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Lanthanide(III)-Catalyzed Synthesis of *trans*-Diaminocyclopentenones from Substituted Furfurals and Secondary Amines via a Domino Ring-Opening/4π-Electrocyclization Pathway

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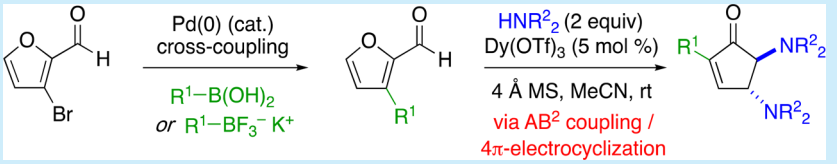
Supporting Information



ABSTRACT: A strategy toward the synthesis of *trans*-4,5-diaminocyclopent-2-enones is described. This core motif is embedded in the marine sponge derived alkaloids agelamadin B and nagelamide J. A variety of 2-substituted *trans*-4,5-diaminocyclopent-2-enones were synthesized in good to quantitative yields using lanthanide(III) catalysis. The products were formed exclusively as the *trans*-diastereomers via a mechanism in which the C4−C5 bond formation occurs through a 4π-conrotatory electrocyclization. The precursor 3-substituted furfurals can be readily accessed using palladium(0)-catalyzed cross-coupling between 3-bromofurfural and boronic acids, trifluoroborate salts, or alkynes.

Highly substituted cyclopentanes are found in a large number of diverse, biologically active natural products and their analogues. The rapid and stereoselective synthesis of cyclopentanes has therefore been the subject of considerable attention among the synthetic organic chemistry community.[1] One important and synthetically extremely challenging class of such compounds is the diaminocyclopentanes. Examples of natural products that incorporate a *trans*-1,2-diaminocyclopentane include the marine sponge derived alkaloids agelastatin A (**1**),[2−4] agelamadins A (**2a**) and B (**2b**),[5] nagelamide J (**3**),[6] the *Streptomyces*-derived pactamycin (**4**)[7,8] and related antibiotic aminocyclopentitols (Figure 1).[9] Agelastatin A, in particular, has been the subject of considerable interest due to its interesting structural features and biological activity.[3,4] The biosynthetically related natural products[10] agelamadins A and B and nagelamide J share many common features with agelastatin, including the key *trans*-1,2-diaminocyclopentane core and bromopyrrole amide functional unit. These molecules also incorporate an additional functionalized aminoimidazole ring appended to the cyclopentane core, while the urea functional group present in agelastatin A is replaced by a guanidine group in **2** and **3**.

The marine sponge alkaloids **1**−**3** thus constitute formidable targets due to the presence of a densely functionalized cyclopentane core, with three to five contiguous stereocenters and unusual bromopyrrole and aminoimidazole heterocycles.[10] Inspired by this structural complexity and the associated antitumor and antimicrobial activity of these alkaloids, we are interested in establishing general synthetic routes to this group of alkaloids. We now report the development of a domino reaction[11] for the synthesis of aryl-substituted *trans*-diaminocyclopentenones from substituted furfurals and secondary amines using lanthanide(III) catalysis, providing the first such approach to the underlying diaminocyclopentenone structure of the agelamadin and nagelamide alkaloids.

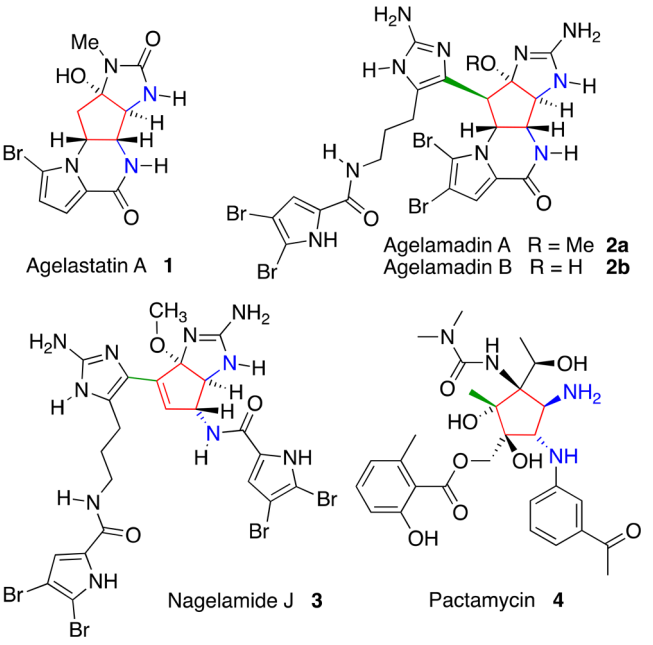


Figure 1. Natural products containing a *trans*-1,2-diaminocyclopentane motif.

