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Solvent Effects on the Steric Course of the [2,3]-Wittig Rearrangement of (*S*,*E*)-[3-(Allyloxy)prop-1-ene-1,3-diyl]dibenzene and Derivatives

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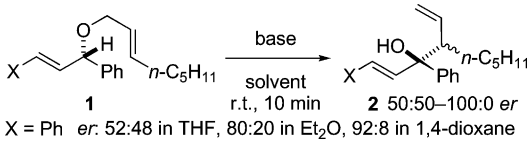
The effect of solvents and additives on the steric course of [2,3]-Wittig rearrangement of the chiral 1,3-diphenyl-1-propenyloxy-2-propen-1-yl carbanion and its derivatives was examined on the basis of chirality transfer in intramolecular trapping.

Introduction

Recently, we have reported on the effect of conjugative electron-withdrawing groups and α-anion-stabilizing heteroatom substituents that distribute charge through a double bond, on the configurational stability of chiral carbanions.[1] The effects can be estimated on the basis of the extent of chirality transfer induced by intramolecular trapping during [2,3]-Wittig rearrangement[2] of chiral 3-substituted 1-phenyl-1-propenyloxy-2-propen-1-yl carbanions of type **1** (Scheme 1).[3] In that paper, we showed that the configurational stability obtained in the system is highly sensitive to a change in solvent. For example, when the reaction was performed in tetrahydrofuran (THF), which is one of the most common solvents used for reactions involving carbanions, racemization occurred with almost all substituents; in contrast, 1,4-dioxane and diethyl ether (Et_2O) gave much better enantiomeric ratios (*er*).



1 **2** 50:50–100:0 *er*

Scheme 1. [2,3]-Wittig rearrangement of **1**.

There are some literature precedents regarding solvent effects on the configurational stability of carbanions. Curtin and Koehl reported that racemization of enantioenriched *sec*-butyllithium in hydrocarbon solvents is greatly accelerated by addition of a small amount of Et_2O.[4] Beak and co-workers also reported that when pyrrolidine derivatives were formed by cyclization of an anion generated enantioselectively using *s*BuLi/(–)-spartein, the extent of the enantiomeric induction was highly dependent on the solvent, affording the product with an enantiomeric ratio ranging from 52:48 (THF) to 96:2 (toluene).[5] In the former case, the comparison was only made between a hydrocarbon solvent and Et_2O, whereas in the latter case the observed trend can be interpreted in terms of competitive binding between the chiral ligand and the solvent toward the organolithium species. Publications by the groups of Hoppe[6] and Gawley[7] have also referred to solvent effects on the configurational stability of benzyl and allyl carbanions, and Kapeller and Hammerschmidt have recently discussed the configurational stability of aroyloxy[D_1]methyllithium in some solvent systems over a range of temperatures.[8]

One of the most elegant and widely used methods for evaluating configurational stability of a chiral carbanion is the Hoffmann test,[9] which is based on kinetic resolution during an electrophilic substitution reaction when using racemic and enantioenriched aldehydes as electrophiles. The test is usually conducted in THF, occasionally in Et_2O, but, to the best of our knowledge, solvent effects in the Hoffmann test have not been explicitly discussed. The reason for this, in addition to the qualitative nature of the test, is probably that the rate of the reaction with an electrophile is not fast enough to reflect the differences between solvents.

In the above [2,3]-Wittig rearrangement, the extent of racemization should be controlled by the relative rates of the racemization of a chiral carbanion and the [2,3]-Wittig rearrangement; these processes are associated with the configurational stability and chemical reactivity of the carbanions, respectively, which may be interrelated. Consequently, solvents and coordinating additives such as tetramethylethylenediamine (TMEDA) can influence the outcome of both processes in either the same or opposite manners. Although, in general, polar solvents or the additives promote the formation of separated ion pairs (SIPs), which facilitates

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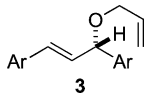
racemization by decreasing the covalent character of the carbon–metal interaction, to the best of our knowledge, no systematic studies on the effects of solvents on the configurational stability of chiral carbanions have been undertaken.

We became interested in examining the influence of solvents and additives on the preservation of the optical purity at the stereogenic centers in [2,3]-Wittig rearrangement of **3**, which should reflect the effects on the entire processes involving deprotonation, racemization, and [2,3]-Wittig rearrangement. We decided to use styryl derivatives **3** (Figure 1) to study these processes because the enantiomeric ratios of their [2,3]-Wittig rearrangement products in a number of solvents were in the appropriate range for comparison.



3

Figure 1. Compound **3**.

