Asymmetric Catalysis | Hot Paper

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Catalytic Enantioselective Synthesis of Functionalized Tropanes Reveals Novel Inhibitors of Hedgehog Signaling**

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Compound classes that are derived from or inspired by natural products (NPs) are biologically prevalidated starting points for the development of bioactive compounds, because they represent areas of chemical space explored by nature in evolution. This reasoning defines the foundation of biology-oriented synthesis (BIOS; a form of analysis) as a hypothesis-generating approach for the design and synthesis of natural-product-inspired compound collections.[1] The use of NPs and NP-inspired compound collections has been particularly rewarding in chemical–biological investigations of cellular signaling cascades.[1] For instance, the hedgehog (HH) pathway is of major importance for the regulation of tissue regeneration, stem cell renewal, and tumorigenesis. In particular, deregulated hedgehog signaling is involved in the development of skin cancer (basal-cell carcinoma) and brain tumors (medulloblastoma). Small-molecule modulators of the hedgehog pathway are currently in clinical development and even already in use.[2] Furthermore, small-molecule modulators of hedgehog signaling may be used to further our understanding of hedgehog biology.[3]

NP scaffolds are frequently structurally complex, and the synthesis of NP-inspired compound collections calls for the development of efficient catalytic enantioselective synthetic methods.[1,4] The tropane scaffold 8-azabicyclo[3.2.1]octane defines the structural core of more than 600 alkaloids (Figure 1). Many natural tropane derivatives are used for the treatment of neurological and psychiatric diseases.[5] However, general methods for the stereoselective synthesis of functionalized tropane collections have not been developed thus far.

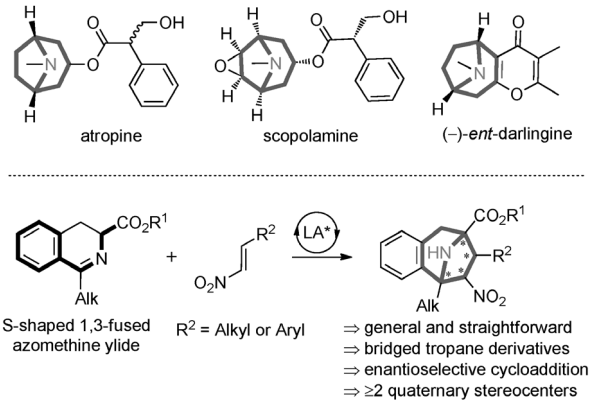

Figure 1. Structures of representative alkaloids with tropane scaffolds and a synthetic disconnection for tropane derivatives.

To address this demand, we envisioned that the 1,3-dipolar cycloaddition of a 1,3-fused azomethine ylide as the dipole and an appropriate alkene as the dipolarophile could efficiently yield the desired tropane scaffold in a stereocontrolled manner (Figure 1); this pathway includes the formation of two new bonds and multiple stereocenters in a single step.[6,7]

The challenges to be met in the development of such a method include 1) the employment of 1,3-fused cyclic azomethine ylides, which have not been used in enantioselective [3+2] cycloadditions to date,[8] 2) the low reactivity of azomethine ylides that are derived from ketones,[9] 3) the low degree of conformational freedom of 1,3-fused azomethine ylides, which restricts binding to the chiral catalyst, 4) the S-shape of the substrates,[7c] and 5) the particularly challenging formation of at least two quaternary stereocenters in the resulting bridged pyrrolidines.

Herein, we report the first catalytic enantioselective approach to the tropane scaffold through a Cu^{I}-catalyzed [3+2] cycloaddition of 1,3-fused cyclic azomethine ylides and nitroalkenes. Furthermore, subjecting a collection of these tropane derivatives to a cell-based screen revealed a novel class of hedgehog-pathway inhibitors.

An initial investigation of suitable reaction partners revealed that the desired cycloaddition efficiently proceeds with nitroalkenes as the dipolarophiles, which are also less commonly used because of their relatively low reactivity compared to other dipolarophiles such as maleimides.[11] Initially, tryptophan derivative **1a** was employed as the dipole and *trans*-β-nitrostyrene (**2a**) as the dipolarophile in

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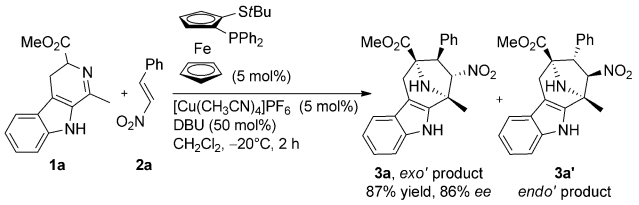


