$.

In the initial studies with cinnamyl derivative **7i**, the use of **15** as the nucleophile gave the same high level of ee (>95%) as dimethyl methylmalonate (**14**). By contrast, the alkylation of **10a** with **15** provided a much lower ee of 80% under the standard conditions (eq 5 and Table 8). While the ee jumped to 90% by simply running the reaction with 2.0 equiv of the nucleophile at 0 °C, the additional increase of the nucleophile to 4.0 equiv did not lead to further improvement. The application of the slow addition protocol to this system proved beneficial again as a comparable result could be obtained with only 1.2 equiv of the nucleophile and a much smaller amount of the catalyst (entry 4).



(5)

Regiochemistry. The ionization of allylic *gem*-dicarboxylates by a Pd(0) catalyst generates π-allylpalladium complex **30** in which the allyl unit is differentially substituted by a carboxy group and an alkyl group (Scheme 2). Due to this unsymmetric structure, the subsequent substitution can occur at either allylic termini to generate regioisomers, the "proximal" and "distal" products with respect to the acyloxy substituent. However, the alkylations of **7i** (R = Ph) and **10a** (R = $TBDPSOCH_2$) uniformly gave single regioisomers of type **31** which were derived from nucleophilic attack at the carbon bearing the acetoxy group (path "a").

To investigate the factors affecting regioselectivity, substrates with different substituents were examined (eq 6 and Table 9). An unsubstituted system (R = H) was first subjected to the alkylation with dimethyl methylmalonate (entries 1−3). The previous work showed that the use of *N,O*-bis(trimethylsilyl)-acetamide (BSA) as base and PPh_3 as ligand generated **34a** arising from distal attack exclusively.[41] In contrast, the alkylation using sodium hydride as base and dppp as ligand reoriented the regioselectivity to the proximal attack to give **33a** as the major product. The alkylation was completed in only 0.5 h to provide 79% of monoalkylated products as a 1.4:1 mixture of inseparable regioisomers and 7% of dialkylation product **35a**. Using chiral ligand **17**, the alkylation under standard conditions generated a 5.5:1 mixture of regioisomers in 81% yield. The major regioisomer **33a** was derived from the proximal attack, and no dialkylated product **35a** was isolated. However, major isomer **33a** had only 13% ee, presumably due to a rapid enantioface interconversion process. The possibility of a background reaction was excluded by a control reaction in the absence of the palladium catalyst which proceeded very slowly

Scheme 2. Regiochemistry of the Nucleophilic Addition to a π-Allyl Complex

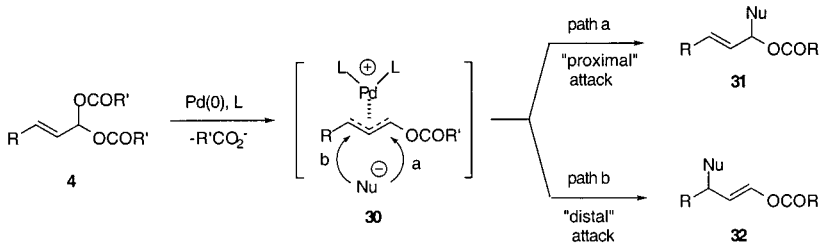
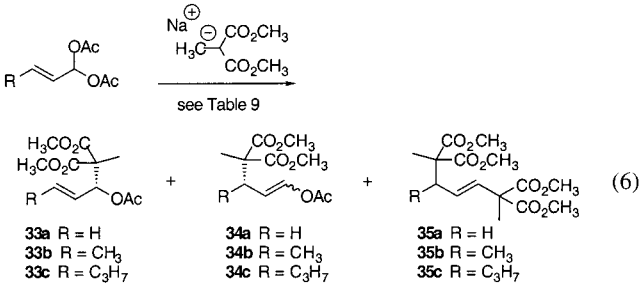


Table 9. Alkylation of *gem*-Diacetate with Dimethyl Methylmalonate[a]

entry	R	ligand	time (h)	% yield[b] **33** + **34**	ratio[c] **33**:**34**	ratio[c] (*E*:*Z*)[c]	% yield[b] **35**	% ee[d]
1[e]	H	PPh_3	11	70	0:1	(20:1)	0	–
2	H	dppp	0.5	79	1.4:1	(9.5:1)	7	–
3	H	**17**	0.5	81	5.5:1	(1.4:1)	0	13 (–)
4	CH_3	PPh_3	0.5	71	2.7:1	(20:1)	0	–
5	CH_3	dppp	2	69	2.9:1	(12:1)	24	–
6	CH_3	**17**	2	86	11:1	(6.3:1)	0	92 (43)[f]
7	$(CH_2)_2CH_3$	PPh_3	4	69	2.5:1	(1.7:1)	0	–
8	$(CH_2)_2CH_3$	dppp	1	62	5.7:1	(2.7:1)	0	–
9[g]	$(CH_2)_2CH_3$	(*S*,*S*)-**17**	5	73	12:1	(2.0:1)	0	93[h] (nd)

[a] All reactions were run at 0 °C in THF with 2.0 equiv of **14** in the presence of 2.5% **16** and 7.5% ligand except for entries 4 and 7 where 5% $Pd(PPh_3)_4$ was used as catalyst. [b] Isolated yields. [c] (*E*)- and (*Z*)-isomeric ratio of the vinyl acetates **34** measured by GC. [d] The ee of the major regioisomer **33** determined by the ^1H NMR integration ratio of the derivatized tris-*O*-methylmandelate esters. [e] Reference 41. [f] The ee of the 11:1 mixture of (*E*)- and (*Z*)-**34b** determined by GC ratio of the derivatized (*S*)-α-methylbenzylamides. [g] Slow addition procedure was applied. [h] The ee of (*ent*)-**33c**.

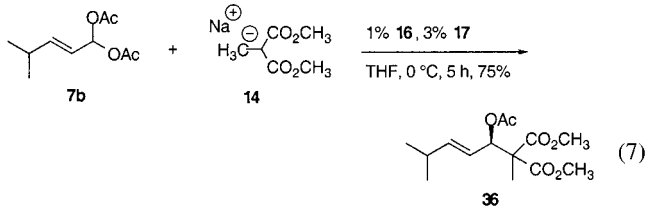
to give only vinyl acetates **34a** as the product in less than 5% yield at room temperature after 24 h.