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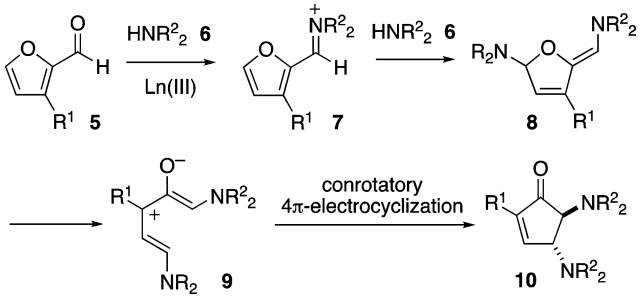
Previous studies in our group had demonstrated the feasibility of using an AB^2 coupling[12]/electrocyclization[13] route to synthesize the core *trans*-1,2-diaminocyclopentane structure embedded within agelastatin A.[3o,14] Mechanistically, the reaction proceeds via a domino condensation/ring-opening/ring-closure process of 2-furaldehyde or furfural **5a** (R^1 = H) and a secondary amine **6** (Scheme 1). The addition of a second

Scheme 1. Proposed Electrocyclization Mechanism for the Lewis Acid Catalyzed Reaction between 2-Furaldehydes 5 and Secondary Amines

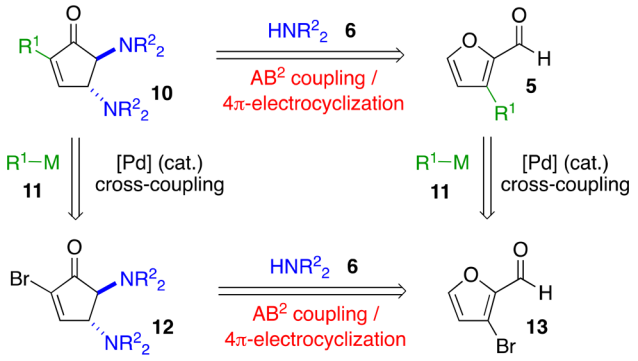


equivalent of secondary amine at the 5-position of the initially formed iminium ion **7**, followed by ring-opening of **8**, generates the conjugated zwitterion **9**.[15] The key ring closure then proceeds to give the product **10**, which is only isolated as the *trans*-diastereomer, consistent with a mechanism involving conrotatory $_\pi4_a$-electrocyclic ring closure of **9** (R^1 = H).[14,16] The electrocyclization reaction is related to the well-known Nazarov cyclization.[17] Our initial studies demonstrated that the use of catalytic Lewis acids such as lanthanide(III) salts [e.g., Dy(OTf)$_3$] facilitates this reaction.[18] Subsequent work has established the use of other catalysts to effect this transformation,[19] the use of dysprosium(III)-catalyzed conditions for the formation of 4-hydroxycyclopent-2-enones via the related Piancatelli reaction,[20] and the formation of 4-aminocyclopent-2-enones via the reaction of 2-furylcarbinols with amines (the aza-Piancatelli reaction).[21]

We envisaged an analogous approach to the alkaloids agelamadin B and nagelamide J in which the differentially functionalized core embedded within **2** and **3** would be accessible from the diaminocyclopentenone **10** ($R^1 \neq$ H). The appended functionalized aminoimidazole moiety of these molecules would necessitate the use of a 3-substituted furfural precursor in the domino ring-opening/electrocyclization reaction. Examples of this reaction using substituted furfurals have not been achieved previously (i.e., for reaction of **5**, $R^1 \neq$ H). However, it is noteworthy that examples of the Piancatelli reaction, using 3- and 4-substituted furyl carbinols under Lewis acidic conditions [Ca(NTf$_2$)$_2$],[22] and the use of bromo-substituted substrates in 4π-electrocyclizations have been reported.[23]

