Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1756–1763
Tetrahedron

Use of zinc enolate, free from other metals, in enantioselective palladium-catalyzed allylic alkylation

Naosumi Kinoshita,[a] Takeo Kawabata,[b,*] Kazunori Tsubaki,[b] Masahiko Bando[a] and Kaoru Fuji[c,*]

[a]*Medicinal Chemistry Research Institute, Otsuka Pharmaceutical Company, Ltd, 463-10 Kagasuno, Kawauchi-cho, Tokushima 771-0192, Japan*
[b]*Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan*
[c]*Faculty of Pharmaceutical Sciences, Hiroshima International University, 5-1-1 Hirokoshingai, Kure, Hiroshima 737-0112, Japan*

Received 12 September 2005; revised 21 November 2005; accepted 22 November 2005

Available online 27 December 2005

This paper is dedicated to the memory of the late Professor Kiyoshi Tanaka.

Abstract—Zinc enolate, free from other metal cations directly prepared from malonate and diethylzinc, was proven to be an excellent nucleophile for enantioselective palladium-catalyzed allylic alkylation, particularly for the allylic cation bearing aromatic rings at the 1- and 3-positions.

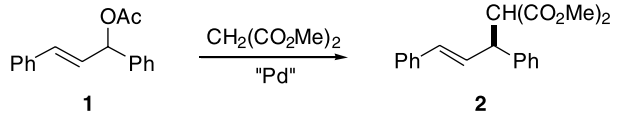
1. Introduction

Diethylzinc is a weak nucleophile used for the nucleophilic addition to aldehydes,[1] 1,4-addition to α,β-unsaturated carbonyl compounds,[2–4] the Simmons–Smith reaction,[5] and the umpolung of π-allylpalladium compounds.[6] It is also known that diethylzinc is a weak Lewis acid coordinating to oxygen, nitrogen, and halogens.[7] Diethylzinc has been rarely used as a base to generate enolates from carbonyl compounds, although limited examples have been reported for the preparation of enolates from dialkyl malonates,[8] and chiral phosphonate anions for the asymmetric Horner–Wadsworth–Emmons reaction.[9] The usefulness of zinc malonate free from other metals has also been reported in iridium-catalyzed allylic alkylation.[10]

Zinc enolates are routinely prepared in situ by metal–metal exchange with other metal enolates.[11] Since the other metals coexist with zinc in the reaction medium, the nature must be quite different from that of the zinc enolate free from other metals, which may affect the stereochemical outcome of the reactions. We have reported a remarkable enhancement of the enantiomeric excess (ee) in a palladium-catalyzed allylic alkylation with (*R*)-BINAP as a chiral ligand using zinc enolates, free from other metals, and generated with diethylzinc as a base.[12] Here, we report a full account of palladium-catalyzed asymmetric allylic alkylation using diethylzinc as a base.

2. Results and discussion

Control of the regio- and stereochemistry of palladium-catalyzed allylic alkylations relies upon the chiral ligand, the structure of a nucleophile and an electrophile, and the nature of counter cations. We have chosen 1,3-diphenylprop-2-enyl acetate (**1**) as a starting material, which gives symmetrical allylic cation, to avoid the ambiguity arising from unsymmetrical allylic cation (Scheme 1). The test reactions were performed with the zinc enolate of dimethyl malonate using triphenylphosphine as a ligand and the



1 **2**

Scheme 1.

Keywords: Enantioselective allylic alkylation; Zinc enolate; Chiral ligand.
* Corresponding authors. Tel.: +81 823 73 8936; fax: +81 823 73 8981; e-mail address: fuji@ps.hirokoku-u.ac.jp

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.053

Table 1. Palladium-catalyzed allylic alkylation of racemic 1,3-diphenylprop-2-enyl acetate (**1**) with dimethyl malonate using Et_2Zn as a base[a]

Entry	Pd source	Pd (mol%)	PPh_3 (mol%)	Solvent	Reaction time (h)	Yield (%)
1	$Pd(OAc)_2$	5	20	THF	20	6
2	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	5	20	THF	19	4
3	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	5	20	CH_2Cl_2	17	79
4	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	2	8	CH_2Cl_2	4	74

[a] Two equivalents of dimethyl malonate and Et_2Zn were used.

Table 2. Palladium-catalyzed enantioselective allylic alkylation[a] of racemic 1,3-diphenylprop-2-enyl acetate (**1**) with Et_2Zn[b] as a base using (*R*)-BINAP[c] as a ligand giving (*S*)-**2**

Entry	Solvent	Temperature (°C)	Reaction time (h)	Product **2**		Recovered **1** yield (%)
				Yield (%)	ee (%)	
1	CH_2Cl_2	0	88	67	14	18
2	CH_3CN	0	65	14	89	53
3	Et_2O	0 to rt	76	26	79	33
4	Toluene	0	45	63	77	13
5	Toluene	rt	17	71	22	0
6	THF	0	39	46	98	36
7	THF	0 to rt	47	73	96	0
8	THF	rt	20	84	99	0
9	THF	Reflux	0.5	90	97	0
10[d]	THF	0 to rt	35	57	88	0
11[e]	THF	rt	134	52	72	10

[a] $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%) was used for all reactions.
[b] Two equivalents for each reaction.
[c] Eight mol% for each reaction.
[d] $Pd_2(dba)_3 \cdot CHCl_3$ was used.
[e] $Pd_2(dba)_3$ was used.

results are shown in Table 1. The alkylated product **2** was obtained in low yields in THF. Change of the solvent to CH_2Cl_2 increased the yield dramatically (entry 3) even with decreased amount of the catalyst (entry 4). Thus, the possible use of diethylzinc was demonstrated for palladium-catalyzed allylic alkylation.

