Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Cascade Radical Cyclization on Alkynyl Vinylogous Carbonates for the Divergent Synthesis of Tetrasubstituted Furans and Dihydrofurans

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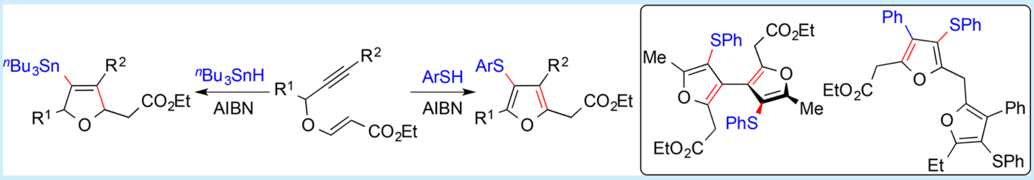
Supporting Information



ABSTRACT: A single alkynyl vinylogous carbonate was elaborated to tetrasubstituted furan or dihydrofuran via a cascade inter-intramolecular radical reaction by changing the radical being added. The strategy could be used in the synthesis of polycyclic heterocycles as well as bis-furan exhibiting atropisomerism. Installation of a new furan motif on the existing one was feasible by iteration. Stannyl dihydrofuran derivative was used in Stille coupling, whereas intramolecular Friedel−Crafts acylation on the furan gave furanonaphthol.

Densely substituted furans constitute important congeners present in many natural products and are fast emerging as an important class of therapeutic agents.[1] These scaffolds are also found in vital fragrances and in various biologically active molecules (Figure 1).[2] They have also proved to be efficient synthons in the total synthesis of various natural products.[3] Not surprisingly, synthesis of furans has attracted enormous attention in recent past.[4] However, transformation of furan to afford tetrasubstituted furans is extremely challenging due to regioselectivity issues, thus necessitating development of new methods consisting of appropriately substituted precursors.[5]

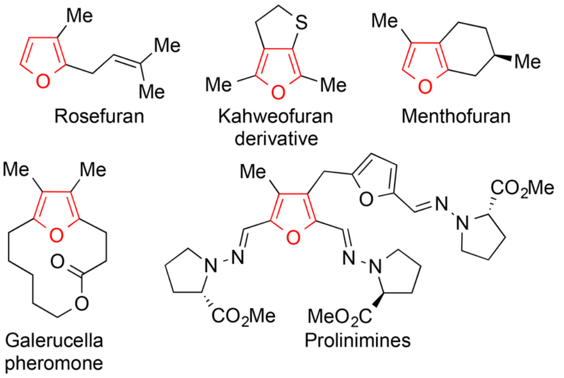


Figure 1. Biologically active substituted furans.

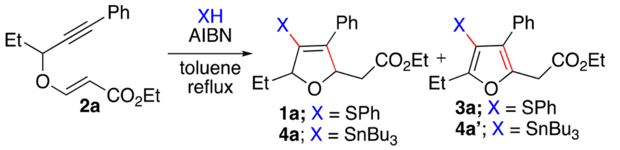
In this context, vinylogous carbonates/esters have been used in the synthesis of substituted furans, which typically involves a metal-assisted Claisen rearrangement (or its variant), followed by cyclization.[6] Interestingly, even though the vinylogous carbonates (β-alkoxy acrylates) are excellent radical precursors for the synthesis of cyclic ethers,[7] their utility for furan/dihydrofuran synthesis remains unexplored. It is also pertinent to mention that general strategies that give access to tetrasubstituted dihydrofuran are uncommon. While radical cyclization using thiyl or stannyl radical addition to terminal alkynes has been explored exhaustively, the same is not true for internal alkynes, perhaps due to regioselectivity problems encountered in these reactions.[8] Recently, we disclosed a highly regioselective addition of thiyl radical to internal alkynes, followed by cyclization for the synthesis of *N*-fused indole and indoline derivatives.[9] In another study, we had used a tandem radical cyclization to vinylogous carbonates for the stereoselective synthesis of angular triquinanes.[10] Herein, we disclose an approach for the divergent synthesis of tetrasubstituted furan/dihydrofuran by a cascade radical cyclization on alkynyl vinylogous carbonates, wherein the outcome is dependent on the hydrogen abstraction ability of the radical being added.

