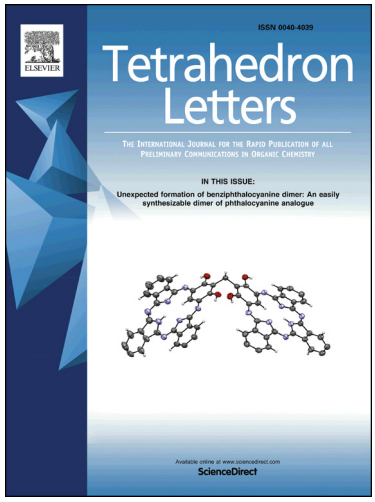

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Enantioselective Organocatalytic α-Sulfamidation of Aldehydes Using Sulfonyl Azides

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Abstract:
Enantioselective organocatalytic α-sulfamidation of unbranched aldehydes is described using MacMillan's second-generation imidazolidinone catalyst and *o*-nitrobenzenesulfonyl azide. The reactions are highly stereoselective (89.9-96.3% ee) with yields up to 71%. A strong correlation between aldehyde structure and product yield was found to exist, with 3-arylpropanals providing the best results. Application to functionalized amino acid synthesis is presented.

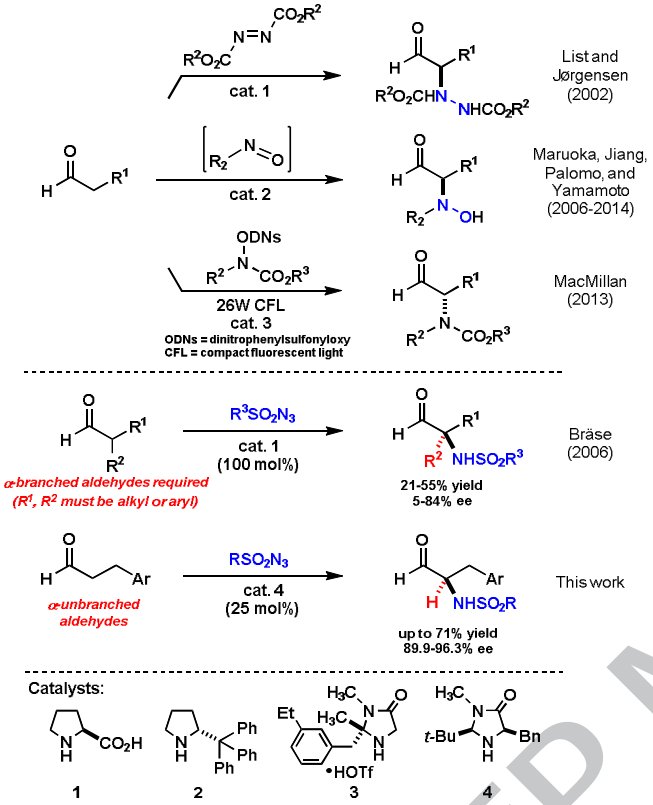
Keywords:
Organocatalysis
Alpha-sulfamidation
Alpha-amination
Sulfonyl azides
MacMillan imidazolidinone

Chiral carbons having bonds to nitrogen are widespread in natural products and medicinal compounds. Among the most highly developed approaches to C–N bond formation is the use of chiral imide and sultam enolates in reactions with electrophilic sources of nitrogen, including azodicarboxylates,[1-3] nitroso compounds,[4] and sulfonyl azides.[5] These transformations have been optimized, and their utility broadened, for decades.[6-8] In recent years, analogous protocols involving organocatalytic C–N bond formation have been reported.[9-11] These methods employ aldehydes, permitting direct transformation of the enantioenriched nitrogen-containing products to target compounds, including amino acids and amino alcohols, with minimal adjustments of oxidation state and without the need to remove chiral auxiliaries.

List and Jørgensen made their seminal contributions to organocatalytic amination using azodicarboxylates as electrophilic sources of nitrogen (Scheme 1).[12-13] Maruoka and others subsequently extended this concept to nitrosobenzene and nitrosocarbonyl reagents,[14-19] and now a range of compounds can be made using these enantioselective protocols. Unmasking the free amine in the transformed reaction products, however, is not trivial and usually requires multiple steps and reductive conditions to cleave the N–N or N–O bond. A more recent development from the MacMillan laboratory takes a notably different approach, using photoredox organocatalysis in radical-mediated aminations (Scheme 1).[20] Removal of the carbamate protecting groups found on the *N*-alkyl carbamate products may be accomplished under a variety of mild conditions to reveal the secondary N-alkyl amines. The continued development of organocatalytic methods providing α-amino carbonyl compounds in which the nitrogen protecting group(s) may be removed in a single step under mild, non-reductive conditions is

essential to extend the range of functional groups compatible with organocatalytic amination and shorten synthetic routes.

