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Chiral Copper Complexes of Phosphino Sulfenyl Ferrocenes as Efficient Catalysts for Enantioselective Formal Aza Diels−Alder Reactions of *N*-Sulfonyl Imines

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Six-membered nitrogen heterocycles are key units in medicinal chemistry and very interesting intermediates in organic synthesis.[1] The catalytic enantioselective Aza Diels−Alder reaction (ADAR) of electron-rich dienes with aldimines is conceptually an extremely powerful strategy for the construction of this type of structures with high enantiopurity.[2] However, to the best of our knowledge, only three catalyst systems have been described to date for this asymmetric process:[3] the zirconium−binaphthol complexes developed by Kobayashi et al.,[4] the silver catalysts of phosphine peptide Schiff bases reported by Snapper and Hoveyda,[5] and the copper complexes of BINAP and phosphino-oxazolines described by Jørgensen et al.[6] Despite the fact that *N*-sulfonyl imines are very appealing heterodienophiles because of their low LUMO energy and the expected high crystallinity of their adducts,[7] the use of such imino dienophiles in catalytic asymmetric ADAR has been essentially restricted to the bidentate and highly reactive *N*-tosyl imine of ethyl glyoxylate.[6]

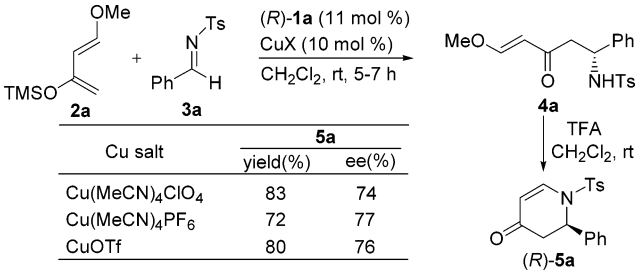
As part of an ongoing program showing the wide potential in enantioselective catalysis of the readily available planar chiral phosphino sulfenyl ferrocenes **1**,[8] we describe herein that the copper(I) complexes of these ligands act as highly efficient chiral Lewis acids in enantioselective formal ADAR of *N*-sulfonyl aldimines with the Danishefsky's diene (**2a**) and derivatives.

We selected as model reaction the ADAR of diene **2a** with the *N*-tosylimine of benzaldehyde (**3a**), process for which the highest reported enantioselectivity was a moderate 48% ee.[6b] As the first experiment, we performed this reaction in the presence of 10 mol % of the enantiopure ligand (*R*)-**1a**[8] and $Cu(MeCN)_4ClO_4$ in CH_2Cl_2 at room temperature. Complete evolution was observed after 5 h, affording mainly the acyclic Mannich-type addition product[2] **4a** rather than the expected Diels−Alder adduct. Nevertheless, the formal Diels−Alder product, the dihydropyridone **5a**, was readily obtained upon addition of TFA to the reaction mixture (83% yield, 74% ee). As shown in Scheme 1, similar results were achieved using other copper(I) salts such as $Cu(MeCN)_4PF_6$ (72% yield, 77% ee) and CuOTf (80% yield, 76% ee). The absolute *R* configuration of **5a** was unambiguously established by X-ray analysis.[9]

To prove the P,S-bidentate character of ligands **1** in this Cu-catalyzed reaction, we turned our attention toward the isolation of their Cu(I) complexes. Simple combination of equimolar amounts of ligands **1**[8] and CuX (X = Cl, Br) in THF/MeOH afforded in nearly quantitative yields the air-stable Cu(I) dimeric complexes **6** and **7** as single epimers at sulfur. The tetrahedral P,S,X,X-coordination at copper and the absolute *R* configuration at sulfur were unambiguously established by X-ray analysis of **6a**[9] (Scheme 2).

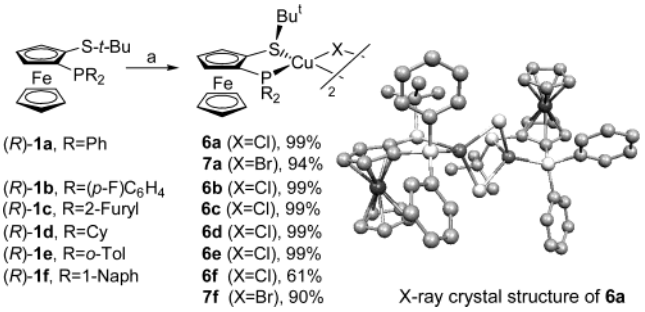
With this set of copper complexes in hand, possessing varied electronic and steric environments around the phosphorus atom, we studied their efficiency as chiral catalysts (5.1 mol %) for the model reaction **2** + **3a** in the presence of 10 mol % of $AgClO_4$[10] as halogen scavenger (Table 1). Under these silver-assisted conditions for in situ generation of the presumed active cationic Cu catalyst, the complex **6a** furnished the ADAR product in similar yield (79%), but with somewhat higher enantioselectivity (80% ee, entry 1) compared with the results obtained in the absence of a silver salt (Scheme 1, 74−77% ee). As expected, the reaction proved

