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Conjugate Additions to Alkylidene Bis(Sulfoxides)

Franck Brebion,[a] Guillaume Vincent,[a] Saloua Chelli,[a] Ophélie Kwasnieski,[a] Francisco Najera,[a] Bénédicte Delouvrié,[a] Ilan Marek,[b] Etienne Derat,[a] Jean-Philippe Goddard,[a] Max Malacria,*[a] and Louis Fensterbank*[a]

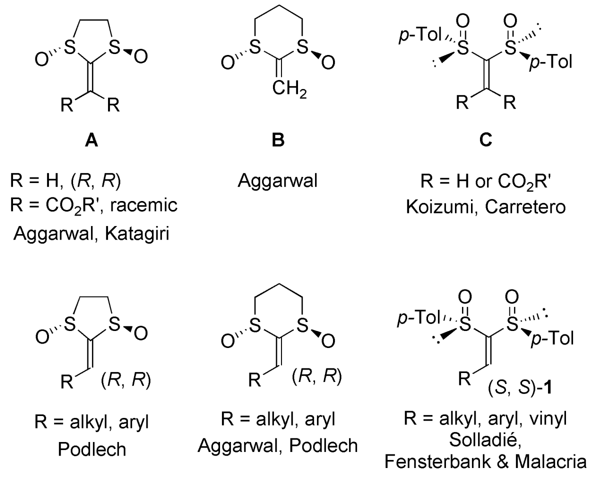
On the occasion of the 150th anniversary of Department of Chemistry, The University of Tokyo

Abstract: A general study on the conjugate addition of anionic nucleophiles to alkylidene bis(sulfoxides) is presented. Alkoxides gave high yielding and diastereoselective addition reactions, which could be influenced by solvents and the counteranion. Azides provided an interesting entry into sulfinyl-substituted triazoles. Organometallics, mainly copper reagents, proved also to be valuable nucleophiles, and complete inversion of the stereoselectivity was achieved in the addition reaction with the latter. Modelizations provide a rationale for the observed diastereoselectivity.

Keywords: azides • bis(sulfoxides) • diastereoselectivity • ketene equivalent • Michael addition

Introduction

Chiral ketene equivalents have attracted the attention of synthetic chemists. While mainly used in cycloaddition reactions,[1] the bis(sulfinyl) congeners,[2,3] which are generally based on simple dioxygenated (*S*,*S*)-acetal templates **A** or **B** (Scheme 1),[4] or bis-*p*-tolyl analogs **C**,[5] have proven to be versatile partners in these reactions. They could, however, also be involved in other key transformations, such as Michael additions,[6] as recently illustrated by Podlech and Wedel with monosubstituted substrates of type **A**[7] and **B**[8] and also demonstrated by our research group with derivatives of type **1**.[9]



Scheme 1. Most commonly used alkylidene bis(sulfoxides).

In this study, we bring some additional elements on the reactivity of conjugate additions[10] to **1**, as well as rationalize the stereochemical outcome of the addition of organometallic reagents.

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[a] Dr. F. Brebion, Dr. G. Vincent, Dr. S. Chelli, Dr. O. Kwasnieski,
Dr. F. Najera, Dr. B. Delouvrié, Dr. E. Derat, Dr. J.-P. Goddard,
Prof. M. Malacria, Prof. L. Fensterbank
UPMC University Paris 06
Institut Parisien de Chimie Moléculaire (UMR CNRS 7201)
4 place Jussieu, C. 229, 75005 Paris (France)
Fax: (+33) 1-44-27-73-60
E-mail: louis.fensterbank@upmc.fr
max.malacria@upmc.fr

[b] Prof. I. Marek
The Mallat Family Laboratory of Organic Chemistry
Schulich Faculty of Chemistry and The Lise Meitner-MinerVa
Center for Computational Quantum Chemistry
Technion-Israel Institute of Technology
Haifa 32 000 (Israel)

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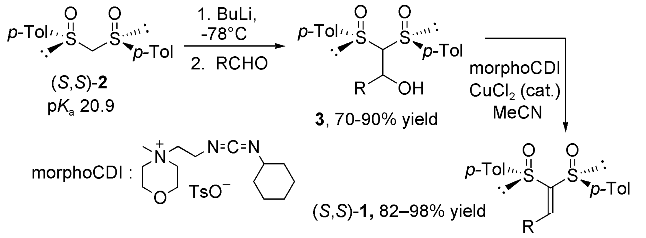
Results and Discussion

Preparation of 1 and Structural Data

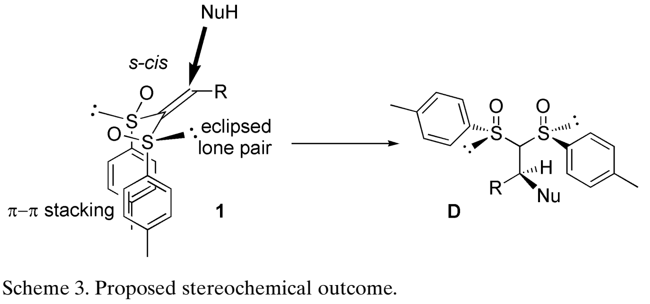
Although, we began to look at asymmetric oxidation processes to prepare precursors **1**,[11] we have relied on following the bis(sulfinyl) methane route (Scheme 2), which we previously described.[12] It should also be noted that bis(sulfinyl) alcohols **3** can be obtained in moderate to very good diastereoselectivities, and that the synthesis of bis(sulfinyl) methane **2** has recently been optimized.[13]



Scheme 2. Synthesis of alkylidene bis(sulfoxides) **1**.

Most precursors of type **1** have been obtained in satisfactory overall yields, and isolated as solids, thus allowing X-ray structure determination of **1a** (R = Ph) and **1b** (R = *i*Pr). These structures established an eclipsed lone pair conformation for the sulfinyl moiety *syn* to the R group and a *s-cis* conformation for the other sulfinyl group;[9a] this is consistent with Tietze's calculations on simpler vinyl sulfoxide systems.[14] Assuming that the same conformational bias would operate in solution, we could anticipate highly diastereoselective Michael additions from the *si* face, thereby avoiding any interaction of the nucleophile with the tolyl groups that lead to adducts **D**. It should be mentioned that Podlech has recently revisited the diastereoselection model for the additions on substrates of type **A** and **B** and has proposed that the stereochemical outcome is controlled by the stabilizing interaction between the forming lone pair at the bis(sulfinyl) center and the S–O σ* of an antiperiplanar S=O group.[15]

Preliminary reports confirmed that amines[9a] could add efficiently and with high to complete diastereoselectivity to a series of substrates **1**, following the proposed stereoinduction of Scheme 3. While these initial findings provided a new entry into the preparation of enantiopure β-aminoalcohols and α-aminoacids, they also illustrated the clear benefit of alkylidene bis(sulfoxides) over simple vinyl sulfoxides in terms of efficiency in the addition step and diastereoselectivity.[10,16] It was also interesting to check if the same reactivity and stereoselectivity could apply to charged nucleophiles. Thus, we examined malonates, ester enolates, and other carbanions.[9a–c] Herein, we focus on new anionic nucleophiles and extend our findings with alkoxides and organometallics.

