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[1,2]-Wittig Rearrangement of Enantio-defined α-Alkoxyalkyllithiums: Structural Requirement and Steric Course at the Li-Bearing Terminus.

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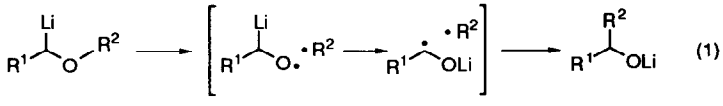
Abstract: The [1,2]-Wittig rearrangements of enantio-defined α-benzyloxypropyllithium and its (*R*)-α-methylbenzyloxy analogs, generated from the enantio-enriched stannanes via Sn / Li exchange, are shown to proceed predominantly with inversion of configuration at the Li-bearing terminus and retention of configuration at the migrating center, and exhibit a significant level of mutual enantiomer recognition in the radical recombination process.

The [1,2]-Wittig rearrangement is a text-book reaction and its mechanism has been a long-standing subject of mechanistic studies. [1] Now widely recognized are: (1) the rearrangement proceeds via the radical dissociation-recombination mechanism, not in a concerted fashion (eq. 1), (2) the alkyl migration occurs with partial retention of configuration at the migrating center, [2] and (3) the migratory aptitude of R^2 increases in the order of *prim-* < *sec-* < *tert*-alkyl < benzyl. However, little is known about: (a) the structural requirement, particularly for the carbanion terminus, (b) the steric course (inversion *vs.* retention) at the Li-bearing terminus,[3] and (c) the possibility of mutual recognition of radical enantiomers [4] in the recombination process.

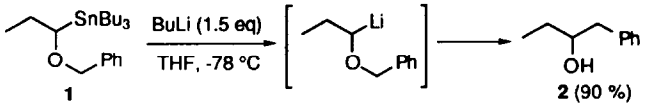
In order to answer these fundamental questions, we have now investigated the [1,2]-Wittig rearrangement using as substrates α-alkoxyalkylstannanes with different alkyl groups and enantio-defined α-alkoxy-stannanes. This paper describes the results relevant to address the three questions.

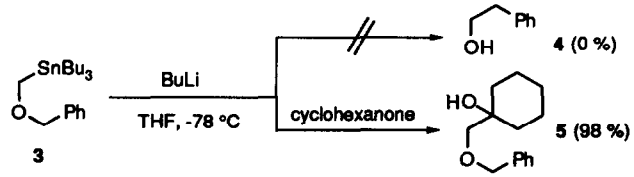


(1)

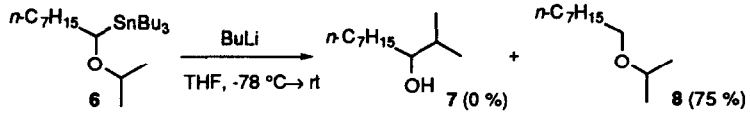
Structural Requirements

In order to define the structural requirements for the [1,2]-Wittig rearrangement, we first studied the rearrangement of benzyl ether **1**, isopropyl ether **6** , tetrahydrofuranyl ethers **9** and **11**. These substrates were prepared as the racemic form from the corresponding stannyl alcohols according to the previously developed procedure [5] or by reaction with 2-chlorotetrahydrofuran. Treatment of benzyl ether **1** with BuLi (THF, -78 °C) was found to afford 90 % of the Wittig product **2**. This result is of special interest in view of Still's observation that benzyloxymethyllithium generated from stannane **3** does not undergo the Wittig rearrangement under similar conditions. [6]