Our initial studies began with the idea of synthesizing tetrasubstituted dihydrofuran **1a** using a cascade radical cyclization from an alkynyl vinylogous carbonate **2a** initiated by an appropriate radical precursor (X = PhS and *n*-Bu$_3$Sn) (Table 1). It was envisaged that the problem of regioselectivity could be circumvented by employing aryl alkynes. To test our hypothesis, alkynyl vinylogous carbonate **2a** was subjected to radical cyclization using PhSH (1.0 equiv) and AIBN (0.3 equiv) in toluene at reflux. Interestingly, the tetrasubstituted dihydrofuran **1a** (X = SPh) was obtained as only minor product along with the tetrasubstituted furan **3a** (X = SPh)

Received: November 16, 2018

DOI: 10.1021/acs.orglett.8b03668

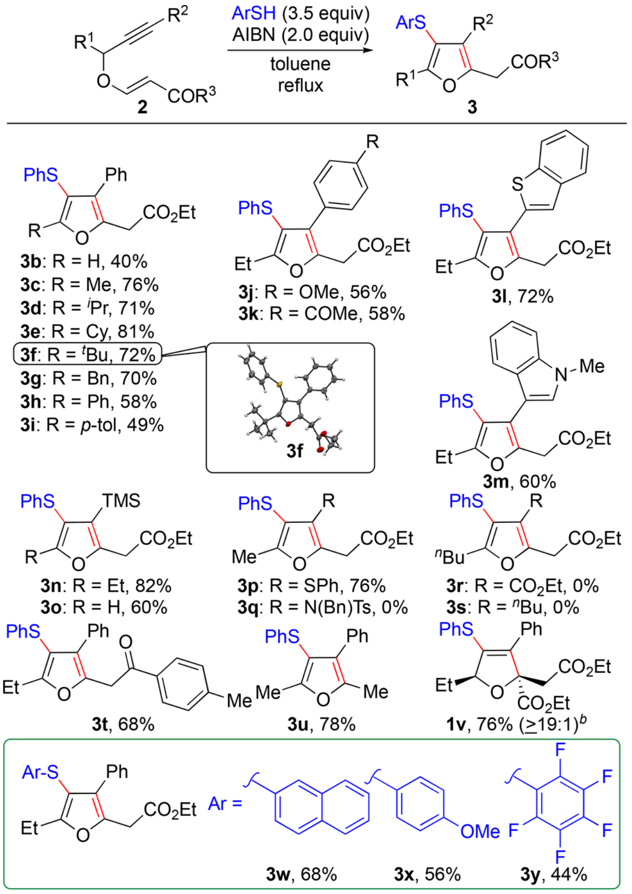
Table 1. Optimization of Cascade Radical Cyclization[a]



sr. no.	XH	equiv	equiv of AIBN	yield (%)[b]	
1	PhSH	1.0	0.3	**1a** (10)[c]	**3a** (42)
2	PhSH	2.0	0.3	–	**3a** (52)
3	PhSH	2.0	0.1	–	**3a** (33)
4	PhSH	3.5	0.1	–	**3a** (46)
5	PhSH	3.5	1.0	–	**3a** (57)
6	PhSH	3.5	2.0	–	**3a** (82)
7	*n*-Bu$_3$SnH	3.5	0.1	**4a** (24)[c]	–
8	*n*-Bu$_3$SnH	3.5	2.0	**4a** (81)[c]	–

[a] In all the cases **2a** (0.39 mmol) was reacted with AIBN and thiophenol/*n*-Bu$_3$SnH at reflux in dry toluene (15 mL) for ca. 6 h. [b] Isolated yield. [c] dr = 1:1, measured on the crude reaction mixture by ^{1}H NMR.

Scheme 1. Synthesis of Tetrasubstituted Furans 3[a]



[a] Isolated yield. [b] Numbers in parentheses refer to dr measured by ^{1}H NMR on the crude reaction mixture.

