Efficient Catalytic Enantioselective Reaction of a Glycine Cation Equivalent with Malonate Anions *via* Palladium Catalysis

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The enantioselective alkylation of Schiff base acetates **1** with malonate types of stabilized carbon nucleophiles in the presence of a stable palladium source $Pd(OAc)_2$ and the chiral ligand (+)-BINAP was developed. The product **2**, a protected β-carboxyaspartic acid (ASA), was obtained in up to 85% enantiomeric excess by varying the ester protecting group on the substrate. The nature of the nucleophile has a significant effect on the enantioselectivity in this (2-aza-π-allyl)palladium system. While a rapid chemical conversion was achieved with Schiff base benzoates **5**, the enantioselectivity was insensitive to the leaving group used. An optically active substrate (51% ee) gave the same level of enantioselectivity as that obtained from the racemate. Temperature effects on the reaction were also studied; the best selectivity was obtained at 0 °C. A laboratory-scale reaction of the reactive nucleophile $KCH(COOCH_3)_2$ with the *tert*-butyl ester substrate **1c** gave, following a single recrystallization, product **2c** with 95.5% ee in an overall chemical yield of 62%.

Introduction

The palladium-catalyzed allylic substitution reaction has been the subject of numerous recent studies.[1] It is a versatile process because of the range of substrates[2] and nucleophiles[3] used. Also, it is possible to obtain excellent chemo-, regio-, and stereocontrol in this reaction. Recently, with the development of a wide variety of chiral ligands,[4] attention has shifted to the modification of the chiral catalyst to achieve high enantioselectivity. The vast majority of allylic systems studied have involved the all-carbon allylic substrates;[5] the synthetic utilization of heteroatom-substituted π-allyl systems is much rarer.[6−8]

Our program for the synthesis of α-amino acids from Schiff base-protected glycine and higher amino acid derivatives has focused on use of the complementary anionic and cationic equivalents for preparation of structurally diversified amino acid products (Scheme 1). Initial studies in the anionic series involved racemic bond construction using phase-transfer catalytic (PTC) alkylation as a mild, room-temperature reaction procedure.[9] Catalytic, enantioselective PTC reactions with these Schiff base substrates have been developed.[10,11] To date, enantioselectivities up to 85% ee have been obtained for monoalkylation and 75% ee for dialkylation PTC chemistry. The principles developed in the PTC reactions of activated anions and substrates have been extended to the selective alkylation of peptide substrates.[12] More recently, the alkylation of resin-bound amino acid and peptide substrates, termed "unnatural peptide synthesis (UPS)", which provides for the attachment of unnatural side chains during normal solid-phase peptide synthesis (SPPS), has been achieved.[13]

The complementary cationic equivalents of glycine, readily available from the parent Schiff base esters, can

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be reacted with various nucleophilic reagents to prepare racemic products.[14] Thus, neutral heteroatom nucleophiles, carbanions, organoboranes, and neutral carbon nucleophiles all react to replace the acetate with the appropriate group regioselectively at the α-carbon.

Of particular interest is the 1990 report of the palladium-catalyzed coupling of malonate anions with Schiff base acetates[15−17] to form racemic β-carboxyaspartic acid (ASA)[18] derivatives. This reaction can be formally represented as involving reaction of a cationic (2-aza-π-allyl)-palladium intermediate with nucleophiles (Scheme 2).

By utilizing the rich chemistry developed in the palladium-catalyzed allylic substitutions, particularly with respect to the choice of chiral ligands and optimized reaction conditions, we were interested in coupling our substrate **1**[19] with malonate-type stabilized carbon nucleophiles in the presence of a palladium catalyst and chiral phosphine ligands. Suitable deprotection of the products **2** provides a convenient route to optically active β-carboxyaspartic acid (ASA) derivatives **3** (Scheme 3).

The starting substrates in these reactions, Schiff base acetates **1**, are readily prepared[15c,20] and undergo the racemic variant of this reaction (Scheme 3, Ar = Ph, R_1 = CH_3 or CH_2Ph) with malonate types of stabilized ("soft") carbon nucleophiles (R_2 = H, R_3 = CH_3 or CH_2Ph) in the presence of the achiral catalyst $(Ph_3P)_4Pd$.[15a] The *in situ* generation of an active catalyst using a stable palladium source ($Pd(OAc)_2$) and various bidentate bisphosphine ligands was developed to bypass catalyst preparation and isolation.[15b] The effect of tether length between the two phosphines on the rate and yield of the reaction is dramatic. Earlier studies demonstrated that at least four methylene groups are needed to give both rapid reaction and high conversion. A number of commercially available chiral phosphine ligands, such as (−)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (DIOP),[21] (−)-(*R*)-*N*,*N*-dimethyl-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine (BPPF),[22] (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (BPPM),[23] and (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[24] were surveyed in the model reaction (Ar = Ph, R_1 = CH_3, R_2 = H, R_3 = CH_3). Although DIOP and BPPF resulted in good chemical conversion, the product was racemic. In contrast, BPPM and BINAP gave low levels of enantioselectivity (8% ee and 27% ee, respectively).[15b] This study represented the first successful enantioselective synthesis of Schiff base glycine derivatives **2** *via* the cationic glycine equivalents. The level of enantioselectivity was increased to 37% with the BPPM ligand by using the *tert*-butyl ester of the substrate (**1c**, Ar = Ph, R_1 = tBu).[15c] The optical purity of the product could be increased further (to 77% ee) by a single recrystallization. Additionally, this product (**2c**) could be subjected to PTC alkylation to produce β-substituted ASA derivatives without epimerization of the α-center.

In this paper, we report further detailed studies using BINAP as the chiral ligand. A systematic study of the various reaction parameters has allowed development of a highly efficient catalytic enantioselective reaction protocol.

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Results and Discussion

Substrate Structural Modification: The Ester. Although the best enantioselectivity was obtained using BINAP in the above model reactions (Schiff base methyl ester acetate, sodium dimethyl malonate, $Pd(OAc)_2$, and (+)-BINAP), this ligand gave extremely slow chemical conversion as well as low yield under the normal catalytic conditions employed (5% $Pd(OAc)_2$, 10% bidentate phosphines). Optimization of the reaction using a stronger nucleophile (sodium dimethyl methylmalonate)[25] illustrated that 10% catalyst (1:2 molar ratio of Pd/P) was needed to ensure both rapid reaction and high conversion of the starting material. These optimized conditions were employed in the following studies.

The effect of the nature of the ester protecting group on the enantioselectivity of the reaction was explored by introducing larger ester groups R (Table 1).[20,26] It was observed that the size of the ester group has a significant impact on the enantioselectivity of the reaction (27−85% ee). The enantioselectivity increased from 27% ee with the methyl ester to 69% ee with the isopropyl ester. *Increasing the size of the ester group to tert-butyl led to an 85% ee.*[27] However, the more sterically demanding

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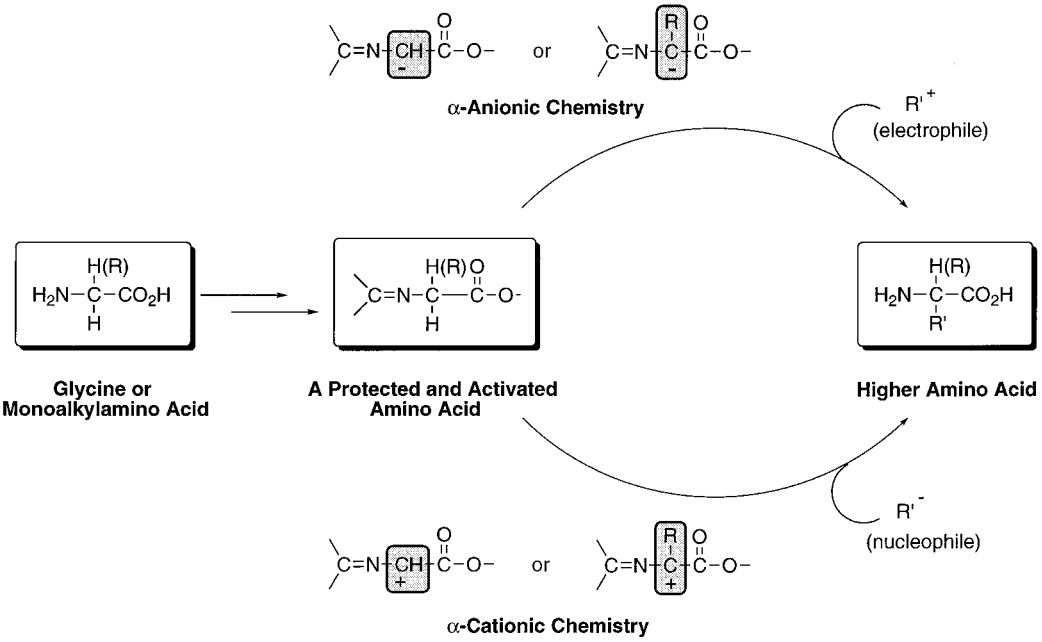
Scheme 1. Schiff Base-Protected Derivatives in Amino Acid Synthesis



group 1,1-diethylpropyl produced a slightly lower enantioselectivity (78% ee).

The above results demonstrate that the optimal substrate in our system requires a relatively bulky ester group.

Substrate Structural Modification: The Imine. Following the success of the above reactions, modification of the imine protecting group was investigated. The initial consideration was introduction of a bulky group on the phenyl rings to examine the steric effect on selectivity at the imine. Therefore, the bis(3,5-dimethyl)-benzophenone imine *tert*-butyl ester acetate **1e** was synthesized.[28] Disappointingly, a lower enantioselectivity was obtained (58% ee), as well as a low chemical yield (38%) and a slow reaction (35 h) (Table 2, entry 2).

The electronic effect of the substituents on the Schiff base was studied next (Table 2, entries 3 and 4). Results show that an electron-donating group ($-OCH_3$) decreased both the yield and the rate of the reaction (47%, 23 h), while an electron-withdrawing group ($-CF_3$) accelerated the reaction substantially and also led to an excellent chemical yield (91%, 0.5 h). The enantioselectivity obtained in these two reactions decreased by about 10% in each case (slightly higher with $-CF_3$ compared to $-OCH_3$), likely due to a steric effect. These results imply that the level of selectivity obtained is a combination of both steric and electronic effects.

Because of the strong electron-withdrawing effect and the minimal steric effect of fluorine, two fluorine-substituted benzophenone Schiff base acetates **1h**,**i** were synthesized next, using the recently published procedure

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(27) The configuration of product **2c** (R = tBu) was determined by the following procedure: 213 mg of sample (0.5 mmol, 85% ee) was treated with ether (2 mL) and 1 N HCl (2 mL) at ambient temperature for 3 h. The acid layer was separated and washed thoroughly with ether to remove benzophenone. Then, 12 N aqueous HCl (2 mL) was added (overall concentration ~6 N). The reaction mixture was heated at 85 °C for 20 h. Solvent was evaporated, and the product was dried under vacuum (0.5 mmHg, 65 °C for 10 h). The resulting aspartic acid hydrochloride (87 mg, 100%) was used directly in the optical rotation determination: $[\alpha]^{25}_D$ +21.0° (*c* = 1, 5 N HCl, S). An authentic sample of (*S*)-aspartic acid purchased from Aldrich gave $[\alpha]^{25}_D$ +24.6° (*c* = 1, 5 N HCl).