We chose the conditions in entry 4, involving the acetate **1** (1 equiv), dimethyl malonate (2 equiv), diethylzinc (2 equiv), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), and the ligand (8 mol%), as a standard procedure for the asymmetric version. The results with (*R*)-BINAP as a chiral ligand are listed in Table 2. All reactions gave (*S*)-**2**, which was confirmed by the comparison of an $[\alpha]_D$ value with that reported by Hayashi[13] and the ee was determined by chiral HPLC analysis. All solvents tested except for CH_2Cl_2 gave moderate to high ee at 0 °C, though the chemical yield was unsatisfactory. Increase in the reaction temperature decreased ee in toluene (entries 4 and 5), while the high ee was kept in THF even under refluxing conditions (entries 6–9). Change of the catalyst to $Pd_2(dba)_3$ was less effective (entries 10 and 11).

We examined the effect of counter cations (Table 3) since their importance for enantioselectivity is well demonstrated in the allylic alkylations,[14,15] The use of NaH decreased the

Table 3. Effects of counter cations in enantioselective allylic alkylation of racemic **1** with dimethyl malonate[a]

Entry	Base	Additive	Temperature (°C)	Reaction time (h)	Yield (%)	ee (%)
1	NaH	None	rt	18	75	35
2	NaH	$ZnCl_2$	rt	48	19 (58)[b]	57
3	KH	None	rt	5	77	59
4	LiH	None	rt	64	68 (89)[b]	72
5	LDA	None	rt	2	87	76
6	LDA	$ZnCl_2$	rt	68	60 (71)[b]	87
7	*n*-BuLi	None	rt	24	91	56
8	*n*-BuLi	$ZnCl_2$	rt	42	19	53
9	Et_2Zn	LiCl	rt	42	67	82
10	Et_2Zn	LiCl	Reflux	1	82	14
11	*t*-Bu–P_4-base	None	rt	3	82	84
12	MeMgBr	None	rt	192	16 (44)[b]	0
13	MeMgBr	None	Reflux	1	81	2
14	MeMgI	None	rt	72	26 (36)[b]	0

[a] Under the standard conditions with (*R*)-BINAP (8 mol%) in THF.
[b] The numbers in the parenthesis are the yields based on the recovered starting material.

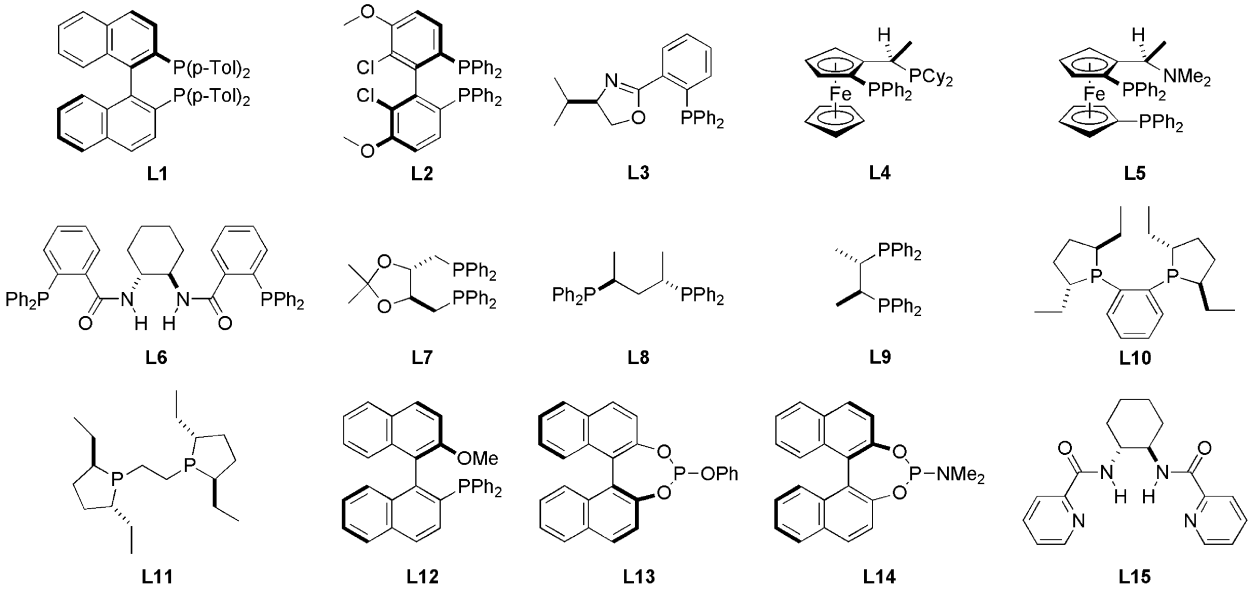
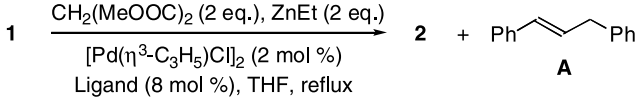


Figure 1. List of ligands tested.

ee to 35% (entry 1).[16] Zinc enolate prepared by the addition of zinc chloride to the sodium enolate gave a higher ee but with a lower yield (entry 2). No significant effect of counter cations was observed under these reaction conditions (entries 3–8). Adding lithium chloride to the pure zinc enolate slightly lowered both the ee and the yield (compare entry 8 in Table 2 with entry 9 in Table 3). The ee was remarkably decreased at refluxing temperature in the presence of lithium chloride (entries 9 vs 10), while decrease in ee was not observed in the absence of lithium chloride at the same temperature (Table 2, entries 8 vs 9). This could be ascribed to the difference in the aggregate structure of the enolate in the former conditions from the latter. The phosphazene base P_4–*t*-Bu, known to generate a metal-free enolate, gave a fairly good yield and ee (entry 11). Magnesium enolate afforded racemic **2** (entries 12–14). The results in Tables 2 and 3 show the advantage of using the zinc enolate, free from other metals, in enantioselective allylic alkylations with (*R*)-BINAP.

