Enantioselective Allylation of Nitro Group-Stabilized Carbanions Catalyzed by Chiral Crown Ether Phosphine−Palladium Complexes

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Enantioselective allylations of α-nitro ketones (**3**) and α-nitro esters (**15**) with allyl acetate were carried out in the presence of 2 equiv of alkali metal fluorides (KF, RbF, CsF) and 1 mol % of palladium catalysts prepared in situ from $Pd_2(dba)_3$·$CHCl_3$ and chiral phosphine ligands. Moderate enantioselectivities were observed in the reaction of nitro ketones **3**, giving products **4** (**4a**, 49% ee; **4b**, 58% ee; **4c**, 44% ee) when rubidium fluoride and ferrocenylphosphine ligands bearing monoaza-15-crown-5 (**1b**) or monoaza-18-crown-6 (**1c**) moieties were used as a base and a chiral ligand, respectively. Optically active allylation product **4a** was converted into 1-methyl-1-azaspiro[4.5]-decan-10-amine (**13**), a precursor to opioid receptor binding agents. Enantioselectivity in the reaction of nitro esters **15** increased in accord with increasing steric demand of the ester alkyl group (Me < Et < *t*-Bu). The highest selectivity (80% ee) for the reaction of *tert*-butyl ester **15c** was observed when the reaction was carried out at −40 °C in the presence of the palladium catalyst with the ligand (**1c**) bearing a monoaza-18-crown-6 moiety, RbF (2 equiv), and $RbClO_4$ (1 equiv). The pronounced effect of the crown ether moiety for both enantioselection and rate acceleration can be explained by assuming the formation of a ternary complex involving the crown ether, rubidium cation, and enolate anion at the stereodifferentiating transition state. Optically active nitro ester (*R*)-**16c** was converted into (*R*)-α-methylglutamic acid (**20**).

Introduction

Stereocontrol by a chiral catalyst in the palladium-catalyzed enantioselective allylation of prochiral stabilized carbanions is an extremely difficult task because a chiral ligand is located far from the prochiral nucleophile attacking the π-allyl carbon of the (π-allyl)palladium(II) intermediate and the nucleophile does not interact with the palladium atom directly at the stereodifferentiating transition state.[1,2] We have previously reported that reasonably high enantioselectivity can be obtained in the allylation of β-diketone enolates by employing properly designed chiral phosphines bearing an aza crown ether moiety as ligands of the palladium catalysts.[3,4] The crown ether phosphines were designed so as to have a secondary interaction with the reacting substrate[5,6] by forming a crown ether−metal enolate inclusion complex. However, the mechanism of stereocontrol remains to be clarified. In order to gain a deeper insight into the stereocontrol by means of the secondary ligand−substrate interaction, it is important not only to expand the scope and limitations of this type of reaction but also to achieve the highest enantioselectivity possible. In this context, we examined several nitro compounds such as α-nitro ketones (**3a**−**c**) and α-nitro esters (**15a**−**c**) as a new class of substrates for the enantioselective palladium-catalyzed allylation.[7] Since the nitro group can be easily converted

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(1) (a) Fiaud, J.-C.; Hibon De Gournary, A.; Larcheveque, M. Kagan, H. B. *J. Organomet. Chem.* **1978**, *154*, 175. (b) Hayashi, T.; Kanehira, K.; Tsuchiya, H.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1162. (c) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113. (d) Ito, Y.; Sawamura, M.; Matsuoka, M.; Matsumoto, Y.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 4849. (e) Genet, J.-P.; Ferroud, D.; Juge, S.; Montes, J. R. *Tetrahedron Lett.* **1986**, *27*, 4573. (f) Genet, J.-P.; Juge, S.; Montes, J. R.; Gaudin, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, 718. (g) Genet, J.-P.; Juge, S.; Achi, S.; Mallart, S.; Montes, J. R.; Levif, G. *Tetrahedron* **1988**, *44*, 5263.

(2) Exceptionally high selectivities have been reported in the enantioselective allylation of 2-cyanopropionate promoted by a palladium−rhodium two-component catalyst system: Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309.

(3) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586.

(4) Reexamination of the enantiomeric excesses of the allylation product of 2-acetylcyclohexanone by GLC analysis with Chiraldex G-TA (0.25 mm × 30 m, 120 °C, base-line separation) revealed that the reported ee values in refs 1c and 3, which had been determined by ^{1}H NMR analyses with a chiral shift reagent and by optical rotations of the allylation product, respectively, had been overestimated by aproximately 15%. The highest ee values for this allylation product reported in ref 1c (81% ee) and ref 3 (75% ee) should be revised to 70% ee and 65% ee, respectively. The ee value (65% ee) for the allylation product of 2-acetylcyclopentanone reported in ref 3, which had been determined by ^{1}H NMR analysis with a chiral shift reagent, was confirmed to be correct by GLC analysis with Chiraldex G-TA (120 °C, base-line separation). Separation of the allylation product of 2-methyl-1-phenylbutane-1,3-dione by chiral GLC was not successful.

(5) For a review, see: Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857.

(6) For recent papers in accord with this concept, see: (a) Sawamura, M.; Kitayama, K.; Ito, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1829. (b) Ward, J.; Börner, A.; Kagan, H. B. *Tetrahedron: Asymmetry* **1992**, *3*, 849. (c) Börner, A.; Holz, J.; Kless, A.; Heller, D.; Berens, U. *Tetrahedron Lett.* **1994**, *35*, 6071. (d) Börner, A.; Ward, J.; Ruth, W.; Holz, J.; Kless, A.; Heller, D.; Kagan, H. B. *Tetrahedron* **1994**, *50*, 10419. (e) Holz, J.; Börner, A.; Kless, A.; Borns, S.; Trinkhaus, S.; Selke, R.; Heller, D. *Tetrahedron: Asymmetry* **1995**, *6*, 1973. (f) Börner, A.; Kless, A.; Kempe, R.; Heller, D.; Holz, J.; Baumann, W. *Chem. Ber.* **1995**, *128*, 767. (g) Börner, A.; Holz, J.; Ward, J.; Kagan, H. B. *J. Org. Chem.* **1993**, *58*, 6814. (h) Börner, A.; Kless, A.; Holz, J.; Baumann, W.; Tillack, A.; Kadyrov, R. *J. Organomet. Chem.* **1995**, *490*, 213. (i) Kless, A.; Kadyrov, R.; Börner, A.; Holz, J.; Kagan, H. B. *Tetrahedron Lett.* **1995**, *36*, 4601. (j) Fields, L. B.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1993**, *4*, 2229. (k) Yamazaki, A.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1993**, *4*, 2287. (l) Yamazaki, A.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 51. (m) Spencer, J.; Gramlich, V.; Häusel, R.; Togni, A. *Tetrahedron: Asymmetry* **1996**, *7*, 41. (n) MacFarland, D. K.; Landis, C. R. *Organometallics* **1996**, *15*, 483. (o) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. (p) Kimmich, B. F. M.; Landis, C. R.; Powell, D. R. *Organometallics* **1996**, *15*, 4141.