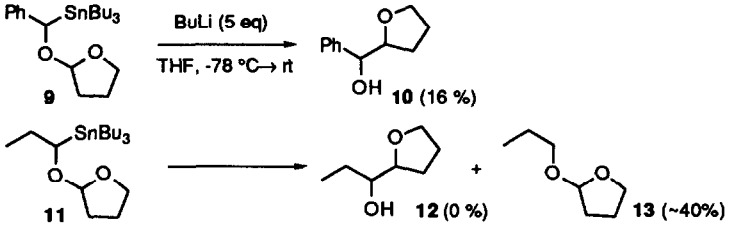




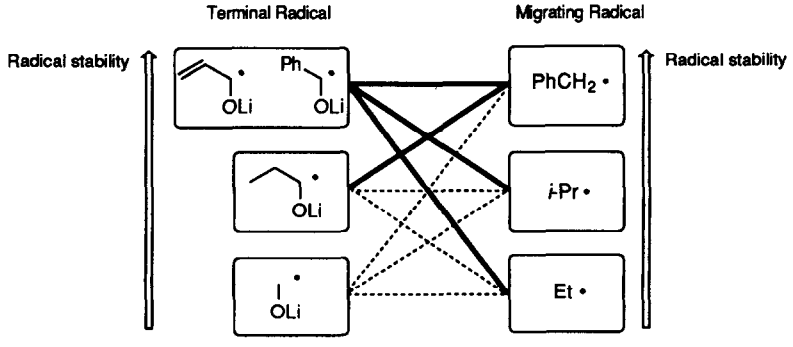
These findings reveal that the Wittig reactivity of the secondary carbanion terminus is much higher than that of the primary counterpart. However, when isopropyl group was employed as the migrating group (cf. **6**) in place of benzyl, no rearrangement occured, instead the destannylated ether **8** resulting.



Next, we examined the rearrangements of stannanes **9** and **11**. Treatment of **9** with butyllithium gave the Wittig product **10** in 16 % yield, whereas **11** gave only the destannylated ether **13**.



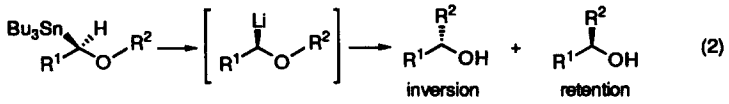
These observations, coupled with the reported ones, [1, 6] reveal that a radical stabilizing factor in either the carbanion terminus or the migrating terminus is required for the facile [1,2]-Wittig rearrangement. In other words, rather stable carbanions that can be generated by direct deprotonation undergo the Wittig rearrangement in most cases, while the rearrangement of relatively unstable radicals requires a migrating group, like benzyl, of which the radical species is substantially stabilized.



Steric Course (Inversion *vs.* Retention) at the Li-bearing Terminus

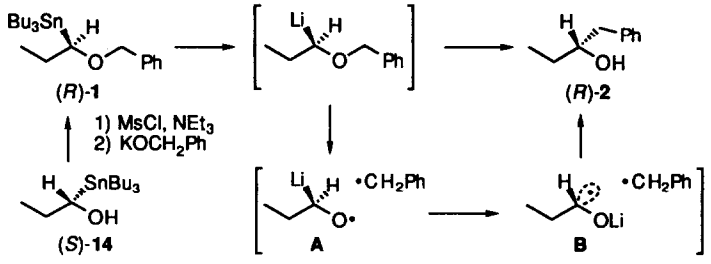
Recently Cohen's and Brückner's groups have presented pieces of evidence for the inversion course in the reductive lithiation-induced rearrangements of sterically biased cyclic systems. [7] In order to definitively answer the stereochemical question, we have now investigated the stereochemistry of the [1,2]-Wittig rearrangements using enantio-defined α-alkoxyalkylstannanes as the substrates (eq. 2). Described here are the stereochemical

outcomes which permit the detailed understanding of the stereochemistry and mechanism of the [1,2]-Wittig rearrangement in general.



(2)

The enantio-defined stannane (*R*)-**1** was prepared from the stannyl alcohol (*S*)-**14** (88% ee) with inversion of configuration according to the previously-developed procedure. [5,8] Treatment of (*R*)-**1** with BuLi (THF, -78°C) was found to afford 90% of the Wittig product (*R*)-**2** in 42% ee. [9] Since the Sn / Li exchange involved is known to occur with complete retention of configuration, [10] this outcome reveals that the reaction proceeds with at least [8] 74% inversion of configuration. This means that the radical recombination occurs within a "solvent cage" after the initially formed *O*-radical **A** might be converted to the *C*-radical **B** of predominantly inverted configuration. [11] It is interesting to note that the inversion stereochemistry in the present 1,2-alkyl shift is in contrast to the retention of configuration observed for the 1,2-silyl shift in the retro-Brook rearrangement (R^1 = alkyls, R^2 = $SiMe_3$). [12]



