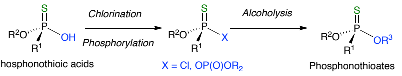
キラリティー転写を利用した*P*-キラル化合物合成法の開発

A03−3

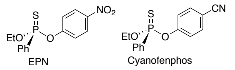
（岐阜大工）村井利昭

Phosphonothioates



Phosphonothioic acids X = Cl, OP(O)OR$_2$ Phosphonothioates

- Pesticides

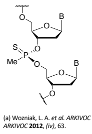


EPN Cyanofenphos

The chirality at the P atom affects biological activities.

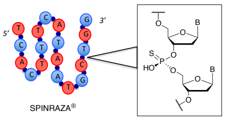
(a) Aaron, H. S. *et al. J. Am. Chem. Soc.* **1958**. (b) Eto, M. *et al. J. Pesticide Sci.* **1984**, *9*, 455.

- ASOs (antisense oligonucleotides)



The “Carbon” effects

- Improving cellular uptake
- Increasing stability toward hydrolysis and nucleases



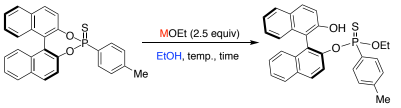
SPINRAZA®
Therapy for
spinal muscular atrophy

2^{17} = 131,072 isomers

(a) Wozniak, L. A. *et al. ARKIVOC* **2004**, *(iii)*, 101. (b) Stawinski, J. and Nawrot, B. *et al. ARKIVOC* **2012**, *(iv)*, 63.

Wada, T. *et al. J. Am. Chem. Soc.* **2002**, *124*, 4962. (g) Baran, P. S. *et al. Science* **2018**, *361*, 1234.

Effect of counter cation and reaction temperature



MOEt	temp. (°C)	time (h)	yield (%)	S.M. (%)	dr[a]
NaOEt	rt	0.5	97(82)	0	81:19
LiOEt	rt	2	91(76)	9	90:10
LiOEt	0	13	97(88)	0	94:6
LiOEt	–20	70	49	51	>95:5

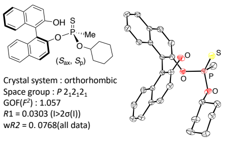
[a] The yields were calculated by ^{31}P NMR analysis of the crude reaction mixtures. Isolated yields are shown in the parentheses. [b] Ratio of diastereomers was determined by ^{31}P NMR analysis of the crude reaction mixtures.

The axis chirality of binaphthyl group transferred to the central chirality of phosphorus atom.

The use of Li salt gave the corresponding product with better yields and dr.

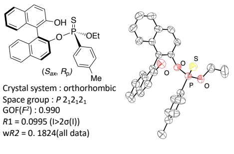
Configurations of P atom

(Solvent: THF)



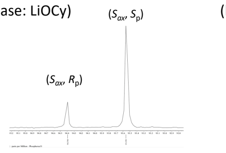
Crystal system : orthorhombic
Space group : *P* $2_12_12_1$
GOF(F^2) : 1.057
*R*1 = 0.0303 (I>2σ(I))
w*R2* = 0. 0768(all data)

(Solvent: EtOH)

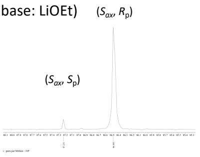


Crystal system : orthorhombic
Space group : *P* $2_12_12_1$
GOF(F^2) : 0.990
*R*1 = 0.0995 (I>2σ(I))
w*R2* = 0. 1824(all data)

(base: LiOCy)

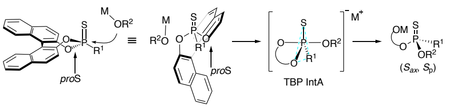


(base: LiOEt)

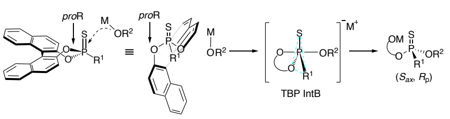


Plausible reaction pathway

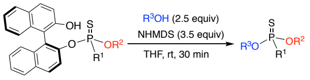
- Path A: Attack of alkoxide to back side of *pro*S P-O bond

