ducts and used without purification. Hydrogen peroxide (Junsei) was commercial product. GC measurements were taken on a Hewlett-Packard 5890 gas chromatograph equipped with a Hewlett-Packard 3390A integrator. Identification of products was made with Hewlett-Packard 5970 GC-MASS. UV-visible spectra were recorded on a Shimadzu Model 2100 spectrophotometer. Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer.

Catalytic Reactions

Catalytic oxidations were carried out in a 25 mL round bottom flask equipped with side arm fitted with a screw capped silicon septum. In a typical experiment, [$PdCl_2$(dppm)] (56 mg, 0.1 mmol) was put into a flask. Solvent (10 mL) was added and followed by a styrene (15 mmol). After stirring for a few minutes, 35% H_2O_2 solution (0.5 mL, 5 mmol) was injected and the temperature was controlled and the time was started. The reaction was monitored with GC by periodic sampling. Relative oxidation rates were calculated from the concentration of product formation and were expressed in TOF (Turn Over Frequency=[oxidation product]/[catalyst]/hr).

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References

1. (a) Dargo, R. S.; *Coord. Chem. Rev.* **1992**, *117*, 185. (b) Akhrem, I. S.; Volpin, M. E. *Russ. Chem. Rev.* **1990**, *59*, 1906. (c) Pignolet, L. H.; *Homogenous Catalysis with Metal Phosphine Complexes*; Plenum Press : New York, 1983. (d) Drent, E.; *Pure & Appl. Chem.* **1990**, 62, 661. (e) Sheldon, R. A.; Kochi, J. K. *Metal Catalyzed Oxidation of Organic Compounds*; Academic: New York, 1981.
2. (a) Cusumano, J. A.; *Chemtech*, **1992**, *22(8)*, 482. (b) Gore, A. *Chemtech* **1995**, *25(3)*, 6.
3. Puddephatt, R. J.; *J. Chem. Soc. Rev.* **1983**, *12*, 99.
4. Sinigalia, R.; Michelin, R. A.; Pinna, F.; Strukul, G. *Organometallics* **1987**, *6*, 728.
5. Strukul, G.; Smigalia, R.; Zanardo, A.; Pinna, F.; Michelin, R. A. *Inorg. Chem.* **1989**, *28*, 554.
6. (a) Appleton, T. G.; Bennet, M. A.; Tomkins, I. B. *J. Chem. Soc. Dalton.* **1976**, 439. (b) Stern, E. W.; Maple, P. K. *J. Catal.* **1972**, *27*, 134.
7. (a) Muir, L. M.; Grossel, M. C.; Brown, M. P. *J. Chem. Soc. Dalton.* **1986**, 1955. (b) Park, Y. C.; Cho, Y. *J. Bull. Kor. Chem. Soc.* **1889**, *10*, 220. (c) Park, Y. C.; Kim, K. C.; Cho, Y. J. *J. Kor. Chem. Soc.* **1992**, *36*, 5, 685.
8. (a) Cooper, S. J.; Brown, M. P.; Puddephatt, R. J. *Inorg. Chem.* **1981**, *20*, 1374. (b) Hunt, C. T.; Balch, A. L. *Inorg. Chem.* **1981**, *20*, 2267.

Liquid Chromatographic Resolution of Racemic Cyclic Amines

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Optically active cyclic amines are abundant in nature and often show significant biological activity.[1] In addition, optically active cyclic amines have been widely employed as important intermediates or chiral building blocks in synthesizing biologically active natural products.[2] Consequently, optically active cyclic amines have been subjected to asymmetric synthesis.[3] In this context, the methods which allow a simple and accurate assessment of the enantiomeric purity of chiral cyclic amines synthesized asymmetrically or obtained from nature are required. Among various techniques, liquid chromatographic separation of enantiomers on chiral stationary phases (CSPs) has been known to be one of the most accurate and convenient means in determining the enantiomeric purity of optically active chemicals.[4]

Previously, several CSPs have been employed in resolving the enantiomers of chiral cyclic amines without much real understanding how CSPs distinguish between enantiomers.[5] However, CSP **1**, recently designed by Pirkle specifically for the resolution of α-arylpropionic acids, commercialized [(S,S)-Whelk-O 1] by Regis Chemical Company (Morton Grove, Illinois, U.S.A.) and found to be applicable in resolving broad spectrum of racemates,[6] has not been utilized in resolving racemic cyclic amines.