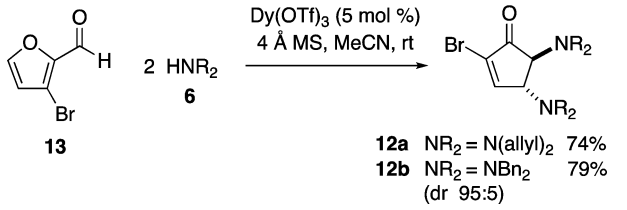
Therefore, our aim in the current study was to establish the feasibility of the AB^2 coupling[24]/electrocyclization route for the formation of diaminocyclopentenones **10** ($R^1 \neq$ H) from 3-substituted furfurals. Initially, we envisaged a late-stage incorporation of the R^1 group in **10** from an organometallic derivative **11** and the corresponding substituted 2-bromodiaminocyclopentenone **12** accessible from the precursor 3-bromofurfural **13** (Scheme 2). Treatment of commercially available 3-bromofuran with sodium hexamethyldisilazide (NaHMDS) and DMF afforded precursor 3-bromofurfural

Scheme 2. Dual synthetic routes toward 10



13.[25] Reaction of **13** under lanthanide triflate catalysis afforded adducts **12a** and **12b** in good yield as the *trans*-diastereomers (≥95:5 by ^{1}H NMR) (Scheme 3), consistent with a $_\pi4_a$

Scheme 3. Lewis acid catalyzed formation of 12



conrotatory electrocyclization of the intermediate **9** (R^1 = Br). Diallylamine or dibenzylamine was chosen as a secondary amine to provide opportunities for deprotection to a primary amine functional group and subsequent functionalization.[3o] In our initial 2007 report[14] on the reaction of furfural **5a** (R^1 = H), 10 mol % of Dy(OTf)$_3$ was used to effect the transformation. However, it was possible to use only 5 mol % of Dy(OTf)$_3$ with a 2:1 stoichiometry of **6**/**5** to provide the 3-substituted products **12** without any detectable decrease in yields or reaction times.[26]

Preliminary attempts using palladium(0) catalysis revealed **12** to be a challenging substrate for cross-coupling reactions (e.g., reactions using Pd(PPh$_3$)$_4$ and arylboronic acids under standard conditions did not result in product formation). Therefore, an alternative approach was explored in which the order of steps for cyclopentenone formation and cross-coupling were reversed. Thus, converting **13** to **5** ($R^1 \neq$ H) followed by domino ring-opening/electrocyclization with **6** would give **10** (Scheme 2). It was first necessary to establish appropriate conditions for the formation of substituted furfurals **5**.[27] A simple alkyl-substituted example, 3-methylfurfural **5a**, was synthesized by the reduction of methyl 3-methyl-2-furoate with lithium aluminum hydride, followed by oxidation with manganese(IV) oxide.[28] For other 3-substituted furfurals, a Pd(0)-catalyzed cross-coupling approach between **13** and boron compounds was utilized (Table 1). Optimal palladium-catalyzed conditions were established for the Suzuki–Miyaura coupling[29] of **13** with both arylboronic acids and aryl and heteroaryltrifluoroborate salts[30] using a variety of ligand/base/Pd sources (Table 1, conditions A–C).[31] In addition to the aryl- and heteroaryl-substituted furfurals **5b–h**, an example of alkynyl-substituted compound **5i** was generated by Sonogashira coupling (Table 1, conditions D). The aldehydes **5** constitute useful synthetic building blocks worthy of further investigation.

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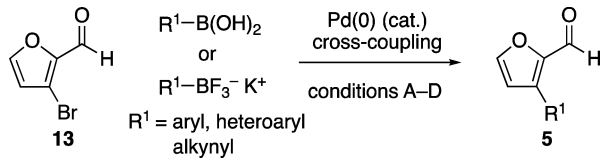
Table 1. Formation of 3-Substituted 2-Furaldehydes 5



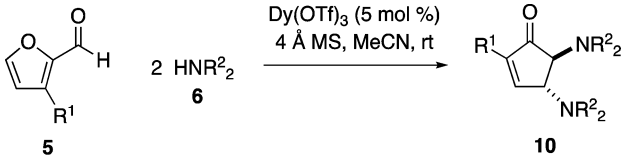
entry	R^1/precursor	conditions[a]	R^1/product	yield (%)
1	C_6H_5	**A**	**5b**	75
2	*p*-MeC_6H_4	**B**	**5c**	quant
3	*p*-$MeOC_6H_4$	**B**	**5d**	58
4	*p*-FC_6H_4	**A**	**5e**	74
5	*o*-MeC_6H_4	**A**	**5f**	48
6	4-pyridyl	**C**	**5g**	45
7	2-thienyl	**C**	**5h**	74
8	ethynyl TMS	**D**	**5i**	64