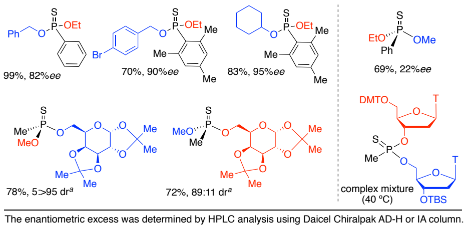


- Path B: Attack of alkoxide to back side of *pro*R P-O bond



Substrate scope



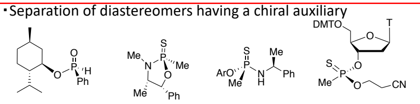


99%, 82%*ee*; 70%, 90%*ee*; 83%, 95%*ee*; 69%, 22%*ee*; 78%, 5:>95 dr[a]; 72%, 89:11 dr[a]; complex mixture (40 °C)

The enantiometric excess was determined by HPLC analysis using Daicel Chiralpak AD-H or IA column.
[a] Ratio of diastereomers was determined by ^{31}P NMR analysis of the crude reaction mixtures.

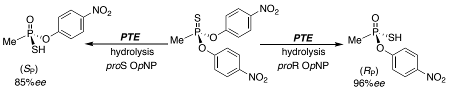
Synthetic methods

- Separation of diastereomers having a chiral auxiliary



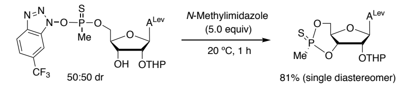
(a) Han, Z. S. *et al. J. Am. Chem. Soc.* **2013**, *135*, 2474. (b) Inch, T. D. *et al. J. Chem. Soc., Chem. Commun.* **1975**, 721. (c) Purnanand, B. S. *et al. Tetrahedron Lett.* **1994**, *35*, 4641. (d) Stec, W. J. *et al. J. Org. Chem.* **1998**, *63*, 9109.

- Stereospecific synthesis (limited examples)



(S_P) 85%*ee* (R_P) 96%*ee*

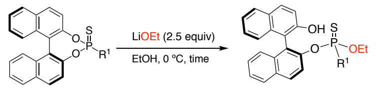
Raushel, F. M. *et al. J. Am. Chem. Soc.* **2002**, *124*, 3498.



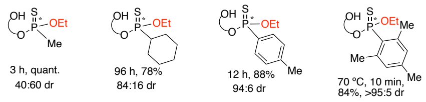
50:50 dr 81% (single diastereomer)

Van Boom, J. H. *et al. Nucleosides & Nucleotides* **1992**, *11*, 141.

Substrate scope



product

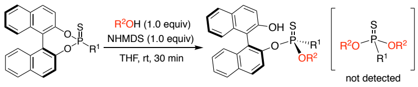


3 h, quant. 40:60 dr; 96 h, 78% 84:16 dr; 12 h, 88% 94:6 dr; 70 °C, 10 min, 84%, >95:5 dr

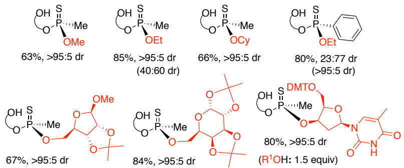
[a] Isolated yields are shown. [b] Ratio of diastereomers was determined by ^{31}P NMR analysis of the crude reaction mixtures.

As substituents on the phosphorus atom, alkyl and aryl groups are available.

Substrate scope



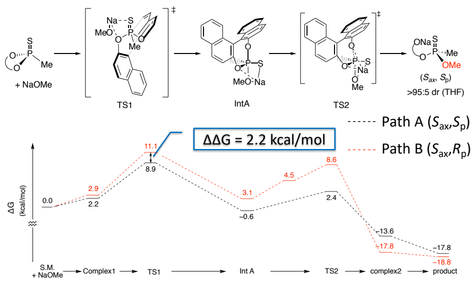
product



63%, >95:5 dr; 85%, >95:5 dr (40:60 dr); 66%, >95:5 dr; 80%, 23:77 dr (>95:5 dr); 67%, >95:5 dr; 84%, >95:5 dr; 80%, >95:5 dr (R¹OH: 1.5 equiv) (NHMDS: 3.0 equiv)

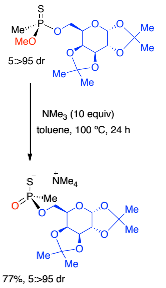
[a] Isolated yields are shown. [b] Ratio of diastereomers was determined by ^{31}P NMR analysis of the crude reaction mixtures.

