Development of a Sulfamate Tethered *Aza*-Michael Cyclization Allows for the Preparation of (-)-Negamycin *tert*-Butyl Ester

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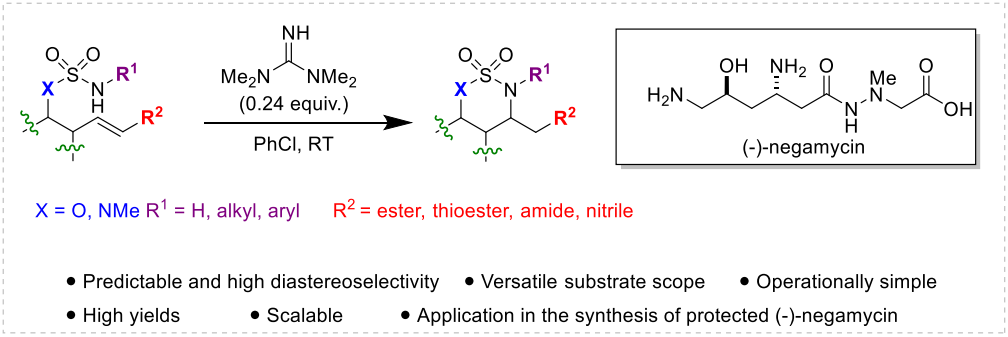
‡ = equal contribution

Supporting Information Placeholder

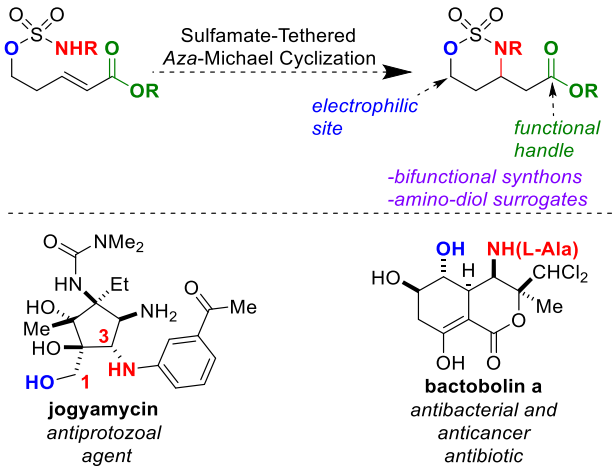


ABSTRACT: We present the first examples of intramolecular *aza*-Michael cyclizations of sulfamates and sulfamides onto pendant α,β-unsaturated esters, thioesters, amides, and nitriles. Stirring substrate with catalytic quantities of the appropriate base delivers product in good yield and excellent diastereoselectivity. The reactions are operationally simple, can be performed open to air, and are tolerant of a variety of important functional groups. We highlight the utility of this technology by using it in the preparation of a (-)-negamycin derivative.

Reactions which make use of tethers are an important subset of intramolecular cyclizations. In such reactions, it is of prime importance that the tether is easily attached prior to cyclization and then detachable post-reaction. "Versatile" tethers allow for highly predictable regioselectivity and diastereoselectivity during the cyclization event and activate the product for a further transformation. This is important from the perspective of step count. One of the drawbacks of auxiliary based chemistry is the expenditure of two steps- one for attachment and the other for removal. As versatile tethers can be manipulated in a productive manner after cyclization, tether attachment becomes the only additional ("extra") step in a synthetic sequence. Sulfamate tethers are particularly versatile.[1-5] They can be conveniently attached to amines and alcohols in the substrate, are excellent *N*-nucleophiles, and can be activated and displaced post-cyclization. Our laboratory has a programmatic focus on the development of sulfamate-tethered chemistry,[6-12] and, here, we disclose the first sulfamate-tethered *aza*-Michael reaction (**Scheme 1**).