Scheme 1. Organocatalytic α-amination of aldehydes

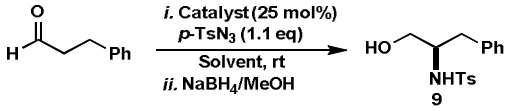


In 2006, Bräse and co-workers reported that proline and derivatives catalyze the reaction of α,α-disubstituted aldehydes with sulfonyl azides to produce α-sulfonamido aldehydes (Scheme 1).[21] The optimized organocatalytic protocol used stoichiometric proline, and delivered reaction products in up to 55% yields and up to 84% ee. Proline failed to catalyze the reaction with linear, unbranched aldehydes, and MacMillan imidazolidinones did not catalyze the reaction at all. Despite the considerable promise of this transformation, to the best of our knowledge no additional studies have appeared since the 2006 publication. Consequently, the described limitations have continued to restrict application of the reaction and prevent its use with classes of aldehydes leading to proteinogenic amino acids and related structures (i.e., secondary amines), that are not fully substituted at the chiral carbon. We report here a study of the enantioselective α-amination of linear, unbranched aldehydes using MacMillan's second-generation imidazolidinone catalyst (**4**, Scheme 1) and sulfonyl azides, providing access to these valuable secondary amino compounds. When *o*-nitrobenzenesulfonyl azide is used in the reaction, the sulfonamide protecting group may be removed from subsequent amine products using Fukuyama's mild protocol.[22]

Our investigation began by exploring the reaction of 3-phenylpropanal with *p*-toluenesulfonyl azide (*p*-TsN_3), catalyzed by imidazolidinone catalyst **4**, in a variety of organic solvents (Table 1) over 24 hours. The amination was successful, producing yields up to 21% in both CH_2Cl_2 and toluene; however, the highest yields were obtained when the reaction was run neat (46%) or in the presence of water (53%). The small improvement in conversion observed when the reaction was run in the presence of water, compared to neat, suggests there is little or no contribution from "on-water" acceleration.[23] The sticky reaction mixture continued to stir in the presence of water, forming a fluid coating around the stir

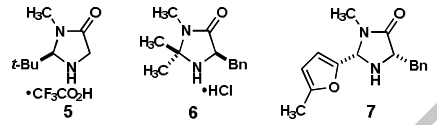
bar, while under neat conditions the stir bar became stuck, preventing efficient mixing of the reaction components.

Table 1. Conditions screen[a]



Entry	Solvent	Catalyst	Time (h)	Yield (%)[b]
1	CH_2Cl_2	**4**	24	21
2	THF	**4**	24	6
3	Acetone	**4**	24	17
4	Toluene	**4**	24	21
5	MeOH	**4**	24	7
6	Neat	**4**	24	46
7	H_2O	**4**	24	53
8	H_2O	**4**	16	49
9	H_2O	**4**	5	46
10	H_2O ($HClO_4$)[c]	**4**	24	58 (60)[d]
11	H_2O	**5**	24	11
12	H_2O	**6**	24	0
13	H_2O	**7**	24	0
14	H_2O	**1**	24	0
15	H_2O	**8**	24	7

[a]Reactions performed using 0.38 mmol of aldehyde and 2 mL of solvent. [b]Determined by NMR using 1,3,5-trioxane as internal standard. [c]$HClO_4$ (1.1 equiv) added. [d]Isolated yield in parentheses (two runs), with 90.5% ee.