Configurational Stability of the Anion Radical Involved

In order to shed further light on the radical recombination process, we examined the double asymmetric versions using the stannyl ethers **15** and **16**, where the both radical fragments are chiral, thus providing a unique opportunity of observing the rarely precedented mutual recognition of radical enantiomers. [4] Table 1 shows the product distributions which were determined by HPLC comparisons of the MTPA esters with those of an authentic mixture prepared by the asymmetric reaction of (±)-2-phenylpropanal with diethylzinc catalyzed by (-)-*N*,*N*-dibutylnorephedrine which affords **19** as the major product. [13]

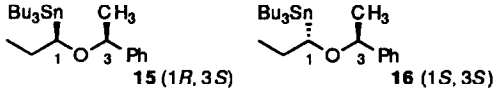
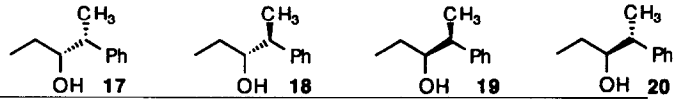


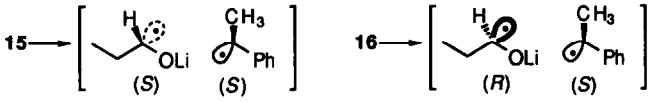
Table 1. Product Distributions in the rearrangements of **15** and **16**.[a)]



Substrate	% yield	Product ratio **17 : 18 : 19 : 20**	% inversion at C1	% retention at C3
15	79	7 : 67 : 23 : 3	74	90
16	87	~0 : 10 : 88 : 2	90	98

a) The stereoisomeric composition were determined by HPLC (Silica gel, hexane / ethylacetate = 500:1) comparisons of the MTPA esters.

These results reveal two important features. First, the rearrangement of **16** compared with that of **15** proceeds with a higher degree of *both* inversion at the Li-bearing terminus and retention at the migrating carbon to afford the inversion/retention product in a higher ratio (88% of **19** from **16** *vs.* 67% of **18** from **15**). [14]
The significant difference in stereospecificity indicates strongly that (*R*)-radical **C** generated from **16** couples more rapidly with the (*S*)-benzylic radical than (*S*)-radical **B** generated from **15**. This means that a substantial level of mutual recognition of radical enantiomers takes place during the recombination process. [15] Second, the degree of inversion at C-1 is significantly lower than that of retention at C-3 in both cases, suggesting that the anion radical fragment is configurationally less stable than the benzylic radical fragment. [16]



B **C**

In summary, we have clearly defined the structural requirments for the [1,2]-Wittig rearrangement, and have convincingly demonstrated that the Wittig rearrangement proceeds predominantly with inversion of configuration at the Li-bearing terminus and retention of configuration at the migrating center. Furthermore, the first example is presented of the mutual recognition of enantiomers in the radical hetero-coupling reactions. [15] Further work is in progress to define the scope and limitation of the Wittig rearrangement.

Experimental Part

General Information: All reactions dealing with air- or moisture sensitive compounds were carried out in a dry reaction vessel under nitrogen. Flash column chromatography was done on Merck 60 silica. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured for $CDCl_3$ solution of a sample with Varian Gemini-300. ^{1}H NMR spectra are reported in parts per million from internal tetramethylsilane and ^{13}C NMR spectra from $CDCl_3$ (77.0 ppm). Coupling constants are reported in Hertz (Hz). IR spectra were recorded with JASCO FT/IR-5000. Absorptions are reported in cm^{-1}. Mass spectra were measured with JEOL JMS-AX-505-HA.