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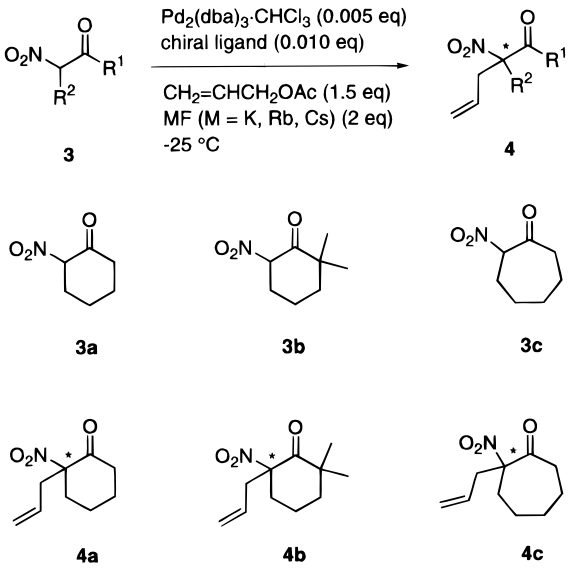
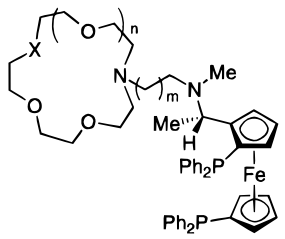
Scheme 1



into an amino group, these reactions may be regarded as equivalents of enantioselective allylations of α-amino ketones and α-amino esters (acids), respectively.[8]

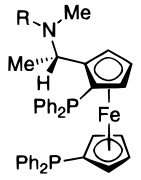
Results and Discussion

Enantioselective Allylation of α-Nitro Ketones (Scheme 1, Tables 1−3). The reaction of 2-nitrocyclohexanone (**3a**) with allyl acetate was carried out at −25 °C in the presence of alkali metal fluorides (MF, 2 equiv; M = K, Rb, Cs) and the palladium catalysts (1 mol %) prepared *in situ* from $Pd_2(dba)_3$·$CHCl_3$ and chiral phosphine ligands.



(*S*)-(*R*)-**1**

a: n = 0, m = 1, X = O
b: n = 1, m = 1, X = O
c: n = 2, m = 1, X = O
d: n = 2, m = 1, X = NMe
e: n = 3, m = 1, X = O
f: n = 2, m = 2, X = O



(*S*)-(*R*)-**2**

a: R = Me
b: R = $CH_2CH_2NMe_2$
c: R = CH_2CH_2OH

Table 1 summarizes the results with the ferrocenylphosphine ligand tethered to monoaza-18-crown-6 with dimethylene group **1c**. The reaction was quenched after 40 h in order to compare the reactivity. Allylation product **4a** was isolated by PTLC, and enantiomeric excesses were determined by GLC analysis with chiral stationary phase column Chiraldex G-TA (0.25 mm × 30 m, 150 °C, base-line separation). The reaction conditions employed for asymmetric allylation of β-diketones, which use KF and mesitylene for a base and a solvent, respectively, gave the product (**4a**) with only 14% ee (*R*) (Table 1, entry 1). Slightly higher selectivities were obtained in toluene, THF, and CH_2Cl_2 (Table 1, entries 2−4). As shown in entries 5 and 6 (Table 1), RbF was found to be a better base, giving (*R*)-**4a** with 29% ee and 38% ee in THF and CH_2Cl_2, respectively. The later selectivity was further improved to 42% by carrying out the reaction at a slightly lower concentration (ca. 0.5 M) (Table 1, entry 7). CsF was less effective in both reactivity and selectivity (Table 1, entry 8).

Then, the effect of the ring size of crown ether and the length of tether were examined for reactivity and enantioselectivity using RbF in CH_2Cl_2 (Table 2). The ligand (**1a**) tethered to monoaza-12-crown-4 with a dimethylene group gave almost racemic product in only 9% yield (Table 2, entry 1). The ligand (**1b**) tethered to monoaza-15-crown-5 was found to be as effective as **1c** in both reactivity and selectivity (Table 2, entry 2). The highest yield was obtained with the ligand bearing 1,10-diaza-18-crown-6 **1d**, while the enantioselectivity was slightly lower than that obtained using **1b** and **1c** (Table 2, entry 4). The enantioselectivity drastically decreased with the

Table 1. Enantioselective Allylation of 2-Nitrocyclohexanone (3a) with Allyl Acetate in the Presence of Pd-(*S*)-(*R*)-1c Catalyst[a]

			3a	**4a**	
entry	base	solvent	concn, M	yield,[b] %	ee,[c] % (confign)
1	KF	mesitylene	1.0	40	14 (*R*)
2	KF	toluene	1.0	47	19 (*R*)
3	KF	THF	1.0	66	25 (*R*)
4	KF	CH_2Cl_2	1.0	33	25 (*R*)
5	RbF	THF	1.0	50	29 (*R*)
6	RbF	CH_2Cl_2	1.0	57	38 (*R*)
7	RbF	CH_2Cl_2	0.5	28	42 (*R*)
8	CsF	CH_2Cl_2	1.0	31	31 (*R*)

[a] Reaction was carried out in 2 mL of solvent at −25 °C for 40 h. **3a** (1 mmol):allyl acetate:base:$Pd_2(dba)_3$·$CHCl_3$:(*S*)-(*R*)-**1c** = 1:1.5:2.0:0.005:0.0105. [b] Isolated yield by PTLC. [c] Determined by GLC analysis of **4a** with Chiraldex G-TA (150 °C, base-line separation).

Table 2. Ligand Effect in the Palladium-Catalyzed Enantioselective Allylation of 2-Nitrocyclohexanone (3a) with Allyl Acetate[a]

		3a	**4a**	
entry	chiral ligand	concn, M	yield,[b] %	ee,[c] % (confign)
1	(*S*)-(*R*)-**1a**	0.5	9	4 (*R*)
2	(*S*)-(*R*)-**1b**	0.5	27	41 (*R*)
3	(*S*)-(*R*)-**1c**	0.5	28	42 (*R*)
4	(*S*)-(*R*)-**1d**	0.5	48	39 (*R*)
5	(*S*)-(*R*)-**1e**	1.0	40	17 (*R*)
6	(*S*)-(*R*)-**1f**	0.5	11	31 (*R*)
7	(*S*)-(*R*)-**2a**	0.7	8	2 (*R*)
8	(*S*)-(*R*)-**2b**	0.7	22	2 (*S*)
9	(*S*)-(*R*)-**2c**	0.7	17	6 (*R*)
10	(*R*)-BINAP	0.5	18	15 (*R*)
11	(*S*,*S*)-CHIRAPHOS	0.5	2	<1
12	(*R*)-DIOP	0.5	14	<1

[a] Reaction was carried out in CH_2Cl_2 (2 mL) at −25 °C for 40 h. RbF was used for base. **3a** (1 mmol):allyl acetate:RbF:$Pd_2(dba)_3$·$CHCl_3$:chiral ligand = 1:1.5:2.0:0.005:0.0105. [b] Isolated yield by PTLC. [c] Determined by GLC analysis of **4a** with Chiraldex G-TA (150 °C, base-line separation).