(6)

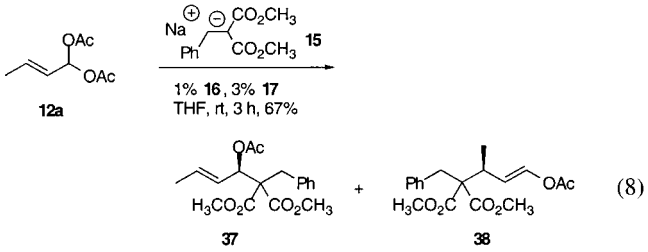
Alkyl substituted *gem*-diacetates were next examined (entries 4−9). The regiochemical preference for the "proximal" attack was more clearly manifested regardless of the ligand employed. Within the achiral reactions, dppp generally provided a better regioselectivity than triphenylphosphine. Unlike the unsubstituted system, the alkylation of these alkyl substituted systems with ligand **17** induced high enantioselectivities, giving **33b** and **33c** in 92% and 93% ee, respectively. Interestingly, the asymmetric reactions exhibited higher regioselectivities than achiral reactions in accord with the results from the unsubstituted system. When the alkyl substituent became significantly bulky as in eq 7, complete regioselection could be achieved. The reaction of isopropyl substituted **7b** furnished **36** as a single product in 95% ee. However, with sterically more congested substrates such as **7d**, **7e**, **7k**, and **13a**, the alkylation did not take place even at an elevated reaction temperature (65 °C). In these cases, the starting *gem*-diacetates or the corresponding α,β-unsaturated aldehydes were recovered.

The nucleophile also had an influence on the regioselectivity. Using less reactive dimethyl sodiobenzylmalonate (**15**) as the



(7)

nucleophile, the alkylation of **12a** gave a 67% yield of two allylic isomers **37** and **38** in a much lowered 2.3:1 regioselectivity (eq 8). In contrast to the alkylation with **14** (see Table 9, entry 6), the minor product possessed only (*E*)-geometry. Surprisingly, a discrepancy between the ee of the major (**37**, 90% ee) and the minor (**38**, 83% ee) isomers was noted.



(8)

While chiral shift studies revealed the ee of the major regioisomers, their absolute configuration was determined by derivatization to the corresponding tris-*O*-methylmandelates in the same manner as Scheme 1. On the other hand, analysis of the minor products was carried out by derivatization to (*S*)-α-methylbenzylamides **41** as shown in Scheme 3.[58] The sequence involving acetalization, oxidation, and amide formation reactions uneventfully furnished the amide derivatives. GC integration of **41** readily revealed the de and thus the ee of **34b** and **38**.

Leaving Group. The key element of chiral induction in the present system is differentiation of the two enantiotopic leaving groups in the ionization step where the two leaving groups experience a chiral recognition process. It was anticipated, therefore, that bulkier leaving groups might give better enantioselection. Along these lines, two series of geminal dipropionates and diisobutyrates were subjected to the alkylation, and their results were compared with those from the *gem*-diacetates (eq 9 and Table 10). Under the standard conditions, *gem*-dipropionate **12b** was reacted with dimethyl methylmalonate to produce a 5.5:1 mixture of isomers **42b** and **44b** in almost quantitative yield (entry 2). The ee's of major isomer **42b** and the mixture of minor products **44b** were determined to be 92 and 51%, respectively. On the other hand, the alkylation of *gem*-diisobutyrate **12c**, containing the bulkiest leaving group within the series, gave a much lower regio- and enantioselectivity (entry 3). In the series of *gem*-dicarboxylates **10**, all of the experiments were performed under the standard conditions and duplicated by using (*S*,*S*)-**17** as the ligand (entries 4−9). While the

(58) Hoye, T. R.; Koltun, D. O. *J. Am. Chem. Soc.* **1998**, *120*, 4638 and references therein.

Scheme 3. Derivatization of the Vinyl Acetates to (*S*)-α-Methylbenzylamides

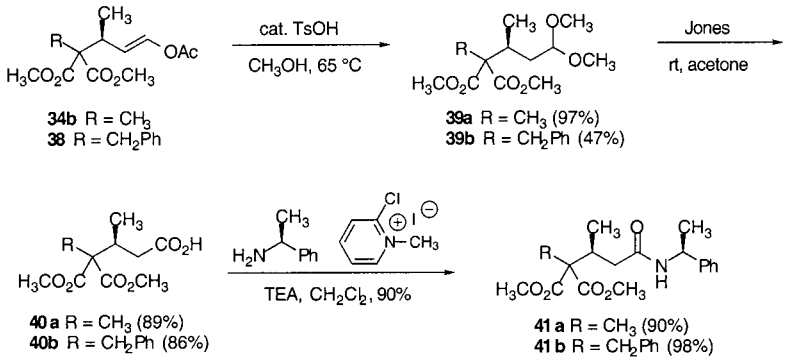
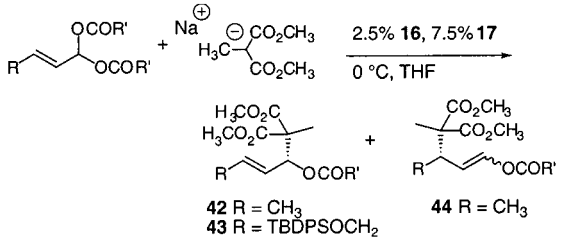


Table 10. Alkylation of *gem*-Dicarboxylate with Dimethyl Methylmalonate[a]

entry	R	R′	ligand	product	% yield[b]	ratio[c]	% ee
1	CH_3	CH_3	(*S*,*S*)-**17**	(*ent*)-**42a** + (*ent*)-**44a**	86	11:1	92[d] (43)[e]
2	CH_3	C_2H_5	(*S*,*S*)-**17**	(*ent*)-**42b** + (*ent*)-**44b**	99	5.5:1	92[d] (51)[e]
3	CH_3	$CH(CH_3)_2$	(*R*,*R*)-**17**	**42c** + **44c**	93	1.6:1	70[d] (nd)
4	$TBDPSOCH_2$	CH_3	(*R*,*R*)-**17**	43a	85	–	91[f]
5	$TBDPSOCH_2$	CH_3	(*S*,*S*)-**17**	(*ent*)-**43a**	76	–	89[f]
6	$TBDPSOCH_2$	C_2H_5	(*R*,*R*)-**17**	43b	95	–	91[f]
7	$TBDPSOCH_2$	C_2H_5	(*S*,*S*)-**17**	(*ent*)-**43b**	97	–	89[f]
8	$TBDPSOCH_2$	$CH(CH_3)_2$	(*R*,*R*)-**17**	43c	87	–	75[f]
9	$TBDPSOCH_2$	$CH(CH_3)_2$	(*S*,*S*)-**17**	(*ent*)-**43c**	83	–	74[f]

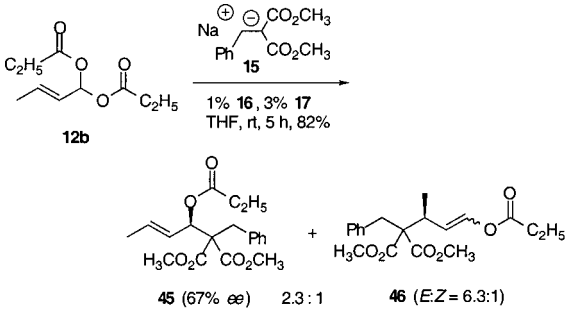
[a] All reactions were run in THF at 0 °C with 2.5% **16** and 7.5% ligand. [b] Isolated yields. [c] Isomeric ratio determined by GC. [d] Determined by ^{1}H NMR integration of the tris-*O*-methylmandelate. [e] The ee of the minor isomer (*E*:*Z* = 6.8:1) determined by GC ratio of the (*S*)-α-methylbenzylamide. [f] Chiral shift studies with (+)-Eu(hfc)$_3$ on the desilylated alcohols.

alkylation in this series gave only one regioisomer as the alkylation product, the ee showed a similar pattern as the methyl-substituted substrates. Namely, the propionate-leaving group gave a comparable ee, and the isobutyrate-leaving group led to a precipitous decrease in ee (entries 8 and 9).