The *aza*-Michael reaction is a 1,4 addition of nitrogen nucleophiles into α,β-unsaturated electrophiles and is a powerful method for the construction of new C–N bonds.[13-15] Intermolecular *aza*-Michael additions are convenient from the perspective of step counts but, depending on the reaction context,

Scheme 1. A robust sulfamate-tethered *aza*-Michael cyclization would supply highly valuable synthetic intermediates.



may suffer from difficulties with regioselectivity and stereoselectivity. Intramolecular *aza*-Michael reactions for the

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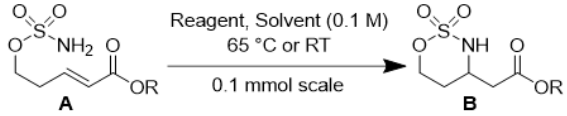
syntheses of pyrrolidine, piperidine, and related heterocycles have been well-explored.[16, 17] The use of versatile tethers in intramolecular *aza*-Michael chemistry has received less attention; such reactions are particularly powerful because they remove the constraint of needing a pre-existing C–N bond in the molecule to forge a new one.[18-25]

For reaction optimization (**Table 1**), we chose substrates that could be prepared in three steps from commercially available 3-[(*tert*-butyldimethylsilyl)oxy]-1-propanal in a sequence of HWE olefination, TBS removal, and sulfamoylation. Treatment of **A** with 10-CSA, (S)-BINOL phosphoric acid, or quinine resulted in low yields of desired cyclized product **B** (**Table 1**, **Entries 1–3**). Phosphines are strong promoters of Michael reactions.[26, 27] Using 1 equivalent of PEt_3 with catalytic (S)-BINOL phosphoric acid gave **B** in an increased yield of 45% (**Table 1**, **Entry 4**). Our laboratory has developed biphasic basic conditions for the ring-opening of epoxides and aziridines by sulfamates[11]; these conditions were only marginally successful here (**Table 1**, **Entry 5**). The most successful results came from switching to either TBAF or 1,1,3,3-tetramethylguanidine (TMG) in CH_2Cl_2 or PhCl (**Table 1**, **Entries 6-9**). The reaction could be made catalytic with respect to TMG, but the time had to be extended to 48 hours for full consumption of starting material (**Table 1**, **Entry 10**).

Table 1. Select Optimization Conditions.

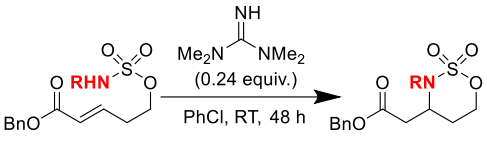


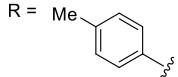
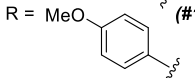
	R	reagent/catalyst (equivalent)	solvent	time (h)	B:A[a]
1[b]	Et	10-CSA[d] (0.3)	MeCN	52	10:70
2[b]	Et	BINOL PA[e] (0.3)	MeCN	52	15:70
3[b]	Et	Quinine (0.3)	MeCN	52	10:50
4[b]	Et	PEt_3 (1.0), BINOL PA (0.3)	MeCN	23	45:0
5[c]	Et	$Bu_4NOH•30H_2O$ (1.0)	H_2O/ $PhCF_3$[h]	22	28:0
6[c]	Et	TBAF[f] (0.5)	CH_2Cl_2	23	85:0
7[c]	Et	TMG[g] (1.0)	CH_2Cl_2	24	67:0
8[c]	Bn	TMG (1.0)	CH_2Cl_2	24	79:0
9[c]	Bn	TMG (1.0)	PhCl	24	89:0
10[c]	Bn	TMG (0.24)	PhCl	48	98:0

(a) yields calculated from ^1H NMR of crude reaction mixture with an internal standard. (b) reaction at 65 °C. (c) reaction at RT. (d) camphorsulfonic acid. (e) (S)-BINOL phosphoric acid. (f) 1 M in THF. (g) 1,1,3,3-tetramethylguanidine. (h) 1/1 biphasic mixture

