

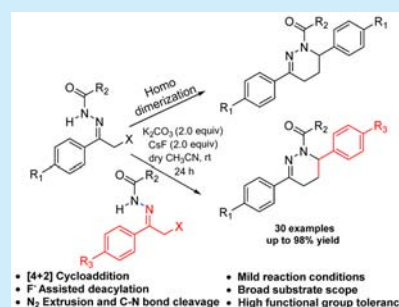
Fluoride-Assisted Synthesis of 1,4,5,6-Tetrahydropyridazines via [4 + 2] Cyclodimerization of in Situ-Generated Azoalkenes Followed by a C–N Bond Cleavage

Anil M. Shelke and Gurunath Suryavanshi*

Chemical Engineering & Process Development Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, Maharashtra 411008, India

S Supporting Information

ABSTRACT: An unexpected CsF-assisted C–N bond cleavage was exploited to synthesize highly functionalized and biologically important 1,4,5,6-tetrahydropyridazine derivatives from α -halo *N*-acylhydrazones in excellent yields. The extrusion of nitrogen and the [4 + 2] cycloaddition between in situ-generated azoalkenes is a key reaction in the process. The identified methodology is suitable for synthesizing a wide variety of analogues of tetrahydropyridazines, which are prevalent in many medicinally important small molecules. The reaction conditions are mild, high-yielding, and amenable for the gram scale.



1,4,5,6-Tetrahydropyridazines¹ and pyridazines² are important six-membered aza-heterocycles widely present as core structures in a large number of natural products (e.g., pyridazomycin³ and azamerone⁴) as well as a structural subunit found in a variety of bioactive molecules and pharmaceuticals^{5,6} such as the antihypertensives hydralzine, dihydralzine, and endralzine and the antidepressants pipofezine and minaprine⁷ (Figure 1).

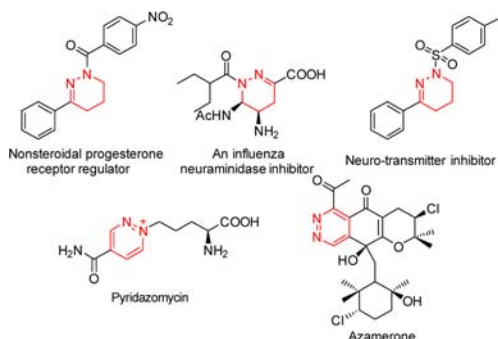


Figure 1. Biologically active tetrahydropyridazine derivatives and natural products containing a pyridazine core.

Moreover, pyridazine derivatives are currently considered to be one of the most developable heterocyclic skeletons for small-molecule-based drug design.^{2,8} As a result, organic chemists are trying to develop and expand new synthetic strategies to make pyridazine and its derivatives.⁹ Several research groups have been engaged in the development of protocols to synthesize these privileged structures using various methods such as aza-Diels–Alder reactions of 1,2-diaza-1,3-dienes with olefins,¹⁰ nucleophilic addition reactions,¹¹ and rearrangement reactions.¹² Conventional methods for tetrahydropyridazine synthesis are

based on the reaction of hydrazine or its derivatives with 1,4-dicarbonyl compounds.^{6a,13,14} Recently, the research groups of Luo¹⁵ and Du¹⁶ have developed an efficient method for the synthesis of 1,4,5,6-tetrahydropyridazines. Later, Werz and co-workers described an alternative method for the preparation of functionalized tetrahydropyridazines using a Lewis acid via a [3 + 3] cycloaddition reaction.¹⁷

