VIP Asymmetric Catalysis

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Catalytic Asymmetric Conjugate Reduction of β,β-Disubstituted α,β-Unsaturated Sulfones**

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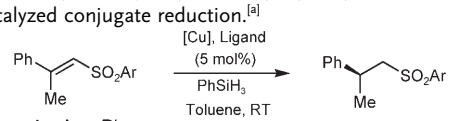
Dedicated to Professor José Luis García Ruano on the occasion of his 60th birthday

The pioneering work reported in 1999 by Buchwald and coworkers[1] on the copper hydride catalyzed asymmetric conjugate reduction of acyclic β,β-disubstituted α,β-unsaturated esters triggered significant progress in this area,[2] including the extension of this methodology to other types of Michael acceptors, such as β-enamido esters[3] and enones,[4] and α,β-unsaturated lactones,[5] lactams,[5] nitriles,[6] and nitro compounds.[7] As a result, the catalytic asymmetric conjugate reduction of β,β-disubstituted Michael acceptors currently represents a useful and practical alternative for the preparation of enantioenriched carbonyl compounds (and related systems) which have a tertiary stereocenter at the β position that nicely complements the catalytic asymmetric conjugate addition[8] of organometallic species to β-substituted Michael acceptors.

In this context, it is interesting to note that despite the great chemical versatility of sulfones in organic synthesis[9] the catalytic asymmetric conjugate reduction of β,β-disubstituted α,β-unsaturated sulfones remains unexplored. We describe herein a general procedure for such novel asymmetric process that relies heavily on the use of 2-pyridylsulfones and provides highly synthetically valuable chiral alkyl 2-pyridylsulfones in excellent yields and enantioselectivities.

As a starting point, the phenyl vinyl sulfone **1** was subjected to the Cu-catalyzed hydrosilylation reaction under typical reaction conditions. In particular, $PhSiH_3$ as the hydrosilane,[10] three copper sources ($Cu(OAc)_2 \cdot H_2O$, $[CuF(PPh_3)_3] \cdot 2\,MeOH$, and CuCl/*t*BuONa), and two chiral ligands (Binap and Josiphos) were considered for the reaction setup. Disappointingly, no reaction was observed with any of the copper catalysts in toluene at room temperature for 24 h, which shows the reluctance of phenyl vinyl sulfones to undergo conjugate reduction (Table 1, entries 1, 3, and 5). On the basis of the knowledge acquired in our previously reported study on the Rh-catalyzed conjugate addition of boronic acids to α,β-unsaturated sulfones, in which the use of a 2-pyridylsulfonyl group produced a dramatic increase in reactivity compared to usual phenyl or tolyl vinyl sulfones,[11] we envisaged that this potentially copper-coordinating sulfonyl group might also result in a strong acceleration of the conjugate reduction. We were pleased to find that under the same reaction conditions tested for the inert phenyl sulfone **1**, the 2-pyridylsulfonyl analogue **2a** was quite reactive, being converted completely into the reduced sulfone **3a** in 8–24 h at room temperature (Table 1, entries 2, 4, and 6).

Table 1: Reactivity of the phenyl and 2-pyridyl vinyl sulfones **1** and **2a** in the Cu-catalyzed conjugate reduction.[a]



1: Ar = Ph
2a: Ar = 2-Py

Entry	Sulfone	[Cu]	Ligand	*t* [h]	Yield [%][b]
1	**1**	$Cu(OAc)_2 \cdot H_2O$	(*R*)-Binap	24	0
2	**2a**	$Cu(OAc)_2 \cdot H_2O$	(*R*)-Binap	24	91
3	**1**	$[CuF(PPh_3)_3] \cdot 2\,MeOH$	Josiphos	8	0
4	**2a**	$[CuF(PPh_3)_3] \cdot 2\,MeOH$	Josiphos	8	96
5	**1**	CuCl/*t*BuONa	(*R*)-Binap	24	0
6	**2a**	CuCl/*t*BuONa	(*R*)-Binap	24	95

[a] Reaction conditions: **1** or **2a** (1 equiv), [Cu]/ligand (5 mol%), $PhSiH_3$ (4 equiv) in toluene (0.2 M) at room temperature. 2-Py: 2-pyridyl; Binap: 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; Josiphos: (*R*)-1-[(*S*)-2-diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine. [b] Yield after chromatography.

