Organic LETTERS

Letter

pubs.acs.org/OrgLett

Inverse Electron-Demand [4 + 2]-Cycloadditions of Ynamides: Access to Novel Pyridine Scaffolds

Guillaume Duret,[†] Robert Quinlan,[†] Rainer E. Martin,[‡] Philippe Bisseret,[†] Markus Neuburger,[§] Vincent Gandon,*[,∥,⊥] and Nicolas Blanchard*[,†]

[†]Laboratoire de Chimie Moléculaire, Université de Strasbourg, CNRS UMR 7509, ECPM, 25 rue Becquerel, 67087 Strasbourg, France

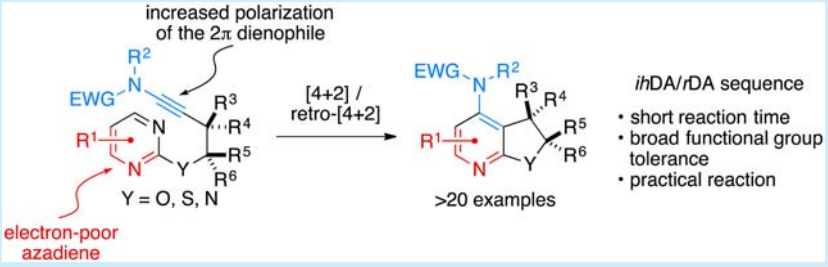
[‡]Medicinal Chemistry, Roche Pharma Research and Early Development (pRED), Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, CH-4070 Basel, Switzerland

[§]Department of Chemistry, University of Basel, Spitalstrasse 51, CH-4056 Basel, Switzerland

[∥]Institut de Chimie Moléculaire et des Matériaux d'Orsay, CNRS UMR 8182, Université. Paris-Sud, Université Paris-Saclay, bâtiment 420, 91405 Orsay cedex, France

[⊥]Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Univ. Paris-Sud, Université Paris-Saclay, 1 Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

Supporting Information



ABSTRACT: Functionalized polycyclic aminopyridines are central to the chemical sciences, but their syntheses are still hampered by a number of shortcomings. These nitrogenated heterocycles can be efficiently prepared by an intramolecular inverse electron demand hetero Diels–Alder (*ih*DA) cycloaddition of ynamides to pyrimidines. This ihDA/rDA sequence is general in scope and affords expedient access to novel types of aminopyridinyl scaffolds that hold great promise in terms of exit vector patterns.

The efficient elaboration of polysubstituted pyridines has been the focus of numerous synthetic methods due to their importance for the chemical sciences in a broad sense.[1] In particular, aminopyridines[2] are valuable ligands, organocatalysts, and building blocks that hold great promise for the agrochemical and pharmaceutical industries with respect to their scaffold diversity and unique patterns of exit vectors.[3] However, their de novo syntheses are still challenging to accomplish, although elegant recent progress has been made with the catalytic hydrodefluorination reactions of fluorinated pyridines.[4]

Inverse electron demand [4 + 2]-Diels–Alder cycloadditions (*ih*DA) of azines are enabling transformations that allow rapid access to pyridines.[5] Quite surprisingly, ynamides have not yet been considered as 2π components in *ih*DA cycloadditions with electron deficient azines, although these nitrogenated alkynes are known to be useful dienophiles in a variety of cycloadditions including [2 + 1]-, [2 + 2]-, [3 + 2]-, [4 + 2]-, [2 + 2 + 1]- and [2 + 2 + 2]-reactions.[6] To the best of our knowledge, only two isolated examples of formal *ih*DA of ynamides have been reported by Movassaghi et al.[7] and Ma et al.[8] (Scheme 1, eqs 1 and 2), while the lack of reactivity of ynamides in silver-catalyzed *ih*DA with 1,2-diazines was reported by Kozmin, Rawal et al.[9]