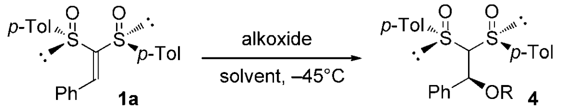


Scheme 3. Proposed stereochemical outcome.

Alkoxides as Nucleophiles

Alkoxides proved to be versatile nucleophiles towards precursor **1a** (Table 1). Optimized conditions involved adding 1.5 equivalents of the alkoxide at −45 °C and quenching the reaction at the same temperature to provide high yields and diastereoselectivities of adducts **4**. Sodium alkoxides gave complete stereoselectivity (Table 1, entries 2 and 5) as determined from the ^{1}H NMR spectrum of the crude product, whereas in some cases a lithium salt resulted in slightly eroded diastereoselectivity (entry 4). Different results were obtained by varying the solvent, as illustrated in entry 3 with a tetrahydrofuran (THF)/MeOH (1.2:1) mixture. In this case, a noticeable reduction in the stereoselectivity (entry 3) was observed. Unfortunately, the reaction in pure methanol could not proceed because **1a** is poorly soluble in this reaction medium. While solvent effects have already been observed in the addition of nucleophiles on simple vinyl sulfoxides by Pyne et al.,[16a] we suspect that methanol might favor hydrogen-bonding interactions with **1a**, thus altering the conformations in the reaction system (Scheme 3).

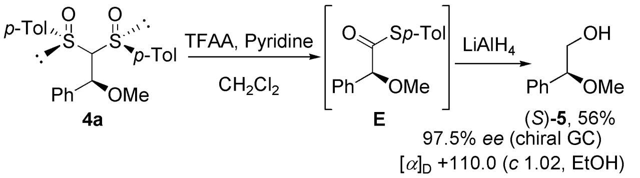
Table 1. Addition of alkoxides on **1a**.



Entry	Alkoxide	Solvent	Product	Yield [%]	d.r.	Abs conf.
1	MeOLi	THF	**4a**	94	>98:2	(*S*)
2	MeONa	THF	**4a**	90	>98:2	(*S*)
3	MeOLi	THF/MeOH[a]	**4a**	100	82:18	(*S*)
4	EtOLi	THF	**4b**	85	96:4	(*S*)
5	EtONa	THF	**4b**	89	>98:2	(*S*)

[a] A THF/MeOH (1.2:1) mixture was used.

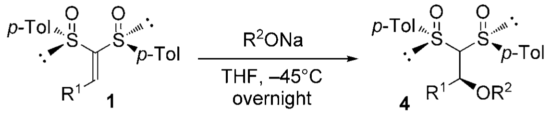
Adduct **4a** was derivatized into the previously described alcohol **5** following a two-step sequence, which involved a Pummerer rearrangement and subsequent reduction of the type-**E** thioester. Correlation with literature data established an (*S*) configuration for **5**.[9a] An enantiomeric excess of 97.5 % was measured by chiral GC for (*S*)-**5**, thereby confirming a highly diastereoselective conjugate addition process and a nonracemizing Pummerer rearrangement (Scheme 4). We deduced by analogy the same (*S*) absolute configuration for all products **4**.



Scheme 4. Derivatization and determination of the absolute configuration of **4a**. TFAA = trifluoroacetic anhydride.

By using these optimized conditions, we could exemplify this addition reaction. High yields of bis(sulfinyl) ethers **4** were observed as well as complete diastereoselectivity (Table 2). A notable exception was the addition of propargyl alcohol; this resulted in a much lower yield (entry 6). A simple change in the reaction conditions, such as adding an excess amount of propargyl alcohol (2 equiv) significantly improved the outcome (64 % yield at 70 % conversion, entry 7). Presumably, protonation of the bis(sulfinyl) anion by excess propargyl alcohol ensures the irreversibility of the addition and results in an improved yield.

Table 2. Addition of alkoxides: yields and diastereoselectivity.

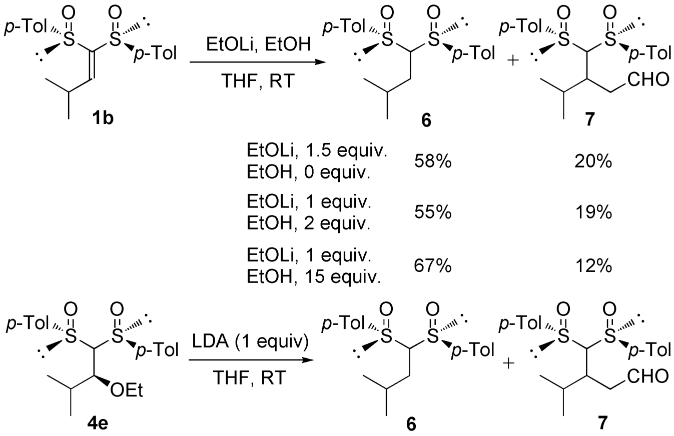


Entry	Precursor	R^1	R^2	Product	Yield [%]	d.r.	Abs conf.
1	**1b**	*i*Pr	Me	**4d**	94	>98:2	(*S*)
2	**1b**	*i*Pr	Et	**4e**	93	>98:2	(*S*)
3	**1b**	*i*Pr	Bn	**4f**	84	>98:2	(*S*)
4	**1b**	*i*Pr	propargyl	**4g**	64[a]	>98:2	(*S*)
5	**1a**	Ph	allyl	**4h**	96	>98:2	(*S*)
6	**1a**	Ph	propargyl	**4i**	15[b,c]	>98:2	(*S*)
7	**1a**	Ph	propargyl	**4i**	64[d]	>98:2	(*S*)

[a] 4 equiv of alkoxide were used and 30 % of **1b** was recovered. [b] 5 equiv of alkoxide were used. [c] 85 % of **1a** was recovered. [d] 2 equiv of alkoxide and 2 equiv of propargylic alcohol were used.

While the addition of sodium ethoxide to **1b** at room temperature resulted in the formation of **4e** in high yield (Table 2, entry 2), lithium ethoxide did not provide the same outcome under similar conditions (Scheme 5). Instead, two new products **6** and **7** were isolated; these products presumably resulted from a Meerwein–Ponndorf–Verley[17] reaction. Thus, hydride conjugate delivery to **1b** with lithium ethoxide would generate **6**. The resulting ethanal by-product would be deprotonated in the basic medium, and the corresponding enolate would also add in a conjugate manner to provide aldehyde **7** as a major diastereomer. We also found that the presence of an excess amount of ethanol does not prevent enolate formation, but results in a slight increase in the yield of **6**.

