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Diastereoselective and Enantiospecific Synthesis of 1,3-Diamines via 2-Azaallyl Anion Benzylic Ring-Opening of Aziridines

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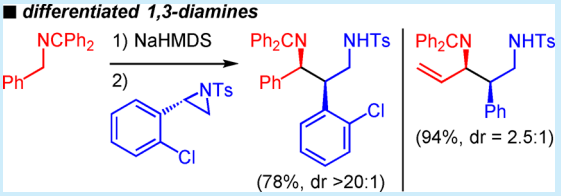
Supporting Information

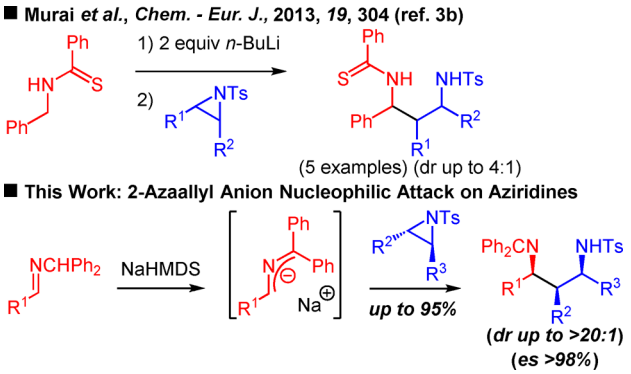
ABSTRACT: The 1,3-diamine motif appears in numerous complex molecules, yet there are few methods for the stereoselective construction of this moiety. Herein, we demonstrate a stereocontrolled synthesis of 1,3-diamines, which bear up to three contiguous stereogenic centers, through benzylic ring-opening of aziridines with 2-azaallyl anion nucleophiles. Reactions proceed efficiently (yield up to 95%), diastereoselectively (dr up to >20:1), site selectively, and enantiospecifically to deliver products with differentiated amino groups.



Numerous natural products and pharmaceutical agents contain multiple stereogenic centers bearing a nitrogen atom; however, there are few approaches that directly and stereoselectively generate a 1,3-diamine via C−C bond formation.[1−5] The majority of methods have relied on Mannich-type reactions of enamides[2b,e] or nitrile enolate equivalents,[2f−j] which require subsequent reduction of the products' imine or nitrile to generate the diamine. Alternatively, an N-substituted carbanion might be added to a two-carbon N-electrophile; largely this has involved reactions with nitroalkenes[2a] or cyanide addition to an aziridine,[2c,d] which also necessitate reduction to obtain the 1,3-diamine. Conversely, Murai has shown that doubly deprotonated thioamides may be added to tosylaziridines to afford 1,3-diamine scaffolds directly (Scheme 1, five examples, dr up to 4:1).[3b]

2-Azaallyl anions have emerged as potent nucleophiles for accessing chiral amines.[6,7] We have recently disclosed 2-azaallyl anion additions to epoxides to prepare 1,3-amino alcohols.[8] In this work, we report that terminal aryl-substituted tosylaziridines react efficiently with azaallyl anions, directly delivering products with a 1,3-diamine framework in up to 95% yield and >20:1 dr, favoring the *syn*-diastereomer (Scheme 1). In most cases, bond formation occurs exclusively between the least hindered position of the nucleophile and the benzylic carbon of the aziridine. All transformations occur with >98% enantiospecificity (es).[9,10] Additionally, 1,3-diamine products with three contiguous stereogenic centers are generated from *trans*-disubstituted aziridines. 2,2-Disubstituted tosylaziridines, unlike epoxides,[8] undergo reaction at the fully substituted position[11] and also with complete inversion of stereochemistry to afford 1,3-diamines bearing a quaternary stereogenic center.