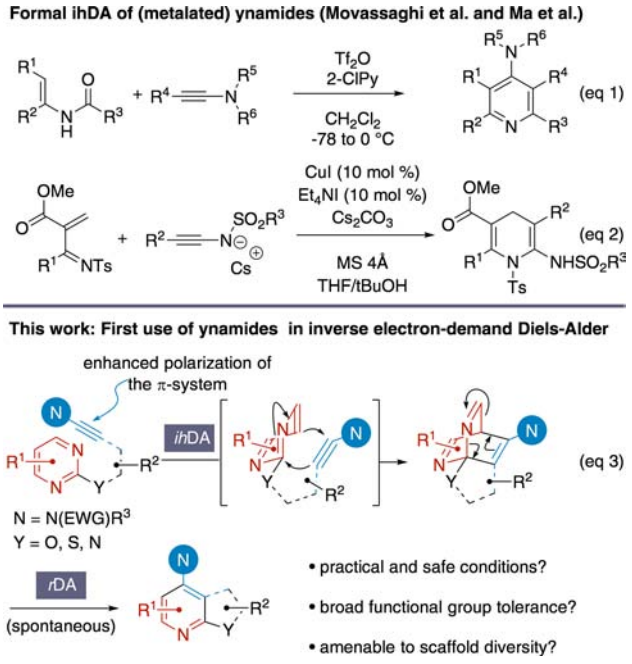
Pyrimidines are among the less reactive electron-deficient azadienes in [4 + 2] reactions.[5] Their cycloadditions spurred only a limited interest in the 1970s and 80s, with Neunhoeffer et al.[10] and van der Plas et al.[5,11] demonstrating that the inter- and intramolecular *ih*DA of pyrimidines with terminal alkynes provide access to (fused) pyridines after a spontaneous retro-Diels–Alder (*r*DA). This *ih*DA/*r*DA sequence demonstrated a very limited scope but was occasionally used as the key step in the partial or total syntheses of naturally and/or biologically occurring products such as streptonigrin,[12] actinidine,[13] the 4-aza analogue of ramelteon,[14] and some chain-breaking antioxidants.[15]

On the basis of these literature precedents, we hypothesized that the electronic tuning of the nitrogen atom of the ynamide

Received: February 18, 2016
Published: March 21, 2016

DOI: 10.1021/acs.orglett.6b00464
Org. Lett. 2016, 18, 1610–1613

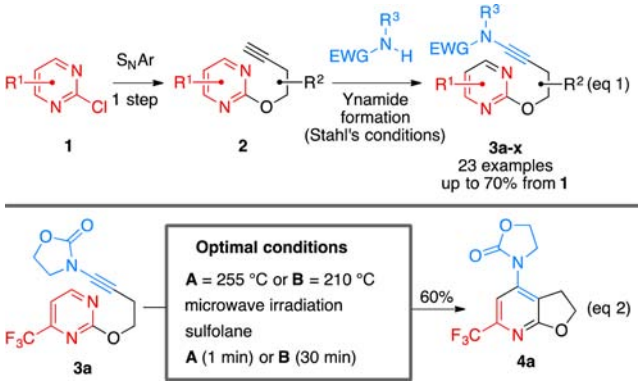
Scheme 1. Formal *ih*DA of Ynamides (eq 1 and 2) and the Proposed First Use of Ynamide in Inverse Electron-Demand Diels–Alder (eq 3)



combined with the induced natural charges of the π-alkynyl system[16] should confer to the ynamide the appropriate reactivity in an *ih*DA/*r*DA sequence with electron-deficient pyrimidines (Scheme 1, eq 3). Provided that high levels of reactivity, regioselectivity and functional group tolerance could be attained during this pericyclic sequence, this could represent a major step forward toward the development of a general route to polycyclic fused and/or spiro aminopyridines.

Synthesis of the ynamide cycloaddition precursors **3a–x** is straightforward and requires only 2 steps from 2-chloropyrimidines **1**, the latter being either commercially available or readily accessible by cross-coupling reactions from 2,4-dichloropyrimidine (Scheme 2, eq 1).[17] Nucleophilic aromatic substitution by homopropargylic sodium alkoxides led to a variety of alkynyl-pyrimidines **2** that were further transformed into the corresponding ynamidyl-1,3-diazines **3a–x** by copper-mediated cross-couplings. The latter reaction required an extensive optimization due to the inherent coordination capacities of the 1,3-diazinyl motif to the copper species.[18] It was finally found that the conditions described by Stahl et al.[19] using $CuCl_2$, cesium carbonate in DMSO at 70 °C under an oxygen atmosphere was the most general and efficient. Due to the electron-poor nature of its pyrimidinyl motif owing to the CF_3 substituent, ynamide **3a** was selected as a model system for the optimization of the *ih*DA/*r*DA sequence (Scheme 2, eq 2).[17] It was quickly found that heating a solution of **3a** in sulfolane for a short time delivered **4a** as the sole product in 60% yield (conditions **A**, 255 °C, 1 min; conditions **B**, 210 °C, 30 min, microwave irradiation). It should also be noted that the cyanhydric acid eliminating during the *retro*-[4 + 2] step, spontaneously polymerizes to a nontoxic solid at high temperature[11f,g,20] that is very easily removed during workup. The choice of the solvent deserves a last comment. Although not often considered in academic laboratories, sulfolane is a cheap, thermally stable and highly dipolar aprotic solvent (μ = 4.68 D) that is readily removed by aqueous washing. Furthermore, it possesses a much-reduced toxicity[21] compared to the classical nitrobenzene[11] and is thus a perfect match for this [4 + 2] reaction.

