Cycloaddition

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Stereocontrolled Syntheses of Seven-Membered Carbocycles by Tandem Allene Aziridination/[4+3] Reaction

*Nels C. Gerstner, Christopher S. Adams, Maik Tretbar, and Jennifer M. Schomaker**

Abstract: *A tandem allene aziridination/[4+3]/reduction sequence converts simple homoallenic sulfamates into densely functionalized aminated cycloheptenes, where the relative stereochemistry at five contiguous asymmetric centers can be controlled through the choice of the solvent and the reductant. The products resulting from this chemistry can be readily transformed into complex molecular scaffolds which contain up to seven contiguous stereocenters.*

Densely functionalized seven-membered rings are valuable synthetic targets occurring in a range of bioactive natural products and their analogues (Figure 1). Several approaches

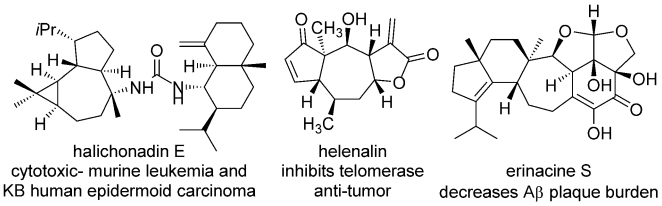
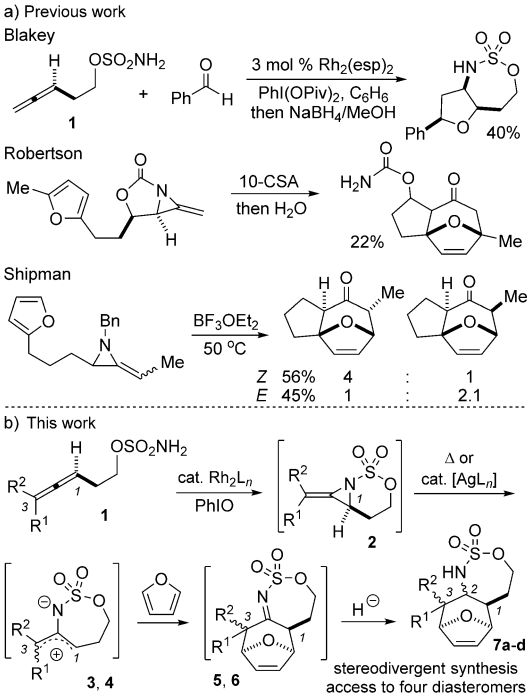


Figure 1. Bioactive natural products with seven-membered carbocyclic cores.

to address the challenge of controlling the stereochemical outcome in the synthesis of seven-membered rings have been developed, including annulations, ring-closing metatheses, and an array of cycloaddition reactions.[1] One powerful strategy involves the [4+3] reaction of a 1,3-diene with a suitable three-carbon coupling partner, analogous to the venerable Diels–Alder reaction, with the potential to form multiple new stereocenters in a highly controlled fashion.[2,3]

Oxyallyl cations are popular coupling partners in [4+3] cycloadditions. However, use of their nitrogen counterparts is far less common. Reactive 2-amidoallyl cations for reported intramolecular [4+3] reactions have been generated from α-chloroenamines, α-chloroimines, allenes, and methylene aziridines (Scheme 1 a).[3–5] Typically, nitrogen is not retained in the product and the stereochemical outcome is dictated by the nature of the substrate. With these limitations in mind, we wanted to develop an intermolecular, stereodivergent [4+3]



Scheme 1. Stereochemical diversity by allene aziridination. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid.

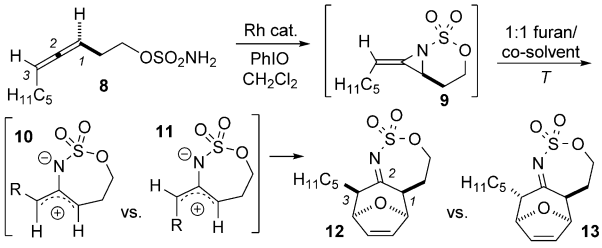
cycloaddition protocol with the ability to rapidly increase molecular complexity from simple allene precursors.