(7) For the palladium-catalyzed allylic alkylations of nitro group-stabilized carbanions, see the following. For α-nitro ketones: (a) Ognyanov, V.; Hesse, M. *Synthesis* **1985**, 645. For α-nitro esters: (b) Genet, J. P.; Ferroud, D. *Tetrahedron Lett.* **1984**, *25*, 3579. (c) Genet, J. P.; Grisoni, S. *Tetrahedron Lett.* **1986**, *27*, 4165. (d) Lalonde, J. J.; Bergbreiter, D. E.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 2323. For nitroalkanes: (e) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523. (f) Deardorff, D. R.; Savin, K. A.; Justman, C. J.; Karanjawala, Z. E.; Sheppeck, J. E., II; Hager, D. C.; Aydin, N. *J. Org. Chem.* **1996**, *61*, 3616.

(8) For the use of 2-nitropropionates for the preparation of α-methylated α-amino acids, see: Robinson, B.; Shepherd, D. M. *J. Chem. Soc.* **1961**, 5037. See also ref 7d.

Table 3. Palladium-Catalyzed Enantioselective Allylation of α-Nitro Ketones (3a−c) with Allyl Acetate[a]

				3	
entry	**2**	chiral ligand	time, h	yield,[b] %	ee,[c] % (confign)
1	**2a**	(*S*)-(*R*)-**1b**	120	74 (**3a**)	49 (*R*)
2	**2b**	(*S*)-(*R*)-**1c**	260	95 (**3b**)	58 (*R*)
3	**2c**	(*S*)-(*R*)-**1b**	94	95 (**3c**)	44 (*R*)

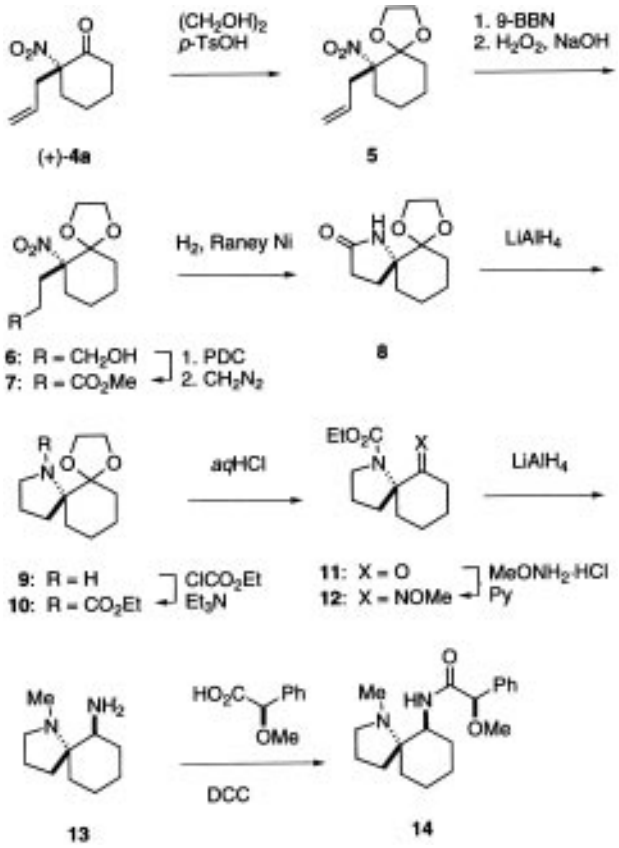
[a] Reaction was carried out in CH_2Cl_2 (2 mL) at −25 °C. RbF was used for base. **3** (1 mmol):allyl acetate:RbF:$Pd_2(dba)_3$·$CHCl_3$:chiral ligand = 1:1.5:2.0:0.005:0.0105. [b] Isolated yield by PTLC. [c] Determined by GLC analysis of **4** with Chiraldex G-TA (150 °C, base-line separation).

ligand-bearing monoaza-21-crown-7 **1e** (Table 2, entry 5). The ligand (**1f**) tethered to monoaza-18-crown-6 by trimethylene group gave (*R*)-**4a** with lower enantiomeric excess (31%) in only 11% yield (Table 2, entry 6). The ferrocenylphosphines lacking the crown ether moiety (**2a**−**c**)[1c,9] and other nonfunctionalized chiral ligands such as BINAP,[10] CHIRAPHOS,[11] and DIOP[12] were much less effective in both reactivity and selectivity, most of them giving almost racemic product (Table 2, entries 7−12), showing the crucial importance of the ligand crown ether moiety.

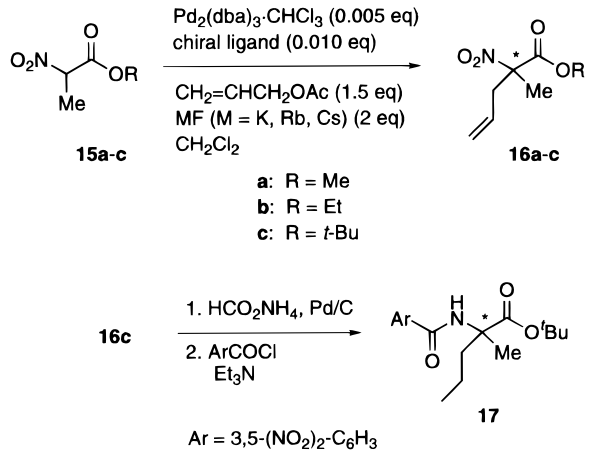
The results of the palladium-catalyzed asymmetric allylation of α-nitro ketones **3a**−**c** in the optimized reaction conditions are summarized in Table 3. The reaction of **3a** in the presence of the palladium catalyst with **1b** was led to completion in 120 h to give (*R*)-**4a** in 74% yield (Table 3, entry 1). It should be noted that the product enantiomeric excess (49% ee) is also significantly improved as compared with that in Table 2, entry 2 (41% ee). Higher enantioselectivity (58% ee) with the same chiral sense was observed for the reaction of 6,6-dimethyl-2-nitrocyclohexanone (**3b**) (Table 3, entry 2). 2-Nitrocycloheptanone (**3c**) was allylated more selectively with ligand **1b** (44% ee, Table 3, entry 3) rather than with **1c** (31% ee).