Scheme 2. Two-Step Synthesis of Cycloaddition Precursors 3a–x (eq 1) and Screening of Optimal *ih*DA/*r*DA Reaction Conditions for 3a (eq 2)



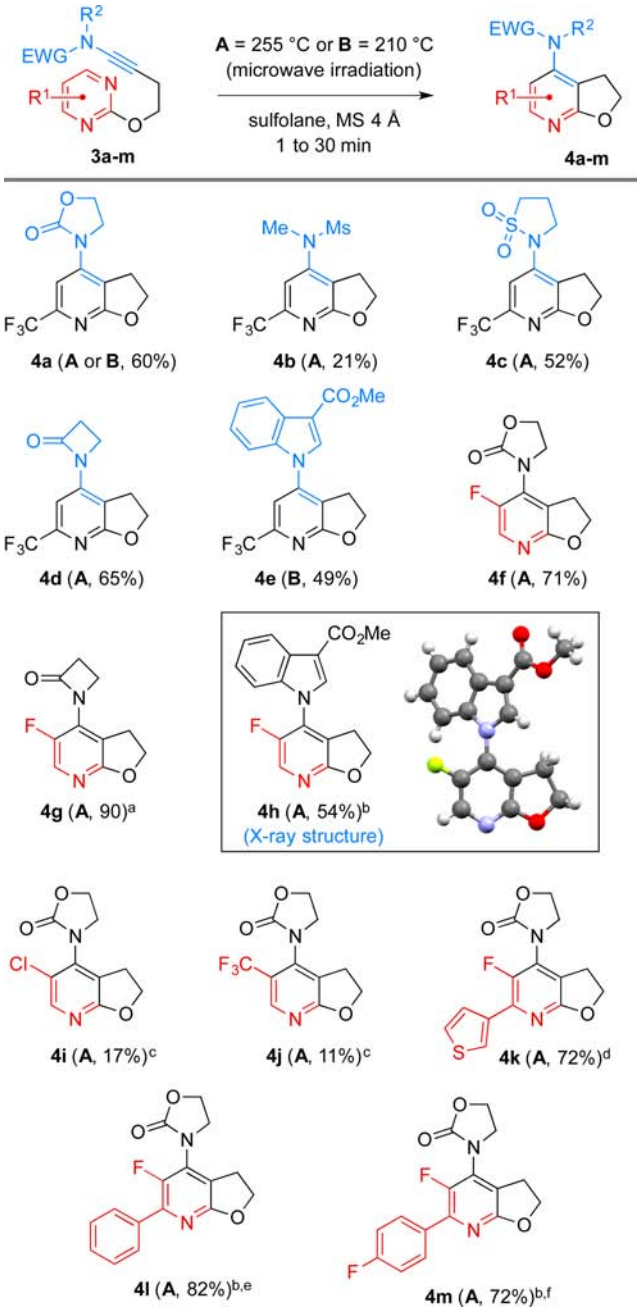
The scope of the *ih*DA/*r*DA reaction of **3a–x** was examined next. As outlined in Scheme 3, various ynamides were evaluated besides **3a**, such as ynamides derived from acyclic or cyclic sulfonamides (**3b** and **3c**, respectively), azetidinone (**3d**) or 3-carbomethoxyindole (**3e**). Except for the acyclic sulfonamide **3b**, the yields of the corresponding 4-amino-2,3-dihydrofuro-[2,3-*b*]pyridines **4a,c–e** were moderate to good after only 1 min at 255 °C. The functional group tolerance on the pyrimidine moiety of the cycloaddition precursors was explored next. In line with previous results,[5,11] it was found that the *ih*DA/*r*DA sequence was sensitive to the steric hindrance at the 5-position of the pyrimidine **3**. A C5-fluorine atom is tolerated as can be seen in the corresponding cycloadducts **4f–h** (71%, 90%, and 54%, respectively), with the latter structure **4h** having been confirmed by X-ray crystallography.[22] On the contrary, a dramatic decrease in yields is observed when ynamides **3** carry bulkier 5-Cl or 5-CF_3 substituents on the pyrimidine core as evidenced by examples **4i** and **4j** (17% and 11%). On the other hand, the 4-position of the pyrimidine could be substituted with a diversity of (hetero) aryl groups, leading to 6-substituted 2,3-dihydrofuro[2,3-*b*]pyridines **4k** (72%) and **4l**, **4m** (82% and 72%). In the latter three cases, the *r*DA step did not follow a unique path, and elimination of the corresponding 3-cyanothiophene, 4-fluorobenzonitrile, and benzonitrile was observed, thus leading to **4f** as a minor product (**4k**/**4f** = 95:5, **4l**/**4f** = 82:18 and **4m**/**4f** = 85:15).