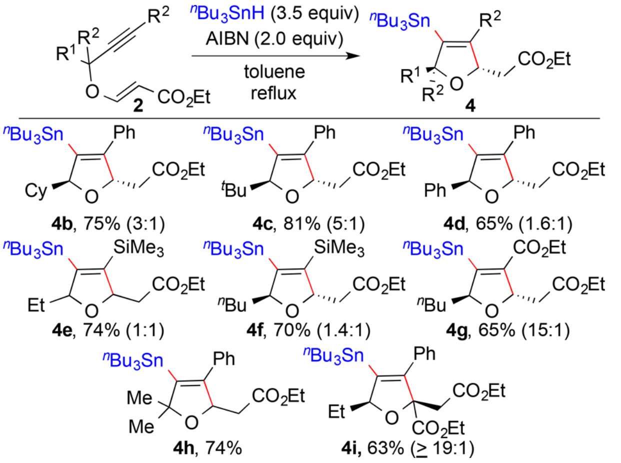
(Table 1, entry 1). Increasing the amount of PhSH resulted in an exclusive formation of furan **3a** (Table 1, entry 2). Reducing the amount of AIBN resulted in poorer yield, whereas increasing equivalents of both PhSH and AIBN resulted in an efficient formation of furan (Table 1, entries 3–6).

Interestingly, when *n*-Bu$_3$SnH was used in place of PhSH, no formation of furan derivative was observed, instead dihydrofuran **4a** (X= SnBu$_3$) was obtained as the only product (Table 1, entries 7 and 8) (see, Supporting Information for details). Given this divergence in the outcome, we decided to explore both these reactions to study their scope and utility.

To begin with, attention was turned toward the synthesis of furan derivatives **3**. Various alkynyl vinylogous carbonates **2b–g** bearing aliphatic substitution at the α position of the oxygen were subjected to optimized reaction conditions to furnish the corresponding tetrasubstituted furans **3b–g** in good to excellent yield (Scheme 1). The structure of furan **3f** was also confirmed by single crystal X-ray diffraction studies.[11] The efficiency of the reaction was found to be unaffected by the steric bulk of the substitution. On the other hand, aromatic substitution at the α position led to tetrasubstituted furans **3h–i** with slightly diminished yields. Electron-donating and -withdrawing groups at the *para* position of the phenyl ring tethered to the alkynyl vinylogous carbonate had little impact on the formation of tetrasubstituted furans **3j–k**. Heterocycles namely, benzothiophene and *N*-methylindole bearing tetrasubstituted furans **3l–m** could also be accessed readily. Trimethylsilyl group too survived the radical cyclization and gave the corresponding tetrasubstituted furans **3n–o** in excellent to good yield. Alkynyl thioethers participated in the reaction with complete regioselectivity, and corresponding bisthiophenyl-substituted furan **3p** was formed as the sole product. Unfortunately, alkynes having alkyl, ester, or amino groups (ynamide) when subjected to optimized radical cyclization condition resulted in only decomposition of the starting compounds, and the corresponding tetrasubstituted furans **3q–s** could not be isolated. Alkynyl vinylogous ester and enol ethers too were found to be good substrates, and corresponding furans **3t–u** were obtained in good yield highlighting that the scope of the reaction is not limited to varied vinylogous carbonates. Moreover, ester-substituted vinylogous carbonate gave the corresponding dihydrofuran **1v** with excellent diastereoselectivity. Interestingly, 2-naphthalenethiol and thiophenols bearing electron-donating as well as -withdrawing substituents proved to be good radical precursors, and the tetrasubstituted furans **3w–y** were obtained in moderate yields. This suggested that differentiation can be brought about in the structure of the furan from very same precursors.

Next, the cascade radical cyclization for the synthesis of tetrasubstituted dihydrofuran was explored using tributyltinhydride as the radical precursor. As anticipated, substitution at the α position of the alkynyl vinylogous carbonate affected the diastereoselectivity of the reaction. Thus, while ethyl-substituted dihydrofuran **4a** was formed with poor diastereoselectivity (cf. Table 1), the cyclohexyl and *t*-butyl-substituted dihydrofurans **4b–c** were obtained with improved diastereoselectivity, with the latter being better (Scheme 2). However, the phenyl group as substitution furnished the dihydrofuran **4d** with reduced diastereoselectivity (dr = 1.6:1). The silyl group survived the radical reaction to form the tetrasubstituted dihydrofuran **4e–f** in excellent yield. Interestingly, the ester-substituted alkynyl vinylogous carbonate, which failed to give furan **3r** under thiyl radical conditions, participated smoothly in stannyl radical-mediated cascade cyclization to form dihydrofuran **4g** in good yield and diastereoselectivity (15:1). Further, alkynyl vinylogous carbonate with ester substitution also gave the corresponding stannyl-substituted dihydrofuran **4i** in good yield as a single