Preparation of α-Hydroxystannanes. All of the racemic α-hydroxystannanes were prepared by the reaction of corresponding aldehydes and Bu_3SnLi as described by Still. [6] The enantio-enriched (*S*)-**14** was prepared by the $TiCl_4$-promoted reaction of (4*S*, 6*S*)-(4,6-dimethyl-1,3-dioxan-2-yl)tributylstannane with ethyl magnesium bromide, followed by oxidation and base treatment. [17]

(1*R*)-1-(Benzoyloxy)-1-(tributylstannyl)-propane (1) (Typical procedure) Methanesulfonyl chloride (57 mg, 39μL, 0.50 mmol) in CH_2Cl_2 (5 mL) was added to a mixture of (*S*)-**14** (88% ee; 90 mg, 0.25 mmol) and Et_3N (76 mg, 104 μL, 0.75 mmol) in CH_2Cl_2 (5 mL) at -20°C; the mixture was stirred for 30 min and quenched with water. After extraction with CH_2Cl_2, the combined extracts were successively washed with 0.5 N HCl, brine, saturated $NaHCO_3$ aqueous solution, and brine. Crude (1*S*)-1-(methanesulfonyloxy)-1-(tributylstannyl)-propane, obtained after drying over Na_2SO_4 and evaporation, was used without further purification for the next step. To a suspension of KH (34% in oil, 146 mg, 1.28 mmol; washed with hexane) in Et_2O (10 mL) was added benzylalcohol (81 mg, 0.75 mmol) in Et_2O (5 mL) at 0°C; the mixture was stirred for 1 h at room temperature. To this solution was added the solution of the crude mesylate (in 5 mL of CH_2Cl_2) and the mixture was stirred for 2 h and then quenched with cold water. Extractive workup and purification with flash chromatography afforded (*S*)-**1** (70 mg, 60% yield) as a colorless oil. ^{1}H NMR; δ 0.9 (m, 15 H), 0.98 (t, *J*=7.1, 3 H), 1.31 (tq, *J*=7.6, 7.6 , 6 H), 1.5 (m, 6 H), 1.89 (dq, *J*=7.1, 7.1, 2 H), 3.86 (t, *J*=7.1, 1 H), 4.43 (s, 2 H), 7.6 (m, 5 H). ^{13}C NMR; δ 9.30, 12.30, 13.69, 27.54, 27.60, 29.27, 72.66, 78.68, 127.27, 127.55, 128.19. HRMS (FAB) *m/z* calcd. for $C_{18}H_{31}OSn$ (M^+ - C_4H_9) 383.1419, found 383.1384.

1-(1'-Methylethoxy)-1-(tributylstannyl)-octane (6) This α-alkoxystannane was prepared by the reaction of the 1-(methanesulfonyloxy)-1-(tributylstannyl)-octane with the potassium salt of isopropanol. ^{1}H NMR; δ 0.9 (m, 18 H), 1.11 (d, *J*=6.0, 6 H), 1.4 (m, 22 H), 1.8 (m, 2 H), 3.42 (hep, *J*=6.0, 1 H), 3.84 (dd, *J*=6.1, 7.6, 1 H). ^{13}C NMR; δ 9.15, 13.74, 14.16, 22.02, 22.70, 22.85, 27.59, 27.98, 29.34, 29.70, 31.91, 35.92, 71.00, 74.35.

(1*R*, 1'*S*)-1-(1'-Methylbenzyloxy)-1-(tributylstannyl)-propane (15) This α-alkoxystannane (>95% ds) was prepared *via* reaction of the (1*S*)-1-(methanesulfonyloxy)-1-(tributylstannyl)-propane (>95% ee) with the potassium salt of (*S*)-α-methylbenzyl alcohol (100% ee). ^{1}H NMR; δ 0.9 (m, 18 H), 1.4 (m, 15 H), 1.8 (m, 2 H), 3.69 (dd, *J*=5.9, 7.6 , 1 H), 4.25 (q, *J*=6.5, 1 H), 7.3 (m, 5 H). IR (NaCl) 2960, 2874, 1456, 1075, 700. Rf 0.6 (hexane / ethylacetate = 20 : 1). HRMS (FAB) *m/z* calcd. for $C_{19}H_{33}OSn$ (M^+ - C_4H_9) 397.1571, found 383.1542.