Our group has reported a suite of highly chemo-, regio-, and stereoselective oxidative aminations which transform allenes into a diverse array of amine stereotriads with control over both the identity and relative stereochemistry of the three heteroatoms at C1–C3.[6] We envisaged extending this concept to controlling the relative stereochemistry at each of the three original allene carbon atoms in the synthesis of aminated cycloheptenes through a tandem aziridination/[4+3]/reduction sequence (Scheme 1 b). This strategy features: 1) a one-pot allene aziridination/ring opening of the C–N bond of **2** to yield a 2-amidoallyl cation (**3** and **4**), 2) intermolecular trapping with inexpensive furan, where the reaction conditions control the relative stereochemistry at C1 and C3 in **5** and **6**, and 3) reagent-controlled reduction of the imine to yield stereodivergent syntheses of all four stereoisomers of **7** containing functionality for further elaboration into useful building blocks.[7]

Initial efforts to convert **8** into the imines **12** and **13** through the intermediacy of **10** and **11** (Table 1) showed a 1:1 THF/furan mixture successfully transformed **9** into the *endo* [4+3] adduct **12** at room temperature (entry 2). The *syn* C1–

[*] N. C. Gerstner, C. S. Adams, Dr. M. Tretbar, Prof. J. M. Schomaker
Department of Chemistry, University of Wisconsin-Madison
1101 University Avenue, Madison, WI 53706 (USA)
E-mail: schomakerj@chem.wisc.edu
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201606195.

Table 1: Solvent screen for the formal [4+3] cycloaddition.



Entry	Cosolvent	Yield [%][a,b] (24 h, RT)	12/13	Yield [%][b] (24 h, 50 °C)	12/13
1	none	0	–	–	–
2	THF	35	>20:1	31	>10:1
3	MeCN	0	–	21	~1:3
4	$MeNO_2$[c]	0	–	31	<1:10
5	CF_3CH_2OH	0	–	26	<1:10

[a] Reactions at room temperature performed in sealed vials. [b] Yields and d.r. values determined by ^{1}H NMR spectroscopy with an internal trimethoxybenzene standard. [c] When run at 65 °C for 7 h, the yield was 45% with about a 1:6 ratio of **12/13**. THF = tetrahydrofuran.

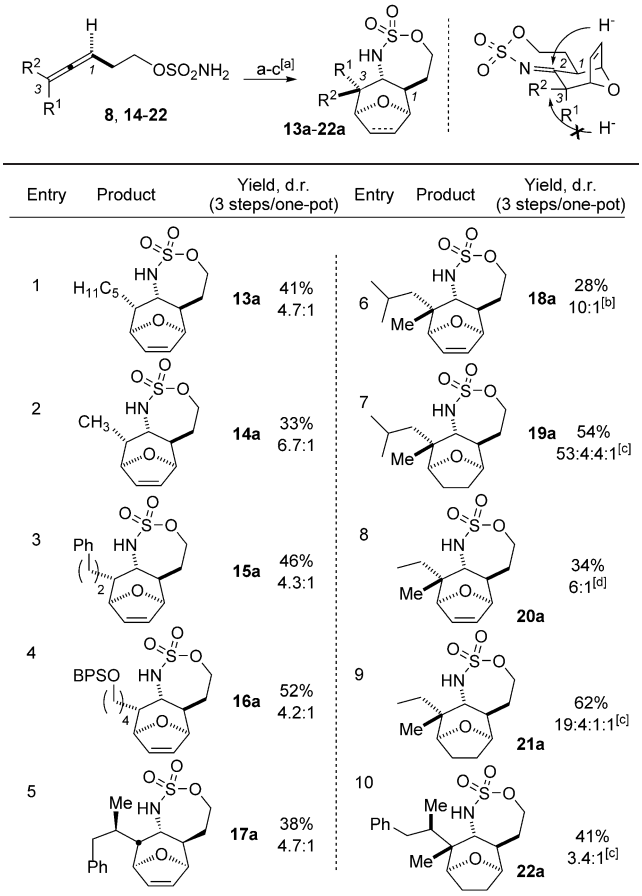
C3 relationship was established by X-ray crystallography (see the Supporting Information). Reactions in polar aprotic solvents, such as MeCN and $MeNO_2$ (entries 3 and 4) did not occur at room temperature, but heating to 50 °C resulted in *endo* cyclization to furnish **13** with a 1,3-*anti* relationship. The yield of **13** was increased to 45% over two steps by heating in $MeNO_2$ at 65 °C, albeit with a slightly lower d.r. value.