Scheme 1. Optimized reaction conditions.

the [3+2] cycloaddition (Scheme 1). Different reaction parameters, such as catalyst, chiral ligand, solvent, base, and reaction temperature, were screened to identify suitable conditions for cycloadduct formation in high yield and with high diastereoselectivity and enantioselectivity (for details, see the Supporting Information). Notably, the formation of the *exo′* and *endo′* products **3a** and **3a′** was observed, whereas the formation of the *exo* and *endo* products was not detected.[11f] This unprecedented selectivity reflects the involvement of the S-shaped azomethine ylide.[12] A combination of $[Cu(CH_3CN)_4]PF_6$ (5 mol%) with (*R*)-Fesulphos (5 mol%; Fesulphos = (*R*)-2-(*tert*-butylthio)-1-(diphenylphosphino)ferrocene) in the presence of DBU (50 mol%; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) in CH_2Cl_2 at −20 °C was identified as the most suitable reaction conditions. Under these conditions, *exo′* isomer **3a** was formed in 87% yield and with 86% *ee* in 2 h, and the formation of other diastereomers was not detected (Scheme 1).

An investigation of the scope of this [3+2] dipolar cycloaddition showed that the reaction is very versatile. For differently substituted nitrostyrenes, regardless of the electronic nature and the position of the substituents on the aryl ring, the reaction proceeded rapidly and efficiently to furnish the expected products in good yields (63–90%) and with excellent diastereoselectivity (>20:1) and enantioselectivity (79–95% *ee*; **3b–3l**, Figure 2). The enantioselectivity of the reaction was found to be generally lower when monosubstituted nitrostyrene derivatives were used instead of di- or trisubstituted derivatives. 2-Fluoro- and 2-bromo-substituted nitrostyrenes provided the corresponding products with 80 and 86% *ee*, respectively (**3e**, **3d**). The enantioselectivity increased to 92% *ee* when the 2,6-dichloro-substituted derivative was used (**3c**). Strongly electron-withdrawing substituents, such as trifluoromethyl or nitro groups, are tolerated, and the corresponding products were obtained with good enantioselectivities (**3f**, **3g**). A variety of dimethoxy-substituted nitrostyrenes, which are frequently found in NPs, smoothly underwent the cycloaddition to furnish the corresponding products with 90% *ee* regardless of the substitution pattern (**3h–3j**), and in good to excellent yields (73–90%). A trisubstituted derivative reacted with the highest enantioselectivity (95% *ee*) among all tested nitrostyrene derivatives (**3k**). Notably, the furan-derived heteroaromatic nitroalkene reacted well to give the corresponding product **3l** in 84% *ee*.

To further explore the scope of this transformation, we turned our attention to less reactive nitroalkene derivatives. To our delight, these nitroalkenes not only reacted very efficiently, but also with high enantioselectivity (**3m–3r**). As the steric bulk at the β-carbon atom of the nitroalkene was gradually increased, an increase in enantioselectivity was observed. 1-Nitroprop-1-ene gave the corresponding product with 87% *ee*. When a more bulky nitroalkene was used, the enantioselectivity increased to 93% *ee*, and the yield reached 83% (**3n**). A derivative with a cyclopropyl group at the β-position of the nitroethene group yielded product **3o** with 91% *ee* and in 86% yield. Isobutyl-, cyclohexyl-, and *n*-pentyl β-substituted nitroethenes furnished the desired products in good yields and with 90–96% *ee* (**3p–3r**). The observed correlation between the steric bulk and the enantioselectivity