We next wished to examine the effect of various sulfamate *N*-substituents on the efficiency of cyclization (**Scheme 2**). Our optimized protocol was compatible with a variety of *N*-alkyl substituents, including methyl, *n*-hexyl, and cyclohexyl (**Scheme 2**, **Entries 2-4**). We were pleased that cyclization was possible even with bulky *N*-aryl groups. With *N*-phenyl sulfamate **9**, the reaction time had to be extended from 48 h to 60 h for optimal product yield (**Scheme 2**, **Entry 5**). In contrast, with *N*-tolyl and *N*-*p*-OMe-phenyl sulfamates **11** and **13**, a normal

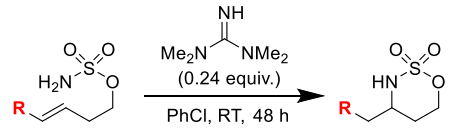
Scheme 2. Structure-Reactivity Relationship with Diverse Sulfamate Esters.

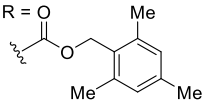
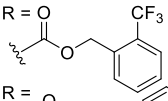
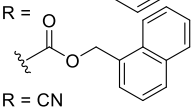
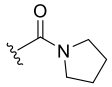


Entry	Substrate		Isolated Yield
1	R = H	***(#1, #2)***[a]	98%
2	R = Me	***(#3, #4)***	95%
3	R = *n*-hex	***(#5, #6)***	85%
4	R = *c*-hex	***(#7, #8)***	17%[b]
5	R = Ph	***(#9, #10)***	46%[c]
6	R = 	***(#11, #12)***	49%
7	R = 	***(#13, #14)***	73%

[a](substrate number, product number)
[b]reaction time extended to 96 h
[c]reaction time extended to 60 h

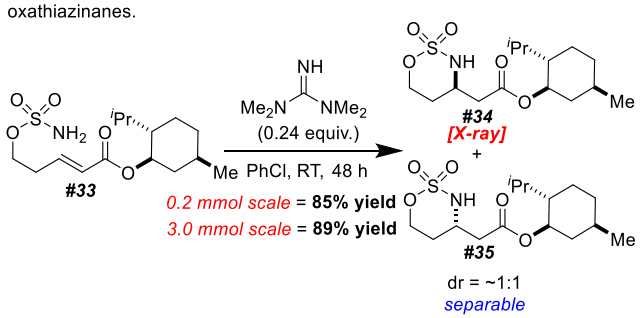
Scheme 3. Exploring Reactivity with Diverse Michael Acceptors.



Entry	Substrate		Isolated Yield
1	R = CO_2Et	***(#15, #16)***[a]	93%
2	R = CO_2t-Bu	***(#17, #18)***	98%
3	R = CO_2Ph	***(#19, #20 [X-ray])***	79%[b]
4	R = $C(O)SC_8H_{17}$	***(#21, #22)***	84%
5	R = 	***(#23, #24)***	98%
6	R = 	***(#25, #26)***	92%
7	R = 	***(#27, #28)***	90%
8	R = CN	***(#29, #30)***	52%
9	R = 	***(#31, #32)***	58%[c]

[a](substrate number, product number)
[b]TBAF/THF (0.5 equiv.), CH_2Cl_2, RT, 24 h, 0.2 mmol scale
The yield is 89% on a 2.7 mmol scale.
[c]Reaction time of 118 h

Scheme 4. Using a menthol ester allows for the synthesis of chiral oxathiazinanes.



reaction time of 48 h was sufficient (**Scheme 2**, **Entries 6-7**).

With *N*-aryl sulfamates, the enhanced nucleophilicity of the attacking nitrogen helps compensate for the increase in steric bulk.