The differing stereochemical outcomes in **12** and **13** obtained by using THF and $MeNO_2$ were intriguing, and control experiments showed neither product epimerized under the reaction conditions. Shimizu[8] noted solvent effects on the d.r. value of [4+3] cycloadditions of 2-oxyallyl cations. In contrast to our results, $MeNO_2$ favored 1,3-*syn* products with a typical d.r. value of 2:1, while THF/Et_2O favored the 1,3-*anti* products, also with a low d.r. value.[8] We hypothesize that under our reaction conditions, **12** results from rapid addition of furan to **11**, while THF permits equilibration of the cation **11** to **10** to relieve the $A^{1,3}$ strain, thus resulting in the *syn* product **12**. This strain relief could occur through rapid reversible addition of the ethereal oxygen atom to the allyl cation, thus permitting bond rotation and equilibration to **11** before addition of furan takes place.

The scope of the thermal [4+3] cycloaddition in $MeNO_2$ was explored first (Table 2). The intermediate imines were reduced using $NaBH_3CN$, thus resulting in attack on the imine through a pseudo-axial trajectory. The allenes **8** and **14**–**16**, with monosubstitution at C3 (entries 1–4), delivered **13a**–**16a** with moderate to good d.r. values. The additional stereocenter α to C3 in **17** (entry 5) exerted an influence on the d.r. value of **17a**, thus resulting in only two major diastereomers in a 4.7:1 ratio.[9,10]

Gratifyingly, **18** (Table 2, entry 6) proved a good substrate for tandem aziridination/cycloaddition to set the all-carbon quaternary stereocenter. While $NaBH_3CN$ gave low conversion, $LiBH_4$ yielded **18a** in 10:1 d.r. When the three-step transformation was performed in one pot, residual rhodium catalyzed the reduction of the olefin with $LiBH_4$ to furnish

Table 2: Scope of the [4+3] reaction in $MeNO_2$ using $NaBH_3CN$ as reductant.

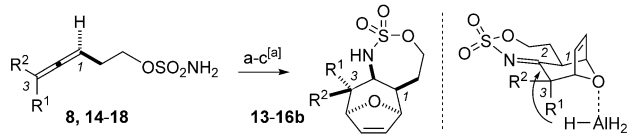


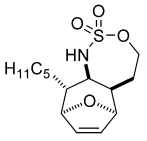
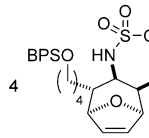
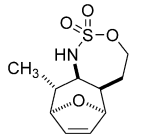
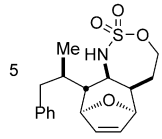
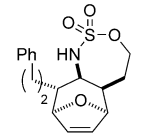
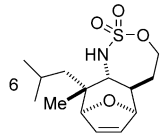
[a] Reaction conditions: a) 1 mol% $Rh_2(TPA)_4$, PhIO, 4 Å M.S., CH_2Cl_2, RT. b) 1:1 $MeNO_2$/furan, 4 Å M.S., 65 °C. c) $NaBH_3CN$, AcOH, MeCN, RT. [b] Treatment with $NaBH_3CN$, AcOH, MeCN, RT, followed by chromatography and reduction of the remaining imine with 5 equiv $LiBH_4$, THF, −78 °C to RT. [c] 500 psi H_2 5% Pd/C, EtOAc; then $LiBH_4$, THF, −78 °C to RT. [d] Purified by column chromatography at the imine stage, then reduced with 5 equiv $LiBH_4$, THF, −78 °C to RT. BPS = *tert*-butyldiphenylsilyl, M.S. = molecular sieves, TPA = triphenylacetic acid.

