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

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The copper-catalyzed enantioselective 1,4-addition of organometallic reagents to z,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 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 NH ligands.8

In contrast to carbonyl compounds, z,β-unsaturated imines have hardly been used for such reactions9,10 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-phosphorimidic 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-ene-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 z-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-arylcyloalkyl 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 pharmacologically 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 stereo- divergent 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-ene-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.
but could be transformed in stereodivergent reductions.13 While partially hydrolyzed upon attempted column chromatography, substrates, imine (hydrolysis of 2a) would be reduced to 0.01 mol% (TON 8900) revealing the outstanding reactivity of N-tosyl imines in this transformation (entry 3). Moreover, good results were also achieved with the simplified ligand L2 (entry 4), and methyl addition proceeded equally well despite the notorious lower reactivity of ZnMe2 in 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-butyloxyl sulfonyl imine 5b derived from cyclopentenone, the respective cycloalkyl amide 6b 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 again proceeded with very high enantio- and diastereoselectivity (entry 3). N-Tosyl imines 1b and 1c with a geminal dissubstitution 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-cyclohexyl amide 4b-Et (entries 4 and 5). Good to very good enantioselectivities were also achieved in the case of substrates 1d...
and 1e with a geminal dissubstitution vicinal to the C,N-double bond, and the 1,4-adducts were reduced with NaBH₄ or tBuNH₂ 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.²⁷ 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 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,⁹⁰ both with the same ligand L1.

Finally, remarkable results were obtained with imine 1i which was prepared from (R)-5-methylcyclohex-2-ene (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.²¹ 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 enamine, 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 desylation 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
than 90% ee with phosphoramidite L1, excellent enantioselectivities have been reported for transformations of the respective enones applying other chiral ligands. 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-alkyleloalkyl 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-enoates for subsequent C,C-bond formations.

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Notes and references


46 The respective enone tosyl imine is problematic to prepare, see ref. 11. 47 For racemic preparation of the trans-diastereomers, see: (b) Zhou and B. List, J. Am. Chem. Soc., 2007, 129, 7498. For racemic preparation of the trans-diastereomers, see: (b) Zhou and B. List, Synlett, 2007, 2037.


18 A TON > 3000 was mentioned by Feringa for transformations of cyclic enones, see ref. 16.


20 The respective N-tosyl imine is problematic to prepare, see ref. 11.


25 For highly enantioselective ZnEt2 additions to the enones corresponding to imines 1d and 5b, see: (a) S. J. Degrado, H. Mizutani and A. H. Hoveyda, J. Am. Chem. Soc., 2001, 123, 755; for the enone corresponding to 1h, see: (b) X. Hu, H. Chen and X. Zhang, Angew. Chem., Int. Ed., 1999, 38, 3518.