Published in final edited form as:

Angew Chem Int Ed Engl. 2016 October 10; 55(42): 13240–13243. doi:10.1002/anie.201606195.

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

Nels C. Gerstner,

Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison, WI 53706 (United States)

Christopher S. Adams,

Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison, WI 53706 (United States)

Dr. Maik Tretbar, and

Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison, WI 53706 (United States)

Prof. Jennifer M. Schomaker

Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison, WI 53706 (United States)

Abstract

A tandem allene aziridination/[4+3]/reduction sequence converts simple homoallenic sulfamates to 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 that contain up to seven contiguous stereocenters.

Graphical Abstract

A tandem allene aziridination/[4 + 3]/reduction sequence converts homoallenic sulfamates to aminated cycloheptanes, where the relative stereochemistry at five contiguous chiral carbons can be controlled through the choice of solvent and reductant.

Keywords

allenes; [4 + 3] cycloaddition; aziridination; stereodivergence

Densely functionalized seven-membered rings are valuable synthetic targets occurring in a range of bioactive natural products and their analogs (Figure 1). Several approaches 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, potential exists to form multiple new stereocenters in a highly controlled fashion.^[2,3]

Oxyallyl cations are popular coupling partners in [4+3] cyclo-additions; 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 1A).^[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] 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 that transform allenes into a diverse array of amine stereotriads with control over both the identity and relative stereochemistry of the three heteroatoms at C1–3.^[6] We envisaged extending this concept to controlling relative stereochemistry at each of the three original allene carbons in the synthesis of aminated cycloheptenes through a tandem aziridination/[4+3]/reduction sequence (Scheme 1B). This strategy features: 1) a one-pot allene aziridination/ring-opening of the C–N bond of **2** to yield 2-amidoallyl cation **3–4**, 2) intermolecular trapping with inexpensive furan, where the reaction conditions control the relative stereochemistry at C1 and C3 in **5–6** 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** to imines **12** and **13** through the intermediacy of **10** and **11** (Table 1) showed a 1:1 THF/furan mixture successfully transformed **9** to the *endo* [4+3] adduct **12** at rt (entry 2). The *syn* C1–C3 relationship was established by X-ray crystallography (see the SI for details). Reaction in polar aprotic solvents, such as MeCN and MeNO₂ (entries 3–4) did not occur at rt, 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 MeNO₂ at 65 °C, albeit in slightly lower *dr*.

The differing stereochemical outcomes in **12** and **13** using THF or MeNO₂ were intriguing; control experiments showed neither product epimerized under the reaction conditions. Shimizu noted solvent effects on the *dr* of [4+3] cycloadditions of 2-oxyallyl cations; in contrast to our results, MeNO₂ favored 1,3-*syn* products in typical *dr* of 2:1, while THF:Et₂O favored the 1,3-*anti* products, also in low *dr*.^[8] We hypothesize under our reaction conditions, **12** results from rapid addition of furan to **11**, while THF permits equilibration of cation **11** to **10** to relieve A^{1,3} strain, resulting in the *syn* product **12**. This

could occur through rapid reversible addition of the ethereal oxygen to the allyl cation, permitting bond rotation and equilibration to **11** before addition of furan takes place.

The scope of the thermal [4+3] cycloaddition in MeNO₂ was explored first (Table 2). The intermediate imines were reduced using NaBH₃CN, resulting in attack on the imine *via* a pseudo-axial trajectory. Allenes **8** and **14–16**, with monosubstitution at C3 (entries 1–4), delivered **13a–16a** in moderate-to-good *dr*. The additional stereocenter α to C3 in allene **17** (entry 5) exerted an influence on the *dr* of **17a**, resulting in only two major diastereomers in a 4.7:1 ratio.^[9,10]

