Synthetic Methods

International Edition: DOI: 10.1002/anie.201509983
German Edition: DOI: 10.1002/ange.201509983

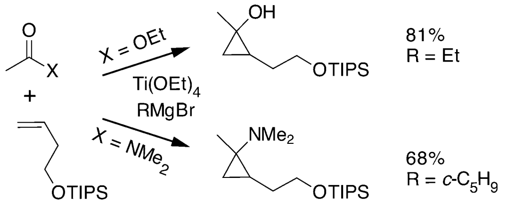
Carbocyclic Amino Ketones by Bredt's Rule-Arrested Kulinkovich–de Meijere Reaction

*Paul B. Finn, Brenden P. Derstine, and Scott McN. Sieburth**

Abstract: *The Ti^{II}-mediated formation of cyclopropylamines from alkenes and amides, the Kulinkovich–de Meijere reaction, involves two carbon–carbon bond-forming steps. Strategic use of a tricyclic intermediate can arrest the process if the second step requires formation of a bridgehead double bond. Use of this Bredt's rule constraint results in the production of carbocyclic amino ketones, key alkaloid building blocks.*

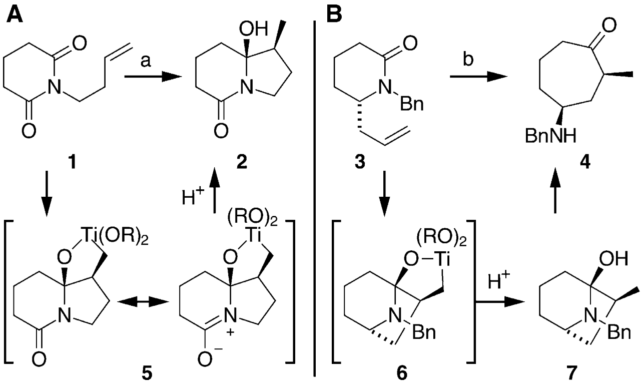
Bredt's rule, the observation that double bonds cannot include bridgehead atoms, has been a cornerstone of organic chemistry since its enumeration in 1924.[1,2] This rule is routinely used to illustrate the concepts of orbital overlap and to explain reactivity in polycyclic molecules, but it has rarely been employed to steer reaction pathways outside of elimination and enolization chemistry.[3]

The extraordinary coupling of an alkene and an ester to give cyclopropanols, mediated by low-valent titanium, has been extensively studied since its discovery in 1989 by Kulinkovich, and was extended to tertiary amides in 1996 by de Meijere to yield cyclopropylamines (Scheme 1).[4–6]



Scheme 1. Kulinkovich (X = OEt) and Kulinkovich–de Meijere (X = NMe$_2$) reactions.[4]

These powerful transformations have been pivotal in syntheses of natural products and pharmaceutical agents.[7] Two sequential carbon–carbon bond forming steps occur in this reaction, and interception of the intermediate can allow the reaction to take alternative pathways, including use of the remaining carbon–titanium bond. The Cha group demonstrated that the Kulinkovich reaction path could be interrupted if an imide substrate was employed, e.g., **1** (Scheme 2A).[8] In this example, following the initial imide carbonyl addition, delocalization of the amide nitrogen electron density stabilizes intermediate **5**, averting cyclopropane formation.



Scheme 2. Interrupted Kulinkovich–de Meijere reactions. A) Cha's imide substrates.[8] B) This work. Reagents and conditions: a) ClTi(O*i*-Pr)$_3$, *c*-C$_5$H$_9$MgBr, THF, rt, 44%; b) Ti(O*i*-Pr)$_4$, *c*-C$_5$H$_9$MgBr, THF, rt, 85%.

An alternative and unexplored strategy involves use of a substrate that would create a bridged intermediate incapable of titanium alkoxide departure. We have found that the readily prepared 6-allyl-2-piperidinone **3** will undergo transannular cyclization under standard Kulinkovich conditions to yield tricyclic **6** (Scheme 2B). Advancement of intermediate **6** to give the normal cyclopropane product would require formation of a bridgehead double bond to nitrogen, but such a nitrogen-assisted elimination of the titanium alkoxide would violate Bredt's rule. Thus confined, intermediate **6** gave, on workup, the *cis*-4-amino-2-methyl cycloheptanone **4** in good yield and as the only product. No trace of a corresponding cyclopropylamine was detected. The ability to transform amides to amino ketones has clear potential in synthesis.[9] We describe here our initial investigation of this new approach to producing these important building blocks.