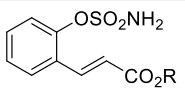
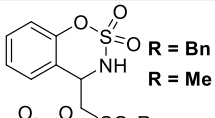
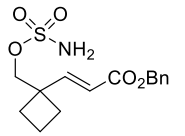
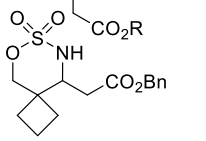
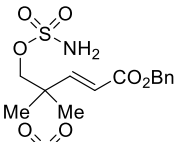
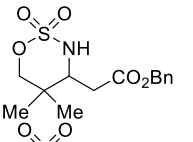
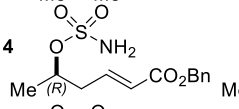
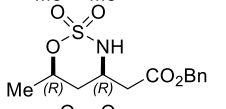
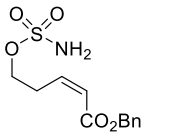
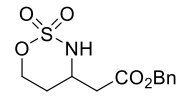
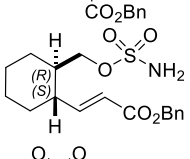
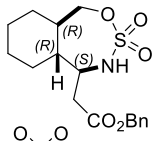
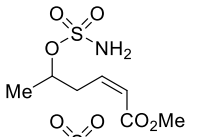
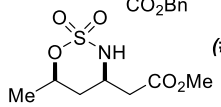
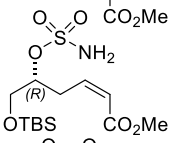
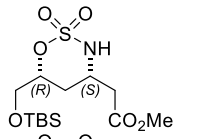
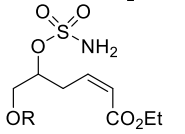
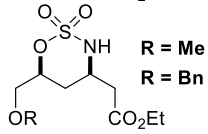
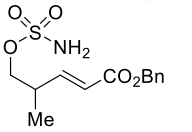
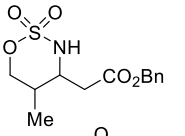
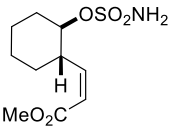
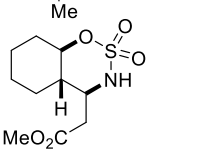
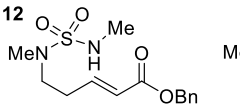
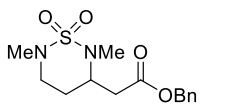
In our optimization studies, we had focused on reactions with α,β-unsaturated ethyl and benzyl esters. We sought to explore this cyclization reaction with other esters and related Michael acceptors (**Scheme 3**). We found that our reaction was productive with a variety of esters, including those with sterically bulky groups such as t-Bu and naphthyl (**Scheme 3**, **Entries 1-3** and **Entries 5-7**). Interestingly, with substrate **19** (**Scheme 3**, **Entry 3**), using TBAF/CH_2Cl_2 in place of TMG/PhCl was essential for a productive reaction; a crystal structure of product **20** (**CCDC 2301582**) allowed us to unambiguously confirm its identity. This reaction was scaled from 0.2 mmol to 2.7 mmol (13.5-fold increase) without a loss of yield. We were pleased that other Michael acceptors such as α,β-unsaturated thioesters, α,β-unsaturated nitriles, and α,β-unsaturated tertiary amides were compatible with our optimized protocol (**Scheme 3**, **Entries 4**, **8**, and **9**). With an ester derived from menthol, chiral oxathiazinanes could be prepared (**Scheme 4**).

