Dependence of the Reactivities of Titanium Enolates on How They Are Generated: Diastereoselective Coupling of Phenylacetic Acid Esters Using Titanium Tetrachloride

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Received December 13, 1995[⊗]

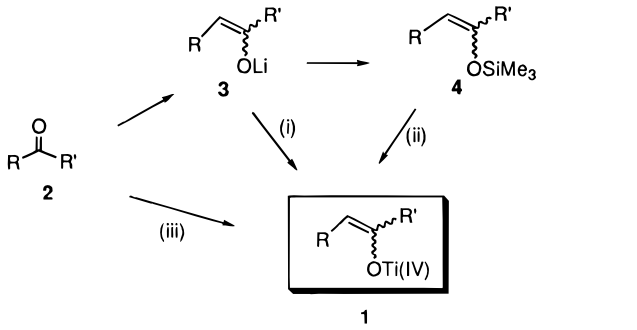
Oxidative coupling of phenylacetic acid esters was easily achieved by treating the esters with $TiCl_4$ and then adding Et_3N to the resulting solution. The products consisted of *dl*- and *meso*-2,3-diphenylsuccinic acid esters with the Claisen condensation product, and the ratio of these products depended on the reaction conditions. Reaction conditions suitable for high *dl* selectivity were determined, and a dimer of titanium enolate was postulated as an intermediate responsible for the high *dl* selectivity. The selectivities were compared with those in known oxidative couplings in which titanium enolate intermediates are prepared through lithium enolates and silyl enol ethers. The results suggest that the reactivities of titanium enolates intermediates depend on how they are generated.

Introduction

Titanium enolates **1**, which are useful intermediates for carbon−carbon bond formation,[1] can be generated from carbonyl compounds **2** by three methods (Scheme 1): (i) transmetalation of lithium enolates **3**, which can be prepared from **2**,[2] (ii) transmetalation of silyl enol ethers **4**, which can be prepared from **3**,[3] and (iii) direct generation from **2**, when **2** are enolizable amides and carbonyl compounds.[4] These three methods give formally identical titanium enolates **1**, but it is not yet clear if the reactivities of **1** depend on how they are generated. Since titanium enolates play important roles in organic synthesis, it is worthwhile to understand all aspects of their reactivities.

Although Ojima *et al*. recently showed that there might be a difference in regioselectivity between titanium enolates generated by methods i and ii,[2] there have been no previous comparisons of the reactivities of titanium enolates generated by these three methods. We identified an efficient homocoupling reaction of phenylacetic acid esters **5** by method iii, the results of which could be compared with those of methods i and ii.[5] Although a variety of methods for oxidative coupling of **5** have been exploited,[6] the stereoselectivity obtained by our new method is the highest among those reported thus far, and the procedure may be the simplest. This paper describes our results and also discusses the dependence of the reactivities of titanium enolates on how they are generated.

Scheme 1



Results and Discussion

The reaction via method iii has been identified as an oxidative homocoupling of methyl phenylacetate (**5a**).

[⊗] Abstract published in *Advance ACS Abstracts,* March 15, 1996.

(1) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: New York, 1986.

(2) Ojima, I.; Brandstadter, S. M.; Donovan, R. J. *Chem. Lett.* **1992**, 1591.

(3) (a) Inaba, S.; Ojima, I. *Tetrahedron Lett.* **1977**, 2009. (b) Hirai, K.; Ojima, I. *Tetrahedron Lett.* **1983**, *24*, 785. (c) Reetz, M. T.; Schwellnus, K.; Hübner, F.; Massa, W.; Schmidt, R. E. *Chem. Ber.* **1983**, *116*, 3708. (d) Totten, G. E.; Wenke, G.; Rhodes, Y. E. *Synth. Commun.* **1985**, *12*, 291.

(4) (a) Lehnert, W. *Tetrahedron Lett.* **1970**, 4723. (b) Harrison, C. R. *Tetrahedron Lett.* **1987**, *28*, 4135. (c) Brocchini, S. J.; Eberle, M.; Lawton, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 5211. (d) Evans, D. A.; Clark, J. S.; Matternich, Nopvack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. (e) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (f) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750. (g) Kise, N.; Tokioka, K.; Matsumura, Y. *J. Org. Chem.* **1995**, *60*, 1100. (h) Dikshit, K.; Bajpai, S. N. *Tetrahedron Lett.* **1995**, *36*, 3231.