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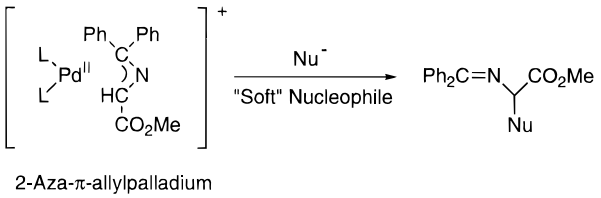
Scheme 2. Reaction of a (2-Aza-π-allyl)palladium Complex with Nucleophiles



2-Aza-π-allylpalladium

of Selva.[29] The enantioselective coupling reaction with sodium dimethyl malonate was then carried out (Table 2, entries 5 and 6). While the better electron-withdrawing *m*-fluoro-substituted substrate gave a faster rate, the enantioselectivity was slightly lower than that with the *p*-fluoro-substituted derivative.

From the above results, it is concluded that the steric effect of the substituents on the Schiff base moiety is the main factor contributing to decreased enantioselectivity. Electron-withdrawing groups increase the rate of the reaction considerably and lead to better yields. However, the enantioselectivity is not influenced greatly by electronic effects. The unsubstituted benzophenone imine still gives the best level of enantioselectivity (85% ee), while the *p*-trifluoromethyl-substituted benzophenone imine results in the fastest reaction and highest chemical yield (0.5 h, 91%).

Because of the cost and availability of precursors (benzophenone, benzophenone imine, and $Ph_2C{=}NCH_2CO_2tBu$ are all commercially available), glycine cation equivalents derived from the benzophenone imine of glycine *tert*-butyl ester are used for the majority of the following studies.

Bases, Counterions, and Additives. Substrate **1c** was coupled with malonate anion under standard conditions with different bases or additives in order to study the selectivity dependence on the nature of the nucleophile and the effect of the counterion on the rate and chemical yield of the reaction (Table 3).

The rate doubles when the reaction is run in an ultrasonic bath (Table 3, entry 2). Similarly, use of a catalytic amount of 15-crown-5 (10%)[30] doubles the rate of the reaction (entry 3). No improvement in enantioselectivity was observed with either of these modifications. Tetraalkylammonium malonate has been reported[31] to exist as a dimer in solution, which presumably increases the size and reactivity (selectivity) of the nucleophile in certain cases.[32] However, it did not have a substantial effect on either the reactivity or the selectivity in the present system (entry 4). These findings imply that the breakup of ion pairs and aggregation does facilitate the nucleophilic attack, but it does not affect the structure of the transition state during the bond-forming step, which is essential to the enantiodifferentiation.

A dramatic effect of the nature of the alkali metal counterion on the reaction rate and yield was discovered by substitution of Na by K or Li. With the counterion potassium,[33] the reaction was completed in 1 h and the high enantioselectivity was maintained (Table 3, entry 5). Use of a catalytic amount of 18-crown-6 in conjunction with KOtBu further increased both the rate and the yield of the reaction (Table 3, entry 6). On the other hand, an extremely slow reaction was observed with lithium (Table 3, entry 7), and the % ee also decreased. The use of BSA with a catalytic amount of KOAc[17k] was found to also decrease both the rate and the % ee of the reaction (Table 3, entry 8).

The above results showed that a rapid reaction can be obtained by using a large alkali metal cation (K^+) with the appropriate complexing agent (18-crown-6).

Substrate Structural Modification: The Leaving Group. The general palladium-catalyzed allylic substitution reaction has been proposed to involve several key steps: (1) initial complexation, (2) oxidative addition and loss of anionic leaving group (i.e., acetate), (3) isomerization, and (4) alkylation.[4c]

The 2-aza-π-allyl system is one of a class of π-allyls[34,35] that can react through diastereomeric π-allyl intermediates, where the chirality of the π-allyl is caused by the different groups on the termini of the allyl system. Since one allyl terminus has identical groups (phenyls), $\pi{-}\sigma{-}\pi$ epimerization can occur. This is synthetically significant because it provides the opportunity for using racemic starting material (e.g., **1** or **5**) to produce chiral, nonracemic product **2**.

To determine if the stereodiscriminating step occurs in the first two steps and to probe if the $\pi{-}\sigma{-}\pi$ epimerization is important in our 2-azaallyl system,[34] it is necessary to study the effect of the leaving group on the enantioselectivity. Attempts to make the Schiff base tosylate, mesylate, and trifluoroacetate failed because it was not possible to isolate and use these very reactive species. However, success was achieved in the synthesis of the Schiff base glycine *tert*-butyl ester benzoates **5**. Thus, our recently developed reduction of the α-keto Schiff base ester **4**[36] using Super-Hydride[15c] followed by quenching with the aroyl halide gave three benzoates with different substituents at the *para* position (Scheme 4).

It is interesting to note that substrates **5a** and **5b** gave the same enantioselectivity as that obtained from the corresponding acetate (Table 2, entry 1: 10 h, 74%, 85% ee). The rate of the reaction generally increased with the benzoate compared to the acetate due to the better leaving group ability of the former. This modification provides the possibility of "tuning" the reactivity of these glycine electrophiles. Substrate **5c** was very unstable and could not be isolated in pure form. It decomposed

(29) Selva, M.; Tundo, P.; Marques, C. A. *Synth. Commun.* **1995**, *25*, 369.

(30) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493.

(31) For the structure of tetrabutylammonium salts in solution, see: (a) Reetz, M. T.; Hutte, S.; Goddard, R. *J. Am. Chem. Soc.* **1993**, *115*, 9339. (b) Reetz, M. T.; Hütte, S.; Goddard, R.; Minet, U. *Chem. Commun.* **1995**, 275.

(32) For the effect of the nature of the ion-pair on rate and enantioselectivity of the reaction, see: (a) Ellington, J. C., Jr.; Arnett, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 7778. (b) Trost, B, M.; Bunt, R. C. *Tetrahedron Lett.* **1993**, *34*, 7513. (c) Trost, B. M.; Bunt R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089 and cited references.

(33) For the use of $KCH(COOCH_3)_2$ as a nucleophile in palladium-catalyzed reaction, see: RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3642 and references cited therein.

(34) (a) Bosnich, B.; Mackenzie, P. B. *Pure Appl. Chem.* **1982**, *54*, 189. (b) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033. (c) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046. (d) Farrar, D. H.; Payne, N. C. *J. Am. Chem. Soc.* **1985**, *107*, 2054.

(35) For examples of all-carbon allyl systems involving $\pi{-}\sigma{-}\pi$ epimerization of palladium complexes, see: (a) Reference 34. (b) Reference 4a. (c) Reference 30. (d) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1995**, *36*, 461. (e) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2535. (f) Bower, J. F.; Williams, J. M. J. *Synlett* **1996**, 685. (g) Reference 1k.

(36) O'Donnell, M. J.; Arasappan, A.; Hornback, W. J.; Huffman, J. C. *Tetrahedron Lett.* **1990**, *31*, 157.

Scheme 3. Preparation of ASA Derivatives by Pd Catalysis

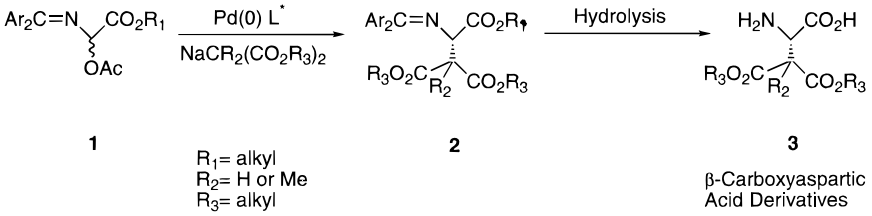
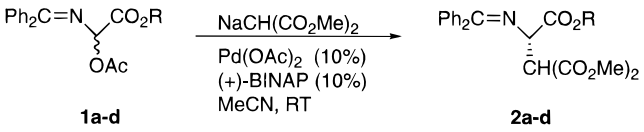


Table 1. Effects of Ester Protecting Group

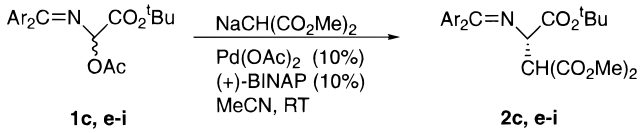


1a-d **2a-d**

entry	substrate (R)	product (% yield[a])	% ee[b]
1	**1a** (−Me)	**2a** (78)	27
2	**1b** (−iPr)	**2b** (59)	69
3	**1c** (−tBu)	**2c** (74)	85
4	**1d** (−CEt_3)	**2d** (71)	78

[a] Yields obtained after flash chromatography. [b] % ee was determined by chiral HPLC using a Chiralcel OD column.

Table 2. Effects of Imine Protecting Groups



1c, e-i **2c, e-i**

entry	substrate (Ar)	time (h)	product (% yield[a])	% ee[b]
1	**1c** (Ph)	10	**2c** (74)	85[c]
2	**1e** (3,5-diMePh)	35	**2e** (38)	58
3	**1f** (4-MeOPh)	23	**2f** (47)	73
4	**1g** (4-CF_3-Ph)	0.5	**2g** (91)	77
5	**1h** (4-FPh)	6	**2h** (79)	82
6	**1i** (3-FPh)	1.5	**2i** (86)	77

[a] Yields were obtained after flash chromatography. [b] % ee was determined by chiral HPLC using Chiralcel OD column. [c] This reaction was also reported in Table 1.

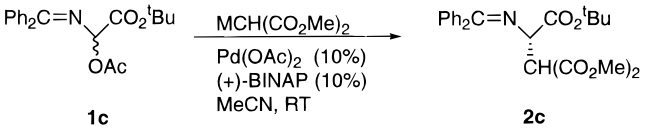
to benzophenone readily during the catalytic reaction, and only ~10% product was observed by TLC.

The optically active Schiff base acetate (**1c**, 51% ee, absolute configuration unknown) was prepared by reduction of **4** with NB-Enantride followed by quenching with acetic anhydride. Reaction of this optically enriched electrophile under conditions identical to those used for the racemic acetate **1c** (Table 2, entry 1) resulted in a result (11 h, 71% yield, 85% ee) identical to that obtained from racemic acetate (10 h, 74% yield, 85% ee). This important finding implies that the chirality of the substrate is completely lost at some point in the catalytic cycle before the formation of final product. The most likely racemization mechanism is $\pi-\sigma-\pi$ epimerization at the α-carbon of the azaallyl.[34] Another possibility is a metal-exchange reaction that occurs via the coordination of a Pd(0)−BINAP "nucleophile" to the exo-face of [*pro-R*-Pd(BINAP)(η^3-azaallyl)]$^+$. This produces the opposite chirality *pro-S*-Pd(II)−BINAP-azaallyl complex, displacing the previously bound metal as Pd(0)−BINAP.[37]

Steric Factors in the Nucleophile and Temperature Effects. The study was continued by employing various malonate types of nucleophiles in combination

(37) Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858.