The results of applying the standard conditions at refluxing temperature to other chiral ligands are listed in Figure 1 and Table 4. The advantage of the zinc enolate free from other metals was not observed with other chiral

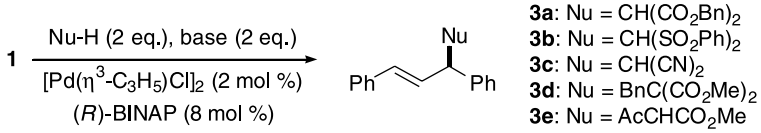
Table 4. Assessment of chiral ligands for the enantioselective allylic alkylation of racemic **1** using Et_2Zn as a base



Entry	Ligand[a]	Reaction time (h)	Yield (%)[b]		ee of **2** (%)[c]
			2	**A**[d]	
1	**L1**:(*R*)-Tol-BINAP	0.5	89	—	91 (*S*)
2	**L2**:(*R*)-Cl-MeO-BIPHEP	0.5	91	—	98 (*S*)
3	**L3**:(*R*)-PHOX	3	72	—	96 (*R*)
4	**L4**:(*R*)-(*S*)-JOSIPHOS	0.5	86	—	84 (*S*)
5	**L5**:(*R*)-(*S*)-BPPFA	0.5	86	—	54 (*S*)
6	**L6**:(*R*,*R*)-Trost ligand	0.5	(3)[e]	—	—
7	**L7**:(*S*,*S*)-DIOP	0.5	86	—	11 (*S*)
8	**L8**:(*S*,*S*)-BDPP	0.5	88	—	36 (*R*)
9	**L9**:(*S*,*S*)-CHIRAPHOS	0.5	0	—	—
10	**L10**:(*R*)-(*R*)-Et-DUPHOS	3	28	—	77 (*S*)
11	**L11**:(*R*)-(*R*)-Et-BPE	3	(10)[e]	—	—
12	**L12**:(*R*)-MeO-MOP	0.5	—	84	—
13	**L13**	1	33	52	34 (*S*)
14	**L14**:(*R*)-MonoPhos	0.5	(5)[e]	—	—
15	**L15**	0.5	—	—	—

[a] Structures of chiral ligands are listed in Figure 1.
[b] Isolated yield.
[c] Determined by HPLC on CHIRALCEL OJ-R (MeOH/H^2O=80:20).
[d] Similar reduction of allyl acetates with alkyl zinc/Pd (0) system has been reported, see Ref. 21.
[e] The number in parenthesis indicates the yield determined by ^1H NMR of crude product.

Table 5. Palladium-catalyzed enantioselective allylic alkylation of the racemic acetate **1** with various nucleophiles (Nu-H) in THF



Entry	Nu-H	Base	Temperature (°C)	Reaction time (h)	Product[a]	Yield (%)[b]	ee (%)
1	$CH_2(CO_2Bn)_2$	Et_2Zn	rt	20	**3a**[c]	81	92[d]
2	$CH_2(CO_2Bn)_2$	Et_2Zn	Reflux	1	**3a**	78	95[d]
3	$CH_2(CO_2Bn)_2$	NaH	rt	2	**3a**	83	0[d]
4	$CH_2(CO_2Bn)_2$	*n*-BuLi	rt	18	**3a**	88	67[d]
5	$CH_2(SO_2Ph)_2$	Et_2Zn	rt	72	**3b**[e]	24 (44)	92[f]
6[g]	$CH_2(SO_2Ph)_2$	Et_2Zn	rt	72	**3b**	43	91[f]
7	$CH_2(SO_2Ph)_2$	Et_2Zn	Reflux	2	**3b**	70	39[f]
8[h]	$CH_2(SO_2Ph)_2$	Et_2Zn	rt	72	**3b**	62 (76)	88[f]
9	$CH_2(SO_2Ph)_2$	NaH	rt	45	**3b**	36 (60)	88[f]
10	$CH_2(CN)_2$	Et_2Zn	rt	48	**3c**[i]	48	85[j]
11	$CH_2(CN)_2$	Et_2Zn	Reflux	1.5	**3c**	89	7[j]
12	$CH_2(CN)_2$	NaH	rt	48	**3c**	33 (62)	75[j]
13	$BnCH(CO_2Me)_2$	Et_2Zn	rt	168	**3d**[k]	47 (53)	70[l]
14	$BnCH(CO_2Me)_2$	Et_2Zn	Reflux	3	**3d**	92	76[l]
15[h]	$BnCH(CO_2Me)_2$	Et_2Zn	rt	168	**3d**	55 (65)	84[l]
16[m]	$BnCH(CO_2Me)_2$	NaH	rt	211	**3d**	45	0[l]
17	$AcCH_2CO_2Me$	Et_2Zn	rt	20	**3e**[n]	13 (76)	96[o]
18	$AcCH_2CO_2Me$	Et_2Zn	Reflux	3	**3e**	70	97[o]
19	$AcCH_2CO_2Me$	NaH	rt	3	**3e**	86	57[o]

