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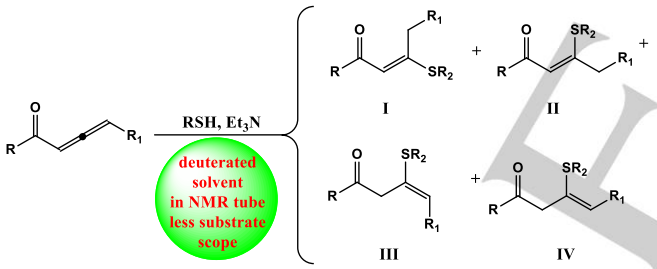
Revisiting the addition of *Insitu* Nucleophiles to Allenic Ketones: An Entry Towards Synthesis of Benzodioxins

Sushree Ranjan Sahoo[a] and Debayan Sarkar[a]*

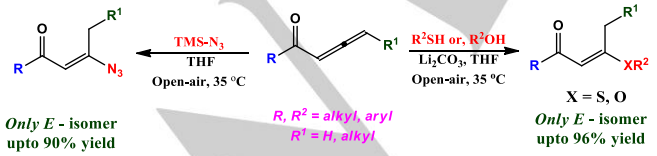
Abstract: The manuscript delineates a revisit towards regioselective addition of *insitu* generated negative nucleophiles to allenic ketones in the presence of a base. A wide variety of allenic ketones as well as nucleophiles are viable in this transformation. A direct ring annulation towards the challenging benzodioxin skeleton synthesis has been developed. Environmentally benign protocol and wide substrate scope are the notable features of this methodology.

Functionalized vinyl sulphides,[1] vinyl ethers[2] and vinyl azides[3] are potential ingredients in organic synthesis. Among these functionalized β-vinyl sulphides, ethers and azides, those containing a Michael acceptors such as a keto group at the adjacent sp^2 carbon, have great synthetic potential. Furthermore, they have combined the chemical reactivity to the molecules associated with these types of reactions. At present, there are very few reports for the preparation of these above vinyl compounds. Sugita[4] reported the formation of sulphides employing allenic ketone and thiol, but the main drawbacks were (1) formation of four different isomers depending upon starting materials and nucleophiles added, (2) reaction was carried out in deuterated solvents, (3) reaction was done in NMR tube, (4) limited substrate scope, (5) applicable to small scale synthesis. (**Scheme-1**)



Scheme 1. Sugita report

The addition of *insitu* generated nucleophiles to allenic ketones to form only one regioselective β-vinyl α,β-unsaturated ketones has been described as under (**Scheme-2**):



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Scheme 2. Regioselective β-vinyl α,β-unsaturated ketone syntheses

Concurrently, the generation of benzodioxin motifs are considered note-worthy. The benzodioxins exhibit a wide range of natural products[5] and drug research (**Figure-1**),[6] as well as building blocks in some organic processes[7]. Furthermore, their unique chemical and structural properties create further curiosity.[8]

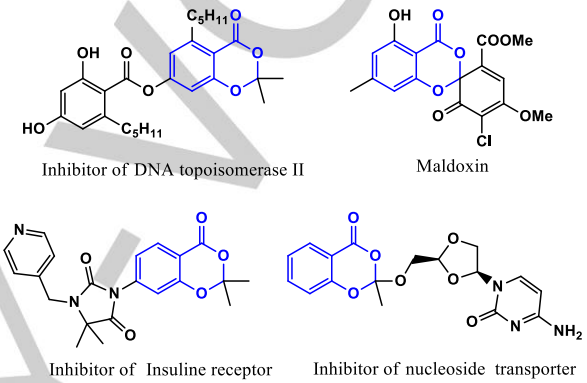
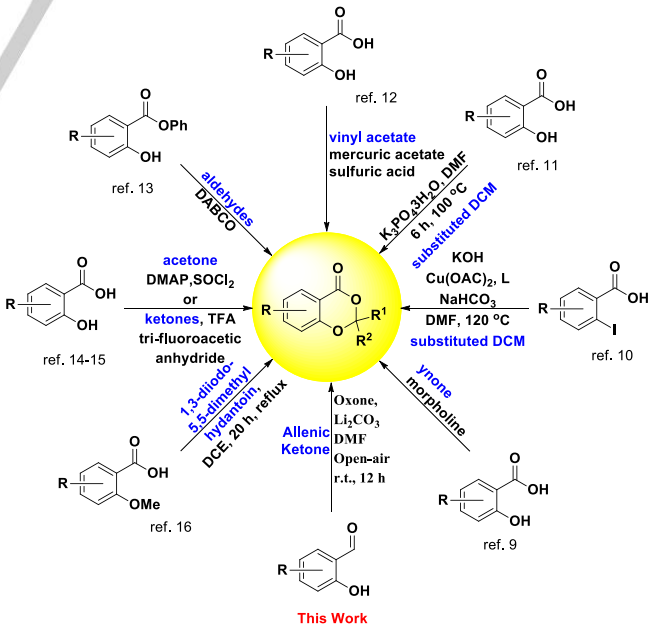