(5) Although 4-isopropyl-3-(phenylacetyl)-2-oxazolidone was coupled by method iii, it gave a complex mixture of products by method i; see ref 4g.

(6) There are a variety of methods for the oxidative homocoupling of phenylacetic acid derivatives. (i) Through enolate anions: (a) Kofron, W. G.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 2085. (b) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605. (c) Tokuda, M.; Shigei, T.; Itoh, M. *Chem. Lett.* **1975**, 621. (ii) Through carboxylic dianions: (d) Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969. (e) Renaud, P. Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745. For the oxidative homocoupling of other esters: (f) Chung, S. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1983**, *48*, 1125. (g) Belletire, J. L.; Fremont, S. L. *Tetrahedron Lett.* **1986**, *27*, 127. (h) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1987**, *52*, 2549. (i) Porter, N. A.; Su, Q.; Harp, J. J.; Rosenstein, I. J.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 4457. (j) Langer, T.; Illich, M.; Helmchen, G. *Tetrahedron Lett.* **1995**, *36*, 4409.

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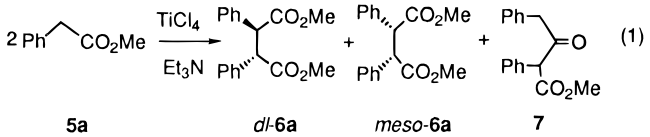


This reaction proceeds smoothly to give both stereoisomers of the dimer, *dl*-**6a** and *meso*-**6a**, with the Claisen condensation product **7**, and the ratios of these products depend on the reaction conditions. The results are summarized in Table 1.

The main features of this reaction are as follows. Although the absence of either $TiCl_4$ or Et_3N did not cause any oxidative coupling of **5a** (Table 1, entries 1 and 2), the use of both $TiCl_4$ and Et_3N[7] gave products consisting of a mixture of stereoisomers of dimer **6a** and the Claisen condensation product **7**. The ratio of these products depended on the order of the addition, the amounts of $TiCl_4$ and Et_3N, and the reaction temperature. The addition of more than 1 equiv of $TiCl_4$ to a solution of **5a** in CH_2Cl_2 followed by the addition of more than 1 equiv of Et_3N to the resulting solution (method A) at −45 °C exclusively gave *dl*-**6a** (Table 1, entries 4 and 5),[8] while the use of less than 1 equiv of $TiCl_4$ or Et_3N (Table 1, entry 3) resulted in the formation of **7** as a main product with a mixture of dimer **6a** in a *dl*/*meso* ratio which was lower than those observed under the conditions for entries 4 and 5 of Table 1. The *dl*/*meso* ratio of **6a** was also decreased by carrying out the reaction at 0 °C (Table 1, entry 6). Furthermore, reversing the order of addition of $TiCl_4$ and Et_3N (method B) decreased the *dl*/*meso* ratio of **6a** and increased the formation of **7**, even though more than 1 equiv of $TiCl_4$ and Et_3N was used (Table 1, entries 7 and 8).

The tentative reaction mechanism is shown in Scheme 2. The first step involves the formation of complex A which is composed of **5a** and $TiCl_4$ in a 1:1 ratio. The formation of A is supported by the fact that peaks of methyl and methylene hydrogens of **5a** in the NMR spectrum were shifted to a lower field by the addition of $TiCl_4$ to a solution of **5a** in $CDCl_3$[9] and plateaus were observed with the addition of 1 equiv of $TiCl_4$ (Figure 1). Upon reaction with an amine, complex A is converted to titanium enolate B or dimer C, in which two phenyl groups may be located opposite two titanium enolates in separate planes. Oxidation of C may lead to *dl*-**6a**, while homocoupling between monomer radical D generated from B or C may favor the formation of *meso*-**6a** rather than *dl*-**6a**, as recognized by the Newman projection E which shows two D's in close proximity. The exclusive formation of *dl*-**6a** under the conditions in entries 4 and 5 (Table 1) suggests that such reaction conditions promote the formation of C. Increasing the reaction temperature may enhance the rate of the transformation of B or C to D and may result in increased *meso*-**6a**.