[a] The absolute configuration was determined by comparison of the $[\alpha]^D$ value with that in the literature.
[b] The number in parenthesis indicates the yield based on the consumed starting material.
[c] New compound. The absolute configuration was not confirmed.
[d] Determined by HPLC on CHIRALPAK AD (hexane/2-propanol=9:1).
[e] Known; see Ref. 17.
[f] Determined by HPLC on CHIRALCEL OJ-R (MeOH).
[g] $CH^2(SO_2Ph)_2$ (10 equiv), base (10 equiv), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), and (*R*)-BINAP (8 mol%) were used.
[h] DMF as a solvent.
[i] Known; see Ref. 18.
[j] Determined by HPLC on CHIRALCEL OJ (hexane/2-propanol=9:1).
[k] Known; see Ref. 16; where the absolute configuration was assigned without evidence. Absolute configuration was postulated from the optical rotation of the corresponding diethyl ester. See Ref. 19.
[l] Determined by HPLC on CHIRALPAK AD (hexane/2-propanol=92:8).
[m] Taken from Ref. 16, where $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.5 mol%), and (*S*)-BINAP (1.2 mol%) were used.
[n] Known; see Ref. 13.
[o] Determined by ^1H NMR with $Eu(hfc)_3$.

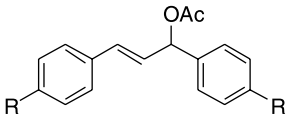
ligands, although modified BINAP analogues (L1 and L2) gave good results comparable to (*R*)-BINAP (entries 1 and 2). Since the combination of (*R*)-BINAP as a chiral ligand and diethylzinc for the generation of enolate was shown to be the best for allylic alkylation, we applied this system to other nucleophiles. The results, together with those with NaH, are compiled in Table 5. The standard conditions were shown to be applicable to other nucleophiles to give high ee's, though yields are sometimes low (entries 5, 10, 13, and 17). The close inspection of Table 5 reveals that the reaction time was remarkably shortened at refluxing temperature without decrease in the ee with the nucleophiles stabilized by carbonyl groups (compare entries 1 and 2, 13 and 14, 17 and 18). Use of NaH dramatically decreased the ee, with these nucleophiles (entries 3, 16, and 19), while nucleophiles stabilized by the sulfonyl or the cyano group gave comparable ee's (compare entries 5 and 9, 10 and 12). Another characteristic disposition of the latter nucleophiles includes low ee's at refluxing temperature (entries 7 and 11). These findings suggest that the structure and/or the aggregation state of the enolates generated from malonate is quite different from those generated from the active methylene compounds with sulfonyl and cyano groups.

The results of enantioselective allylic alkylation of racemic acetates **4**–**7** and **12** with dimethyl malonate are listed in Table 6. All of the starting material except for the nitro substituted compound **7** showed characteristic features associated with a combination of a malonate and diethylzinc, in which the high ee's were kept under refluxing conditions (entries 2, 6, 10, and 17). The (*S*)-configuration of the carbon center, newly created in **9**, was determined by X-ray crystallography (Fig. 2). The same absolute configurations for other products **8**, **10**, **11**, and **13** can be postulated by the reaction mechanism, though direct evidence is lacking. The advantage of diethylzinc as a base was not observed with 1,3-dialkylallylic esters **14**, **15**, and **17**–**19** (Table 7).

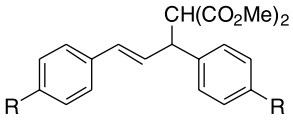
3. Conclusion

Zinc enolate free from other metal cations, directly prepared from malonate, was proven to be a good

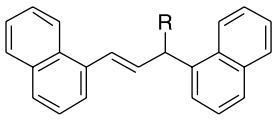
Table 6. Palladium-catalyzed enantioselective allylic alkylation of the racemic acetate **4**–**7** and **12** with dimethyl malonate in THF[a]



4: R = Cl
5: R = Br
6: R = Me
7: R = NO_2



8: R = Cl
9: R = Br
10: R = Me
11: R = NO_2



12: R = OAc
13: R = $CH(CO_2Me)_2$

Entry	Substrate	Base	Temperature (°C)	Reaction time (h)	Product	Yield (%)	ee (%)
1	**4**	Et_2Zn	rt	20	**8**	92	97
2	**4**	Et_2Zn	Reflux	0.5	**8**	95	96
3	**4**	NaH	rt	4	**8**	88	30
4[b]	**4**	NaH	rt	1	**8**	91	0
5	**5**	Et_2Zn	rt	40	**9**	60[c]	97
6	**5**	Et_2Zn	Reflux	1	**9**	40	97
7	**5**	NaH	rt	4	**9**	90	34
8[b]	**5**	NaH	rt	1	**9**	84	0
9	**6**	Et_2Zn	rt	72	**10**	73	78
10	**6**	Et_2Zn	Reflux	1	**10**	91	80
11	**6**	NaH	rt	4	**10**	78	19
12[b]	**6**	NaH	rt	1	**10**	83	0
13	**7**	Et_2Zn	rt	72	**11**	21	32
14	**7**	NaH	rt	24	**11**	44	36
15[b]	**7**	NaH	rt	0.5	**11**	75	0
16	**12**	Et_2Zn	rt	48	**13**	73	88
17	**12**	Et_2Zn	Reflux	2	**13**	95	90
18	**12**	NaH	rt	8	**13**	88	67
19[b]	**12**	NaH	rt	10	**13**	83	0

[a] Unless otherwise stated, dimethyl malonate (2 equiv), base (2 equiv), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), and (*R*)-BINAP (8 mol%) were used for all of the reactions.
[b] PPh^3 was used as a ligand.
[c] A 7% of starting material was recovered.