Figure 1. Biologically important natural products based on the benzodioxin skeleton

However, methodologies available for the construction of benzodioxin skeletons are documented below (**Scheme-3**):



Scheme 3. Strategies for the synthesis of benzodioxin moiety

The study was initiated by evaluating the parameters of the reaction, including the variation of bases, solvents, and temperature in the reaction of allenic ketone **1f** with *p*-

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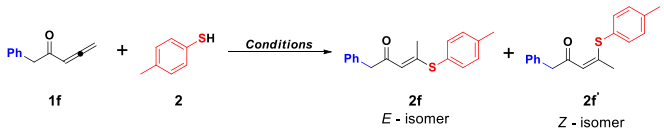
thiocresol **2** (**Table-1**). Firstly, bases were screened with THF as the solvent at r.t. - 35 °C. Li_2CO_3 was found to be the most effective base, with the reaction providing the desired sole product **2f** in 96 % yield (**Table-1**, entry 7) at 35 °C. On screening of solvents (**Table-1**, entries 9-13), our observation suggested that THF was optimum for the present reaction. Similar experiments were conducted in deuterated chloroform ($CDCl_3$) as a solvent and varying the base. The results are enlisted below (**Table-1**, entries 16-17).

Table 1. Optimization of reaction conditions[a] for the formation of **2f** and **2f'**



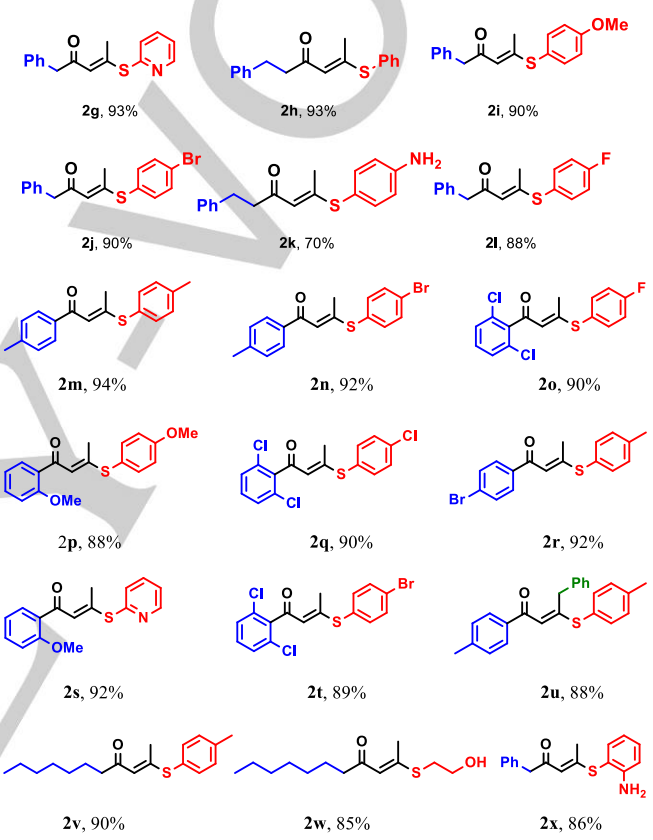
Entry No.	Solvent	Base	Temp. °C	Yield (%)[b] (**2f**:**2f'**)
1	CH_3CN	K_2CO_3	r.t.	60 (60:40)
2	THF	K_2CO_3	r.t.	70 (65:35)
3	THF	Na_2CO_3	r.t.	75 (65:35)
4	THF	Na_2CO_3	40	80 (85:15)
5	THF	Cs_2CO_3	40	70 (85:15)
6	THF	Li_2CO_3	40	85 (90:10)
7	THF	Li_2CO_3	35	96 (100:0)
8	THF	Li_2CO_3	r.t.	96 (55:45)
9	Dioxane	Li_2CO_3	35	85 (100:0)
10	Benzene	Li_2CO_3	35	70 (65:35)
11	$CHCl_3$	Li_2CO_3	35	78 (100:0)
12	DCM	Li_2CO_3	35	75 (100:0)
13	DCE	Li_2CO_3	35	80 (100:0)
14	THF	Et_3N	35	75 (83:17)
15	THF	Pyridine	35	70 (65:35)
16	$CDCl_3$	Et_3N	35	72 (80:20)
17	$CDCl_3$	Li_2CO_3	35	80 (100:0)

