Organic LETTERS

Letter

pubs.acs.org/OrgLett

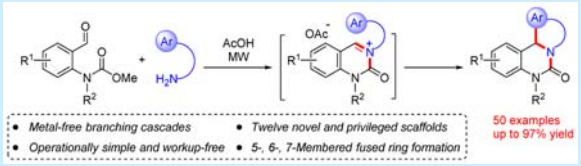
Microwave-Assisted Branching Cascades: A Route to Diverse 3,4-Dihydroquinazolinone-Embedded Polyheterocyclic Scaffolds

Rajiv T. Sawant, Marc Y. Stevens, Christian Sköld, and Luke R. Odell*

Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Center, Uppsala University, P.O. Box 574, SE-751 23 Uppsala, Sweden

Supporting Information

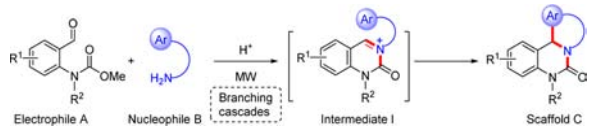
ABSTRACT: A novel metal-free microwave-assisted branching cascades strategy for the efficient synthesis of 3,4-dihydroquinazolinone-embedded polyheterocyclic scaffolds is reported. Starting from in situ generated key *N*-acyliminium ion precursors, 12 distinct and skeletally diverse polycyclic frameworks were accessed in a single step/pot via adjustment of the nucleophile(s) and reaction conditions. Postcascade functionalization of these compounds was also demonstrated, proving the utility of this method in accessing structurally diverse chemical entities.



The iterative design−make−test−analyze cycle of small molecule libraries in the quest for new bioactive chemical modulators is one of the central research themes for chemists and biologists in modern drug discovery and chemical biology.[1] In the search for skeletally and functionally diverse small molecule libraries exploring biologically relevant chemical space, a number of methods for library generation have been developed.[2] In particular, the field of diversity-oriented synthesis (DOS)[3] has emerged as a powerful technique to fulfill the rising demand for novel and diverse small organic molecules to facilitate the identification of new chemical leads.[4] DOS includes different strategies[5] such as branching pathways,[6] folding pathways,[7] the build-couple-pair strategy,[8] the click−click−cyclize strategy,[9] and the fragment-based approach.[10]

The branching cascades technique[11] has attracted considerable interest over the past decade for the efficient creation of polyfunctionalized diverse and complex framework libraries. The major advantage of this approach is that diversity is generated in a one-step/pot process by treating one or more polyfunctionalized precursors with different reagents/reactants or under various reaction conditions. Kumar and co-workers used chromone-based precursors[12] and more recently a de novo branching cascades approach to access complex molecular frameworks.[13] The O'Connell and Stockman groups reported a 12-fold branching pathway to access diverse natural product-like polycyclic scaffolds from a single keto-diester intermediate.[14] Patil and co-workers have disclosed a relay catalytic branching cascade technique utilizing alkynoic acids or alkynols[15] to access diverse polyheterocyclic scaffolds.[16] More recently, the same group developed an electrophile-induced branching cascades strategy to produce drug-like polyheterocycles from 2-alkynylbenzaldehydes.[17] Despite these elegant and powerful developments,[18] the existing pathways require either a battery of different reaction conditions or expensive transition metal catalysts to generate structural diversity. Moreover, the majority of reported transformations require long reaction times, detracting from their appeal as chemical tools to enable rapid compound optimization.

Scheme 1. Proposed Metal-Free Microwave-Assisted Branching Cascades Strategy to Diverse Polycyclic Scaffolds