The influence of the linker between the 1,3-diazine and the ynamide was also studied (Scheme 4). In contrast with the two-carbon chain tether (**3a** → **4a**) (60%), the corresponding three- (n = 1) and four-carbon (n = 2) tethers did not lead to any productive *ih*DA/*r*DA reaction (**4n**, **4o**).[23]

On the other hand, the use of cyclic linkers led to a range of unique cycloadducts. Fused- and spiro-tricyclic pyridines such as **4p–u** were obtained in good to excellent yields after very short reaction times. As anticipated, the *ih*DA/*r*DA sequence was favored by cyclic tethers that entropically favor the cyclization.[11a,24,25] This reactivity enhancement is quite obvious in three series, differing only by the nature of the ynamide. In the oxazolidinone-derived ynamides series, adding a cyclic tether such as a fused-*trans*-cyclohexyl to **3a** increases the yields of the cycloadducts (**4a** vs **4p**).

DOI: 10.1021/acs.orglett.6b00464
Org. Lett. 2016, 18, 1610–1613

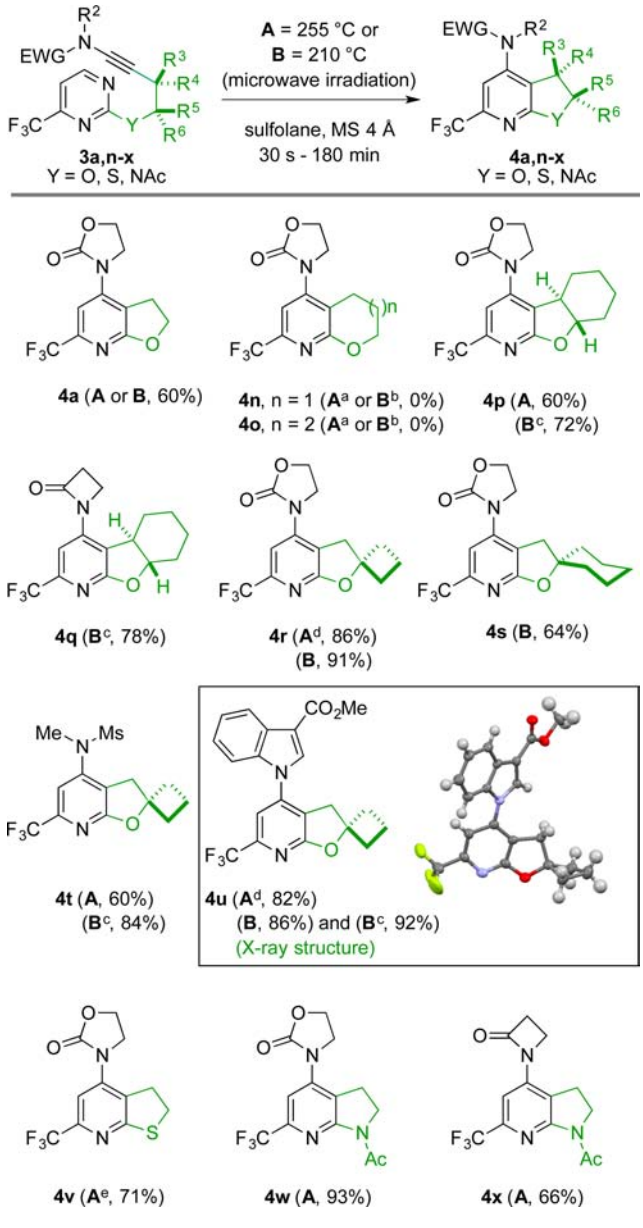
Scheme 3. *ih*DA/*r*DA of Ynamides 3a−m



[a](a) 2 min; (b) 10 min; (c) NMR yields using an internal standard; (d) ratio **4k**/**4f** = 95:5 by ^{19}F NMR, see text; (e) ratio **4l**/**4f** = 82:18 by ^{19}F NMR, see text; (f) ratio **4m**/**4f** = 85:15 by ^{19}F NMR, see text.