[a] Reaction conditions: **1** (1 equiv.), **2** (1.1 equiv.), base (1.1 equiv.), dry solvent (5 mL), for 5 h under air atmosphere. [b] *E*/*Z* is determined by ^{1}H-NMR.

With the optimized reaction conditions in hand, the scopes of the β- vinyl thioethers were investigated and the results are summarized in **Table-2**. The reaction is quite general and delivered a wide substrate scope of substituted aromatic allenic ketones and aliphatic allenic ketones. Both electron-donating as well as electron-withdrawing groups in different substituents of the aromatic ring smoothly afforded the desired products in high to excellent yields. Likewise, both electron-donating as well as electron-withdrawing groups containing aromatic thiol and aliphatic thiol, delivered the scopes of the β- vinyl thioethers in excellent yields.

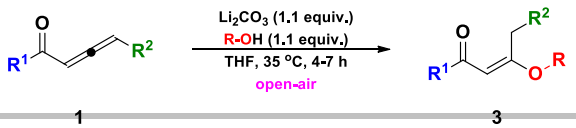
Table 2. Substrate scope for synthesis of (*E*) β-vinyl thioether

1 2 *E* - isomer

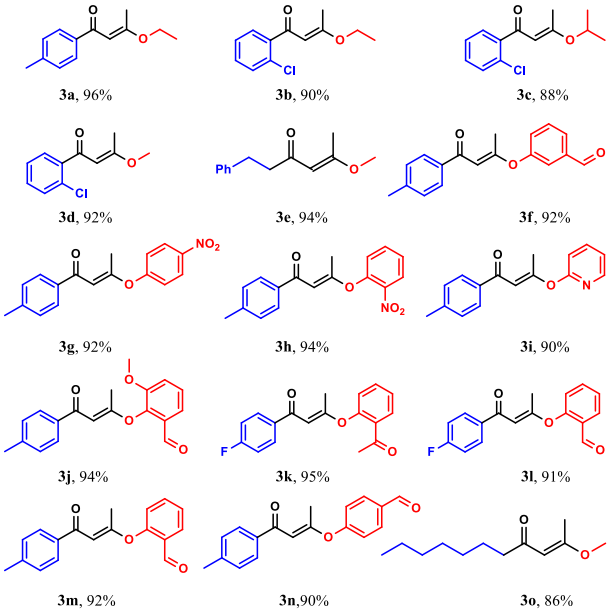


With the wider substrate scope of β-vinyl thioether in hand, the next target was to expand the synthetic utility of our methodology with the replacement of substituted thiophenols to substituted phenols, which delivered the regioselective β-vinyl ethers in good to excellent yields in the standard conditions and the results are summarized in **Table-3**. In this case also, the reaction was quite general and delivered for a wide substrate scope of substituted aromatic allenic ketones and aliphatic allenic ketones. Both electron-donating as well as electron-withdrawing groups in different substituents of the aromatic ring smoothly afforded the desired products in high to excellent yields. At the same point, both electron-donating as well as electron-withdrawing groups containing aromatic phenol and aliphatic alcohol delivered the scopes of the β-vinyl ethers in excellent yields.