Results

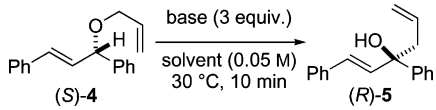
The results obtained when (*S*)-**4** was treated with *n*BuLi at 30 °C are shown in Table 1. Reactions in acyclic ethers, except those containing more than one oxygen atom, afforded moderate to good enantiomeric ratios and showed a general increase of this ratio with increasing steric bulk of the alkyl groups (Table 1, Entries 1–3). With solvents containing more than one oxygen atom, almost complete racemization and recovery of the starting material were observed, probably because of their higher donor ability (Table 1, Entries 4 and 5).[1g] The reactions of cyclic ethers other than 1,4-dioxane (Table 1, Entry 10) resulted in either poor enantiomeric ratios or complete racemization, whereas less polar hydrocarbon solvents afforded relatively high enantiomeric ratios (Table 1, Entries 12 and 13).

When lithium diisopropylamide (LDA) was used as a base in a range of solvents, a similar trend was observed, but slightly higher enantiomeric ratios were achieved in most cases (Table 1, Entries 1–3, 10, and 13). Changing the counter cation from lithium to potassium, however, resulted in complete racemization, except when the reactions were conducted in less polar hydrocarbon solvents in which low enantiomeric ratios were observed. These results suggest that racemization is accelerated more by an increased ionic character of the counter cation[10] than the acceleration of the [2,3]-Wittig rearrangement due to the enhanced reactivity of the carbanion.

Because the reactions afforded high enantiomeric ratios even in nonpolar solvents such as hexane, we cannot exclude the possibility that the rearrangement product **5** stems from a [1,2]-Wittig rearrangement[11] proceeding through a radical-pair mechanism with inversion of the lithium-bearing terminus in most cases. This led us to examine the reaction using 1,1-dideuterioallyl derivative [D_2]-**4**[12] in selected solvents (Table 2). Under these conditions, only a trace amount of [1,2]-Wittig rearrangement product [1,1-D_2]-**5** was detected in solvents other than toluene and hexane, in which ca. 15% of [1,1-D_2]-**5** to [2,3]-Wittig rearrangement product [3,3-D_2]-**5** was formed, suggesting that [1,2]-Wittig rearrangement is not the major reaction pathway even in nonpolar solvents.

We then examined the influence of temperature on the reaction, because we had obtained preliminary results that indicated that, in contrast to normal trends, performing the reactions at higher temperatures gives higher enantiomeric

Table 1. [2,3]-Wittig rearrangement of (*S*)-**4** in various solvents.

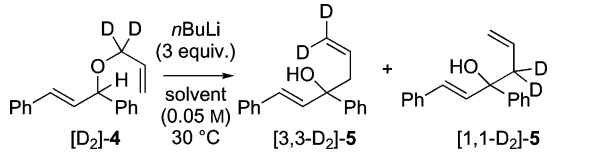


(*S*)-**4** (*R*)-**5**

Entry	Solvent[a,b]	*n*BuLi			LDA			KHMDS[c]		
		(*R*)-**5**		(*S*)-**4**[d]	(*R*)-**5**		(*S*)-**4**[d]	(*R*)-**5**		(*S*)-**4**[d]
		Yield [%]	*er*	Yield [%]	Yield [%]	*er*	Yield [%]	Yield [%]	*er*	Yield [%]
1	Et_2O	76	67:33	–	71	71:29	–	61	50:50	22
2	CPME	76	73:27	–	67	82:18	8	59	50:50	12
3	MTBE	69	80:20	–	74	92:8	–	63	50:50	14
4	DME	18	51:49	74	[e]	[e]	[e]	[e]	[e]	[e]
5	diglyme	17	50:50	79	[e]	[e]	[e]	[e]	[e]	[e]
6	THF	95	50:50	–	76	50:50	–	28	50:50	58
7	THP	89	55:45	–	[e]	[e]	[e]	[e]	[e]	[e]
8	1,3-dioxolane	0	–	38	[e]	[e]	[e]	[e]	[e]	[e]
9	1,3-dioxane	96	50:50	–	[e]	[e]	[e]	[e]	[e]	[e]
10	1,4-dioxane	70	86:14	–	70	87:13	–	41	50:50	35
11	NMM	91	74:26	–	83	74:26	–	47	50:50	35
12	toluene	38	86:14	52	52	82:18	20	66	52:58	0
13	hexane	41	91:9	44	41	92:8	19	67	54:46	0

[a] Cyclopentyl methyl ether (CPME), *tert*-butyl methyl ether (MTBE), dimethoxyethane (DME), tetrahydropyran (THP), *N*-methylmorpholine (NMM). [b] In the reactions of *n*BuLi and LDA, 7.5% of *n*-hexane originating from *n*BuLi solution was also present. [c] Potassium hexamethyldisilazane. [d] Compound **4** was recovered without any loss of optical purity. [e] Not conducted.