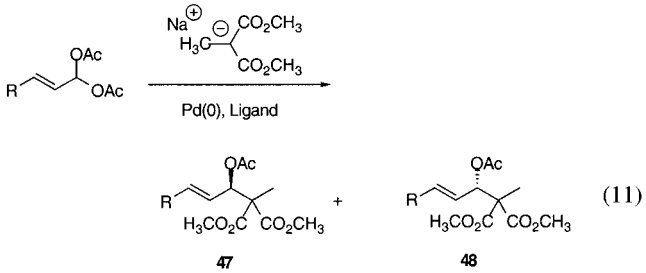
(9)

The adverse effect of a larger leaving group was more clearly noted when the alkylation was carried out with **15**. With this nucleophile, even the propionate-leaving group no longer provided a result comparable to that of the acetate (eq 10). The alkylation of dipropionate **12b** with **15** gave rise to a mixture of regioisomers in which the major isomer **44** had only 67% ee. Furthermore, the reaction occurred more slowly, giving a much lowered 2.3:1 regioselectivity. This result stands in contrast to those from the alkylation of **12a** with **14** (Table 9 entry 6) and the alkylation of **12a** with **15** (eq 8).



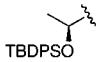
(10)

Diastereoselective Alkylation. So far, all of the substrates employed in these asymmetric reactions had been achiral. However, substrates possessing a stereogenic center adjacent to the allylic alkylation site may experience effects on their diastereoselectivity, thereby creating an issue of reagent versus substrate stereocontrol. To address this issue, two chiral substrates were subjected to the alkylation with dimethyl sodiomethylmalonate (eq 11, Table 11). The alkylation of d-mannitol derived **7c** exhibited rather strong stereochemical bias when achiral triphenylphosphine was used as ligand. The use of (*R*,*R*)-**17** reinforced the preference increasing the dr to 96:4. On the other hand, the formation of a 1:1 diastereomeric mixture was observed with (*S*,*S*)-**17** which apparently caused a mismatched event. Similarly, acyclic chiral substrate **13c** was also examined (entries 4−7). The alkylation using dppp ligand occurred in a nonselective fashion resulting in the formation of the two diastereomers in equal amounts. Employment of triphenylphosphine revealed a small stereochemical bias of the substrate. The reversal of intrinsic bias, albeit to a small degree, was realized by the use of (*R*,*R*)-**17**. However, the reaction suffered from poor conversion as the starting material was mostly recovered after prolonged reaction time. The slight preference for **48b** by triphenylphosphine ligand was switched to complete control of diastereoselectivity by chiral ligand (*S*,*S*)-**17**, which in this case represented a matched ligand.



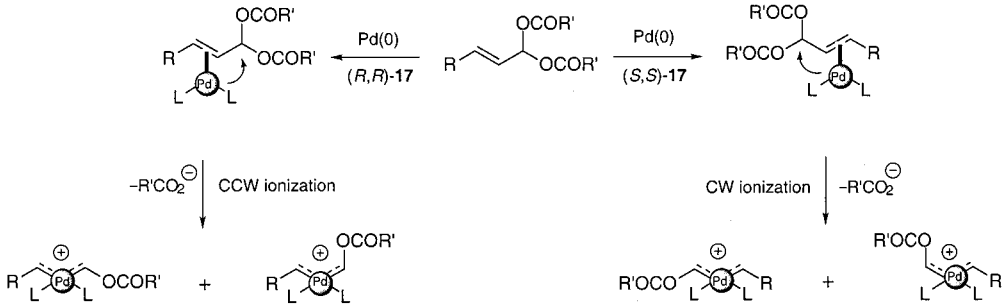
(11)

Table 11. Diastereoselective Alkylation

Entry	R	Ligand	Time (h)	Product	% Yield[a]	dr[b] 47 : 48
1	 **7c**	PPh_3	8	**47a + 48a**	50	88 : 12
2		(*R,R*)-**17**	4		77	96 : 4
3		(*S,S*)-**17**	6		81	50 : 50
4	 **13c**	dppp	8	**47b + 48b**	50	50 : 50
5		PPh_3	8		50	38 : 62
6		(*R,R*)-**17**	12		21	54 : 46
7		(*S,S*)-**17**	8		55	0 : 100

[a] Isolated yields. [b] Diastereomeric ratio determined by ^{1}H NMR integration.

Scheme 4. Mode of Enantioselective Ioinzation and Stereochemical Mnemonic



Discussion

The results of the present investigation demonstrate the feasibility of discriminating two enantiotopic geminal leaving groups by the AAA reaction. The allylic substitution reactions using ligand **17** give only the mono-alkylated product with high regio- and enantioselectivity. It is worth noting that the corresponding desymmetrization by enzymatic hydrolysis or acylation is not feasible with these 1,1-diol derivatives. Moreover, the absolute stereochemistry of the product can be correctly predicted on the basis of a simple stereochemical mnemonic which provides a structural and physical link between the ligand chirality and the mode of ionization.[13,42] High ee's of the alkylation product suggest that the clockwise or counterclockwise rotation of the ligand with respect to the substrate occur in a highly selective fashion (see Scheme 4 and earlier work[51] for a fuller description of this type of model). Apparently, this ionization process accompanies control of the *syn*- and *anti*-orientation of the allylic substituent within one mode of ionization since the *syn*- and *anti*-π-allyl complexes would lead to the formation of enantiomeric products.

The selection processes in the ionization and alkylation steps can be understood by a simple model as depicted in Figure 2.[59] This cartoon model retains the predictive power of the simple clockwise or counterclockwise rotation-based mnemonic, and more significantly, imparts physical interpretations. While the model adopts a representation involving C_2 symmetry, this representation does not likely describe the instantaneous structure. The ligand bound to the metal likely adopts conformations leading to non-C_2 symmetrical structures whose dynamic behavior creates a functional equivalent of C_2 symmetry. The observed memory effects[60] and an X-ray structure[55] in a related series supports this interpretation. Nevertheless, for simplicity, the cartoon depicts the time-average situation. Considering the effective C_2-symmetry of the ligand and the geometry of the allyl unit (M or W shape), there are four possible transition states for the ionization. First, two different trajectories, *exo* and *endo*, for the ionization arise due to the structure of the π-allyl complex in which the metal cants toward the *anti* substituents to allow a better overlap between the metal and the allyl unit. These two pathways differ in their orientation relative to the π-allyl. The *exo* pathway involves departure of the leaving group from the side of the *syn* substituent whereas in the *endo* pathway the same event takes place from the side of the *anti* substituent. Within these two pathways, the *exo* pathway should be preferred since this trajectory is closer to the optimum angle with respect to the newly forming palladium−carbon bond. Given this stereoelectronic argument, the additional consideration of a steric interaction provided by the chiral ligand suggests that the expulsion of the leaving group through the raised flap should be favored. It is conceivable that the difference in the transition-state energy between ionization of this fashion and that of other modes becomes larger since the development of an anionic charge on the leaving group is accompanied by solvation in the transition state. This transition state argument, to a first-order approximation, is equally applicable to the nucleophilic addition step based on the principle of microscopic reversibility ($X^{\delta-} = Nu^{\delta-}$ in Figure 2).