Table 3. Substrate scope for (*E*) β-vinyl ether

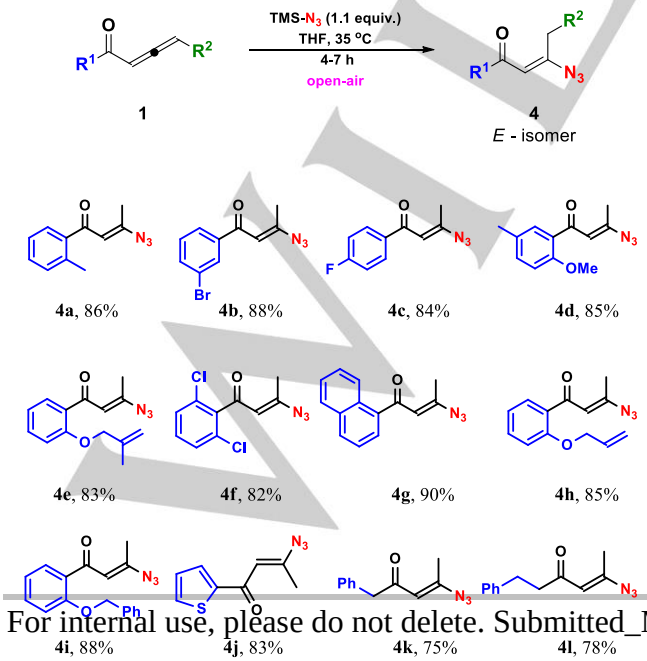


1 3 *E* - isomer



After this regioselective β-vinyl thioether and β-vinyl ether synthesis, our next target was to extend this methodology for the regioselective synthesis of β-vinyl azide. Fortunately, we were able to get our desired regioselective β-vinyl azides were achieved employing TMS-N_3 as a nucleophile in good to excellent yields without any external base and the results are summarized in **Table-4**. Both electron-donating as well as electron-withdrawing groups placed as substituents in the aromatic ring and aliphatic allenic ketones smoothly afforded the desired products in high to excellent yields.

Table 4. Substrate scope for (*E*) β-vinyl azides



The relative stereo-chemistry has been confirmed with multiple nOe for β-vinyl derivatives. (**Figure-2**)

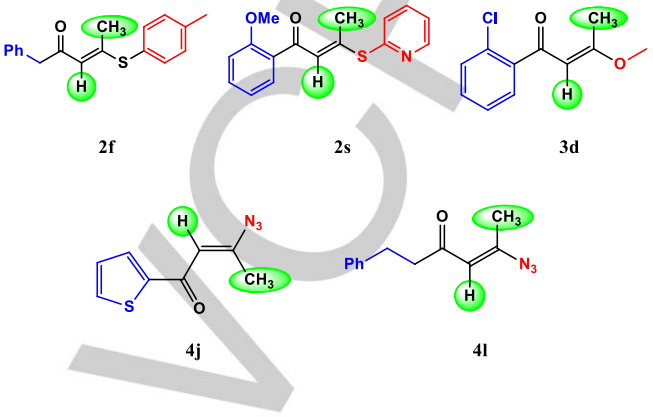
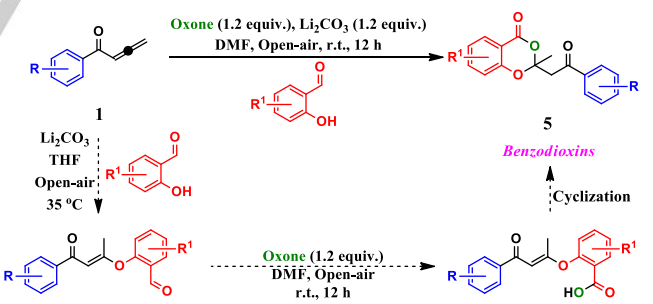
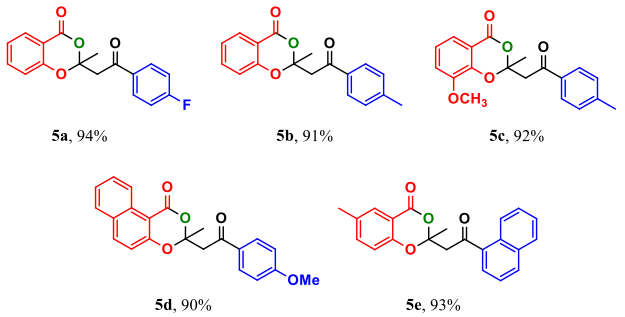