In this study, we wish to report that CSP **1** can be successfully utilized in resolving the enantiomers of racemic cyclic amines **2-4** as their *N*-α- and/or *N*-β-naphthoyl derivatives and wish to propose a possible chiral recognition mechanism based on the chromatographic resolution results and from the study of CPK molecular models. In addition, the resolution of the corresponding derivatives of cyclic amino esters **5**, which are structurally similar to cyclic amines, is reported.

CSP **1** possesses a strong π-acidic 3,5-dinitrobenzamide group. To utilize the strong π-acidic group of CSP **1** for the enantioselective π-π donor acceptor interaction with analytes,[7] racemic cyclic amines **2-4** available from prior study[5c] and cyclic amino esters **5** were derivatized by treating with α-naphthoyl and/or β-naphthoyl chloride. The strong π-basic na-

ture of the derivatizing group is expected to allow the enantioselective strong π–π donor-acceptor interaction between the CSP and the analyte.

Table 1 summarizes the chromatographic results for resolving *N*-α-naphthoyl and/or *N*-β-naphthoyl derivatives of cyclic amines **2-4** and cyclic amino esters **5**. As shown in Table 1, the chromatographic resolution results are reasonable. Previously *N*-α-naphthoyl derivatives of racemic cyclic amines have been reported to be resolvable with marginal separation factors on a CSP derived from (R)-*N*-(3,5-dinitrobenzoyl)phenylglycine.[5b] However, the enantioselectivity on CSP **1** turns out to be much greater than that on the CSP derived from (R)-*N*-(3,5-dinitrobenzoyl)phenylglycine. The *N*-α-naphthoyl derivatives are generally resolved better on CSP **1** than the *N*-β-naphthoyl derivatives. The greater enantioselectivity for the *N*-α-naphthoyl derivatives of cyclic amines might be expected to stem from the conformational rigidity engendered by the peri-hydrogen of the α-naphthoyl group.[8] However, the reason for the slightly greater enantioselectivity for the *N*-β-naphthoyl derivatives of cyclic amines in which the chiral center is far from the secondary amino group (analyte **2c** and **2h**) is not clear yet. From Table 1 it is also noted that the size of the alkyl group at the chiral center of cyclic amines **2** influences the enantioselectivity. For example, the separation factor increases continuously as the size of the alkyl group of cyclic amines **2** increases from methyl to ethyl and octyl moiety (analyte **2e**, **2f** and **2g**). The elution orders shown in Table 1 determined by injecting configurationally known samples are all consistent in a sense of chiral recognition. Note that the apparent opposite elution orders for resolving the derivatives of cyclic amines **2** and cyclic amino esters **5** are resulted simply from the inversion of the Cahn-Ingold-Prelog priority sequence for assignment of absolute configuration.

Based on the chromatographic resolution results shown in Table 1 and from the study of CPK molecular models, we propose a chiral recognition model as shown in Figure 1. In the chiral recognition model shown in Figure 1, we used (S, S)-4-[*N*-(3,5-dinitrobenzoyl)]amino-3-methyl-1,2,3,4-tetrahydrophenanthrene, **6**, as a model compound for the chiral selector of CSP **1** and (S)-*N*-α-naphthoyl-2-methylpyrrolidine (α-naphthoyl derivative of **2a**) as a representative compound for α-naphthoyl derivatives of (S)-cyclic amines. In the chiral recognition model, (S,S)-4-[*N*-(3,5-dinitrobenzoyl)] amino-3-methyl-1,2,3,4-tetrahydrophenanthrene is viewed from X-ray crystallographic data to have a semirigid framework containing a π-acidic 3,5-dinitrobenzamide group perpendicular to a π-basic naphthalene group, the amide N-H hydrogen being situated in the cleft formed by the two aromatic systems.[6c] In this instance, the perpendicular π-acidic and π-basic aromatic group present in the chiral selector are capable of simultaneous face to face and face to edge π–π interaction with an aromatic group present in the analyte.[6d] (S)-*N*-α-Naphthoyl-2-methylpyrrolidine is assumed to adopt a conformation in which the plane of the carboxamide system is out of the plane of the naphthalene ring because of the steric hindrance exerted by the peri-hydrogen.[9] In addition, it is also assumed that the *Z*-conformation of the car-