The few interesting methods known in the literature for the synthesis of 1,4,5,6-tetrahydropyridazines^{15–17} suffer from many disadvantages, such as limited substrate scope,^{10d,g–i,k,18,19} the requirement of a large excess of alkene as the dienophile partner,¹⁵ and harsh reaction conditions.^{16,10m} Therefore, the development of more general strategies that allow rapid access to these structurally diversified 1,4,5,6-tetrahydropyridazines from readily accessible starting materials is still highly desirable and challenging in synthetic organic chemistry. Herein we report a simple, versatile, and novel route to highly functionalized 1,4,5,6-tetrahydropyridazine derivatives from α -halo *N*-acylhydrazones as the only starting material, which acts as both the diene and the dienophile. Azoalkenes (1,2-diaza-1,3-dienes),²⁰ which can be easily generated in situ from α -halo hydrazones, have been commonly introduced as a valuable synthetic intermediate for the construction of various N-heterocycles. Recently, a broad range of transformations has been established using azoalkenes as a suitable chemical handle.

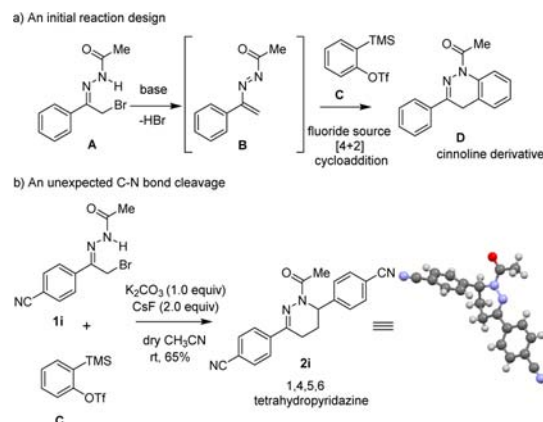
In this context, considering the high reactivity of azoalkenes and as a part of our ongoing efforts to transform readily accessible substrates into synthetically important N-heterocycles,²¹ we envisioned that treatment of α -halo *N*-acylhydrazone **A** with base

Received: June 15, 2016

Published: August 5, 2016

would afford azadiene **B** in situ, which upon treatment with aryne precursor **C** would facilitate an intermolecular [4 + 2] cycloaddition reaction to offer cinnoline derivative **D** (Scheme 1). In order to test our hypothesis, α -halo *N*-acylhydrazone **1i**

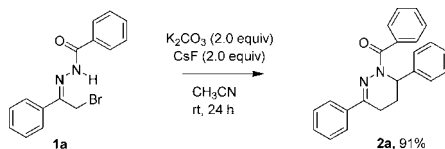
Scheme 1. Initial Reaction Design and an Unexpected C–N Bond Cleavage



was treated with K_2CO_3 (1.0 equiv) in the presence of freshly generated benzyne in CH_3CN at room temperature. After 24 h, a single product **2i** (65% yield) was observed, which was confirmed unambiguously as 4,4'-(1-acetyl-1,4,5,6-tetrahydropyridazine-3,6-diyl)dibenzonitrile by single-crystal XRD analysis.²² 1,2-Diaza-1,3-dienes bearing no substituents at C4 show a tendency to self-condense, giving cyclic dimers in the presence of base when unsuitable or inefficient partners for the cycloaddition reaction are present.²³ Although the desired cinnoline derivative was not obtained, we were surprised to observe an unexpected C–N bond cleavage in the presence of fluoride leading to 1,4,5,6-tetrahydropyridazine derivatives in quite good yields under very mild reaction conditions. This result inspired us to examine the scope and generality of the present methodology.