In the *exo* ionization event that occurs through the raised flap, the substrate can ionize through another transition state, leading to the formation of a *syn,anti*-π-allyl complex (Figure 3). However, this transition state involves the development of

(59) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.

(60) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235. Also see: Lloyd-Jones, G. G.; Sephen, S. C. *Chem. Eur. J.* **1998**, *4*, 2539; Poli, G.; Scolastico, C. *Chemtracts: Org. Chem.* **1999**, *12*, 837.

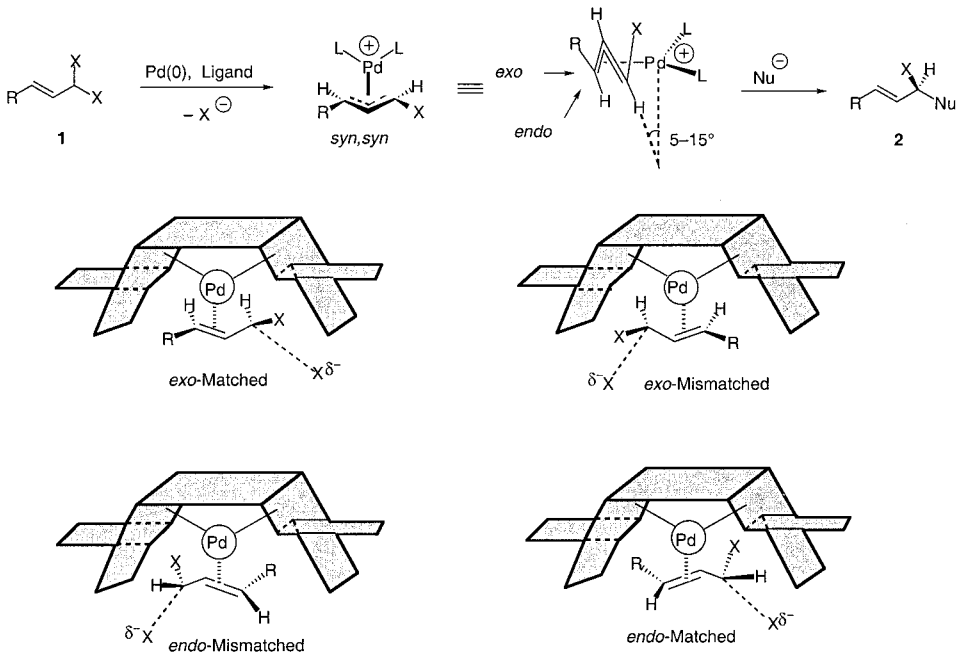


Figure 2. Transition state models for ionization (and nucleophilic addition).

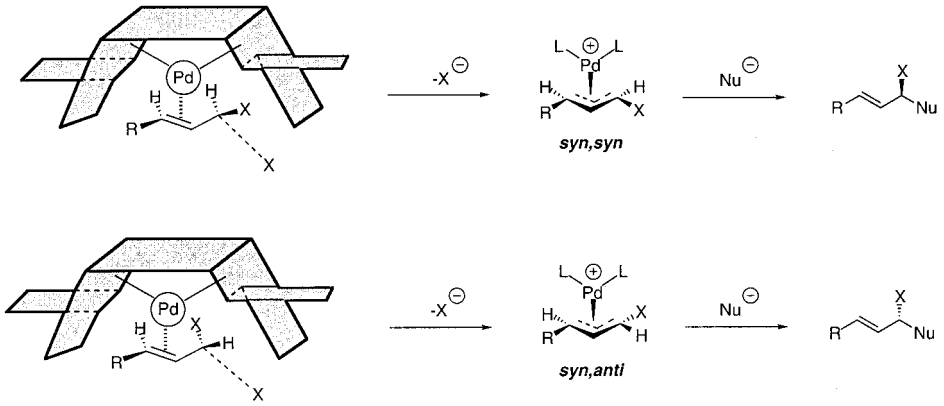


Figure 3. Transition states for *syn,syn*- and *syn,anti*-π-allyl complex formation.

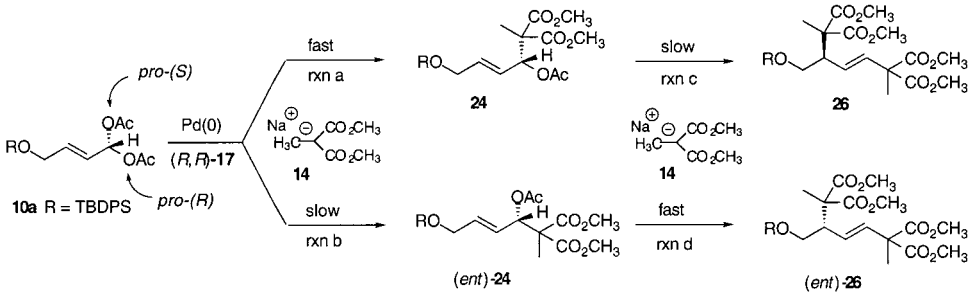
unfavorable $A^{1,3}$-allylic strain between the *anti*-substituent and the *anti*-hydrogen, and the steric hindrance between the *anti*-substituent and the wall of the chiral pocket. Furthermore, the preference for a *syn,syn*-geometry by ligand **17** is consistent with all of the results from other acyclic systems such as the 1,3-dimethylallyl system.[61,62] Thus, the high enantioselectivity obtained from the present reaction is believed to stem initially from the preference for the formation of the diastereomeric *syn,syn*-π-allyl intermediate. Although this intermediate is not necessarily the most stable π-allyl species, it may well be the most reactive intermediate since the nucleophilic addition process undergoes a reverse mechanistic pathway of ionization with respect to the interactions between the chiral ligand and the substrate. Therefore, this model can be applied to both the ionization and nucleophilic addition steps to fully explain the observed pattern of enantio- and regioselectivities.

In contrast to the alkylations using achiral ligands, asymmetric reactions produce only the monoalkylated product. The dialkylation seems to be a result of the rapid second ionization by the sterically less demanding palladium(0)−dppp complex. The lack of formation of the dialkylated product **26** is important in interpretating the resulting enantioselectivity due to the kinetic picture shown in Scheme 5. In the first alkylation, because (*R,R*)-**17** favors the ionization of the *pro-S* leaving group, reaction "a" should be faster than reaction "b", leading to an excess of enantiomer **24** over (*ent*)-**24**. On the other hand, this same ligand may promote the second alkylation via the ionization of (*ent*)-**24** to a greater extent than **24**. As a consequence, the ee of **24** can be enriched by over-reaction at the expense of the yield. Since the dialkylation was never observed in the reactions using chiral ligand **17**, the obtained ee should reflect the true chiral discrimination. From the ligand-screening experiments, the strong dependence of the enantioselectivity on all of the components of the ligand is readily noted. Although it is rather difficult at this point to formulate the requirements for a good ligand in this reaction, the results clearly support that all of the structural and electronic elements of the parent ligand **17** are significant for the successful alkylation.