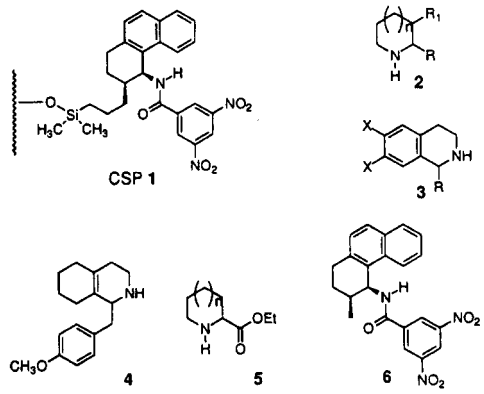

Table 1. Resolution of *N*-α- and/or *N*-β-naphthoyl derivatives of cyclic amines **2-4** and cyclic amino ethyl esters **5** on CSP **1**[a]

Anal.	R	R_1	X	n	α-Naph	Deriv.	Conf.[d]	β-Naph	Deriv.	Conf.[d]
					k_1[b]	α[c]		k_1[b]	α[c]	
2a	Me	H		0	7.27	1.72	S	4.94	1.68	S
b	Octyl	H		0	4.73	1.91				
c	H	Me		0	9.62	1.06		6.06	1.10	
d	H	Octyl		0	6.87	1.07				
e	Me	H		1	7.53	1.77	S	6.22	1.46	S
f	Ethyl	H		1	4.50	2.18		4.16	1.81	
g	Octyl	H		1	3.73	2.54		3.43	2.09	
h	H	Me		1	8.22	1.10		5.22	1.16	
3a	Phenyl		H		2.30	3.41				
b	Me		MeO					44.65	1.83	
4								8.22	1.62	
5a				0	7.55	2.44	R	10.46	1.10	R
b				1	5.69	2.14	R	6.37	1.17	R

[a] Chromatography was performed with an HPLC system consisting of a Waters model 510 pumpm, a Waters model U6k Liqid chromatographic injector, a Waters model 441 absorbance detector and a Waters model 740 data module recorder. All data were obtained by using 20% isopropyl alcohol in hexane as a mobile phase with a flow rate of 2 mL/min. at 254 nm UV. [b] Capactiy factor of the first eluted enamitioner. [c] Separation factor. [d] Absolute configuration of the second eluted enantiomer. For blanks, elution orders have not been established.

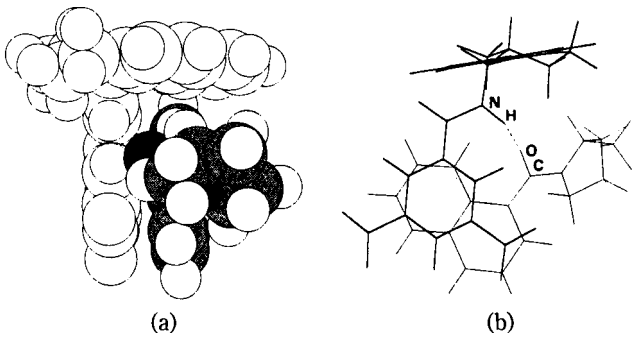

Figure 1. (a) Computer-generated three dimensional space filling chiral recognition model showing the enantioselective interaction between (S,S)-4-[*N*-(3,5-dinitrobenzoyl)]amino-3-methyl-1,2,3,4-tetrahydrophenanthrene, **6**, and *N*-α-naphthoyl derivative of (S)-2-methylpyrrolidine, **2a**. (b) Compuer-generated three dimensional stick chiral recognition model viewed from different angle.

boxamide part of (S)-*N*-α-naphthoyl-2-methylpyrrolidine is more favorable in solution than its *E*-conformation.[9,10]