Table 2. Wittig rearrangements of [D_2]-**4**.

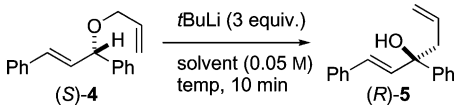


Solvent[a]	Yield [%]		
	[3,3-D_2]-**5**	[1,1-D_2]-**5**	[D_2]-**4**
Et_2O	80	2	–
CPME	83	2	–
MTBE	78	2	–
THF	81	2	–
1,4-Dioxane	82	3	–
NMM	82	3	–
Toluene	29	4	53
Hexane	33	5	36

[a] 7.5% of *n*-hexane originating from *n*BuLi solution was also present.

ratios in Et_2O. The results in some selected solvents are shown in Table 3.[13] In almost all cases, other than the reactions in THF in which complete racemization was observed, the same trend as observed in the previous case was found. These results suggest that acceleration of the rate with increasing temperature is greater for the [2,3]-Wittig rearrangement than for racemization, with the latter rate exceeding that of the former at lower temperatures. Thus, the rates of racemization and [2,3]-Wittig rearrangement seem to be of the same order of magnitude. This allowed the above system, by using [2,3]-Wittig rearrangement of **1**, to be used as a tool for evaluating the effect of substituents on the configurational stability of chiral carbanions.[3]

Table 3. [2,3]-Wittig rearrangement of (*S*)-**4** at lower temperatures.

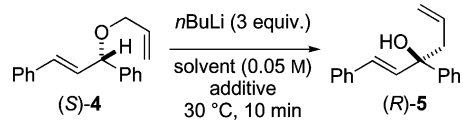


Solvent[a]	*T* [°C]	(*R*)-**5**		(*S*)-**4**	
		Yield [%]	*er*	Yield [%]	*er*
Et_2O	–60	46	51:49	0	–
Et_2O	–25	30	59:41	0	–
Et_2O	30	30	68:32	0	–
MTBE	–60	74	77:23	15	100:0
MTBE	–25	44	87:13	0	–
MTBE	30	32	90:10	0	–
THF	–60	87	50:50	0	–
THF	–25	88	50:50	0	–
THF	30	88	50:50	0	–
NMM	–60	90	54:46	0	–
NMM	–25	86	59:41	0	–
NMM	30	40	71:29	0	–
Hexane	–60	10	69:31	64	99:1
Hexane	–25	17	79:21	28	98:2
Hexane	30	12	79:21	0	–

[a] 7.5% of pentane originating from *t*BuLi solution was also present.

We then examined the influence of coordinating additives capable of solvating the lithium ion, such as TMEDA, Me_2NEt, hexamethylphosphoramide (HMPA), and THF.[14] Addition of TMEDA resulted in lower enantiomeric ratios in all solvents (Table 4, Entries 1, 5, 9, 13, 16, 20, 24, and 28), but was particularly noticeable in hydrocarbon solvents. In contrast, the enantiomeric ratios obtained with Me_2NEt, a non-chelating analogue of TMEDA, were either comparable or better than those observed in the absence of an additive in solvents other than the hydrocarbon solvents (Table 4, Entries 2, 6, 10, 14, 17, 21, 25, and 29). The lower enantiomeric ratios observed in the presence of TMEDA relative to those with Me_2NEt in ethereal solvents might indicate the importance of the bidentate interaction of the former additive with lithium ions in the solvent. In contrast, all the reactions conducted in THF and those with HMPA resulted in complete racemization (Table 4, Entries 3, 7, 11, 13–15, 18, 22, 26, and 30). The reduction in the enantiomeric ratio observed when THF was used as an additive seemed to be most pronounced in acyclic ethereal solvents (Table 4, Entries 4, 8,

Table 4. Effect of additives on the chirality transfer in the [2,3]-Wittig rearrangement of (*S*)-**4**.