Computational analysis



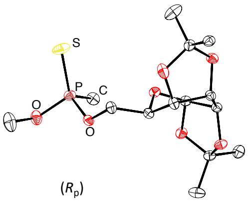
B3LYP/6-31G(d,p) scrf=(solvent=THF)//B3LYP/6-31G(d,p) (@298 K, 1 atm)

Configuration of P atom



5:>95 dr

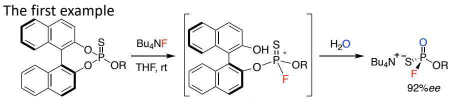
77%, 5:>95 dr
G6P analog



(R_p)
Crystal system : orthorhombic
Space group : *P* $2_12_12_1$
GOF(F^2) : 1.040
*R*1 = 0.0248 (I>2σ(I))
w*R2* = 0. 0660 (all data)

Axis-to-Center chirality transfer

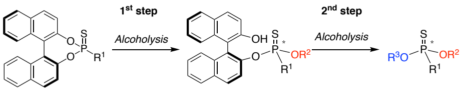
The first example



Chem. Commun. **2014**, *50*, 12473.

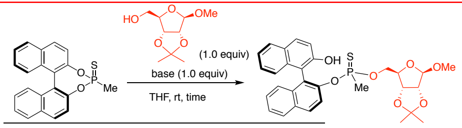
- Nucleophilic attack of F⁻ and hydrolysis proceeded with high stereoselectivities.
- The Intermediates were readily hydrolyzed.

Our new strategy



- No need to separate of stereoisomers.

Optimization of reaction conditions



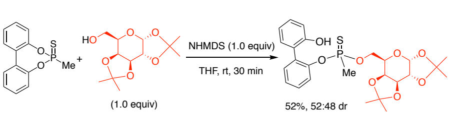
base	additive	time (h)	yield (%)[a]	dr[b]
NHMDS	-	1	89 (67)	>95:5
LHMDS	-	1	41	79:21
NHMDS	18-crown-6	1	100	82:18
DBU	-	1.5	86 (62)	75:25
^{t}BuMgCl	-	1.5	n.r.	-

[a] The yields were calculated by ^{31}P NMR analysis of the crude reaction mixtures. Isolated yields are shown in the parentheses.
[b] Ratio of diastereomers was determined by ^{31}P NMR analysis of the crude reaction mixtures.

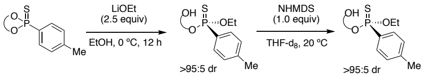
NHMDA worked efficiently in the reaction in THF.

Control experiment

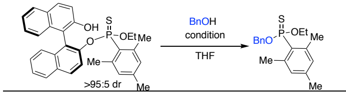
✔Binaphthyl group controlled the stereoselectivities.



✔Epimerization of the product did not occur.



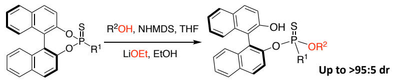
Second alcoholysis: effect of base



condition	M	base	S.M.	time (h)	yield (%)	*ee* (%)[a]
BnOM (3.5 equiv)	Na	-	(R_{ax}, *S*)	0.5	72	–88
	Li	-	(R_{ax}, *S*)	4	86	–58
BnOM (2.5 equiv)	Na	NHMDS	(S_{ax}, *R*)	0.5	70	>99
	Li	*n*-BuLi	(R_{ax}, *S*)	4	84	<-99
BnOM (2.5 equiv)	-	DBU	(S_{ax}, *R*)	24	15	66
Base (3.5 equiv)	-	NHMDS	(R_{ax}, *S*)	0.5	92	>99

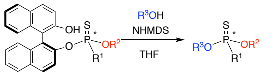
Isolated yields are shown. [a] The enantiometric excess was determined by HPLC analysis using Daicel Chiralpak IA column. [b] *n*-BuLi was added at –78 °C. [c] The reaction was carried out at rt.

Summary



Up to >95:5 dr

- Alcoholysis proceeded via axis-to-center chirality transfer.
- The stereoselectivities depend on the solvents and the counter cation.
- The coordination induces high diastereoselectivities.



- NHMDS was necessary to improve the stereoselectivities.
- 2nd step alcoholysis proceeded in ‘almost’ with inversion of configuration at the phosphorus atom.
- Both enantiomers were synthesized starting from single phosphonothioates.

Kuwabara, K.; Maekawa, Y.; Minoura, M.; Maruyama, T.; Murai, T. *J. Org. Chem.* doi.org/10.1021/acs.joc. 0c00687.