Sulfamates could be conveniently synthesized from phenols and were compatible with our optimized protocol (**Scheme 5**, **Entry 1)**. Products with a variety of substituent patterns could be prepared, including [6,4]-spirocycles (**Scheme 5**, **Entry 2**). Substrates with *cis* α,β-unsaturated esters (**Scheme 5**, **Entries 5, 7, 8, 9, and 11**) cyclized with efficiencies comparable to related ones bearing *trans* α,β-unsaturated esters. 7-membered rings could be forced to form, but the efficiency of cyclization dropped (**Scheme 5**, **Entry 6**); the bond angle of the sulfamate tether strongly favors the formation of 6-membered rings.[1, 6] Overall, the diastereoselectivity of this reaction was excellent, and, in many cases, a single diastereomer of product was furnished within the limits of ^{1}H NMR detection (**Scheme 5**, **Entries 4, 6, 7, 8, 9, and 11**). Our optimized protocol tolerated a variety of functional groups including TBS, methyl, and benzyl ethers (**Scheme 5**, **Entries 8 and 9**). In addition to sulfamates, sulfamides were also compatible with the reaction conditions and gave 1,3-diamine products (**Scheme 5**, **Entry 12**).

To further highlight the utility of our method, we chose to prepare an ester of the highly polar, heteroatom rich compound (-)-negamycin (**Scheme 6**). (+)-Negamycin is a natural product antibiotic which has remarkable activity against both Gram-positive and Gram-negative bacteria by interfering with multiple steps of the protein synthesis pathway.[28-32] While (+)-negamycin has been the target of numerous synthetic efforts,[33, 34] its antipode has only been synthesized once.[35] To our knowledge, the biological activity of (-)-negamycin has not been delineated; often, the non-natural enantiomers of natural products and natural-product like compounds have divergent, surprising, and useful activity.[36, 37]

Our synthesis commenced by deprotonation of methyl propiolate with *n*-BuLi and regioselective addition into commercial (*S*)-*N*-glycidylphthalimide. Lindlar reduction gave α,β-unsaturated ester **64**, which was converted into sulfamate **65** (**CCDC 2301583**) using a Johnson-Magolan sulfamoylation.[38] Our sulfamate tethered *aza*-Michael cyclization converted **65** into oxathiazinane **66** (**CCDC 2301584**) with good yield and >20:1 diastereoselectivity. To activate oxathiazinane **66** for ring-opening, a Cbz group was appended using K_2CO_3 and CbzCl in CH_3CN. Ring-opening proceeded smoothly by heating with KOAc in CH_3CN. The methyl ester was selectively cleaved using Nicolaou's Me_3SnOH protocol.[39]

Scheme 5. Assessing Functional Group Compatibility and Diastereoselectivity.