Gratifyingly, trisubstituted allene **18** (Table 2, entry 6) proved a good substrate for tandem aziridination/cycloaddition to set the all-carbon quaternary stereocenter. While NaBH₃CN gave low conversion, LiBH₄ yielded **18a** in 10:1 *dr*. When the three-step transformation was performed in one pot, residual Rh catalyzed the reduction of the olefin with LiBH₄ to furnish **19a**. Ultimately, we found olefin hydrogenation (entry 7, using Pd/C and H₂) prior to imine reduction gave reproducible high yields of **19a** in excellent *dr*.^[10] The chemistry could even distinguish between a Me and an Et group at C3 of allene **20** to yield **20a** (entry 8) or **21a** (entry 9, Pd/C and H₂ to reduce the alkene) in good *dr*.^[10] Finally, trisubstituted allene **22**, containing an additional stereocenter α to C3, gave **22a** (entry 12) in *dr* comparable to the disubstituted allene **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, AlH₃•Me₂NEt furnished the desired stereochemical outcome. Presumably, AlH₃ binds to the oxygen 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 *dr* and scope (Table 3, entries 1–3) compared to the 1,2-*anti*:2,3-*syn* diastereomers. Alane did not tolerate a Si-protected oxygen in **16** or branching α to C3 in **17** as **16b** and **17b** were observed only in trace amounts (entry 4 and 5). Axial reduction was noted for trisubstituted Allenes (entry 6); despite the lower *dr*, the use of AlH₃•Me₂NEt gave more reproducible access to **18a**, as compared to the use of LiBH₄ (Table 2, entry 6).

The next goal was to improve access to 1,3-*syn* imines of the form **12** (Table 1). Reaction of **8** with a Rh catalyst, followed by [4+3] in THF at 50 °C (entry 2) resulted in only a 31% yield of **12**. A variety of Lewis acids (see the SI for details) were tested, with 10 mol % of AgPF₆ providing optimal results. Adoption of these conditions furnished the 1,3-*syn* imine **30** (Table 4) in typical *dr* > 10:1. To achieve tunable reduction of **30**, we postulated that less bulky hydride sources (NaBH₃CN) should approach from the top face of **30** to favor the 1,2-*anti*:2,3-*anti* diastereomers. In contrast, bulkier reductant such as LiBHEt₃ 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, NaBH₃CN reduced *syn* imines to the *anti:anti* products **13–16c** (Table 4, entries 1, 3, 5, 7) in good-to-excellent *dr*. Switching the reductant to LiBHEt₃ delivered the *syn:syn* products **13–16d** (entries 2, 4, 6, 8), also in good *dr*.

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 SI for details). Nonetheless, the ability to racemize the axial chirality of the allene during the cycloaddition process could be used to advantage to transfer chirality at the sp^3 carbon of **31** to the three carbons of the initial racemic allene to yield **32** (Scheme 2) in moderate *dr* and excellent *ee*.^[10,11]

The cycloheptenes from the tandem allene aziridination/formal [4+3] are flexible scaffolds for further diversification, as **12** has four primary reactive functional handles that can be manipulated (Scheme 3). For example, reduction of **12**, activation of the sulfamate and nucleophilic attack with thiophenol or diethyl malonate delivers **23** and **24** in good yields.^[11,12] Ring contraction to pyrrolidine **25**^[13] 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 regioisomers **26** and **27**.^[14] Dihydroxylation of the alkene yields **28** in high *dr*; this sequence sets seven contiguous stereocenters in high *dr* over four steps from a simple allene.^[10,15] Carbon nucleophiles also add to imine **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 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 analogs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

JMS thanks the NIH 1R01GM111412-01 and NSF-CAREER Award 1254397 for funding. The NMR facilities at UW-Madison are funded by NSF (CHE-9208463, CHE-9629688) and NIH (RR08389-01). The National Magnetic Resonance Facility at UW-Madison is supported by NIH (P41GM103399, S10RR08438, S10RR029220) and NSF (BIR-0214394). Lu Liu, Josh Taylor and Nick Dolan of UW-Madison are thanked for starting materials and assistance with NOE studies. Adrian Amador is acknowledged for his assistance with SFC analyses.