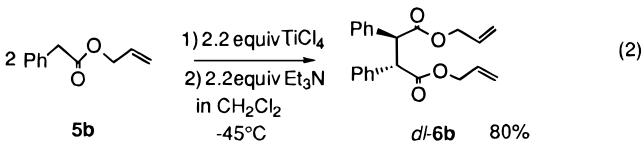
The absence of **5a** in the reaction system at the formation of B or C seems to be a key point in preventing the formation of **7**. If **5a** exists in the reaction system when B or C is formed, either of these as nucleophiles may attack **5a** to give **7**. The reaction conditions which use less than 1 equiv of $TiCl_4$ (Table 1, entry 3) and the reverse addition (method B) (Table 1, entries 7 and 8) might be such cases.

Table 1. Oxidative Coupling of Methyl Phenylacetate (5a) by Method iii[a]

				product **6a**		product **7**
entry	method[b]	molar ratio **5a**:$TiCl_4$:Et_3N	reaction temp (°C)	yield (%)	*dl*:*meso*	yield (%)
1		1:1.1:0	0 or −45	0		0[c]
2		1:0:1.1	0 or −45	0		0[d]
3	A	1:0.5:0.5	−45	18	75:25	50
4	A	1:1.1:1.1	−45	86	95:5	0
5	A	1:2.2:1.1	−45	83	99:1	0
6	A	1:2.2:1.1	0	73	85:15	0
7	B	1:1.1:1.1	−45	46	75:25	24
8	B	1:2.2:1.1	−45	20	80:20	50

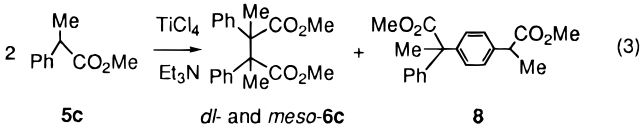
[a] The reaction was carried out for 1.5 h. [b] Method A: addition of $TiCl_4$ to **5a** followed by addition of Et_3N. Method B: addition of Et_3N to **5a** followed by addition of $TiCl_4$. [c] Recovery of starting compound was 93%. [d] Recovery of starting compound was 91%.

Under reaction conditions similar to those in entry 5, allyl phenylacetate (**5b**) gave the dimer *dl*-**6b** stereoselectively in 80% yield with no *meso* isomer, no condensation products, and no cyclized products (eq 2).



Using these data, we attempted to compare the selectivities of methods i, ii, and iii. However, the homocoupling of **5a** by method i has not been reported, and the stereoselectivity of the homocoupling of **5a** by method ii has not been described.[3a] Thus, we attempted the coupling of **5a** by method i and reexamined the reaction by method ii. The results with method iii are summarized in Table 2, which shows the advantage of method iii, with respect to product yields and diastereoselectivities, in comparison with methods i and ii.

We also compared these three methods in the homocoupling reaction of methyl α-methylphenylacetate (**5c**) (eq 3, Table 3). In this reaction, both stereo- and regio-



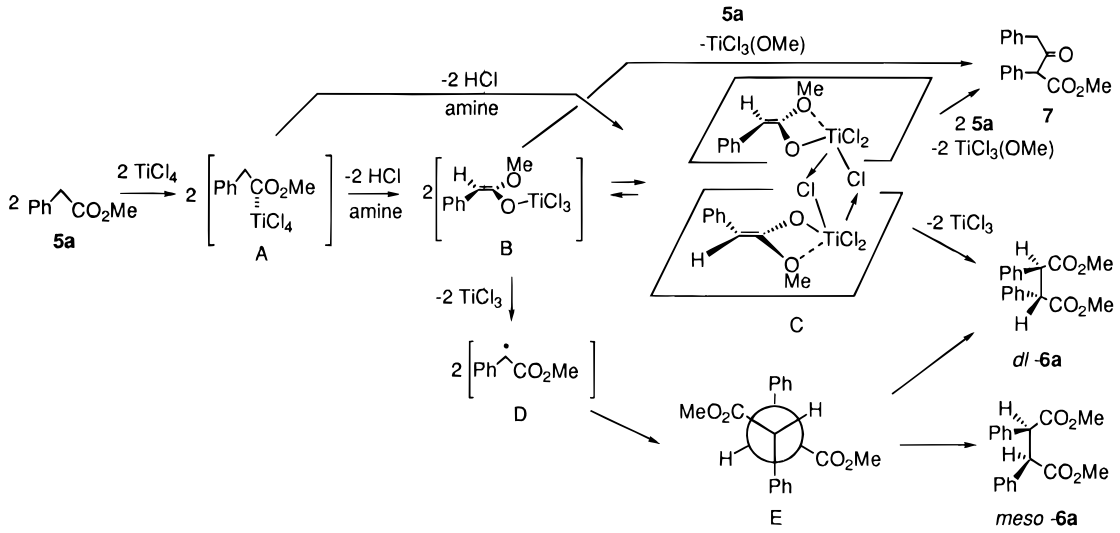
selectivities differed between the three methods. Thus, both a mixture of the stereoisomers of the homocoupling product **6c**[11] with a *dl*/*meso* ratio of ∼50/50 and the α,*p*-coupling product **8** were formed using methods i and ii, while method iii gave **6c** with a *dl*/*meso* ratio of 30/70 and no **8**. In the latter reaction, a dimeric intermediate similar to C may also play an important role.