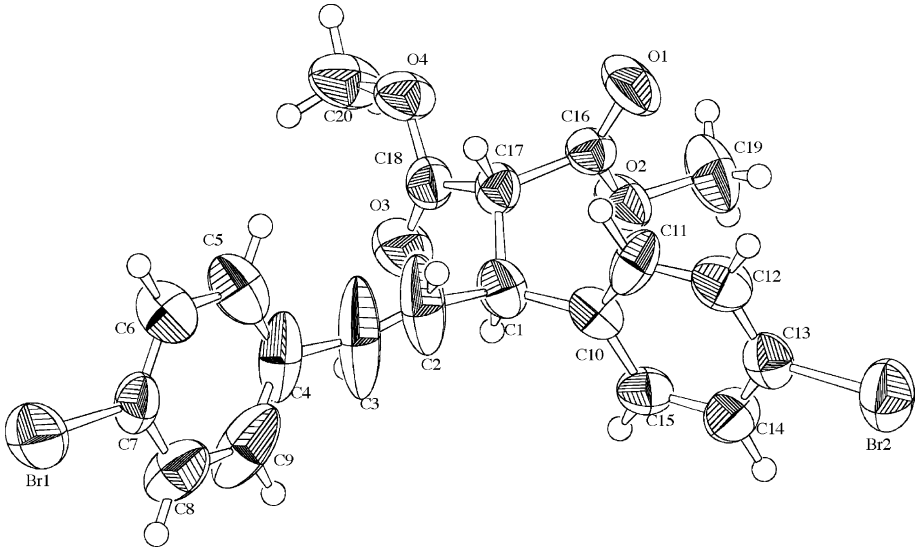
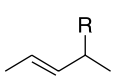


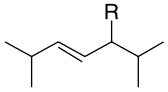
Figure 2.

nucleophile for palladium-catalyzed allylic alkylation to give a product with good yield and high ee. In particular, the allylic cation bearing aromatic rings at the 1- and 3-positions gave excellent results with BINAP or modified BINAP analogues. Advantage to use zinc enolates free from other metals involves marked decrease in the reaction time by using refluxing conditions without any loss of the ee. The present results may suggest that the use of zinc enolates free from other metals is the method of choice to increase ee's and/or chemical yields in other types of enantioselective reactions involving enolates.

Table 7. Enantioselective allylic alkylation of the racemic 1,3-dialkyl allyl ester derivatives **14**, **15**, and **17–19** under the standerd conditions



14: R = OAc
15: R = OCO_2Me
16: R = $CH(CO_2Me)_2$



17: R = OAc
18: R = OCO_2Me
19: R = $OPO(OEt)_2$
20: R = $CH(CO_2Me)_2$

Entry	Substrate	Solvent	Temperature (°C)	Reaction time (h)	Product	Yield (%)[a]	ee (%)[b]
1	**14**	THF	Reflux	0.5	**16**	54	41
2	**14**	THF	rt	6	**16**	21	63
3	**14**	THF	rt	24	**16**	40	45
4	**15**	THF	rt	24	**16**	63	41
5	**15**	DMF	rt	24	**16**	27	28
6	**17**	THF	Reflux	16	**20**	62	66
7	**17**	DMF	70	36	**20**	31	77
8[c]	**17**	THF	Reflux	1	**20**	88	68
9	**18**	THF	rt	360	**20**	0	—
10	**18**	THF	Reflux	4	**20**	16	82
11	**18**	DMF	70	8	**20**	23	78
12	**19**	THF	Reflux	8	**20**	67	78

[a] Isolated yield.
[b] Determined by GLC (Chirasil-DXE CB) for **16**[20] and ^{1}H NMR with Eu(hfc)$_3$ for **20**.[20]
[c] NaH was used as a base.

4. Experimental

4.1. Standard procedure of allylic alkylation (entry 9 in Table 2)

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.82 mg, 0.005 mmol, 2 mol%), and (*R*)-BINAP (12.5 mg, 0.02 mmol, 8 mol%) were dissolved in THF (0.5 ml) and stirred for 1 h at room temperature. After cooling to 0 °C, 1,3-diphenylprop-2-enyl acetate (1.59 mg, 0.25 mmol) in THF (0.5 ml) was added to prepare the solution A. Diethylzinc (1.0 M in hexane, 0.5 ml, 0.5 mmol) was added to a solution of dimethyl malonate (67 mg, 0.5 mmol) in THF (1.5 ml) and stirred for 1 h at room temperature, to which the solution A was introduced via Teflon tube. After the mixture was stirred at refluxing temperature for 30 min, it was diluted with 1 N HCl followed by the extraction with AcOEt. Organic layer was successively washed with aq $NaHCO_3$ and brine and dried over $MgSO_4$. Evaporation of the solvent gave an oil, which was purified by PTLC over silica gel (AcOEt/hexane=1:7).