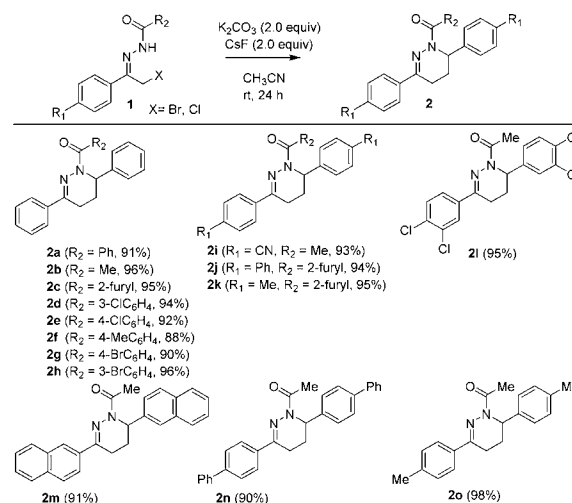
We started our investigation by taking **1a** as a model substrate to determine the optimal reaction conditions for the cyclodimerization reaction to form **2a**. Several experiments were performed to investigate the effect of solvent, base, and fluoride source on the reaction (see the Supporting Information for a detailed optimization table), and we were pleased to find that the cyclodimerization reaction proceeded very well in the presence of K_2CO_3 (2.0 equiv) and CsF (2.0 equiv) in CH_3CN as the solvent, resulting in a 91% yield of **2a** (Scheme 2). Attempts to decrease the amounts of both the fluoride source and the base resulted in much lower yields of the desired product **2a**.

Scheme 2. 1,4,5,6-Tetrahydropyridazine Synthesis



With these optimized reaction conditions in hand, the substrate scope of this unique transformation and limitations of the homocyclodimerization reaction were studied by evaluating a variety of α -halo *N*-acylhydrazones in order to investigate the generality of this reaction. As illustrated in Scheme 3, the reaction proceeded effectively with several

Scheme 3. Scope of the Homocyclodimerization Reaction^{a,b}



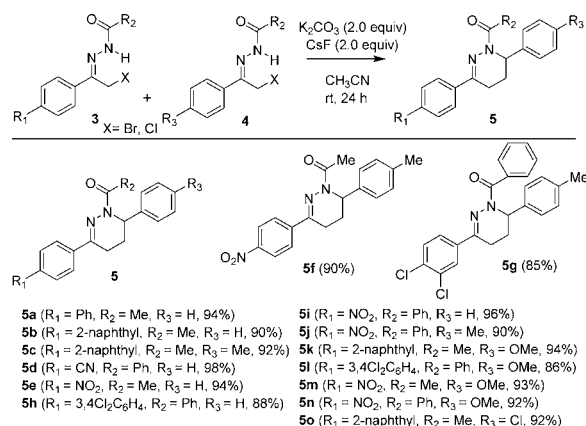
^aThe reactions were carried out with **1** (0.5 mmol), K_2CO_3 (1.0 mmol), CsF (1.0 mmol), and CH_3CN (dry, 3 mL) at rt for 24 h.

^bIsolated yields after column chromatographic purification are shown.

substrates and was not found to be much dependent on the electronic nature of the substituents, affording a wide range of 1,4,5,6-tetrahydropyridazines (**2a–o**) in good to excellent yields. In most of the cases, 1,4,5,6-tetrahydropyridazines could be isolated in greater than 90% yield after column chromatography on silica gel. The flexibility of the process allows the strategic placement of functional groups. For instance, **2d**, **2e**, **2g**, **2h**, and **2l**, which contain chlorine and bromine atoms, were easily prepared and could be additionally derivatized, thereby providing a convenient alternative for the generation of a broad range of analogues.

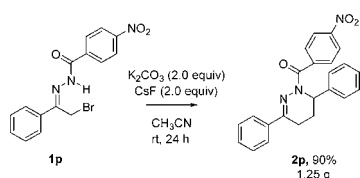
To our delight, not much electronic effect of R_2 on the aromatic ring was observed. Electron-donating, -withdrawing, and -neutral groups gave almost similar yields of 1,4,5,6-tetrahydropyridazines (Scheme 3). *Meta*-substituted derivatives also worked well, providing comparatively better yields than their *para*-substituted counterparts (**2d** vs **2e** and **2h** vs **2g**). Notably, 2-furoic hydrazones could undergo homocyclodimerization, giving good yields of the desired products (**2c**, **2j**, and **2k**). Variations of the R_1 group were also tested. As can be seen from Scheme 3, electron-donating and -withdrawing groups could be equally applied in this reaction, giving good yields of products. The formation of products **2a–o** was confirmed by NMR and HRMS analysis.