Optimization of the reaction conditions, which would presumably involve the use of an aluminum alkoxide from an alcohol leading to a nonenolizable carbonyl derivative might provide an alternative route for the preparation of primary alkyl-substituted bis(sulfinyl) compounds of type **6**, which so far have been little described. Methyl-substituted product is known.[18] However, Trost and Bridges have shown that simple alkylation of the bis(phenylsulfinyl) anion with an allyl bromide or a primary alkyliodide requires relatively harsh conditions, which leads to sulfinic acid elimination products.[19] Also, in our hands this alkylation reaction has proved to be troublesome so far (yields <50 %).[20]



Scheme 5. Meerwein–Ponndorf–Verley reaction and reversibility of the alkoxide additions.

Further experiments gave us a better insight into this reaction and suggested the reversible nature of the addition of the alkoxides (Scheme 5). Thus, treating adduct **4e** with lithium diisopropylamide (LDA) at room temperature provided a mixture of **6** and **7**, thus suggesting that retroaddition took place, liberating lithium ethoxide, which triggers the Meerwein–Ponndorf–Verley sequence.

Trapping of the Bis(Sulfinyl) Carbanion

Aforementioned, the alkylation of bis(sulfinyl) anions is difficult. We could also confirm this by trying to add electrophiles to the bis(sulfinyl) anion, which results from the addition of alkoxides. For instance, the trapped product was not detected with methyl iodide. Another attempt consisted of bubbling oxygen through the reaction mixture to hydroxylate the bis(sulfinyl) position, and this should give a transient intermediate that rapidly evolves into a carboxylate derivative. However, no discrete product was isolated with these attempts. Finally, ourselves and others have shown that addition of nucleophiles armed with a leaving group, thus allowing an intramolecular electrophilic trapping, could

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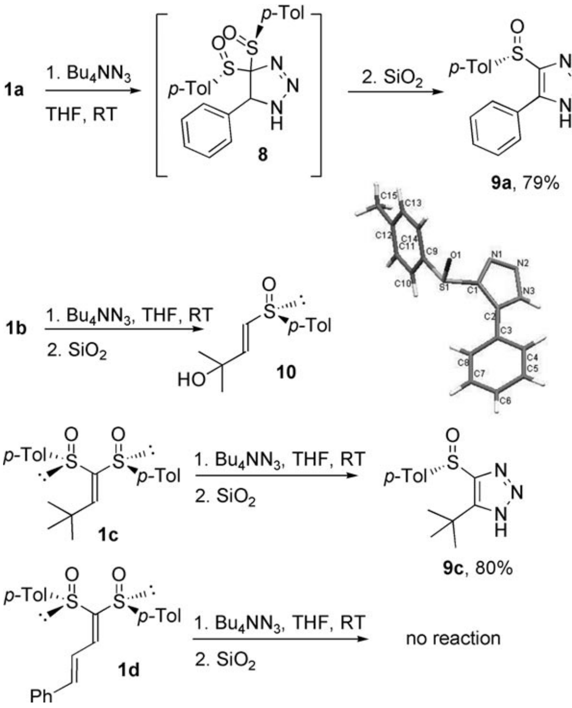
give high yields of cyclopropyl products as single diastereomers,[9a,c,e] which originates from attack of the nucleophile from the *si* face.[21]

Azides

In the same vein, aiming at the formation of triazoles, we also examined the addition of azides. While sodium azide did not afford any addition product with **1a**, presumably for solubility reasons, tetrabutylammonium azide led to triazole **9a** in good yield, the structure of which was confirmed by X-ray crystallography analysis (Scheme 6).[22a] This transformation, which formally corresponds to a Huisgen-type cycloaddition has some precedent with other Michael acceptors to an acetylenic sulfoxide,[23] however, to the best of our knowledge it remains unknown with vinyl sulfoxides. The putative intermediate **8** was observed in the NMR spectrum of the crude product but sulfinic acid elimination during flash chromatography on silica gel took place. Alkyl precursor **1b** gave the Evans–Mislow product **10** as a single diastereomer in good yield.[24] Presumably, with alkyl derivatives, the basic medium would trigger isomerization to the allyl bis(sulfinyl) derivative, thereby setting the stage for an Evans–Mislow rearrangement. The *tert*-butyl substrate **1c** did not follow the Evans–Mislow pathway and it could also be operative, thus leading to triazole **9c** in good yield. Another limitation in this reaction was observed with diene precursor **1d**, which did not afford any adduct in significant yield.

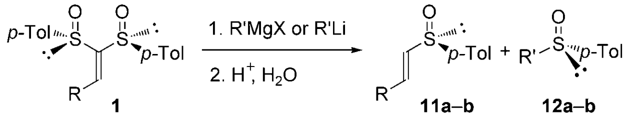


Scheme 6. Formation of triazoles.

Organometallics

Organometallics were obvious candidates to explore.[25] Not surprisingly, lithium or Grignard reagents favor a 1,2-type addition, which corresponds to a thiophilic attack and after displacement of the sulfinyl group[26] leads to a vinyl sulfoxide carbanion and the corresponding *p*-tolyl sulfoxide derivative with an inversion in configuration. It should be noted that a slight erosion in the enantiomeric excess was observed with the (*R*)-methyl-*p*-tolyl sulfoxide (Table 3, entries 1–3). It is known that vinyl sulfoxide lithium carbanions isomerize to give, after protonation, the corresponding (*E*)-vinyl sulfoxides.[27] Indeed, compounds (*E*)-**11a** and (*E*)-**11b** were isolated in good yields.

Table 3. Addition of lithium reagents and Grignards.

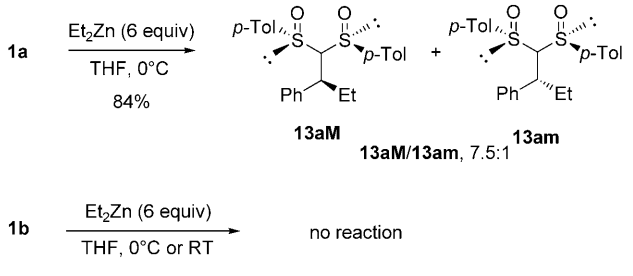


Entry	Precursor	Organometallic (equiv)	(*E*)-11 [%]	12 [%]
1	**1a**	MeMgCl, 1	**11a**, 85	12a, 63[a]
2	**1a**	MeMgBr, 1	**11a**, 83	12a, 82[b]
3	**1a**	MeMgI, 1.1	**11a**, 31	12a, 43[c]
4	**1a**	(nBu)$_2$Mg, 1	**11a**, 75	12b, 83
5	**1a**	MeLi, 1.2	**11a**[d]	12a[d]
6	**1b**	MeLi, 1.2	**11b**[d]	12a[d]

[a] $[\alpha]_D = -144.2$ ($c = 1.25$, acetone). Literature data for (*R*)-methylsulfoxyde is $[\alpha]_D = +146.0$ ($c = 2.0$, acetone). [b] $[\alpha]_D = -137.0$ ($c = 1.25$, acetone). [c] $[\alpha]_D = -132.0$ ($c = 0.98$, acetone). [d] Observed by ^{1}H NMR spectroscopy on the crude product but not isolated.