Scheme 1. Copper-Catalyzed Reaction of Danishefsky's Diene with *N*-Sulfonyl Imine **3a** in the Presence of Ligand (*R*)-**1a**



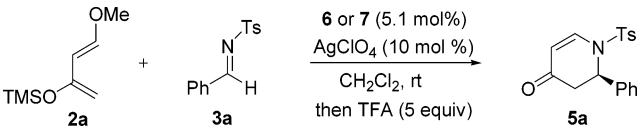
Cu salt	5a yield(%)	5a ee(%)
$Cu(MeCN)_4ClO_4$	83	74
$Cu(MeCN)_4PF_6$	72	77
CuOTf	80	76

Scheme 2. Preparation of Chiral Cu(I) Complexes of Ligands (*R*)-**1**



[a] CuX (X = Cl, Br), THF/MeOH, rt, 10 min.

Table 1. Optimization of the Cu(I) Catalyst



entry	Cu complex	time (h)	yield (%)[a]	ee (%)[b]
1	**6a**	6	79	80
2	**6b**	20	70	71
3	**6c**	20	58	71
4	**6d**	20	60	55
5	**6e**	20	66	57
6	**6f**	3	96	80
7	**7a**	2	89	80
8	**7f**	1	90	93(97)[c]

[a] Isolated yield after column chromatography. [b] Determined by HPLC (Chiralpak AD column). [c] $T = -20$ °C (1 h, 87% yield).

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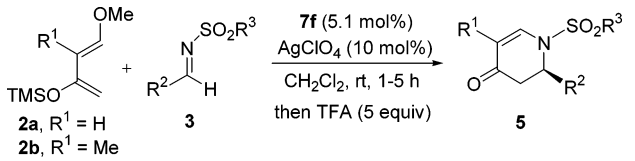
Table 2. Scope of the ADAR Catalyzed by Complex **7f**



ent	R^1	R^2	R^3	prod	yield(%)[a]	ee(%)[b]
1	H	Ph	*p*-Tol	**5a**	90	93(97)[c]
2	H	*o*-Tol	*p*-Tol	**5b**	82	93
3	H	(*p*-F)C_6H_4	*p*-Tol	**5c**	78	88(93)[c]
4	H	(*p*-OMe)C_6H_4	*p*-Tol	**5d**	76	91
5	H	(*p*-NMe_2)C_6H_4	*p*-Tol	**5e**	39	93
6	H	2-Naph	*p*-Tol	**5f**	85	86(93)[c]
7	H	PhCH=CH	*p*-Tol	**5g**	66	83(96)[c]
8	H	*n*-Pr	*p*-Tol	**5h**	65[c]	73[c](82)[d]
9	Me	Ph	*p*-Tol	**5i**	64	87(92)[e]
10	Me	PhCH=CH	*p*-Tol	**5j**	57	88[c]
11	H	Ph	(*p*-OMe)C_6H_4	**5k**	61	94
12	H	(*p*-F)C_6H_4	(*p*-OMe)C_6H_4	**5m**	78	90
13	H	2-Naph	(*p*-OMe)C_6H_4	**5n**	56	82
14	H	PhCH=CH	(*p*-OMe)C_6H_4	**5o**	58	76
15	H	Ph	(*p*-NO_2)C_6H_4	**5p**	58	90

[a] Isolated yield. [b] Determined by HPLC. Absolute configuration assigned by analogy with that of **5a**.[9] [c] $T = -20$ °C. [d] $T = -78$ °C. [e] $T = 0$ °C.

to be deeply influenced by the substitution at phosphorus. Complexes **6b**−**e** afforded the dihydropyridone **5a** in lower yields and enantioselectivities (entries 2−5) than the model complex **6a**. On the contrary, the bulky α-naphthylphosphino derivative **6f** proved to be more reactive than **6a** (3 h instead of 6 h), affording **5a** in excellent yield (96%, entry 6) with the same enantioselectivity (80% ee).

Interestingly, the dimeric (bromo)Cu complexes **7** showed a remarkable higher reactivity (entries 7 and 8). To our delight, complex **7f**, having the highly sterically demanding α-naphthylphosphine moiety, exhibited excellent values of reactivity, chemical yield (87−90%) and asymmetric induction (93% ee at room temperature and 97% ee at −20 °C, entry 8).

Next, with optimized catalyst **7f** in hand, a variety of other *N*-sulfonyl imines were prepared and tested under our standard reaction conditions. Table 2 delineates the wide scope of this catalytic ADAR. A survey of representative imino dienophiles revealed a high degree of stereochemical fidelity with a number of electronically varied aromatic imines (entries 1−6, 86−93% ee at room temperature; 93−97% ee at −20 °C). The high reactivity and enantioselectivity displayed by the tosyl imine of cinnamaldehyde (83% ee, entry 7) are noteworthy. Lowering the reaction temperature to −20 °C enhanced the enantioselectivity to 96% ee, the reaction being complete within 1 h (82% yield). As far as we know, this is the first example of a catalytic enantioselective ADAR of α,*β*-unsaturated imino dienophiles.[11] This procedure was also successfully applied to the highly reactive aldimines of enolizable aliphatic aldehydes, a kind of heterodienophiles scarcely studied in enantioselective ADAR.[4c] Thus, the tosylimine of butyraldehyde (**3h**) reacted with Danishefsky's diene in 30 min at −20 °C, in the presence of the catalyst system **7f**/$AgClO_4$, to provide the dihydropyridone **5h** in 73% ee (entry 8). The aliphatic tosylimine **3h** is so reactive that the reaction can be carried out even at −78 °C, raising the enantioselectivity to 82% ee

Interestingly, the presence of an additional substituent at the diene (diene **2b**, entries 9 and 10) or a change in the nature of the arylsulfonyl group of the heterodienophile (entries 11−15) provided similar results in terms of both chemical yield and enantioselectivity. The first issue is important for the synthesis of more substituted dihydropyridones (compounds **5i** and **5j**), whereas the second aspect offers varied possibilities for the deprotection of the amino group of the *N*-sulfonyl dihydropyridones **5**.[12] Finally, from a practical point of view, it is important to note that products **5** are quite stable and easy-to-handle crystalline solids, giving rise to enantiopure samples (>99.5% ee) upon a single recrystallization.[13]

In summary, novel copper(I) Lewis acid catalysts, relying on planar chiral 1-phophino-2-sulfenylferrocenes, show excellent activity, enantioselectivity, and structural scope in asymmetric ADAR between *N*-sulfonylaldimines and Danishefsky's type dienes. The mechanistic origin of the high enantiocontrol and the extension of this study to other heterodienophiles and dienes are under current investigation.

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Supporting Information Available: Experimental procedures and characterization data of new compounds, copies of NMR spectra, and X-ray crystallography data of (+)-**5a** and (+)-**6a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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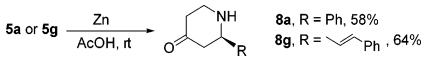
(9) See Supporting Information for detailed X-ray data.

(10) This formal ADAR also takes place using the catalytic pair ligand **1** + $AgClO_4$, instead of the halo copper complexes **6** − **7** + $AgClO_4$. However, this Ag-catalyzed process is slower and less enantioselective than the Cu-mediated reaction. For instance, in the presence of 10 mol % of $AgClO_4$ and 10.2 mol % of ligand (*R*)-**1a** or (*R*)-**1f** the model reaction **2a** + **3a** requires 24 h for completion (CH_2Cl_2, rt), giving rise to the dihydropyridine **5a** in 55% ee from (*R*)-**1a** and 73% ee from (*R*)-**1f** (67−68% chemical yield).

(11) For recent examples of α,*β*-unsaturated imino dienophiles in ADAR, see: (a) Loncaric, C.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2003**, *345*, 475. (b) Loncaric, C.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 574.

(12) For instance, the tosylamides **5a** and **5g**, having an aryl and an alkenyl group at C-2 respectively, afforded the chiral 4-oxopiperidines **8a** and **8g** in satisfactory yields (58−64%, unoptimized) upon treatment with Zn/AcOH at room temperature.



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(13) For instance, from samples of dihydropyridones **5a** and **5h** of 92 and 78% ee, respectively, a single recrystallization from *n*-hexanes−CH_2Cl_2 provided enantiomerically pure compounds (>99.5% ee, 60−70% yield).

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