Although solvents participate in many different aspects of the reaction, often making interpretation of their specific role very difficult, they have an effect on the ionization and nucleophilic addition steps in the catalytic cycle which involve charge development and neutralization processes.[57] The degree

(61) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520.
(62) Trost, B. M.; Radinov, R. *J. Am. Chem. Soc.* **1997**, *119*, 5962.

Scheme 5. Kinetic Amplification of Enantioselectivity by Dialkylation



of chiral recognition can vary due to the differential solvation of the incipient ionic π-allyl complex in the enantio-discriminating ionization step. Similarly, the rate of nucleophilic addition is affected by solvation of the electrophile and the nucleophile, both of which are charged species. The observations from the solvent-screening experiments indicate that the origin of the effect on the ee lies both in the polarity of solvents and their coordinating ability. Ethereal solvents of intermediate polarity (e.g. THF, DME, and 1,4-dioxane) provide the best results. Nonpolar solvents appear to be a medium for good chiral recognition although the subsequent nucleophilic addition is sluggish due to their poor ability to solvate the nucleophile. To the extent that the ionization is reversible, the slow rate of the nucleophilic addition fails to reflect the initial enantiodiscrimination because the "mismatched" ionization becomes more competitive in this situation. The opposite may be true for cases with polar solvents. The good ee's obtained with ethereal solvents suggest that an optimal compromise may be reached between the degree of enantioselective ionization and the rate of the nucleophilic addition owing to the relatively nonpolar, yet coordinating nature of these solvents.

The nonlinear relationship between ee and the ionic radius of the cation attests to the complex nature of these alkylations. Given that the enantio-discriminating event occurs in the ionization step, the nature of the nucleophile should, a priori, not affect the initial asymmetric induction process. Therefore, the observed variance of ee appears to be the consequence of an indirect effect derived from the rate of the nucleophilic addition.[62] Since the different counterions can cause the differential solvation and aggregation of the nucleophile, it is conceivable that the efficiency of quenching the π-allyl intermediate by a nucleophile can vary, depending on the counterion. In cases where the nucleophile is slow to react, reversal of the "matched" ionization occurs and ultimately leads to significant competition of the "mismatched" ionization. Since 0.5−2.5% of $(\eta^3\text{-}C_3H_5PdCl)_2$ (**16**) was used as a palladium source, the reaction mixture always contains 1.0−5.0% chloride ion. Therefore, it is likely that the additive effects reside mostly in the cation rather than anion.[63] The addition of alkylammonium salts did promote solvation of the nucleophile, providing homogeneous reaction mixtures. However, this increased solubility did not translate into an increase in the reaction rate. Instead, nucleophiles with an alkylammonium cation generally retarded the reaction, with the retardation increasing with increasing size,[64] and decreased the ee. Interestingly, the smaller alkylammonium cations give higher ee's in accord with the trend observed in the solvent-screening experiment; faster reactions give higher ee's. This effect is again opposite to that observed when nucleophilic attack is the enatiodiscriminating event.[17]

The results from the effect of temperature and concentration lead to a simple conclusion that a lower reaction temperature and a higher nucleophile concentration give a better enantioselectivity. The increase in ee observed in cooling from 25 °C to 0 °C seems to arise from better chiral recognition at a lower reaction temperature. However, no improvement of the ee by further lowering the reaction temperature suggests that the good enantio-discrimination achieved in the ionization step should be followed by a fast nucleophilic addition. Given the fact that the enantioselectivity of these alkylations is rather insensitive to the amount of the catalyst, the direct metal−metal displacement mechanism is unlikely to be the source of lowering the ee. The slow addition procedure, which would make occurrence of this process more likely due to the increased catalyst concentration with respect to that of substrate, generally gives better ee's instead.

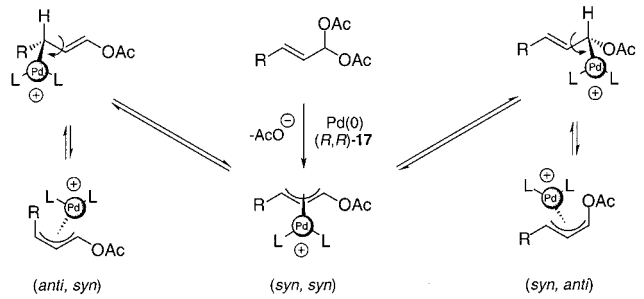
The regioselectivity of the alkylation is primarily reflective of the strong electronic effect of an oxygen atom that stabilizes the α-cation through resonance favoring nucleophilic attack at that carbon. This preference is reinforced by the effect of the substituents as in the case of **7i** (R = Ph) and **10a** (R = $TBDPSOCH_2$). While the aromatic ring favors formation of the regioisomers in which the resultant double bond is conjugated with the phenyl group (path "a" in Scheme 2), the silyloxymethyl substituent in **10a** disfavors nucleophilic attack at the adjacent carbon (path "b") due to its destabilizing effect on a partial cationic charge, and thus leads to a "proximal" alkylation product. In addition to these substrate originated factors, the ameliorative influence of the chiral ligand on the regioselectivity is readily apparent from the results. The higher regiocontrol in the asymmetric reaction relative to achiral reactions stems from the chiral recognition by ligand **17**. If the chiral ligand favors a certain mode of ionization, the reverse pathway, which involves a nucleophilic attack at carbon where the leaving group was placed, should also be favored.

The formation of (*E*)- and (*Z*)-alkenes in the minor regioisomer is indicative of the presence of the $\pi-\sigma-\pi$ isomerization among the π-allyl intermediates prior to the nucleophilic addition (Scheme 6). This isomerization represents an enantioface interconversion process in the case of R = H, presumably leading to the poor enantioselectivity of the unsubstituted system. It is important to note that (*Z*)-alkene was never observed as the major isomer. This fact suggests that the *anti*,*syn*-complex is not formed or that other π-allyl complexes are more reactive. It is also possible that the *anti*,*syn*-complex undergoes nucleophilic attack exclusively at the distal carbon. The much lower ee's of the minor products relative to the major isomer is in part derived from the fact that the ee was determined from a mixture of (*E*)- and (*Z*)-isomers. The configuration of the distal carbon in the *syn*,*syn*- and *syn*,*anti* -isomers would be opposite to each other because the $\pi-\sigma-\pi$ mechanism entails a π-facial interconversion process, leading to a change

(63) Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155.

(64) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 70.