Conclusion

This paper presents a simple and convenient procedure for the stereoselective homocoupling of phenylacetic acid esters to give *dl*-2,3-diphenylsuccinic acid esters. The *dl*-dimer was obtained with high stereoselectivity by treating phenylacetic acid esters with more than 1 equiv of $TiCl_4$ in CH_2Cl_2 and then adding Et_3N at low tempera-

(7) Diisopropylethylamine and spartein also gave similar results.
(8) The coupling also took place at −78 °C, but a longer reaction time was required (after 4.5 h, *dl*-**6a**/*meso*-**6a** = 95/5, 85% yield).
(9) Oxidative coupling of **5a** took place in $CHCl_3$.
(10) We obtained a yield of 27%, while a yield of 76% was described in ref 3a.
(11) de Luca, C.; Insei, A.; Rampazzo, L. *J. Chem. Soc., Perkin Trans. 2*, **1982**, 1403.
(12) The numbers in parentheses are in ref 2.

Scheme 2



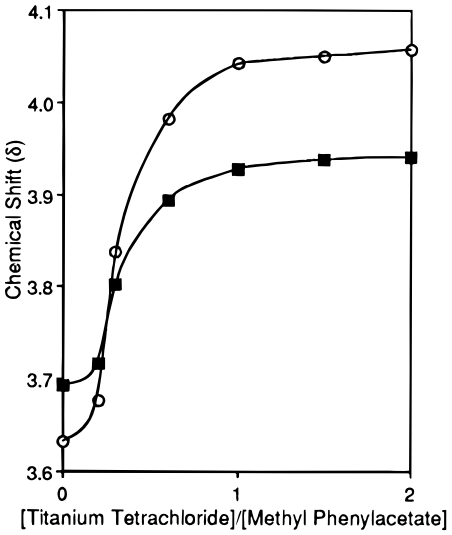


Figure 1. NMR chemical shifts of methyl phenylacetate (**5a**): (■) methyl group, (○) methylene group.

Table 2. TiCl4-Promoted Oxidative Coupling of 5a

method	yield (%) of **6a** (*dl* + *meso*)	*dl*-**6a**/*meso*-**6a**
i[a]	40	50/50
ii[b]	27 (76)[d]	63/37
iii[c]	83	99/1

[a] Successive addition of LDA (1.25 equiv) and $TiCl_4$ (1.25 equiv) to a solution of **5a** in THF at −78 °C. [b] Addition of LDA to **5a**, addition of TMSCl, followed by addition of $TiCl_4$ (1.1 equiv) at 0 °C. [c] Successive addition of $TiCl_4$ (2.2 equiv) and Et_3N (1.1 equiv) to a solution of **5a** in CH_2Cl_2 at −45 °C. [d] See ref 10.

ture. Furthermore, the results in this paper clearly show that the stereo- and regioselectivities in the homocoupling reactions depend on the method used to generate titanium enolates from phenylacetic acid esters. Although further studies on the reaction mechanism must be carried out, the high *dl* selectivity is tentatively explained in terms of the formation of a dimer of titanium enolates.

Experimental Section

General. All solvents were dried and distilled by standard techniques. Titanium tetrachloride, triethylamine, and methyl phenylacetate (**5a**) were obtained commercially. Allyl phenylacetate (**5b**)[13] was prepared by the reaction of phenylacetyl chloride with allyl alcohol in the presence of triethylamine in $CHCl_3$. Methyl α-methylphenylacetate (**5c**)[2] was prepared by esterification of commercially available phenylpropionic acid.