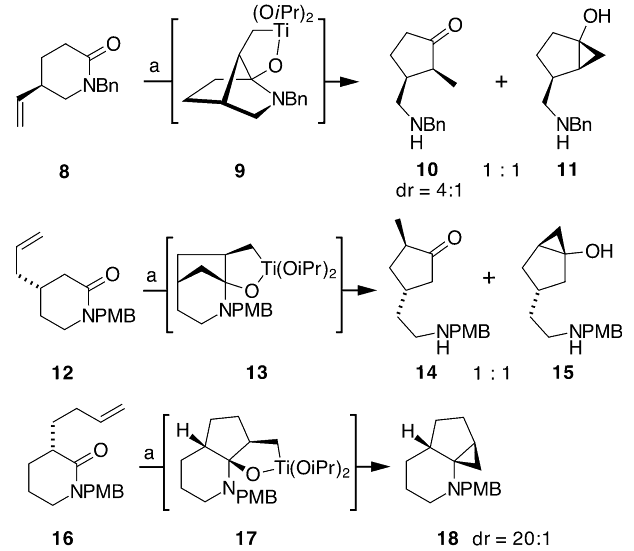
Following the demonstration that ene-amide **3** would undergo the initial carbon–carbon bond-formation of the Kulinkovich–de Meijere reaction, despite the need for transannular attack, we investigated three additional examples in which the alkene was attached at the other positions around the ring (Scheme 3). Each of these reactions would form a tricyclic intermediate incorporating a five-membered carbocycle through coupling of the internal alkene carbon and the amide carbonyl. For 5- and 4-substituted piperidinones **8** and **12**, two products were formed, the now expected amino ketones **10** and **14**, as well as unexpected aminocyclopropanols **11** and **15**. With the 3-(3-butenyl) substitution in **16**, cyclopropylamine **18** was isolated in good yield.

---

[*] P. B. Finn, B. P. Derstine, Prof. S. McN. Sieburth
Department of Chemistry, Temple University
1901 N. 13th St., Philadelphia, PA 19122 (USA)
E-mail: scott.sieburth@temple.edu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509983.

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 3. Reaction of alkenes at other positions around the piperidinone. Reagents and conditions: a) Ti(O*i*-Pr)$_4$, *c*-C$_5$H$_9$MgBr, THF, rt, (33 % for **10**, 40 % for **14**+**15**, 73 % for **18**).

These examples further illustrate the Bredt's rule effect. Substrate **16** leads to intermediate **17** that can readily eliminate the titanium alkoxide and form an unstrained iminium ion, leading to the normal Kulinkovich–de Meijere product **18** in good yield and with a high degree of stereocontrol.[10] In contrast, the bridged, polycyclic intermediates **9** and **13** from **8** and **12**, cannot eliminate the alkoxide, yielding amino ketones **10** and **14** on workup. The surprising formation of aminocyclopropanol products **11** and **15** are also consequences of Bredt's rule. These are among the first examples of aminocyclopropanols formed during a Kulinkovich–de Meijere reaction and the proportion of cyclopropanol products in Scheme 3 are some of the highest for the substrates we have examined.[11] Departure of the anionic amine group from **9** and **13** was unexpected but the intermediate oxonium ions, leading to cyclopropanols **11** and **15**, are relatively unstrained and therefore accessible. The diminished yields for the reactions of **8** and **12** are likely a consequence of the strain of the intermediates **9** and **13**.

In his seminal review of Bredt's rule, Fawcett defined the term *S* as the sum of the bridging atoms of a bicyclic system, $x+y+z$ (Figure 1).[3] Using that analysis, he determined that when the sum of the bridging atoms totalled less than nine, providing that none of the bridges had a length of zero, a bridgehead alkene would be too strained to form. For bicyclic **19**, the iminium ion potentially derived from intermediate **13**, the ring system is too small to accommodate the double bond. In contrast, for iminium ion **20** derived from **17**, bridge *y* has a length of zero and the iminium ion is therefore easily formed and leads to product **18**.

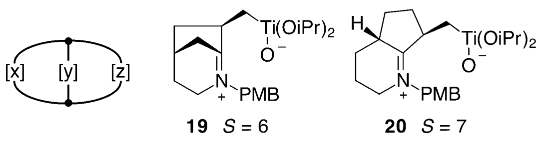
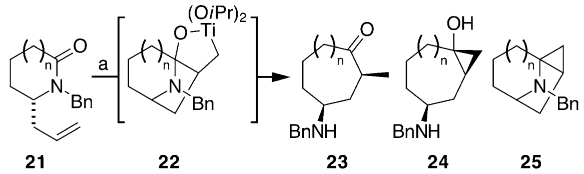


Figure 1. $S = x+y+z$.