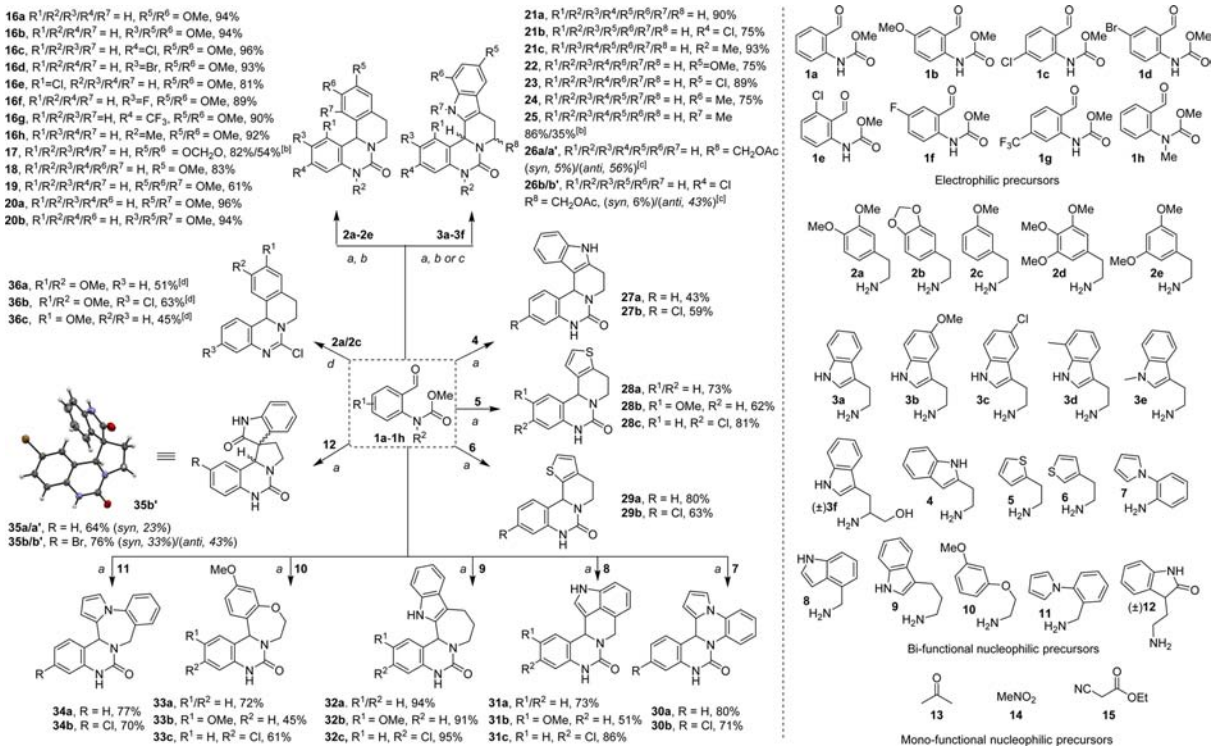
Accordingly, the development of an expedient, metal-free, and environmentally benign branching cascades protocol, requiring short reaction times to generate diverse scaffold libraries, would be of considerable interest.

As part of our continued interest in diversity-oriented synthesis of *N*-heterocycles,[19] we recently reported[20] a novel approach to highly functionalized and biologically significant[21] 3,4-dihydroquinazolinones (DHQs) based on *N*-acyliminium ion chemistry.[22] We envisioned that *N*-acyliminium ion intermediates (**I**), generated in situ from an *o*-formyl carbamate electrophile (**A**) and an amine nucleophile (**B**) under microwave irradiation, would undergo *N*-acyliminium ion cyclization with an appropriate pendant aromatic/heteroaromatic ring system to provide direct access to diverse polyheterocyclic DHQ scaffolds (**C**)[23] (Scheme 1). With the aim of discovering an efficient, flexible approach to build skeletal diversity in a rapid fashion, we sought to develop a new microwave-assisted, branching cascades protocol via a novel cascade imine/cyclization/*N*-acyliminium ion cyclization reaction sequence. To the best of our knowledge, this is the first report highlighting the use of both branching cascades and microwave irradiation to create extensive skeletal diversity requiring short (20−30 min) reaction times. Herein, we report a highly efficient, metal-free microwave-assisted branching cascades strategy to access natural product-like libraries of 3,4-dihydroquinazolinone-embedded polyheterocyclic frameworks using precursors that

Received: September 14, 2016
Published: October 11, 2016

DOI: 10.1021/acs.orglett.6b02774
Org. Lett. 2016, 18, 5392−5395

Scheme 2. Microwave-Assisted Branching Cascades Route to Diverse 3,4-Dihydroquinazolinone Polyheterocyclic Scaffolds