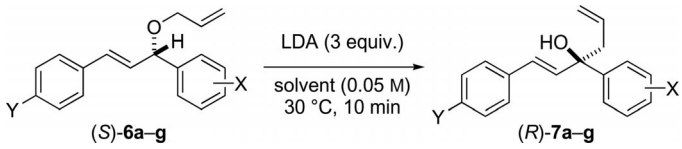


Entry	Solvent	Additive	(*R*)-**5**	
			Yield [%]	*er*
1	Et_2O	TMEDA	74	63:37
2	Et_2O	Me_2NEt	77	67:33
3	Et_2O	HMPA	79	50:50
4	Et_2O	THF	87	57:43
5	CPME	TMEDA	75	56:44
6	CPME	Me_2NEt	74	77:23
7	CPME	HMPA	90	50:50
8	CPME	THF	85	58:42
9	MTBE	TMEDA	80	66:34
10	MTBE	Me_2NEt	71	81:19
11	MTBE	HMPA	83	50:50
12	MTBE	THF	94	58:42
13	THF	TMEDA	95	50:50
14	THF	Me_2NEt	81	50:50
15	THF	HMPA	85	50:50
16	1,4-dioxane	TMEDA	82	78:22
17	1,4-dioxane	Me_2NEt	87	84:16
18	1,4-dioxane	HMPA	50	50:50
19	1,4-dioxane	THF	89	71:29
20	NMM	TMEDA	80	66:34
21	NMM	Me_2NEt	85	74:26
22	NMM	HMPA	85	50:50
23	NMM	THF	87	63:37
24	toluene	TMEDA	79	65:35
25	toluene	Me_2NEt	47	63:37
26	toluene	HMPA	79	50:50
27	toluene	THF	90	62:38
28	hexane	TMEDA	74	77:23
29	hexane	Me_2NEt	44	63:37
30	hexane	HMPA	77	50:50
31	hexane	THF	92	73:27

and 12), whereas those in cyclic ethers and hydrocarbon solvents (Table 4, Entries 19, 23, 27, and 31) were more modest.

To obtain information on the influence of the solvents on the inductive and resonance stabilization of carbanions, we focused on substrates (*S*)-**6a**–**f**, which bear either an inductively anion-stabilizing halogen atom or a cyano group at the *meta*- or *para*-positions, and (*S*)-**6g**, a vinylogous *p*-cyanophenyl derivative. The results are shown in Table 5.[15,16] The halogen derivatives (*S*)-**6b**–**d**, other than the *meta*-fluoro derivative (*S*)-**6a**, resulted in similar or slightly higher enantiomeric ratios (Table 5, Entries 2–4) than those observed in the case of the parent compound (*S*)-**4**, which afforded lower enantiomeric ratios (Table 1, Entries 1–3 and 10–13). In contrast, the enantiomeric ratios obtained with the cyano derivatives (*S*)-**6e**–**g** depended on the solvent (Table 5, Entries 5–7). Thus, a lowering of the enantiomeric ratio, which was ascribed to the resonance effect of the *para*-cyano group relative to its *meta*-substituted counterpart, was observed in solvents other than hexane, in which the enantiomeric ratio was slightly increased (Table 5, Entries 5 and 6). The lowering was remarkable in 1,4-di-

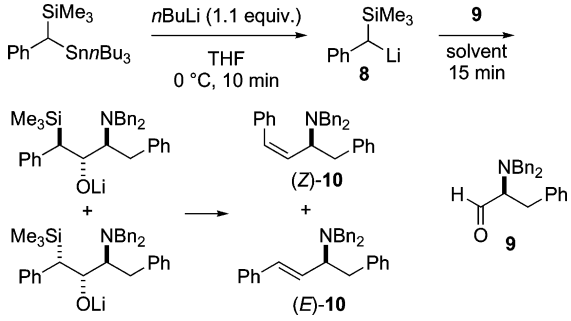
Table 5. [2,3]-Wittig rearrangement of (*S*)-**6a**–**g**.



(*S*)-**6a**–**g** (*R*)-**7a**–**g**

Entry		X	Y	Et_2O		CPME		MTBE		1,4-Dioxane		NMM		Toluene		Hexane	
				Yield [%]	*er*	Yield [%]	*er*	Yield [%]	*er*	Yield [%]	*er*	Yield [%]	*er*	Yield [%]	*er*	Yield [%]	*er*
1	**6a**	*m*-F	H	80	71:29	75	82:18	78	90:10	75	82:18	63	66:34	72	82:18	67	90:10
2	**6b**	*m*-Cl	H	74	72:28	75	85:15	77	93:7	81	87:13	75	67:33	76	84:16	80	92:8
3	**6c**	*m*-Br	H	77	75:25	74	86:14	76	93:7	79	88:12	78	68:32	64	86:14	70	92:8
4	**6d**	*p*-Cl	H	78	75:25	81	85:15	86	93:7	82	88:12	82	68:32	77	82:18	77	89:11
5	**6e**	*m*-CN	H	30	67:33	41	75:25	40	87:13	41	65:35	48	60:40	14	90:10	13	81:19
6	**6f**	*p*-CN	H	14	66:34	32	70:30	40	76:24	37	56:44	38	53:47	29	70:30	33	83:17
7	**6g**	H	CN	33	70:30	32	77:23	35	82:18	38	68:32	45	64:36	20	80:20	10	82:18

Table 6. Hoffmann test by using the reaction of **8** with **9**.