Scheme 6. Isomerization of π-Allyl Complexes via $\pi-\sigma-\pi$ Mechanism



in both the configuration of the stereogenic center and the geometry of the olefin. Therefore, the ee obtained from the (*E*) and (*Z*) mixture of **34** should reflect the consequence of the isomerization process to give a much lower ee than that of the major isomer **33**.

However, the lower ee of **38** relative to **37** raises an interesting mechanistic question as to the origin of the minor product. The factors that lead to higher ee's (i.e. high concentration of the nucleophile or slow addition of the substrate) suggest the existence of a mechanism eroding the ee before the nucleophilic addition step. Although the background reaction could form vinyl acetate **38** in a racemic fashion, the slow rate of this process in the control experiment and the exclusive (*E*)-geometry make this possibility less likely to be responsible for the lower ee. Instead, a simple rationalization evolves from the possibility that the generated π-allylpalladium intermediates may have differential reactivities toward the nucleophile. As is shown in Scheme 7, ligand **17** generates the two diastereomeric π-allylpalladium intermediates **47** and **48** with different rates. In the case of the matched ionization, the nucleophilic addition leading to the formation of allylic acetate **37** should be favored since it constitutes another matched process (i.e. microscopic reverse of the ionization). When the subsequent nucleophilic addition is slow, the return of the π-allylpalladium intermediate to starting diacetate **12a** competes with alkylation. With the less reactive nucleophile **15**, more significant competition between the matched and mismatched ionization would cause an erosion of the ee. Furthermore, "distal attack" of the nucleophile to the mismatched intermediate **48** becomes a matched process leading to preferential formation of enantiomeric vinyl acetate (*ent*)-**38**. Consequently, the ee of minor isomer **38** and the regioselectivity of the overall alkylation deteriorate. Therefore, for the maximum chiral induction and regioselection, the kinetically preferred π-allyl intermediate **47** must be captured by the nucleophile before it undergoes any kind of selectivity-lowering process.

The similar acidity (pK_a) of acetic (4.75), propionic (4.86), and isobutyric (4.84) acids suggests that the unexpected inverse relationship between the ee and the size of the leaving group may be mostly steric in origin. In particular, precipitous drops of the ee's by changing leaving groups from a linear propionate to a branched isobutyrate indicates that chiral ligand **17** has a well defined chiral pocket to differentiate the branching in the leaving group. However, the complicated nature of the chiral recognition process, which originates from the two prochiral elements, the two faces of the double bond, and the two enantiotopic leaving groups, makes it rather difficult to rationalize these results. Nevertheless, a simplified picture wherein only counterclockwise ionization is considered, may explain the observed results (Scheme 8). Upon coordination of the palladium(0)−**17** complex to the double bond, the two enantiotopic leaving groups become diastereotopic. While the leaving group *anti* to the η^2-palladium−olefin complex is ionized, the rotation about the C1−C2 bond can change the orientation of the leaving group. To the extent that a preequilibrium between these two species is established via this bond rotation and the reversible complexation, the ionization favors the formation of (*syn*)-**50** over (*anti*)-**50**. If the R′ group is sterically demanding, steric interactions between the carboxylate in **49s** and the pocket might begin to disfavor **49s** relative to **49a**. The fact that 1,3-disubstituted allyl systems bearing sterically bulky substituents are poor substrates with these catalysts support this contention.[65] As a consequence, the degree of differentiation between the two species becomes smaller, and thus competitive formation of (*ent*)-**2** lowers the ee. Alternatively, it is possible that the preference of the remaining carboxy group to assume the *anti* position becomes larger as the steric demand increases. Indeed, such change of *syn* versus *anti* preference by chiral ligand **17** has been utilized in the stereoselective synthesis of a (*Z*)-alkene.[66]

The results of the diastereoselective alkylations attest to the presence of the matched and mismatched ionizations. As is evident from the results with achiral ligands, the two substrates have a stereochemical bias. It is interesting to note that the structural feature of these systems permits an opportunity for 1,4-asymmetric induction, and thus the alkylation product is equivalent to a vinylogous Felkin−Anh adduct. The bias is believed to arise from the conformational preference of the allylic systems upon coordination to Pd(0) (Scheme 9). In the case of achiral ligands, the initial facial selectivity in the complexation more or less determines the de of the reaction. On the other hand, a certain mode of ionization (clockwise vs counterclockwise) is favored by the chiral ligands. Since the coordination is reversible, this two-stage selection process allows the chiral ligands to amplify the inherent stereochemical bias of the substrates in the matched cases.

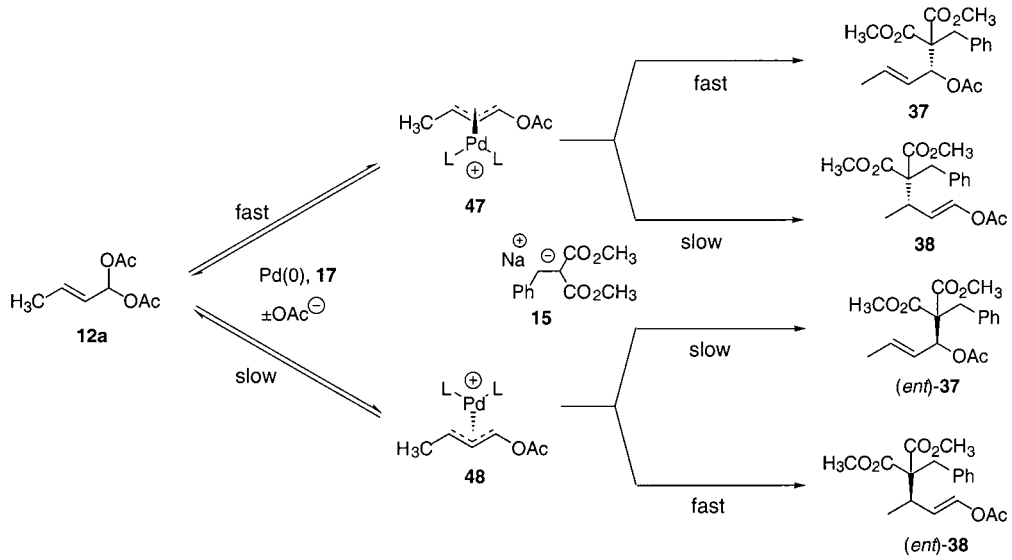
Considering the factors discussed thus far, a unified kinetic picture that outlines the pathways for enantio- and regioselective alkylation of *gem*-dicarboxylates can be formulated (Scheme 10). In this scheme, all of the favored pathways are drawn as a solid line. With ligand (*R*,*R*)-**17**, the initial ionization that occurs in a counterclockwise motion and generates a *syn*,*syn*-π-allyl intermediate is kinetically preferred. While this intermediate can undergo an isomerization process via a $\pi-\sigma-\pi$ mechanism to generate isomeric π-allyl complexes, the mode of the nucleophilic addition to each complex is again influenced by the chiral pocket, providing control of regioselectivity. The major product is derived from a series of kinetically favored events, each of which constitutes a matched process. It is remarkable that the alkylation using ligand **17** produces the major product out of numerous kinetic possibilities in a highly enantio- and regioselective fashion.