Table 3. $TiCl_4$-Promoted Oxidative Coupling of 5c

method	yield (%) of **6c**	*dl*-**6c**/*meso*-**6c**	yield (%) of **8**
i[a]	41 (63)[d]	51/49	22 (18)[d]
ii[b]	50	50/50	13
iii[c]	87	30/70	0

[a] Successive addition of LDA (1.0 equiv) and $TiCl_4$ (1.0 equiv) to a solution of **5c** in THF at −78 °C. [b] Addition of LDA to **5c**, addition of TMSCl, followed by addition of $TiCl_4$ (1.1 equiv) at 0 °C. [c] Successive addition of $TiCl_4$ (5.0 equiv) and Et_3N (5.0 equiv) to a solution of **5c** in CH_2Cl_2 at −45 °C. [d] See ref 12.

Selective Formation of *dl*-2,3-Diphenylsuccinic Acid Dimethyl Ester (*dl*-6a). To a solution of methyl phenylacetate (**5a**) (3 mmol, 0.45 g) in CH_2Cl_2 (10 mL) was added $TiCl_4$ (6.6 mmol, 0.72 mL) with a syringe at −45 °C, and the solution was stirred for 30 min. Triethylamine (6.6 mmol, 0.92 mL) was then added, and the solution was stirred at −45 °C for 1.5 h. The solution was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried on $MgSO_4$, and the solvent was evaporated *in vacuo* to give a white solid. The solid was subjected to column chromatography (Merck silica gel 60, 70−230 mesh) with hexane/AcOEt (5/1) to give pure *dl*-2,3-diphenylsuccinic acid dimethyl ester (*dl*-**6a**) in 83% yield. Under these reaction conditions, *meso*-**6a** was obtained in a trace amount, and the resulting Claisen condensation product **7** was negligible. Although *dl*-**6a** is a known compound, only its mp and elemental analysis data are described in the literature.[1] Spectroscopic data of the resulting *dl*-**6a** were as follows.

dl-**6a**: mp 163−164 °C (lit.[14] mp 165−166 °C); IR (KBr) 3030, 2990, 2950, 1730, 1435, 1305, 1250, 1155, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H), 4.25 (s, 1H), 6.95−7.08 (m, 2H), 7.08−7.16 (m, 3H); MS 298, 266, 238, 206, 179, 165, 149, 139, 121 (P), 102, 91, 77, 60, 52.

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.38; H, 6.10.

Preparation of *dl*-2,3-Diphenylsuccinic Acid Dimethyl Ester (*dl*-6a), *meso*-2,3-Diphenylsuccinic Acid Dimethyl Ester (*meso*-6a), and 2,4-Diphenyl-3-oxobutyric Acid Methyl Ester (7). To a solution of methyl phenylacetate (**5a**) (3 mmol, 0.45 g) in CH_2Cl_2 (10 mL) was added $TiCl_4$ (1.5 mmol, 0.16 mL) with a syringe at −45 °C, and the solution was stirred for 30 min. Triethylamine (1.5 mmol, 0.21 mL) was then added, and the solution was stirred at −45 °C for 1.5 h. The

(13) Cadogan, J. I. G.; Hey, D. H.; Ong, S. H. *J. Chem. Soc.* **1965**, 1939.
(14) Wren, H.; Still, C. J. *J. Chem. Soc.* **1915**, *107*, 444.

solution was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried on $MgSO_4$, and the solvent was evaporated *in vacuo* to give a residue. The residue was subjected to column chromatography (Merck silica gel 60, 70−230 mesh) with hexane/AcOEt (5/1) to give *dl*-**6a**, *meso*-**6a**, and **7**.

***dl*-6a**: 13.5%.

***meso*-6a**: 4.5%; sublimation temperature 174−179 °C (lit.[14] mp 218−219 °C); IR (KBr) 2960, 1730, 1500, 1455, 1435, 1300, 1150, 995, 880, 733, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (s, 3H), 4.40 (s, 1H), 7.25−7.42 (m, 3H), 7.43−7.53 (m, 2H); MS 298, 266, 238, 179, 165, 149 (P), 135, 121 102, 96, 91, 85, 77, 57.