[a]Reaction conditions: Unless otherwise stated, reactions were performed with 1 equiv of *o*-formyl carbamate (**1a**−**1h**), 1.3 equiv of amine (**2a**−**2e**, **3a**−**3f**, **4**−**12**) in 1 mL of AcOH, 140 °C, MW, 10−120 min. [b]HCl salt of amine used. [c]Two-step protocol for **26a**/**a**′−**26b**/**b**′: (i) AcOH, MW, 140 °C, 1 h; (ii) DMAP, Ac_2O (1.5 equiv), CH_2Cl_2, rt, 1 h. [d]Two-step protocol for **36a**−**36c**: (i) AcOH, MW, 140 °C, 20 min; (ii) $POCl_3$, reflux, 4 h.

either are commercially available or can be easily prepared by literature methods.[20]

We began our investigation by screening various solvents, acid promoters, temperatures, and reaction times under microwave irradiation (see Supporting Information), and after exhaustive optimization, we were pleased to identify productive reaction conditions. The reaction between **A** and **B** in AcOH under microwave irradiation at 140 °C and/or further treatment with different reagents produced a library of skeletally diverse 3,4-dihydroquinazolinone scaffolds (**C**, **16**−**36**) with 12 distinct frameworks (Scheme 2).

For the initial study, amine **2a** was reacted with eight different carbamates (**1a**−**1h**) in AcOH at 140 °C under microwave irradiation to afford fused 3,4-diydroquinazolinone heterocycles **16a**−**16h** in up to 96% yield (Scheme 2). Notably, the reaction worked well with carbamates containing halogen, electron-donating and -withdrawing groups to afford DHQs in excellent yields. Similarly, amines **2b**−**2d** reacted smoothly with carbamate **1a** to furnish DHQs **17**−**19** in good to excellent yields (61−83%). The reaction also performed well with amine **2e** and carbamates **1a** and **1b** to give **20a** and **20b** in excellent yield. Next, the scope of tryptamine **3a** was investigated with carbamates **1a**, **1c**, and **1h**, and we were pleased to observe the formation of fused indoloquinazolinones **21a**−**21c** in up to 93% yield. Furthermore, the substituted tryptamines **3b**−**3e** reacted efficiently with carbamate **1a** to afford pentacyclic DHQs **22**−**25** in up to 89% yield. Interestingly, upon treatment with carbamate **1a** and **1c**, amine **3f** gave a mixture of pentacyclic acetate diastereomers **26a** (*syn*, 5%), **26a**′ (*anti*, 56%) and **26b** (*syn*, 6%), **26b**′ (*anti*, 43%), respectively, in satisfactory yield based on a two-step reaction sequence. Notably, both diastereomers were easily separated by column chromatography. In addition, a significant preference for use of the amine nucleophile in free-base form was observed using **2b** and **3e** rather than the corresponding HCl salts. In both cases, the isolated yields of products **17** and **25** were substantially higher using the free-base nucleophile rather than the HCl salt (82% vs 54% and 86% vs 35%). Reaction of **4** with carbamates **1a** and **1c** was found to be sluggish and gave DHQ scaffold **27a** and **27b** in moderate to fair yields of 43% and 59%, respectively. Thiophene-2-ethylamine **5** also reacted smoothly with different carbamates **1a**−**1c** to produce thienoquinazolinones **28a**−**28c** in good yield (62−81%). Similarly, thiophene-3-ethylamine **6** gave the isomeric DHQ scaffold **29a** and **29b** in up to 80% yield without any side reaction derived from competing nucleophilic attack at the 4-position of the thiophene ring.

To further expand the scope of developed protocol, we subjected a range of amines (**7**−**12**) to our reaction conditions to create significant skeletal diversity. In this process, aniline derivative **7** reacted smoothly to provide pyrroloquinazolinones **30a** and **30b** in 80% and 71% yield, respectively. Cascade cyclization of the indole nucleus was also successfully induced by a 4-aminomethyl substituent in **8** to furnish quinazolinone scaffolds **31a**−**31c** in up to 86% yield. Aiming for seven-membered fused polyheterocyles, we subjected amine **9** to our reaction conditions in the presence of carbamates **1a**−**1c** to afford azepino-quinazolinones **32a**−**32c** in excellent yield (91−95%). The strategy also worked well for resorcinol amine derivative **10** to afford seven-membered fused oxazepinoquinazolinones **33a**−**33c** in moderate to good yield (45−72%) (Scheme 2). In addition, the structure of **33a** was confirmed by X-ray crystallographic analysis and shows a near perpendicular orientation of the two aromatic rings consistent with a substantial deviation from