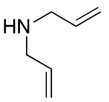
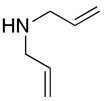
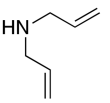
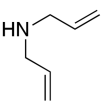
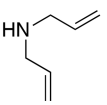
[a]Conditions A: $Pd(OAc)_2$ (0.5 mol %), $ArBF_3K$ (1.3 equiv), K_2CO_3 (3.0 equiv), MeOH, reflux. Conditions B: $PdCl_2(PPh_3)_2$ (1.7 mol %), $ArB(OH)_2$ (1.5 equiv), K_2CO_3 (2.5 equiv), DMF/H_2O (3:1), 75 °C. Conditions C: $Pd(OAc)_2$ (3 mol %), RuPhos (6 mol %), $HetArBF_3K$ (1.1 equiv), Na_2CO_3 (2.0 equiv), EtOH, reflux. Conditions D: $PdCl_2(PPh_{32})$ (5 mol %), CuI (5 mol %), $HCCSi(CH_3)_3$ (1.2 equiv), NEt_3 (1.4 equiv), THF, 60 °C.

A variety of secondary amines were found to provide the 2-substituted *trans*-4,5-diaminocyclopent-2-enones **10** in good to quantitative yields as the *trans*-diastereomers (≥95:5 by ^{1}H NMR) using the standard conditions[26] and 3-substituted 2-furaldehydes **5** as precursors (Table 2). The sterically least encumbered substituted precursor, 3-methylfurfural **5a**, was converted to give **10a** (R^1 = CH^3, NR^2_2 = morpholine) in quantitative yield. 3-Phenylfurfural was converted in good yields to adducts **10b** and **10c** (Table 2, entries 2 and 3). Various substituted 3-arylfurfurals **5c−f** also underwent reactions using a variety of acyclic and cyclic secondary amines to give products **10d−j** (Table 2, entries 4−10). In addition, heteroaryl functional units were also tolerated, as exemplified in the formation of the 4-pyridyl- and 2-thienyl-substituted products **10k** and **10l**, respectively (Table 2, entries 11 and 12). Finally, the TMS-alkynyl-substituted furfural **5i** only afforded a relatively low yield of **10m** (Table 2, entry 13).[32] In general, yields of the diallylamine-derived adducts were slightly lower than those of the other adducts (e.g., **10b** versus **10c**, **10d** versus **10e**).

In conclusion, we have demonstrated that 3-substituted furfurals undergo a domino condensation/rearrangement process with secondary amines. 2-Substituted diaminocyclopentenone products **10** and **12** are obtained in good to quantitative yields, exclusively as the *trans*-diastereomers, through a $_\pi4_a$ conrotatory electrocyclization mechanism that is analogous to the Nazarov cyclization. The precursor 3-substituted furfurals can be readily accessed directly from 3-bromofurfural without the need for protection of the aldehyde group using Pd(0)-catalyzed cross-coupling with boronic acids or trifluoroborate salts. Overall, this method is an attractive alternative to traditional approaches to synthesize highly substituted cyclopentenones, involving a domino reaction, and employing readily accessible furaldehyde precursors. Specifically, the 2-step protocol establishes that substituents are tolerated in this reaction. As such, this opens up the use of this strategy to the synthesis of the heretofore unaddressed highly functionalized marine alkaloids agelamadin B and nagelamide J. Further studies on applying this strategy to their synthesis, and extending the method to related systems, including homochiral synthesis, is the subject of ongoing research in our laboratory.

Table 2. $Dy(OTf)_3$-Catalyzed Reaction between Substituted Furaldehydes 5 and Secondary Amines 6



entry	R^1	HNR^2_2	product[a]	yield (%)
1	Me		**10a**	quant
2	C_6H_5		**10b**	87
3	C_6H_5		**10c**	quant
4	*p*-MeC_6H_4		**10d**	70
5	*p*-MeC_6H_4		**10e**	97
6	*p*-$MeOC_6H_4$		**10f**	94
7	*p*-FC_6H_4		**10g**	85
8	*p*-FC_6H_4		**10h**	93
9	*p*-FC_6H_4		**10i**	84
10	*o*-MeC_6H_4		**10j**	quant
11	4-pyridyl		**10k**	73
12	2-thienyl		**10l**	quant
13	ethynyl TMS		**10m**	41

[a]Products were exclusively obtained as the *trans*-diastereomers (≥95:5 by ^{1}H NMR).