19a. Ultimately, we found olefin hydrogenation (entry 7; using Pd/C and H_2) prior to imine reduction gave reproducibly high yields of **19a** with excellent d.r. values.[10] The chemistry could even distinguish between a Me and Et group at C3 of **20** to yield either **20a** (entry 8) or **21a** (entry 9, Pd/C and H_2 to reduce the alkene) with good d.r. values.[10] Finally, the trisubstituted allene **22**, containing an additional stereocenter α to C3, gave **22a** (entry 12) with a d.r. value comparable to that of **17** (entry 5).

Access to the 1,2-*syn*/2,3-*anti* diastereomer **13b** requires the hydride to approach the 1,3-*anti* imine from the same face as any substituents at C3 of the allene precursor (Table 3). DIBAL-H and triisobutylaluminum gave **13b** as the minor diastereomer, however, $AlH_3{\cdot}Me_2NEt$ furnished the desired stereochemical outcome. Presumably, AlH_3 binds to the oxygen atom of the [3.2.1] bicyclic ring to direct reduction to the hindered imine face, although coordination to the sulfamate O or to the imine is also possible. The challenge of overriding substrate control is reflected in lower d.r. value

Table 3: Scope of the [4+3] cycloaddition in $MeNO_2$ with $AlH_3{\cdot}Me_2NEt$ as the reductant.



Entry	Product	Yield, d.r. (3 steps)	Entry	Product	Yield, d.r. (3 steps)
1	 **13b**	30% 4.9:1.1:1	4	 **16b**	trace N/A
2	 **14b**	29% 4.9:1	5	 **17b**	trace N/A
3	 **15b**	46% 12:2:2:1	6	 **18a**	36%[b] 3:1

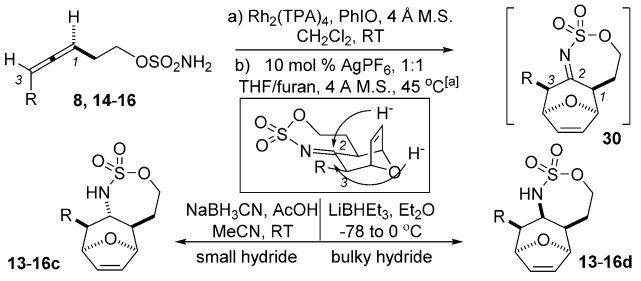
[a] a) 1 mol% $Rh_2(TPA)_4$, PhIO, 4 Å M.S., CH_2Cl_2, RT. b) 1:1 $MeNO_2$/furan, 4 Å M.S.,65 °C. c) $AlH_3{\cdot}Me_2NEt$, $PhCH_3$, RT. [b] Yield determined by ^1H NMR spectroscopy.

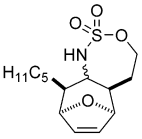
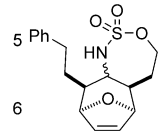
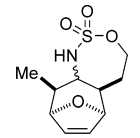
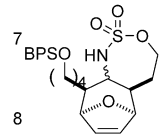
and scope (entries 1–3) compared to the 1,2-*anti*/2,3-*syn* diastereomers. Alane tolerated neither a silicon-protected oxygen atom in **16** nor branching α to C3 in **17** as **16b** and **17b** were observed only in trace amounts (entries 4 and 5). Axial reduction was noted for trisubstituted allenes (entry 6), and despite the lower d.r. value, the use of $AlH_3{\cdot}Me_2NEt$ gave more reproducible access to **18a**, as compared to the use of $LiBH_4$ (Table 2, entry 6).