The success in the homocyclodimerization prompted us to investigate the cross-cyclodimerization reaction. Competition experiments between an α -halo *N*-acylhydrazone with another α -halo *N*-acylhydrazone in excess resulted in the formation of the heterocyclodimerization products in good yields (e.g., **5a–o** in Scheme 4). As presented in Scheme 4, both electron-donating and -withdrawing groups on the aromatic ring of the α -halo *N*-acylhydrazone were compatible with this cross-cyclodimerization reaction, yielding the desired products in 85–98% yield. This indicates the broad substrate scope and importance of the present reaction. Alkyl-substituted hydrazones, α -substituted aryl hydrazones, other electron-deficient olefins, and alkynes failed to give the desired products. To show the synthetic potential of our present methodology, we carried out the reaction of (*Z*)-*N'*-(2-bromo-1-phenylethylidene)-*N*-4-nitrobenzoyl hydrazide (**1p**) under our optimized reaction conditions, which afforded **2p**,

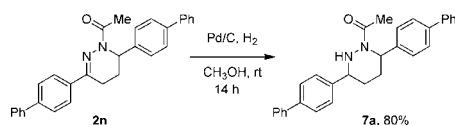
Scheme 4. Scope of the Cross-Cyclodimerization Reaction^{a,b}

^aThe reactions were carried out with **3** (0.5 mmol), **4** (0.25 mmol), K_2CO_3 (1.0 mmol), CsF (1.0 mmol), and CH_3CN (dry, 3 mL) at rt for 24 h. ^bIsolated yields after column chromatographic purification are shown.

an analogue of a nonsteroidal progesterone receptor regulator, on a gram scale (1.25 g, 90% yield; **Scheme 5**).¹⁵

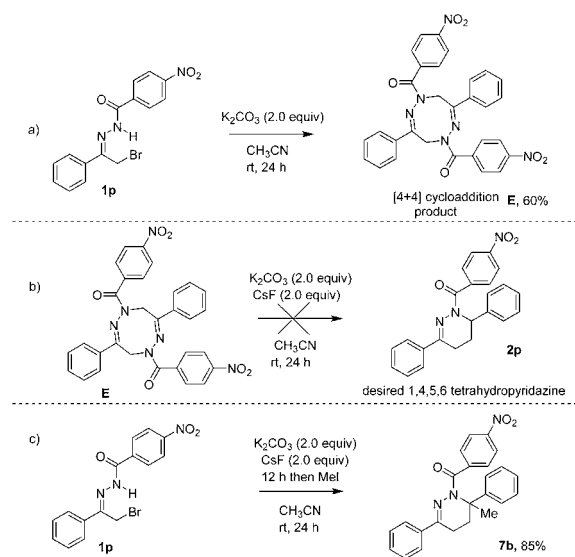
Scheme 5. Gram-Scale Synthesis of **2p**, an Analogue of a Nonsteroidal Progesterone Receptor Regulator

Furthermore, to demonstrate the utility of the reaction, product **2n** was subjected to hydrogenation reaction conditions using Pd/C as the catalyst to give hexahydropyridazine **7a** in 80% yield, which could be further converted to a pharmaceutically important 1,4-diamine adduct (**Scheme 6**).²⁴