DOI: 10.1021/acs.orglett.6b02774
Org. Lett. 2016, 18, 5392−5395

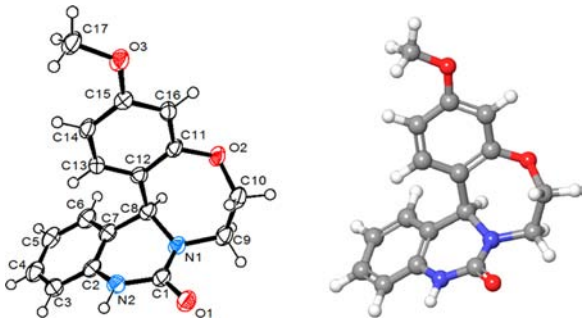


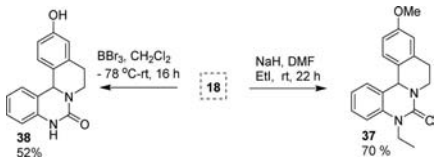
Figure 1. 3D structure of **33a**: ORTEP plot (left) and 3D structure from conformational analysis (right).

planarity imparted by the benzylic sp^3 center (see Figure 1).[25] A conformational analysis of **33a** identified a lowest energy conformation that was in excellent agreement with the crystal structure (RMSD = 0.2151 Å). Conformational analyses were then performed on representative compounds from all the scaffolds depicted in Scheme 2, and a similar perpendicular orientation of the DHQ and pendant aromatic rings was noted (see Supporting Information for details). This is important, as it shows that the compounds in Scheme 2 possess not only structural but also three-dimensional complexity, which is a key consideration in the design of diverse compound libraries.

The pyrrole-derived amine **11** also performed well to produce benzodiazepino DHQs **34a** and **34b** in 77% and 70% yield, respectively. Gratifyingly, the reaction of **12** with carbamate **1a** and **1c** provided the novel spirocycles **35a/a′** and **35b/b′** as diastereomeric mixtures in 64% and 76% yield, respectively. Thereafter, the diastereomers were separated by column chromatography and carbamate **1a** afforded **35a** (*syn*, 23%) while carbamate **1c** gave **35b** (*syn*, 33%) and **35b′** (*anti*, 43%), respectively. The spirocyclic skeleton and relative stereochemistry of **35b′** was confirmed by X-ray crystallographic analysis (see Scheme 2).[26] The two-pot reaction sequence of carbamates **1a** and **1c** with amine **2a/2c** followed by $POCl_3$ provided the advanced chloroquinazoline intermediates **36a** (51%), **36b** (63%), and **36c** (45%), respectively. The developed protocol offers a simple and easy approach for the rapid synthesis of libraries of nitrogen- and oxygen-containing five-, six-, and seven-membered fused heterocycles, including the useful 2-chloroquinazolines **36a**–**36c** and numerous halogen-bearing derivatives (e.g., **16c**, **16c**, **27a**, **30a**) which are all highly amenable for further elaboration into second generation libraries.

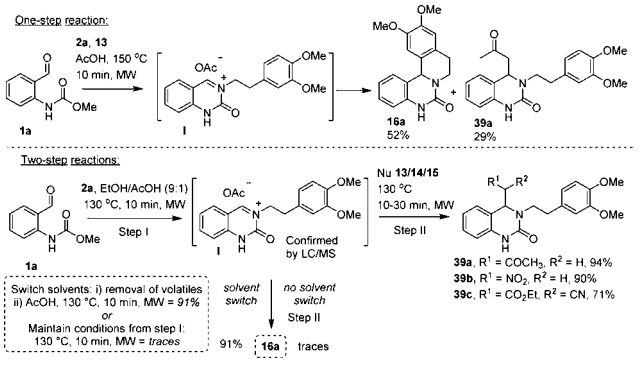
To further explore the utility of these compounds for second generation library development, we sought to exploit the *N*-1 moiety, which is present in almost all compounds in Scheme 2, as a synthetic handle for postcyclization elaboration (Scheme 3). After some experimentation, we were pleased to identify conditions suitable for selective *N*-1 alkylation and *N*-ethyl DHQ **37** was prepared in 70% yield by treating scaffold **18** with ethyl iodide and NaH at ambient temperature. Many of the derivatives in Scheme 2 contain a latent phenolic group, which if unmasked would provide a versatile site for subsequent scaffold modification. To investigate this strategy, the demethylation of **18** was conducted using BBr_3, and this afforded the phenolic DHQ derivative **38** in 52% yield.