To test the limits of this approach to interception of the Kulinkovich–de Meijere intermediate we have probed alternative *S* values in homologues of **3** and **12** (Table 1 and Table 2). For the ω-allyl lactams, varying the lactam ring size from five to nine, **21a** to **21e**, changes the *S* value for the intermediate **22** from five to nine (Table 1). With the exception of the nine-membered lactam substrate **21e**, the yields are uniformly good. For lactam ring sizes between five and seven-membered, **21a–c** with $S=5$–7, only **23** and **24** are produced, with the amino ketone **23** making up 66–100 % of the product mixture, without formation of cyclopropylamine **25**. When the *S* value of **22** reaches 8 however, Bredt's rule can be violated and there is an abrupt changeover, with **21d** and **21e** giving only aminocyclopropanes **25d** and **25e** as products.

Table 1: Kulinkovich–de Meijere reaction with ω-allyl lactams.



	n	*S*[b]	Yield [%][c]	Ratio **23**:**24**:**25**[d]
a	0	5	65	5:1:0
b	1	6	85	1:0:0
c	2	7	60	2:1:0
d	3	8	73	0:0:1
e	4	9	34	0:0:1

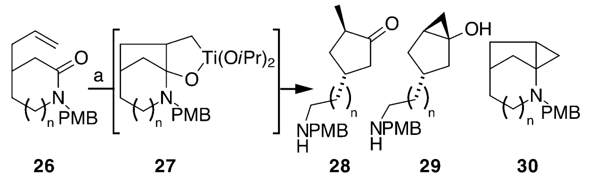
[a] Reagents and conditions: Ti(O*i*-Pr)$_4$, *c*-C$_5$H$_9$MgBr, THF, rt. [b] Total number of bridging atoms in **22**.[3] [c] Isolated yields. [d] **21b**, **23b** = 3, 4.

With an allyl group beta to the carbonyl, **26**, cyclization between the alkene and the amide carbonyl also forms a five-membered ring (**27**, Table 2). This cyclization leads to a cyclopentanone product **28** with a side chain carrying a secondary amine. In the example of intermediate **27a** with $S=6$, Bredt's rule prevents formation of a cyclopropylamine; only amino ketone **28a** and cyclopropanol **29a** are observed, with the former comprising 50 % of the mixture. With **26c** and **26d**, $S=8$ and 9 respectively, the *S* value is compatible with a bridgehead double bond and iminium ion formation and cyclopropylamines **30c** and **30d** were the only products formed. For the intermediate case of **26b** where $S=7$, the product mixture is difficult to purify and appears to be largely cyclopropanol **29b**. This may be a consequence of a strained transition structure in these transannular reactions.

Two additional examples with $S=7$ intermediates are shown in Scheme 4. These Bredt's rule-arrested transformations utilize the smaller lactams with longer alkenyl chains. For piperidinone **31** carrying a 4-(1-butene) beta to the carbonyl, cyclization was expected to lead to an azabicyclo[3.3.1]nonane framework. The result was formation of cyclohexanone **33** and cyclopropanol **34**, favouring the former. Similarly, a pentenyl chain attached adjacent to the nitrogen

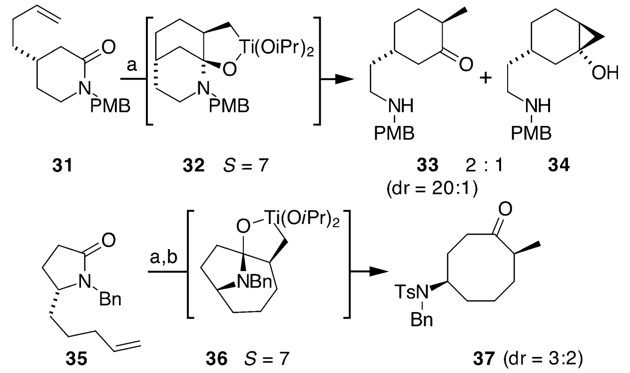
© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 2: Kulinkovich–de Meijere reaction with β-allyl lactams.