Entry	Solvent	**9**	*T* [°C]	Ratio	Yield [%]	Conclusion
1	1,4-dioxane[a]	*rac*-**9**	5	42:58	91	stable
2	1,4-dioxane[a]	(*S*)-**9**	5	48:52	88	
3	NMM[a]	*rac*-**9**	5	56:44	87	stable
4	NMM[a]	(*S*)-**9**	5	50:50	88	
5	NMM[a]	*rac*-**9**	–50	68:32	83	unstable
6	NMM[a]	(*S*)-**9**	–50	68:32	79	
7	Et_2O[a]	*rac*-**9**	–78	78:22	84	unstable
8	Et_2O[a]	(*S*)-**9**	–78	76:24	86	
9	CPME[a]	*rac*-**9**	–78	74:26	85	unstable
10	CPME[a]	(*S*)-**9**	–78	75:25	84	
11	toluene[a]	*rac*-**9**	–78	76:24	80	unstable
12	toluene[a]	(*S*)-**9**	–78	76:24	84	
13	hexane[a]	*rac*-**9**	–78	76:24	75	unstable
14	hexane[a]	(*S*)-**9**	–78	76:24	75	
15	THF	*rac*-**9**	–78	70:30	91[b]	unstable
16	THF	(*S*)-**9**	–78	70:30	93[b]	

[a] Contains 9% of THF. [b] See Hoffmann et al.[9c]

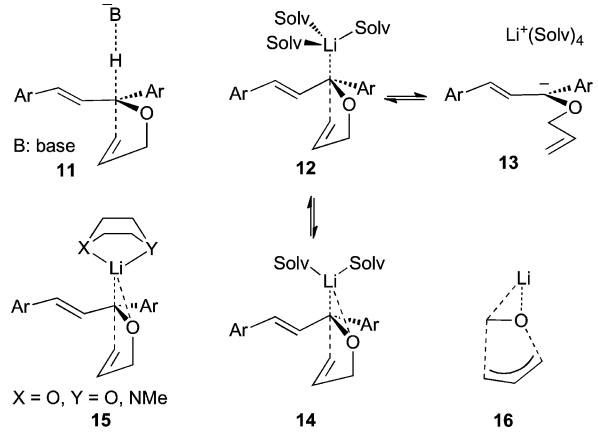
oxane (65:35 to 56:44) and NMM (60:40 to 53:47). The resonance effect of the *para*-cyano group through a double bond was smaller than that of the same group on the 1-phenyl moiety (Table 5, Entry 7).

Because it is possible that the effects of solvents and additives could operate solely on the rate of the [2,3]-Wittig rearrangement, we became interested in determining whether the effects could also be observed in carbanion-trapping reactions other than [2,3]-Wittig rearrangement. Thus, we decided to conduct the Hoffmann test[9] by using [phenyl(trimethylsilyl)methyl]lithium (**8**) and Reetz aldehyde **9**[17] in the above solvents (Table 6). The substrate **8** has been reported to be configurationally unstable in THF (Table 6, Entries 15 and 16).[9c] The diastereomeric ratio was determined by using the stereospecificity of the Peterson elimination to give (*Z*)- or (*E*)-**10**. In acyclic ethers and hydrocarbon solvents, reactions using *rac*-**9** proceeded smoothly to give **10** in ratios of 70–78% *rac*-(*E*)-**10** to 22–30% *rac*-(*Z*)-**10** (Table 6, Entries 7, 9, 11, and 13). Experiments using (*S*)-**9** resulted in almost the same diastereomeric ratios as those obtained from the first set of experiments described above (Table 6, Entries 8, 10, 12, and 14), indicating that the carbanion is configurationally unstable on the timescale of the reaction with aldehyde. Reactions of **8** with *rac*-**9** in cyclic ethers, 1,4-dioxane, or NMM, at 5 °C, gave (*E*)-**10** and (*Z*)-**10** in ratios of 42:58 and 56:44, respectively (Table 6, Entries 1 and 3), indicating the low intrinsic diastereoselectivity under these conditions, probably because of the relatively high reaction temperature. The ratios in the reactions with (*S*)-**9** changed to 48:52 and 50:50 (Table 6, Entries 2 and 4), respectively. Because it was difficult to draw definitive conclusions from the subtle changes in the ratios, we carried out the reaction in NMM at –50 °C, expecting to observe an enhancement in the diastereoselectivity.[18] Identical ratios (68:32) were obtained in both experiments, showing that the carbanion is configurationally unstable at lower temperatures.[19] These results suggest that the ratios obtained at 5 °C in the solvents are significant, even if the differences are small, and that the behavior of the cyclic ethers are different to those of the other solvents with respect to the configurational stability of the carbanions. Consequently, the solvent effects can, at least in part, determine the configurational stability of chiral carbanions.