References

1. For selected reviews, see: Nguyen TV, Hartmann JM, Enders D. *Synthesis*. 2013; 45:845. Battiste MA, Pelphrey PM, Wright DL. *Chem. Eur. J.* 2006; 12:3438. [PubMed: 16402402] Pellissier H. *Adv. Synth. Catal.* 2011; 353:189. Foley DA, Maguire AR. *Tetrahedron*. 2010; 66:1131.
2. For reviews dedicated to [4+3] cycloadditions, see Hartung IV, Hoffmann HMR. *Angew. Chem. Int. Ed.* 2004; 43:1934. Harmata M. *Acc. Chem. Res.* 2001; 34:595. [PubMed: 11456477] Harmata M.

- Chem. Comm. 2010; 46:8886. [PubMed: 21057692] Hoffmann HMR. Angew. Chem. Int. Ed. 1984; 23:1.
3. For selected reviews on heteroatom-substituted allyl cations in [4+3] cycloadditions, see: Lohse AG, Hsung RP. Chem. Eur. J. 2011; 17:3812. [PubMed: 21384451] Harmata M. Chem. Comm. 2010; 46:8904. [PubMed: 21063614]
4. a) Kende AS, Huang H. Tetrahedron Lett. 1997; 38:3353.b) Schmid R, Schmid H. Helv. Chim. Acta. 1981; 64:813.c) Robertson J, Feast GC, White LV, Steadman VA, Claridge TDW. Org. Biomol. Chem. 2010; 8:3060. [PubMed: 20480094] d) Prié G, Prévost N, Twin H, Fernandes SA, Hayes JF, Shipman M. Angew. Chem. Int. Ed. 2004; 43:6517.
5. For recent examples of reactions believed to occur through the intermediacy of 2-amidoallyl cations, see: Stoll AH, Blakey SB. Chem. Sci. 2011; 2:112. Stoll AH, Blakey SB. J Am. Chem. Soc. 2010; 132:2108. [PubMed: 19968304] Thorton AR, Martin VI, Blakey SB. J Am. Chem. Soc. 2009; 131:2434. [PubMed: 19193003]
6. a) Adams CS, Grigg RD, Schomaker JM. Chem. Sci. 2014; 5:3046.b) Adams CS, Grigg RD, Schomaker JM. Tetrahedron. 2014; 70:4128.c) Adams CS, Boralsky LA, Guzei IA, Schomaker JM. J Am. Chem. Soc. 2012; 134:10807. [PubMed: 22708990]
7. For examples of generating 2-oxyallyl cations from allenes and their use in [4+3] cycloadditions, see: Fernández I, Mascareñas JL. Org. Biomol. Chem. 2012; 10:699. [PubMed: 22159300] Xiong H, Hsung RP, Berry CR, Rameshkumar C. J Am. Chem. Soc. 2001; 123:7174. [PubMed: 11459504] Huang J, Hsung RP. J Am. Chem. Soc. 2005; 127:50. [PubMed: 15631443] Lohse AG, Hsung RP, Leider MD, Ghosh SK. J Org. Chem. 2011; 76:3246. [PubMed: 21449577]
8. Shimizu N, Tanaka M, Tsuno Y. J Am. Chem. Soc. 1982:1330.
9. For examples of stereocenters adjacent to either the diene or the 2-oxyallyl cation affecting the *dr* of a [4+3] cycloaddition, see: Giguere RJ, Tasseley SM, Tose MI. Tetrahedron Lett. 1990; 31:4577. Lautens M, Aspiotis R, Colucci J. J Am. Chem. Soc. 1996; 118:10930. Chung WK, Lam SK, Lo B, Liu LL, Wong W-T, Chiu P. J Am. Chem. Soc. 2009; 131:4556. [PubMed: 19281161] Cho SY, Lee JC, Cha JK. J Org. Chem. 1999; 64:3394. [PubMed: 11674457] Harmata M, Rashatasakhon P. Org. Lett. 2000; 2:2913. [PubMed: 10964397] Stark CBW, Eggert U, Hoffmann HMR. Angew. Chem. Int. Ed. 1998; 37:1266. Harmata M, Jones DE, Kahraman M, Sharma U, Barnes CL. Tetrahedron Lett. 1999; 40:1831. Montaña AM, Grima PM. Tetrahedron Lett. 2002; 43:2017.
10. The relative stereochemistry of product was determined by NOE studies.
11. Duran F, Leman L, Ghini A, Burton G, Dauban P, Dodd RH. Org. Lett. 2002; 4:2481. [PubMed: 12123356]
12. a) Bower JF, Švenda J, Williams AJ, Charmant JPH, Lawrence RM, Szeto P, Gallagher T. Org. Lett. 2004; 6:4727. [PubMed: 15575671] b) Moss TA, Alonso B, Fenwick DR, Dixon DJ. Angew. Chem. Int. Ed. 2010; 49:568.
13. For examples of pyrrolidine formation, see ref. [6a] Thorton AR, Martin VI, Blakey SB. J Am. Chem. Soc. 2009; 131:2434. [PubMed: 19193003]
14. Lautens M, Abd-El-Aziz AS, Lough A. J Org. Chem. 1990; 55:5305.
15. He S, Hsung RP, Presser WR, Ma Z-X, Haugen BJ. Org. Lett. 2014; 16:2180. [PubMed: 24701990]