Scheme 1. Synthesis of 1,3-Diamines by Stereoselective Additions to Aziridines



We commenced by exploring the addition of phenyl-substituted **1a** to tosylaziridine **3a** (Table 1). Our investigations indicate that the diphenylketimine activating group of **1a** is crucial for obtaining the desired site isomer of product **4a** and that the tosyl group of the aziridine is essential for reactivity at −78 °C (at which maximum diastereoselectivity is achieved).[12] Although the base identity has little effect at higher temperature,[12] the role of the cation on reaction efficiency and stereoselectivity at −78 °C is profound. The reaction is inefficient with a Li cation (55% conv, dr = 6.0:1) (Table 1, entry 1), unlike in reactions with epoxides where it is essential,[8] and though the K salt delivers 84% conversion to **4a**, it is less stereoselective (5.0:1 dr) (Table 1, entry 3). The nucleophile generated with NaHMDS (Table 1, entry 2), however, leads to 76% conversion (68% yield) to **4a**, which is generated as an 8.0:1 mixture of diastereomers, each as a single enantiomer (es >98%). Increasing to 2 equiv of nucleophile (Table 1, entry 4) improves conversion to product (95% yield, dr = 8.0:1, es >98%). The reaction is completely site selective under all conditions, with C−C bond formation occurring solely between the less substituted position of the anion and the aziridine's benzylic carbon.[13] In all cases, *syn*-**4a** is the major diastereomer.[14]

The tautomeric aldimine **2a** also efficiently undergoes deprotonation with NaHMDS under the optimized conditions

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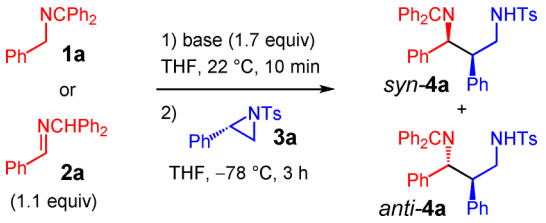
Table 1. Azaallyl Anion Counterion Effects[a]



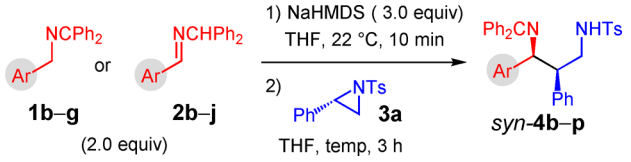
entry	imine	base	conv (%)[b]	yield (%)[c]	4a dr[d] syn/anti	es (%)[e]
1	**1a**	LiHMDS	55	nd	6.0:1	nd
2	**1a**	NaHMDS	76	68	8.0:1	>98
3	**1a**	KHMDS	84	nd	5.0:1	nd
4[f]	**1a**	NaHMDS	>98	95	8.0:1	>98
5[f]	**2a**	NaHMDS	>98	90	8.5:1	>98

[a]Reactions run with 0.1 mmol **3a**. See the Supporting Information for experimental details. [b]Based on consumption of **3a** as determined by 500 MHz ^{1}H NMR spectroscopy of the unpurified mixture in comparison with an internal standard. [c]Isolated yield of purified product as a mixture of diastereomers. [d]Determined by 500 MHz ^{1}H NMR spectroscopy of the unpurified mixture. [e]Determined by HPLC analysis of purified products. [f]2.0 equiv of imine with 3.0 equiv of NaHMDS; nd = not determined.

for ketimine **1a** to generate the same resonance-stabilized 2-azallyl anion. As expected, C−C bond formation with aziridine **3a** is just as efficient and stereoselective (dr = 8.5:1, es >98%), and diamine **4a** is isolated in 90% yield (Table 1, entry 5).

Diphenylketimines **1b−g** and benzhydrylaldimines **2b−j** serve as azaallyl anion precursors for preparing 1,3-diamines (Table 2). Additions of aryl-substituted nucleophiles with *para*- or *meta*-substitution undergo diastereoselective reaction with aziridine **3a** (dr = 6.0−9.5:1) (Table 2, entries 1−3 and 7−11). Reactions with *ortho*-substituted aryl-containing nucleophiles are efficient but less selective (Table 2, entries 4, 12, and 13). Heteroaromatic-substituted azaallyl anions (Table 2, entries 5, 6 and 14,15) are also competent reaction partners with the thiophenyl nucleophile leading to the highest stereoselectivity (dr = 9.0:1). Contrastingly, reaction with the furyl-substituted nucleophile requires warming to −45 °C,[15] generating **4f** in 4.0:1 dr. In all cases, azaallyl anion attack upon aziridine **3a** generates a single product with the exception of the *para*-methoxyphenyl-containing azaallyl anion (entry 2).[12]