Table 3. Effects of Different Bases, Counterions, and Additives



1c **2c**

entry	M	base and additives used	time (h)	% yield[i]	% ee[j]
1	Na	NaH[a]	10	74	85[b]
2	Na	NaH[a,c]	4.5	82	85
3	Na	NaH + 15-crown-5[a,d]	5	84	85
4	$(C_8H_{17})_4N$	NaH + $(C_8H_{17})_4NBr$[e]	9	72	84
5	K	KOtBu[f]	1	90	83
6	K	KOtBu + 18-crown-6[f,g]	0.6	92	77
7	Li	BuLi[f]	70	32	64
8	K	KOAc + BSA[h]	47	60	72

[a] 1.8 equiv of base was added to 3.0 equiv of dimethylmalonate. [b] This reaction also reported in Table 1. [c] The reaction was run in an ultrasonic bath at a constant temperature of 28 °C. [d] 10% of 15-crown-5 was added to the reaction. [e] Stoichiometric amounts of NaH and $(C_8H_{17})_4NBr$ added to 3.0 equiv of dimethyl malonate. [f] 2.0 equiv of base was added to 3.0 equiv of dimethyl malonate. [g] 10% 18-crown-6 was added to the reaction. [h] 10% KOAc added to stoichiometric amount of BSA + 3.0 equiv of dimethyl malonate. [i] Yields obtained after flash chromatoghaphy. [j] % ee was determined by chiral HPLC using a Chiralcel OD column.

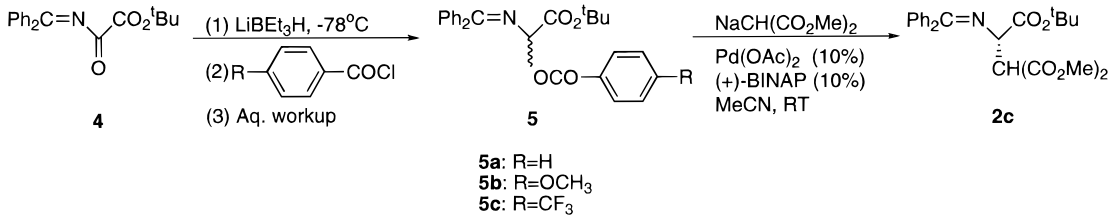
with methyl or *tert*-butyl ester Schiff base acetates **1a** and **1c** to study dependence of the enantioselectivity on the nucleophile (Table 4).

Surprisingly, the structure of the nucleophile has a considerable effect on the enantioselectivity in this 2-aza-π-allyl system, in contrast to the findings of Bosnich with the related all-carbon system (Ph_2C=CHCH(OAc)Ph). In the latter case, optical yields were insensitive to the nature of the nucleophiles used.[34b] In the case of methyl ester Schiff base acetate **1a**, the enantioselectivity increased (27% to 40% and 62%) with increasing size of the ester in the nucleophiles (Table 4, entries 1−3). However, with the corresponding *tert*-butyl ester **1c**, the % ee decreased considerably (85% ee to 50% ee) with the more sterically demanding nucleophile (Table 4, entries 7 and 8). These results demonstrate that the nucleophile participates in the enantiodifferentiating step and a high level of selectivity can be achieved by a judicious choice of the nucleophile and the substrate.

Temperature control experiments (Table 4, entries 3−6 and 9−12) showed that the optical yields were sensitive to temperature employed[38] and that the highest % ee was obtained at 0 °C.[25] It has been suggested by Sharpless[38c] that such temperature-dependent enantioselectivities

(38) For the effect of temperature on selectivity in transition-metal-catalyzed reactions, see: (a) Muchow, G.; Vannoorenberghe, Y.; Buono, G. *Tetrahedron Lett.* **1987**, *28*, 6163. (b) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477. (c) Göbel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1329. (d) Markó, I. E., Chesney, A.; Hollinshead, D. M. *Tetrahedron: Asymmetry* **1994**, *5*, 569. (e) Brunne, J.; Hoffmann, N.; Scharf, H.-D. *Tetradehron* **1994**, *50*, 6819 and references cited therein.

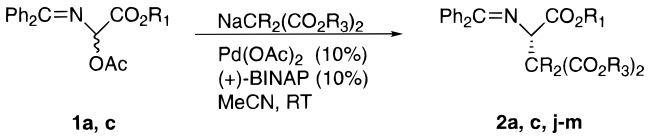
Scheme 4. Preparation and Utilization of Schiff Base Benzoates



5a: R=H
5b: R=OCH_3
5c: R=CF_3

SM	Time (h)	% Yield	ee %
5a	2	73	84
5b	4	89	84

Table 4. Effects of Nucleophiles and Temperature



entry	substrate (R_1)	nucleophile $NaCR_2(COOR_3)_2$	*T* (°C)	time (h)	product (% yield[a])	% ee
1	**1a** (Me)	$NaCH(COOMe)_2$	25	4	**2a** (78)	27[b,c]
2	**1a** (Me)	$NaCH(COOtBu)_2$	25	2	**2j** (52)	40[b]
3	**1a** (Me)	$NaCMe(COOMe)_2$	25	1	**2k** (55)	62[d]
4	**1a** (Me)	$NaCMe(COOMe)_2$	0	2.5	**2k** (56)	68[d]
5	**1a** (Me)	$NaCMe(COOMe)_2$	−10	2.5	**2k** (66)	59[d]
6	**1a** (Me)	$NaCMe(COOMe)_2$	−40	3	**2k** (69)	50[d]
7	**1c** (tBu)	$NaCH(COOMe)_2$	25	10	**2c** (74)	85[b,c]
8	**1c** (tBu)	$NaCH(COOtBu)_2$	25	5	**2l** (83)	50[b]
9	**1c** (tBu)	$NaCMe(COOMe)_2$	25	3	**2m** (69)	80[b]
10	**1c** (tBu)	$NaCMe(COOMe)_2$	0	7	**2m** (77)	86[b]
11	**1c** (tBu)	$NaCMe(COOMe)_2$	−10	10	**2m** (72)	85[b]
12	**1c** (tBu)	$NaCMe(COOMe)_2$	−40	11	**2m** (20)	84[b]

[a] All yields were obtained after flash chromatography. [b] % ee was determined by chiral HPLC using a chiral OD column. [c] This reaction was also reported in Table 1. [d] % ee was determined by NMR using $Eu(hfc)_3$ as shift reagent.

imply that the reaction pathway may contain at least two enantioselective steps and that each step contributes differentially at different temperatures.

Attempts at Isolation of η^3-(Azaallyl)palladium Intermediates. In order to rationalize the results obtained from the catalytic reactions, efforts were made to isolate intermediates that would account for the high levels of selectivity. In particular, we focused on rational approaches to the synthesis and characterization of stable η^3-(azaallyl)palladium complexes. First, actual catalyst solutions were examined by ^{31}P NMR spectroscopy. A solution containing stoichiometric amounts of $Pd(OAc)_2$, (*R*)-(+)-BINAP, and substrate **1c** in CH_3CN revealed no signals of AB or AX quartets expected of a diastereomeric substrate−catalyst η^3-complex. Only signals corresponding to the known complexes $Pd(OAc)_2$−(+)-BINAP and Pd[(+)-BINAP]$_2$ were observed.[39] Upon addition of malonate nucleophile, these signals diminished and gave a complex spectrum that defies interpretation. We conclude that any η^3-(azaallyl) intermediates must be present at very low concentration and that equilibrium favors starting materials.

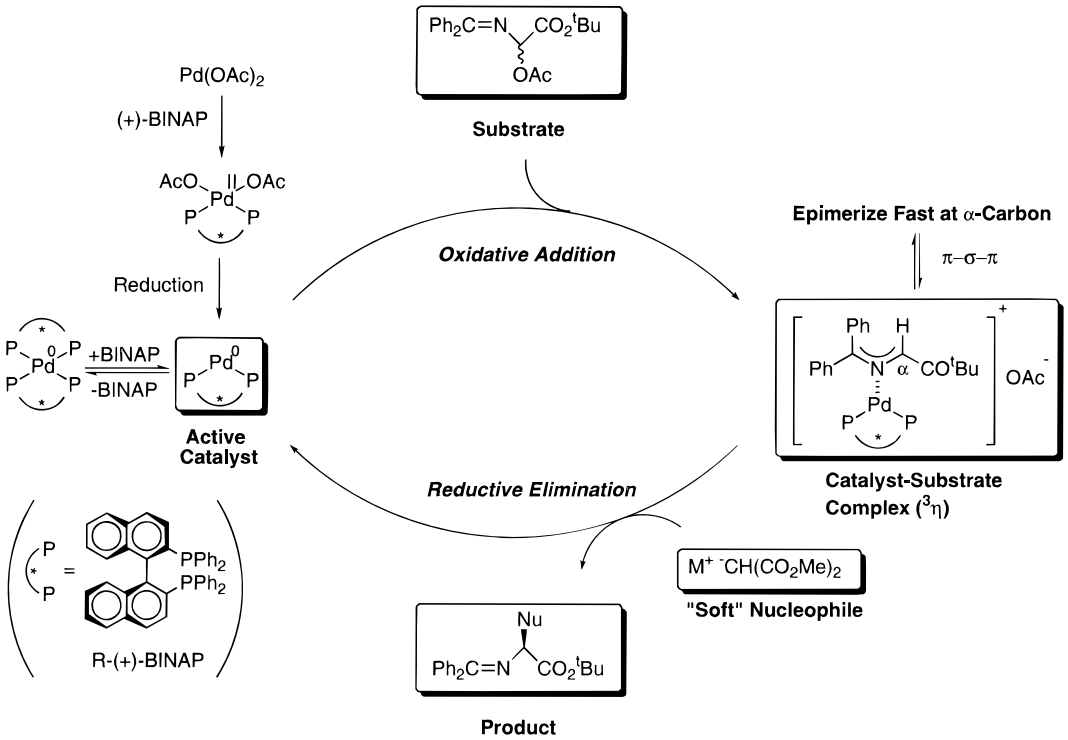
Second, precedented procedures for the synthesis of palladium η^3-allyl complexes from organopalladium precursors and allyl acetate were attempted using *tert*-butyl(acetyloxy)[(diphenylmethylene)amino] acetate (**1c**). Trogler has reported that UV photolysis of (dppe)Pd(C_2O_4) leads to decarboxylation and the formation of the highly reactive 14 e, Pd(0) intermediate Pd(dppe).[40] In a control experiment, we photolyzed (dppe)Pd(C_2O_4) in the presence of allyl acetate and observed by $^{31}P\{^1H\}$ NMR a singlet at 52.2 ppm that corresponds to [Pd(η^3-C_3H_5)(dppe)]$^+$.[40] Some side reactions that give rise to weaker $^{31}P\{^1H\}$ signals at 57.6 and 61.3 ppm were also observed. These side products also result from irradiation of (dppe)Pd(C_2O_4) without substrate. Irradiation of (dppe)Pd(C_2O_4) in the presence of substrate **1c** resulted only in $^{31}P\{^1H\}$ signals of these side products. However, isolated residues from these photolyses produce a plasma desorption mass spectrum (PDMS) signal at *m/e* 798, consistent with an azaallylpalladium dppe cation.