Once we established the superiority of the pyridyl sulfonyl group,[12] a broad survey or reaction conditions was undertaken to optimize the enantioselectivity of the conjugate reduction of **2a**, including a variety of copper sources,[13] chiral ligands, solvents,[14] and mode of addition of the reagents.[15] The best reactivity/enantioselectivity profile was observed with $Cu(AcO)_2$ and, especially, CuCl/*t*BuONa in toluene. Table 2 shows the enantioselectivity of the process in the presence of common chiral ligands employed in asymmetric reductions of α,β-unsaturated carbonyl compounds. For this model reaction we found that the axial chiral ligands binap, Segphos, and DTBM-Segphos (Table 2, entries 1–3) were much more efficient than the planar chiral ligands Josiphos and Taniaphos[16] (entries 4 and 5) and provided the known

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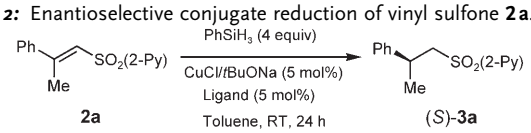
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 2: Enantioselective conjugate reduction of vinyl sulfone **2a**.



Entry	Ligand[a]	Yield [%][b]	*ee* [%][c]
1	(*R*)-Binap	>98	94
2	(*R*)-Segphos	>98	94
3	(*R*)-DTBM-Segphos	70	91
4	(*R,S*)-Josiphos	>98	73
5	Taniaphos	>98	72

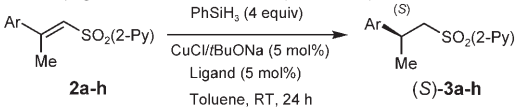
[a] Structures of the chiral ligands are given in the Supporting Information. [b] Conversion yield determined by NMR spectroscopy. [c] Determined by HPLC (Chiralpak IA column).

chiral sulfone (*S*)-**3a**[11a] with very high enantioselectivities (91–94% *ee*).

With the optimal ligands Binap and Segphos, we next studied the enantioselectivity of the reduction of a variety of β-methyl β-aryl α,β-unsaturated 2-pyridylsulfones. These vinyl sulfones **2** were readily prepared in high yields and with complete *E* stereoselectivity by addition of the α-sulfonyl carbanion of methyl 2-pyridylsulfone to the corresponding acetophenone, followed by formal dehydration (TFAA, Et_3N, DMAP).[17] As it is deduced from the data in Table 3, Binap proved to be much more efficient than Segphos with regard to both reactivity and asymmetric induction and afforded the chiral sulfones **3a**–**h** with chemical yields and enantioselectivities higher than 90% regardless of the substitution at the β-aryl ring.[18] The only exception to this general trend was the naphthyl substrate **2h**, which provided the chiral sulfone with 70% *ee* (Table 3, entry 14).

To broaden the synthetic interest of this highly enantioselective procedure, a set of structurally diverse vinyl sulfones, including β,β-dialkyl-substituted substrates, cyclic substituents, and *E*/*Z* stereoisomers, was prepared and submitted to the optimized Cu-catalyzed hydrosilylation conditions (Table 4). Gratifyingly, all vinyl sulfones provided the reduced products in high yield (89–93%) and with excellent enantioselectivity (90–93% *ee*), regardless of the substitution at β-position. In addition, as expected, the *E* and *Z* stereoisomers of the same vinyl sulfone led to opposite enantiomers (Table 4, entries 1–4).

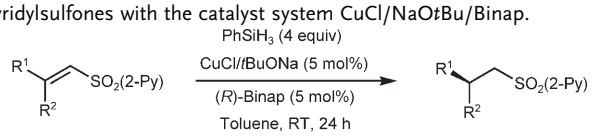
Table 3: Enantioselective conjugate reductions of β-aryl β-methyl α,β-unsaturated 2-pyridylsulfones.