Figure 1.

Bioactive natural products with seven-membered carbocyclic cores.

A Previous work

Blakey

Robertson

Shipman

B This work **Scheme 1.**Stereochemical diversity *via* allene aziridination.

Scheme 2.
Enantioenriched cycloheptenes *via* [4 + 3] reactions.

Scheme 3.

Synthetic utility of cycloheptene products.

a: NaBH₃CN, AcOH, MeCN; 41%, 16:1 *dr* from **8**. *b*: Boc₂O, cat. DMAP, Et₃N, CH₂Cl₂, rt.
c: thiophenol, K₂CO₃, CH₃CN, rt; 75% from **13**. *d*: diethyl malonate, TBAB, Cs₂CO₃, MeCN, rt; 58% from **13**. *e*: KO*t*-Bu, DMAP, CH₂Cl₂, 0 °C, then Ac₂O, rt; 96%. *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% OsO₄, NMO, acetone, H₂O, *t*-BuOH, rt; 65%, >20:1 *dr*. *i*: *n*-Bu₄NCN, MeCN, rt; 80% yield from **12**.

Table 1

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

co-solvent	entry	% yield at 24 h, rt ^{a,b}	12:13	% yield at 24 h, 50 °C ^b	12:13
none	1	0	-	-	-
THF	2	35	> 20:1	31	> 10:1
MeCN	3	0	-	21	~1:3
MeNO₂^c	4	0	-	31	< 1:10
CF ₃ CH ₂ OH	5	0	-	26	< 1:10

Table 2

Scope of the [4+3] reaction in MeNO₂ using NaBH₃CN as reductant.

entry	product	yield, dr (3 steps/one-pot)	entry	product	yield, dr (3 steps/one-pot)
1		41% 4.7:1	6		28% 10:1 ^a
2		33% 6.7:1	7		54% 53:4:4:1 ^b
3		46% 4.3:1	8		34% 6:1 ^c
4		52% 4.2:1	9		62% 19:4:1:1 ^b
5		38% 4.7:1	10		41% 3.4:1 ^b

Table 3

Scope of the [4+3] in MeNO₂ with AlH₃•Me₂NEt as the reductant.

entry	product	yield, dr (3 steps)	entry	product	yield, dr (3 steps)
1		30% 4.9:1.1:1	4		trace N/A
2		29% 4.9:1	5		trace N/A
3		46% 12:2:2:1	6		36% ^b 3:1

Table 4

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

entry	product	yield, <i>dr</i> (3 steps)	entry	product	yield, <i>dr</i> (3 steps)
1		<i>anti:anti</i> 41% 13c 16:1	5		<i>anti:anti</i> 29% 15c 3.2:1
2		<i>syn:syn</i> 30% 13d 10:1	6		<i>syn:syn</i> 22% 15d 7.5:1
3		<i>anti:anti</i> 26% 14c 10:1	7		<i>anti:anti</i> 46% 16c 18:1
4		<i>syn:syn</i> 20% 14d 15:1	8		<i>syn:syn</i> 34% 16d 11:1