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.05; H, 6.13.

7: 50%; mp 58−60 °C; IR (KBr) 3480, 3140, 2950, 1745, 1720, 1500, 1460, 1435, 1220, 1165, 1060, 715, 700, 550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.43 (s, 0.66H), 3.67 (s, 0.99H), 3.69 (d, J = 16 Hz, 0.67H), 3.71 (s, 2.01H), 3.78 (d, J = 16 Hz, 0.67H), 4.81 (s, 0.67H), 7.05−7.43 (m, 10H), 13.05 (s, 0.33H); MS 268, 236, 209, 191, 177, 165, 150, 145, 136, 116, 105, 91(P), 77, 65.

Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.01; H, 6.08.

Preparation of *dl*-2,3-Diphenylsuccinic Acid Diallyl Ester (*dl*-6b). To a solution of allyl phenylacetate (**5b**) (2 mmol, 0.35 g) in CH_2Cl_2 (10 mL) was added $TiCl_4$ (4.4 mmol, 0.48 mL) with a syringe at −45 °C, and the solution was stirred for 30 min. Triethylamine (4.4 mmol, 0.61 mL) was then added, and the solution was stirred at −45 °C for 1.5 h. The solution was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried on $MgSO_4$, and the solvent was evaporated *in vacuo* to give a white solid. The solid was subjected to column chromatography with hexane/AcOEt (10/1) to give pure *dl*-**6b** in 80% yield. Under these reaction conditions, the *meso*-isomer and the Claisen condensation product were not observed. The stereochemistry of *dl*-**6b** was determined by its conversion to *dl*-**6a**: i.e., heating of *dl*-**6b** in methanol containing NaOMe at reflux temperature for 7 h followed by acidifying the resulting solution to give the corresponding diacid, which was transformed to *dl*-**6a** by heating in methanol containing hydrogen chloride.

***dl*-6b**: mp 49−54 °C; IR (KBr) 3060, 3040, 2945, 1725, 1600, 1495, 1455, 1370, 1300, 1240, 1160, 985, 940, 735, 700, 570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.29 (s, 1H), 4.55−4.65 (m, 2H), 5.10−5.28 (m, 2H), 5.73−5.95 (m, 1H), 6.95−7.20 (m, 5H); MS 352, 336, 292, 280, 264, 251, 223, 207, 193, 180, 165, 149, 147, 129, 119, 105, 91, 83, 69, 57.

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.29; H, 6.41.

Preparation of *dl*- and *meso*-2,3-Dimethyl-2,3-diphenylsuccinic Acid Dimethyl Ester (6c). To a solution of methyl α-methylphenylacetate (**5c**) (2 mmol, 0.33 g) in CH_2Cl_2 (10 mL) was added $TiCl_4$ (10.0 mmol, 1.10 mL) with a syringe at −45 °C, and the solution was stirred for 30 min. Triethylamine (10.0 mmol, 1.40 mL) was then added, and the solution was stirred at −45 °C for 1.5 h. The solution was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried on $MgSO_4$, and the solvent was evaporated *in vacuo* to give a white solid. The solid was subjected to column chromatography with CH_2Cl_2 to give a mixture of *dl*- and *meso*-2,3-dimethyl-2,3-diphenylsuccinic acid dimethyl ester (**6c**) in 87% yield. *dl*- and *meso*-**6c** are known compounds,[11] and the *dl*/*meso* ratio was determined by NMR. α,*p*-Coupling product **8** was not observed in this reaction. The authentic sample of **8** was prepared as previously reported.[2] The spectroscopic (IR and ^1H NMR spectra) data of **8** were as follows.

8: IR (KBr) 2988, 2951, 1728, 1599, 1495, 1433, 1240, 1167, 1080, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.48 (d, J = 7.1 Hz, 3H), 1.90 (s, 3H), 3.63 (s, 3H), 3.67 (m, 1H), 3.69 (s, 3H), 6.81−7.32 (m, 9H).

Oxidative Coupling of 5a and 5c by Methods i and ii. Oxidative coupling by methods i and ii was carried out by the procedures described in the literature.[2,3a]

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (No. 236) and for Scientific Research (No. 07672272) from the Ministry of Education, Science and Culture, Japan.

JO952204H