In Figure 1, (S)-*N*-α-naphthoyl-2-methylpyrrolidine is shown to interact with (S,S)-4-[*N*-(3,5-dinitrobenzoyl)]amino-3-methyl-1,2,3,4-tetrahydrophenanthrene through the π–π interaction between the face of the α-naphthyl group of the analyte model compound and the face of the 3,5-dinitrobenzoyl group of the CSP model compound and the simultaneous edge to face π–π interaction between the edge of the α-naphthyl group of the analyte model compound and the face of the naphthalene ring of the CSP model compound. In addition the hydrogen bonding between the carbonyl oxygen of the (S)-analyte model compound and the amide N-H hydrogen of the CSP model compound acts as an important associate force between the two model compounds. In this event, as shown in Figure 1, the large methyl group at the chiral center of the (S)-analyte model compound directs away from the tetrahydrophenanthrene group of the CSP model compound while the small hydrogen at the chiral center of the (S)-analyte model compound directs towards the tetrahydrophenanthrene group of the CSP model compound. However, the same interaction between the (R)-analyte model compound and the CSP model compound is expected to have the large methyl group at the chiral center of the (R)-analyte direct towards the tetrahydrophenanthrene group of the CSP model compound, invoking some steric hindrance between them. Consequently, it is concluded that the (S)-analyte interacts with the CSP more strongly than the (R)-analyte and the (S)-analyte is retained longer on the CSP. In this event, the larger alkyl group than the methyl group at the chiral center of the analyte invokes even more steric hindrance between the alkyl group at the chiral center of the (R)-analyte and the CSP and consequently the enantioselectivity for the enantiomers on CSP **1** is expected to increase as the size of the alkyl group at the chiral center of the analyte increases. These are exactly consistent with the experimental observations shown in Table 1.

In summary, in this study, we demonstrated that commercially available CSP **1** can be successfully employed in resolving the enantiomers of various chiral cyclic amines and cyclic amino esters as their *N*-α-naphthoyl and/or *N*-β-naphthoyl derivatives. Based on the chromatographic resolution results and from the study of CPK molecular models, we proposed a chiral recognition model which utilizes the face to face π–π interaction between the α-naphthoyl group of the analyte and the 3,5-dinitrobenzoyl group of the CSP and the simultaneous face to edge π–π interaction between the α-naphthoyl group of the analyte and the naphthalene ring of the CSP, the hydrogen bonding interaction between the carbonyl oxygen of the analyte and the amide N-H hydrogen of the CSP, and the stereoselective steric interaction between the substituents at the stereogenic center of the analyte and the tetrahydrophenanthrene group of the CSP. The proposed chiral recognition model was successful in rationalizing the experimental observations. However, the chiral recognition model proposed herein may be modified or improved as more chromatographic and/or spectroscopic evidences are accumulated.

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References

1. Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiely: New York, U.S.A., 1985; Vol. 3, pp 1-90.
2. Apsimon, J. Ed. *The Total Synthesis of Natural Products*; Wiely: New York, U.S.A., 1977; Vol. 3.
3. For example, see (a) Meyers, A. I.; Fuentes, L. M.; Kubota, Y. *Tetrahedron* **1984**, *40*, 1361. (b) Kerrick, S.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (c) Freville, S.; Celerier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron Asymm.* **1995**, *6*, 2651.
4. (a) Krstulovic, A. M. Ed. *Chiral Separations By HPLC: Applications to Pharmaceutical Compounds*; Ellis Horwood: Chichester, England, 1989. (b) Ahuja, S. Ed. *Chiral Separations by Liquid Chromatography*, ACS Symposium Series 471, American Chemical Society; Washington, DC. 1991. (c) Taylor, D. R.; Maher, K. *J. Chromatogr. Sci.* **1992**, *30*, 67. (d) Hyun, M. H.; Mim, C.-S. *Bull. Kor. Chem. Soc.* **1996**, *17*, 1117.
5. (a) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117. (b) Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* **1984**, *49*, 2504. (c) Pirkle, W. H.; McCune J. E. J. *Chromatogr.* **1988**, *441*, 311. (d) Hyun, M. H.; Kim, M.-S. *Bull. Kor. Chem. Soc.* **1991**, *12*, 104.
6. (a) Pirkle, W. H.; Welch, C. J.; Lamm, B. *J. Org. Chem.* **1992**, *57*, 3854. (b) Pirkle, W. H.; Chris, C. J. *J. Liq. Chromatogr.* **1992**, *15*, 1947. (c) Welch, C. J. Ph. D. Dissertation, University of Illinois, Champaign-Urbana, IL. 1992. (d) Pirkle, W. H.; Chris, C. J. *Tetrahedron Asymm.* **1994**, *5*, 777.
7. Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347.
8. Hyun, M. H.; Kim, M. H. *J. Liq. Chromatogr.* **1990**, *13*, 3229.
9. Pirkle, W. H.; Welch, C. J.; Zych, A. J. *J. Chromatogr.*

1993, *648*, 101.
10. Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. *Tables of Spectral Data for Structure Determination of Organic Compouds ^{13}C-NMR ^{1}H NMR IR MS UV/VIS*, Translated by Biemann, K.: Springer-Verlag: Berlin, Germany, 1989; p H160.