(1*S*, 1'*S*)-1-(1'-Methylbenzyloxy)-1-(tributylstannyl)-propane (16) This α-alkoxystannane (>95% ds) was prepared by chromatographic separation of the epimeric mixture prepared from (±)-**14** and (*S*)-α-methylbenzyl alcohol (100% ee). ^{1}H NMR; δ 0.8 (m, 15 H), 0.94 (t, *J*=7.4, 3 H), 1.3 (m, 15 H), 1.7 (m, 1 H), 1.9 (m, 1 H), 3.69 (dd, *J*=5.2, 6.8, 1 H), 4.44 (q, *J*=6.5, 1 H), 7.3 (m, 5 H). Rf 0.7 (hexane / ethylacetate = 20 : 1).

(Phenyl)(tetrahydropyran-2-yloxy)(tributylstannyl)methane (9) 1-(Tributylstannyl)benzyl alcohol (4.3 g, 11.0 mmol) was dissolved in 10 mL of THF. A THF (10 mL) solution of Et_3N (4.0 g, 5.54 mL, 40 mmol) and a THF (30 mL) solution of 2-chlorotetrahydrofuran (10 mmol) were added and the resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$. Extractive work-up and purification with flash chromatography afforded **9** (1.7 g, 36% yield) as a colorless oil. ^{1}H NMR; δ 0.8 (m, 15 H), 1.3 (m, 12 H), 1.9 (m, 4 H), 3.7 (m, 1.2 H), 3.9 (m, 0.8 H), 5.1 (m, 2 H).

Procedure for the [1,2]-Wittig rearrangements Rearrangement of stannane (*R*)-**1** (Typical procedure): To a THF (3 mL) solution of (*R*)-**1** (70 mg, 0.15 mmol; 88% ee) was added BuLi (1.6 M in hexane, 0.14 mL, 0.23 mmol) at -78 °C. After 10 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl. Extractive work-up and purification with flash chromatography afforded (*R*)-**2** (23 mg, 90% yield) as a colorless oil. ^{1}H NMR; δ 1.00 (t, *J*=7.3, 3 H), 1.5 (m, 2 H), 2.64 (dd, *J*=8.3, 13.5, 1 H), 2.84 (dd, *J*=4.3, 13.5, 1 H), 3.8 (m, 1 H), 7.3 (m, 5 H). ^{13}C NMR; δ 10.05, 29.58, 43.58, 74.03, 126.41, 128.53, 129.40. IR (NaCl); 3200, 3070, 2958, 1734, 1454, 1272, 1172, 1125. $[\alpha]_D^{22}$ -12.6 ° (*c* 1.0, $CHCl_3$) 42 % ee (*R*). [9]

Ether 8 from α-alkoxystannane 6 To a THF solution of stannane **6** (100 mg, 0.21 mmol) was added BuLi (1.6 M in hexane, 0.65 mL, 1.05 mmol) at -78 °C. The stirring was continued for 30 min at -78 °C, and allowed to warm to 25°C. The reaction was quenched with a saturated aqueous solution of NH_4Cl. Extractive work-up and purification by flash chromatography afforded ether **8** (27 mg, 75% yield) as a colorless oil. ^{1}H NMR; δ 0.9 (m, 3 H), 1.15 (d, *J*=6.1, 6 H), 1.4 (m, 12 H), 3.39 (t, *J*=6.7, 2 H), 3.54 (hep, *J*=6.1, 1 H).

Rearrangement of α-alkoxystannane 9 To a THF solution of stannane **9** (100 mg, 0.22 mmol) was added BuLi (1.6 M in hexane, 0.69 mL, 1.10 mmol) at -78 °C. The stirring was continued for 30 min at -78 °C, and allowed to warm to 25 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl. Extractive work-up and purification by flash chromatography afforded alcohol **10** (6.0 mg, 16% yield) as a colorless oil. ^{1}H NMR; δ 1.8 (m, 4H), 2.60 (brs, 1H), 4.0 (m, 3H), {4.45 (d, *J*=7.5) and 4.93 (d, *J*=3.8) (1H)}, 7.3 (m, 5H).

Rearrangement of α-alkoxystannane 15 Use of the typical procedure with stannane **15** (97 mg, 0.21 mmol) gave 2-phenylheptan-3-ol (27 mg, 79% yield) as a colorless oil. The stereoisomeric compositions were determined by HPLC (silica gel, hexane / ethylacetate = 500 : 1) comparisons of the α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters.