Discussion

Although the influence of the solvent on the relative rates of racemization and rearrangement, and on the aggregation state of the bases and the carbanion in the system, are unknown at present, we are tempted to assume that the solvents and additives would not significantly affect the relative rate of the [2,3]-Wittig rearrangement, based on the results of the low-temperature experiments (Table 3) and of the Hoffmann test (Table 6).

The clearest difference between the [2,3]-Wittig rearrangement approach and other systems that have been used to trap chiral carbanions is that a carbanion can be generated in the presence of a trapping agent in the former case. Consequently, processes involving concerted deprotonation and trapping of the generated carbanion were also considered. The reaction in hexane is a case in which such a concerted deprotonation/[2,3]-Wittig rearrangement may be a major pathway (Scheme 2, **11**).[20] This is supported by the findings that the enantiomeric ratios were relatively high, that the starting material was recovered without any loss of optical purity at lower temperatures (Table 1, Entries 12 and 13), and that planarization due to resonance stabilization by the *para*-cyano group shows a less pronounced effect on the enantiomeric ratio (Table 5, Entry 6).[21] Because THF, 1,2-dimethoxyethane (DME), and diglyme can operate as strong solvating agents, albeit inferior to HMPA (Table 1, Entries 4–6; Table 4 Entry 3, 7, 11, 13–15, 18, 22, 26, and 30), this suggests that these solvents can drive the conversion of a contact ion pair (CIP) **12** into a separated ion pair **13**. Cyclic ethers, 1,4-dioxane, and NMM seem to behave differently to acyclic ethers, particularly regarding the resonance effect of the *para*-cyano group (Table 5, Entry 6). Thus, the enantiomeric ratios in the former solvents were much lower than those in the acyclic ethers. In similar reactions with the corresponding crotyl derivatives **1** (X = Me), only slight racemization was observed in THF, Et_2O, and 1,4-dioxane (98–97:2–3 *er* in THF; 100–98:0–2 *er* in Et_2O; 99–97:1–3 *er* in 1,4-dioxane).[3] Consequently, marked differences in the enantiomeric ratios obtained with different solvents in the reaction of (*S*)-**4** can be ascribed to the extent of ion separation, which depends on the nature of solvent and/or additive. Thus, conversion of CIP into SIP caused by trapping of lithium ions by the solvent and/or additive, allows charge delocalization into the double bond and the phenyl ring to occur, which can lead to racemization.[6,22,23]



Scheme 2. Process of chirality transfer in the [2,3]-Wittig rearrangement of **4**.

How can the fact that reactions provide higher enantiomeric ratios in bulkier acyclic ethereal solvents and in 1,4-dioxane be explained? We propose the following speculative hypothesis that accommodates the above observations. Solvation of the lithium cation, which loosens the C–Li coordi-

nation and increases the fraction of SIP, becomes less effective in bulkier solvents such as MTBE and CPME due to the steric repulsion with **13**.[24] Although a similar type of repulsion can also exist in **12**, this is reduced when the solvent molecule is replaced with the allyl ether oxygen, as found in **14**. This is consistent with a reactant-like (early) transition structure, such as **16**, for the [2,3]-Wittig rearrangement of allyl lithiomethyl ether, as calculated by ab initio methods by Wu, Houk and Marshall in which a lithium atom coordinates with the ether oxygen atom.[25] With bulkier ethers, the concerted mechanism proceeding through **11** may also operate.

The fact that the use of 1,4-dioxane led to higher enantiomeric ratios than the use of acyclic ethers in the reactions of (*S*)-**4** with *n*BuLi, can be explained by assuming that the former solvent acts as a bidentate ligand to form a strained complex **15** (X, Y = O),[26] which is more stable than **14** (Solv = acyclic ether). Although there is no report on the use of *N*-methylmorpholine as an additive, to the best of our knowledge, it may act in a manner similar to that of 1,4-dioxane, albeit with lower coordinating ability presumably because of steric repulsion of the methyl group. The differing behavior of 1,4-dioxane and *N*-methylmorpholine to the other solvents assessed in the Hoffmann test, also suggests their participation as a bidentate ligand. Consequently, the solvent effect operates mainly on the configurational stability of chiral carbanions and not on the [2,3]-Wittig rearrangement.