In the control reaction of (dppb)Pd(C_2O_4) with allyl acetate, an intense $^{31}P\{^1H\}$ signal at 21.1 ppm is observed that corresponds to [Pd(η^3-C_3H_5)(dppb)]$^+$. Some side reactions that give rise to weaker $^{31}P\{^1H\}$ signals at 30.7 and 30.8 ppm were also observed. As in the dppe case, these side products also result from irradiation of (dppb)-Pd(C_2O_4) without substrate. Irradiation of (dppb)Pd-(C_2O_4) in the presence of substrate **1c** resulted only in $^{31}P\{^1H\}$ signals of these side products. Crude residues from these photolyses produce a PDMS signal at *m/e* 826, which is consistent with an (aza−allyl)palladium−dppb complex. We conclude that under the photolysis conditions Pd(diphosphine) reactive intermediates do not

(39) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.

(40) Paonessa, R. S.; Prignano, A. L.; Trogler, W. C. *Organometallics* **1985**, *4*, 647.

Scheme 5. Proposed Model for the Palladium Catalysis



react with substrate **1c** at rates that are competitive with side reactions known to occur in the absence of any substrate.

The complex (η^3-allyl)(η^5-cyclopentadienyl)palladium(II) is a convenient precursor to Pd(0) organometallic complexes. The reaction of (η^3-allyl)(η^5-cyclopentadienyl)-palladium(II) with allyl acetate at room temperature in the presence of dppe or dppb led to the clean conversion to [Pd(η^3-C_3H_5)(dppe)][OAc][40] and [Pd(η^3-C_3H_5)(dppb)]-[OAc],[41] respectively. Reaction of (η^3-allyl)(η^5-cyclopentadienyl)palladium(II) with substrate **1c** in the presence of dppe and one of the noncoordinating anions PF_6^- or BPh_4^- led to the prompt appearance of an AX quartet in the $^{31}P\{^1H\}$ spectrum. However, this intermediate was too unstable to be isolated as a solid. In a similar vein, $Pd(PCy_3)_2$ is a two-coordinate 14-electron palladium(0) complex. A consequence of the bulky tricylcohexylphosphine ligands is that reactivity of the PdL_2 species is lower than that of Pd(dppe) or Pd(dppb). $Pd(PCy_3)_2$ is an isolable complex that is sufficiently stable to be stored in a drybox for months. In the control reaction of Pd-$(PCy_3)_2$ with allyl acetate only the monophosphine complex, [Pd(η^3-C_3H_5)(OAc)(PCy_3)], is obtained due to the steric demands of the PCy_3 ligand.[42] Normally, [Pd(η^3-C_3H_5)Cl]$_2$ reacts with dppe or other phosphines to give bis-phosphine complexes, [Pd(η^3-C_3H_5)L_2]$^+$.[34c] The reaction of [Pd(η^3-C_3H_5)Cl]$_2$ with PCy_3 leads to the initial formation of [Pd(η^3-C_3H_5)Cl(PCy_3)].[42] $AgPF_6$ in the presence of excess PCy_3 is required to convert [Pd(η^3-C_3H_5)-Cl(PCy_3)] to [Pd(η^3-C_3H_5)(PCy_3)$_2$][PF_6].[43] The attempted oxidative addition reaction of **1c** to $Pd(PCy_3)_2$ in the presence of NH_4PF_6 or other noncoordinating anions such as BPh_4^- gave clean AX multiplet $^{31}P\{^1H\}$ spectra. This asymmetric complex could not be isolated as a solid.

We conclude that η^3-(azaallyl)palladium complexes are likely intermediates in the oxidative addition reaction of substrate **1c** to palladium(0)−phosphine complexes. These η^3-(azaallyl)palladium−phosphine complexes appear to be quite unstable and have consistently eluded our best attempts at isolation. The often mutually exclusive relationship between stable intermediates and active catalyst systems has complicated many detailed mechanistic studies in the field of homogeneous catalysis.[44,45]

Mechanistic Model. A number of different aspects of selectivity need to be considered in this reaction. In terms of chemoselectivity, the reaction occurs at the Pd-coordinated cationic π-allyl system rather than the isolated ester group. The regioselectivity also strongly favors reaction of the malonate at the α-carbon rather than the γ-carbon or the enolate oxygen of the ester. Similar high levels of chemo- and regioselectivity have been observed with the related anionic glycine equivalents [($Ph_2C{=}NCHCO_2tBu$)$^-$].[9] The lack of reaction at the γ-carbon likely results from the considerable steric effect of the two phenyl groups at this position.

Several important conclusions can be drawn from the experiments reported in this paper concerning the stereochemical outcome of the reaction: (1) the ester protecting group on the substrate affects the % ee significantly (a relatively large group is preferred); (2) steric bulk on the diphenylketimino group decreases the % ee; (3) various leaving groups do not affect the enantioselectivity; (4) the optically active Schiff base acetate (51% ee) gives the same % ee as that obtained with the racemic acetate; and (5) the nature of the nucleophile has a considerable effect on the enantioselectivity.

A working mechanistic model is presented in Scheme 5 for the palladium-catalyzed reaction of malonate anion with the Schiff base acetate **1c**. Initially, $Pd(OAc)_2$ is complexed with BINAP to give a $Pd(OAc)_2$−BINAP

(41) Kumobayashi, H.; Mitsuhashi, S.; Akutagawa, S.; Ohtsuka, S. *Chem. Lett.* **1986**, 157.
(42) Yamamoto, T.; Saito, O; Yamamoto, A. *J. Am. Chem. Soc.* **1981**, *103*, 5600.
(43) Carturan, G.; Biasiolo, M.; Daniele, S.; Mazzocchin, G. A.; Ugo, P. *Inorg. Chim. Acta* **1986**, *119*, 19.
(44) Halpern, J. *Science* **1982**, *217*, 401.
(45) Alcock, N. W.; Brown, J. M.; Derome, A. E.; Lucy, A. R. *Chem. Commun.* **1985**, 575.

complex. This is then reduced to generate the active catalyst, Pd(0)−BINAP.[39,46] With the introduction of substrate **1c**, a cationic palladium−BINAP-η^3-azaallyl substrate complex is formed by nucleophilic displacement of acetate by Pd(0). The η^3-azaallyl species, once formed, is present in low concentration. Finally, nucleophilic attack by malonate anion on the cationic allylic complex produces, by reductive elimination, the product and regenerates the active catalyst.

This mechanism is similar to that proposed by Bosnich and co-workers for their [Pd((*S*,*S*)-chiraphos)(η^3-allyl)]$^+$ catalyst system.[34] The kinetic situation, however, appears to be quite different. Bosnich found that Pd(0)−(*S*,*S*)-chiraphos reacts in high yield with a variety of substituted allyl acetates to produce stable [Pd((*S*,*S*)-chiraphos)(η^3-allyl)]$^+$ complexes that were carefully studied. The oxidative addition of *racemic*-1,1,3-trisubstituted allyl acetates to Pd(0)-(*S*,*S*)-chiraphos produces two diastereomeric [Pd((*S*,*S*)-chiraphos)(η^3-((*R*)-, or (*S*)-allyl)]$^+$ complexes in ratios that track the final enantioselectivity of the catalyzed nucleophilic substitution by malonate anion. Thus, the primary enantioselectivity of the Bosnich system arose from the thermodynamic stability of the two diastereomeric [Pd((*S*,*S*)-chiraphos)(η^3-((*R*)-, or (*S*)-allyl)]$^+$ complexes, coupled with the nucleophilic attack of the malonate nucleophile on these diastereomers. The rate-determining step in the Bosnich system is the attack of the nucleophile on the diastereomeric [Pd((*S*,*S*)-chiraphos)(η^3-((*R*)-, or (*S*)-allyl)]$^+$ complex.

The current Pd(BINAP)/**1c** system is quite different. Here, the rate-determining step is the initial oxidative addition of substrate **1c** to the Pd(0)−BINAP catalyst. The fact that we do not see any appreciable amounts of the [Pd(BINAP)(η^3-azaallyl)]$^+$ complex in solution implies that it is not very stable and that nucleophilic attack to give either product or starting substrate is at least as fast or, most likely, faster (*vide infra*) than the oxidative addition of substrate to the Pd(0)−BINAP species. Otherwise, we would have observed the buildup of diastereomeric [Pd(BINAP)(η^3-azaallyl)]$^+$ complexes as seen with [Pd((*S*,*S*)-chiraphos)(η^3-allyl)]$^+$.

The instability of the [Pd(BINAP)(η^3-azaallyl)]$^+$ complex is probably mainly electronic in origin and involves the difference between allyl and azaallyl ligands. The anionic azaallyl ligand with an electron-withdrawing central nitrogen atom and ester group will not be as good a donor ligand to the cationic electron-deficient Pd(II)−BINAP complex after oxidative addition of the starting azaalkene acetate substrate to the Pd(0)−BINAP. The poorer Pd−azaallyl bonding changes the thermodynamics to make the [Pd(BINAP)(η^3-azaallyl)]$^+$ complex unstable enough to favor the starting Pd(0) complex.

On the other hand, the electron-withdrawing groups on **1c** should enhance the kinetics of the nucleophillic attack of the Pd(0)−BINAP complex at the α-carbon site. Similarly, when the [Pd(BINAP)(η^3-azaallyl)]$^+$ complex is formed there will be an increased shift of electron density away from the γ- and especially the α-carbon allyl donor atoms by the electron-withdrawing ester group, nitrogen atom, and cationic Pd^{2+} center. This should significantly enhance the electrophilicity and reactivity of the α-allyl carbon atom with respect to nucleophillic attack by malonate (or acetate) anions.

(46) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009.