Table 2. Aryl Group Variation within Azaallyl Anions[a]

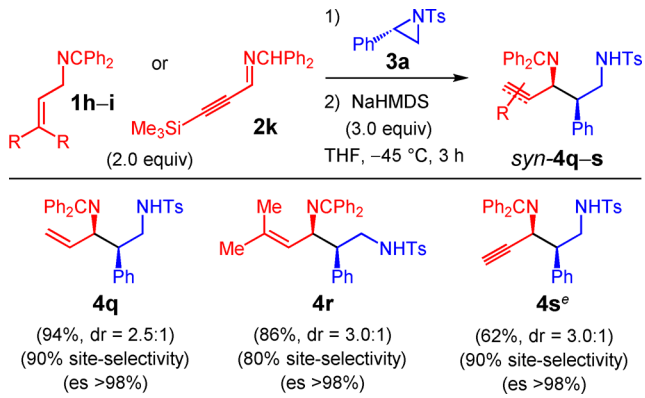


entry	imine	4, Ar	temp (°C)	yield (%)[b]	dr[c]	es (%)[d]
1	**1b**	4-BrC_6H_4	−78	73	9.5:1	>98
2	**1c**	4-OMeC_6H_4	−78	93[e]	8.0:1	>98
3	**1d**	3-$CF_3C_6H_4$	−78	89	7.5:1	>98
4	**1e**	2-ClC_6H_4	−60	91	1.5:1	>98
5	**1f**	2-furyl	−45	87	4.0:1	>98
6	**1g**	2-thiophenyl	−78	82	9.0:1	>98
7[f]	**2b**	4-CNC_6H_4	−60	72	6.0:1	>98
8	**2c**	4-FC_6H_4	−78	69	6.5:1	>98
9	**2d**	3-OMeC_6H_4	−78	78	7.5:1	>98
10	**2e**	3-BrC_6H_4	−78	73	7.5:1	>98
11	**2f**	3-PhC_6H_4	−78	83	7.5:1	>98
12[g]	**2g**	2-MeC_6H_4	−78	92	4.0:1	>98
13[h]	**2h**	2,6-$Cl_2C_6H_3$	−45	91	4.0:1	>98
14[i]	**2i**	4-pyridyl	−60	74	6.0:1	>98
15[j]	**2j**	3-pyridyl	−60	79	5.5:1	>98

[a]Reactions run with 0.1 mmol **3a**. [b]Isolated yield of purified product as a mixture of diastereomers. [c]Determined by 500 MHz ^{1}H NMR spectroscopy of the unpurified mixture. [d]Determined by HPLC analysis of purified products. [e]Contains ca. 12% of an inseparable site isomer. [f]Reaction for 5 h. [g]Deprotonation for 2 h. [h]0.8 mmol scale. [i]Reaction for 10 h. [j]Reaction for 6 h.

Azaallyl anions with vinyl and alkynyl substituents effectively participate in reactions with aziridines (Scheme 2), delivering allylic and propargylic amines that provide handles for further functionalization. In these cases, low temperature deprotonation in the presence of the electrophile avoids nucleophile decomposition and affords diamines **4q−s** in 62−94% yield (dr = 2.5−3.0:1, es >98%) with 80−90% site selectivity.

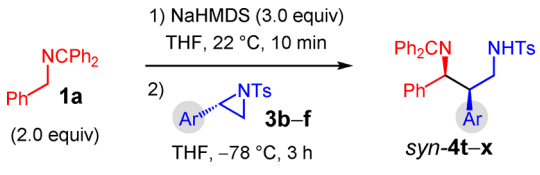
Scheme 2. Vinyl- and Alkynyl-Substituted Azaallyl Anion Additions[a−d]



[a−d]See Table 2. [e]Isolated as the terminal alkyne from the Me_3Si-alkyne upon K_2CO_3/MeOH workup. See the Supporting Information.