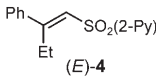
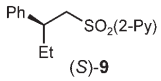
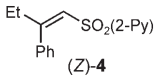
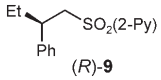
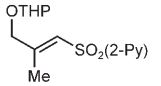
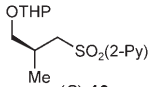
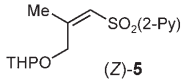
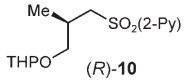
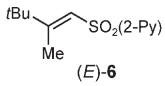
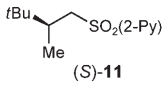
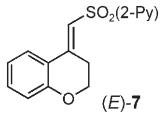
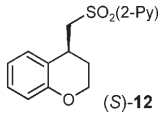
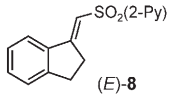
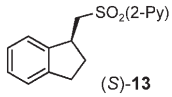


Entry	Substrate	Ar	Ligand[a]	Product	Yield [%][b]	*ee* [%][c]
1	**2a**	Ph	A	**3a**	95	94
2	**2a**	Ph	B	**3a**	95	94
3	**2b**	*p*-MeO-C_6H_4	A	**3b**	92	91
4	**2c**	*p*-NO_2-C_6H_4	A	**3c**	93	89
5	**2c**	*p*-NO_2-C_6H_4	B	**3c**	50[d]	78
6	**2d**	*p*-Br-C_6H_4	A	**3d**	92	92
7	**2d**	*p*-Br-C_6H_4	B	**3d**	78[d]	83
8	**2e**	*p*-CF_3-C_6H_4	A	**3e**	95	92
9	**2e**	*p*-CF_3-C_6H_4	B	**3e**	75[d]	77
10	**2f**	*o*-Me-C_6H_4	A	**3f**	93	93
11	**2f**	*o*-Me-C_6H_4	B	**3f**	45[d]	71
12	**2g**	*o*-Br-C_6H_4	A	**3g**	90	94
13	**2g**	*o*-Br-C_6H_4	B	**3g**	17[d]	nd
14	**2h**	2-naphthyl	A	**3h**	89	70
15	**2h**	2-naphthyl	B	**3h**	<10[d]	nd

[a] A: (*R*)-Binap; B: (*R*)-Segphos. [b] Yield after chromatography. [c] Determined by chiral HPLC (Chiralpak IA column). [d] Conversion yield determined by ^1H NMR spectroscopy on the crude mixture.

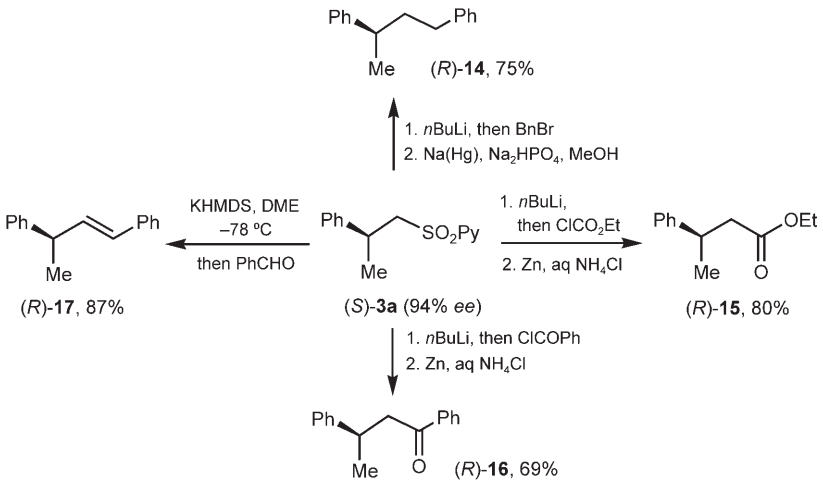
Table 4: Enantioselective conjugate reduction of α,β-unsaturated 2-pyridylsulfones with the catalyst system CuCl/NaO*t*Bu/Binap.



Entry[a]	Substrate	Product	Yield [%][b]	*ee* [%][c]
1	 (*E*)-**4**	 (*S*)-**9**	92	93
2	 (*Z*)-**4**	 (*R*)-**9**	92	91
3	 (*E*)-**5**	 (*S*)-**10**	89	91
4	 (*Z*)-**5**	 (*R*)-**10**	91	91
5	 (*E*)-**6**	 (*S*)-**11**	93	91
6	 (*E*)-**7**	 (*S*)-**12**	93	90
7	 (*E*)-**8**	 (*S*)-**13**	91	90

[a] Reaction conditions: vinyl sulfone (1 equiv), [Cu]/(*R*)-Binap (5 mol%), $PhSiH_3$ (4 equiv) in toluene (0.2 M) at room temperature. [b] Yield after chromatography. [c] Determined by chiral HPLC (Chiralpak IA column). THP: tetrahydropyranyl.

