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[2,3]-Wittig Rearrangement of Enantiomerically Enriched 3-Substituted 1-Propenyloxy-1-phenyl-2-propen-1-yl Carbanions: Effect of Heteroatoms and Conjugating Groups on Planarization of an α-Oxy-Benzylcarbanion through a Double Bond

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Abstract: The effect of conjugating electron-withdrawing groups and α-anion-stabilizing heteroatom substituents on configurational stability of chiral carbanions through a double bond was examined on the basis of extent of chirality transfer in intramolecular trapping in [2,3]-Wittig rearrangement of chiral 3-substituted 1-propenyloxy-1-phenyl-2-propen-1-yl carbanions.

Keywords: carbanions · configuration analysis · Wittig reactions

Introduction

Because the enantioselective formation of a chiral carbanion and its reaction with an electrophile in a stereodefined manner is very attractive for asymmetric carbon–carbon bond formation, investigations on the relative configurational stability of the anion would be important for the successful preparative application of the process.[1] One of the most widely used and elegant methods for evaluating configurational stability of a chiral carbanion is the Hoffmann test,[2] which is based on a kinetic resolution during the electrophilic substitution step using racemic and enantioenriched aldehydes as an electrophile.

We have recently found that [2,3]-Wittig rearrangement can trap a chiral carbanion generated between a double bond and a phenyl group, which has been considered difficult to generate due to their high tendency toward racemization, almost without racemization even at room temperature, indicating that the rearrangement is very fast.[3,4] The finding that the asymmetric induction changes greatly depending on the nature of the ethereal solvents used is noteworthy. Thus, reactions in 1,4-dioxane and Et_2O showed excellent and good asymmetric induction, respectively, in sharp contrast to the reaction in THF, the most common solvent for the rearrangement, in which almost complete racemization was observed. These findings led us to the general idea that the rearrangement can be used as a tool for estimation of the effect of substituents on the configurational stability of chiral lithium compounds using substrates like **1**, in which a substituent X is a heteroatom or a conjugating group such as a cyano and a carbonyl group (Scheme 1). Thus, the extent of chirality transfer in the rearrangement would reflect the difference in stereochemical stability of chiral carbanions next to the substituent X. The Hoffmann test may be less suitable particularly for electron-withdrawing conjugating groups due to the relatively slower intermolecular process. Although Brückner has used [2,3]-thia-Wittig rearrangement of diastereomeric organolithiums for an estimation of the configurational stability of α-lithio sulfide[5] and Hammerschmidt has tested the microscopic configurational stability of homochiral oxymethyllithium in [1,2]-retro-Brook and [2,3]-Wittig rearrangement,[6] to the best of our knowledge there have been no systematic studies on the effects of conjugating groups including a cyano group and the α-anion-stabilizing heteroatom substituents on the configurational stability of chiral carbanions.

Herein we report our results using vinylogous derivatives **2**, in which a heteroatom or an electron-withdrawing conjugating group is placed at a vinylogous position. We chose **2** to remove any steric bias in **1** with respect to the difference

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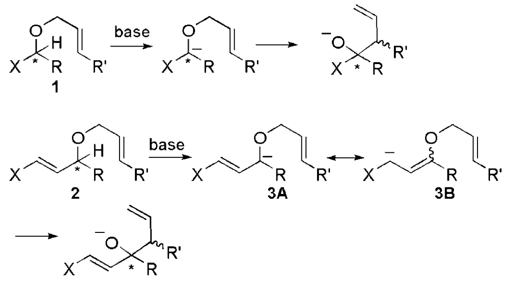
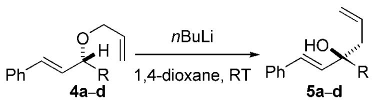


Scheme 1. [2,3]-Wittig rearrangement as a tool for estimation of the effect of group X on the configurational stability of chiral carbanions.

in rate of the rearrangement arising from the difference in the bulkiness of X. That is based on results of preliminary experiments performed using **4** (Table 1).

Table 1. [2,3]-Wittig rearrangement of **4a**–**d**.