The next goal was to improve access to 1,3-*syn* imines of the form **12**. Reaction of **8** with a rhodium catalyst, followed by [4+3] in THF at 50 °C (Table 1, entry 2) resulted in only a 31% yield of **12**. A variety of Lewis acids (see the Supporting Information) were tested, with 10 mol% of $AgPF_6$ providing optimal results. Adoption of these reaction conditions furnished the 1,3-*syn* imine **30** (Table 4) in a typical d.r. of greater than 10:1. To achieve tunable reduction of **30**, we postulated that less bulky hydride sources ($NaBH_3CN$) should approach from the top face of **30** to favor the 1,2-*anti*/2,3-*anti* diastereomers. In contrast, a bulkier reductant, such as $LiBHEt_3$, would be expected to favor reduction from the face opposite the alkene bridge to give the all-*syn* stereotriads. The 1,3-*syn* imines were much easier to reduce than the corresponding 1,3-*anti* imines. For example, $NaBH_3CN$ reduced *syn* imines to the *anti/anti* products **13–16c** (entries 1, 3, 5, and 7) with good to excellent d.r. values. Switching the reductant to $LiBHEt_3$ delivered the *syn/syn* products **13–16d** (entries 2, 4, 6, and 8), also in good d.r.

In our previous work, aziridination and subsequent functionalization of enantioenriched allenes gave excellent transfer of axial to point chirality.[6a,c] However, the intermediacy of an amidoallyl cation in the [4+3] precludes chirality transfer (see the Supporting Information). Nonetheless, the

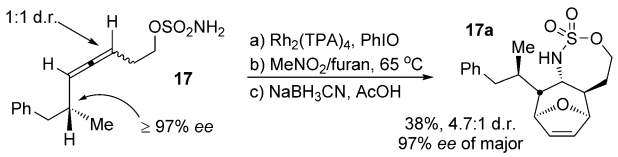
Table 4: Scope of the [4+3] cycloaddition/reduction in THF.



Entry	Product		Yield, d.r. (3 steps)	Entry	Product		Yield, d.r. (3 steps)
1		*anti/anti* **13c**	41% 16:1	5		*anti/anti* **15c**	29% 3.2:1
2		*syn/syn* **13d**	30% 10:1	6		*syn/syn* **15d**	22% 7.5:1
3		*anti/anti* **14c**	26% 10:1	7		*anti/anti* **16c**	46% 18:1
4		*syn/syn* **14d**	20% 15:1	8		*syn/syn* **16d**	34% 11:1

[a] Reaction conditions: a) 1 mol% $Rh_2(TPA)_4$, PhIO, 4 Å M.S., CH_2Cl_2, RT. b) 10 mol% $AgPF_6$, 1:1 THF/furan, 4 Å M.S., 45 °C.

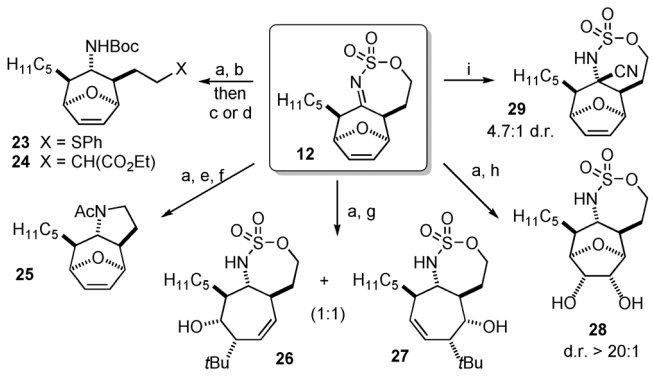
ability to racemize the axial chirality of the allene during the cycloaddition process could be used to an advantage to transfer chirality at the sp^3 carbon atom of **17** to the three carbon atoms of the initial racemic allene to yield **17a** (Scheme 2) in moderate d.r. and excellent *ee* values.[10,11]



Scheme 2. Enantioenriched cycloheptenes by [4+3] reactions.