Figure 2. nOe experiments

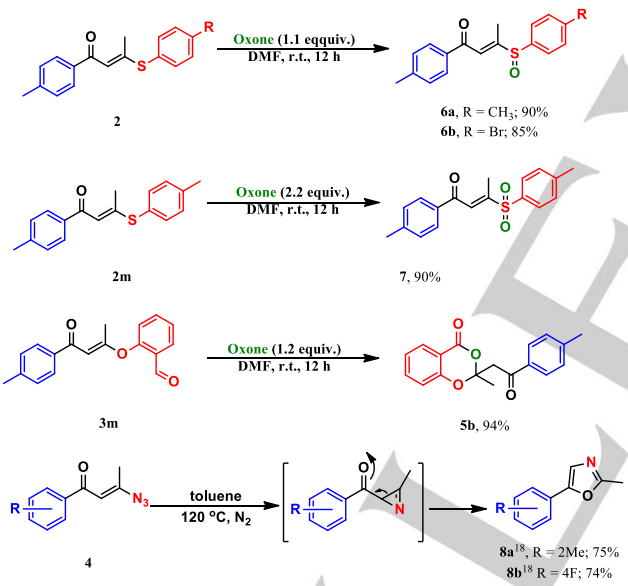
With the wider substrate scope of β-vinyl ketones in hand, the next target was to expedite the synthetic utility of our methodology with different allenic ketones and substituted *ortho*-hydroxyl benzaldehydes to deliver the challenging benzodioxin molecular skeletons in good to excellent yields (**Table-5**) in the presence of Li_2CO_3 and oxone with DMF solvent at room temperature under open-air conditions. The utility of this reaction concludes in transforming three reaction steps into a single step, which is an effective development towards the molecule.

Table 5. Substrate scope for benzodioxin skeleton synthesis





The β- vinyl thioether **2** was further functionalized by treating with oxone in DMF solvent to access β-vinyl sulfone **6** and **7** with an excellent yield at room temperature under open-air conditions due to sulfones containing molecules are bioactive in nature.[17] (**Scheme-4**) Similarly, when β-vinyl ether **3m** was treated with oxone in DMF solvent, it delivered the benzodioxins **5b** with 94 % at room temperature under open-air conditions. This further proved the reaction sequence of above one pot synthesis of benzodioxin skeletons. Further synthesis of exciting 2,5-disubstituted oxazoles **8** was executed with thermolysis of β-vinyl azides **4** by just heating at 120 °C in toluene under a nitrogen atmosphere with excellent yields *via* 2H-azirines.[3]



Scheme 4. Post-functionalization of the products

In summary, a revisit to addition of negative nucleophiles to allenic ketones has been demonstrated. This protocol shows regioselective tolerance with a broad range of functional groups and is environmentally benign. The reaction takes place through the sequence of allenic ketones and substituted *orho*-hydroxy benzaldehyde addition cascade towards the synthesis of the benzodioxin skeleton. Thus, the approach represents an economic and eco-friendly reaction pathway towards the adducts.

Experimental Section

General procedure (A) for vinyl α,β-unsaturated ketone: Allenic Ketones (1 equiv.) was taken in an oven dried single neck round bottom flask (10 mL capacity) equipped with a magnetic stir within THF (5 mL) in open atmosphere followed by addition of Li_2CO_3 (1.1 equiv.) (except azide) and corrsponding nucleophile (1.1 equiv.) and left it at 35 °C for 4-7 h. The progress of the reaction was monitored by TLC. After the complication of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate (3 X 20 mL). The organic part was washed with brine solution and dried over anhydrous sodium sulphate. Then, the solvent was evaporated under reduced pressure and the obtained crude mass was purified by column chromatography using silica gel in a specified solvent combination to deliver the desired compounds with expected purity.