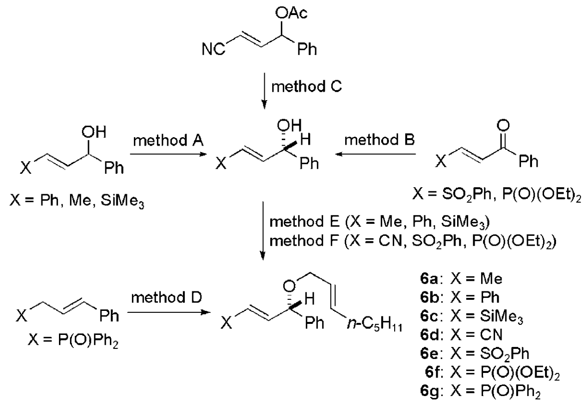


4	R	Yield [%]	*ee* [%]
a	Ph	70	72
b	Me	21	2
c	*o*-tol	33	8
d	*p*-tol	88	66

The reaction of α-methyl derivative **4b**, in which there should be much better asymmetric induction than that in the reaction of the phenyl counterpart **4a**, resulted in a much poorer *ee*, which was speculated to be caused by deceleration of the rearrangement due to steric repulsion in the transition state in the rearrangement. This assumption was supported by the fact that *o*-tolyl derivative **4c** afforded the corresponding rearrangement product in a much smaller *ee* than that in the case of *p*-tolyl derivative **4d**. Furthermore, a pentyl group was introduced as the R in the allyl group to enable us to distinguish whether the product **5** was formed via [2,3]- or [1,2]-Wittig rearrangement, the latter proceeding via a radical pathway. We envisioned that the system can provide information about the effect of the substituent X on the configurational stability of chiral carbanions through a double bond.

Results and Discussion

The preparation of **6a**–**g** is shown in Scheme 2. As a group X we selected methyl, phenyl, trimethylsilyl, cyano, benzenesulfonyl, diethoxyphosphoryl and diphenylphosphinoyl groups. Enantioenriched alcohol precursors were obtained using Sharpless kinetic resolution,[8] (−)-*B*-chlorodiisopinocamphenylborane reduction,[9] lipase-mediated kinetic resolution,[10] or Sharpless asymmetric dihydroxylation.[11]



method A: $Ti(OiPr)_4$, L-(+)-DIPT, TBHP, CH_2Cl_2
method B: 1) (−)-*B*-chlorodiisopinocamphenylborane; 2) diethanolamine
method C: Amano lipase PS, THF/H_2O
method D: 1) AD-mix α, $MeSO_2NH_2$, *t*BuOH/H_2O; 2) $SOCl_2$, NEt_3, CH_2Cl_2; 3) DBU, CH_2Cl_2; 4) method F
method E: NaH, *n*-$C_5H_{11}CH{=}CHCH_2Br$, DMF
method F: Ag_2O, *n*-$C_5H_{11}CH{=}CHCH_2Br$, Et_2O or CH_2Cl_2

Scheme 2. Preparation of **6a**–**g**.

Wittig rearrangement of **6a**–**g** was conducted using *n*BuLi or LDA as a base[12] in 1,4-dioxane, Et_2O, and THF at room temperature. The results are shown in Table 2.[13]

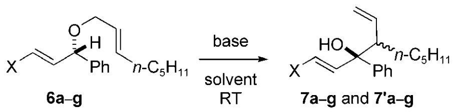
Particularly notable is the fact that substrates bearing electron-withdrawing groups such as a cyano group[10,14] can partly retain their stereochemical information without complete racemization. Regarding the relationship between solvent and asymmetric induction, the same general trend as that with the orginal system[3] was observed only for X = phenyl and $SiMe_3$ groups; that is, the enantiomeric excesses in their reactions decreased in the order of 1,4-dioxane > Et_2O > THF. In the case of methyl and cyano groups or other heteroatom substituents, a clear correlation was not observed.

In principle, the major diastereomer of the rearrangement products **7** and **7′**, which is a faster rearrangement product, should posses a higher *ee* value than that of the minor isomer. This trend was observed in most cases but not all cases. The latter may be due to the difference in stability of the two diastereomers.

The noteworthy points from Table 2 are as follows: 1) when X is an anion-unstabilizing group such as a methyl group, little racemization was observed regardless of the solvent used (entries 1–3); 2) in the case of conjugating groups, phenyl and cyano groups (entries 4–6; 10–12), racemization occurs depending on the extent of their electron-withdrawing nature, and the phenyl group is very sensitive to changes in solvent; and 3) α-carbanion-stabilizing heteroatom substituents other than the silyl group cause considerable racemization.

Studies on configurational stability of α-heteroatom-substituted carbanions using the Hoffmann test have shown that organolithiums α to phosphorus[15] and silicon are configurationally unstable on a microscopic timescale, while lithiated sulfones[16] are configurationally stable on a microscopic timescale.[17] The results of the Hoffmann test also

Table 2. [2,3]-Wittig rearrangement of **6a–g**.