This increase in yield is even greater with the spiro-cyclobutyl tether as can be seen for the oxazolidinone- (**4a** vs **4r**), the sulfonamide- (**4b** vs **4t**), and the indole-derived ynamide series (**4e** vs **4u**).[22] Finally, extension of this *ih*DA/*r*DA sequence to 2-thio and 2-*N*-acetyl-pyrimidines **3v** and **3w**, **3x** (respectively) was briefly investigated (Scheme 4). Good to excellent yields of the corresponding cycloadducts **4v**, **4w**, and **4x** were obtained after 1 to 2 min (method **A**), thus highlighting the versatility of this method for the preparation of 4-amino pyridines possessing various fused oxygen-, sulfur-, and nitrogen-containing heterocycles.

Scheme 4. *ih*DA/*r*DA of Ynamides 3a,n−u



[a](a) 10 min; (b) 180 min; (c) 60 min; (d) 30 s; (e) 2 min.

In summary, we have developed an efficient route to structurally diverse polycyclic fused- and spiro-aminopyridines through the first inverse electron demand hetero Diels−Alder cycloadditions of ynamides. This reaction is practical to set up and calls for a rapid heating under microwave irradiation in an underutilized solvent, sulfolane. These exciting results open new avenues for the previously unknown inverse-electron-demand hetero Diels−Alder cycloadditions of ynamides, both in intramolecular and intermolecular fashion.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00464.

Crystallographic data for **4u** (CIF)
Crystallographic data for **4h** (CIF)

DOI: 10.1021/acs.orglett.6b00464
Org. Lett. 2016, 18, 1610−1613

Full experimental procedures, spectroscopic characterizations, copies of NMR (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: vincent.gandon@u-psud.fr
*E-mail: n.blanchard@unistra.fr

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the Université de Strasbourg, the CNRS, the Université Paris-Sud, the Université Paris-Saclay and the Région Alsace. We are grateful to Dr. Didier Le Nouën (Université de Haute-Alsace) for his NMR expertise and to Sophie Brogly (Hoffmann-La Roche, Ltd.) for HRMS analysis. V.G. thanks IUF.

REFERENCES

(1) For selected recent reviews, see: (a) Allais, C.; Grassot, J.-M.; Rodriguez, J.; Constantieux, T. *Chem. Rev.* **2014**, *114*, 10829. (b) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. For recent contributions, see: (c) Fier, P. S.; Hartwig, J. F. *Science* **2013**, *342*, 956. (d) Loy, N. S. Y.; Singh, A.; Xu, X.; Park, C.-M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2212. (e) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95. (f) Chen, M. Z.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 1352. (g) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 14411.

(2) (a) Mittal, N.; Lippert, K. M.; De, C. K.; Klauber, E. G.; Emge, T. J.; Schreiner, P. R.; Seidel, D. *J. Am. Chem. Soc.* **2015**, *137*, 5748. (b) Dias Pires, M. J.; Poeira, D. L.; Marques, M. M. B. *Eur. J. Org. Chem.* **2015**, *2015*, 7197. (c) De Rycke, N.; Couty, F.; David, O. R. P. *Chem. - Eur. J.* **2011**, *17*, 12852.

(3) (a) Brown, N. *Scaffold Hopping in Medicinal Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2013. (b) Hajduk, P. J.; Galloway, W. R. J. D.; Spring, D. R. *Nature* **2011**, *470*, 42. (c) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun.* **2010**, *1*, 80. (d) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74.

(4) (a) McKay, D.; Riddlestone, I. M.; Macgregor, S. A.; Mahon, M. F.; Whittlesey, M. K. *ACS Catal.* **2015**, *5*, 776. (b) Podolan, G.; Jungk, D.; Lentz; Zimmer, R.; Reissig, H.-U. *Adv. Synth. Catal.* **2015**, *357*, 3215. (c) Podolan, G.; Lentz, D.; Reissig, H.-U. *Angew. Chem., Int. Ed.* **2013**, *52*, 9491.

