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Letter

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Silyl Imine Electrophiles in Enantioselective Catalysis: A Rosetta Stone for Peptide Homologation, Enabling Diverse *N*-Protected Aryl Glycines from Aldehydes in Three Steps

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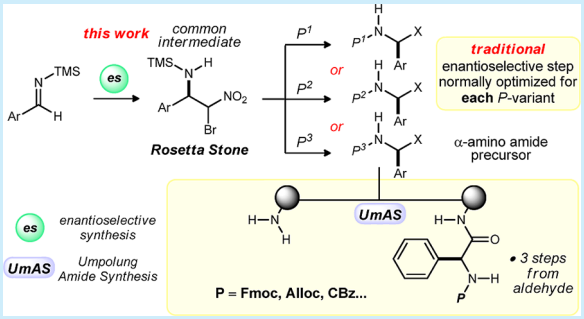
Supporting Information

ABSTRACT: We report that *N*-(trimethylsilyl)imines serve in the Bis(AMidine)-catalyzed addition of bromonitromethane with a high degree of enantioselection. This allows for the production of a range of protected α-bromo nitroalkane donors (including Fmoc) for use in Umpolung Amide Synthesis (UmAS). Hence, peptide homologation with nonnatural aryl glycine amino acids is achieved in three steps from aromatic aldehydes, which are plentiful and inexpensive. Epimerization during the homologation step is circumvented by avoiding an α-amino acid intermediate.



Despite the tremendous achievements of conventional dehydrative amide synthesis,[1] opportunities abound for the study of peptides containing nonnatural amino acids. As an increasing number of peptides reach commercial end points,[2,3] the demand for new methods that might address amide and peptide preparatory needs has only increased.[4,5] Umpolung Amide Synthesis (UmAS), an amide preparation that expresses the ability of α-halo nitroalkanes (**D**, Figure 1) to function as carboxylic acid surrogates in a direct synthesis of amides,[6] may play a key role in solving this problem. Chiral nonracemic donors **D** were prepared from *N*-Boc-imine electrophiles (**B**, R = O^{t}Bu),[7] but we soon realized that alternative protecting groups at nitrogen would be desirable, if not preferred, for applications in complex peptide synthesis (e.g., aryl glycine-rich natural products).[8] This report describes access to aryl glycine donors for UmAS using *N*-(trimethylsilyl)imines (**A**) as unlikely electrophiles for the enantioselective aza-Henry addition of bromonitromethane. Furthermore, the silyl amine intermediates (**C**) may be functionalized by a range of protecting groups, including Fmoc.[9] The resulting procedure can be used to homologate an amine with a non-natural amino acid in the shortest sequence yet from inexpensive starting materials.

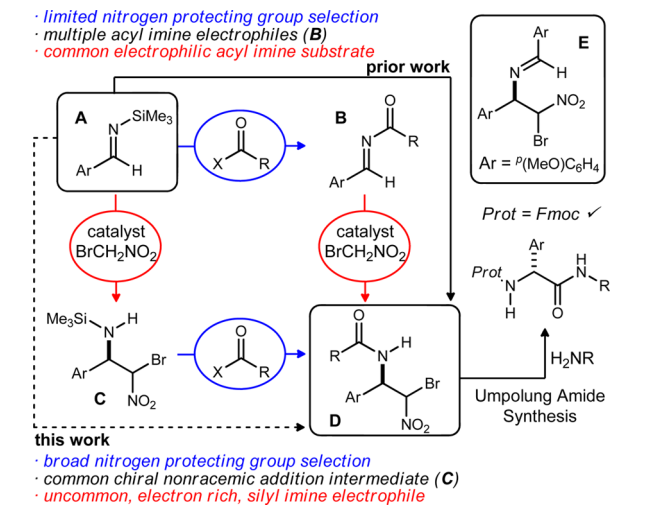


Figure 1. Parallel strategies to prepare aryl glycine α-bromo nitroalkane donors for Umpolung amide synthesis.

The early impact of *N*-silylimine substrates was driven heavily by nucleophilic addition reactions of strong nucleophiles.[10] Itsuno reported the use of *N*-silylimines in enantioselective synthesis with organoborane additions, providing the products of carbon nucleophilic addition in up to 96% ee.[11,12] These transformations utilize a stoichiometric amount of the chiral amino alcohol but provide convenient access to a range of homoallylic amines since the nitrogen−silicon bond is cleaved hydrolytically during workup.[12] More recent work has established that silyl imines are competent electrophiles for fluoronium catalysis[13] and α-amino boronic acid synthesis.[14] Insofar as *N*-TMS imines are considerably more Lewis basic and less electrophilic than *N*-acylimines,[15] a catalyst complement would need to simultaneously activate the imine and mitigate both imine polymerization and further addition of the desired adduct to imine. Indeed, our early attempts were plagued by the formation of products such as **E**.