In order to determine the absolute configuration and to show a synthetic utility, allylation product **4a** was converted into 1-methyl-1-azaspiro[4.5]decan-10-amine (**13**),[13] whose *N*-acyl derivatives are reported to show potent opioid receptor binding activity (Scheme 2). The carbonyl group of nitro ketone **4a** with rotation $[\alpha]^{20}_D$ +47.8 ($CHCl_3$) (36% ee) was protected as acetal, and then the vinyl group of acetal **5** was converted to carboxylic acid by sequential oxidation with 9-BBN/H_2O_2 and PDC. Esterification of the carboxylic acid gave nitro ester **7**. The nitro group of **7** was hydrogenated in the presence of Raney Ni to form an amino ester, which underwent ring closure during the hydrogenation to give spiro lactam **8**. The lactam was then reduced to secondary amine **9** with $LiAlH_4$ and converted into carbamate **10**. The hydrolysis of acetal followed by condensation with *O*-methylhydroxylamine gave *N*-methoxyimine **12**. Diastereoselective reduction of **12** with $LiAlH_4$[13] gave desired diamine **13** (100% de), whose configuration was

Scheme 2



Scheme 3



determined to be R by X-ray crystal structure analysis of the major diastereomer of amide **14**, which was obtained by the condensation with (*R*)-*O*-methylmandelic acid.

The absolute configuration of **4b** was determined by comparing its CD spectrum with that of **4a** (see the supporting information). The configuration of **4c** was assigned on the basis of the comparison of the sign of the optical rotations and the pattern of GLC (Chiraldex G-TA) separation with those of **4a** and **4b**.

Enantioselective Allylation of α-Nitro Esters (Scheme 3, Table 4). The enantioselective allylation of 2-nitro-2-propionates (**15a**−**c**) with different ester alkyl groups were first carried out in CH_2Cl_2 at −25 °C in the

(9) (a) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138. (b) Hayashi, T.; Yamazaki, A. *J. Organomet. Chem.* **1991**, *413*, 295.

(10) (*R*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl: Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(11) (*S*,*S*)-1,2-Bis(diphenylphosphino)butane: Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.

(12) (*S*,*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane: Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

(13) Fujimoto, R. A.; Boxer, J.; Jackson, R. H.; Simke, J. P.; Neale, R. F.; Snowhill, E. W.; Barbaz, B. J.; Williams, M.; Sills, M. A. *J. Med. Chem.* **1989**, *32*, 1259.

Table 4. Palladium-Catalyzed Enantioselective Allylation of 2-Nitropropionates (15) with Allyl Acetate[a]

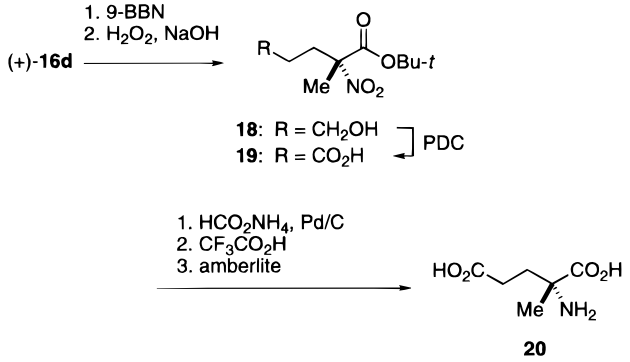
						16	
entry	R (**15**)	chiral ligand	base	additive[b]	*T*, °C	yield,[c] %	ee,[d] % (confign)
1	Me (**15a**)	(*S*)-(*R*)-**1c**	KF		−25	43 (**16a**)	23 (*R*)
2	Et (**15b**)	(*S*)-(*R*)-**1c**	KF		−25	44 (**16b**)	37 (*R*)
3	*t*-Bu (**15c**)	(*S*)-(*R*)-**1c**	KF		−25	95 (**16c**)	51 (*R*)
4	*t*-Bu (**15c**)	(*S*)-(*R*)-**1c**	RbF		−25	95 (**16c**)	60 (*R*)
5	*t*-Bu (**15c**)	(*S*)-(*R*)-**1c**	CsF		−25	91 (**16c**)	34 (*R*)
6[e]	*t*-Bu (**15c**)	(*S*)-(*R*)-**1c**	RbF		−25	88 (**16c**)	64 (*R*)
7[e]	*t*-Bu (**15c**)	(*S*)-(*R*)-**1c**	RbF	$RbClO_4$	−25	98 (**16c**)	69 (*R*)
8[e,f]	*t*-Bu (**15c**)	(*S*)-(*R*)-**1c**	RbF	$RbClO_4$	−40	92 (**16c**)	80 (*R*)
9	*t*-Bu (**15c**)	(*S*)-(*R*)-**1b**	KF		−25	95 (**16c**)	20 (*R*)
10	*t*-Bu (**15c**)	(*S*)-(*R*)-**1b**	RbF		−25	91 (**16c**)	18 (*R*)
11	*t*-Bu (**15c**)	(*S*)-(*R*)-**1d**	RbF		−25	60 (**16c**)	51 (*R*)
12	*t*-Bu (**15c**)	(*S*)-(*R*)-**1e**	RbF		−25	89 (**16c**)	11 (*R*)
13	*t*-Bu (**15c**)	(*S*)-(*R*)-**2a**	RbF		−25	72 (**16c**)	12 (*S*)
14	*t*-Bu (**15c**)	(*S*)-(*R*)-**2c**	RbF		−25	14 (**16c**)	1 (*S*)

[a] Reaction was carried out in CH_2Cl_2 (2 mL) for 40 h unless otherwise noted. **15** (1 mmol):allyl acetate:MF:$Pd_2(dba)_3$·$CHCl_3$:chiral ligand = 1:1.5:2.0:0.005:0.0105. [b] **15**:$RbClO_4$ = 1:1. [c] Isolated yield by PTLC. [d] Determined by GLC analysis of the products with Chiraldex G-TA (90 °C) for **16a**,**b** and by HPLC analysis of **17** (see Scheme 3 and Experimental Section for the transformation) with SUMICHIRAL OA-4400 (hexane:$ClCH_2CH_2Cl$:EtOH = 225:20:1) for **16c** (base-line separation except for **16a**). [e] Reaction was carried out in 6 mL of CH_2Cl_2. [f] Reaction time was 70 h.

presence of 2 equiv of KF and 1 mol % of the palladium catalyst containing the ferrocenylphosphine ligand (**1c**) tethered to 18-crown-6 by a dimethylene group, and the rates of reactions were compared on the basis of isolated yields (PTLC) of allylation products **16a**−**c** (Table 4, entries 1−3). The enantioselectivity for the *R*-isomer increased continuously from 23% to 51% with increasing steric demand of the ester alkyl group (Me < Et < *t*-Bu). The observed reactivities were not expected; i.e., while methyl (**15a**) and ethyl ester (**15b**) gave only 43% and 44% yields, complete conversion was observed for the reaction of the sterically most demanding *tert*-butyl ester (**15c**). Aggregation of enolates in the cases of the sterically less demanding nitro esters might be responsible for the unexpected reactivities. As in the cases of the reaction of nitro ketone **3a**, the enantioselectivity was dependent on the counter cations of metal fluoride bases (Table 4, entries 3−5), and the highest selectivity was again observed with RbF (60% ee). The selectivity was improved by using a large amount of CH_2Cl_2 solvent (64% ee, Table 4, entry 6) with $RbClO_4$ (69% ee, Table 4, entry 7) and then further improved to 80% ee (92% yield) by carrying out the reaction at −40 °C for 70 h (Table 4, entry 8).[14] We speculate that the added $RbClO_4$ might have increased a ratio of Rb^+-bound ligand to free ligand.[15] When the ligand (**1b**) tethered to monoaza-15-crown-5 was used, the reactions proceeded smoothly but the selectivities were only 20% ee and 18% ee with KF and RbF, respectively (Table 4, entries 9 and 10). The ligands bearing 1,10-diaza-18-crown-6 (**1d**) were less efficient in terms of both catalytic activity and enantioselectivity compared with **1c** (Table 4, entry 11). As shown in entries 12−14 (Table 4), the reactions using of the ligand bearing a monoaza-21-crown-7 moiety (**1e**) and the ferrocenylphosphines (**2a**,**c**) lacking a crown ether moiety gave almost racemic product.

