



Cite this: *Chem. Commun.*, 2014, 50, 15897

Received 10th September 2014,
Accepted 25th September 2014

DOI: 10.1039/c4cc07134d

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

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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 zirconocenes⁴ 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 spent 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}

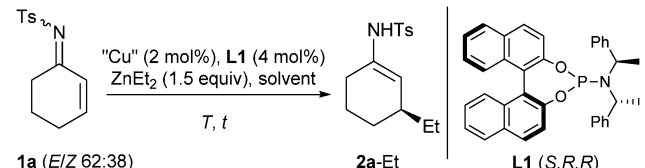
Recently, we reported the first preparation of cycloalk-2-enone-derived *N*-sulfonyl imines¹¹ as well as their transformation in highly enantioselective Rh(i)/binap-catalyzed additions of methyl- and arylaluminium reagents. The 1,2- versus 1,4-selectivity of this reaction was influenced by several factors, 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-aryl-cycloalkyl 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 $-30\text{ }^{\circ}\text{C}$ proved to be optimal, partial catalyst decomposition being observed at $0\text{ }^{\circ}\text{C}$

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† 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 ZnEt₂ addition


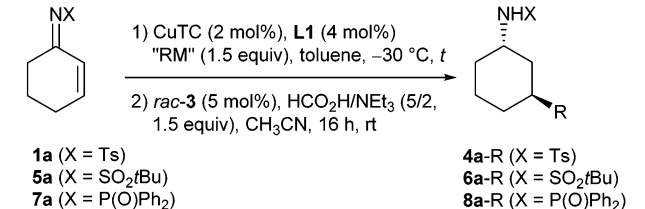
Entry	"Cu"	Solvent	T (°C)	t (h)	Yield ^a (%)	ee ^b (%)
1	Cu(OTf) ₂	Toluene	-30	1	97	96
2	Cu(OTf) ₂	Toluene	-78	16	92	47
3	Cu(OTf) ₂	Toluene	0	1	96	96
4	Cu(OTf) ₂	Toluene	rt	1	92	92
5	Cu(OTf) ₂	CH ₂ Cl ₂	-30	1	98	91
6	Cu(OTf) ₂	Et ₂ O	-30	1	87	96
7	Cu(OTf) ₂	THF	-30	1	86	51
8	Cu(OTf) ₂ ^c	Toluene	-30	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 ¹H 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.

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 ZnEt₂ 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*BuNH₂·BH₃ 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 ZnMe₂ in

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


Entry	"RM"	Product	t (h)	dr ^a (<i>trans/cis</i>)	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

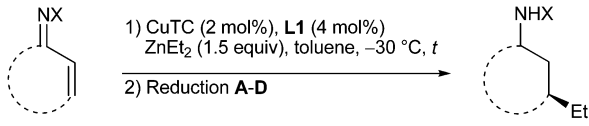
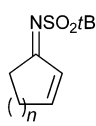
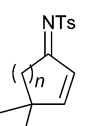
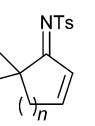
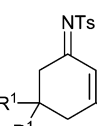
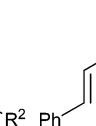
^a Determined by ¹H NMR analysis of the crude product. ^b Isolated yield of the diastereomerically pure product. ^c Determined by HPLC. ^d Reduction performed with *t*BuNH₂·BH₃ in CH₂Cl₂. ^e Performed with 0.01 mol% CuTC and 0.02 mol% L1. ^f L2 as the ligand. ^g 1,4-Addition in Et₂O. ^h Reduction performed with *t*-selectride in THF.

comparison with that of ZnEt₂ (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 5b²⁰ 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 stereoselection in the case of *N*-sulfonyl imines. Transformation of the cycloheptenone-derived imine 5c²⁰ 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 NaBH₄ 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

						
						
5b (<i>n</i> = 1)	1b (<i>n</i> = 1)	1d (<i>n</i> = 1)	1f (<i>R</i> ¹ = Me, <i>R</i> ² = H)	1h		
5c (<i>n</i> = 3)	1c (<i>n</i> = 2)	1e (<i>n</i> = 2)	1g (<i>R</i> ¹ = H, <i>R</i> ² = Me)			
Entry	Imine	<i>t</i> (h)	Reduction ^a	dr ^b (<i>trans/cis</i>)	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**: *t*BuNH₂·BH₃, CH₂Cl₂.

^b Determined by ¹H NMR analysis of the crude product. ^c Isolated yield.

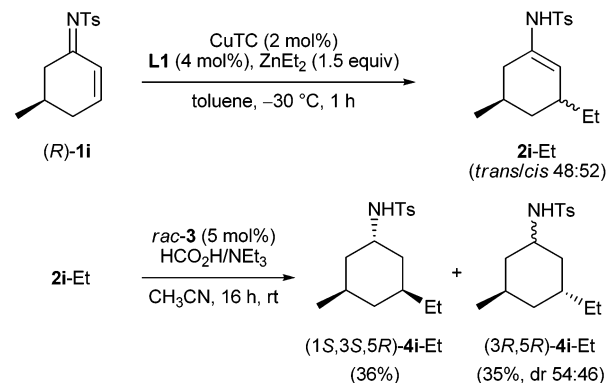
^d Determined by HPLC; values in parentheses were reported for transformation of the respective enone using the same chiral ligand.

^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 *t*BuNH₂·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

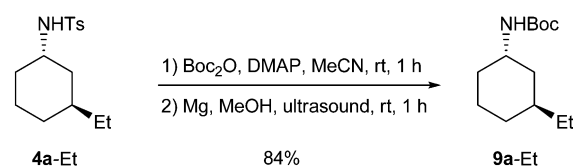
Scheme 1 Synthesis of the *cis*-3,5-disubstituted amide (1*S*,3*S*,5*R*)-**4i**-Et.

transformation of the chalcone itself at −25 °C²² 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-substituted 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.

The authors are indebted to Jan Herritsch and Christoph Priem, Philipps-Universität Marburg, for technical assistance and to the BASF SE, Ludwigshafen for the generous donation of chemicals. J. W. thanks the Konrad-Adenauer-Stiftung, Sankt Augustin, for a scholarship.

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