The cycloheptenes from the tandem allene aziridination/formal [4+3] are flexible scaffolds for further diversification, as **12** has four primary reactive functional handles which can be manipulated (Scheme 3). For example, reduction of **12**, activation of the sulfamate and nucleophilic attack with either thiophenol or diethyl malonate delivers **23** or **24**, respectively, in good yields.[11,12] Ring contraction to the pyrrolidine **25**[5c,6a] can be achieved or the ether bridge cleaved in an S_N2' fashion using *t*BuLi as a nucleophile to give a 1:1 mixture of the regioisomers **26** and **27**.[13] Dihydroxylation of the alkene yields **28** with high d.r. value, and this sequence sets seven contiguous stereocenters with high d.r. values over four steps from a simple allene.[10,14] Carbon nucleophiles also add to **12**, as evidenced by a Strecker reaction to afford **29**.

In conclusion, we have described the first examples of intermolecular [4+3] reactions occurring via 2-amidoallyl cations arising from direct allene aziridination. The ability to manipulate the stereochemistry of the intermediate amidoallyl cation leads to stereodivergent syntheses of all four possible diastereomeric cycloheptenes resulting from *endo* cyclization. The functional-group diversity of the products



Scheme 3. Synthetic utility of cycloheptene products. a) $NaBH_3CN$, AcOH, MeCN; 41%, 16:1 d.r. from 8. b) Boc_2O, cat. DMAP, Et_3N, CH_2Cl_2, RT. c) Thiophenol, K_2CO_3, CH_3CN, RT; 75% from **13**. d) Diethyl malonate, TBAB, Cs_2CO_3, MeCN, RT; 58% from **13**. e) KO*t*Bu, DMAP, CH_2Cl_2, 0°C; then Ac_2O, RT; 96%. f: f) NaI, DMF, 60°C; then NaH, 40 to 60°C; 83%. g) *t*BuLi, THF, −40°C; 61% of a 1:1 mixture of regioisomers. h) 10 mol% OsO_4, NMO, acetone, H_2O, *t*BuOH, RT; 65%, >20:1 d.r. i) nBu_4NCN, MeCN, RT; 80% yield from **12**. Boc = *tert*-butoxycarbonyl, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, NMO = *N*-methylmorpholine *N*-oxide, TBAB = tetra-*n*-butylammonium bromide.

enables access to an array of densely functionalized synthetic building blocks in a few simple steps. While the stereoablative nature of the chemistry prevents direct transfer of axial-to-point chirality, the presence of an additional stereocenter can be employed to yield enantioenriched aminated carbocycles. Future work is focused on expanding the scope of both allenes and coupling partners, as well as applying this methodology to the syntheses of both bioactive natural products and their aminated analogues.

Acknowledgments

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Keywords: allenes · cycloaddition · heterocycles · rhodium · synthetic methods

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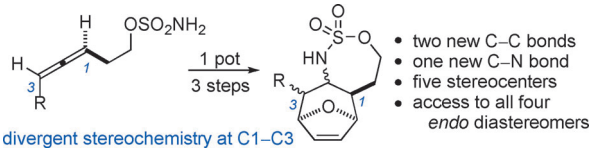
Communications

Cycloaddition

N. C. Gerstner, C. S. Adams, M. Tretbar, J. M. Schomaker* ———— ▮▮▮▮–▮▮▮▮

Stereocontrolled Syntheses of Seven-Membered Carbocycles by Tandem Allene Aziridination/[4+3] Reaction



Magic seven: A tandem allene aziridination/[4+3]/reduction sequence converts homoallenic sulfamates into aminated cycloheptanes, where the relative stereochemistry at five contiguous chiral carbon atoms can be controlled through the choice of solvent. The resulting products can be readily transformed into complex molecular scaffolds that contain up to seven contiguous stereocenters.