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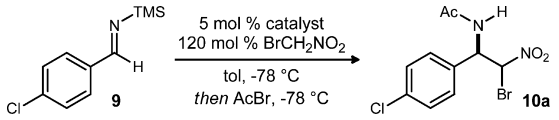
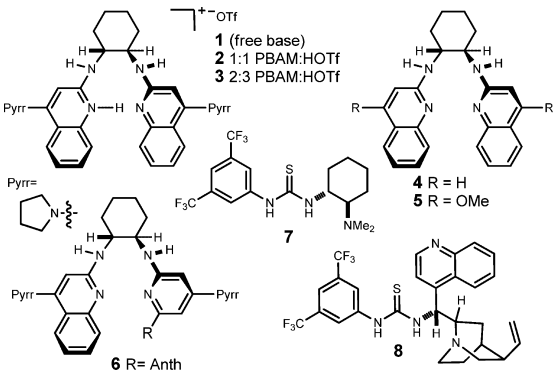
Table 1. Enantioselective Additions of Bromonitromethane to *N*-TMS Imines: Catalyst Investigation



entry[a]	catalyst	ee[b] (%)	yield[c] (%)
1	PBAM (**1**)	80, 81	56
2	PBAM·HOTf 1:1 (**2**)	60, 61	19
3	PBAM·HOTf 2:3 (**3**)	38, 40	10
4	H-Quin-BAM (**4**)	33, 32	18
5	4-MeO-BAM (**5**)	24, 23	17
6	Anth-PBAM (**6**)	35, 32	47
7	thiourea **7**	−16, −17	42
8	thiourea **8**	8, 3	34
9[d]	PBAM (**1**)	32, 30	40
10[d]	PBAM (**1**)	89, 88	8
11[d]	PBAM (**1**)	93, 91	78

[a]Reactions stirred at −78 °C for 8 h. Then acetyl bromide was added, and the reactions were stirred additional 2 h before being quenched with water at −78 °C. [b]Adducts isolated as a mixture of diastereomers (dr = 1:1 up to 3:1, see the Supporting Information), ee's reported for (major, minor) diastereomer. [c]Low yields generally correspond to poor reactivity of the catalyst, resulting in low conversions. [d]Bromonitromethane used: entry 9, 300 mol %; entry 10, 30 mol %; entry 11, 20 mol % added every 2 h, 100 mol % total, and 10 mol % catalyst.



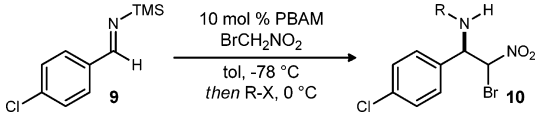
Our studies began with the preparation of *p*-chloro *N*-TMS benzaldimine **9** (**A**, Figure 1) using the Collet protocol[16] and its conversion to the corresponding *N*-Fmoc derivative (**A** → **B**, Figure 1) by treatment with Fmoc-Cl. This acylation suffered from poor conversion, and the *N*-Fmoc derivative was not isolated in pure form. However, when the crude product was subjected to bromonitromethane and catalyst PBAM (**1**)[17,18] at −20 °C, the addition product was obtained in 28% yield (two steps, as a mixture of diastereomers) with 84/83% ee (for the major/minor diastereomer, respectively). While the ee of this reaction was pleasing, the low yield led us to explore other options—specifically, a direct aza-Henry addition to the *N*-TMS-imine. Our experience with aza-Henry adducts from *N*-alkylimines has shown that they undergo reversible addition upon standing, leading to racemization. That behavior, combined with the large silyl group at the putative substrate binding site and less polarized azomethine, suggested a low possibility for success. Notwithstanding, the *N*-TMS-imine was subjected to bromonitromethane directly with electron-rich bis(amidine) catalyst **1** at ambient temperature. Though the resulting adduct could not be isolated, it could be observed directly by NMR ($^{1}H/^{13}C$).[19] Immediate treatment of the crude adduct with Fmoc-Cl delivered the α-bromo nitroalkane (**10e**) in 43% yield and 11% ee (for each diastereomer) from **9**.