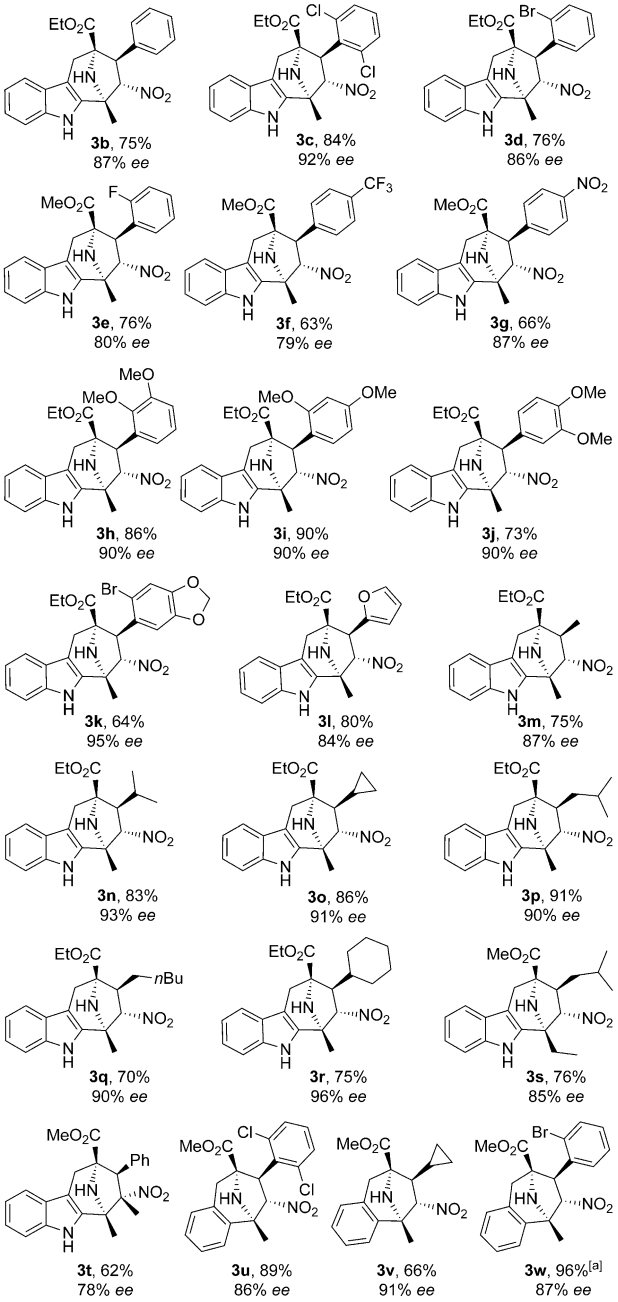


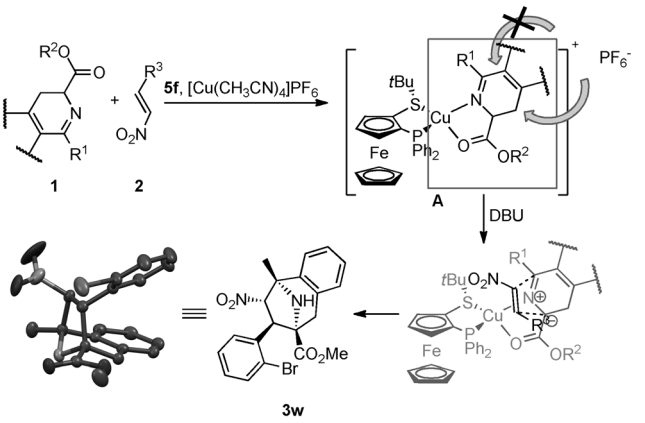
Figure 2. Scope of the catalytic enantioselective [3+2] cycloaddition reaction for the synthesis of annulated tropanes. Under the optimized reaction conditions (Scheme 1), the products were obtained with a d.r. of >20:1. [a] Products were isolated as a mixture of diastereomers (*exo′*/*endo′* = 2.6:1). The structure of the major diastereomer is shown.

indicates that the steric demand of the substituent at the β-position of the nitroethene has an advantageous effect on the enantioselectivity of this [3+2] cycloaddition. The fact that the cycloaddition proceeds equally well with nitrostyrene derivatives and various nitroalkenes demonstrates the generality of this approach for the synthesis of tropane-inspired compounds.

After a broad investigation into the use of disubstituted nitroalkenes as dipolarophiles, we explored the use of trisubstituted nitroalkenes under the developed reaction conditions. Gratifyingly, β-methyl nitrostyrene reacted equally well to give the corresponding product **3t** in 62% yield and with 78% *ee*. This is remarkable, because the product embodies three quaternary and one tertiary stereocenter out of a maximum of four contiguous stereocenters in the five-membered pyrrolidine cycle of **3t**.

Finally, variations in the cyclic azomethine ylide part were explored. When the methyl group at the C1 position of 3,4-dihydro-β-carboline was exchanged for a comparably more bulky ethyl group, the enantioselectivity of the reaction was reduced to 85% *ee*, but the transformation proceeded with a good yield of 76% and essentially formed only a single diastereomer (**3s**). Employing 3,4-dihydro-β-carboline with a phenyl group at the C1 position led to formation of a mixture of diastereomers (for details, see the Supporting Information). The corresponding substrate without a substituent at C1 position was found to react in a complex way. To further extend the scope of the transformation, the backbone of the azomethine ylide precursor was changed from indole to phenyl (with a phenylalanine-derived precursor). With this dihydroisoquinoline precursor, the [3+2] cycloaddition proceeded with an efficiency similar to that for dihydrocarboline **1a** and provided the corresponding products with high enantioselectivity and good yield and diastereoselectivity (**3u**, **3v**). However, the use of *ortho*-bromo-substituted nitrostyrene resulted in reduced diastereoselectivity of the transformation into product **3w**. The absolute stereochemistry of **3w** was determined by crystal structure analysis (see the Supporting Information for details). The absolute configurations of all other compounds were assigned by analogy. Overall, the developed cycloaddition is very efficient and offers straightforward access to tropane-inspired compounds with high enantiomeric excess (78–96% *ee*), high yields (62–91%), and excellent diastereoselectivities.