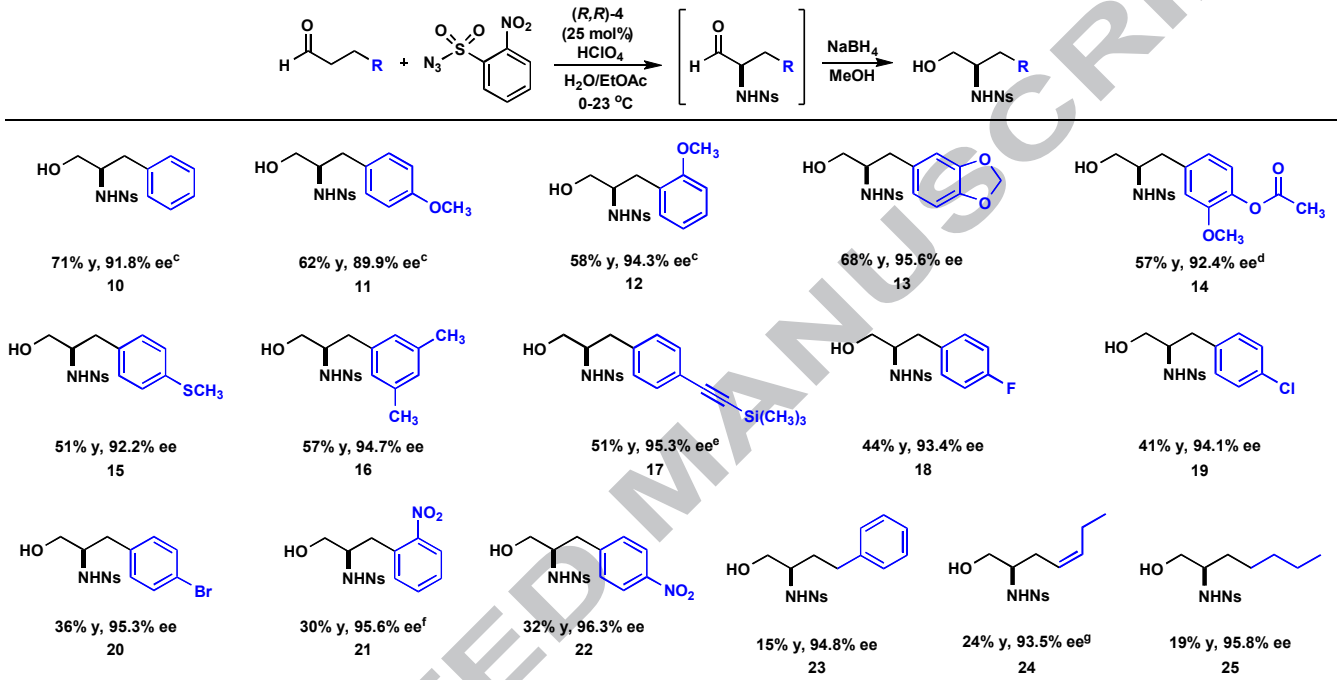


Having identified water as the optimal reaction medium, we screened other commercially-available MacMillan imidazolidinone catalysts (**5**-**7**), as well as proline (**1**) and a representative TMS-protected diphenylprolinol derivative (**8**). Surprisingly, the relatively small changes in structure encountered going from catalyst **4** to catalysts **5**-**8** resulted in either a complete loss or steep decline in the desired reactivity. We also examined the possibility of improving yield through control of reaction time, stoichiometry, and use of additives.[24] Varying the stir time from 5-16 hours, the reaction was observed to be mostly complete after 5 hours (entry 9). Inclusion of $HClO_4$ was also found to improve product yield (Entry 10).[25] Follow-up reactions indicated that isolated yields of tosyl-protected amino alcohol **9** averaged 60%, with 90.5% ee.

A brief survey of sulfonyl azides identified *o*-nitrobenzenesulfonyl azide (NsN_3) as providing the optimal combination of yield and enantiomeric excess with 3-phenylpropanal.[24] Thus, attention was turned to a study of aldehyde substrate scope using NsN_3 as nitrogen source (Table 2). While 3-phenylpropanal is a liquid at room temperature, permitting the formation of a fluid organic phase, semisolid aldehydes performed better when a small amount of ethyl acetate was added to the reaction mixture, enabling more efficient mixing of reactants. Therefore, small quantities of ethyl acetate (3-7% of total solvent volume) were used in subsequent amination reactions. 3-Arylpropanals were initially pursued, and a striking relationship was found to exist between the nature of the aromatic ring and the isolated yield of amination product. When the aromatic ring was substituted with electron-donating groups, including ethers (**11**-**13**), esters (**14**), thioethers (**15**), alkyl groups (**16**), and alkynes (**17**), the highest yields (51-68%) of amination products were obtained. When 3-arylpropanals bearing electron-

withdrawing groups, including halogens (**18**-**20**) and nitro groups (**21**-**22**), were used, considerably lower yields resulted (30-44%). Enantioselectivities >90% were generally observed. Three additional modifications were made to the aldehyde, including the insertion of a carbon atom between the carbonyl and the aromatic ring (**23**), replacement of the aromatic ring with an olefin (**24**), and replacement of the aromatic ring with an alkyl chain (**25**). In all three cases, a dramatic drop in yield was observed (15-24%).[26] However, enantioselectivities remained high (>93% ee). Notably, *cis*-4-heptenal gave consistently higher yields than heptanal.