Scheme 3. Second-Generation DHQ Library Strategies



Finally, to validate the proposed cascade imine/cyclization/*N*-acyliminium ion cyclization reaction pathway in Scheme 1, *N*-acyliminium ion (**I**) intermediate trapping experiments were also performed employing Mannich-type reactions.[27] We have recently reported intermolecular Mannich-type reactions between unactivated ketones and *N*-acyliminium ion intermediates to afford *β*-amino ketones in good yields.[20b] The one-step three-component reaction between carbamate **1a**, amine **2a**, and acetone (**13**) in AcOH gave **16a** in only 52% yield along with 29% of *β*-amino ketone **39a** (Scheme 4). We were delighted to observe formation of **39a**, as it suggested the intermediacy of the putative *N*-acyliminium ion (**I**) and, more importantly, that it is possible to trap this intermediate with an external nucleophile despite the presence of a pendant arene nucleophile. Pleasingly, by changing the solvent from AcOH to EtOH/AcOH (9:1), the competing intramolecular cyclization could be completely suppressed and a one-pot two-step reaction sequence afforded **39a** in 94% yield under optimal reaction conditions. Similarly, other nucleophiles **14** and **15** also produced C-4-substituted DHQs **39b** and **39c** in 90% and 71% yields, respectively (Scheme 4). To further validate our mechanistic hypothesis, a two-step reaction protocol using carbamate **1a** and amine **2a** in EtOH/AcOH (9:1) gave the *N*-acyliminium ion (**I**) (confirmed by LC/MS), which upon further heating in AcOH underwent intramolecular cyclization to afford **16a** in 91% yield whereas heating in the absence of additional AcOH provided only traces of **16a** (Scheme 4). Taken together, these results indicate that the reaction can be directed exclusively through an intra- or intermolecular cascade sequence by simply changing the solvent composition. Intramolecular cyclization requires the use of stoichiometric AcOH, suggesting that further Brønsted acid activation of the *N*-acyliminium ion intermediate is required to promote intramolecular attack by the pendent arene ring. The combination of EtOH/AcOH (9:1) allows the reaction to be paused at the *N*-acyliminium ion stage and selectively functionalized at the C4-position through the addition of external nucleophiles even in the presence of a highly electron-rich pendant arene moiety. These results are consistent with the proposed mechanistic pathway depicted in Scheme 1. In addition, the microwave-assisted reaction of amine **2b**, **2d**, **2e**, **4**, and **7** with *o*-formyl carbamates **1a** and **1c** also showed formation of traces of competing Pictet–Spengler[28] cyclization products (confirmed by LC/MS), which did not undergo further cyclization upon

Scheme 4. Mechanistic Study and Solvent-Controlled Branching Pathway to 3,4-Dihydroquinazolinones[a]



[a]For structures of nucleophiles **13**, **14**, and **15**, see Scheme 2.

DOI: 10.1021/acs.orglett.6b02774
Org. Lett. 2016, 18, 5392–5395

prolonged heating. This provides further evidence for the formation of an *N*-acyliminium ion intermediate in this process, as opposed to a cyclic amine derivative derived from the trapping of a linear imine intermediate via a Pictet−Spengler cyclization.