Therefore, we turned our attention to softer organometallics and initially examined the reactivity of zinc reagents. Our initial endeavors focused on the use of the commercially available diethylzinc reagent solution (Scheme 7) with alkylidene **1a**. At −30 °C with 6 equivalents of reagent, no reaction took place, however, running the reaction at 0 °C provided adducts **13** in good yield (84 %) as a 7.5:1 mixture of **13aM/13am** stereoisomers.[28] In sharp contrast, isobutylidene **1b** proved to be unreactive toward diethyl zinc.

Because of these moderate results in terms of diastereoselectivity and reactivity, we then turned our attention to copper-based derivatives.[25c–f] Our preliminary findings with copper reagents (RLi/CuX, 1:1) or cuprates (RLi/CuX, 2:1) show that these reagents efficiently add to alkylidene bis(-



Scheme 7. Addition of diethylzinc.

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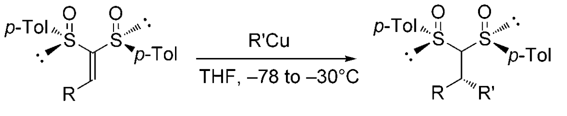
sulfoxides) in good yields with high and identical stereoselectivity, as generally only one diastereomer was isolated from these reactions (Table 4, entries 1–4). We also found that the reactions had to be carried out under very anhydrous conditions, as hydroxy anions, which could originate from the presence of water also add and give the corresponding bis(sulfinyl) alcohol **3**. We found that cuprates, probably due to their increased basicity, resulted in less clean reactions, for example, primary alkyl derivatives (**1e** and **1f**), which bear allylic hydrogens can suffer from Evans–Mislow-type rearrangements. Therefore, we used copper reagents with these substrates. In some cases, the addition of minor amounts of methylate, presumably originating from the oxidation of methyllithium, were observed (products of type **4**).

Table 4. Addition of copper reagents.



1

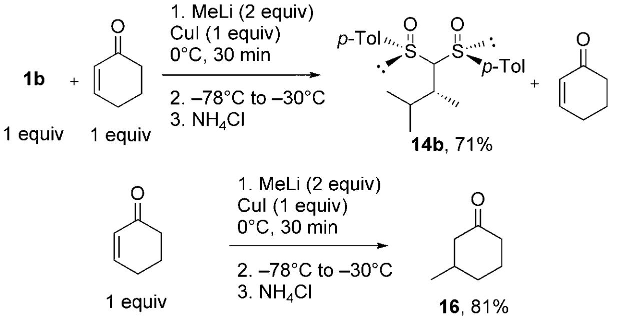
13–15, 1 diastereomer

Entry	precursor, R	R′Cu (equiv)	Product	Yield [%]
1	**1a**, Ph	MeCu, 1	**14a**	70[a,b]
2	**1a**, Ph	MeCu, 2	**14a**	96
3	**1a**, Ph	*n*BuCu, 2	**15a**	85
4	**1a**, Ph	EtCu, 2	**13am**	80
5	**1b**, *i*Pr	MeCu, 1	**14b**	42[c,d]
6	**1b**, *i*Pr	MeCu, 2	**14b**	96
7	**1b**, *i*Pr	Me_2CuLi, 1	**14b**	73[a]
8	**1b**, *i*Pr	Me_2CuLi, 2	**14b**	96
9	**1b**, *i*Pr	*n*BuCu, 2	**15b**	100
10	**1e**, *n*Bu	MeCu, 2	**14e**	85
11	**1f**, CH_2OTBS	MeCu, 2	**14f**	83[b]
12	**1f**, CH_2OTBS	*n*BuCu, 2	**15f**	52[d]

[a] Around 20% of **1a** was recovered. [b] Traces of methylate addition product of type **4**. [c] Around 20% of **1b** was recovered. [d] Bis(sulfinyl) alcohol of type **3** was isolated (10–15%).

By examining the results in Table 4, it appears that higher yields are obtained when two equivalents of the copper or cuprate reagent are used instead of one (compare entries 1 and 2, and 5–8). We also excluded a radical mechanism in these additions, as when methylcopper was added to a mixture of **1b** and isopropyliodide, no addition product of the isopropyl radical that could be generated under these conditions[29a,b] was observed and **14a** is obtained in high yield. To gain further insight into this reactivity, a competitive experiment was run (Scheme 8). Thus, an equimolar mixture of **1b** and cyclohexenone was treated with one equivalent of the methylcuprate reagent, however, only adduct **14b** was isolated, thus suggesting much faster addition on the alkylidene bis(sulfinyl) substrate compared to that of cyclohexenone. As a control experiment, the methylcuprate was added efficiently to cyclohexenone to afford **16**.

Importantly, adducts **13–15** were obtained as single diastereomers (Table 4). The relative configuration of adducts **14a** and **14e** was determined by derivatization.[9a] In the case of **14a**,[22b] it was confirmed by X-ray crystallography analysis, as well as for **14b**.[22c] From these data, we deduced the configurations for other adducts. All these stereochemical determinations mark a sharp contrast with the previous cases and are consistent with an attack from the *re* face with copper reagents.



Scheme 8. Competitive experiment.

It is noteworthy that the diastereoselectivity in the addition between the ethylcopper and diethylzinc reagents to **1a** is opposite (**13aM**/**13am** ratio shifts from 0:1 to 7.5:1, see Scheme 7 and Table 4, entry 4). A possible explanation for this would be that in the case of the reaction with the zinc reagent, a radical Michael addition is involved, as proposed recently by different research groups.[29] The free ethyl radical would follow the diastereoselectivity of a simple nonorganometallic nucleophile (Figure 1).