Entry		X	Solvent	Base[a]	Yield [%]	**7**/**7'**	ee [%]	
							7	**7'**
1	**6a**	Me	1,4-dioxane	A	77	32:68	94	98
2	**6a**	Me	Et_2O	A	79	38:62	95	100
3	**6a**	Me	THF	A	87	31:69	93	96
4	**6b**	Ph	1,4-dioxane	A	70	45:55	84	92
5	**6b**	Ph	Et_2O	A	64	51:49	60	71
6	**6b**	Ph	THF	B	61	43:57	3	4
7	**6c**	$SiMe_3$	1,4-dioxane	B	80	47:53	85	86
8	**6c**	$SiMe_3$	Et_2O	B	78	51:49	82	79
9	**6c**	$SiMe_3$	THF	B	79	47:53	56	62
10	**6d**	CN	1,4-dioxane	B	31	50:50	8	9
11	**6d**	CN	Et_2O	B	31	44:56	8	6
12	**6d**	CN	THF	B	40	50:50	2	3
13	**6e**	SO_2Ph	1,4-dioxane	B	49	63:37	5	12
14	**6e**	SO_2Ph	Et_2O	B	71	49:51	7	17
15	**6e**	SO_2Ph	THF	B	75	60:40	0	7
16	**6f**	$P(O)(OEt)_2$	1,4-dioxane	B	18	76:24	2	14
17	**6f**	$P(O)(OEt)_2$	Et_2O	B	27	49:51	1	18
18	**6f**	$P(O)(OEt)_2$	THF	B	8	75:25	12	7
19	**6g**	$P(O)Ph_2$	1,4-dioxane	B	58	57:43	5	12
20	**6g**	$P(O)Ph_2$	Et_2O	B	52	33:67	10	4
21	**6g**	$P(O)Ph_2$	THF	B	50	65:35	14	22

[a] A: *n*BuLi; B: LDA.

are consistent with the calculated inversion energies ($^-CH_2SiH_3$: 0.8 kcal mol^{-1}; $^-CH_2SH$: 2.8 kcal mol^{-1}).[18] Consequently, the results showing that more racemization occurred in the sulfonyl derivative **6e** than in the silyl derivative **6c** deserve some comments. This suggests that in allyl carbanion **3**, the contribution of the resonance form **3B** should be more significant in the sulfone derivative **6e** than in the silyl derivative **6c**, which is consistent with the expectation based on pK_a[19] values of their α-proton, and that the carbanion in **3B** can be rather planarized. In other words, the chirality of β-heteroatom-substituted allylic carbanions would not be transferred into the α-position to the heteroatom through a double bond in the above system. This is supported by the fact that an obvious solvent effect was observed only for the phenyl and trimethylsilyl derivatives, which have a less electron-withdrawing nature than that of the cyano group and other heteroatom substituents. We previously proposed that the origin of the excellent enantioselectivity observed in 1,4-dioxane is the decreased rate of racemization by chelation of the lithium cation with the two oxygens. Increased contribution of the resonance form **3B** and of the planar structure of the anion α to the group X would make chelation by the 1,4-dioxane in **3A** less important.

The method described herein offers an advantage compared with the Hoffmann test. The surprisingly high reaction rates of [2,3]-Wittig rearrangements make the method a particular sensitive test for highly configurationally labile carbanions. This is based on the logical differences between the two methods. While the Hoffmann test 1) captures the carbanion moiety by an external electrophile, and 2) allows inference from stereochemical analysis of the products whether a configurational loss occurs on the time scale of that capture, the method using [2,3]-Wittig rearrangement 1) captures the carbanion moiety by an internal allyl transfer and 2) allows inference from stereochemical analysis of the products how much configurational loss occurs on the time scale of that capture.

Conclusion

We have examined the possibility that the extent of chirality transfer in [2,3]-Wittig rearrangement employing a chiral β-substituted allyl benzyl carbanion is used as a tool for evaluation of the effect of substituents on the configurational stability of a chiral carbanion through a double bond, and found that in the behavior of the conjugative electron-withdrawing groups and α-anion-stabilizing heteroatoms on the configurational stability of chiral carbanions, there is no direct correlation between the groups themselves and their vinylogous variants.

Experimental Section

General methods and additional procedures are available in the Supporting Information.

Representative procedure: A solution of *n*BuLi (1.86 M in hexane, 289 μL, 0.54 mmol) was added at room temperature to a solution of **6b**

(>99% *ee*, 57.8 mg, 0.18 mmol) in dioxane (3.6 mL). After stirring at the same temperature for 10 min, a few drops of saturated aqueous NH_4Cl solution was added. The mixture was diluted with Et_2O, dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 7 g, elution with hexane/AcOEt 22:1) to give **7b** and **7′b** (40.5 mg, 70%, **7b**/**7′b** 45:55).

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