A Convenient Synthesis of β-Keto Phosphonates from Diethylphosphonoacetic Acid

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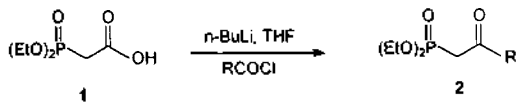
β-Keto phosphonates are valuable intermediates for organic synthesis, especially for the preparation of α,β-unsaturated carbonyl compounds by the Horner-Wadsworth-Emmons condensation.[1] Commonly, β-keto phosphonates are prepared by the Arbuzov reaction and acylation of alkylphosphonate anions. The Arbuzov reaction of trialkyl phosphite and a-halogeno ketones leads to β-keto phosphonates. The latter method is restricted to highly reactive α-halogeno ketones or a-halogeno ketones containing a carbonyl protecting group, because of the nucleophilicity of phosphites and competition from the Perkow reaction to give enol phosphates.[2] The most commonly used method for preparing β-keto phosphonates is acylation of alkylphosphonate a-anions with carboxylic acid esters,[3] carboxylic acid chlorides,[4] N-methoxy-N-methylcarboxamides.[5] or nitriles followed by hydrolysis.[6] Recently, β-keto phosphonates were also obtained by either base-induced isomerization of enol phosphates or reaction of ketone enolates with dialkylphosphorochloridite followed by aerial oxidation.[7] Other miscellaneous methods include acylation of 1-(trimethylsilyl)vinylphosphonates,[8] hydrolysis of vinylogous phosphoramides,[9] reaction of 2-(diethoxyphosphinyl)carboxylic acid chlorides with organometallic reagents,[10] the use of (diethoxyphosphoryl)acetonitriles oxides,[11] *via* allene oxide,[12] nucleophilic addition of allenic phosphonate with diethylamine and subsequent hydrolysis,[13] Pd(0)-catalyzed rearrangement of the 2,3-epoxyalkyl phosphonates,[14] reaction of phosphite with epoxysulfones,[15] chloroepoxide,[16] or α-nitro epoxides,[17] oxidation of β-hydroxyalkylphosphonates,[18] reaction of silyl enol ethers with phosphite using hypervalent iodine compound,[19] alkylation of β-keto phosphonates,[20] acylation of triethyl phosphonoacetate,[21] and reaction of nitroalkenes with phosphite.[22]

Herein we wish to report a convenient synthesis of β-keto phosphonates **2** from diethylphosphonoacetic acid **1**. Under anhydrous conditions diethylphosphonoacetic acid was treated with 2.2 equiv. of *n*-butyllithium in THF at − 78 °C. The resulting diethyl phosphonoacetate dianion underwent a facile reaction with carboxylic acid chlorides. On aqueous workup β-keto phosphonates 2 were isolated in good yields. Noteworthy was that both aromatic and aliphatic carboxylic acid chlorides were compatible with this methodology and both gave high yields.

Table 1. Preparation of β-keto phosphonates **2** from diethylphosphonoacetic acid **1**

Entry	R	Product	Yield[a]
1	Ph	**2a**	88
2	*p*-$C_6H_4CH_3$	**2b**	87
3	*p*-C_6H_4Cl	**2c**	81
4	*m*-C_6H_4Br	**2d**	78
5	*trans*-CH=CHPh	**2e**	90
6	C_2H_5	**2f**	73
7	*n*-C_5H_{11}	**2g**	78
8	cyclo-C_6H_{11}	**2h**	74
9	$CH(OAc)CH_3$	**2i**	65

[a] Isolated yields are based on diethylphosponoacetic acid.



1 2

The aromatic carboxylic acid chlorides containing electron rich and electron deficient substituents reacted with equal efficiency (entry 1-4). In the aliphatic carboxylic acid chlorides series, primary and secondary acid chlorides gave good yields (entry 5-9). Compared with general synthetic route for the preparation of β-keto phosphonates by the acylation of alkylphosphonate,[3-6] the present procedure is inexpensive and convenient.

In conclusion, we have developed a new convenient procedure for the preparation of β-keto phosphonates based on the acylation of diethyl phosphonoacetate dianion with carboxylic acid chlorides in THF.

Experimental Section

All reactions were carried out under nitrogen atmosphere. ^{1}H and ^{13}C NMR were measured at 200 and 50 MHz, respectively, in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded on HP 5985A or Jeol HX100/HX110.