Since the nitro group can be easily converted into an amino group, the allylation product thus obtained is considered to be useful synthetic intermediate for optically active α-methylated α-amino acids.[16] For example, the conversion of (*R*)-**16d** to α-methylglutamic acid (**20**)[17] was carried out as shown in Scheme 4. The allylation

Scheme 4



product (*R*)-**16d** (64% ee) was subjected to hydroboration−oxidation (9-BBN/H_2O_2) to give alcohol **18**. The alcohol was then oxidized to carboxylic acid **19** with PDC. The reduction of nitro group by catalytic transfer hydrogenation (Pd/C, HCO_2NH_4)[18] followed by hydrolysis of *tert*-butyl ester with CF_3CO_2H gave, after treatment with an ion-exchange column, optically active α-methylglutamic acid **20**. The absolute configuration of **16d** was determined by comparing the optical rotation of this amino acid with the reported value.[17]

Mechanism of Enantioselection. Unlike the enantioselective allylation of β-diketones,[3] relatively high enantioselectivities were obtained with rubidium fluoride rather than potassium fluoride in the reaction of both nitro ketones and nitro esters. It is obvious that relatively high reactivity and enantioselectivity were observed when a ferrocenylphosphine bearing a proper crown ether moiety was employed as a chiral ligand of palladium catalyst. The ligand bearing a monoaza-18-crown-6 moiety (**1c**), whose ring size is complementary with the size of rubidium cation, generally gave good results in terms of both reactivity and selectivity, while the ligand bearing the crown ether moiety of smaller ring size (**1b**) showed the comparable enantioselectivities only

(14) The ee was not further improved by lowering the reaction temperature to −50 °C; 7 days, 77% yield, 79% ee.

(15) No effect of $RbClO_4$ was observed in the enantioselective allylation of nitro ketone **3a**.

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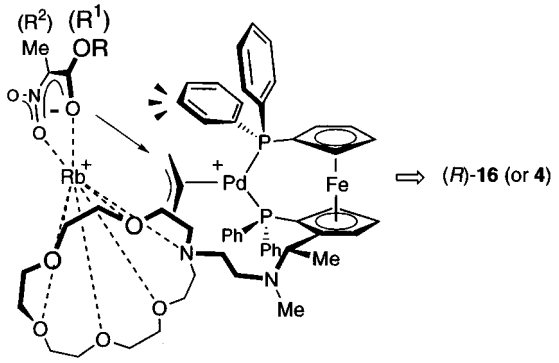

Figure 1. Illustration of possible nucleophilic attack of the rubidium enolate of **15** (or **3**) to the π-allylpalladium(II) complex bearing chiral ligand (*S*,*R*)-**1c**.

in the case of the reaction of nitro ketones (**3**). Even though more work is needed to understand the role of the rubidium cation and monoaza crown ether, the pronounced effect of the monoaza crown ether suggests that this metal cation-binding site interacts with the rubidium enolate attaking the π-allylpalladium complex and that such an interaction plays an important role for the enantioselection as well as the rate acceleration. On the basis of the absolute configuration of products, we speculate that enolate anion of the nitro compound attacks one of the terminal π-allyl carbon atom in such a way that a bulky substituent (R^1 for **3**, OR for **15**) can avoid the steric repulsion against one of the ligand phenyl groups as visualized in Figure 1.[19]

Conclusion

We presented a new example of enantioselective reaction in which a secondary interaction between a chiral ligand and a substrate plays an important role for the stereocontrol. An enantioselectivity as high as 80% was achieved in the palladium-catalyzed asymmetric allylation of nitro ester with a bulky ester alkyl group (**15c**) through the modification of chiral phosphine ligand with metal cation-binding crown ether moiety while the selectivity was moderate for the reaction of nitro ketones (**3**). We believe that the results presented here may be helpful for future mechanistic studies of palladium-catalyzed enantioselective allylic alkylation and that our chiral crown ether phosphine ligands are potentially applicable to other enantioselective catalytic processes involving main group metal ion species such as metal enolates, alkoxides and acetylides.

Experimental Section

Materials. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. α-Nitro ketones **3a**,**c**,[20] $Pd_2(dba)_3$·$CHCl_3$,[21] and ferrocenylphosphines **1a**−**f**[3] and **2a**−**c**[1c,9] were prepared according to the literature procedures. 2-Nitropropionates **15a**,**b** were distilled before use. Preparative medium-pressure liquid chromatography (MPLC) was performed with a silica gel prepacked C.I.G. (Kusano) column. The chiral stationary phase columns Chiraldex G-TA (for GLC, 0.25 mm × 30 m) and Sumichiral OA-4400 (for HPLC) were purchased from Advanced Separation Technologies, Inc., and Sumitomo Chemical Co., respectively.

6,6-Dimethyl-2-nitrocyclohexanone (3b) was prepared from 9.8 g (77 mmol) of 6,6-dimethylcyclohexanone[22] according to the literature procedure[20] for the preparation of **3a** as colorless crystals in 40% yield: mp 98.5−100 °C; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.16 (s, 3H), 1.27 (s, 3H), 1.58−1.99 (m, 4H), 2.27−2.61 (m, 2H), 5.53 (dd, J = 12.8, 6.3 Hz, 1H); ^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, TMS) δ 18.81, 24.20, 24.97, 31.99, 40.21, 46.31, 89.67, 202.86. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18. Found: C, 55.98; H, 7.88; N, 8.02.

General Procedure for the Palladium-Catalyzed Enantioselective Allylations of α-Nitro Ketones 3 and α-Nitro Esters 15. In a small glass vessel, chiral ligand (0.0105 mmol) and $Pd_2(dba)_3$·$CHCl_3$ (0.0050 mmol) were dissolved in 1 mL of reaction solvent. After being stirred for 1 h at rt, the solution was transferred to a 20-mL Schlenk tube containing metal fluoride (2.0 mmol) by using 1 mL of solvent (in the case of Table 4, entries 6−8, 4 mL more of solvent was added here). The nitro compound (**3** or **15**, 1.00 mmol) was added to the suspension at rt, and the mixture was cooled to a given reaction temperature before addition of allyl acetate (1.5 mmol). The reaction mixture was kept for a given reaction time at the same temperature. The reaction was quenched with 5% hydrochloric acid and extracted with ether four times. The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The allylation product (**4** or **16**) was isolated by PTLC on silica gel.