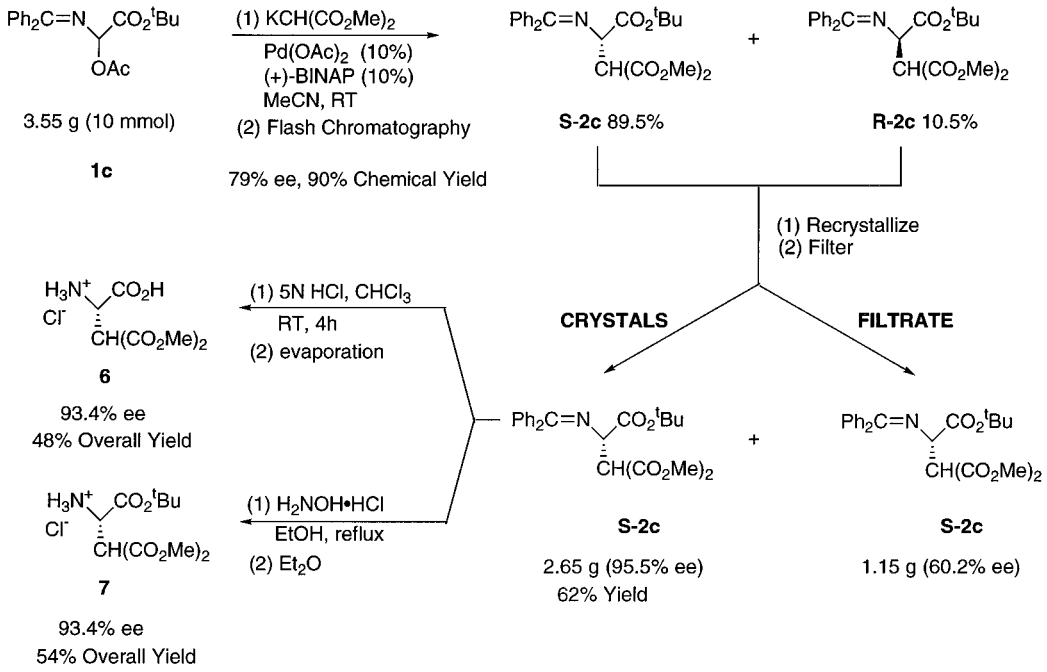
The net prediction from this electronic analysis is that the rate of the nucleophilic attack step is likely to be considerably faster than that seen in the Bosnich system. The experimental results appear to support this proposition. Under proper conditions, we observe the conversion of 10 equiv of **1c** in as little as 1 h (entry 5, Table 3; average rate 10 turnovers/h), while in the Bosnich system at least 5 h was needed to convert 200 equiv of substrate (average rate 40 turnovers/h). We know from our ^{31}P NMR studies that the amount of [Pd(BINAP)(η^3-azaallyl)]$^+$ complex present in solution is less than 2%, while in the Bosnich system the [Pd((*S*,*S*)-chiraphos)(η^3-allyl)]$^+$ concentration is nearly 100%. Taking into account the amount of Pd(II) complex present in each system during the nucleophilic step (100% vs <2%), the rate constant for this step in our system could be at least 12 times faster (a factor of 0.25 for the rate-determining step, and another factor of 50 for concentration) than that seen with the Bosnich [Pd((*S*,*S*)-chiraphos)(η^3-allyl)]$^+$ catalyst.

It was demonstrated that the Bosnich catalyst had time to allow sufficient $\pi-\sigma-\pi$ epimerization to produce Curtin−Hammett conditions, under which the enantioselectivity only depends on the difference in free energy of the two diastereomeric transition states during nucleophillic attack. There is every indication that the $\pi-\sigma-\pi$ epimerization rate in this system is considerably faster than the rate-determining step, indicating that we are also working under Curtin−Hammett conditions.

One final experiment demonstrates how much faster the current catalyst system is relative to the Bosnich [Pd((*S*,*S*)-chiraphos)(η^3-allyl)]$^+$ system. We examined the possibility that the observed product enantioselectivity could be lowered by side reactions with the excess base present. Reaction product **2c** was purified to 96.8% ee and used as starting material for this experiment. The reaction of (*S*)-**2c** (1.0 equiv, 96.8% ee) with $Pd(OAc)_2$ (0.1 equiv), (*R*)-(+)-BINAP (0.1 equiv), NaH (1.8 equiv), and dimethylmalonate (3.0 equiv) in acetonitrile at room temperature produced product [(*S*)-**2c**] of 85.4% ee as quickly as the reaction could be mixed and analyzed. The enantioselectivity of the product in the reaction mixture then stayed constant over the course of the reaction (85.2% ee at 28 h). This experiment reveals a number of interesting features about the catalytic reaction: (1) the product can very readily back-react with the catalyst to reenter the catalytic cycle; (2) the excess base does not participate in any deprotonation/racemization reactions with the free product; and (3) the $\pi-\sigma-\pi$ epimerization to produce Curtin−Hammett conditions is very fast. Finally, the conversion of 96.8% ee product **2c** within a few minutes to 85.4% ee product indicates that the rate of catalysis is also very fast (but not faster than the rate of epimerization), in agreement with the previous discussion.

Selective Deprotection and Scale-Up Reaction To Prepare Enantiomerically Enriched Product. The ultimate goal of asymmetric synthesis is to obtain optically pure products in high chemical yield and short reaction times. General methods to increase the enantioselectivity are necessary even though the reaction has already produced high levels of optical yields. Since the products of our coupling reaction are often crystalline, it was found that the % ee of products can often be increased by recrystallization. Scheme 6 illustrates the sequence used in the laboratory-scale preparation of

Scheme 6. Laboratory-Scale Reaction To Produce Enantiomerically Enriched Products



highly optically enriched product (*S*)-**2c** (95.5% ee) and selective deprotection to produce optically active ASA derivative **6** and **7**. Schiff base *tert*-butyl acetate **1c** (3.55 g, 10 mmol) was coupled with potassium dimethyl malonate using $Pd(OAc)_2$−(+)-BINAP to generate product (*S*)-**2c** (79% ee, 90% yield). A single recrystallization gave enriched (*S*)-**2c** (95.5% ee, 62% yield). The crystals were selectively hydrolyzed to 1,1-dimethyl 2-amino-2-carboxy-(*S*)-1,1-ethanedicarboxylate hydrochloride (**6**) (93.4% ee, 48% overall yield) or to the 2-*tert*-butyl 1,1-dimethyl 2-amino-(*S*)-1,1,2-ethanetricarboxylate hydrochoride (**7**) (93.4% ee, 54% overall yield).

Conclusions

In summary, a systematic study of substrate, nucleophile, additives, and reaction conditions has led to a simple, highly stereoselective synthesis of β-carboxyaspartic acid derivatives using palladium catalysis. The optical purity of the products can be increased by recrystallization. Studies on the identification of the reaction intermediate and use of other potential nucleophiles are currently underway.

Experimental Section

General Methods. All reactions using palladium catalysis were performed under argon or nitrogen using standard Schlenk line and drybox techniques. CH_3CN and CH_2Cl_2 were distilled from CaH_2. Benzene was degassed and dried over molecular sieves. THF and ether were distilled from sodium benzophenone ketyl. All chemicals were commercially available and reagent grade unless otherwise specified. The ligands (*R*)-BINAP((*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), tricyclohexylphosphine, dppe (1,2-bis(diphenylphosphino)-ethane), and dppb (1,2-bis(diphenylphosphino)butane) were purchased from Strem Chemical, Inc. Allyl acetate and allyl chloride were purchased from Aldrich Chemical Co. The diphosphinepalladium(II) oxalate complexes,[47] (η^3-allyl)(η^5-cyclopentadienyl)palladium(II),[48] and bis(tricyclohexylphosphine)palladium(0)[49] were prepared according to published procedures.

HPLC analyses of product samples were performed using a Chiralcel OD column (5 μm, 4.6 × 250 mm) and, unless otherwise noted, 100:1 hexane/iPrOH (v/v) as mobile phase at a flow rate of 1.0 mL/min and UV detection at 254 nm.

General Procedure for the Preparation of Starting Material. For the individual alkyl (acetyloxy)[(substituted diphenylmethylene)amino]acetate **1**, the corresponding alkyl *N*-(substituted diphenylmethylene)glycinate was first prepared[20] and then oxidized according to the published procedure:[15c]

Isopropyl (acetyloxy)[(diphenylmethylene)amino]-acetate (1b): yield 37%; white crystals; mp 92.5−93.5 °C; IR (KBr) 1738, 1629, 1241, 1103, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (dd, 6H, J = 3.0, 3.0 Hz), 2.17 (s, 3H), 5.05 (dq, 1H, J = 6.0 Hz), 6.13 (s, 1H), 7.30−7.69 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.6, 69.9, 84.4, 127.9, 128.1, 128.4, 129.2, 129.3, 131.3, 135.5, 138.6, 166.3, 169.9, 174.3. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.99; H, 6.26; N, 4.19.

1,1-Diethylpropyl (acetyloxy)[(diphenylmethylene)-amino]acetate (1d): yield 35%; colorless oil; IR (neat) 1745, 1625, 1237, 1134, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (t, 9H, J = 7.5 Hz), 1.82 (dq, 6H, J = 6.0 Hz), 2.16 (s, 3H), 6.09 (s, 1H), 7.29−7.69 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 7.4, 20.9, 26.7, 84.5, 91.0, 127.8, 128.0, 128.2, 128.4, 129.1, 129.3, 131.1, 135.5, 138.7, 165.4, 169.7, 173.9; HRMS m/z (M^+) calcd 396.2175, found 396.2171.

***tert*-Butyl *N*-[bis(3,5-dimethylphenyl)methylene]glycinate:** yield 85%; colorless oil; IR (neat) 1742, 1626, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.28 (s, 6H), 2.34 (s, 6H), 4.12 (s, 2H), 6.78 (s, 2H), 7.04 (d, 2H, J = 6.9 Hz), 7.29 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 21.1, 21.2, 28.0, 56.1, 80.7, 125.0, 126.4, 130.1, 131.9, 136.3, 137.3, 137.9, 139.4, 169.9, 172.4; HRMS m/z (M^+) calcd 352.2277, found 352.2259.

***tert*-Butyl (acetyloxy)[[bis(3,5-dimethylphenyl)methylene]amino]acetate (1e):** yield 38%; colorless oil; IR (neat) 1739, 1626, 1240, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.17 (s, 3H), 2.29 (s, 6H), 2.35 (s, 6H), 6.02 (s, 1H), 6.87 (s, 2H), 7.07 (s, 2H), 7.28 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.1, 21.3, 27.9, 82.6, 84.8, 125.4, 127.0, 130.6, 132.9, 135.7, 137.5, 137.8, 138.9, 165.9, 169.9, 174.7; HRMS m/z (M^+) calcd 410.2331, found 410.2335.

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***tert*-Butyl (acetyloxy)[[bis(4-methoxyphenyl)methylene]amino]acetate (1f):** yield 39%; colorless oil; IR (neat) 1739, 1616, 1250, 1155, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.16 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 6.05 (s, 1H), 6.84 (d, 2H, J = 8.7 Hz), 6.97 (d, 2H, J = 8.7 Hz), 7.24 (d, 2H, J = 8.7 Hz), 7.63 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 21.1, 27.9, 55.3, 82.7, 84.9, 113.3, 113.7, 127.8, 129.6, 131.2, 131.9, 160.0, 162.1, 166.1, 170.0, 173.5; HRMS m/z (M^+) calcd 414.1917, found 414.1905.

***tert*-Butyl (acetyloxy)[[bis[4-(trifluoromethyl)phenyl]methylene]amino]acetate (1g):** yield 59%; colorless oil; IR (neat) 1749, 1631, 1326, 1231, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.17 (s, 3H), 5.98 (s, 1H), 7.49 (d, 2H, J = 8.4 Hz), 7.62 (d, 2H, J = 8.4 Hz), 7.74−7.79 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 20.9, 27.8, 83.6, 84.2, 125.2, 125.3, 125.5, 125.6, 125.7, 128.5 (2C), 129.4 (2C), 131.5, 132.0, 132.9, 133.3, 138.5, 141.1, 165.0, 169.8, 170.8; HRMS m/z (M^+) calcd 490.1453, found 490.1438.