Even the low level of stereoselection observed in this reaction was surprising, and it prompted an expanded investigation of catalysts that might promote the addition (Table 1). The reaction temperature was lowered to −78 °C, and acetyl bromide was used to quench the resulting TMS-adduct. This provided an increase in stereoselection to the 80% ee level (Table 1, entry 1). Use of a single equivalent, as well as a slight excess of triflic acid relative to the ligand, led to progressively lower reactivities and enantioselectivities (Table 1, entries 2 and 3).[20] Less electron-rich bis(amidine) catalysts provided lower enantioselection (Table 1, entries 4 and 5),[21] and a catalyst that had provided excellent enantioselection with *N*-Boc-imine substrates also fared poorly with the corresponding silyl imine (Table 1, entry 6).[6] Finally, an examination of two catalysts common to the thiourea catalysis field provided disappointing preliminary results (Table 1, entries 7 and 8).[22]

A significant sensitivity of enantioselection to bromonitromethane concentration was also uncovered. If an excess of bromonitromethane was used, the apparent reactivity was lowered along with the measured ee for the adducts (Table 1, entry 9). Conversely, limiting the pronucleophile concentration provided an enhancement of ee from 81 to 89% (Table 1, cf. entries 1 and 10). Addition of bromonitromethane in 20 mol % increments evenly over 10 h led to excellent enantioselection at the 93/91% ee level (Table 1, entry 11) with a 10 mol % catalyst loading to ensure low bromonitromethane concentrations throughout the reaction.

Our primary goal of this study was to address the need to extend UmAS to carboxylic acid surrogates containing *N*-protecting groups other than Boc. Therefore, immediately after formation of the aza-Henry adduct, the acylation reagent was

Table 2. Enantioselective α-Bromo Nitroalkane Synthesis: Functionalization of the Silyl Amine Adduct[a]



entry	RX		ee[b] (%)	yield (%)	entry	RX		ee[b] (%)	yield (%)
1	AcBr	**a**	93, 91	78	5	N_3AcCl	**d**	91, 91	82
2	AcCl	**a**	92, 91	83	6	FmocCl	**e**	91, 91	76
3	BzCl	**b**	94, 95	70	7	CbzCl	**f**	91, 90	72
4	PivCl	**c**	96, 97	67	8	AllocCl	**g**	91, 91	85

[a]100 mol % bromonitromethane added in aliquots over 10 h (0.2 equiv/2 h) before stirring overnight. The acylating agent (1 equiv) was then added and an ice−water bath applied. [b]Adducts isolated in dr = 1:1 up to 3:1 (see the Supporting Information); ee's reported for (major, minor).

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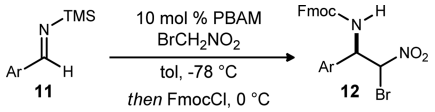
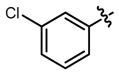
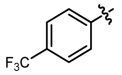
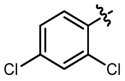
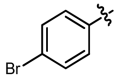
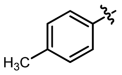
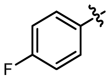
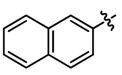
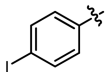
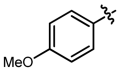
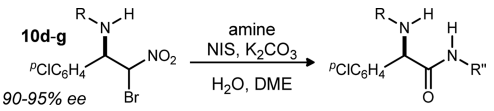
Table 3. Enantioselective Synthesis of Fmoc-Protected α-Bromonitroalkanes[a]

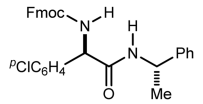
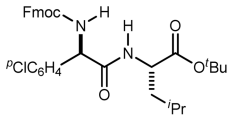
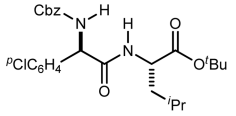
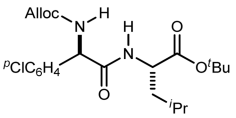
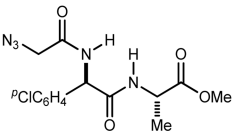


entry	Ar	product	ee (%)[b]	yield (%)	entry	Ar	product	ee (%)[b]	yield (%)
1		**a**	82,83	63	6		**f**	80,76	66
2		**b**	90,91	70	7		**g**	65,66	63
3		**c**	86,85	64	8		**h**	70,71	63
4		**d**	86,86	74	9		**i**	83,84	63
5		**e**	88,88	83	10		**j**	62,62	76

[a]100 mol % bromonitromethane added in aliquots over 10 h (0.2 equiv/2 h) before stirring overnight. The acylating agent (1 equiv) was then added and an ice−water bath applied. See the Supporting Information for complete experimental details and analytical data. [b]Adducts isolated as a mixture of diastereomers (dr = 1:1 up to 3:1, see the Supporting Information), ee's reported for (major, minor) diastereomer.