General procedure (B) for benzodioxin synnthesis: Allenic Ketones (1 equiv.) was taken in an oven dried single neck round bottom flask (10 mL capacity) equipped with a magnetic stir within DMF (5 mL) in open atmosphere followed by addition of Li_2CO_3 (1.2 equiv.), substituted *ortho*-hydroxy benzaldehyde (1.1 equiv.) and oxone (1.2 equiv.), left it at room temperture (25 °C) for 12 h. The progress of the reaction was monitored by TLC. After the complication of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate (3 X 20 mL). The organic part was washed with brine solution and dried over anhydrous sodium sulphate. Then, the solvent was evaporated under reduced pressure and the obtained crude mass was purified by column chromatography using silica gel in a specified solvent combination to deliver the desired compounds with expected purity.

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Keywords: •regioselective •*insitu* nucleophiles •β-vinyl •benzodioxins

[1] (a) G. Perin, E. J. Lenardao, R. G. Jacob, R. B. Panatieri, *Chem. Rev.* **2009**, *109*, 1277; (b) T. Kondo, T. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205.

[2] (a) R. A. Jr. Longley, W. S. Emerson, *J. Am. Chem. Soc.* **1950**, *72*, 3079-3801; (b) A. C. Cope, H. L. Jr. Dryden, C. F. Howell, *Organic Syntheses*; Wiley & Sons: New York, 1963; Collect. *Vol. IV*, pp 816-819.

[3] G. Labbe, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 775-782.

[4] T. Sugita, M. Eida, H. Ito, N. Komatsu, K. Abe, M. Suama, *J. Org. Chem.* **1987**, *52* (17), 3789-3793.

[5] (a) L. Liu, *Mycology* **2011**, *2*, 37-45; (b) M. O. Adeboya, R. L. Edwards, T. Lassae, D. J. Maitland, L. Shields, A. J. S. Whalley, R. B. Gardens, B. Sciences, L. John, B. Street, T. Lassoe, D. J. Maitland, L. Shields, A. J. S. Whalley, *J. Chem. Soc. Perkin Trans.* **1996**, ***1***, 1419-1425.

[6] (a) G. Attardo, B. Zacharie, R. Rej, J. F. Lavallee, L. Vaillancourt, R. Denis, S. Levesque, US Pat, US2003013660(A1), **2003**; (b) H. Strobel, S. Ruf, D. Lesuisse, C. Nemecek, S. Guessregen, A. Lebrun, K. Ritter, J. L. Malleron, US Pat, WO2006/ 010642A1, **2007**; (c) H. Lin, T. Annamalai, P. Bansod, Y.-C. Tse-Dinh, D. Sun, *Med. Chem. Comm.* **2013**, *4*, 1613-1618.

[7] (a) A. Furstner, O. R. Thiel, G. Blanda, *Org. Lett.* **2000**, *2*, 3731-3734; (b) J. S. S. Rountree, P. V. Murphy, *Org. Lett.* **2009**, *11*, 871-874; (c) G. A. Holloway, H. M. Hügel, M. A. Rizzacasa, C. Herb, A. Bayer, M. E. Maier, *J. Org. Chem.* **2003**, *68*, 2200-2204; (d) P. A. Evans, M.-H. Huang, M. J. Lawler, S. Maroto, *Nat. Chem.* **2012**, *4*, 680-684; (e) T. Yoshino, I. Sato, M. Hirama, *Org. Lett.* **2012**, *14*, 4290-4292; (f) B. X. Li, K. Yamanaka, X. Xiao, *Bioorg. Med. Chem.* **2012**, *20*, 6811-6820; (g) J. S. Yadav, A. K. Mishra, S. S. Dachavaram, S. Ganesh Kumar and S. Das,

Tetrahedron Lett. **2014**, *55*, 2921-2923; (h) R. Mukkamala, A. Hossain, I. Singh Aidhen, *Nat. Prod. Res.* **2017**, *31*, 1085-1090; (i) R. Wisastra, M. Ghizzoni, A. Boltjes, H. J. Haisma, F. J. Dekker, *Bioorg. Med. Chem.* **2012**, *20*, 5027-5032; (j) N. Bajwa, M. P. Jennings, *J. Org. Chem.* **2006**, *71*, 3646-3649; (k) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681-7684; (l) D. C. Elliott, T. K. Ma, A. Selmani, R. Cookson, P. J. Parsons, A. G. M. Barrett, *Org. Lett.* **2016**, *18*, 1800-1803; (m) S. Kamisuki, S. Takahashi, Y. Mizushina, S. Hanashima, K. Kuramochi, S. Kobayashi, K. Sakaguchi, T. Nakata, F. Sugawara, *Tetrahedron* **2004**, *60*, 5695-5700.