(5) (a) Foster, R. A. A.; Willis, M. C. *Chem. Soc. Rev.* **2013**, *42*, 63. (b) van der Plas, H. C. In *Advances in Heterocyclic Chemistry*; Katritsky, R. A., Ed.; Academic Press, 2003; Vol. *84*, p 31. (c) van der Plas, H. C. *Chem. Heterocycl. Compd.* **1994**, *30*, 1427. (d) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (e) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (f) For a DFT analysis of azadienes *ih*DA, see: Yang, Y.-F.; Liang, Y.; Liu, F.; Houk, K. N. *J. Am. Chem. Soc.* **2016**, *138*, 1660. (g) Talbot, A.; Devarajan, D.; Gustafson, S. J.; Fernández, I.; Bickelhaupt, F. M.; Ess, D. H. *J. Org. Chem.* **2015**, *80*, 548. (h) Hayden, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 4084.

(6) (a) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (c) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.

(7) (a) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096. (b) Wezeman, T.; Zhong, S.; Nieger, M.; Bräse, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 3823.

(8) Yan, X.; Ling, F.; Zhang, Y.; Ma, C. *Org. Lett.* **2015**, *17*, 3536.

(9) Türkmen, Y. E.; Montavon, T. J.; Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 9062.

(10) (a) Neunhoeffer, H.; Lehmann, B. *Liebigs Ann. Chem.* **1975**, *1975*, 1113. (b) Neunhoeffer, H.; Werner, G. *Liebigs Ann. Chem.* **1974**, *1974*, 1190.

(11) (a) Frissen, A. E.; Marcelis, A. T. M.; Geurtsen, G.; de Bie, D. A.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 5151. (b) Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 803. (c) Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron Lett.* **1987**, *28*, 1589. (d) Marcelis, A. T. M.; van der Plas, H. C. *J. Org. Chem.* **1986**, *51*, 67. (e) Charushin, V. N.; van der Plas, H. C. *Tetrahedron Lett.* **1982**, *23*, 3965. (f) Martin, R. E.; Lenz, M.; Alzieu, T.; Aebi, J. D.; Forzy, L. *Tetrahedron Lett.* **2013**, *54*, 6703. (g) Martin, R. E.; Morawitz, F.; Kuratli, C.; Alker, A. M.; Alanine, A. I. *Eur. J. Org. Chem.* **2012**, 47.

(12) Martin, J. C. *J. Heterocycl. Chem.* **1980**, *17*, 1111.

(13) Davies, L. B.; Greenberg, S. G.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1909.

(14) Koike, T.; Hoashi, Y.; Takai, T.; Uchikawa, O. *Tetrahedron Lett.* **2011**, *52*, 3009.

(15) Wijtmans, M.; Pratt, D. A.; Brinkhorst, J.; Serwa, R.; Valgimigli, L.; Pedulli, G. F.; Porter, N. A. *J. Org. Chem.* **2004**, *69*, 9215.

(16) Hentz, A.; Retailleau, P.; Gandon, V.; Cariou, K.; Dodd, R. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8333.

(17) See Supporting Information for details.

(18) Jouvin, K.; Evano, G. In *Copper-Mediated Cross-Coupling Reactions*; Evano, G., Blanchard, N., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2013; p 187.

(19) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.

(20) (a) de la Fuente, J. L.; Ruiz-Bermejo, M.; Nna-Mvondo, D.; Minard, R. D. *Polym. Degrad. Stab.* **2014**, *110*, 241. (b) He, C.; Lin, G.; Upton, K. T.; Imanaka, H.; Smith, M. A. *J. Phys. Chem. A* **2012**, *116*, 4751.

(21) Tilstam, U. *Org. Process Res. Dev.* **2012**, *16*, 1273.

(22) CCDC 1411129 (**4h**) and 1437398 (**4u**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

(23) The sequence does not even proceed at 285 °C for 10 min; this could be attributed to an unfavorable conformational bias for the cycloaddition step and will be addressed in future DFT investigations.

(24) For an earlier example involving a *gem*-dinitrile, see: (a) Frissen, A. E.; Marcelis, A. T. M.; Geurtsen, G.; de Bie, D. A.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 547. (b) Frissen, A. E.; Marcelis, A. T. M.; Melger, W. C.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 6891.

(25) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

DOI: 10.1021/acs.orglett.6b00464
Org. Lett. 2016, 18, 1610−1613