Scheme 2. Synthesis of Tetrasubstituted Dihydrofurans 4[a,b]

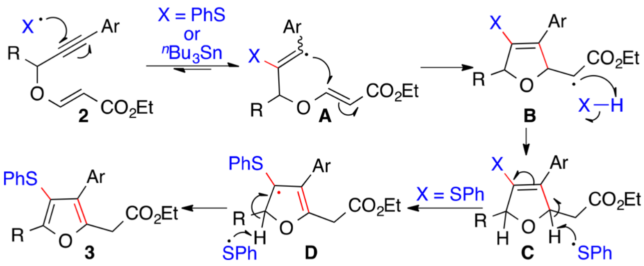


[a]Numbers in parentheses refer to dr measured by ^{1}H NMR on the crude reaction mixture. [b]Isolated yield.

diastereomer. Dihydrofurans **4h–i** are noteworthy as they contain tertiary ether linkages, which are otherwise difficult to access in good yields and diastereoselectivity by conventional methods.

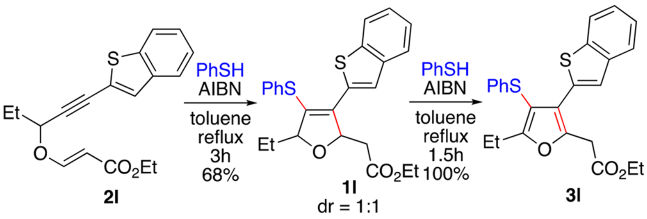
The divergent outcome of thiyl and stannyl radical initiated radical cyclization leading to furan or dihydrofuran could be explained as follows (Scheme 3): The intermolecular addition of initial thiyl or stannyl radical to alkyne in a regioselective manner generates the aryl vinyl radical **A**. The regioselectivity is perhaps the outcome of the relative stability of the vinyl radical.[8] Alternatively, the reversible addition of the thiyl or stannyl radical to the alkyne followed by the favored 5-*exo-trig* radical cyclization to vinylogous carbonate enables the equilibrium to shift in the forward direction to furnish **B**. This radical, formed α to the ester, **B** abstracts hydrogen from n-Bu$_3$SnH or PhSH to give the dihydrofuran derivative **C**. When the reaction is carried out with excess of PhSH and AIBN, another radical process is initiated in which PhS$^\bullet$ picks up hydrogen from the (either of the) second position of the dihydrofuran **C** (only one side abstraction of H is shown) to generate resonance stabilized allylic radical **D**. Abstraction of another hydrogen from the (corresponding) fifth position of the dihydrofuran **D** to gain aromaticity results in the formation of a highly substituted furan skeleton **3**.

Scheme 3. Plausible Mechanism



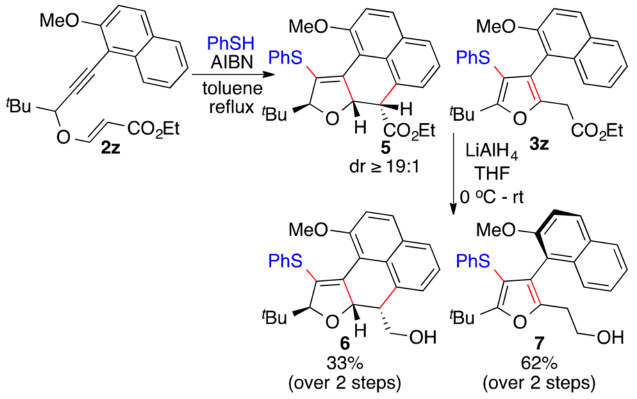
We carried out some experiments to test the proposed step of conversion of the dihydrofuran to furan (cf. **C** → **D** → **3** in Scheme 3). Thus, the vinylogous carbonate **2l** was subjected to radical condition, and reaction was stopped after 3 h to furnish the tetrasubstituted dihydrofuran **1l** (Scheme 4). When this dihydrofuran **1l** was further subjected to radical reaction using PhSH/AIBN in refluxing toluene, the corresponding oxidized tetrasubstituted furan **3l** was obtained quantitatively. On the other hand, when the stannyl-substituted dihydrofurans were resubjected to the radical conditions using n-Bu$_3$SnH/AIBN (or PhSH/AIBN), it only resulted in decomposition. Thus, it was apparent that thiyl radical enables 5-*exo-trig* cyclization as well as oxidation to give furan. It could be argued that since the bond energy of PhS-H is greater than that of n-Bu$_3$Sn-H, the thiyl radical can participate in oxidation of dihydrofurans to the corresponding furans.[12]