2-Allyl-2-nitrocyclohexanone (4a):[7a] $[\alpha]^{25}_D$ +54.5 (*c* 1.35, $CHCl_3$) (41% ee); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.55−1.91 (m, 4H), 1.91−2.16 (m, 1H), 2.47−2.71 (m, 3H), 2.71−2.95 (m, 2H), 5.05−5.25 (m, 2H), 5.59−5.82 (m, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 21.2, 26.7, 36.0, 39.6, 39.8, 96.7, 120.7, 130.1, 200.1. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.27; H, 7.30; N, 7.69.

2-Allyl-6,6-dimethyl-2-nitrocyclohexanone (4b): $[\alpha]^{25}_D$ +55.0 (*c* 1.30, $CHCl_3$) (57% ee); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.12 (s, 3H), 1.15 (s, 3H), 1.58−2.09 (m, 5H), 2.63 (dd, J = 13.0, 7.0 Hz, 1H), 2.78−2.99 (m, 2H), 5.07−5.22 (m, 2H), 5.52−5.73 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, TMS) δ 17.31, 25.90, 26.91, 34.13, 39.44, 41.72, 46.93, 94.41, 120.97, 130.33, 203.80. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.84; H, 8.25; N, 6.65.

2-Allyl-2-nitrocycloheptanone (4c): $[\alpha]^{25}_D$ +11.1 (*c* 1.51, $CHCl_3$) (43% ee); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.40−2.06 (m, 7H), 2.36−2.80 (m, 4H), 3.02 (dd, J = 14.2, 6.7 Hz, 1H), 5.10−5.22 (m, 2H), 5.59−5.80 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, TMS) δ 24.37, 25.39, 29.27, 33.64, 41.21(2C), 99.15, 121.11, 130.16, 202.15. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.84; H, 7.67; N, 7.10. Found: C, 60.95; H, 7.80; N, 7.13.

(*R*)-6-Nitro-6-(2′-propenyl)-1,4-dioxaspiro[4.5]decane (5). A solution of (*R*)-**3a** (2.27 g, 12.4 mmol, 36% ee), *p*-TsOH·H_2O (180 mg, 0.95 mmol), and ethylene glycol (14 mL, 251 mmol) in 70 mL of benzene was refluxed for 7 days. Saturated aqueous $NaHCO_3$ was added and extracted with ether four times. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was distilled (108−109 °C/0.5 mmHg) and purified by preparative HPLC (YMC-SH 543−5, hexane:AcOEt = 14:1) to afford 1.01 g (36%) of (*R*)-**5**: $[\alpha]^{25}_D$ +14.5 (*c* 1.78, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.21−1.50 (m, 1H), 1.58−1.82 (m, 5H), 2.08 (dt, J = 14.5, 4.3 Hz, 1H), 2.39 (td, J = 13.1, 3.2 Hz, 1H), 2.59 (dd, J = 14.4, 8.0 Hz, 1H), 3.36 (dd, J = 14.7, 6.4 Hz, 1H), 3.87−4.01 (m, 4H), 5.11−5.21 (m, 2H), 5.42−5.63 (m, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 21.5, 22.4, 29.4, 33.6, 35.8, 65.2, 94.6, 109.6, 120.4, 130.3. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.19. Found: C, 58.38; H, 7.50; N, 6.19.

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(*R*)-6-(3′-Hydroxypropyl)-6-nitro-1,4-dioxaspiro[4.5]-decane (6). A solution of (*R*)-**5** (1.01 g, 4.44 mmol) in 5 mL of THF was added to a solution of 9-BBN (2.17 g, 8.89 mmol) in 10 mL of THF at 0 °C. The mixture was stirred for 3.5 h at 0 °C and for 1 h at rt and then treated with 0.1 mL of water. After the mixture was cooled to 0 °C, 3 N NaOH (2.6 mL) and 30% H_2O_2 (3.65 mL) was carefully added in this order. Water was added and extracted with AcOEt three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/AcOEt) to afford 1.04 g (95%) of (*R*)-**6**: $[\alpha]^{25}_D$ −3.9 (*c* 1.71, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.10−1.14 (m, 4H), 1.14−1.85 (m, 5H), 1.92−2.15 (m, 2H), 2.44 (dddd, J = 9.9, 9.9, 3.8, 1.2 Hz, 1H), 3.52−3.80 (m, 2H), 3.86−4.02 (m, 4H) (OH not detected); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 21.6, 22.4, 26.2, 27.7, 29.3, 33.6, 62.2, 65.1, 65.2, 95.0, 109.9. Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.86; H, 7.80; N, 5.74. Found: C, 54.08; H, 8.00; N, 5.55.

(*R*)-6-[2′-(Methoxycarbonyl)ethyl]-6-nitro-1,4-dioxaspiro[4.5]decane (7). PDC (5.57 g, 14.79 mmol) was added to a solution of (*R*)-**6** (1.04 g, 4.23 mmol) in 11 mL and stirred at rt for 36 h. The mixture was diluted with ether, passed through a pad of Celite, and concentrated by heating at 45 °C under a reduced pressure. This procedure was repeated once more to give crude carboxylic acid (961 mg). For esterification, the carboxylic acid was dissolved in 5 mL of THF and 10 mL of ether and treated with a solution of CH_2N_2 in ether. The excess CH_2N_2 was decomposed with AcOH. The mixture was washed with saturated aqueous $NaHCO_3$, extracted with ether three times, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by MPLC (silica gel, hexane:AcOEt = 2:1) afforded 597 mg (52%) of (*R*)-**7**: $[\alpha]^{25}_D$ −5.8 (*c* 0.92, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.17−1.47 (m, 1H), 1.47−1.82 (m, 5H), 1.97 (dtd, J = 13.8, 4.0, 1.7 Hz, 1H), 2.10−2.34 (m, 3H), 2.46 (dddd, J = 15.9, 12.3, 3.8, 1.1 Hz, 1H), 2.91 (dddd, J = 17.5, 11.6, 3.1, 1.4 Hz, 1H), 3.68 (s, 3H), 3.86−4.02 (m, 4H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 21.6, 22.3, 26.5, 28.2, 29.5, 33.5, 51.8, 65.2, 94.3, 109.7, 172.6. Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.75; H, 7.15; N, 5.06.

(*R*)-1,3-Dioxolane-2-spirocyclohexane-2′-spiro-5″-2″-pyrrolidinone (8). Raney Ni (W7) (ca. 200 mg) was added to a solution of (*R*)-**7** (113 mg, 0.413 mmol) in MeOH (2 mL), and the mixture was stirred in an autoclave at 30 °C at a hydrogen pressure of 100 atm. After the mixture was stirred for 2 d, progress of the reaction was checked by TLC, which indicated the remains of the starting material. Raney Ni (ca. 200 mg) was added, and the mixture was again subjected to the hydrogenation for 4 d. After the completion of reaction was confirmed by TLC, the mixture was passed through a pad of Celite and evaporated. The residue was then purified by chromatography on silica gel (hexane:AcOEt, Et_2NH) followed by bulb-to-bulb distillation (200 °C/0.2 mmHg) to afford 52 mg (60%) of (*R*)-**8**: $[\alpha]^{25}_D$ −9.6 (*c* 1.07, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.18−1.93 (m, 9H), 2.22−2.40 (m, 2H), 2.44−2.65 (m, 1H), 3.83−4.10 (m, 4H), 5.64 (br s, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 21.7, 22.9, 28.5, 30.5, 32.0, 37.5, 64.5, 65.3, 65.7, 111.0, 177.9; HRMS (EI) calcd for $C_{11}H_{17}NO_3$ (M^+) 211.1207, found 211.1196. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.16; N, 6.66. Found: C, 61.97; H, 8.24; N, 6.59.