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data for all compounds including copies of ^{1}H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02711.

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Full experimental details and characterization data for all compounds including copies of ^{1}H and ^{13}C NMR spectra(PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Simeonov, S. P.; Nunes, J. P. M.; Guerra, K.; Kurteva, V. B.; Afonso, C. A. M. *Chem. Rev.* **2016**, *116*, 5744−5893.

(2) (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305−1306. (b) Guerriero, A.; D'Ambrosio, M.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1895−1902.

(3) Total syntheses of agelastatin A: (a) Stien, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.-H.; Weinreb, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 9574−9579. (b) Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060−9061. (c) Domostoj, M. M.; Irving, E.; Scheinmann, F.; Hale, K. J. *Org. Lett.* **2004**, *6*, 2615−2618. (d) Davis, F. A.; Deng, J. *Org. Lett.* **2005**, *7*, 621−623. (e) Trost, B. M.; Dong, G. *J. Am. Chem. Soc.* **2006**, *128*, 6054−6055. (f) Ichikawa, Y.; Yamaoka, T.; Nakano, K.; Kotsuki, H. *Org. Lett.* **2007**, *9*, 2989−2992. (g) Yoshimitsu, T.; Ino, T.; Tanaka, T. *Org. Lett.* **2008**, *10*, 5457−5460. (h) Davis, F. A.; Zhang, J.; Zhang, Y.; Qiu, H. *Synth. Commun.* **2009**, *39*, 1914−1919. (i) Dickson, D. P.; Wardrop, D. J. *Org. Lett.* **2009**, *11*, 1341−1344. (j) Hama, N.; Matsuda, T.; Sato, T.; Chida, N. *Org. Lett.* **2009**, *11*, 2687−2690. (k) Yoshimitsu, T.; Ino, T.; Futamura, N.; Kamon, T.; Tanaka, T. *Org. Lett.* **2009**, *11*, 3402−3405. (l) Wehn, P. M.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3802−3805. (m) Movassaghi, M.; Siegel, D. S.; Han, S. *Chem. Sci.* **2010**, *1*, 561−566. (n) Reyes, J. C. P.; Romo, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 6870−6873. (o) Duspara, P. D.; Batey, R. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10862−10866. (p) Han, S.; Siegel, D. S.; Morrison, K. C.; Hergenrother, P. J.; Movassaghi, M. *J. Org. Chem.* **2013**, *78*, 11970−11984. (q) Yao, Y.; Wang, X.; Liang, G. *Tetrahedron* **2017**, *73*, 4538−4544.

(4) For a review on agelastatin total syntheses, see: Dong, G. *Pure Appl. Chem.* **2010**, *82*, 2231−2246.

(5) Kusama, T.; Tanaka, N.; Sakai, K.; Gonoi, T.; Fromont, J.; Kashiwada, Y.; Kobayashi, J. *Org. Lett.* **2014**, *16*, 3916−3918.

(6) Araki, A.; Tsuda, M.; Kubota, T.; Mikami, Y.; Fromont, J.; Kobayashi, J. *Org. Lett.* **2007**, *9*, 2369−2371.

(7) Argoudelis, A. D.; Jahnke, H. K.; Fox, J. A. *Antimicrob. Agents Chemother.* **1962**, 191−198.

(8) (a) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Lecomte, F.; DelValle, J. R.; Zhang, J.; Deschênes-Simard, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 3497−3450. (b) Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science* **2013**, *340*, 180−182. (c) Kisunzu, J. K.; Sarpong, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 10694−10696. (d) Sharpe, R. J.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 17990−17998.

(9) Jogyamycin: (a) Iwatsuki, M.; Nishihara-Tsukashima, A.; Ishiyama, A.; Namatame, M.; Watanabe, Y.; Handasah, S.; Pranamuda, H.; Marwoto, B.; Matsumoto, A.; Takahashi, Y.; Otoguro, K.; Omura, S. *J. Antibiot.* **2012**, *65*, 169−171. Cranomycin: (b) Kondo, S.; Shimura, M.; Sezaki, M.; Sato, K.; Hara, T. *J. Antibiot.* **1964**, *17*, 230−233 TM-026: . (c) Guha, G.; Lu, W.; Li, S.; Liang, X.; Kulesz-Martin, M. F.; Mahmud, T.; Indra, A. K.; Ganguli-Indra, G. *PLoS One* **2015**, *10*, e0125322.