Rearrangement of α-alkoxystannane 16 Use of the typical procedure with stannane **16** (131 mg, 0.29 mmol) gave 2-phenylheptan-3-ol (41 mg, 87% yield) as a colorless oil. The stereoisomeric compositions were determined by HPLC (silica gel, hexane / ethylacetate = 500 : 1) comparisons of the MTPA esters.

Acknowledgment : This work was supported by the Grant-in-Aid for Scientific Research, Ministry of Education, Science and Culture, Japan.

References and Notes

1. For reviews on [1,2]- and [2,3]-Wittig rearrangement, see: Schöllkopf, U. *Angew. Chem.* **1970**, *82*, 795. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 763. Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885. Marshall, J. A. In *Comprehensive Organic Synthesis*, Pattenden, G., Ed.; Pergamon Press: London, **1991**; Vol. 3, 975.
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3. It should be noted that 100 % inversion of configuration at the lithium bearing terminus has been observed in the [2,3]-Wittig rearrangements described. [5, 7a] Also note that the same problem arises in the retro-Brook rearrangement ($R^2 = SiR_3$), which has been the current subject of controversy (*vida infra*).
4. For reviews on mutual recognition of enantiomers, see (a) Noyori, R.; Kitamura, M. In *Frontiers in Organic Synthesis*, Mukaiyama, T., Ed.; Tokyo Kagaku Dojin: Tokyo, **1992**; 233. (b) Noyori, R.; Okada, S. *J. Synth. Org. Chem. , Jpn.* ***1990***, *48*, 447. *Chem. Abstr.* **1990**, *113*, 131262m.
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6. Still, W. C.; *J. Am. Chem. Soc.* **1978**, *100*, 1481.
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8. Neither the configuration and optical purity of (*R*)-**1** were determined. In view of the previously-proved reactions, [5] however, it is reasonable to presume that the S*N*2 reaction concerned proceeds with complete inversion of configuration.
9. The ee value of **2** was determined by ^1H NMR comparison of the corresponding MTPA ester.; $[\alpha]_D^{22}$ -12.6° (*c* 1.0, $CHCl_3$). The literature value for the (*R*)-isomer (73% ee): $[\alpha]_D$ -20.2° (*c* 7.16, $CHCl_3$): Ziffer, H.; Kawai, K.; Kasai, M.; Imuta, M.; Froussios, C. *J. Org. Chem.* **1983**, *48*, 3017.
10. (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.
11. At this stage, it is not clear whether the incompleteness of inversion of configuration is due to the incomplete stereospecificity in the Li-migration step (**A**→**B**) and / or partial inversion of *C*-radical **B** thus formed.
12. Linderman, R. J.; Ghannam, A. *J. Am. Chem. Soc.* **1990**, *112*, 2392. They have proposed a non-radical pathway that involves a silicate intermediate. Strange enough, however, the retro-Brook rearrangement of (*S*)-α-deuterobenzyl silyl ether has been reported to proceed with nearly complete inversion of configuration: Wright, A.; West, R. *J. Am. Chem. Soc.*, **1974**, *96*, 3227.
13. Niwa, S.; Hatanaka, T.; Soai, K. *J. Chem., Soc. Perkin Trans. 1* **1991**, 2025. The product ratio obtained in our hands: **17: 18: 19: 20** = 11: 1: 60: 28, consistent with the literature values (13: 1: 62: 24).
14. Also revealed is that the Li-migrating step concerned [11] proceeds with at least 90% stereospecificity.
15. For examples of mutual recognition of enantiomers in radical homo-coupling reaction, see; (a) Touboul, E.; Dana, G.; *C. R. Acad. Sci., Ser. C.* **1974**, *278*, 1063. (b) Wynberg, H.; Feringa, B. *Tetrahedron*, **1976**, *32*, 2831. (c) Merrifield, J. H.; Lin, G.-Y.; Kiel, W. A.; Gladysz, J. A. *J. Am. Chem. Soc.* ***1983***, *105*, 5811.
16. Pertinent theoretical works are awaited to determine the relative configurational stabilities of anion radical species.
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