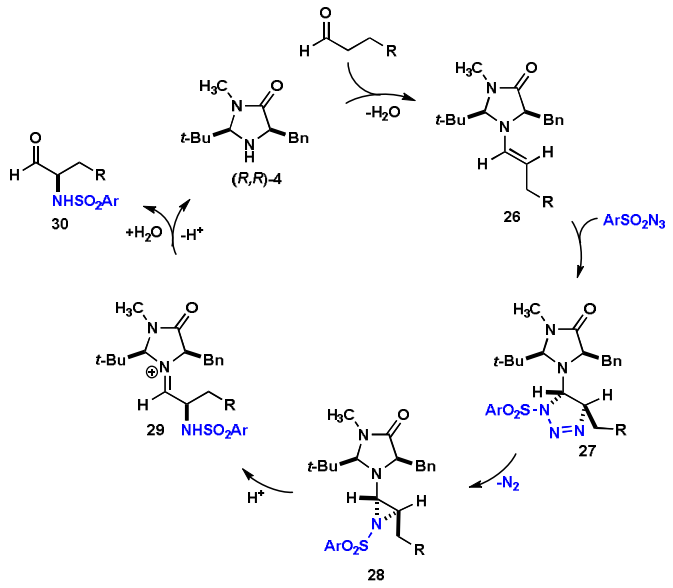
Table 2. Aldehyde substrate scope[a,b]



[a]Reactions performed using 0.38 mmol of aldehyde, 0.41 mmol of azide (NsN_3), and 0.38 mmol of $HClO_4$ in H_2O (2 mL)/EtOAc (0.06-0.15 mL). [b]Data are an average of two or more runs. [c]EtOAc excluded. [d]Yield of aldehyde. [e]On 1.0 mmol scale, 39% y, 95.1% ee. [f]On 1.0 mmol scale, 25% y, 94.0% ee. [g]cis/trans ratio = 9:1.

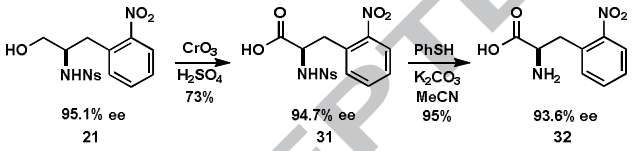
Scheme 2 depicts the catalytic cycle proposed by Bräse for proline,[21] used to rationalize the stereoinduction observed with MacMillan's second generation catalyst, (*R,R*)-**4**. Condensation with the aldehyde produces enamine **26**, in which the double bond has the *E* configuration and is rotated away from the bulky *tert*-butyl group. The *Si* face of the enamine is shielded from reaction with the sulfonyl azide by catalyst substituents, directing regioselective [3+2] cycloaddition[27] to the unobstructed *Re* face. This rationale has been used to explain enantioinduction in a variety of transformations using catalyst **4**.[28-33] Decomposition of triazoline **27** with loss of nitrogen (N_2) delivers aziridine intermediate **28**. Opening of the aziridine and migration of the sulfonamide produces iminium ion **29**, affording the substituted aldehyde (**30**) upon hydrolysis.[34-35] The major enantiomer obtained in the reaction (*R*-configuration, confirmed for **10** and **25**) indicates a retention of configuration in going from **27** to **30**.

Scheme 2. Proposed catalytic cycle



The products of these reactions, α-sulfonamido alcohols and aldehydes, are precursors to functionalized α-amino acids. To demonstrate their utility, oxidation of sulfonamide-protected amino alcohol **21**, substituted with an aromatic nitro group, was followed by removal of the *o*-nosyl protecting group using Fukuyama's method (Scheme 3).[22] The susceptibility of aromatic nitro groups to reduction[36] would render the synthesis of amino acid **32**, under conditions requiring N–N or N–O bond cleavage, challenging.

Scheme 3. Functionalized amino acid synthesis



In conclusion, conditions for the organocatalytic α-amination of unbranched aldehydes using MacMillan's second generation imidazolidinone catalyst and sulfonyl azides have been developed, and a study of the aldehyde substrate scope has been conducted. The transformation proceeds with high enantioselectivites in all cases examined, but the best yields are obtained using 3-arylpropanals bearing electron-rich aromatic rings. Further work to understand the reaction mechanism and optimize catalyst structure is ongoing to broaden substrate scope and improve scalability. The results will be reported in due course.

Acknowledgments

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Supplementary Data

Supplementary data (general experimental details, ^{1}H and ^{13}C NMR spectra, and HPLC data) associated with this article can be found, in the online version, at http://

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Graphical Abstract