Several aryl-substituted terminal aziridines **3b−f** efficiently participate in reactions with azaallyl anions to afford diamine products **4t−x** in 5.5 to >20:1 dr and 61−91% yield (Table 3). Electron-withdrawing groups in the arene's *para*-position are well-tolerated (Table 3, entry 1). An electron-donating *para*-methyl affords diamine **4u** in 61% yield (dr = 5.5:1) (Table 3,

Table 3. Addition of Azaallyl Anions to Aryl-Substituted Aziridines[a]



entry	aziridine	4, Ar	yield (%)[b]	dr[c]	es (%)[d]
1	**3b**	**4t**, 4-$CF_3C_6H_4$	88	5.5:1	>98
2[e]	**3c**	**4u**, 4-MeC_6H_4	61	5.5:1	>98
3	**3d**	**4v**, 3-MeC_6H_4	80	8.0:1	>98
4	**3e**	**4w**, 2-MeC_6H_4	91	>20:1	>98
5	**3f**	**4x**, 2-ClC_6H_4	78	>20:1	>98

[a−d]See Table 2. [e]Reaction at −60 °C.

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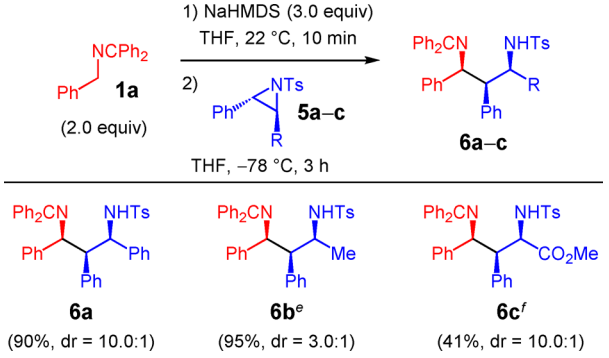
entry 2); however, the more donating *para*-methoxy substituent leads only to aziridine decomposition under the reaction conditions. Both *meta*- and *ortho*-substituted aziridine aryl groups are amenable to azaallyl anion additions, as well (diamines **4w,x**) (Table 3, entries 3−5). All transformations proceed with >98% enantiospecificity. As the aromatic substituent is moved from the *para*- to the *ortho*-position, stereoselectivity steadily improves with *ortho* groups leading to >20:1 dr.

1,3-Diamines **6a−c**, bearing three contiguous stereogenic centers, are generated when 1,2-disubstituted aziridines **5a−c** undergo ring-opening with the anion of ketimine **1a** (Scheme 3).

Scheme 3. Azaallyl Anion Additions to 1,2-Disubstituted Aziridines[a-d]

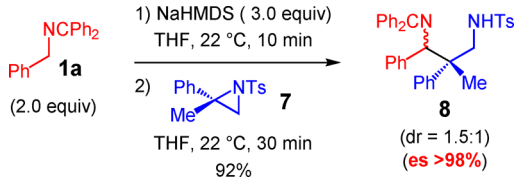


[a-d]See Table 2. [e]Reaction performed at −45 °C. [f]Obtained using 2.0 equiv of NaHMDS in 95.5:4.5 er from **5c** of equal enantiopurity.

Triphenylpropyldiamine **6a**, whose symmetry is broken only by the differentiated N groups, is obtained as a single enantiomer with good diastereoselectivity and yield via azaallyl anion addition (90%, dr = 10.0:1). Diamine **6b**, with a smaller Me group, is generated in 95% yield but with a diminished 3.0:1 dr. The more sensitive nature of aziridine **5c** requires that no excess base be added to avoid partial aziridine elimination to the unsaturated α-aminoester. Under these optimal conditions, α,γ-diaminoester **6c** is formed in 41% yield and 10.0:1 dr. The product is obtained with >98% es, thereby indicating that it arises via direct anion attack upon the aziridine and not through conjugate addition to the unsaturated aminoester byproduct.

We have also examined azaallyl anion addition to 2,2-disubstituted aziridine **7** (Scheme 4). Despite the added steric