(*R*)-1,3-Dioxolane-2-spirocyclohexane-2′-spiro-2″-pyrrolidine (9). $LiAlH_4$ (168 mg, 4.42 mmol) was added at 0 °C to a solution of (*R*)-**8** (232.6 mg, 1.10 mmol) in 5 mL of THF. The mixture was then refluxed for 40 h and quenched at 0 °C by sequential additions of water (168 μL), 15% NaOH (168 μL), and water (504 μL). After the mixture was stirred at rt for 30 min, the aluminum salts were filtered off with a pad of Celite and washed with THF. The filtrate and washings were combined and concentrated under reduced pressure. The residue was then purified by bulb-to-bulb distillation (120 °C/0.2 mmHg) to afford 182 mg (84%) of (*R*)-**9**: $[\alpha]^{25}_D$ −0.9 (*c* 0.86, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.22−1.98 (m, 13H), 2.83−3.04 (m, 2H), 3.92−4.11 (m, 4H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 22.7, 23.1, 26.1, 32.2, 32.3, 37.3, 46.7, 64.8, 65.0, 67.0, 112.3; HRMS (EI) calcd for $C_{11}H_{19}NO_3$ (M^+) 211.1207, found 211.1196. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H,9.71; N, 7.10. Found: C, 66.71; H, 10.00; N, 6.97.

(*R*)-1,3-Dioxolane-2-spirocyclohexane-2′-spiro-2″-1″-(ethoxycarbonyl)azacyclopentane (10). A solution of ethyl chloroformate (603 mg, 5.56 mmol) in 3 mL of CH_2Cl_2 was slowly added to a solution of (*R*)-**9** (182.2 mg, 0.92 mmol) in 1.3 mL of Et_3N. After 1 h of stirring at rt, the mixture was combined with water and extracted with AcOEt three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (180 °C/0.2 mmHg) to afford 224.9 mg (90%) of (*R*)-**10**: $[\alpha]^{25}_D$ +7.0 (*c* 1.46, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.19−2.84 (m, 9H), 1.25 (t, 3H), 1.91−2.15 (m, 1H), 2.21−2.37(m, 1H), 3.12−3.34 (m, 1H), 3.35−3.66 (m, 2H), 3.76−3.96 (m, 4H), 4.02−4.23 (m, 2H); ^{13}C-{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 14.8, 21.6, 23.3, 23.5, 34.4, 35.1, 36.6, 49.6, 65.0, 65.1, 66.2, 70.0, 113.0, 155.4; HRMS (EI) calcd for $C_{14}H_{23}NO_4$ (M^+) 269.1626, found 269.1625. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 61.65; H, 8.45; N, 5.27.

(*R*)-6-Oxo-1-(ethoxycarbonyl)-1-azaspiro[4.5]decane (11). A solution of (*R*)-**10** (224.9 mg, 0.84 mmol) in 0.5 mL of CH_2Cl_2 was treated with 22 mL of 10% hydrochloric acid and stirred for 19 h at rt. The mixture was extracted with AcOEt three times, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by MPLC (silica gel, hexane:AcOEt = 1:1) followed by bulb-to-bulb distillation to afford 132 mg (70%) of (*R*)-**11**: $[\alpha]^{25}_D$ −10.2 (*c* 1.14, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.23 (dt, J = 14.2, 7.2 Hz, 3H), 1.47−2.17 (m, 9H), 2.23−2.45 (m, 1H), 2.46−2.80 (m, 2H), 3.46−3.67 (m, 2H), 4.03−4.22 (m, 2H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 14.0 and 14.7 (2 s), 22.3 and 22.9 (2 s), 23.3 and 23.5 (2 s), 24.6 and 24.7 (2 s), 35.6 and 36.7 (2 s), 37.1 and 38.2 (2 s), 39.8 (s), 47.8 and 48.4 (2 s), 60.77 and 60.85 (2 s), 71.1 and 71.5 (2 s), 154.5 and 154.9 (2 s), 208.0 and 208.3 (2 s). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.82; H, 8.65; N, 6.03.

(*R*)-1-(Ethoxycarbonyl)-6-(methoxyimino)-1-azaspiro-[4.5]decane (12). A solution of (*R*)-**11** (122 mg, 0.54 mmol) in 1.3 mL of pyridine was treated with H_2NOMe·HCl (301 mg, 3.60 mmol) and stirred for 23 h at rt. The reaction mixture was diluted with 3 mL of water, made alkaline with 3 N NaOH, and extracted with CH_2Cl_2 three times. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC (silica gel, hexane:AcOEt = 1:1) to afford 120 mg (87%) of (*R*)-**12**: $[\alpha]^{25}_D$ +16.7 (*c* 1.44, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.24 (dt, J = 6.7, 6.7 Hz, 3H), 1.30−1.97 (m, 9H), 2.02−2.16 (m, 1H), 2.48−2.68 and 2.84−3.03 (m, 1H + 1H′), 3.18−3.25 and 3.25−3.32 (m, 1H + 1H′), 3.36−3.50 (m, 1H), 3.77 (s, 3H), 3.96−4.27 (m, 2H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 14.7 and 14.9 (2 s), 21.2 and 21.4 (2 s), 23.1 and 23.2 (2 s), 23.36 and 23.43 (2 s), 23.9 (s), 36.2 and 37.1 (2 s), 38.5 and 39.6 (2 s), 47.9 and 48.5 (2 s), 60.2 and 60.4 (2 s), 61.6 (s), 65.7 and 66.4 (2 s), 154.4 and 155.7 (2 s), 157.3 and 157.9 (2 s). Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.11; H, 8.95; N, 10.89.

(*R*)-1-Methyl-1-azaspiro[4.5]decan-6-amine (13).[13] $LiAlH_4$ (170 mg, 4.47 mmol) was added to a solution of (*R*)-**12** (105 mg, 0.414 mmol) in 4.5 mL of THF at 0 °C. After 7 h of stirring at rt, the mixture was diluted with 5 mL of ether and cooled to 0 °C before being quenched by sequential additions of water (170 μL), 15% NaOH (170 μL), and water (510 μL). The mixture was stirred for 1 h at rt, and aluminum salts were filtered off with a pad of Celite and washed with THF. The combined filtrate and washings were concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (180 °C/16 mmHg) to afford 65 mg (93%) of (*R*)-**13**: $[\alpha]^{25}_D$ −1.20 (*c* 1.25, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.10−1.95 (m, 14H), 2.23 (s, 3H), 2.46−2.67 (m, 2H), 2.87−2.98 (m, 1H).