In conclusion, we have developed a highly efficient, metal-free, workup-free microwave-assisted branching cascades strategy to generate skeletally diverse 3,4-dihydroquinazolinone-embedded polyheterocyclic scaffolds in a one-pot operation. This protocol offers a rapid and direct approach to generate a library of more than 50 polyfunctionalized polyheterocyclic DHQs bearing 12 distinct scaffolds in excellent yields, starting from readily available and stable *o*-formyl carbamate precursors with a broad substrate scope. We have also described successful strategies for preparation of second-generation libraries through functionalization of the DHQ scaffold. Mechanistic investigations of the cascade cyclization confirmed the intermediacy of an *N*-acyliminium ion intermediate and led to the discovery of a solvent-controlled process for directing the reaction through an intra- or intermolecular cyclization cascade sequence. Thus, this reaction manifold allows access to an enormous range of diverse DHQ derivatives covering novel chemical space, and further investigations to explore the biological activity of these compounds are underway 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.6b02774.

Full experimental details and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: luke.odell@orgfarm.uu.se.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by Uppsala University and we thank Dr. Lisa Haigh (Imperial College London) and Dr. Anatoly Mishnev (Latvian Institute of Organic Synthesis) for assistance with accurate mass and X-ray structure determination.

■ REFERENCES

(1) (a) Li, J.; Ballmer, S. G.; Gillis, E. P.; Fujii, S.; Schmidt, M. J.; Palazzolo, A. M. E.; Lehmann, J. W.; Morehouse, G. F.; Burke, M. D. *Science* **2015**, *347*, 1221. (b) Galloway, W. R. J. D.; Stokes, J. E.; Spring, D. R. *Small Molecule Medicinal Chemistry*; John Wiley & Sons, Inc.: 2015; pp 77−101. (c) Stockwell, B. R. *Nature* **2004**, *432*, 846. (d) Tavassoli, A.; Hamilton, A. D.; Spring, D. R. *Chem. Soc. Rev.* **2011**, *40*, 4269.

(2) Galloway, W. R. J. D.; Diáz-Gavilán, M.; Isidro-Llobet, A.; Spring, D. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1194.

(3) Schreiber, S. L. *Science* **2000**, *287*, 1964.

(4) (a) Grabowski, K.; Baringhaus, K.-H.; Schneider, G. *Nat. Prod. Rep.* **2008**, *25*, 892. (b) Kaiser, M.; Wetzel, S.; Kumar, K.; Waldmann, H. *Cell. Mol. Life Sci.* **2008**, *65*, 1186. (c) Lenci, E.; Guarna, A.; Trabocchi, A. *Molecules* **2014**, *19*, 16506. (d) Spring, D. R. *Chem. Soc. Rev.* **2005**, *34*, 472. (e) Dobson, C. M. *Nature* **2004**, *432*, 824. (f) Thomas, G. L.; Wyatt, E. E.; Spring, D. R. *Curr. Opin. Drug Discovery Devel.* **2006**, *9*, 700. (g) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867. (h) Garcia-Castro, M.; Zimmermann, S.; Sankar, M. G.; Kumar, K. *Angew. Chem., Int. Ed.* **2016**, *55*, 7586.

(5) Dandapani, S.; Marcaurelle, L. A. *Curr. Opin. Chem. Biol.* **2010**, *14*, 362.

(6) (a) Kwon, O.; Park, S. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 13402. (b) Ko, S. K.; Jang, H. J.; Kim, E.; Park, S. B. *Chem. Commun.* **2006**, 2962. (c) Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. *Chem. Commun.* **2006**, 3296.

(7) (a) Oguri, H.; Schreiber, S. L. *Org. Lett.* **2005**, *7*, 47. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

(8) (a) Ascic, E.; Le Quement, S. T.; Ishoey, M.; Daugaard, M.; Nielsen, T. E. *ACS Comb. Sci.* **2012**, *14*, 253. (b) Luo, T.; Schreiber, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5667. (c) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48.

(9) Rolfe, A.; Lushington, G. H.; Hanson, P. R. *Org. Biomol. Chem.* **2010**, *8*, 2198.

(10) (a) Hung, W.; Ramek, A.; Wang, Y.; Kaya, T.; Wilson, J.; Clemons, P.; Young, D. W. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6799. (b) Murray, C. W.; Rees, D. C. *Nat. Chem.* **2009**, *1*, 187. (c) Hajduk, P. J.; Greer, J. *Nat. Rev. Drug Discovery* **2007**, *6*, 211.