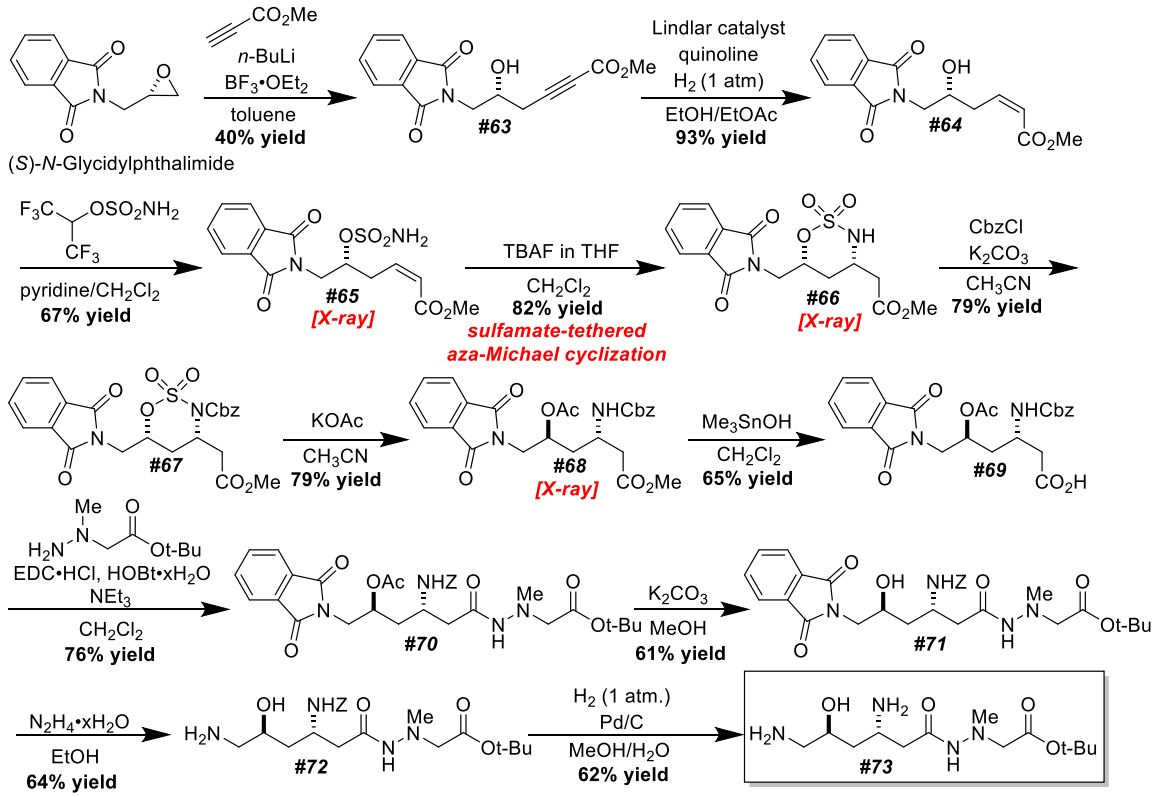
Entry	Substrate	Product		Isolated Yield[a]
1			R = Bn R = Me	*(#36, #37)*[b] 80% *(#38, #39)* 80%
2				*(#40, #41)* 98%
3				*(#42, #43)* 94%
4				*(#44, #45)* 95%[c] *3.34 mmol scale* 97%
5				*(#46, #2)* 71%
6				*(#47, #48)* 22%[c,f]
7				*(#49, #50)* 76%[c]
8				*(#51, #52)* 87%[d]
9			R = Me R = Bn	*(#53, #54)* 85%[d] *(#55, #56)* 86%[d]
10				*(#57, #58)* 95%[e] *dr = 3.8:1*
11				*(#59, #60)* 97%[c]
12				*(#61, #62)* 96%

[a]1,1,3,3-tetramethylguanidine (0.24 equiv.), PhCl, 23 °C, 48 hours
[b](substrate number, product number). Relative stereochemistry shown unless stereocenters are explicitly assigned.
[c]Stereochemistry assigned by nOe analysis.
[d]Stereochemistry assigned by analogy to other products.
[e]Relative stereochemistry unassigned.
[f]1,1,3,3-tetramethylguanidine (1 equiv.), PhCl, 60 °C, 72 hours

Commercially available *tert*-butyl 2-(1-methylhydrazinyl)acetate was coupled with carboxylic acid **69** using EDC•HCl and

HOBt in CH_2Cl_2. The acetate group was removed using K_2CO_3, and the phthalimide was cleaved with hydrazine hydrate. Finally, the Cbz group was removed by hydrogenolysis. This completed a synthesis of (-)-negamycin *tert*-butyl ester.

Scheme 6. Synthesis of a protected (-)-negamycin.



In summary, we have developed protocols for the intramolecular *aza*-Michael cyclization of sulfamates and sulfamides onto pendant α,β-unsaturated esters, thioesters, amides, and nitriles. Stirring substrate with catalytic quantities of the appropriate base delivers product in good yield and excellent diastereoselectivity. The reactions are operationally simple, can be performed open to air, and are tolerant of a variety of important functional groups. We have demonstrated the utility of this new reaction by applying it as a key step in the preparation of a (-)-negamycin derivative. Overall, we expect this technology to find much use for the controlled preparation of 1,3-aminoalcohols in both academic and industrial contexts.

ASSOCIATED CONTENT

Supporting Information

Supporting Information contains additional experimental details and NMR spectra.

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