***tert*-Butyl (acetyloxy)[[bis(4-fluorophenyl)methylene]amino]]acetate (1h):** yield 58%; colorless oil; IR (neat) 1755, 1629, 1235, 1153, 1051 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.17 (s, 3H), 5.99 (s, 1H), 7.03 (t, 2H, J = 8.7 Hz), 7.18 (t, 2H, J = 8.7 Hz), 7.29−7.34 (m, 2H), 7.63−7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.0, 27.8, 83.2, 84.4, 115.1, 115.4, 115.6, 115.8, 130.0 (2C), 131.1, 131.4, 131.5, 134.8 (2C), 161.4, 163.1, 164.7, 165.6, 166.5, 169.9, 171.7; HRMS m/z (M^+) calcd 390.1517, found 390.1525.

***tert*-Butyl (acetyloxy)[[bis(3-fluorophenyl)methylene]amino]acetate (1i):** yield 57%; colorless oil; IR (neat) 1755, 1629, 1235, 1159, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.17 (s, 3H), 6.00 (s, 1H), 7.08−7.50 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 21.0, 27.9, 83.4, 84.3, 115.2, 115.5 (2C), 115.8, 116.4, 116.7, 118.3, 118.6, 123.5, 125.2, 129.6, 129.7, 130.4, 130.5, 136.9, 137.0, 140.3, 140.4, 160.8, 161.0, 164.1, 164.3, 165.2, 169.9, 170.9; HRMS m/z (M^+) calcd 390.1517, found 390.1525.

Preparation of Optically Active Schiff Base Acetate: *tert*-Butyl (Acetyloxy)[(diphenylmethylene)amino]acetate (1c). A solution of NB-Enantride (0.5 M, 24 mL, 12 mmol) was added dropwise to a solution of freshly prepared **4**[36] (3.09 g, 10 mmol) in THF (20 mL) over 10 min at −78 °C. The mixture was stirred at −78 °C for 30 min. Acetic anhydride (1.53 g, 15 mmol) was added, and the mixture was stirred for 30 min at −78 °C and then at ambient temperature for 5 h. The solvent was evaporated, and the residue was dissolved in methylene chloride (50 mL). The organic phase was washed with saturated $NaHCO_3$ (2 × 30 mL), dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (hexane:EtOAc = 12:1) to give **2c** (918 mg, 26%) as a colorless oil. The purified product, an oil, was analyzed by chiral HPLC (column: Chiral BakerBond; hexane:iPrOH = 600:1): 51% ee [34.6 min, 35.6 min]. Recrystallization from ether/hexane gave white crystals: mp 105−106 °C; IR (KBr) 1740, 1625, 1232, 1153, 1059 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.20 (s, 3H), 6.10 (s, 1H), 7.30−7.70 (m, 10 H); ^{13}C-NMR ($CDCl_3$) δ 21.0, 27.8, 82.8, 84.6, 127.9, 128.0, 128.3, 129.1, 129.3, 131.2, 135.6, 138.8, 165.7, 169.8, 173.9. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.41; H, 6.48; N, 3.99.

General Procedure for the Preparation of Schiff Base Benzoates: *tert*-Butyl (Benzoyloxy)[(diphenylmethylene)amino]acetate (5a). A solution of Super Hydride (1.0 M, 12 mL, 12 mmol) was added dropwise to a solution of freshly prepared **4**[36] (3.09 g, 10 mmol) in THF (20 mL) over 10 min at −78 °C. The mixture was stirred at −78 °C for 30 min. Benzoyl chloride (2.11 g, 15 mmol) was added dropwise, and the mixture was stirred for 30 min at −78 °C and then at ambient temperature for 2 h. The solvent was evaporated, and the residue was dissolved in methylene chloride (50 mL). The organic phase was washed with saturated $NaHCO_3$ (2 × 30 mL), dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (hexane:EtOAc = 10:1) to give **5a** (1.953 g, 47%) as a colorless oil: IR (neat) 1727, 1622, 1269, 1108, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 6.30 (s, 1H), 7.33−7.49 (m, 10H), 7.71 (d, 2H, J = 7.2 Hz), 8.14 (d, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 27.9, 82.8, 84.9, 128.0 (2C), 128.3, 128.4, 129.1, 129.3, 129.6, 130.0, 131.1, 133.2, 135.7, 138.9, 165.4, 165.8, 174.0; HRMS m/z (M^+) calcd 416.1862, found 416.1870.

***tert*-Butyl [(4-methoxybenzoyl)oxy][(diphenylmethylene)amino]acetate (5b):** yield 2.54 g, 57%; colorless oil; IR (neat) 1720, 1624, 1264, 1102, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 3.86 (s, 3H), 6.26 (s, 1H), 6.92 (d, 2H, J = 8.7 Hz), 7.34−7.71 (m, 10H), 8.09 (d, 2H, J = 8.7 Hz); ^{13}C NMR (CDCl3) δ 27.9, 55.4, 82.8, 84.7, 113.5, 122.0, 128.0 (2C), 128.4, 129.2, 129.4, 131.1, 132.1, 135.7, 138.9, 163.6, 165.1, 166.0, 173.9; HRMS m/z (M^+) calcd 446.1967, found 446.1959.

***tert*-Butyl [[4-(trifluoromethyl)benzoyl]oxy][(diphenylmethylene)amino]acetate (5c):** light-yellow oil as crude product, decomposed on column; IR (neat) 1731, 1625, 1325, 1271, 1101, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9H), 6.31 (s, 1H), 7.32−7.71 (m, 12H), 8.25 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 27.9, 83.2, 85.3, 125.3−138.8 (m), 164.2, 165.5, 174.4; HRMS m/z (M^+) calcd 484.1736, found 484.1741.

General Procedure for the Asymmetric Coupling Reaction Using Pd Catalysis: 2-*tert*-Butyl 1,1-Dimethyl 2-[(Diphenylmethylene)amino]-(*S*)-1,1,2-ethanetricarboxylate (2c). Palladium acetate (45 mg, 0.2 mmol) and (+)-BINAP (125 mg, 0.2 mmol) were added to a three-necked round-bottom flask (flask A, 50 mL) equipped with a gas bubbler, magnetic stirring bar, and rubber septum. NaH (60%, 144 mg, 3.6 mmol) was added to a similar flask (flask B, 25 mL). Flasks A and B were both connected to a vacuum line, allowed to deoxygenate under reduced pressure, and then flushed with argon using a manifold. This operation was repeated three times. Acetonitrile (5 mL) was added to flask A in one portion, and the mixture was stirred for 5 min at ambient temperature. Then, *tert*-butyl (acetyloxy)[(diphenylmethylene)amino]acetate (**1c**) (706 mg, 2 mmol) in acetonitrile (5 mL) was introduced by syringe to the flask A, and the reaction mixture was stirred for an additional 5 min. At the same time, dimethyl malonate (792 mg, 6 mmol) in acetonitrile (5 mL) was added to flask B. After bubbling (H_2) had ceased, the light-gray solution in flask B was transferred dropwise by syringe to flask A. The entire mixture was then stirred at ambient temperature for 10 h until TLC (EtOAc:hexane = 1:4) showed complete disappearance of starting material. The reaction mixture was quenched with H_2O (50 mL, added in one portion), and then EtOAc (70 mL) was added. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a red oil as the crude product. This product was purified by flash chromatography (hexane:EtOAc = 8:1) to yield 2-*tert*-butyl 1,1-dimethyl 2-[(diphenylmethylene)amino]-1,1,2-ethanetricarboxylate (**2c**) (629 mg, 74%) as a colorless oil, which solidified on standing. The purified product (oil) was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 100:1): 85% ee [10.15 min (*R*), 20.52 min (*S*)]. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 98−98.5 °C; IR (KBr) 1752, 1623, 1262, 1148, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 3.69 (s, 3H), 3.70 (s, 3H), 4.32 (d, 1H, J = 8.4 Hz), 4.67 (d, 1H, J = 8.4 Hz), 7.28−7.59 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 27.8, 52.5, 55.1, 65.2, 82.1, 127.9, 128.1, 128.2, 128.8, 129.0, 130.4, 135.7, 139.5, 167.6, 167.7, 168.3, 172.6. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.95; H, 6.45; N, 3.24.

2-Isopropyl 1,1-Dimethyl 2-[(Diphenylmethylene)amino]-(*S*)-1,1,2-ethanetricarboxylate (2b). Following the general procedure for the asymmetric coupling reaction using palladium catalysis gave **2b**: 481 mg, 59% yield. The purified product (oil) was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 100:1): 69% ee [13.04 min (*R*), 18.85 min (*S*)]. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 83.5−84.2 °C; IR (KBr) 1755, 1625, 1288, 1149, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 6H, J = 6.6 Hz), 3.69 (s, 3H), 3.70 (s, 3H), 4.37 (d, 1H, J = 8.4 Hz), 4.75 (d, 1H, J = 8.4 Hz), 5.02 (dq, 1H, J = 6.3 Hz), 7.28−7.59 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.6, 52.5, 55.0, 64.6, 69.3, 128.0, 128.2, 128.3, 128.8, 129.0, 130.5, 135.7, 139.5, 167.6, 167.7, 168.8, 173.0. Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 66.95; H, 6.07; N, 3.38.

2-(1′,1′-Diethylpropyl)-1,1-dimethyl 2-[(diphenylmethylene)amino]-(*S*)-1,1,2-ethanetricarboxylate (2d). Following the general procedure for the asymmetric coupling

reaction using palladium catalysis gave **2d**: 661 mg, 71% yield. The purified product (oil) was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 100:1): 78% ee [7.55 min (*R*), 10.21 min (*S*)]. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 78.0−79.0 °C; IR (KBr) 1751, 1617, 1277, 1154, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (t, 9H, J = 7.5 Hz), 1.81 (dq, 6H, J = 7.2 Hz), 3.67 (s, 3H), 3.69 (s, 3H), 4.36 (d, 1H, J = 8.7 Hz), 4.75 (d, 1H, J = 8.4 Hz), 7.27−7.56 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 7.4, 26.6, 52.5, 54.9, 65.2, 90.5, 127.9, 128.1, 128.3, 128.8, 129.0, 130.4, 135.6, 139.5, 167.7, 168.0, 172.4. Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.41; H, 7.05; N, 3.01.