Conclusions

We have demonstrated that the steric course of the [2,3]-Wittig rearrangement of 1,3-diphenyl-1-propenyloxy-2-propen-1-yl carbanion (*S*)-**4** and its derivatives (*S*)-**6a**–**g** is greatly affected by the solvent and the additive. We have proposed that the differences can be attributable to the configurational stability of the chiral carbanions, which depends on the solvent and which reflects the ratio of CIP and SIP associated with their solvated structures.

Experimental Section

General: Infrared spectra were recorded with an FTIR spectrometer. ^{1}H NMR spectra were recorded with a 500 MHz spectrometer with samples in $CDCl_3$ referenced to $CHCl_3$ (δ = 7.26 ppm). ^{13}C NMR spectra were measured with a 125 MHz spectrometer with samples in $CDCl_3$ referenced to the $CDCl_3$ triplet (δ = 77.2 ppm). Resonance multiplicities are described as singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br.). Mass spectra were obtained either in the EI mode or in the FAB mode either with NBA as the matrix or without any matrix. For routine chromatography, the following adsorbents were used: silica gel 60N, particle size 63–210 μm, for column chromatography; precoated silica gel 60 F-254 plates for analytical thin-layer chromatography. All moisture-sensitive reactions were performed under a positive pressure of nitrogen. Anhydrous $MgSO_4$ was used to dry all organic solvent extracts during workup, and the removal of the solvents was performed with a rotary evaporator. Anhydrous solvents and reagents were obtained according to standard procedures.

General Procedure for [2,3]-Wittig Rearrangement of 4: To a solution of **4** (100:0 *er*, 50.1 mg, 0.20 mmol) in dioxane (4 mL), was added a solution of *n*BuLi (2.17 M in hexane, 276 μL, 0.60 mmol) at 30 °C. The reaction mixture was stirred at room temperature for 10 min, and 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, 5 g; hexane/Et_2O, 5:1) to give **5** (35.3 mg, 70%); 86:14 *er* [Chiralcel OD; hexane/*i*PrOH, 9:1; flow rate 1.0 mL/min; detection at 254 nm; t_R = 7.35 min (major) and 8.38 min (minor)].

General Procedure for the Preparation of Compounds (*S*)-6a–g: Compounds (*S*)-**6a**, (*S*)-**6b**, (*S*)-**6e**, (*S*)-**6f**, and (*S*)-**6g** were prepared starting from known or commercially available enones through Luche reduction, Sharpless kinetic resolution, and allylation. Compounds (*S*)-**6c** and (*S*)-**6d** were prepared from known alcohol derivatives.[27] It was assumed that the allylation of the alcohols proceeded without any loss in the enantiomeric ratio.

(*S*,*E*)-1-[1-(Allyloxy)-3-phenylallyl]-3-fluorobenzene [(*S*)-6a]: To a cooled (ice/water) solution of (*E*)-1-(3-fluorophenyl)-3-phenylprop-2-en-1-one[28] (2.00 g, 8.24 mmol) and $CeCl_3 \cdot 7H_2O$ (3.07 g, 8.24 mmol) in MeOH (66 mL) and CH_2Cl_2 (16.5 mL), was added $NaBH_4$ (312 mg, 8.24 mmol). The reaction mixture was warmed to room temperature, and, after being stirred at the same temperature for 30 min, the mixture was diluted with Et_2O (80 mL) and 10% aqueous NH_4Cl solution (80 mL). The mixture was separated, and the aqueous phase was extracted with Et_2O (3 × 80 mL). The combined organic phases were washed with saturated brine (30 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 40 g; hexane/AcOEt, 5:1) to give (*E*)-1-(3-fluorophenyl)-3-phenylprop-2-en-1-ol (1.93 g, 96%).