(11) (a) Sharada, D. S.; Shinde, A. H.; Patel, S. M.; Vidyacharan, S. *J. Org. Chem.* **2016**, *81*, 6463. (b) Patil, N. T.; Bansode, A. H.; Chimala, P. *ChemCatChem.* DOI 10.1002/cctc.201600766.

(12) (a) Liu, W.; Khedkar, V.; Baskar, B.; Schürmann, M.; Kumar, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 6900. (b) Murali, A.; Medda, F.; Winkler, M.; Giordanetto, F.; Kumar, K. *Bioorg. Med. Chem.* **2015**, *23*, 2656.

(13) Garcia-Castro, M.; Kremer, L.; Reinkemeier, C. D.; Unkelbach, C.; Strohmann, C.; Ziegler, S.; Ostermann, C.; Kumar, K. *Nat. Commun.* **2015**, *6*, 6516.

(14) Robbins, D.; Newton, A. F.; Gignoux, C.; Legeay, J.-C.; Sinclair, A.; Rejzek, M.; Laxon, C. A.; Yalamanchili, S. K.; Lewis, W.; O'Connell, M. A.; Stockman, R. A. *Chem. Sci.* **2011**, *2*, 2232.

(15) Bansode, A. H.; Shaikh, A. C.; Kavthe, R. D.; Thorat, S.; Gonnade, R. G.; Patil, N. T. *Chem. - Eur. J.* **2015**, *21*, 2319.

(16) Patil, N. T.; Shinde, V. S.; Sridhar, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 2251.

(17) Patil, N. T.; Konala, A.; Sravanti, S.; Singh, A.; Ummanni, R.; Sridhar, B. *Chem. Commun.* **2013**, *49*, 10109.

(18) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104.

(19) Sawant, R. T.; Stevenson, J.; Odell, L. R.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2013**, *24*, 134.

(20) (a) Stevens, M. Y.; Wieckowski, K.; Wu, P.; Sawant, R. T.; Odell, L. R. *Org. Biomol. Chem.* **2015**, *13*, 2044. (b) Sawant, R. T.; Stevens, M. Y.; Odell, L. R. *Eur. J. Org. Chem.* **2015**, *2015*, 7743. (c) Sawant, R. T.; Stevens, M. Y.; Odell, L. R. *Molbank* **2015**, *2015*, M866.

(21) (a) Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *J. Med. Chem.* **2000**, *43*, 2019. (b) Barrow, J. C.; Rittle, K. E.; Reger, T. S.; Yang, Z.-Q.; Bondiskey, P.; McGaughey, G. B.; Bock, M. G.; Hartman, G. D.; Tang, C.; Ballard, J.; Kuo, Y.; Prueksaritanont, T.; Nuss, C. E.; Doran, S. M.; Fox, S. V.; Garson, S. L.; Kraus, R. L.; Li, Y.; Marino, M. J.; Kuzmick Graufelds, V.; Uebele, V. N.; Renger, J. J. *ACS Med. Chem. Lett.* **2010**, *1*, 75.

(22) (a) Maryanoff, B. E.; Zhang, H.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Yazici, A.; Pyne, S. *Synthesis* **2009**, *2009*, 339. (d) Yazici, A.; Pyne, S. *Synthesis* **2009**, *2009*, 513.

(23) (a) Diness, F.; Beyer, J.; Meldal, M. *Chem. - Eur. J.* **2006**, *12*, 8056. (b) Kano, S.; Yuasa, Y.; Shibuya, S. *Synthesis* **1984**, *1984*, 1071. (c) Klein, G.; Ostresh, J. M.; Nefzi, A. *Tetrahedron Lett.* **2003**, *44*, 2211.

(24) (a) Hasegawa, H.; Muraoka, M.; Matsui, K.; Kojima, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 727. (b) Hasegawa, H.; Muraoka, M.; Matsui, K.; Kojima, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3471.

(25) CCDC 1473149 contains the crystallographic data for **33a**.

(26) CCDC 1473153 contains the crystallographic data for **35b′**.

(27) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.

(28) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.

DOI: 10.1021/acs.orglett.6b02774
Org. Lett. 2016, 18, 5392−5395