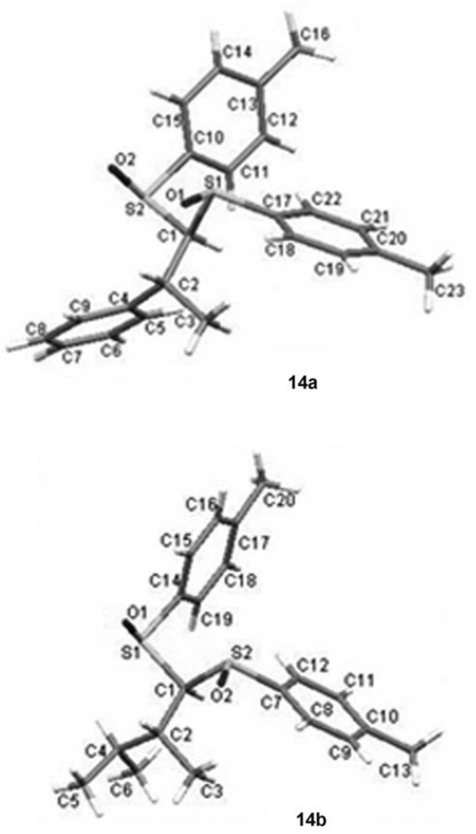
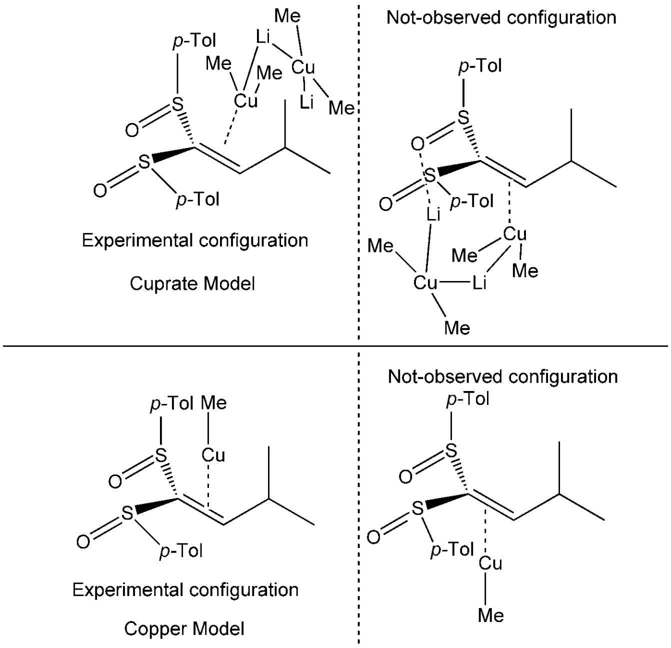


Figure 1. X-Ray structures of **14a** and **14b**.

To account for this inversion in stereoselectivity, we initially invoked a chelate of the sulfinyl groups with the copper salt.[9a] All our experiment attempts using different copper salts to stabilize a copper chelate either failed by sulfur or oxygen complexation. To understand more precisely if indeed a chelate effect can explain the selectivity, we ran quantum mechanics calculations on different models.[30] First, we choose to compare the reactivity between a copper and cuprate reagent (Scheme 9). The copper model uses a simple CuMe to describe the organometallic substrate, while the cuprate model uses two Me_2CuLi subunits, following previous calculations by Nakamura;[31] these results are summarized in Table 5. For the copper model, the barrier for the observed experimental configuration is around 40 kcal mol^{-1}, while the barrier for the other (not observed) configuration is much lower (21 kcal mol^{-1}). A similar barrier was observed (around 21 kcal mol^{-1}) with the cuprate model, comparing the not observed and the experimental configuration. Therefore, we can exclude these models for further investigations of the mechanism.



Scheme 9. Stereoselectivity model.

Table 5. Relative energies for addition of copper and cuprate reagents calculated at the B3LYP/LACVP(d) level, including ZPC. See Scheme 9 for a description of the chemical system.

Model system		Reactant	Transition State	Product
Cuprate	Exp.	21.43	44.16	−24.72
	Non Exp	0.00	20.77	−27.26
Copper	Exp.	0.00	39.56	−2.27
	Non Exp.	0.12	21.37	−24.40

We can notice from these calculations that when lithium is complexed between the two oxygen atoms of the bis(sulfoxide) (cuprate case, in the configuration not observed experimentally), the structure is much more stable. To elucidate the mechanism and the stereoselectivity, this kind of chelation must be taken into account (leading to structures **A-X** and **A-X′**). As it is known that cuprates are monomeric in a tetrahydrofuran solution,[32] we decided to use only one cuprate to study the reactivity and add specific solvent effects, namely, by adding a molecule of dimethylether or tetrahydrofuran. Results are summarized in Figure 2. It can be seen that the gap between the two configurations is reduced and the barriers are lower (ca. 15 kcal mol^{-1}) than in our previous models. Without taking into ac-

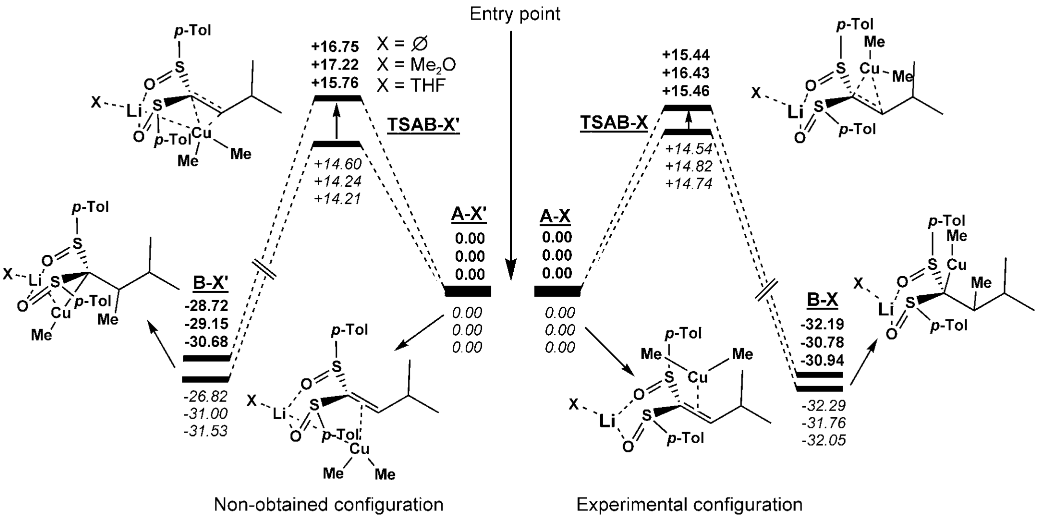


Figure 2. Energetic profiles for the addition or organocuprate reagent on alkylidene bis(sulfoxides), calculated at the B3LYP/LACVP(d) level. Energies are in kcal mol^{-1}. All three value sets corresponding to each calculated structure are given in the following order, from top to bottom: without ligand, with dimethyether, with THF. Italic: without entropy and bold: with entropy.

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count entropy, the not observed configuration is still favored, with or without one solvent molecule complexed to lithium. When entropy is included, we observed a selectivity inversion. Barriers are slightly favored: 15.44 vs. 16.75 kcal mol^{-1} without solvent, 16.43 vs. 17.22 kcal mol^{-1} with dimethylether and 15.46 vs. 15.76 kcal mol^{-1} with tetrahydrofuran (compare **TSAB-X** vs. **TSAB-X'** in Figure 2). We can attribute this entropy effect to the fact there is one more degree of freedom in the experimental configuration, as there is no bonding between copper and lithium (each of them being on the opposite face of the alkylidene bis(sulfoxides)).