Table 4. Coupling of Protected α-Bromo Nitroalkane Donors to Amines Using UmAS[a]



entry	product		dr[d]	yield (%)
1[a]		**13**	>20:1	66
2[b]		**14**	>20:1	62
3[b]		**15**	>20:1	63
4[b]		**16**	>20:1	68
5[c]		**17**	>20:1	50

[a]Reaction run in THF, with 1.2 equiv of amine for 24 h at 0 °C. [b]Reaction run with 2 equiv of amine, for 24 h at 0 °C, under an atmosphere of O_2. [c]Reaction run with 1.2 equiv of amine, for 4 h at 0 °C, under an atmosphere of O_2. [d]Measured by ^{1}H HMR.

added to the reaction mixture at low temperature. We found it prudent to replace the cryogenic bath with an ice−water bath at this point, since the acylation was relatively slow in some cases. This practice ensured complete conversion of the intermediate silyl amine. Both acetyl bromide and acetyl chloride provided similar outcomes (Table 2, entries 1 and 2). Aromatic and hindered acid chlorides provided highly enantioenriched products in comparable yield (Table 2, entries 3 and 4). α-Azido acetyl chloride also performed well, delivering the product in 82% yield and 91% ee for both diastereomers (Table 2, entry 5). The heavy reliance on Fmoc-protected amino acids in solid-phase peptide synthesis made it a priority problem to solve (Table 2, entry 6). The versatile Cbz- and Alloc-protected amino acids are also now available through the synthesis of both **10f** and **10g** in good yield and with good enantioselection (Table 2, entries 7 and 8).

The initial scope of this approach to aryl glycine donors for use in UmAS was elucidated in the context of Fmoc-protected donor synthesis (Table 3). Halogenated aryl glycines bearing a variety of substitution patterns provided good enantioselection and good overall isolated yields of the Fmoc-protected α-bromo nitroalkanes 12a-e (Table 3, entries 1−5). Electron-deficient and neutral silyl aldimines (Table 3, entries 6 and 7, respectively) provided slightly depressed enantioselection that would correspond to approximately 9:1 dr after UmAS coupling with a chiral amine. This behavior is improved slightly with the tolyl and 2-naphthyl cases (Table 3, entries 8 and 9), and our initial investigation of the *p*-methoxy case (Table 3, entry 10) places it within this category as well. In all cases, it is significant to note that the diastereomeric addition products are homochiral (*R*) at the benzylic carbon.[23]

The enantioselectivity with which adducts **10a−g** are formed (Table 2) correlates directly to the diastereomeric ratio of the amide products resulting from their coupling to enantiopure amino acids using UmAS (Table 4). For example, α-bromonitroalkanes **10d−g**, listed in Table 2, were coupled to a variety of chiral nonracemic α-amino esters and amines to establish the overall efficiency of this approach to aryl glycinamide synthesis (Table 4). In all cases, the enantiomeric ratio of the donors translated into high diastereomeric ratios for the amide products, indicating the absence of epimerization. Of

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particular note is the tolerance of the Fmoc-protected donor to the basic reaction conditions.

In summary, we have discovered that *N*-TMS imines are effective electrophiles in the BAM-catalyzed enantioselective addition of bromo nitromethane and that the intermediate *N*-TMS adduct can be acylated in situ. This provides a range of adducts that can be used in Umpolung amide synthesis, delivering the amino acid derivative, homologated by an aryl glycine, with high diastereomeric purity. In some cases, such as Fmoc-protected **10e**, the product can be prepared by either pathway via **B** or **C** (Figure 1) with similarly high enantioselection.[24] However, the low yield observed in the former case further emphasizes the practical value of the pathway through **C**. In other comparisons, such as the acyl-protected **10a**, the increased reactivity of the acyl imine intermediate leads to poor enantioselection and yield. The development of *N*-TMS imines as substrates in the enantioselective synthesis of amides and peptides both decreases the length from aryl aldehyde to peptide to three steps and broadens the nitrogen substituent choices, including Fmoc protection without extensive redevelopment of the enantioselective reaction for each case. In this way, silyl amines **C** are Rosetta Stones for α-amino amide synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Complete preparatory and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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