Scheme 4. Support for the Proposed Mechanism



In one of the experiments, when β-methoxy naphthyl-substituted alkynyl vinylogous carbonate **2z** was subjected to cascade radical cyclization under optimized conditions, formation of an inseparable mixture of the dihydrofuranyl tetracyclic-fused framework **5** along with the corresponding tetrasubstituted furan **3z** was observed. The mixture upon reduction with LiAlH$_4$ furnished a separable mixture of alcohols **6** and **7** in 95% over two steps (Scheme 5).

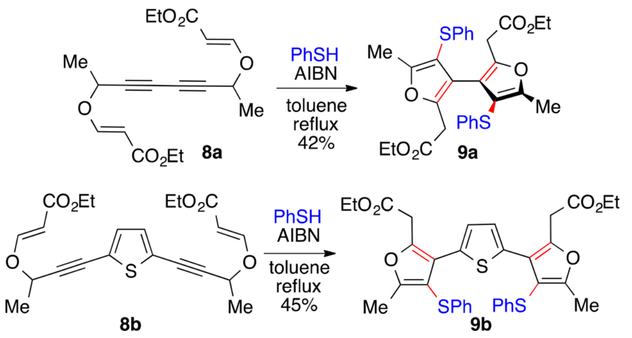
Scheme 5. Radical Cascade Cyclization Involving Intramolecular Aryl Trapping



Formation of the fused dihydrofuran **5** could be explained by the fact that, due to the proximity of the aryl ring tethered onto the alkyne, the radical α to the ester (cf. intermediate **B**, Scheme 3) adds to the former giving a six-membered ring stereoselectively. These experiments gave further support to the proposed mechanism. Interestingly, based on ^{1}H NMR, we observed that compound **7** demonstrated atropisomerism.

To probe this atropisomeric behavior further, we subjected diyne vinylogous carbonate **8a** to cascade 5-*exo-trig* radical cyclization and obtained the tetrasubstituted bis-furan **9a** in moderate yield. Surprisingly, this molecule **9a** also exhibited atropisomerism, which could be identified by the occurrence of an AB quartet for the CH$_2$ protons α to the ester in ^{1}H NMR spectrum. To the best of our knowledge, such atropisomerism displayed by a bis-furan molecule **9a** is unprecedented to date,[13] thus enhancing the uniqueness and importance of the method developed (Scheme 6). Further, 2,5-disubstituted

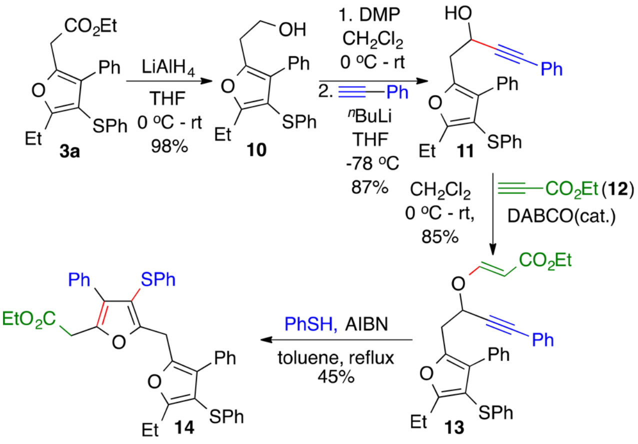
Scheme 6. Cascade Radical Cyclization on Diynes To Form Polyheterocycles



thiophene alkynyl vinologous carbonate **8b**, under the standard thiophenyl radical cascade condition, gave the tricyclic tetrasubstituted furanyl thiophene **9b** in moderate yield, which did not exhibit atropisomerism.