Scheme 6. Transformation of Product **2n** into **7a**

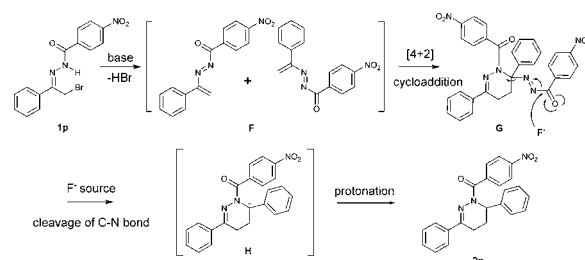
In order to gain insight into the mechanistic details of the reaction, we conducted the following experiments (**Scheme 7**): (a) When α -bromo N -acylhydrazone **1p** was treated with K_2CO_3 in the absence of CsF , we did not observe the formation of the desired product **2p**; instead we got [4 + 4] cycloaddition product **E** (structure confirmed by ^1H , ^{13}C , and 2D NMR and HRMS analyses) in 60% yield, which proves the significant role of cesium fluoride to get **2p**. (b) Next, we subjected compound **E** to our optimized reaction conditions, but unfortunately, the starting material remained intact and was not converted into the expected product **2p**. This control experiment suggests that the reaction does not go through compound **E** as an intermediate. (c) Additionally, when **1p** was subjected to our optimized reaction conditions in the presence of excess methyl iodide (>5.0 equiv), interestingly, the methylated product **7b** (85% yield) was obtained, confirming the generation of the carbanion at the

Scheme 7. Control Experiments



benzylic position during the course of the cyclodimerization reaction. This experiment also suggests that compound **G** is undoubtedly the key intermediate in the reaction (**Scheme 8**).

Scheme 8. Proposed Mechanism



On the basis of the above control experiments and literature precedents,²⁵ a probable mechanism is proposed in **Scheme 8**. Treatment of the α -halo hydrazone with base generates azoalkene **F** (1,2-diaza-1,3-diene), which then undergoes cyclodimerization (regioselective intermolecular [4 + 2] cycloaddition of the transient azoene) to give pyridazine **G**. Since fluoride is the only active nucleophilic species under rigorously anhydrous conditions, the most likely mechanism for the C–N bond cleavage is regioselective nucleophilic attack of fluoride anion at one of the acyl carbonyl groups of **G** followed by nitrogen elimination and breaking of the C–N bond, resulting in unstable carbanion intermediate **H**, which undergoes protonation to afford the desired 1,4,5,6-tetrahydropyridazine. Notably, the fluoride anion attack is highly regioselective. Nitrogen elimination may be the driving force for this high regioselectivity.

In summary, we have demonstrated a simple and facile transformation of α -halo N -acylhydrazones into highly functionalized 1,4,5,6-tetrahydropyridazines in excellent yields using CsF and K_2CO_3 under very mild reaction conditions via fluoride-assisted unexpected C–N bond cleavage. Mild reaction conditions, readily accessible starting materials, high yields, and broad functional group tolerance are some of the notable features of the present methodology. Mechanistically, this reaction involves cyclodimerization (regioselective intermolecular [4 +

2] cycloaddition of the transient azoene followed by regioselective deacylation) and the extrusion of nitrogen using cesium fluoride as the nucleophile. The asymmetric version of the present methodology and biological studies of the products are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b01551](https://doi.org/10.1021/acs.orglett.6b01551).

Experimental procedures and analytical data (PDF)
Crystallographic data for **2i** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gm.suryavanshi@ncl.res.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.M.S. thanks UGC, New Delhi, India for the award of research fellowship and SERB-DST (GAP302326), New Delhi for funds. The authors thank Dr. Rajesh G. Gonnade and Mr. Samir Shaikh (Centre for Materials Characterization, CSIR-NCL) for assistance with X-ray crystallography.