Conclusions

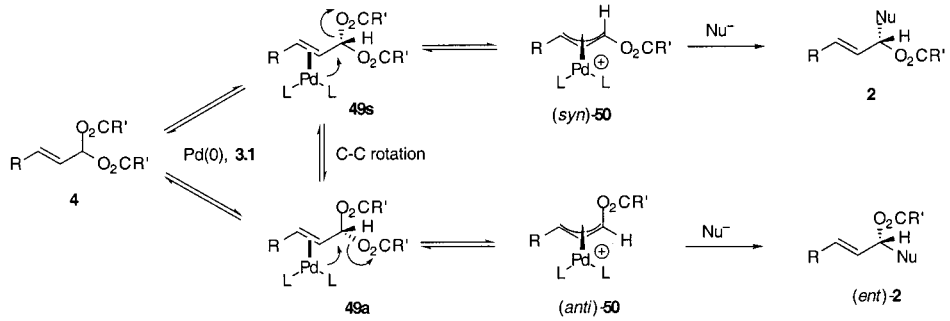
In summary, a new strategy in the enantioselective allylic alkylation reaction has been developed using allylic *gem*-dicarboxylates as substrates and alkylmalonates as nucleophiles. The complex derived from palladium(0) and ligand **17** was most effective, giving rise to the alkylation product in high enantio- and regioselectivities. The sense of induced stereochemistry can be correctly predicted on the basis of a simple stereochemical mnemonic. Simple comparison of the results from the achiral

(65) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057.
(66) Trost, B. M.; Heinemann, C.; Ariza, X.; Weigand, S. *J. Am. Chem. Soc.* **1999**, *121*, 8667.

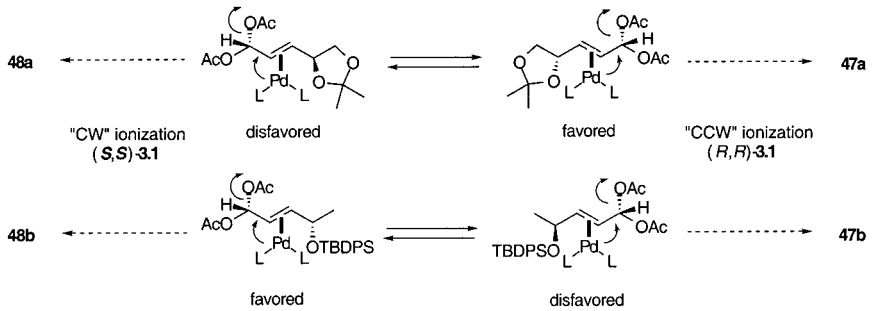
Scheme 7. Matched and Mis-matched Ionization and Nucleophilic Addition



Scheme 8. Effect of Leaving Group and Mechanism



Scheme 9. Matched and Mis-matched Coordination and Ionization



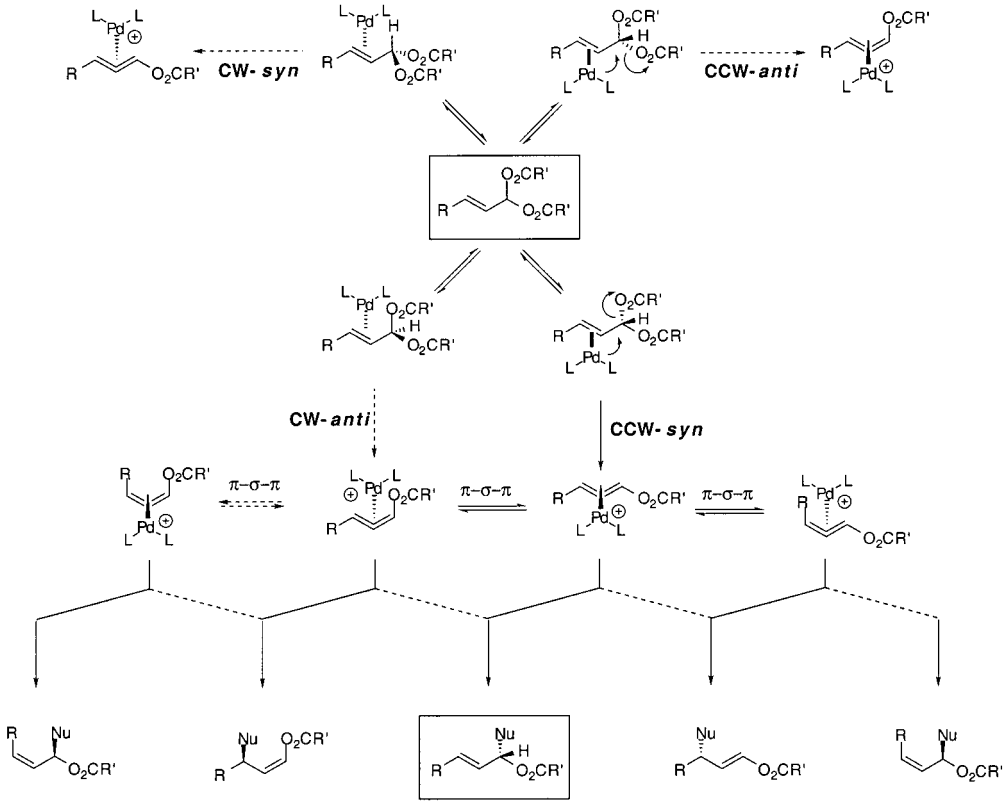
reactions and their asymmetric version reveals that chiral ligand **17** not only performs the alkylation in a highly enantioselective fashion but also provides excellent chemo- and regioselectivities. By systematic studies, various factors affecting the stereochemical outcome of the reaction have been probed and analyzed. Proper control of reaction conditions proves critical for obtaining high ee's (>90%). Among reaction parameters, the solvent and the concentration of the nucleophile are most important. The observed solvent and concentration effects suggest that two conditions must be met in order to obtain good enantio- and regiocontrol of the reaction: (1) a good level of chiral recognition in the ionization step and (2) the effective capture of the kinetic π-allyl intermediate in the nucleophilic addition. A comparison of the results from reactions of structurally different geminal diesters such as diacetates, dipropionates, and diisobutyrates provides further mechanistic insight into the chiral recognition process and the kinetic picture of the reaction. The mode of asymmetric induction achieved in the present study represents a novel process of differentiation between two geminal carbon−oxygen bonds, a difficult transformation by enzymatic methods. Synthetically, the present reaction constitutes the equivalent of a stabilized nucleophile addition to a carbonyl group with high asymmetric induction.

Experimental Section

1-Methoxy-1-(3′,3′-diacetoxy-1′(*E*)-propen-1′-yl)-cyclopentane (13a). Procedure A. Freshly distilled acetic acid (0.70 mL, 12.2 mmol) was added to a solution of Pd_2dba_3·$CHCl_3$ (41.4 mg, 0.040 mmol) and triphenylphosphine (105 mg, 0.400 mmol) in degassed toluene (30 mL) at room temperature. After the solution stirred for 5 min, a solution of **6a** (0.785 g, 4.00 mmol) in toluene (20 mL) was added, and the resultant mixture was heated at 110 °C for 4 h. The reaction mixture was cooled, concentrated, and purified by flash chromatography on a silica gel column (hexanes/ethyl acetate 15:1) to yield diacetate **13a** as a clear oil (0.897 g, 87%).