After these encouraging results showed that the stereoselectivity can be different depending of the presence or absence of solvent, we decided to include a second molecule of solvent, namely, tetrahydrofuran (Figure 3).

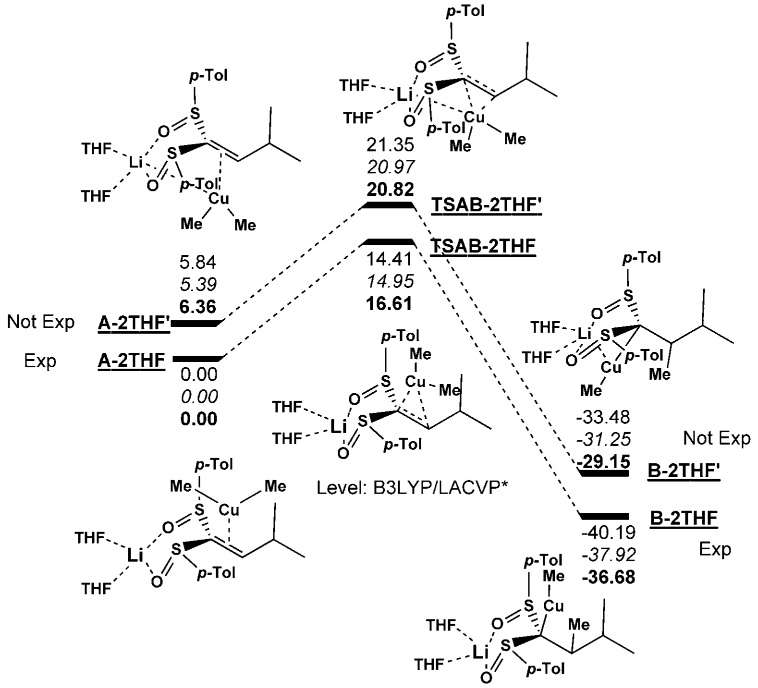

Figure 3. Energetic profiles for the addition of organocuprate reagent on alkylidene bis(sulfoxides) with two THF molecules, calculated at the B3LYP/LACVP(d) level. Italic values correspond to energies with ZPC included. Bold values also include entropy. Energies are in kcal mol^{-1}.

Results with two tetrahydrofuran molecules are summarized in Figure 3. The starting alkylidene-cuprate complex (**A-2THF**) that gives finally the observed product is more stable by approximately 6 kcal mol^{-1}. It should be noted that **A-2THF** can be seen as a Cu^{I} or as a Cu^{III} complex, as two mesomeric structures can be drawn to describe the copper-alkylidene interaction.[31] The stability of **A-2THF** is mainly due to the fact that the second tetrahydrofuran molecule can be close to the lithium atom in that case, whereas when both lithium and copper are on the same side of the alkylidene bis(sulfoxides), some unfavorable steric interaction is developed with tetrahydrofuran. As a result, we computed a barrier of 16.61 kcal mol^{-1} for the experimentally observed diastereoisomer (**B-2THF**) and a barrier of 20.82 kcal mol^{-1} for the other. Also, the product is more stable when the lithium is on the opposite face of copper, as in this case tetrahydrofuran molecules can interact well with the cation to stabilize it.

In summary, DFT calculations suggest that a copper reagent is not likely to be the alkylating agent in solution. A cuprate model is found to be more favored. This could be corroborated by the fact that better yields are obtained when two equivalents of copper reagent are used. Lithium chelation of the alkylidene bis(sulfoxides) together with explicit solvent effect are found to be necessary to account for the observed diastereoselectivity.

Conclusions

In conclusion, we have shown that alkylidene bis(sulfoxides) of type **1** are remarkable Michael acceptors towards various anionic nucleophiles. Very good yields and complete stereoselectivities are observed in most cases with heteronucleophiles as well as copper reagents, the latter yielding reversed facial selectivity, which could be rationalized by DFT calculations.

Experimental Section

General Procedure for the Addition of Sodium Alkoxides to Alkylidene Bis(Sulfoxides)

At 0 °C, NaH (60 % suspension in mineral oil, 1.5 equiv) was added to a solution of alcohol (1.5 equiv) in THF (4.5 mL mmol^{-1}). The solution was stirred for 5 min, cooled to −45 °C, and a solution of alkylidene bis(sulfoxide) **1** (1 equiv) in THF (6.5 mL mmol^{-1}) was canulated. The reaction mixture was stirred at −45 °C for 14 h and quenched with an aqueous saturated solution of NH_4Cl. Then it was diluted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography to afford the corresponding product **4**.

General Procedure for the Addition of Lithium and Grignards reagents to Alkylidene Bis(Sulfoxides)

At −78 °C, a solution of the organometallic reagent (1 equiv) was added to a solution of alkylidene bis(sulfoxide) **1** (1 equiv) in THF (10 mL mmol^{-1}). These reagents are used from the commercial solutions: CH_3MgBr (3 M) in diethyl ether, CH_3MgCl (3 M) in THF, CH_3MgI (0.5 M) in toluene, Bu_2Mg (1 M) in THF, CH_3Li (1.6 M) in diethyl ether. After 5 min at −78 °C, the reaction mixture turned to an orange-brown color and an aqueous saturated solution of ammonium chloride was added.

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The crude mixture was extracted with dichloromethane and the organic phase was successively washed with water and brine, dried over magnesium sulfate. The solvents were removed under vacuum and the crude was purified by silica gel chromatography (pentane/ethyl acetate from 80:20 to 0:100). Two fractions were obtained containing the vinyl sulfoxide **11** and the sulfoxide **12**.

General Procedure for the Addition of Copper and Cuprate Reagents on Alkylidene Bis(Sulfoxides)

(MeCu, LiI) and (Me$_2$CuLi, LiI) were prepared according the following procedure: MeLi (1.6 M in diethyl ether, 1 equiv for the organocopper and 2 equiv for the cuprate) was slowly added to a THF (2 mL mmol^{-1}) suspension of CuI (1 equiv) at 0 °C. Stirring was continued for 30 min at this temperature. The solution became yellow. (EtCu, LiI) and (*n*BuCu, LiI) were prepared according the following procedure: EtLi (0.5 M in benzene/cyclohexane 9:1, 1 equiv) or *n*BuLi (2.5 M in hexanes, 1 equiv) was slowly added to a THF (2 mL mmol^{-1}) suspension of CuI (1 equiv) at −50 °C; stirring was continued for 30 min at this temperature.