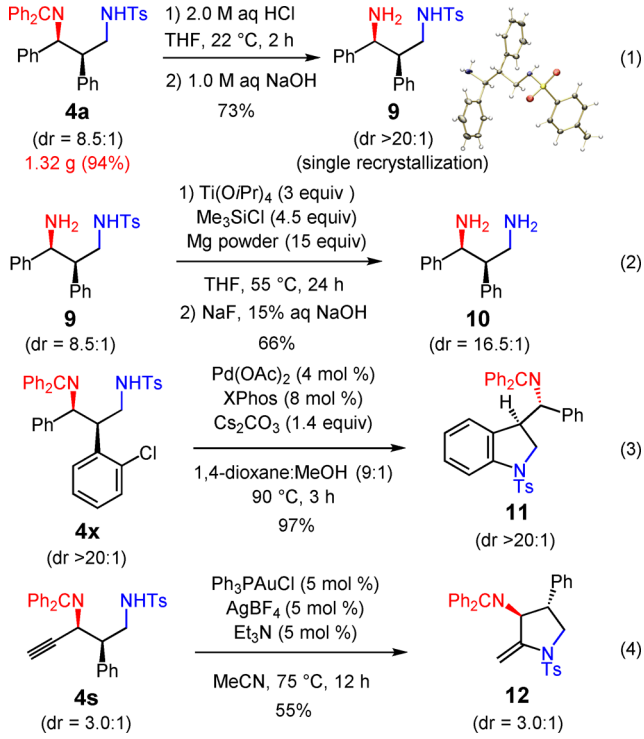
Scheme 4. Enantiospecific Synthesis of a Stereogenic Quaternary Carbon Center by Azaallyl Anion Addition Aziridine 7



congestion at the benzylic site, nucleophilic attack exclusively takes place there to deliver quaternary carbon-containing diamine **8** in 92% yield, opposite site selectivity to that observed with analogous epoxides.[8] Diastereoselectivity in the transformation is low and was not improved upon cooling; however, both diastereomers of **8** are obtained in the same enantiopurity as aziridine **7** (es >98%), suggesting an S_N2-like process.[11]

An advantage of this method is the differentiation of the two masked amines within the products, with the benzophenone imine serving as a double protecting group for one N atom while the sulfonamide allows for monofunctionalization of the other (Scheme 5). Hydrolysis of the imine within **4a**, prepared on a

Scheme 5. Diversification of the Differentiated Amines within the 1,3-Diamine Products



gram-scale,[12] proceeds under mildly acidic conditions to reveal the nucleophilic primary amine within **9** (73%, dr >20:1 after a single recrystallization) (Scheme 5, eq 1).[16] Subsequent Ti-mediated removal of the *N*-tosyl group[17] delivers diamine **10** (66%, dr = 16.5:1) (Scheme 5, eq 2).

Conversely, the sulfonamide within the protected diamine may be functionalized while retaining the imine, leading to heterocyclic compounds via intramolecular C−N bond formations. For example, the sulfonamide in **4x** takes part in Buchwald−Hartwig coupling to furnish dihydroindoline **11** (Scheme 5, eq 3).[9g,18] Additionally, the terminal alkyne of **4s** undergoes Au-catalyzed cyclization of the sulfonamide to deliver 3-aminopyrrolidine **12** (Scheme 5, eq 4).[19]

2-Azaallyl anions are useful building blocks for constructing chiral amines through C−C bond formation. In this study, we demonstrate that aziridines efficiently react with azaallyl anions to prepare 1,3-diamines. Aryl-substituted terminal aziridines are attacked at their benzylic position in a diastereoselective and enantiospecific manner to deliver enantioenriched 1,3-diamines that contain vicinal stereogenic centers. 1,2-Disubstituted aziridines similarly undergo benzylic ring-opening to afford diamine products with three contiguous stereogenic centers. A 2,2-disubstituted aziridine reacts enantiospecificially at the sterically congested benzylic center, affording a 1,3-diamine with a quaternary stereogenic center. The differentially protected amines within the products facilitate downstream synthesis.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01886.

X-ray data for rds504 (CIF)

Experimental procedures, analytical data for new compounds, spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(13) Alkyl-substituted aziridines undergo terminal ring-opening but deliver diamines with low diastereoselectivity (dr < 2.0:1).

(14) Identity of the major stereoisomer was determined by single-crystal X-ray diffraction of imine hydrolysis product **9** (Scheme 5). All other stereochemical assignments are made by inference.

(15) Several azaallyl anions are unreactive with **3a** at −78 °C; however, at either −60 or −45 °C, those reactions proceed to >98% conversion to the 1,3-diamine within 3−10 h.

(16) Hydrolysis may be carried out directly in the workup of the nucleophilic addition. See the Supporting Information for details.

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