4.1.1. Dibenzyl[(1,3-diphenyl)prop-2-enyl]malonate (3a). The crude product obtained through the standard procedure was purified by PTLC over silica gel (Et_2O/CH_2Cl_2/hexane=1:1:5). Oil (95% ee, determined by CHIRALPAC AD, hexane/2-propanol=9:1, flow rate 0.5 ml/min., detection at 254 nm, t_R 47 and 59 min), $[\alpha]_D^{20}$ −7.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.04 (d, J=10.9 Hz, 1H), 4.30 (dd, J=10.8, 8.5 Hz, 1H), 4.93 (dd, J=17.5, 12.3 Hz, 2H), 5.11 (dd, J=16.3, 12.2 Hz, 2H), 6.31 (dd, J=15.7, 8.5 Hz, 1H), 6.41 (d, J=15.8 Hz, 1H), 7.04–7.06 (m, 2H), 7.20–7.28 (m, 18H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.3, 57.8, 67.1, 67.4, 126.4, 127.2, 127.5, 127.9, 128.1, 128.2, 128.3, 128.4, 128.4, 128.5, 128.7, 129.0, 131.9, 135.1, 135.1, 136.7, 140.1, 167.2, 167.6. IR (neat) cm^{-1}: 1758, 1773, 1469, 1455, 1375, 1257, 1216, 1150, 966, 744, 695. MS *m*/*z*: 476 (M^+), 385, 341, 91 (base peak). HRMS *m*/*z*: Calcd for $C_{32}H_{28}O_4$ (M^+): 476.1988. Found: 476.1996. Anal. Calcd for $C_{32}H_{28}O_4$: C, 80.65; H, 5.92. Found C, 80.72; H, 5.96.

4.1.2. (*E*)-1,3-Bis(4-methylphenyl)prop-2-enyl acetate (6). To a suspension of (*E*)-1,3-bis(4-methylphenyl)propenone (1.18 g, 5.0 mmol) and $CeCl_3\cdot 7H_2O$ (1.86 g, 5.0 mmol) in MeOH was added $NaBH_4$ (0.19 g, 5.0 mmol) portionwise under ice-cooling and the mixture was stirred for 30 min. Usual extractive work-up with Et_2O afforded (*E*)-1,3-bis(4-methylphenyl)prop-2-en-1-ol (1.1 g, 94%). To a solution of (*E*)-1,3-bis(4-methylphenyl)prop-2-en-1-ol (0.55 g, 2.3 mmol) and DMAP (2.8 mg, 0.01 equiv) in CH_2Cl_2 (2 ml) was successively added Et_3N (0.38 ml, 2.7 mmol) and Ac_2O (0.24 ml, 2.5 mmol) under ice-cooling and the mixture was stirred for 1 h. Extractive work-up with Et_2O afforded **6** (0.61 g, 95%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.11 (s, 3H), 2.32 (s, 3H), 2.35 (s, 3H), 6.29 (dd, J=15.8, 6.8 Hz, 1H), 6.40 (d, J=6.9 Hz, 1H), 6.58 (d, J=15.8 Hz, 1H), 7.10 (d, J=8.0 Hz, 2H), 7.18 (d, J=8.0 Hz, 2H), 7.26–7.31 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2, 21.2, 21.4, 76.2, 126.6, 127.1, 129.2, 129.3, 132.3, 133.4, 136.4, 137.9, 137.9, 170.1. IR (neat) cm^{-1}: 1738, 1513, 1369, 1233, 1017, 965, 818, 800. MS *m*/*z*: 280 (M^+), 238, 220 (base peak), 205, 129, 119. HRMS *m*/*z*: Calcd for $C_{19}H_{20}O_2$ (M^+): 280.1463. Found: 280.1452. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.60; H, 7.24.

4.1.3. (*E*)-1,3-Bis(4-nitrophenyl)prop-2-enyl acetate (7). To a suspension of (*E*)-1,3-bis(4-nitrophenyl)propenone (2.98 g, 10.0 mmol) and $CeCl_3\cdot 7H_2O$ (3.73 g, 10.0 mmol) in MeOH was added $NaBH_4$ (0.38 g, 10.0 mmol) portionwise under ice-cooling and the mixture was stirred for 2 h. Usual extractive work-up with Et_2O afforded (*E*)-1,3-bis(4-nitrophenyl)prop-2-en-1-ol (2.2 g, 75%) after column chromatography over silica gel (AcOEt/hexane=35:65). To a solution of (*E*)-1,3-bis(4-nitrophenyl)prop-2-en-1-ol (2.18 g, 7.26 mmol) and DMAP (9 mg, 0.01 equiv) in CH_2Cl_2 (15 ml) was successively added Et_3N (1.21 ml,

8.71 mmol) and Ac_2O (0.82 ml, 8.71 mmol) under ice-cooling and the mixture was stirred for 30 min. Extractive work-up with Et_2O followed by column chromatography over silica gel (AcOEt/hexane=20:80) afforded **7** (1.76 g, 71%) as yellow needles, mp 127–129 °C (from AcOEt–hexane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 3H), 6.46 (dd, J=15.7, 6.6 Hz, 1H), 6.52 (d, J=6.8 Hz, 1H), 6.74 (d, J=15.7 Hz, 1H), 7.51–7.53 (m, 2H), 7.59–7.60 (m, 2H), 8.18–8.19 (m, 2H), 8.26 (dd, J=6.9, 1.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1, 74.5, 124.0, 124.1, 127.4, 127.8, 130.7, 131.4, 141.9, 145.4, 147.5, 147.8, 169.6. IR (KBr) cm^{-1}: 1736, 1600, 1516, 1346, 1233, 859. MS *m/z*: 342 (M^+), 300 (base peak), 282, 271, 236, 189, 178. HRMS *m/z*: Calcd for $C_{17}H_{14}N_2O_6$ (M^+): 342.0852. Found: 342.0874. Anal. Calcd for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12. Found: C, 59.69; H, 4.09.

4.2. Products in Table 6

All reactions were performed with the same ratio of the substrate and reagents as those of described in standard procedure and under the conditions in Table 6.