■ REFERENCES

- (1) (a) Xu, S.; Chen, R.; Qin, Z.; Wu, G.; He, Z. *Org. Lett.* **2012**, *14*, 996. (b) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (c) Shen, L.; Sun, L.; Ye, S. *J. Am. Chem. Soc.* **2011**, *133*, 15894. (d) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550. (e) Oelke, A. J.; France, D. J.; Hofmann, T.; Wuitschik, G.; Ley, S. V. *Angew. Chem.* **2010**, *122*, 6275; *Angew. Chem., Int. Ed.* **2010**, *49*, 6139.
- (2) Ritchie, T. J.; Macdonald, S. J. F.; Peace, S.; Pickett, S. D.; Luscombe, C. N. *MedChemComm* **2012**, *3*, 1062.
- (3) (a) Bockholt, H.; Beale, J. M.; Rohr, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1648. (b) Grote, R.; Chen, Y.; Zeeck, A.; Chen, Z.; Zähler, H.; Mischnick-Lübbecke, P.; König, W. A. *J. Antibiot.* **1988**, *41*, 595.
- (4) Cho, J. Y.; Kwon, H. C.; Williams, P. G.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2006**, *8*, 2471.
- (5) Boger, D. L.; Ledebor, M. W.; Kume, M.; Jin, Q. *Angew. Chem., Int. Ed.* **1999**, *38*, 2424.
- (6) (a) Combs, D. W.; Reese, K.; Phillips, A. J. *Med. Chem.* **1995**, *38*, 4878. (b) Combs, D. W.; Reese, K.; Cornelius, L. A. M.; Gunnet, J. W.; Cryan, E. V.; Granger, K. S.; Jordan, J. J.; Demarest, K. T. *J. Med. Chem.* **1995**, *38*, 4880.
- (7) Wermuth, C. G.; Schlewer, G.; Bourguignon, J. J.; Maghioros, G.; Bouchet, M.-J.; Moire, C.; Kan, J.-P.; Worms, P.; Biziere, K. *J. Med. Chem.* **1989**, *32*, 528.
- (8) Abed, H. B.; Mammoliti, O.; Bande, O.; Van Lommen, G.; Herdewijn, P. *J. Org. Chem.* **2013**, *78*, 7845.
- (9) (a) Mason, J. W.; Aldous, D. L. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley-Interscience: New York, 1973; Vol. 28, p 24. (b) Coates, W. J.; McKillop, A. *Synthesis* **1993**, *1993*, 334. Wang, D.; Kuang, L.; Li, Z.; Ding, K. *Synlett* **2008**, *2008*, 69.
- (10) For selected examples, see: (a) Vors, J.-P. *J. Heterocycl. Chem.* **1991**, *28*, 1043. (b) Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1179. (c) Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Raynor, C. M.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2591. (d) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Fringuelli, F.; Mantellini, F.; Matteucci, M.; Piermatti, O.; Pizzo, F. *Helv. Chim. Acta* **2001**, *84*, 513. (e) Arroyo, Y.; Rodríguez, J. F.; Santos, M.; Tejedor, M. A. S.; Vaca, I.; Ruano, J. L. G. *Tetrahedron: Asymmetry* **2004**, *15*, 1059. (f) Rossi, E.; Abbiati, G.; Attanasi, O. A.; Rizzato, S.; Santeusano, S. *Tetrahedron* **2007**, *63*, 11055. (g) D'Auria, M.; Racioppi, R.; Attanasi, O. A.; Mantellini, F. *Synlett* **2010**, *2010*, 1363. (h) Lopes, S. M. M.; Brigas, A. F.; Palacios, F.; Lemos, A.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2012**, *2012*, 2152. (i) Gao, S.; Chen, J.-R.; Hu, X.-Q.; Cheng, H.-G.; Lu, L.-Q.; Xiao, W.-J. *Adv. Synth. Catal.* **2013**, *355*, 3539. (j) Attanasi, O. A.; Bianchi, L.; D'Auria, M.; Mantellini, F.; Racioppi, R. *Curr. Org. Synth.* **2013**, *10*, 631. (k) Tong, M.-C.; Chen, X.; Li, J.; Huang, R.; Tao, H.; Wang, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 4680. (l) Attanasi, O. A.; Favi, G.; Mantellini, F.; Mantenuto, S.; Moscatelli, G.; Nicolini, S. *Synlett* **2015**, *26*, 193. (m) Yang, X.-L.; Peng, X.-X.; Chen, F.; Han, B. *Org. Lett.* **2016**, *18*, 2070.