Finally, to highlight the chemical versatility of these β-substituted highly enantioenriched sulfones in the preparation of differently functionalized chiral compounds, Scheme 1 shows the one-step or two-step straightforward conversion of (*S*)-**3a** (94% *ee*) into the benzylated compound (*R*)-**14**, the β-substituted ester (*R*)-**15**,[1] the β-substituted ketone (*R*)-**16**,[19] and the allylic substituted alkene (*R*)-**17**.[11a,20] The first three transforma-



Scheme 1. Examples of synthetic applications of chiral nonracemic 2-pyridylsulfones. HMDS: hexamethyldisilazide; DME: 1,2-dimethoxyethane.

tions are based on the generation of the highly nucleophilic α-sulfonyl carbanion, formation of the C–C bond by reaction with an appropriate carbon electrophile (benzyl bromide, ethyl chloroformate, or benzoyl chloride), and final desulfonylation. On the other hand, the Julia–Kocienski olfefination[21] of (*S*)-**3a** with benzaldehyde afforded directly the alkene (*R*)-**17** (87%) with complete *E* stereoselectivity and similar optical purity (94% *ee*) as the starting sulfone, thus proving that this olefination process occurs without racemization at the allylic stereogenic center.

In summary, we have developed an efficient protocol for the catalytic asymmetric conjugate reduction of β,β-disubstituted α,β-unsaturated sulfones. Key factors in the success of this reaction are the use of 2-pyridylsulfones as substrates and CuCl/*t*BuONa/Binap as the chiral catalytic system. This procedure has a broad scope regarding the substitution at the vinyl sulfone and provides β-substituted 2-pyridylsulfones in excellent chemical yields and with excellent enantioselectivities (typically 90–94% *ee*). These enantioenriched sulfones are versatile intermediates in the preparation of a wide variety of functionalized chiral compounds.

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[10] A much lower reactivity was observed in the reduction of the model sulfone **2a** when PMHS was used instead of $PhSiH_3$.

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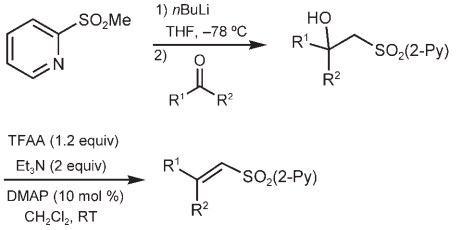
[13] CuF_2, $[CuF(PPh_3)_3]\cdot 2MeOH$, $[Cu(acac)_2]$ (acac: acetylacetonate), $Cu(OAc)_2\cdot H_2O$, CuI/*t*BuONa, and CuCl/*t*BuONa were tested.

[14] The effect of the solvent was systematically studied in the case of the $Cu(OAc)_2$/Binap-mediated reduction of the model substrate **2a**. Toluene provided the best result (90% *ee*), while the reduction was less enantioselective in dioxane (83% *ee*), acetonitrile (77% *ee*), and THF (64% *ee*), and very low reactivity was observed in dichloromethane and DMSO.

[15] We observed a higher reactivity when all the species (copper source, ligand, substrate, and silane) were added directly to the solution, rather than aging the copper source and ligand for 30 min before the addition of the substrate and silane (see Supporting Information).

[16] Other commercially available chiral ligands such as TolBinap, Chiraphos, Norphos, Phanephos, and Mandyphos were also surveyed in the Cu-catalyzed reduction of the model substrate **2a**, but they provided very low asymmetric inductions (0–40% *ee*).

[17] All vinyl pyridyl sulfones (substrates **2a–h** and **4–8**) were prepared in good yields (44–75%) from methyl 2-pyridylsulfone and the corresponding ketone according to the two-step sequence shown below. Only the reaction with propiophenone (substrate **4**) and the THP derivative of hydroxyacetone (substrate **5**) were not completely *E*-stereoselective (the mixture of *E*/*Z* isomers was readily separated by silica gel chromatography). TFAA: trifluoracetic anhydride; DMAP: 4-(*N*,*N*-dimethylamino)pyridine.



[18] The *S* configuration of the major enantiomer of products **3** was assumed by analogy with the case of the known (*S*)-**3a**. In agreement with this stereochemical assignment, the enantiomers of sulfones **3a–h** show a homogeneous behavior in chiral HPLC (the *S* enantiomer always appears at higher retention time; column IA, 0.6 mL min^{-1}, hexane/isopropyl alcohol 90:10).

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