2-*tert*-Butyl 1,1-Dimethyl 2-[[Bis(3,5-dimethylphenyl)-methylene]amino]-(*S*)-1,1,2-ethanetricarboxylate (2e). Following the general procedure for the asymmetric coupling reaction using palladium catalysis gave **2e**: 312 mg, 38% yield. The purified product (oil) was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 100:1): 58% ee [7.24 min (*R*), 10.36 min (*S*)]. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 109−109.5 °C; IR (KBr) 1738, 1621, 1258, 1152 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.27 (s, 6H), 2.35 (s, 6H), 3.68 (s, 3H), 3.71 (s, 3H), 4.29 (d, 1H, J = 8.7 Hz), 4.65 (d, 1H, J = 8.7 Hz), 6.86 (s, 2H), 7.04 (d, 2H, J = 10.8 Hz), 7.17 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 21.4, 27.9, 52.4 (2C), 55.2, 65.2, 81.9, 125.8, 126.8, 130.3, 132.1, 136.0, 137.3, 137.5, 139.9, 167.6, 167.8, 168.6, 173.4. Anal. Calcd for $C_{28}H_{35}NO_6$: C, 69.83; H, 7.33; N, 2.91. Found: C, 69.66; H, 7.54; N, 2.88.

2-*tert*-Butyl 1,1-Dimethyl 2-[[Bis(4-methoxyphenyl)-methylene]amino]-(*S*)-1,1,2-ethanetricarboxylate (2f). Following the general procedure for the asymmetric coupling reaction using palladium catalysis gave **2f**: 453 mg, 47% yield (colorless oil). The purified product was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 97:3): 73% ee [12.09 min (*R*), 22.49 min (*S*)]: IR (neat) 1739, 1619, 1251, 1153, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 3.67 (s, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 3.87 (s, 3H), 4.29 (d, 1H, J = 8.7 Hz), 4.68 (d, 1H, J = 8.7 Hz), 6.81 (d, 2H, J = 8.7 Hz), 6.97 (d, 2H, J = 8.7 Hz), 7.24 (d, 2H, J = 8.7 Hz), 7.52 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 27.8, 52.5 (2C), 55.1, 55.2 (2C), 65.1, 81.8, 113.2, 113.4, 128.2, 129.8, 130.6, 132.9, 159.8, 161.5, 167.6, 167.7, 167.9, 168.6; HRMS m/z (M^+) calcd 486.2128, found 486.2123.

2-*tert*-Butyl 1,1-Dimethyl 2-[[Bis[4-(trifluoromethyl)-phenyl]methylene]amino]-(*S*)-1,1,2-ethanetricarboxylate (2g). Following the general procedure for the asymmetric coupling reaction using palladium catalysis gave **2g**: 1021 mg, 91% yield. The purified product (oil) was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 100:1): 77% ee [6.97 min (*R*), 9.36 min (*S*)]. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 101−101.5 °C; IR (KBr) 1742, 1626, 1317, 1265, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 3.72 (s, 3H), 3.73 (s, 3H), 4.35 (d, 1H, J = 8.4 Hz), 4.58 (d, 1H, J = 8.4 Hz), 7.48 (d, 2H, J = 8.7 Hz), 7.58 (d, 2H, J = 8.4 Hz), 7.66 (d, 2H, J = 8.4 Hz), 7.77 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 27.8, 52.6 (2C), 54.8, 65.4, 82.8, 125.1, 125.2, 125.4, 125.5, 125.6, 128.8 (2C), 129.1 (2C), 131.2, 131.6, 132.3, 132.7, 138.7, 141.9, 167.5 (2C), 167.6, 169.9. Anal. Calcd for $C_{26}H_{25}F_6NO_6$: C, 55.62; H, 4.49; N, 2.49; F, 20.30. Found: C, 55.75; H, 4.56; N, 2.48; F, 20.34.

2-*tert*-Butyl 1,1-Dimethyl 2-[[Bis(4-fluorophenyl)methylene]amino]-(*S*)-1,1,2-ethanetricarboxylate (2h). Following the general procedure for the asymmetric coupling reaction using palladium catalysis gave **2h**: 724 mg, 79% yield. The purified product (oil) was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 100:1): 82% ee [10.04 min (*R*), 19.71 min (*S*)]. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 134−135 °C; IR (KBr) 1736, 1624, 1242, 1222, 1152 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 3.69 (s, 3H), 3.72 (s, 3H), 4.30 (d, 1H, J = 8.1 Hz), 4.60 (d, 1H, J = 8.1 Hz), 6.99 (t, 2H, J = 8.7 Hz), 7.16 (t, 2H, J = 8.7 Hz), 7.29−7.33 (m, 2H), 7.53−7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.8, 52.5 (2C), 54.9, 65.1, 82.4, 114.9, 115.2, 115.3, 115.6, 130.2, 130.3, 131.0, 131.1, 131.3, 131.4, 135.6 (2C), 161.3, 162.7, 164.5, 166.0, 167.7 (2C), 168.1, 170.5. Anal. Calcd for $C_{24}H_{25}F_2NO_6$: C, 62.47; H, 5.46; N, 3.04; F, 8.23. Found: C, 62.61; H, 5.48; N, 3.06; F, 8.40.

2-*tert*-Butyl 1,1-Dimethyl 2-[[Bis(3-fluorophenyl)methylene]amino]-(*S*)-1,1,2-ethanetricarboxylate (2i). Following the general procedure for the asymmetric coupling reaction using palladium catalysis gave **2i**: 790 mg (colorless oil), 86% yield. The purified product was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 100:1): 77% ee [9.60 min (*R*), 12.77 min (*S*)]: IR (neat) 1739, 1627, 1271, 1253, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 3.71 (s, 3H), 3.73 (s, 3H), 4.32 (d, 1H, J = 8.1 Hz), 4.61 (d, 1H, J = 8.1 Hz), 7.05−7.50 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 27.8, 52.5 (2C), 54.8, 65.2, 82.5, 115.1, 115.3, 115.4, 115.6, 116.0, 116.3, 117.5, 117.8, 123.9, 124.8, 129.5, 129.6, 130.1, 130.2, 137.1, 137.2, 141.0, 141.1, 160.8, 160.9, 164.1, 164.2, 167.5, 167.6, 167.8, 169.8; HRMS m/z (M^+) calcd 462.1728, found 462.1728.

1,1-Di-*tert*-butyl 2-Methyl 2-[(Diphenylmethylene)-amino]-(*S*)-1,1,2-ethanetricarboxylate (2j). Following the general procedure for the asymmetric coupling reaction using palladium catalysis gave **2j**: 486 mg, 52%. The purified product (oil) was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 100:1): 40% ee [8.49 min (*R*), 10.12 min (*S*)]. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 103.5−104.5 °C; IR (KBr) 1740, 1625, 1278, 1136, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.42 (s, 9H), 3.71 (s, 3H), 4.13 (d, 1H, J = 9 Hz), 4.73 (d, 1H, J = 9 Hz), 7.28−7.61 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 27.9, 52.3, 57.3, 64.6, 81.6, 81.8, 127.9, 128.2, 128.4, 128.8, 129.1, 130.4, 135.6, 139.6, 166.6, 170.3, 172.5. Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.49; H, 6.96; N, 3.03.

Trimethyl 1-[(Diphenylmethylene)amino]-(*S*)-1,2,2-propanetricarboxylate (2k). Following the general procedure for the asymmetric coupling reaction using palladium catalysis gave **2k**: 437 mg, 55% yield. The purified product (oil) was analyzed by NMR using $Eu(hfc)_3$ as chiral shift reagent: 62% ee. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 125−125.5 °C; IR (KBr) 1752, 1629, 1258, 1105, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (s, 3H), 3.67 (s, 3H), 3.71 (s, 3H), 3.78 (s, 3H), 4.73 (s, 1H), 7.18−7.60 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 18.5, 52.4, 52.7, 52.8, 58.3, 68.7, 127.6, 128.0, 128.5, 128.9, 129.0, 130.7, 135.9, 139.3, 170.1, 170.4, 170.9, 172.7. Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.52; H, 5.88; N, 3.54.

Tris-*tert*-butyl 2-[(Diphenylmethylene)amino]-(*S*)-1,1,2-ethanetricarboxylate (2l). Following the general procedure for the asymmetric coupling reaction using palladium catalysis gave **2l**: 845 mg, 83% yield. The purified product (oil) was analyzed by chiral HPLC (column: Chiralcel OD; hexane: iPrOH = 97:3): 50% ee [9.16 min (*R*), 10.45 min (*S*)]. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 95−95.5 °C; IR (KBr) 1730, 1619, 1257, 1151, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.41 (s, 9H), 1.44 (s, 9H), 4.16 (d, 1H, J = 9 Hz), 4.61 (d, 1H, J = 9 Hz), 7.27−7.61 (m, 10H); ^{13}C NMR($CDCl_3$) δ 27.9, 57.1, 65.5, 81.4, 81.6, 81.7, 127.8, 128.0, 128.5, 128.7, 129.1, 130.2, 135.7, 139.9, 166.8, 166.9, 168.7, 172.0. Anal. Calcd for $C_{30}H_{39}NO_6$: C, 70.70; H, 7.71; N, 2.73. Found: C, 70.82; H, 7.64; N, 2.74.

1-*tert*-Butyl 2,2-Dimethyl 1-[(Diphenylmethylene)-amino]-(*S*)-1,2,2-propanetricarboxylate (2m). Following the general procedure for the asymmetric coupling reaction using palladium catalysis gave **2m**: 586 mg, 69% yield. The purified product (oil) was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 100:1): 80% ee [14.17 min (*S*), 18.26 min (*R*)]. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 98.5−99.5 °C; IR (KBr) 1740, 1627, 1242, 1151, 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.62 (s, 3H), 3.65 (s, 3H), 3.76 (s, 3H), 4.58 (s, 1H), 7.21−7.60 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 18.4, 27.8, 52.5, 58.3, 69.0, 81.9, 127.7, 127.9, 128.4, 128.7, 128.9, 130.4, 136.2, 139.4, 168.2, 170.4, 170.9, 171.9. Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.22; H, 6.55; N, 3.19.

Photochemical Reactions of *tert*-Butyl (Acetyloxy)-[(diphenylmethylene)amino]acetate with (Diphosphine)palladium(II) Oxalate (Diphosphine = dppb, dppe). To (diphosphine)Pd(C_2O_4) (0.01 mmol) in a quartz tube was added 3 mL of CH_3CN to form a suspension. *tert*-Butyl

(acetyloxy)[(diphenylmethylene)amino]acetate (35.3 mg, 0.1 mmol) in 1 mL of CH_3CN was then added dropwise into the tube. The mixture was irradiated ($\lambda = 254$ nm) at 5 °C with an Oriel 1000W Xe arc lamp for 30 min to give a yellow solution along with a trace of colloidal palladium. The solids were filtered from the solution, and the solvent was removed under vacuum, leaving a yellow solid. Similar reactions were done using only the phosphine complexes and no acetate. $^{31}P\{^1H\}$ (CD_3CN) for the dppe reactions was δ 57.2, 61.0, 66.8 (with or without substrate) and for the dppb reactions δ 30.3, 30.8 (with or without substrate).