To a cooled (–20 °C) solution of (*E*)-1-(3-fluorophenyl)-3-phenylprop-2-en-1-ol (1.84 g, 7.5 mmol), L-(+)-diisopropyl tartrate [L-(+)-DIPT; 703 mg, 3.00 mmol] and molecular sieves (4 Å; 703 mg) in CH_2Cl_2 (30 mL), were added $Ti(OiPr)_4$ (619 μL, 2.25 mmol) and *tert*-butyl hydroperoxide (TBHP; 5.0–6.0 M in decane, 1.05 mL). After the mixture had been stirred at the same temperature for 2.5 h, a solution of $FeSO_4 \cdot 7H_2O$ (6.81 g) and tartaric acid (2.27 g) in water (31 mL) was added. After stirring for 10 min, the mixture was extracted with Et_2O (2 × 46 mL), and the combined organic phases were washed with water (31 mL) and saturated brine (31 mL) and then dried and concentrated. The residual oil was subjected to column chromatography (silica gel, 170 g; hexane/CH_2Cl_2, 1:3) to give (*S*,*E*)-1-(3-fluorophenyl)-3-phenylprop-2-en-1-ol (710 mg, 39%); 100:0 *er* [Chiralcel OD-H; hexane/*i*PrOH, 7:1; flow rate 1.0 mL/min; detection at 254 nm; t_R = 11.7 min (major) and 16.9 min (minor)]; colorless oil; R_f = 0.34 (hexane/AcOEt, 3:1); $[\alpha]_D^{21}$ = –13.7 (*c* = 1.04, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3334, 3064, 3031, 2925, 2861 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.06 (d, $^3J_{H,H}$ = 3.5 Hz, OH), 5.39 (dd, $^3J_{H,H}$ = 6.4, 3.5 Hz, 1 H, 1-H), 6.34 (dd, $^3J_{H,H}$ = 15.8, 6.4 Hz, 2-H), 6.70 (d, $^3J_{H,H}$ = 15.8 Hz, 1 H, 3-H), 6.97–7.40 (m, 9 H, PhH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 74.7, 113.3 (d, $J_{C,F}$ = 21.9 Hz), 114.6 (d, $J_{C,F}$ = 21.0 Hz), 122.0, 126.8, 128.2, 128.8, 130.2, 130.3, 131.1, 131.4, 136.4, 145.5, 145.6, 162.2 (d, $J_{C,F}$ = 244.2 Hz) ppm. HRMS: calcd. for $C_{15}H_{13}FO$ 228.0950; found 228.0950.

To a cooled (ice/water) solution of (*S*,*E*)-1-(3-fluorophenyl)-3-phenylprop-2-en-1-ol (667 mg, 2.73 mmol) and allyl bromide (666 mg, 5.45 mmol) in DMF (12.6 mL) was added NaH (60% oil suspension, 218 mg, 5.45 mmol). The reaction mixture was warmed to room temperature, and, after stirring at the same temperature for 40 min, the mixture was diluted with saturated aqueous NH_4Cl solution (10 mL), and extracted with Et_2O (2 × 20 mL). The com-

bined organic phases were successively washed with water (2 × 10 mL) and saturated brine (10 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 30 g; hexane/AcOEt, 22:1) to give (*S*)-**6a** (640 mg, 82%); colorless oil; R_f = 0.65 (hexane/AcOEt, 3:1); $[\alpha]_D^{28}$ = 9.04 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3082, 3060, 3025, 2981, 2923, 2857 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.00–4.11 (m, 2 H, 1-H′′), 4.98 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 1-H′), 5.22 (ddd, $^3J_{H,H}$ = 10.3, 3.0, 1.4 Hz, 1 H, 3-H′′), 5.32 (ddd, $^3J_{H,H}$ = 17.2, 3.2, 1.6 Hz, 1 H, 3-H′′), 5.93–6.01 (m, 1 H, 2-H′′), 6.25 (dd, $^3J_{H,H}$ = 16.0, 7.3 Hz, 1 H, 2-H′), 6.64 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, 3-H′), 6.96–7.40 (m, 9 H, PhH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 69.6, 81.3, 113.8, 114.0 (d, $J_{C,F}$ = 22 Hz), 114.6 (d, $J_{C,F}$ = 21 Hz), 114.8, 117.3, 122.6, 122.6, 126.8, 128.1, 128.8, 129.8, 130.1, 130.2, 132.2, 134.8, 136.6, 144.1, 144.2, 162.3 (d, $J_{C,F}$ = 244.2 Hz) ppm. HRMS: calcd. for $C_{18}H_{17}FO$ $[M - H]^+$ 267.1180; found 267.1191.

General Procedure for the Hoffmann Test with 8 and 9: To a solution of benzyltrimethylsilane (114 mg, 0.25 mmol) in anhydrous THF (750 μL) was added a solution of *n*BuLi (2.38 M in hexane, 116 μL, 0.275 mmol) at 0 °C. After stirring at the same temperature for 10 min, a solution of (*S*)-2-(dibenzylamino)-3-phenylpropionaldehyde (**9**; 165 mg, 0.50 mmol) in 1,4-dioxane (7.5 mL) was added by using a cannula over 2 min. After stirring at 5 °C for 10 min, acetic acid (1 M in 1,4-dioxane, 0.275 mL) was added dropwise, and the mixture was diluted with Et_2O (5 mL) and 10% aqueous NH_4Cl (5 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic phases were washed with saturated brine (30 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 30 g; hexane/CH_2Cl_2, 1:1) to give alkene **10** (88.6 mg, 88%) in an (*E*)/(*Z*) ratio of 48:52. The alkenes were characterized by their NMR spectra.

For the reaction of **8** with racemic aldehyde **9**, the same procedure was performed as described above.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds.

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