(10) For reviews on the bromopyrrole alkaloids, see: (a) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753−1783. (b) Weinreb, S. M. *Nat. Prod. Rep.* **2007**, *24*, 931−948. (c) Al-Mourabit, A.; Zancanella, M. A.; Tilvi, S.; Romo, D. *Nat. Prod. Rep.* **2011**, *28*, 1229−1260. (d) Wang, X.; Ma, Z.; Wang, X.; De, S.; Ma, Y.; Chen, C. *Chem. Commun.* **2014**, *50*, 8628−8639. (e) Lindel, T. *Alkaloids: Chemistry and Biology* **2017**, *77*, 117−219.

(11) (a) *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K., Eds.; Wiley-VCH: Weinheim, 2006. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186. (c) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993−3009.

(12) Powell, D. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7569−7573.

(13) For a review, see: Bian, M.; Li, L.; Ding, H. *Synthesis* **2017**, *28*, 4383−4413.

(14) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2007**, 3759−3761.

(15) Compound **9** is the deprotonated form of a Stenhouse salt: Stenhouse, J. *Justus Liebigs Ann. Chem.* **1850**, *74*, 278−297.

(16) For general reviews on the chemistry of Stenhouse salts, see: (a) Lewis, K. G.; Mulquiney, C. E. *Tetrahedron* **1977**, *33*, 463−475. (b) Gomes, R. F. A.; Coelho, J. A. S.; Afonso, C. A. M. *Chem. - Eur. J.* **2018**, *24*, 9170−9186. For a review on their photochemistry, see: (c) Lerch, M. M.; Szymanski, W.; Feringa, B. L. *Chem. Soc. Rev.* **2018**, *47*, 1910−1937.

(17) For selected reviews on the Nazarov cyclization, see: (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N.Y.)* **1994**, *45*, 1−158. (b) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479−6517. (c) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577−7606. (d) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676−5688. (e) Shimada, N.; Stewart, C.; Tius, M. A. *Tetrahedron* **2011**, *67*, 5851−5870. (f) Spencer, W. T., III; Vaidya, T.; Frontier, A. *J. Eur. J. Org. Chem.* **2013**, *2013*, 3621−3633. (g) Tius, M. A. *Chem. Soc. Rev.* **2014**, *43*, 2979−3002. (h) Di Grandi, M. *Org. Biomol. Chem.* **2014**, *12*, 5331−5345. (i) Wenz, D. R.; Read de Alaniz, J. *Eur. J. Org. Chem.* **2015**, *2015*, 23−37. (j) Sheikh, N. S. *Org. Biomol. Chem.* **2015**, *13*, 10774−10796. (k) Vinogradov, M. G.; Turova, O. V.; Zlotin, S. G. *Org. Biomol. Chem.* **2017**, *15*, 8245−8269.

(18) (a) Shibasaki, M.; Yamada, K.-I.; Yoshikawa, N., Lanthanide Lewis Acids Catalysis. In *Lewis Acids in Organic Synthesis*; Wiley-VCH, 2000; pp 911−944. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227−2302. (c) Veits, G. K.; Read de Alaniz, J. *Tetrahedron* **2012**, *68*, 2015−2026.