Addition onto Alkylidene Bis(Sulfoxides)

At −78 °C a solution of alkylidene bis(sulfoxide) **1** (1 equiv) in THF (4 mL mmol^{-1}) was canulated into a solution of the copper or cuprate reagent (1 or 2 equiv) in THF (2 mL mmol^{-1}). After 30 min at −78 °C, the reaction mixture was allowed to warm to −30 °C for another 30 min, then it was diluted in Et$_2$O and quenched with an aqueous saturated solution of ammonium chloride. The organic layer was successively washed with water and brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to afford the corresponding compounds **13**, **14**, or **15**.

All the experimental details and the characterization data of the new compounds are reported in the Supporting Information.

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---

[1] a) J.-L. Reymond, P. Vogel, *Tetrahedron: Asymmetry* **1990**, *1*, 729–736; b) W. R. Roush, B. B. Brown, *J. Org. Chem.* **1992**, *57*, 3380–3387; c) J. Martynow, M. Dimitroff, A. G. Fallis, *Tetrahedron Lett.* **1993**, *34*, 8201–8204; d) R. López, J. C. Carretero, *Tetrahedron: Asymmetry* **1991**, *2*, 93–96.

[2] For a review on bis(sulfoxides), see: B. Delouvrié, L. Fensterbank, F. Nájera, M. Malacria, *Eur. J. Org. Chem.* **2002**, 3507–3525.

[3] For recent reviews on the use of sulfoxides in asymmetric synthesis, see: a) I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651–3705; b) H. Pellissier, *Tetrahedron* **2006**, *62*, 5559–5601; c) M. C. Carreño, G. Hernández-Torres, M. Ribagorda, A. Urbano, *Chem. Commun.* **2009**, 6129–6144.

[4] a) N. Katagiri, S. Ise, N. Watanabe, C. Kaneko, *Chem. Pharm. Bull.* **1990**, *38*, 3242–3248; b) V. K. Aggarwal, M. Lightowler, S. D. Lindell, *Synlett* **1992**, 730–732; c) V. K. Aggarwal, Z. Gültekin, R. S. Grainger, H. Adams, P. L. Spargo, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2771–2781; d) V. K. Aggarwal, R. S. Grainger, H. Adams and P. L. Spargo, *J. Org. Chem.* **1998**, *63*, 3481–3485; e) V. K. Aggarwal, S. Roseblade and R. Alexander, *Org. Biomol. Chem.* **2003**, *1*, 684–691; f) see also: O. De Lucci, D. Fabbri, V. Lucchini, *Synlett* **1991**, 565–568 and Ref. [2] for other references; see also: g) S. Yoshida, H. Yorimitsu, K. Oshima, *Org. Lett.* **2009**, *11*, 2185; h) T. Kobatake, S. Yoshida, H. Yorimitsu, K. Oshima *Angew. Chem.* **2010**, *122*, 2390–2393; *Angew. Chem. Int. Ed.* **2010**, *49*, 2340–2343.

[5] a) Y. Arai, S. Kuwayama, Y. Takeuchi, T. Koizumi, *Synth. Commun.* **1986**, *16*, 233–244; b) J. C. Carretero, J. L. García Ruano, L. M. Martín Cabrejas, *Tetrahedron: Asymmetry* **1997**, *8*, 409–416; c) For recent use of bis-*p*-tolylsulfinyl substrates in organocatalysis, see: I. Fernández, V. Valdivia, M. Pernía Leal, N. Khiar, *Org. Lett.* **2007**, *9*, 2215–2218; d) For recent applications of chiral bis-*p*-tolylsulfinyl substrates as ligands for platinum, see: R. Martinez Mallorquin, S. Chelli, F. Brebion, L. Fensterbank, J.-P. Goddard, M. Malacria, *Tetrahedron: Asymmetry* **2010**, *21*, 1695–1700.

[6] An initial example of highly diastereoselective Michael addition has been reported by Aggarwal in the study of the epoxidation of a substrate of type **B** (R = Ph) with H$_2$O$_2$, NaOH, see: V. K. Aggarwal, J. K. Barrell, J. M. Worrall and R. Alexander, *J. Org. Chem.* **1998**, *63*, 7128–7129.

[7] T. Wedel, J. Podlech, *Synlett* **2006**, 2043–2046.

[8] T. Wedel, J. Podlech, *Org. Lett.* **2005**, *7*, 4013–4015.

[9] a) F. Brebion, B. Delouvrié, F. Nájera, L. Fensterbank, M. Malacria, J. Vaissermann *Angew. Chem.* **2003**, *115, 5500–5503; Angew. Chem. Int. Ed.* **2003**, 42, 5342–5345; *Angew. Chem. Int. Ed.* **2003**, *42*, 5342–5345; b) F. Brebion, J.-P. Goddard, C. Gomez, L. Fensterbank, M. Malacria, *Synlett* **2006**, 713–716; c) F. Brebion, J.-P. Goddard, L. Fensterbank, M. Malacria, *Synthesis* **2005**, 2449–2452; d) J.-P. Goddard, C. Gomez, F. Brebion, S. Beauvière, L. Fensterbank, M. Malacria, *Chem. Commun.* **2007**, 2929–2931; e) A. Abramovitch, L. Fensterbank, M. Malacria, I. Marek, *Angew. Chem.* **2008**, *120*, 6971–6974; *Angew. Chem. Int. Ed.* **2008**, *47*, 6865–6868; f) For Michael conjugate radical addition, see: F. Brebion, M. Vitale, L. Fensterbank, M. Malacria, *Tetrahedron: Asymmetry* **2003**, *14*, 2889–2896.

[10] For important references on the Michael addition to vinylsulfoxides, see: a) M. C. Carreño, *Chem. Rev.* **1995**, *95*, 1717–1760; b) G. Hanquet, F. Colobert, S. Lanners, G. Solladié, *Arkivoc* **2003**, *(vii)*, 328–401; c) P. Łyżwa, A. Jankowiak, M. Kwiatkowska, M. Mikołajczyk, P. Kiełbasiński, A. Betz, P.-A. Jaffres, A.-C. Gaumont, M. Gulea, *Tetrahedron Lett.* **2007**, *48*, 351 and references therein.

[11] a) S. Colonna, V. Pironti, J. Drabowicz, F. Brebion, L. Fensterbank, M. Malacria, *Eur. J. Org. Chem.* **2005**, 1727–1730; b) Vanadium-catalyzed asymmetric oxidation has furnished promising results, M. Vitale, L. Fensterbank, M. Malacria, unpublished results, see also: c) J. Skarzewski, E. Ostrycharz, R. Siedlecka, *Tetrahedron: Asymmetry* **1999**, *10*, 3457–3461; d) C. Bolm, F. Bienewald, *Angew. Chem.* **1995**, *107*, 2883–2885; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2640–2642.

[12] B. Delouvrié, F. Nájera, L. Fensterbank, M. Malacria, *J. Organomet. Chem.* **2002**, *643–644*, 130–135.

