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

Johannes Westmeier and Paultheo von Zezschwitz*

In copper(I)/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 $ZnMe_2$ 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 $ZnEt_2$ 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]

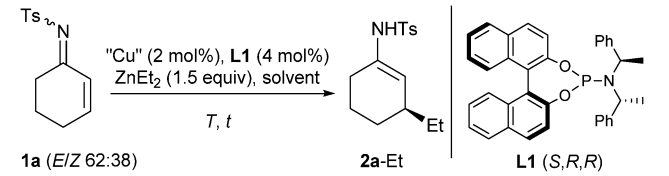
Recently, we reported the first preparation of cycloalk-2-enone-derived *N*-sulfonyl imines[11] as well as their transformation in highly enantioselective Rh(I)/binap-catalyzed additions of methyl- and arylaluminium reagents. The 1,2- *versus* 1,4-selectivity of this reaction was influenced by several 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(I)/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 $AlMe_3$ 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 $ZnEt_2$ 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

Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Straße, 35032 Marburg, Germany. E-mail: zezschwitz@chemie.uni-marburg.de

† Electronic supplementary information (ESI) available: Experimental procedures, analytical data, and NMR spectra for all new compounds. See DOI: 10.1039/c4cc07134d

Table 1 Optimization of the Cu-catalyzed $ZnEt_2$ addition

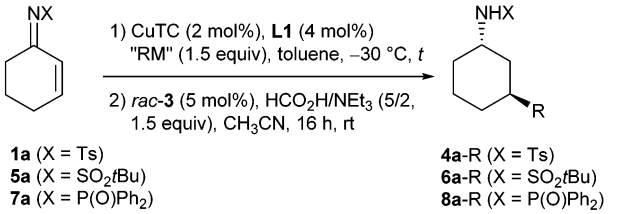


1a (*E*/*Z* 62:38) 2a-Et L1 (*S*,*R*,*R*)

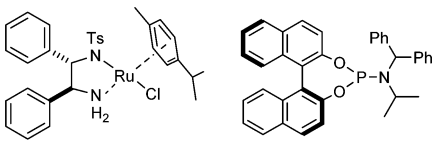
Entry	"Cu"	Solvent	T (°C)	t (h)	Yield[a] (%)	ee[b] (%)
1	$Cu(OTf)_2$	Toluene	−30	1	97	96
2	$Cu(OTf)_2$	Toluene	−78	16	92	47
3	$Cu(OTf)_2$	Toluene	0	1	96	96
4	$Cu(OTf)_2$	Toluene	rt	1	92	92
5	$Cu(OTf)_2$	CH_2Cl_2	−30	1	98	91
6	$Cu(OTf)_2$	Et_2O	−30	1	87	96
7	$Cu(OTf)_2$	THF	−30	1	86	51
8	$Cu(OTf)_2$[c]	Toluene	−30	1	62	0
9	—[d]	Toluene	−30	1	14	0
10	$Cu(OAc)_2{\cdot}2H_2O$	Toluene	−30	1	91	97
11	CuCl	Toluene	−30	1	96	97
12	$(CuI)_4(DMS)_3$	Toluene	−30	1	88	97
13	$Cu(MeCN)_4BF_4$	Toluene	−30	1	78	97
14	CuTC	Toluene	−30	1	91	97

[a] Determined by ^{1}H NMR analysis of the crude product against diphenylmethane 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**.

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



1a (X = Ts) **4a**-R (X = Ts)
5a (X = SO_2tBu) **6a**-R (X = SO_2tBu)
7a (X = P(O)Ph_2) **8a**-R (X = P(O)Ph_2)



3 L2

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 tBuNH$_2{\cdot}$BH$_3$ in CH_2Cl_2. [e] Performed with 0.01 mol% CuTC and 0.02 mol% **L1**. [f] **L2** as the ligand. [g] 1,4-Adddition in Et_2O. [h] Reduction performed with L-selectride in THF.

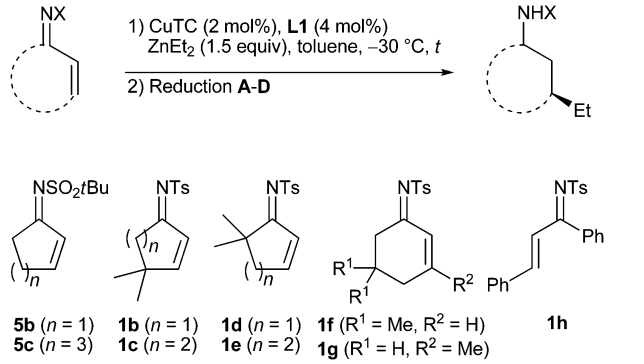
and rt (entries 1–4). Moreover, some other solvents were screened but toluene appeared to be the most suitable solvent (entries 5–7 *vs.* 1).

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 tBuNH$_2{\cdot}$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 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

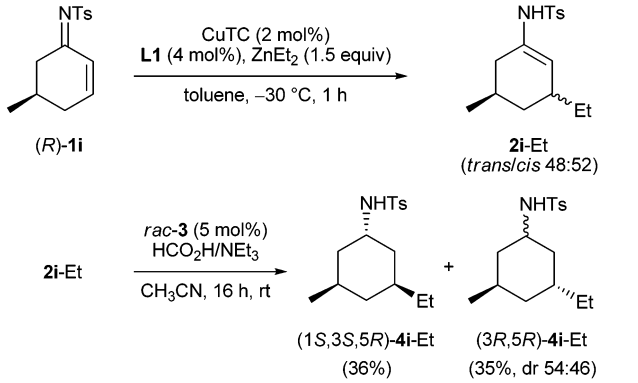


Entry	Imine	t (h)	Reduction[a]	dr[b] (*trans*/*cis*)	Yield[c] (%)	ee[d] (%)
1	**5b**	24	**A**	23 : 77	52	64 (10)
2	**5b**	20	**B**	23 : 77	72	69
3	**5c**	16	**A**	96 : 4	66	~92 (>98)
4	**1b**	5	**C**	7 : 93	70	91
5	**1c**	18	**A**	>97 : 3	87	96 (>98)
6	**1d**	20	**C**	64 : 36	89	80
7	**1e**	16	**D**	<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**), $HCOOH/NEt_3$ (5/2), CH_3CN; **B**: As in **A**, but (*S*,*S*)-**3**; **C**: $NaBH_4$, EtOH; **D**: $tBuNH_2{\cdot}BH_3$, CH_2Cl_2. [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 $NaBH_4$ or $tBuNH_2{\cdot}BH_3$ 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 $ZnEt_2$ 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



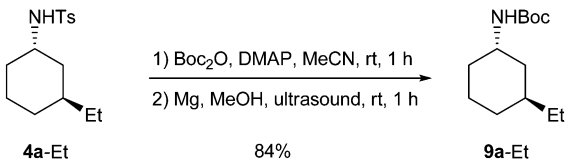
Scheme 1 Synthesis of the *cis*-3,5-disubstituted amide (1*S*,3*S*,5*R*)-**4i**-Et.

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 (1*S*,3*S*,5*R*)-**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 enantioselectivities 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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