[8] A. Ooguri, K. Nakai, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2009**, *131*, 13194-13195; (b) V. Kumbaraci, B. Aydogan, N. Talinli, Y. Yagci, *J. Polym. Sci. Part A: Polym. Chem.* **2012**, *50*, 2612-2618.

[9] X. He, Y. Li, M.g Wang, H.-X. Chen, B. Chen, H. Liang, Y. Zhang, J. Pang, L. Qiu, *Org. Biomol. Chem.* **2018**, *16*, 5533-5538.

[10] Y. Liu, M. Huang, L. Wei, *New J. Chem.* **2017**, *41*, 4776-4778.

[11] F. Lin, Q. Song, Y. Gao, X. Cui, *RSC Adv.* **2014**, *4*, 19856-19860.

[12] (a) D. T. Mowry, US 2510036 A, Dayton and Ohio, **1946**; (b) D. T. Mowry, W. H. Yanko, E. L. Ringwald, *J. Am. Chem.Soc.* **1947**, *69*, 2358.

[13] P. Perlmutter, E. Puniani, *Tetrahedron Lett.* **1996**, *37*, 3755.

[14] (a) A. Hadfield, H. Schweitzer, M. P. Trova, K. Green, *Synth. Commun.* **1994**, *24*, 1025; (b) I. Shibuya, Y. Gama, M. Shimizu, M. Goto, *Heterocycles* **2002**, *57*, 143.

[15] (a) N. Bajwa, M. P. Jennings, *J. Org. Chem.* **2006**, *71*, 3646; (b) T. Yoshino, I. Sato, M. Hirama, *Org. Lett.* **2012**, *14*, 4290; (c) R. G. Dushin, S. J. Danishefsky, *J. Am. Chem. Soc.* **1992**, *114*, 655.

[16] K. Kulbitski, G. Nisnevich, M. Gandelman, *Adv. Synth. Catal.* **2011**, ***353***, 1438.

[17] M. Y. Ansari, N. Kumar, A. Kumar, *Org. Lett.* **2019**, *21*, 3931-3936 and references therein.

[18] C. Songhuia, B. Donghua, S. Fenga, L. Jiana, L. Chunjua, J. Xueshun, *Chin. J. Chem.* **2012**, *29*, 1-6.

10.1002/ejoc.202000076

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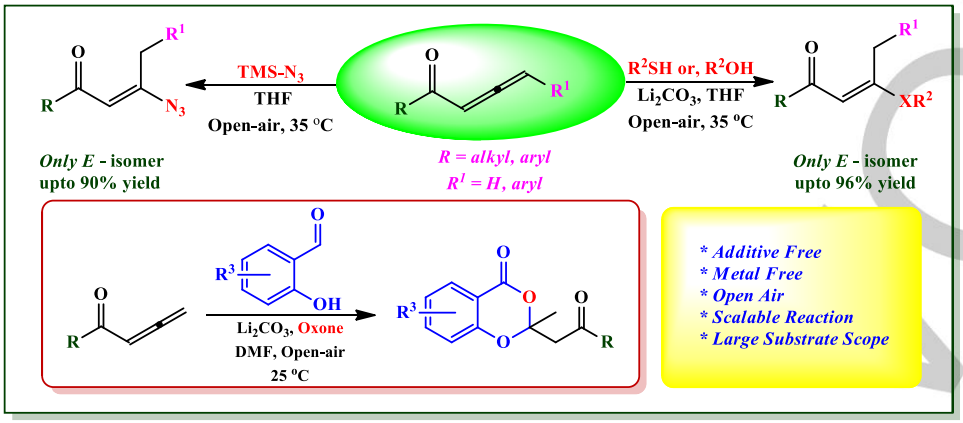

A revisit towards regioselective addition of *insitu* generated negative nucleophiles to allenic ketones in the presence of a base. A direct ring annulation towards the benzodioxin skeleton synthesis has been developed. In the process, the obtained *E*-vinyl kenones were readily transformed into sulfones and 2,5-disubstituted oxazole.

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Keywords: *Nucleophilic addition; allenyl ketones*