- (11) For selected examples, see: (a) Hughes, P.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 3260. (b) Boger, D. L.; Schüle, G. *J. Org. Chem.* **1998**, *63*, 6421. (c) Potikha, L. M.; Kovtunen, V. A.; Turov, A. V. *Chem. Heterocycl. Compd.* **2009**, *45*, 815. (d) Handy, E. L.; Totaro, K. A.; Lin, C. P.; Sello, J. K. *Org. Lett.* **2014**, *16*, 3488.
- (12) For selected examples, see: (a) Yoshida, Z.; Harada, T.; Tamaru, Y. *Tetrahedron Lett.* **1976**, *17*, 3823. (b) Viswanathan, N.; Sidhaye, A. R. *Tetrahedron Lett.* **1979**, *20*, 5025.
- (13) Rybczynski, P. J.; Combs, D. W.; Jacobs, K.; Shank, R. P.; Dubinsky, B. *J. Med. Chem.* **1999**, *42*, 2403.
- (14) Zhang, L.; Williams, M. A.; Mendel, D. B.; Escarpe, P. A.; Chen, X.; Wang, K.-Y.; Graves, B. J.; Lawton, G.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1751.
- (15) (a) Zhong, X.; Lv, J.; Luo, S. *Org. Lett.* **2015**, *17*, 1561. (b) Zhong, X.; Lv, J.; Luo, S. *Org. Lett.* **2016**, *18*, 3150.
- (16) Wang, W.; Meng, W.; Du, H. *Dalton Trans.* **2016**, *45*, 5945.
- (17) Garve, L. K. B.; Petzold, M.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2016**, *18*, 564.
- (18) For recent examples, see: (a) Attanasi, O. A.; Favi, G.; Filippone, P.; Perrulli, F. R.; Santeusano, S. *Org. Lett.* **2009**, *11*, 309. (b) Attanasi, O. A.; Favi, G.; Filippone, P.; Mantellini, F.; Moscatelli, G.; Perrulli, F. R. *Org. Lett.* **2010**, *12*, 468. (c) Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusano, S. *Adv. Synth. Catal.* **2011**, *353*, 1519. (d) Hu, X.-Q.; Chen, J.-R.; Gao, S.; Feng, B.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2013**, *49*, 7905. (e) Hu, X.-Q.; Chen, J.-R.; Wei, Q.; Liu, F.-L.; Deng, Q.-H.; Beauchemin, A. M.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 12163.
- (19) (a) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924. (b) Guo, C.; Sahoo, B.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17402.
- (20) (a) Reese, C. B.; Sanders, H. P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2719. (b) Attanasi, O. A.; De Crescentini, L. D.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusano, S. *Eur. J. Org. Chem.* **2009**, *2009*, 3109. (c) Hatcher, J. M.; Coltart, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 4546.
- (21) (a) Reddy, R. S.; Chouthaiwale, P. V.; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. *Chem. Commun.* **2010**, *46*, 5012. (b) Shelke, A. M.; Suryavanshi, G. *Org. Biomol. Chem.* **2015**, *13*, 8669. (c) Shaikh, T. M.; Karabal, P. U.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett.* **2009**, *50*, 2815.
- (22) CCDC 1477217 contains the supplementary crystallographic data for **2i**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- (23) (a) Banert, K.; Hagedorn, M. *Tetrahedron Lett.* **1992**, *33*, 7331. (b) Gilchrist, T. L.; Wasson, R. C.; King, F. D.; Wootton, G. J. *Chem. Soc., Perkin Trans. 1* **1987**, 2511. (c) Curtin, D. Y.; Tristram, E. W. *J. Am. Chem. Soc.* **1950**, *72*, 5238.
- (24) Sinha, M.; Dola, V. R.; Soni, A.; Agarwal, P.; Srivastava, K.; Haq, W.; Puri, S. K.; Katti, S. B. *Bioorg. Med. Chem.* **2014**, *22*, 5950.
- (25) Attanasi, O. A.; De Crescentini, L. D.; Favi, G.; Mantellini, F.; Mantenuto, S.; Nicolini, S. *J. Org. Chem.* **2014**, *79*, 8331.