4.2.1. Dimethyl [1,3-bis(4-chlorophenyl)prop-2-enyl]malonate (8) in entry 1. An oil, purified by PTLC (silica gel, AcOEt/hexane=1:6), 97% ee, determined by HPLC (CHIRALPAK AD, 2-propanol/hexane=15:85, flow rate 0.8 ml/min, detection at 254 nm, t_R 19, 25 min), $[\alpha]_D^{20}$ −3.1 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.55 (s, 3H), 3.70 (s, 3H), 3.89 (d, J=10.7 Hz, 1H), 4.26 (dd, J=10.6, 8.7 Hz, 1H), 6.26 (dd, J=15.7, 8.5 Hz, 1H), 6.40 (d, J=15.8 Hz, 1H), 7.21–7.26 (m, 6H), 7.28–7.30 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 48.4, 52.6, 52.7, 57.4, 127.6, 128.7, 129.0, 129.2, 129.3, 131.1, 133.1, 133.4, 135.1, 138.5, 167.5, 167.9. IR (neat) cm^{-1}: 1758, 1739, 1491, 1435, 1255, 1159, 1093. MS *m/z*: 394 (M^+), 392 (M^+), 263, 261 (base peak), 226, 191, 149. HRMS *m/z*: Calcd for $C_{20}H_{18}O_4Cl_2$ (M^+): 394.0553, 392.0582. Found: 394.0541, 392.0604. Anal. Calcd for $C_{20}H_{18}O_4Cl_2$: C, 61.08; H, 4.61. Found: C, 61.36; H, 4.57.

4.2.2. Dimethyl [1,3-bis(4-bromophenyl)prop-2-enyl]malonate (9) in entry 5. An oil, purified by PTLC (silica gel, AcOEt/hexane=1:7), 97% ee, determined by HPLC (CHIRALPAK AD, 2-propanol/hexane=20:80, flow rate 0.6 ml/min, detection at 254 nm, t_R((*R*)-**9**) 25 min, t_R((*S*)-**9**) 35 min), $[\alpha]_D^{20}$ +3.1 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.55 (s, 3H), 3.70 (s, 3H), 3.89 (d, J=10.7 Hz, 1H), 4.22 (dd, J=10.6, 8.7 Hz, 1H), 6.27 (dd, J=15.7, 8.4 Hz, 1H), 6.39 (d, J=15.8 Hz, 1H), 7.16 (d, J=8.2 Hz, 4H), 7.39 (d, J=8.4 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 48.5, 52.6, 52.7, 57.3, 121.2, 121.6, 127.9, 129.3, 129.6, 131.2, 131.7, 131.9, 135.5, 139.0, 167.5, 167.9. IR (neat) cm^{-1}: 1758, 1738, 1487, 1434, 1255, 1161, 1072, 1010, 757. MS *m/z*: 484 (M^+), 482 (M^+), 480 (M^+), 353, 351, 349, 272, 270, 191 (base peak), 189. HRMS *m/z*: Calcd for $C_{20}H_{18}O_4Br_2$ (M^+): 483.9531, 481.9552, 479.9572. Found: 483.9534, 481.9573, 479.9546. Anal. Calcd for $C_{20}H_{18}O_4Br_2$: C, 49.82; H, 3.76. Found: C, 49.98; H, 3.74.

A crystal for the X-ray analysis was obtained from MeOH, mp 78–80 °C. X-ray crystallographic data: $C_{20}H_{18}O_4Br_2$, Mr=482.17, orthorhombic, space group $P2_12_12_1$, a=13.655 (3) Å, b=25.107 (5) Å, c=5.796 Å, α=90°, β=90°, γ=90°, V=1987 (2) Å^3, Z=4, D_c=1.612 g/cm^3, $F(000)$=960 and μ=41.128 cm^{-1}. The structure was refined to R=0.200, Rw=0.114. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 282742. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2.3. Dimethyl[1,3-bis(4-methylphenyl)prop-2-enyl]malonate (10) in entry 10. Purified by PTLC (silica gel, AcOEt/hexane=1:6), 80% ee determined by HPLC (CHIRALPAK AD, 2-propanol/hexane=6:94, flow rate 0.5 ml/min, detection at 254 nm, t_R 29, 40 min), $[\alpha]_D^{20}$ −13.4 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.30 (s, 6H), 3.53 (s, 3H), 3.69 (s, 3H), 3.92 (d, J=10.9 Hz, 1H), 4.21 (dd, J=10.7, 8.8 Hz, 1H), 6.25 (dd, J=15.7, 8.7 Hz, 1H), 6.42 (d, J=15.7 Hz, 1H), 7.07 (d, J=8.0 Hz, 2H), 7.11 (d, J=7.9 Hz, 2H), 7.18 (dd, J=13.6, 8.1 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0, 21.1, 48.9, 52.4, 52.6, 57.8, 126.3, 127.7, 128.3, 129.1, 129.4, 131.5, 134.1, 136.7, 137.3, 137.3, 167.9, 168.3. IR (neat) cm^{-1}: 1760, 1739, 1513, 1434, 1321, 1256, 1159. MS *m/z*: 352 (M^+), 221 (base peak), 129. HRMS *m/z*: Calcd for $C_{22}H_{24}O_4$ (M^+): 352.1675. Found: 352.1689. Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.75; H, 6.74.