[13] a) Ref. [9c]; b) M. Reggelin, H. Weinberger, V. Spohr, *Adv. Synth. Catal.* **2004**, *346*, 1295–1306.

[14] a) L. F. Tietze, A. Schuffenhauer, P. R. Schreiner, *J. Am. Chem. Soc.* **1998**, *120*, 7952–7958; b) For similar directing effect of the sulfinyl moiety, see also: G. Sklute, I. Marek, *J. Am. Chem. Soc.* **2006**, *128*, 4642–4649.

[15] T. Wedel, T. Gehring, J. Podlech, E. Kordel, A. Bihlmeier, W. Klopper, *Chem. Eur. J.* **2008**, *14*, 4631.

[16] Additions of amines to simple vinylsulfoxides are slower and less selective, see: a) S. G. Pyne, P. Bloem, S. L. Chapman, C. E. Dixon, R. Griffith, *J. Org. Chem.* **1990**, *55*, 1086–1093; b) D. J. Abbott, S. Colonna, J. M. Stirling, *J. Chem. Soc. Perkin Trans. 1* **1976**, 492–498.

[17] M. B. Smith, J. March in *Advanced Organic Chemistry*, *5th ed.*, Wiley, **2001**, New York, p. 1199.

[18] a) N. Khiar, I. Fernandez, F. Alcudia, *Tetrahedron Lett.* **1993**, *34*, 123–126; b) see also: Ref. [9d].

[19] a) B. M. Trost, A. J. Bridges, *J. Org. Chem.* **1975**, *40*, 2014–2016; b) For an application of the sulfinic acid elimination in the diastereoselective synthesis of vinylsulfoxides, see: F. Brebion, J.-P. Goddard, L. Fensterbank, M. Malacria, *Org. Lett.* **2008**, *10*, 1917–1920.

[20] C. Gomez, J.-P. Goddard, M. Malacria, L. Fensterbank, unpublished results.

[21] For epoxidation, see: Ref. [6].

[22] The following CCDC files contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif: a) **9a**: CCDC 777833; b) **14a**: CCDC 779148; c) **14b**: CCDC 779149.

[23] a) F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2004**, *69*, 2315; b) Z. Dong, K. A. Hellmund, S. G. Pyne, *Aust. J. Chem.* **1993**, *46*, 1431.

[24] a) F. Brebion, F. Nàjera, B. Delouvrié, E. Lacôte, L. Fensterbank, M. Malacria, *Synthesis* **2007**, 2273–2278; see also the SPAC reaction (Sulfoxide Piperidine Aldehyde Condensation): b) V. Guerrero-de la Rosa, M. Ordoñez, F. Alcudia, J. M. Llera, *Tetrahedron Lett.* **1995**, *36*, 4889–4892; c) K. Burgess, J. Cassidy, I. Henderson, *J. Org. Chem.* **1991**, *56*, 2050–2058.

[25] For organometallics addition to vinylsulfoxides, see: a) J. P. Marino, A. de Dios, L. J. Anna, R. Fernndez de La Pradilla, *J. Org. Chem.* **1996**, *61*, 109–117; b) J. P. Marino, A. Viso, R. Fernández de La Pradilla, P. Fernández, *J. Org. Chem.* **1991**, *56*, 1349–1351. For copper reagent additions, see: c) E. Nakamura, N. Yoshikai in *The Chemistry of Organocopper Compounds* (Ed. Z. Rappoport I. Marek), Wiley New-York, **2009**, pp. 1–23; d) S. Mori, E. Nakamura in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 315–346; e) W. Henze, T. Gärtner, R. Gschwind, *J. Am. Chem. Soc.* **2008**, *130*, 13718–13726; f) B. Breit, Y. Schmidt, *Chem. Rev.* **2008**, *108*, 2928–2951.

[26] For sulfoxide-metal exchange, see Ref. [9e] and references therein.

[27] a) S. House, P. R. Jenkins, J. Fawcett, D. R. Russell, *J. Chem. Soc. Chem. Commun.* **1987**, 1844–1845; b) J. Fawcett, S. House, P. R. Jenkins, N. J. Lawrence, D. R. Russell, *J. Chem. Soc. Perkin Trans. 1* **1993**, 67–73; c) M. Mikołajczyk, W. Perlikowska, J. Omelańczuk, H.-J. Cristau, A. Perraud-Darcy, *J. Org. Chem.* **1998**, *63*, 9716–9722.

[28] The determination of configuration is based by comparison with results obtained in the copper reagent series (see Table 4, line 4) which presumably gives **13am** as a major diastereomer.

[29] a) H. O. House, *Acc. Chem. Res.* **1976**, *9*, 59–67; b) K. Li, A. Alexakis *Angew. Chem.* **2006**, *118, 7762–7765; Angew. Chem. Int. Ed.* **2006**, 45, 7600–7603; *Angew. Chem. Int. Ed.* **2006**, *45*, 7600–7603; c) S. Bazin, L. Feray, N. Vanthuyne, M. P. Bertrand, *Tetrahedron* **2005**, *61*, 4261–4274; d) F. Denes, S. Cutri, A. Pérez-Luna, F. Chemla, *Chem. Eur. J.* **2006**, *12*, 6506–6513; e) Conjugate Addition of Organometallic Reagents, K. Tomioka, Y. Nagaoka in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H., Yamamoto), Springer, New York, **1999**, *3*, 1105–1120; f) B. L. Feringa, R. M. Kellog, H. van der Deen, *Org. Lett.* **2000**, *2*, 1593–1595; g) T. Cohen, H. Gibney, R. Ivanov, E. A.-H. Yeh, I. Marek, D. P. Curran, *J. Am. Chem. Soc.* **2007**, *129*, 15405–15409.

[30] Computational methods: All the structures were calculated by DFT using the hybrid functional B3LYP, and the double-zeta basis set, LACVP(d), which includes effective core potential for heavier elements like Cu. In geometry optimization procedures, we use JAGUAR 6.5, and subsequently employ GAUSSIAN03/09 for analytic frequency calculations. Reaction pathways were verified by a scan along a given coordinate, while optimizing freely all other coordinates. The data are summarized is the Supporting Information (SI) deposited with this paper, while the text focuses on the key results.

[31] a) N. Yoshikai, S.-L. Zhan, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 12862–12863; S. Mori, E. Nakamura, *Chem. Eur. J.* **1999**, *5*, 1534–1543; b) E. Nakamura, S. Mori, K. Morokuma, *J. Am. Chem. Soc.* **1997**, *119*, 4900–4910; c) E. Nakamura, S. Mori, *Angew. Chem.* **2000**, *112*, 3902–3924; *Angew. Chem. Int. Ed.* **2000**, *39*, 3750–3771.

[32] A. Gerold, J. T. B. H. Jastrzebski, C. M. P. Kronenburg, N. Krause, G. von Koten, *Angew. Chem.* **1997**, *109*, 778–780; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 755–757.

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