A mechanistic and stereochemical proposal for the [3+2] cycloaddition reaction is depicted in Scheme 2. In the first step of the reaction, copper(I) is simultaneously coordinated by the bidentate chiral ligand (*R*)-Fesulphos and the substrate **1** in a tetrahedral arrangement to form the catalytic complex **A**. This proposal is in agreement with previous studies based on NOE experiments.[6d] In the next step, deprotonation by DBU leads to the formation of the azomethine ylide, the active substrate for the cycloaddition. This active substrate then undergoes a cycloaddition with nitroalkene **2** to furnish product **3**. The approach of the nitroalkene takes place from the less-hindered face, in this case the front side, to avoid unfavorable steric interactions with the bulky *tert*-butyl group of the ligand. A plausible mechanism could also involve stepwise transformations.[11a]



Scheme 2. Proposed mechanism and model of the origin of stereoselectivity for the enantioselective [3+2] cycloaddition reaction.

The Michael addition of complex **A** to nitroalkene **2** creates two stereocenters. The following intramolecular aza-Henry reaction forms the thermodynamically favorable *exo*′ product **3**.

To investigate whether the tropane-inspired compounds modulate biological pathways, 84 tropane derivatives were synthesized and subjected to different cell-based assays, which included monitoring the hedgehog signal transduction pathway (Figure 3). Hedgehog proteins are secreted lip-

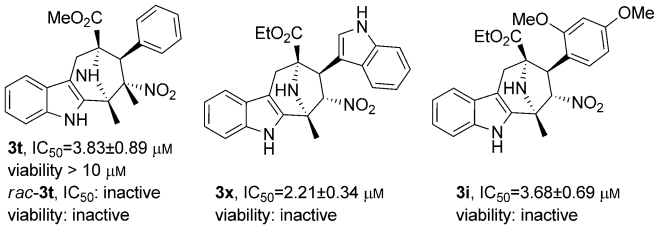


Figure 3. Representative results of hedgehog-pathway inhibition. For inactive compounds, cell viability remained above 80% at 10 μM (see the Supporting Information).

ophilic proteins that bind the transmembrane protein Patched 1 (PTCH1). Upon ligand binding, PTCH1 triggers a signaling cascade that includes a transmembrane protein called smoothened (SMO), which results in the activation of glioma-associated oncogene homologues (GLI) and subsequent transcription of HH pathway target genes.[2,3]

For assaying the HH pathway, mouse embryonic mesoderm fibroblast C3H10T1/2 cells were used. These multipotent mesenchymal progenitor cells can differentiate into osteoblasts upon treatment with the SMO agonist Purmorphamine. During differentiation, osteoblast-specific genes, such as alkaline phosphatase (ALK), are strongly expressed. The activity of ALK can be directly monitored by following substrate hydrolysis, which yields a highly luminescent product. Inhibition of the pathway results in a reduction of luminescence.[3,13]

To our delight, the compound collection contained potent inhibitors of the HH-signaling cascade, with IC_{50} values in the low μM range for several compounds (Figure 3; see also the Supporting Information). To the best of our knowledge, modulation of the hedgehog signaling pathway by tropanes or analogues thereof has not been observed before. Nevertheless, other natural-product-derived compounds, such as cyclopamine ($IC_{50} = 46$ nM) and estrone derivatives ($IC_{50} =$ 20–200 nM), are potent inhibitors of this pathway.[14]

In conclusion, we have developed a very efficient Cu^I-catalyzed highly diastereoselective and enantioselective [3+2] cycloaddition reaction of 1,3-fused cyclic azomethine ylides and nitroalkenes. For the first time, S-shaped azomethine ylides were successfully used in an enantioselective catalytic process. This novel method provides an unprecedented and general access to functionalized tropane scaffolds that embody quaternary and tertiary stereocenters in a stereoselective manner. It allows the generation of stereochemically complex products in a single step under mild reaction conditions, and is characterized by a broad scope and versatility. Furthermore, the investigation of a tropane-inspired compound collection in a process that monitored signaling through the hedgehog pathway revealed a novel class of hedgehog-signaling inhibitors.

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