4.2.4. Dimethyl[1,3-bis(4-nitrophenyl)prop-2-enyl]malonate (11) in entry 14. An oil, purified by PTLC (Silica gel, AcOEt/hexane=1:2), 36% ee determined by HPLC (CHIRALCEL OJ-R, MeOH/H_2O=85:15, flow rate 0.4 ml/min, detection at 300 nm, t_R 79, 87 min), $[\alpha]_D^{20}$ −127.7 (c 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.58 (s, 3H), 3.74 (s, 3H), 3.99 (d, J=10.5 Hz, 1H), 4.44 (dd, J=10.4, 8.1 Hz, 1H), 6.50 (dd, J=15.8, 8.1 Hz, 1H), 6.57 (d, J=15.8 Hz, 1H), 7.45–7.50 (m, 4H), 8.15–8.17 (m, 2H), 8.20–8.23 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 48.7, 52.9, 53.0, 56.7, 124.0, 124.2, 127.1, 128.9, 131.3, 132.2, 142.5, 146.9, 147.3, 167.1, 167.5. IR (neat) cm^{-1}: 1755, 1738, 1597, 1520, 1346, 858, 756. MS *m/z*: 414 (M^+, base peak), 354, 295, 283, 249, 237, 203, 191. HRMS *m/z*: Calcd for $C_{20}H_{18}N_2O_8$ (M^+): 414.1063. Found: 414.1078. Anal. Calcd for $C_{20}H_{18}N_2O_8$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.90; H, 4.40; N, 6.82.

4.2.5. Dimethyl(1,3-di-naphthalen-1-ylprop-2-enyl)malonate (13) in entry 17. Purified by PTLC (silica gel, AcOEt/hexane=2:9). The sample for $[\alpha]_D$ measurement was obtained by recycling preparative HPLC followed by recrystallization from Et_2O–hexane, mp 82–85 °C, 94% ee determined by HPLC (CHIRALPAK AD, 2-propanol/hexane=10:90, flow rate 1.0 ml/min, detection at 295 nm, t_R 10, 22 min), $[\alpha]_D^{20}$ −37.5 (c 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.45 (s, 3H), 3.75 (s, 3H), 4.31 (d, J=10.7 Hz, 1H), 5.30–5.34 (m, 1H), 6.43 (dd, J=15.5, 8.6 Hz, 1H), 7.30 (d, J=15.5 Hz, 1H), 7.34–7.60 (m, 8H), 7.72 (d, J=8.1 Hz, 1H), 7.77–7.81 (m, 2H), 7.87 (d, J=8.1 Hz, 1H), 7.95–7.97 (m, 1H), 8.39 (d, J=8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 44.2, 52.5, 52.7, 57.4, 123.4, 123.8,

124.0, 124.3, 125.4, 125.5, 125.7, 125.8, 126.0, 126.4, 127.9, 127.9, 128.4, 129.0, 130.0, 131.1, 131.4, 132.3, 133.5, 134.2, 134.7, 136.3, 167.8, 168.6. IR (neat) cm^{-1}: 1760, 1733, 1432, 1252, 1158, 797, 778, 757. MS *m/z*: 424 (M^+), 293, 165 (base peak), 141. HRMS *m/z*: Calcd for $C_{28}H_{24}O_4$ (M^+): 424.1675. Found: 424.1653. Anal. Calcd for $C_{28}H_{24}O_4$: C, 79.22; H, 5.70. Found: C, 79.27; H, 5.71.

References and notes

1. Kitamura, M.; Oka, H.; Suga, S.; Noyori, R. *Org. Synth.* **2003**, *79*, 139–145.
2. Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999–1014.
3. Liang, L.; Au-Yeng, T. T. L.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 3799–3801.
4. Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660–5667.
5. Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013–12026.
6. Kimura, M.; Ogawa, Y.; Shimidu, M.; Sueishi, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1998**, *39*, 6903–6906.
7. For example; see: Ozaki, H.; Hirano, A.; Nakahara, S. *Macromol. Chem. Phys.* **1995**, *196*, 2099–2111.
8. Kawakami, Y.; Tsuruta, T. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 247–257.
9. (a) Tanaka, K.; Watanabe, T.; Shimamoto, K.; Sahakitpichan, P.; Fuji, K. *Tetrahedron Lett.* **1999**, *40*, 6599–6602. (b) Yamazaki, J.; Bedekar, A. V.; Watanabe, T.; Tanaka, K.; Fuji, K. *Tetrahedron: Asymmetry* **2002**, *13*, 729–734.
10. Kinoshita, N.; Marx, K. H.; Tanaka, K.; Tsubaki, K.; Kawabata, T.; Yoshikai, N.; Nakamura, E.; Fuji, K. *J. Org. Chem.* **2004**, *69*, 7960–7964.
11. Zinc enolates of ketones free from other metals were generated from α-iodoketones or α-iodoaldehydes with diethylzinc; see: Ito, S.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 5253–5256.
12. Fuji, K.; Kinoshita, N.; Tanaka, K. *Chem. Commun.* **1999**, 1895–1896.
13. Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191–194.
14. Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089–4090.
15. O'Donnell, M. J.; Chen, N.; Zhou, C.; Murray, A.; Kubiak, C. P.; Yang, F.; Stanley, G. G. *J. Org. Chem.* **1997**, *62*, 3962–3975.
16. (*R*)-**2** was obtained in 30% ee under the similar conditions with (*S*)-BINAP. See: Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M. *Tetrahedron: Asymmetry* **1991**, *2*, 663–666.
17. Kubota, H.; Koga, K. *Heterocycles* **1996**, *42*, 543–547.
18. Martin, C. J.; Rawson, D. J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3723–3730.
19. Chen, X.; Guo, R.; Li, Y.; Chen, G.; Yeung, C.-H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 213–217.
20. Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905–7920.
21. Matsushita, H.; Negishi, E. *J. Org. Chem.* **1982**, *47*, 4161–4165.