(2*R*,5′*R*)-*N*-(1′-Methyl-1′-azaspiro[4.5]dec-6′-yl)-2-methoxy-2-phenylacetamide (14). A solution of (*R*)-**13** (6.5 mg, 38.5 μmol) in 150 μL of CH_2Cl_2 was added to a mixture of (*R*)-α-methoxy-α-phenylacetic acid (13 mg, 78.2 μmol), DCC (15.7

mg, 76.1 μmol), and CH_2Cl_2 (100 μL) and stirred for 23 h at rt. The mixture was filtered and concentrated under reduced pressure. The residue was treated with AcOEt and cooled to 0 °C. The precipitates were filtered off, and the filtrate was concentrated under reduced pressure. The ^{1}H NMR spectrum of the residue indicated that the diastereomer ratio is in the range of 2:1 to 3:1. From this mixture, the major isomer (5.5 mg) was isolated by PTLC (silica gel, AcOEt, Et_2NH): ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.12−1.48 (m, 5H), 1.57−1.88 (m, 6H), 2.12 (s, 3H), 2.16−2.30 (m, 1H), 2.52−2.70 (m, 1H), 2.82−2.96 (m, 1H), 3.37 (s, 3H), 3.61−3.74 (m, 1H), 4.57 (s, 1H), 6.84 (br d, J = ca. 5 Hz, 1 H), 7.27−7.48 (m, 5H).

The configuration of the major isomer was determined to be (2*R*,5′*R*) by X-ray structure analysis of a single crystal obtained from a ligroin solution by slow evaporation of the solvent.

***tert*-Butyl 2-nitropropionate (15c)** was prepared in 72% yield according to the literature procedure[23] for the preparation of a related compound (MPLC): ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.49 (s, 9H), 1.75 (d, J = 7.1 Hz, 3H), 5.11 (q, J = 7.0 Hz, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 15.6, 27.6, 83.9, 84.4, 164.0.

Methyl (*R*)-2-methyl-2-nitro-4-pentenoate (16a):[7d] $[\alpha]^{25}_D$ +4.7 (*c* 1.00, $CHCl_3$) (12% ee); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.77 (s, 3H), 2.88 (dd, J = 14.2, 7.3 Hz, 1H), 3.00 (dd, J = 14.2, 7.2 Hz, 1H), 3.28 (s, 3H), 5.14−5.27 (m, 2H), 5.56−5.77 (m, 1H).

Ethyl (*R*)-2-methyl-2-nitro-4-pentenoate (16b): $[\alpha]^{25}_D$ +9.4 (*c* 1.11, $CHCl_3$) (35% ee); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.29 (t, J = 7.2 Hz, 3H), 1.76 (s, 3H), 2.87 (dd, J = 14.1, 7.5 Hz, 1H), 2.99 (dd, J = 14.1, 7.3 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 5.16−5.28 (m, 2H), 5.56−5.77 (m, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 13.8, 21.0, 40.8, 62.8, 92.0, 121.5, 129.6, 167.0. Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.46; H, 7.14; N, 7.54.

***tert*-Butyl (*R*)-2-methyl-2-nitro-4-pentenoate (16c):** $[\alpha]^{25}_D$ +12.5 (*c* 1.26, CHCl3) (66.0% ee); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.47 (s, 9H), 1.72 (s, 3H), 2.83 (dd, J = 14.1, 7.3 Hz, 1H), 2.95 (dd, J = 14.1 Hz, 7.1 Hz, 1H), 5.15−5.27 (m, 2H), 5.56−5.77 (m, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 21.0, 27.6, 40.9, 84.0, 92.5, 121.2, 129.8, 165.8. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.79; H, 8.22; N, 6.42.

***tert*-Butyl (*R*)-5-Hydroxy-2-methyl-2-nitropentanoate (18).** A solution of (*R*)-**16c** (1.07 g, 4.95 mmol, 64% ee) in 10 mL of THF was added to a solution of 9-BBN (1.22 g, 10.0 mmol) in 10 mL of THF at 0 °C. The mixture was stirred for 30 min at 0 °C and for 2.5 h at rt and then treated with 0.12 mL of water. After the mixture was cooled to 0 °C, 3 N NaOH (2.8 mL) and 30% H_2O_2 (4.1 mL) were carefully added in this order. The mixture was stirred at rt for 1.5 h. Water was then added and the mixture extracted with AcOEt three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/AcOEt) to afford 0.892 g (77%) of (*R*)-**18**: $[\alpha]^{25}_D$ +4.1 (*c* 1.39, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.48 (s, 9H), 1.43−1.71 (m, 2H), 1.76 (s, 3H), 2.10−2.40 (m, 2H), 3.67 (t, J = 6.5 Hz, 2H) (OH not detected); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$, TMS) δ 21.2, 26.8, 27.5, 32.9, 61.8, 84.0, 93.0, 166.2. Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N, 6.00. Found: C, 51.48; H, 8.39; N, 5.84.

(*R*)-4-(*tert*-Butoxycarbonyl)-4-nitropentanoic Acid (19). PDC (4.42 g, 11.74 mmol) was added to a solution of (*R*)-**18** (783 mg, 3.36 mmol) in 9.2 mL and the resulting mixture stirred for 3 h at 0 °C and then for 12 h at rt. The mixture was diluted with ether, passed through a pad of Celite, and concentrated by heating at 45 °C under reduced pressure. The residue was purified by chromatography on silica gel (hexane/AcOEt/MeOH) to afford crude (*R*)-**19**, which was used without further purification: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.48 (s, 9H), 1.76 (s, 3H), 2.38−2.55 (m, 4H) 8.03 (s, 1H).

(*R*)-2-Methylglutamic Acid (20). To a solution of (*R*)-**19** (605 mg, 2.45 mmol) in 16 mL of MeOH were successively added 10% Pd/C (302 mg) and HCO_2NH_4 (1.76 g, 28 mmol). After 32 h of stirring at rt, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residual colorless solid was dissolved in 5 mL of CF_3CO_2H and stirred overnight. After evaporation of CF_3CO_2H, the residue was subjected to an ion-exchange column (Amberlite IR-120B H^+ form). The column was washed with water. Elution with 5% aqueous NH_4OH followed by evaporation gave crude amino acid **20**, which was then recrystallized from a mixture of ether and MeOH to afford 201 mg (51%) of colorless crystals: $[\alpha]^{25}_D$ −4.6 (*c* 2.02, 6 N HCl) [lit.[16a] $[\alpha]^{rt}_D$ −12.1 (*c* 4, 6 N HCl) for (*R*) isomer]; ^{1}H NMR (200 MHz, D_2O, TPS) δ 1.49 (s, 3H), 1.97−2.09 (m, 2H), 2.23−2.34 (m, 2H).

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **8** and **10** and CD spectra of **4a**,**b** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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