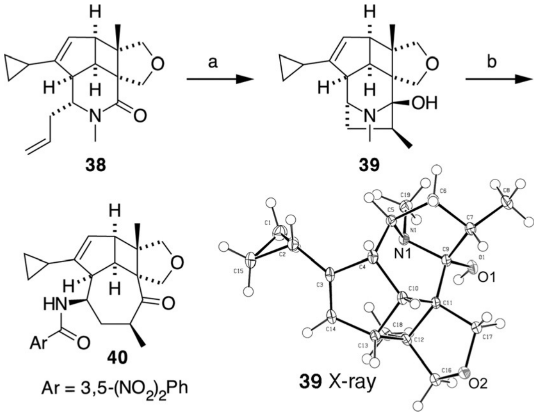


	n	*S*[b]	Yield [%][c]	Ratio **28:29:30**[d]
a	1	6	40[e]	1:1:0
b	2	7	–	See text
c	3	8	64	0:0:1
d	4	9	75	0:0:1

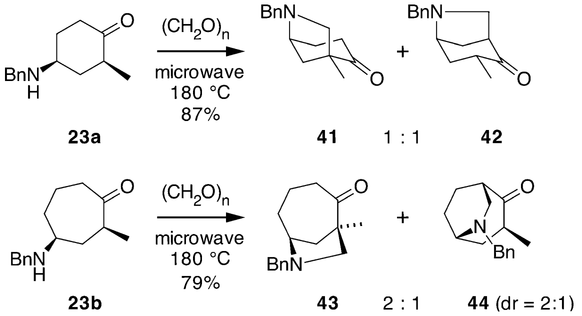
[a] Reagents and conditions: Ti(O*i*-Pr)$_4$, *c*-C$_5$H$_9$MgBr, THF, rt. [b] Total number of bridging atoms in **27**.[3] [c] Isolated yields. In some cases the amines were derivatized before isolation, see Supporting Information for details. [d] **26a**, **28a**, **29a** = **12**, **14**, **15**. [e] Isolated yield of **28a**.



Scheme 4. Changes in side chain length. Reagents and conditions: a) Ti(O*i*-Pr)$_4$, *c*-C$_5$H$_9$MgBr, THF, rt, b) TsCl, pyridine (40% for **33**: 27% for **37** as a 3:2 mixture of diastereomers).



Scheme 5. Polycyclic substrate. Reagents and conditions: a) Ti(O*i*-Pr)$_4$, *c*-C$_5$H$_9$MgBr, THF, rt, 93%; b) 3,5-(O$_2$N)$_2$C$_6$H$_3$COCl, Et$_3$N, 75%.



Scheme 6. Intramolecular Mannich reaction of **23a** and **23b**.

of a 2-pyrrolidinone was expected to form an azobicyclo[4.2.1]nonane intermediate. This transformation yields only the cyclooctanone **37**, albeit in modest yield.

Complex structures are also compatible with these reaction conditions and may benefit from the additional structural rigidity (Scheme 5). Tetracyclic substrate **38**,[12] under standard conditions, yields the pentacyclic product **39** in near quantitative yield. In this case the product is stable as the aminal, a structure confirmed by X-ray crystallography. Treatment of this aminal with 2,5-dinitrobenzoyl chloride gave the corresponding ketoamide **40** in quantitative yield, also confirmed by an X-ray structure analysis (see Supporting Information).

These amino ketone products can be elaborated using the Mannich reaction. Microwave heating of aminocyclohexanone **23a** with paraformaldehyde resulted in a high yield of Mannich products **41** and **42** (Scheme 6), despite the inherently poor orbital overlap of a 5-*endo*-trig cyclization.[13,14] Homologous ketone **23b** under identical conditions yields bicyclics **43** and **44**, favouring quaternary **43**.

The intermediate formed during the two-step Kulinkovich–de Meijere cyclopropanation can be prevented from consummating the second step if the substrate leads to a bicyclic structure incapable of the requisite elimination. This Bredt's rule constraint allows the reaction to convert alkene-substituted lactams into amino-substituted carbocyclic ketones under mild conditions and in some cases with a high degree of stereocontrol. The examples here have even greater potential in the form of the second and unused carbon–titanium bond.

Acknowledgements

We gratefully acknowledge support from the National Science Foundation (CHE-1152159). We also thank Professor Michael J. Zdilla, Clifton R. Hamilton and Charles M. Stockdale for the crystal structures.