(19) (a) Ramesh, D.; Reddy, T. S.; Narasimhulu, M.; Rajaram, S.; Suryakiran, N.; Mahesh, K. C.; Venkateswarlu, Y. *Chem. Lett.* **2009**, *38*, 586−587. (b) Liu, J. Q.; Yu, J. J.; Zhu, M. Y.; Li, J.; Zheng, X. Z.; Wang, L. M. *Synthesis* **2013**, *45*, 2165−2170. (c) Nunes, J. P. M.; Afonso, C. A. M.; Caddick, S. *RSC Adv.* **2013**, *3*, 14975−14978. (d) Griffiths, K.; Gallop, C. W. D.; Abdul-Sada, A.; Vargas, A.; Navarro, O.; Kostakis, G. E. *Chem. - Eur. J.* **2015**, *21*, 6358−6361. (e) Griffiths, K.; Kumar, P.; Mattock, J. D.; Abdul-Sada, A.; Pitak, M. B.; Coles, S. J.; Navarro, O.; Vargas, A.; Kostakis, G. E. *Inorg. Chem.* **2016**, *55*, 6988−6994. (f) Procopio, A.; Costanzo, P.; Curini, M.; Nardi, M.; Oliverio, M.; Sindona, G. *ACS Sustainable Chem. Eng.* **2013**, *1*, 541−544. (g) Estevão, M. S.; Afonso, C. A. M. *Tetrahedron Lett.* **2017**, *58*, 302−304. (h) Nardi, M.; Costanzo, P.; De Nino, A.; Di Gioia, M. L.; Olivito, F.; Sindona, G.; Procopio, A. *Green Chem.* **2017**, *19*, 5403−5411. (i) Estevao, M. S.; Afonso, C. A. M. *Tetrahedron Lett.* **2017**, *58*, 302−304. (j) Gomes, R. F. A.; Esteves, N. R.; Coelho, J. A. S.; Afonso, C. A. M. *J. Org. Chem.* **2018**, *83*, 7509−7513.

(20) (a) Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, *17*, 3555−3558. (b) Piutti, C.; Quartieri, F. *Molecules* **2013**, *18*, 12290−12312.

(21) (a) Veits, G. K.; Wenz, D. R.; Read de Alaniz, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 9484−9487. (b) Palmer, L. I.; Read de Alaniz, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7167−7170. (c) Subba Reddy, B. V.;

DOI: 10.1021/acs.orglett.8b02711
Org. Lett. XXXX, XXX, XXX−XXX

Narasimhulu, G.; Subba Lakshumma, P.; Vikram Reddy, Y.; Yadav, J. S. *Tetrahedron Lett.* **2012**, *53*, 1776−1779. (d) Yu, D.; Thai, V. T.; Palmer, L. I.; Veits, G. K.; Cook, J. E.; Read de Alaniz, J.; Hein, J. E. *J. Org. Chem.* **2013**, *78*, 12784−12789. (e) Wenz, D. R.; Read de Alaniz, J. *Org. Lett.* **2013**, *15*, 3250−3253. (f) Veits, G. K.; Wenz, D. R.; Palmer, L. I.; St. Amant, A. H.; Hein, J. E.; Read de Alaniz, J. *Org. Biomol. Chem.* **2015**, *13*, 8465−8469. (g) Li, H.; Tong, R.; Sun, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 15125−15128. (h) Cai, Y.; Tang, Y.; Atodiresei, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 14126−14130.

(22) LeBœuf, D.; Schulz, E.; Gandon, V. *Org. Lett.* **2014**, *16*, 6464−6467.

(23) Rosocha, G.; Batey, R. A. *Tetrahedron* **2013**, *69*, 8758−8768.

(24) Powell, D. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7569−7573.

(25) Zhao, H.; Dankwardt, J. W.; Koenig, S. G.; Singh, S. P. *Tetrahedron Lett.* **2012**, *53*, 166−169.

(26) On the basis of TLC analysis, the reactions were generally complete after 4−5 h. However, since no decrease in yield or decomposition of products was observed with extended reaction times, the reactions were often left to stir overnight for convenience.

(27) For a review of methods for furan synthesis, see: Moran, W. J.; Rodriguez, A. *Org. Prep. Proced. Int.* **2012**, *44*, 103−130.

(28) Saitman, A.; Theodorakis, E. A. *Org. Lett.* **2013**, *15*, 2410−2413.

(29) Han, F. S. *Chem. Soc. Rev.* **2013**, *42*, 5270−5298.

(30) For reviews of organotrifluoroborates, see: (a) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275−286. (b) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623−3658. (c) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288−325. (d) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412−443.

(31) Conditions were chosen using modified literature conditions applied to other systems. Conditions A: (a) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302−4314. Conditions B: (b) Raheem, M.−A.; Nagireddy, J. R.; Durham, R.; Tam, W. *Synth. Commun.* **2010**, *40*, 2138−2146. Conditions C: (c) Molander, G. A.; Canturk, B.; Kennedy, L. *J. Org. Chem.* **2009**, *74*, 973−980.

(32) Reactions of **5i** using other secondary amines also led to similar results. Product **10m** was shown to be unstable, particularly upon exposure to silica gel, producing a new, bright pink product in acidic media. We speculate that this compound may be the corresponding ring-opened Stenhouse salt. See ref 16.

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