Reaction of (η^3-Allyl)(η^5-cyclopentadienyl)palladium(II) with dppe and Allyl Acetate. A benzene solution of dppe (39.8 mg, 0.1 mmol) and allyl acetate (20 mg, 0.2 mmol) mixture was added to a benzene solution of (η^3-allyl)(η^5-cyclopentadienyl)palladium(II) (21.0 mg, 0.1 mmol). After addition, the solution was stirred at ambient temperature for 10 h and dried under vacuum. $^{31}P\{^1H\}$ (CD_3CN) δ 52.2 (s). Similar reaction using dppb instead of dppe gave $^{31}P\{^1H\}$ (CD_3CN) δ 20.9 (s). Reaction using *tert*-butyl (acetyloxy)-[(diphenylmethylene)amino]acetate instead of allyl acetate together with 2 equiv of $NaBPh_4$ in CH_3CN resulted in an AX quartet: $^{31}P\{^1H\}$ (CD_3CN) NMR δ 38.90, 47.79 ($J_{AX} = 7.3$ Hz).

Reaction of *tert*-Butyl (Acetyloxy)[(diphenylmethylene)amino]acetate with Bis(tricyclohexylphosphine)-palladium(0). *tert*-Butyl (acetyloxy)[(diphenylmethylene)-amino]acetate (53.0 mg, 0.15 mmol) and NH_4PF_6 (33 mg, 0.2 mmol) in 3 mL of CH_3CN was added dropwise to a benzene solution of $Pd(PCy_3)_2$ (66.6 mg, 0.10 mmol). The orange solution was stirred overnight at room temperature. Solvents were removed under vacuum, leaving an orange solid: $^{31}P\{^1H\}$ (CD_3CN) AX quartet, δ 34.17, 42.50 ($J_{AX} = 21.8$ Hz), and PF_6^- septet, δ −143.7.

Product Racemization Study. Palladium acetate (8 mg, 0.036 mmol), (*R*)-(+)-BINAP (23 mg, 0.036 mmol), and 2-*tert*-butyl 1,1-dimethyl 2-[(diphenylmethylene)amino]-(*S*)-1,1,2-ethanetricarboxylate (**2c**) (153 mg, 0.36 mmol, 96.8% ee) were added to a three-necked round-bottom flask (flask A, 50 mL) equipped with a gas bubbler, magnetic stirring bar and rubber septum. NaH (60%, 26 mg, 0.648 mmol) was added to a similar flask (flask B, 25 mL). Flasks A and B were both connected to a vacuum line, allowed to deoxygenate under reduced pressure, and then flushed with argon using a manifold. This operation was repeated three times. Acetonitrile (1 mL) was added to flask A in one portion, and the mixture was stirred for 5 min at ambient temperature. At the same time, dimethyl malonate (143 mg, 1.08 mmol) in acetonitrile (1.25 mL) was added to flask B. After bubbling (H_2) had ceased, the light-gray solution in flask B was transferred dropwise by syringe to flask A. A sample (0.1 mL) was taken from the reaction mixture at the indicated time intervals, filtered through cotton, and diluted with 5 mL of mixed solvent (hexane and isopropyl alcohol), and then the solution was injected onto the chiral HPLC column. HPLC results: 0 min (immediately following above mixing), 85.5% ee; 20 min, 85.4% ee; 40 min, 85.5% ee; 1 h, 85.6% ee; 1.5 h, 85.8% ee; 3 h, 86.0% ee; 5 h, 86.0% ee.

After 5 h, half of the reaction mixture from above was transferred to a second flask. To the first flask, an amount of catalyst and ligand equivalent to that initially used was added: palladium acetate (8 mg, 0.036 mmol) and (*R*)-(+)-BINAP (23 mg, 0.036 mmol). To the second flask, an amount of base (substrate anion) equivalent to that initially used was added: base made from NaH (60%, 26 mg, 0.648 mmol) and dimethyl malonate (143 mg, 1.08 mmol) in acetonitrile (1.25 mL). Samples (0.1 mL) were taken from the two reaction mixtures at the indicated time intervals, filtered through cotton, and diluted with 5 mL of mixed solvent (hexane and isopropyl alcohol), and then the solutions were injected onto the chiral HPLC column. HPLC results: (a) with extra catalyst: 6 h, 86.3% ee; 28 h, 85.2% ee; with extra base: 6 h, 85.8% ee; 28 h, 87.2% ee.

Laboratory-Scale Preparation of 2-*tert*-Butyl 1,1-Dimethyl 2-[(Diphenylmethylene)amino]-(*S*)-1,1,2-ethanetricarboxylate (2c) and the Selective Deprotection to Optically Active ASA Derivatives. Palladium acetate (229 mg, 1 mmol) and (+)-BINAP (635 mg, 1 mmol) were added to a three-necked round-bottom flask (flask A, 100 mL) equipped with a gas bubbler, magnetic stirring bar, and rubber septum. Dimethyl malonate (3.964 g, 30 mmol) was added to a similar flask (flask B, 50 mL). Flasks A and B were both connected to a vacuum line, allowed to deoxygenate under reduced pressure, and then flushed with argon using a manifold. This operation was repeated three times. Acetonitrile (25 mL) was added to flask A in one portion, and the mixture was stirred for 10 min at ambient temperature. Then, *tert*-butyl (acetyloxy)[(diphenylmethylene)amino]acetate (**1c**) (3.53 g, 10 mmol) in acetonitrile (25 mL) was introduced by syringe to the flask A, and the reaction mixture was stirred for an additional 10 min. At the same time, KOtBu (20 mL, 1.0 M solution in THF) was added to flask B. After bubbling (H_2) had ceased, flask B with the white milky solution was connected to an oil pump to remove all the THF. Acetonitrile (25 mL) was then added to flask B. The resulting white milky solution was transferred to flask A by syringe. The entire mixture was then stirred at ambient temperature for 1 h until TLC (EtOAc:hexane = 1:4) showed complete disappearance of starting material. The reaction mixture was quenched with H_2O (100 mL, added in one portion), and then EtOAc (150 mL) was added. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a red oil as the crude product. This product was purified by flash chromatography (hexane: EtOAc = 8:1) to yield 2-*tert*-butyl 1,1-dimethyl 2-[(diphenylmethylene)amino]-1,1,2-ethanetricarboxylate (**2c**) (3.83 g, 90%) as a colorless oil, which solidified on standing. The purified product (oil) was analyzed by chiral HPLC (column: Chiralcel OD; hexane:iPrOH = 100:1): 79% ee [10.15 min (*R*), 20.52 min (*S*)]. All of the purified product was transferred to a 500 mL round-bottom flask, and mixed solvent (hexane:iPrOH=100:1, 450 mL) was added. The mixture was stirred until a homogenous solution was obtained. The flask was then kept in a freezer at −10 °C for 24 h. After recrystallization was complete, the white needle-like crystals were separated from the filtrate, washed with a small amount of hexane (20 mL), and dried on a vacuum line. A yield of 62% (2.65 g) was obtained with an optical purity of 95.5% ee (*S*). The filtrate was evaporated to dryness and found to be 60.2% ee (*S*, 1.15 g). An analytical sample (20 mg) of 99.8% ee (*S*) was obtained by recrystallization of the optically enriched product (79% ee, *S*) in a mixed solvent of hexane/iPrOH (100:1) at ambient temperature. The optical rotation was determined to be $[\alpha]^{25}_D$ −238.5° ($c = 1.3$, MeOH).

1,1-Dimethyl 2-Amino-2-carboxy-(*S*)-1,1-ethanedicarboxylate Hydrochloride (6). To a 50 mL round-bottom flask was added 2-*tert*-butyl 1,1-dimethyl 2-[(diphenylmethylene)-amino]-1,1,2-ethanetricarboxylate (**2c**) (2.65 g, 6.24 mmol, 95.5% ee, *S*), 5 N HCl (10 mL), and $CHCl_3$ (10 mL). The reaction mixture was stirred at ambient temperature for 4 h until TLC showed complete disappearance of starting material. The $CHCl_3$ layer was then removed, the aqueous layer was washed with $CHCl_3$ (3 × 20 mL) and separated, and the solvent was evaporated to give 1,1-dimethyl 2-amino-(*S*)-1,1,2-ethanetricarboxylate hydrochloride (1.16 g, 77%, overall 48% from acetate) as a white solid: IR (KBr) 3350−2340 (br), 1751, 1736, 1509, 1241 cm^{-1}; ^1H NMR (CD_3COOD) δ 3.82 (s, 3H), 3.84 (s, 3H), 4.54 (bs, 1H), 4.89 (bs, 1H); ^{13}C NMR (CD_3COOD) δ 52.9, 54.3 (2C), 167.8, 167.9, 169.8; MS (FAB, *m/z*) 206, 192, 160. The optical purity was determined by hydrolyzing a small sample (118 mg, 0.4 mmol) in 6 N HCl at 85 °C for 20 h. The solvent was evaporated to yield (*S*)-aspartic acid (66 mg, 97%), which was analyzed by chiral HPLC (column: CrownPack; perchloric acid solution, pH 1.5, 0 °C): 93.4% ee [6.42 min (*R*), 8.53 min (*S*)] and compared with a commercial sample of (S)-aspartic acid (Aldrich).

2-*tert*-Butyl 1,1-Dimethyl 2-Amino-(*S*)-1,1,2-ethanetricarboxylate Hydrochoride (7). To a 50 mL round-bottom flask was added 2-*tert*-butyl 1,1-dimethyl 2-[(diphenylmethylene)amino]-1,1,2-ethanetricarboxylate (**2c**) (2.65 g, 6.24 mmol, 95.5% ee, *S*), $NH_2OH{\cdot}HCl$ (402 mg, 6.24 mmol), and absolute ethanol (30 mL). The reaction mixture was refluxed for 2 h until TLC showed complete disappearance of starting material. Ethanol was then evaporated, and the crude product (white

solid) was washed with ether (3 × 20 mL), filtered, and dried to give 2-*tert*-butyl 1,1-dimethyl 2-amino-(*S*)-1,1,2-ethanetricarboxylate hydrochoride (1.59 g, 86%, overall 54% from acetate). Recrystallization from $EtOH/Et_2O$ gave white crystals: mp 128−128.5 °C; IR (KBr) 3300−2350 (br), 1759, 1741, 1509, 1220 cm^{-1}; ^1H NMR (CD_3OD) δ 1.50 (s, 9H), 3.81 (s, 3H), 3.83 (s, 3H), 4.29 (d, 1H, $J = 3.9$ Hz), 4.57 (d, 1H, $J = 3.9$ Hz); ^{13}C NMR (CD_3OD) δ 28.0, 52.9, 53.9 (2C), 86.3, 166.7, 167.6, 167.8; MS (FAB, *m*/*z*) 262, 206, 192, 160. The optical purity was determined by hydrolyzing a small sample (150 mg, 0.5 mmol) in 6 N HCl at 85 °C for 20 h. The solvent was evaporated to yield (*S*)-aspartic acid (84 mg, 98%), which was analyzed by chiral HPLC (column: CrownPack; perchloric acid solution, pH 1.5, 0 °C): 93.4% ee [6.49 min (*R*), 8.82 min (*S*)] and compared with a commercial sample of (*S*)-aspartic acid (Aldrich).

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