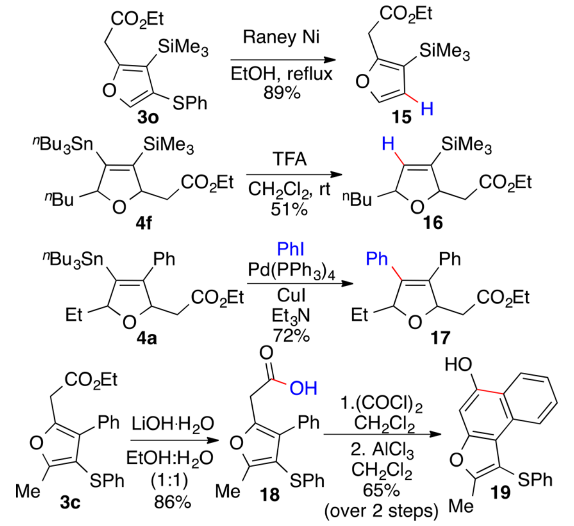
We envisioned that the ester group of the product furan is a good handle for allowing iteration of the reaction sequence. To test this, the tetrasusbstituted furan **3a** was reduced to the corresponding alcohol **10** (Scheme 7). Oxidation of alcohol **10** followed by addition of lithiated phenylacetylene to the resultant aldehyde furnished the secondary alcohol **11**. DABCO catalyzed Michael addition of the alcohol **11** to ethyl propiolate (**12**) gave the corresponding vinylogous carbonate **13**, which when subjected to cascade radical cyclization installed the second tetrasubstituted furan **14** in moderate overall yield.

Scheme 7. Iterative Strategy for the Synthesis of Non-Adjacent Tetrasubstituted Bis-furans



We also explored functionalization of the furans **3** and dihydrofurans **4**. Thus, desulfurization of the furan **3o** led to the disubstituted silyl-furan **15**, which could be a potential synthon for rosefuran or its sila-analogue.[2] In another direction, acid-mediated destannylation of **4f** gave trisubstituted dihydrofuran **16**, a potential synthon for Hagen's gland lactone.[14] Stannyl-dihydrofuran **4a** also proved to be an excellent Stille coupling partner, and the tetrasubstituted dihydrofuran **17** was obtained in good yield (Scheme 8). Finally, base-mediated hydrolysis of the ester **3c** gave the acid **18**. Conversion of the acid **18** to its acid chloride followed by intramolecular Friedel–Crafts acylation gave a furanonaphthol derivative **19**.

Scheme 8. Functionalization of Furans 3 and Dihydrofurans 4



In conclusion, we have developed a robust, chemodivergent, cascade thiyl and stannyl radical cyclization on alkynyl vinylogous carbonates to gain an expeditious access to tetrasubstituted furans and dihydrofurans, respectively. The reaction displayed broad substrate scope even with thiophenols. Interestingly, PhSH not only acts as radical precursor but also acts as an oxidant (along with AIBN) converting the dihydrofurans to furans. Cascade radical cyclization on diynes gave the first example of atropisomeric bis-furan and is applicable to the synthesis of polyheterocyclic systems. The reaction sequence could be iterated to install a new furan ring. The dihydrofurans and furans could be elaborated to useful derivatives such as furanonaphthols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03668.

Synthetic procedures and characterization data of products (PDF)

Accession Codes

CCDC 1878359 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank SERB, New Delhi, for financial support. We acknowledge the efforts of Mr. Pradeep Billas (M.Sc., IIT Bombay) for carrying out the initial experiments in this project. We thank Mr. Darshan Mhatre of the X-ray facility of the Department of Chemistry, IIT Bombay, for collecting the crystallographic data and IRCC, IIT Bombay, for funding. We are grateful to IIT Bombay for the award of research fellowship to Padmaja and CSIR, New Delhi, to V.P. and Y.G.S.

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Org. Lett. XXXX, XXX, XXX−XXX