Procedure B. Acetic acid (0.43 mL, 7.52 mmol) was added to a solution of $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) in degassed toluene (20

Scheme 10. Reaction Pathways for Asymmetric Alkylation of *gem*-Dicarboxylates



mL) at room temperature. After the solution stirred for 5 min, acetate **6a** (0.985 g, 5.02 mmol) in toluene (10 mL) was added, and the resultant mixture was heated at 110 °C for 12 h. The reaction mixture was cooled, concentrated, and purified by flash chromatography on a silica gel column (hexanes/ethyl acetate 15:1) to yield diacetate **13a** (1.150 g, 89%): t_r = 7.94 min (GC); IR (film) ν_{max} 1766, 1676, 1436, 1373, 1242, 1204, 1069, 1009, 961 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (dd, J = 6.0, 0.9 Hz, 1H), 6.02 (dd, J = 16.0, 0.9 Hz, 1H), 5.65 (dd, J = 16.0, 6.0 Hz, 1H), 3.11 (s, 3H), 2.09 (s, 6H), 1.89−1.83 (m, 2H), 1.80−1.57 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 139.7, 122.9, 89.3, 86.1, 50.9, 35.7, 23.0, 20.8; Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.82; H, 7.71.

(*S*)-1,1-Diacetoxy-4-(*tert*-butyldimethylsilyloxy)-pent-2(*E*)-ene (13b). Freshly distilled acetic acid (0.028 mL, 0.490 mmol) was added to a solution of $Pd_2(dba)_3$·$CHCl_3$ (2.5 mg, 0.0022 mmol) and tri(*o*-methoxyphenyl)phosphine (6.8 mg, 0.019 mmol) in degassed toluene (1.5 mL) at room temperature. A solution of acetate **6b** (62 mg, 0.242 mmol) in toluene (1 mL) was added, and the resultant mixture was heated at 110 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated and chromatographed on a silica gel column (hexanes/ethyl acetate 15:1) to yield diacetate as **13b** a clear oil (46.5 mg, 61%): t_r = 8.02 min (GC); $[\alpha]_D$ +0.11 (*c* 2.37, $CHCl_3$); IR (film) ν_{max} 1766, 1682, 1473, 1442, 1372, 1247, 1205, 1142, 1094, 1051, 1007, 964 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 6.3 Hz, 1H), 6.02 (ddd, J = 15.5, 4.4, 0.8 Hz, 1H), 5.70 (ddd, J = 15.5, 6.3, 1.1 Hz, 1H), 4.39−4.30 (m, 1H), 2.08 (s, 6H), 1.21 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.82, 166.79, 141.3, 121.4, 89.2, 67.7, 25.7, 23.7, 20.7, 18.1, −4.9, −5.0; HRMS Calcd for $C_{13}H_{25}O_3Si$ ($M^+ - C_2H_3O_2$) 257.1573, Found 257.1576.

Pd-Catalyzed Asymmetric Allylic Alkylation. General Procedures. A. Standard Procedure. To a suspension of sodium hydride in THF (or an indicated solvent) was added dimethyl methyl- or benzylmalonate at 0 °C. The mixture was stirred until evolution of hydrogen ceased. To this mixture was added a solution of π-allylpalladium chloride dimer (**16**), ligand **17** (or an indicated ligand), and the geminal dicarboxylate in THF (or an indicated solvent) via cannula. The resulting orange solution was stirred at 0 °C (or room temperature), and the progress was monitored by TLC or GC. After complete consumption of the starting material or cessation of the reaction, the reaction mixture was poured into 10% aqueous $NaHSO_4$ and extracted with ether or ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, concentrated, and purified by flash chromatography on a silica gel column with ethyl acetate/hexanes (or petroleum ether) mixture as an eluent.

B. Slow Addition Procedure. The nucleophile (**14** or **15**) was generated in the same manner as described in the standard procedure. A solution of the palladium catalyst and the ligand in THF was added to the nucleophile solution via a cannula. To this mixture was added a solution of the geminal dicarboxylate in THF by a syringe pump over an indicated period of time (3−5 h). After the addition was complete, the reaction mixture was stirred for an additional hour and worked up in the same manner as the standard procedure.

Dimethyl (2′*E*,1′*R*)-2-[1′-Acetoxy-4′-(*tert*-butyldiphenylsilyloxy)-2′-buten-1′-yl]-2-methylmalonate (24). Following the standard procedure, the reaction of diacetate **10a** (0.325 g, 0.762 mmol) with dimethyl sodiomethylmalonate (**14**), prepared from sodium hydride (60% dispersion, 50 mg, 1.25 mmol) and dimethyl methylmalonate (0.200 g, 1.37 mmol), was performed in THF (1.5 mL) at room temperature for 2 h in the presence of π-allylpalladium chloride dimer **16** (7.0 mg, 0.019 mmol) and (*R*,*R*)-**17** (42 mg, 0.061 mmol). Purification by flash chromatography on a silica gel column (hexanes/ethyl acetate 15:1) afforded acetate **24** as a colorless oil (0.265 g, 68%, 89% ee). Following the slow addition procedure, **10a** (0.410 g, 0.964 mmol) in THF (3 mL) was reacted with **14** by adding to a mixture of sodium hydride (48.7 mg, 1.93 mmol), dimethyl methylmalonate (0.325 g, 2.41 mmol), **16** (1.8 mg, 0.0049 mmol), and **17** (10.0 mg, 0.0145 mmol) in THF (2 mL) via a pump driven syringe at −5 °C over 3 h. After stirring for an additional hour followed by a standard workup, flash chromatography on a silica gel column (hexanes/ethyl acetate 15:1) gave **24** as a colorless oil (0.429 g, 87%, 93% ee): $[\alpha]_D$ −8.95 (*c* 1.05, $CHCl_3$); IR (film) ν_{max} 1748, 1590, 1429, 1372, 1227, 1112, 1022, 824 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4H), 7.43−7.35 (m, 6H), 6.02−5.99 (m, 1H), 5.84−5.83 (m, 2H), 4.19 (s, 2H), 3.71 (s, 3H), 3.70 (s, 3H), 2.05 (s, 3H), 1.47 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.7, 169.4, 135.6, 135.5, 134.7,

133.5, 133.4, 129.7, 127.7, 127.6, 122.9, 74.1, 63.2, 57.6, 52.6, 52.5, 26.6, 20.8, 19.0, 15.6; Anal. Calcd for $C_{28}H_{36}O_7Si$: C, 65.60; H, 7.08. Found: C, 65.79; H, 6.86.

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Supporting Information Available: Experimental procedures for the preparation of all new compounds as well as characterization data are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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