Keywords: amino ketones · Bredt's rule · Kulinkovich reaction · Mannich reaction · titanium

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 2536–2539
Angew. Chem. **2016**, *128*, 2582–2585

---

[1] J. Bredt, *Justus Liebigs Ann. Chem.* **1924**, *437*, 1–13.
[2] E. H. Krenske, C. M. Williams, *Angew. Chem. Int. Ed.* **2015**, *54*, 10608–10612; *Angew. Chem.* **2015**, *127*, 10754–10758.
[3] Reviews: F. S. Fawcett, *Chem. Rev.* **1950**, *47*, 219–274; V. Prelog, *J. Chem. Soc.* **1950**, 420–428; G. Köbrich, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 464–473; *Angew. Chem.* **1973**, *85*, 494–503; G. L. Buchanan, *Chem. Soc. Rev.* **1974**, *3*, 41–63; R. Keese, *Angew.*

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Chem. Int. Ed. Engl. **1975**, *14*, 528 – 538; *Angew. Chem.* **1975**, *87*, 568 – 578; K. J. Shea, *Tetrahedron* **1980**, *36*, 1683 – 1715; P. M. Warner, *Chem. Rev.* **1989**, *89*, 1067 – 1093; B. R. Bear, S. M. Sparks, K. J. Shea, *Angew. Chem. Int. Ed.* **2001**, *40*, 820 – 849; *Angew. Chem.* **2001**, *113*, 864 – 894; Ref. [2].

[4] J. K. Cha, O. G. Kulinkovich, *Org. React.* **2012**, *77*, 1 – 159; J. C. Lee, M. J. Sung, J. K. Cha, *Tetrahedron Lett.* **2001**, *42*, 2059 – 2061; J. Lee, J. K. Cha, *J. Org. Chem.* **1997**, *62*, 1584 – 1585.

[5] O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, T. S. Pritytskaya, *Zh. Org. Khim.* **1989**, *25*, 2244 – 2245; O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, A. I. Savchenko, T. S. Pritytskaya, *Zh. Org. Khim.* **1991**, *27*, 294 – 298.

[6] V. Chaplinski, A. de Meijere, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 413 – 414; *Angew. Chem.* **1996**, *108*, 491 – 492; A. De Meijere, V. Chaplinski, A. Kourdioukov (Bayer AG), DE-19647615, **1998**.

[7] Review: I. Haym, M. A. Brimble, *Org. Biomol. Chem.* **2012**, *10*, 7649 – 7665; Selected examples: J. S. Kingsbury, E. J. Corey, *J. Am. Chem. Soc.* **2005**, *127*, 13813 – 13815; F. Lecornué, R. Paugam, J. Ollivier, *Eur. J. Org. Chem.* **2005**, 2589 – 2598; O. Lack, R. E. Martin, *Tetrahedron Lett.* **2005**, *46*, 8207 – 8211; C. A. Faler, M. M. Joullié, *Org. Lett.* **2007**, *9*, 1987 – 1990; K. A. Keaton, A. J. Phillips, *Org. Lett.* **2007**, *9*, 2717 – 2719; C. Madelaine, O. Buriez, B. Crousse, I. Florent, P. Grellier, P. Retailleau, Y. Six, *Org. Biomol. Chem.* **2010**, *8*, 5591 – 5601.

[8] J. Lee, J. D. Ha, J. K. Cha, *J. Am. Chem. Soc.* **1997**, *119*, 8127 – 8128; S.-H. Kim, Y. Park, H. Choo, J. K. Cha, *Tetrahedron Lett.* **2002**, *43*, 6657 – 6660; S. Santra, N. Masalov, O. L. Epstein, J. K. Cha, *Org. Lett.* **2005**, *7*, 5901 – 5904.

[9] See: A. Gomtsyan, *Org. Lett.* **2000**, *2*, 11 – 13; S. Baktharaman, R. Hili, A. K. Yudin, *Aldrichimica Acta* **2008**, *41*, 109 – 119, and references therein.

[10] The *cis* fusion of **18** was determined by nOe studies.

[11] Reactions of *N*-acylated Oppolzer's sultam have been found to yield cyclopropanols. R. Mizojiri, H. Urabe, F. Sato, *Angew. Chem. Int. Ed.* **1998**, *37*, 2666 – 2668; *Angew. Chem.* **1998**, *110*, 2811 – 2814.

[12] P. B. Finn, S. Kulyk, S. McN. Sieburth, *Tetrahedron Lett.* **2015**, *56*, 3567 – 3570.

[13] J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, R. C. Thomas, *J. Chem. Soc. Chem. Commun.* **1976**, 736 – 738.

[14] C. P. Johnston, A. Kothari, T. Sergeieva, S. I. Okovytyy, K. E. Jackson, R. S. Paton, M. D. Smith, *Nat. Chem.* **2015**, *7*, 171 – 177.

Received: October 26, 2015
Published online: January 14, 2016

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim