COMMUNICATION

Copper-catalyzed enantioselective 1,4-addition of alkyl groups to *N*-sulfonyl imines†

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In copper(ɪ)/phosphoramidite-catalyzed asymmetric 1,4-additions of dialkylzinc, *N*-sulfonyl imines are more reactive and furnish higher enantiomeric excesses than the respective cycloalk-2-enones. This enables formation of a quaternary stereocenter as well as a *cis*-selective addition to an imine derived from 5-methylcyclohex-2-enone. The 1,4-adducts can be transformed in stereodivergent reductions yielding *cis*- or *trans*-3-alkylcycloalkyl amides.

The copper-catalyzed enantioselective 1,4-addition of organometallic reagents to α,β-unsaturated acceptors is a fundamental transformation in organic synthesis.[1] Originally reported with dialkylzinc, it has been developed towards the use of other types of nucleophiles such as organoaluminium reagents,[2] Grignard reagents,[3] and zirconocenes[4] as well as towards addition of unsaturated residues such as aryl and alkenyl groups.[5] While the latter can also be efficiently performed under rhodium catalysis,[6] use of copper is highly attractive due to its lower price. Moreover, much effort is being spend on the study of 1,4-additions to β,β-disubstituted compounds to create quaternary stereocenters.[7] In the case of unactivated, plain enones, this can be achieved by the use of more reactive aluminium or Grignard reagents and/or more reactive catalysts with NHC ligands.[8]

In contrast to carbonyl compounds, α,β-unsaturated imines have hardly been used for such reactions[9,10] which is surprising in view of the enormous importance of nitrogen-containing moieties in natural and artificial bioactive molecules. Tomioka *et al.* reported on the 1,4-addition of dialkylzinc to *N*-sulfonyl imines derived from cinnamaldehyde and achieved up to 91% ee using a Cu/amidophosphane catalyst if the sulfonyl group carried a bulky aryl substituent.[9a] Carretero *et al.* studied the 1,4-addition of ZnMe₂ to *N*-sulfonyl imines derived from chalcones. Up to 80% ee was achieved using a Cu/binol-phosphoramidite catalyst in the
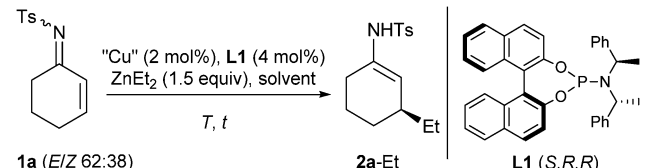
case of *N*-2-pyridylsulfonyl imines, while no conversion occurred with the respective tosyl derivatives.[9b] Finally, Palacios *et al.* reported up to 88% ee in the 1,4-addition of ZnEt₂ to acyclic β,γ-unsaturated *N*-aryl α-iminoesters using a Cu/taddol-phosphoramidite catalyst.[9c] In all reports, the 1,4-adducts were either hydrolyzed to the respective carbonyls or transformed by oxidative cleavage of the C,C-double bonds in the tautomeric enamines. Subsequent transformation to amines was reported in only one example in which hydrogenation over Pd/C furnished an 82:18 mixture of diastereomers.[9c]

Recently, we reported the first preparation of cycloalk-2-enone-derived *N*-sulfonyl imines[11] as well as their transformation in highly enantioselective Rh(ɪ)/binap-catalyzed additions of methyl- and arylaluminium reagents. The 1,2- *versus* 1,4-selectivity of this reaction was influenced by several factors, and we initially performed optimization towards 1,2-addition to deliver valuable α-tertiary cycloalk-2-enyl amides.[12] Moreover, we developed regio- and enantioselective Rh(ɪ)/binap-catalyzed 1,4-additions of arylzinc halides to these substrates. After subsequent stereodivergent reduction, *cis*- or *trans*-3-arylcycloalkyl amides were obtained which can oxidatively be degraded to deliver 3-aminocycloalkanecarboxylic acids.[13] Both 3-aryl- as well as 3-alkyl-substituted cycloalkyl amines are commonly found in pharmaceutically active molecules.[14,15] Based on our previous results, a Rh-catalyzed enantioselective 1,4-addition of AlMe₃ should be feasible, but we decided to study economically more attractive Cu-based catalysts. This communication describes the first highly regio- and enantioselective 1,4-additions of alkyl groups to cyclic *N*-sulfonyl ketimines with subsequent stereodivergent reduction. Catalyzed by a Cu–phosphoramidite complex, these transformations surpass those of the corresponding carbonyl derivatives in both reactivity and enantioselectivity.

As a model reaction, the addition of ZnEt₂ to the cyclohex-2-enone-derived *N*-tosyl imine **1a** was studied by applying classical conditions with Feringa's phosphoramidite **L1** (Table 1).[16] Using toluene as the solvent, excellent results were achieved from the very beginning, and a reaction temperature of −30 °C proved to be optimal, partial catalyst decomposition being observed at 0 °C

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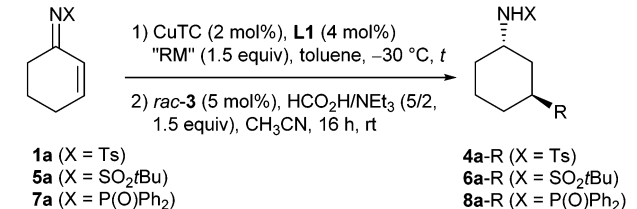
Table 1 Optimization of the Cu-catalyzed ZnEt$_2$ addition

Entry	"Cu"	Solvent	T (°C)	t (h)	Yield^a (%)	ee^b (%)
1	Cu(OTf)$_2$	Toluene	−30	1	97	96
2	Cu(OTf)$_2$	Toluene	−78	16	92	47
3	Cu(OTf)$_2$	Toluene	0	1	96	96
4	Cu(OTf)$_2$	Toluene	rt	1	92	92
5	Cu(OTf)$_2$	CH$_2$Cl$_2$	−30	1	98	91
6	Cu(OTf)$_2$	Et$_2$O	−30	1	87	96
7	Cu(OTf)$_2$	THF	−30	1	86	51
8	Cu(OTf)$_2$^{c}	Toluene	−30	1	62	0
9	—^{d}	Toluene	−30	1	14	0
10	Cu(OAc)$_2$·2H$_2$O	Toluene	−30	1	91	97
11	CuCl	Toluene	−30	1	96	97
12	(CuI)$_4$(DMS)$_3$	Toluene	−30	1	88	97
13	Cu(MeCN)$_4$BF$_4$	Toluene	−30	1	78	97
14	CuTC	Toluene	−30	1	91	97

^{a} Determined by ^{1}H NMR analysis of the crude product against diphenyl-methane as an internal standard. ^{b} Determined by GC after hydrolysis to the respective ketone. ^{c} Without ligand **L1**. ^{d} Without the Cu salt and ligand **L1**.

and rt (entries 1–4). Moreover, some other solvents were screened but toluene appeared to be the most suitable solvent (entries 5–7 *vs.* 1).

In the absence of the chiral ligand and even without the copper salt, some background reactivity was observed (entries 8 and 9), and screening of several copper(I) and copper(II) sources led to only slight variations in the yields (entries 10–14). In the end, CuTC (TC = thiophene-2-carboxylate) was chosen due to its chemical stability, and the reaction was monitored using continuous IR detection which revealed an induction period of about 0.5 min after addition of ZnEt$_2$ to the catalyst–substrate mixture (see ESI†). In all these transformations, the 1,4-adduct was obtained exclusively as enamide **2a**-Et, and not as the tautomeric imine, and the (*E*)- and the (*Z*)-isomer of substrate **1a** underwent the reaction. The facial selectivity of this 1,4-addition is identical with both types of substrates, imine **1a** and the respective enone, as proven by hydrolysis of **2a**-Et and comparison with an authentic sample of (*S*)-3-ethylcyclohexanone.

Similar to the respective 3-aryl derivatives, enamide **2a**-Et partially hydrolyzed upon attempted column chromatography, but could be transformed in stereodivergent reductions.[13] While pure *trans*-3-ethylcyclohexyl amide **4a** was obtained after transfer hydrogenation catalyzed by racemic RuCl(*p*-cymene)[Ts-DPEN][17] (*rac*-**3**), reduction with *t*BuNH$_2$·BH$_3$ furnished a 90:10 *cis*/*trans* mixture which could be separated by chromatography to deliver *cis*-**4a**-Et in a 64% yield (Table 2, entries 1 and 2). The catalyst loading could be reduced to 0.01 mol% (TON 8900) revealing the outstanding reactivity of *N*-tosyl imines in this transformation (entry 3).[18] Moreover, good results were also achieved with the simplified ligand **L2**[4b] (entry 4), and methyl addition proceeded equally well despite the notorious lower reactivity of ZnMe$_2$ in

Table 2 Scope of organometallic reagents and *N*-substituents

Entry	"RM"	Product	t (h)	dr^a (*trans/cis*)	Yield^b (%)	ee^c (%)
1	ZnEt$_2$	**4a**-Et	1	>97:3	85	98
2	ZnEt$_2$	**4a**-Et	1	10:90^d	64	96
3^e	ZnEt$_2$	**4a**-Et	1	>97:3	89	87
4^f	ZnEt$_2$	**4a**-Et	1	>97:3	83	91
5	ZnMe$_2$	**4a**-Me	1	>97:3	87	98
6^g	AlEt$_3$	**4a**-Et	1.5	—	0	—
7^g	AlMe$_3$	**4a**-Me	1.5	>97:3	28	96
8	ZnEt$_2$	**6a**-Et	20	>97:3	60	95
9	ZnEt$_2$	**8a**-Et^h	20	>97:3	62	0

^{a} Determined by ^{1}H NMR analysis of the crude product. ^{b} Isolated yield of the diastereomerically pure product. ^{c} Determined by HPLC. ^{d} Reduction performed with *t*BuNH$_2$·BH$_3$ in CH$_2$Cl$_2$. ^{e} Performed with 0.01 mol% CuTC and 0.02 mol% **L1**. ^{f} **L2** as the ligand. ^{g} 1,4-Addition in Et$_2$O. ^{h} Reduction performed with L-selectride in THF.

comparison with that of ZnEt$_2$ (entry 5). In contrast, aluminium reagents appeared to be less suitable for this transformation (entries 6 and 7).[2] Besides *N*-tosyl imine **1a**, the *N-tert-*butylsulfonyl imine **5a** could also be reacted, yet the reactivity and the chemoselectivity were inferior (entry 8). Nevertheless, these types of substrates are synthetically useful, because the *tert-*butylsulfonyl group can be cleaved under acidic conditions.[19] The *N*-phosphinoyl imine **7a**, however, furnished a racemic 1,4-adduct (entry 9).

Besides the cyclohex-2-enone-derived substrates, various additional imines were transformed in this addition-reduction sequence (Table 3). Starting with the *N-tert-*butylsulfonyl imine **5b**[20] derived from cyclopentenone, the respective cycloalkyl amide **6b**-Et was obtained as a 23:77 *trans/cis* mixture after transfer hydrogenation with the racemic Ru-catalyst **3** (entry 1). The use of the (*S*,*S*)-enantiomer of **3** led to a significantly higher yield and also to a slight increase of enantiopurity (entry 2). At first, this 64–69% ee appeared to be insufficient, however, given that ligand **L1** leads to only 10% ee with cyclopent-2-enone,[16] these results reveal a significantly higher stereoinduction in the case of *N*-sulfonyl imines. Transformation of the cycloheptenone-derived imine **5c**[20] again proceeded with very high enantio- and diastereoselectivity (entry 3). *N*-Tosyl imines **1b** and **1c** with a geminal disubstitution vicinal to the C,C-double bond underwent the 1,4-addition with a similar efficiency as the related enones,[16,21] the 1,4-adduct **2b**-Et was reduced with NaBH$_4$ to furnish the *cis*-cyclopentyl amide **4b**-Et (entries 4 and 5). Good to very good enantioselectivities were also achieved in the case of substrates **1d**

Table 3 Scope of substrates

Entry	Imine	t (h)	Reduction[a]	dr[b] (trans/cis)	Yield[c] (%)	ee[d] (%)
1	5b	24	A	23:77	52	64 (10)
2	5b	20	B	23:77	72	69
3	5c	16	A	96:4	66	~92 (>98)
4	1b	5	C	7:93	70	91
5	1c	18	A	>97:3	87	96 (>98)
6	1d	20	C	64:36	89	80
7	1e	16	D	<3:97	76	91
8	1f	1	A	>97:3	83	94 (84–88)
9	1g	20[e]	B	82:18	54	94
10	1h	2.5	—[f]	—	68	72 (75)

[a] **A**: racemic RuCl(p-cymene)[Ts-DPEN] (rac-3), HCOOH/NEt₃ (5/2), CH₃CN; **B**: As in A, but (S,S)-3; **C**: NaBH₄, EtOH; **D**: tBuNH₂·BH₃, CH₂Cl₂. [b] Determined by ¹H NMR analysis of the crude product. [c] Isolated yield. [d] Determined by HPLC; values in parentheses were reported for transformation of the respective enone using the same chiral ligand. [e] Performed at −15 °C with 10 mol% CuTC and 12 mol% ent-L1. [f] Isolated as enamide 2h-Et.

and **1e** with a geminal disubstitution vicinal to the C,N-double bond, and the 1,4-adducts were reduced with NaBH₄ or tBuNH₂·BH₃ due to failure of the transfer hydrogenation (entries 6 and 7). Transformation of the 5,5-dimethyl substituted compound **1f** again demonstrated a higher enantioselectivity compared to that of the respective enone (entry 8).[16]

With an increased catalyst loading and at increased temperature, 82% conversion was achieved in the 1,4-addition to the 3-methyl substituted imine **1g**, and hydrolysis of the 1,4-adduct delivered the respective ketone with 86% ee. Towards formation of the cycloalkyl amide $trans$-**4g**-Et, best results were obtained when performing the 1,4-addition with the (R,S,S)-enantiomer of ligand **L1** and the transfer hydrogenation with (S,S)-3. This combination is obviously the matched pair and led to a slight amplification of the enantiopurity to 94% ee and to a good 82:18 dr (entry 9). Thus, this protocol even enables construction of quaternary stereocenters which is highly remarkable because copper–phosphoramidite complexes fail to catalyze ZnEt₂ addition to unactivated β,β-disubstituted enones, more reactive organometallic reagents and/or catalysts being needed.[7,8] As an example for an acyclic substrate, the chalcone-derived N-tosyl imine **1h** was converted, and its 1,4-adduct proved to be more stable than those of the cyclic imines. Thus, the enamide **2h**-Et could be purified by column chromatography and was obtained in a good yield with 72% ee (entry 10). This compares well with the 75% ee reported by Feringa et al. for
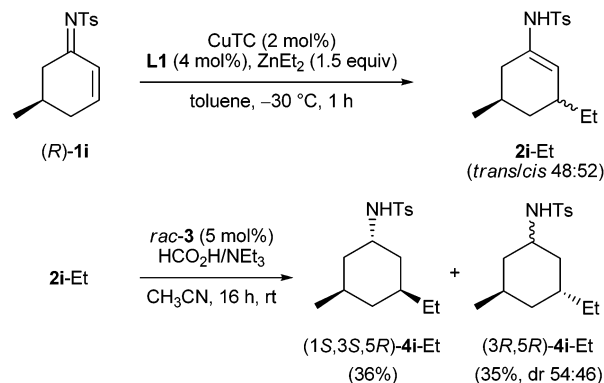

Scheme 1 Synthesis of the cis-3,5-disubstituted amide (1S,3S,5R)-**4i**-Et.

transformation of the chalcone itself at −25 °C[22] and the 60% ee reported by Carretero et al. for transformation of the N-2-pyridylsulfonyl imine of the chalcone at −78 °C,[9b] both with the same ligand **L1**.

Finally, remarkable results were obtained with imine **1i** which was prepared from (R)-5-methylcyclohex-2-enone (Scheme 1): copper-catalyzed 1,4-additions to such 5-alkyl-substitued cyclohex-2-enones are always dominated by a very strong $trans$-directing substrate control, which cannot be overcome by catalyst control.[23] Thus, it is not possible to obtain cis-3,5-dialkyl substituted cyclohexanones from Cu-catalyzed 1,4-additions. This substrate control was also observed in the case of imine (R)-**1i**: using a racemic phosphoramidite ligand in the 1,4-addition, the enamide $trans$-**2i**-Et was formed as a single diastereomer. With ligand **L1**, however, a 48:52 mixture of the $trans$- and cis-configured 1,4-adducts was obtained, reflecting comparable strength of the substrate and catalyst control. Transfer hydrogenation of this diastereomeric mixture delivered exclusively (1S,3S,5R)-**4i**-Et from the cis-configured enamide, while a 54:46 mixture of epimers was obtained from the $trans$-diastereomer.

$tert$-Butylsulfonyl groups can readily be removed under acidic conditions,[19] while cleavage of tosyl groups frequently requires rather harsh conditions. After Boc protection, however, the detosylation of amide $trans$-**4a**-Et occurred under mild conditions in a high yield (Scheme 2),[24] which proves the general synthetic applicability of this 1,4-addition-reduction sequence.

In summary, the 1,4-addition of dialkylzinc reagents to cyclic N-sulfonyl imines outpaces transformations of the respective enones in both reactivity and stereoselectivity. This is highlighted by the formation of a cis-3,5-dialkyl substituted adduct from imine **1i** and the formation of a quaternary stereocenter from imine **1g**. While some imines furnished less
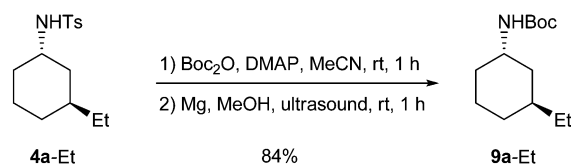
Scheme 2 Detosylation of cyclohexyl amide **4a**.

than 90% ee with phosphoramidite **L1**, excellent enantio-selectivities have been reported for transformations of the respective enones applying other chiral ligands.[25] Thus, better selectivities can certainly be achieved with these imines, too. Anyway, the broad scope of applicable cyclic imines and the stereodivergence of the subsequent reduction offer a highly flexible access to synthetically and biologically important 3-alkylcycloalkyl amines. We are now working on employing other organometallic reagents in this copper-catalyzed 1,4-addition and on using the initially formed zinc aza-enolates for subsequent C,C-bond formations.

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