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Iodine(III) Promoted Ring Contractive Cyanation of Exocyclic β-enaminones to Cyanocyclopentanones Synthesis

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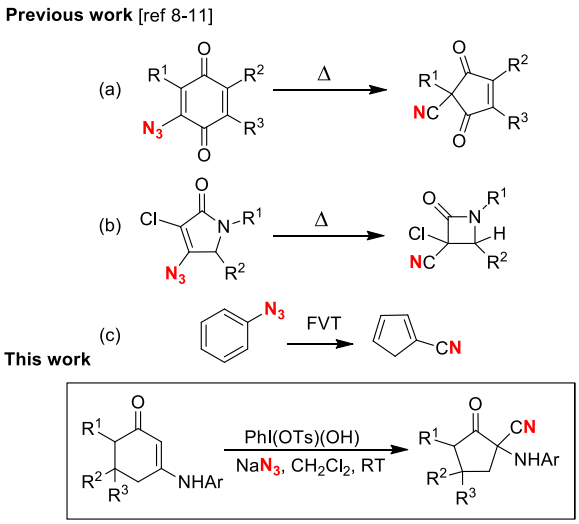
Abstract. A highly efficient hypervalent iodine promoted regiocontrolled ring contractive cyanation (RCC) reaction of exocyclic β-enaminones to cyanocyclopentanone (CCP) synthesis was demonstrated at ambient temperature with wide substrate scope. The methodology offers a facile technique to construct amino carbonitrile containing quaternary stereocenter at the α-position of cyclopentanone in good yields. The sequence of substrates addition can facilitate the reaction to follow the different pathways (free radical/ non radical) to afford the same final product was critically investigated.

Keywords: hypervalent iodine; cyclopentanone; ring contraction; *β*-enaminone; sodium azide



Scheme 1: common strategies of ring contractive cyanation.

Cyclopentanone derivatives with a quaternary stereocenter serve as basic structural skeletons in numerous biologically active natural products such as opaliferin[1], guanacastepene A[2] and estrone.[3] Traditional methods of cyclopentanone synthesis includes pyrolysis of adipic acid and its derivatives,[4] the oxidation of cyclopentenes[5] and ring expansion reactions.[6] Further, the ring contraction reaction is an alternative approach for cyclopentanone analogue synthesis from epoxy-/ unsaturated-cyclohexanones.[7]

Among the reported protocols of ring contraction reactions, the area of ring contractive cyanation (RCC) remains less explored, which attracted our attention to work in this area. However, Moore *et al.* described a conventional approach for the synthesis of 2-azetidinones *via* RCC reaction which is restricted to 4-azido-2-pyrrolinone compounds at elevated temperatures.[8a] Moreover, ring contraction and concurrent cyanation of 2-azido-1,4-quinone *via* a zwittazido cleavage mechanism has also been demonstrated.[8b,8c] Recently, flash vacuum thermolysis (FVT) has been applied for cyanocyclopentadiene synthesis from phenyl azide and isatin at 500-715 °C following cycloperambulatory mechanism.[9] Tichy *et al.* developed nitrile substituted cyclopentadiene from *N*-phenyl-3-nitropyridinium ion through vibrationally excited singlet nitrene formation.[10] The thermolytical decomposition of 2-azidopyridine-1-oxide to 2-cyano-1-hydroxy pyrroles in toluene,[11] are among the most highlighted protocols for the RCC reactions. In general, the use of organic azides as starting materials that led to the formation of nitrene intermediate under photolytic or thermal conditions paved the way to ring rearrangement and simultaneous cyanation reaction.

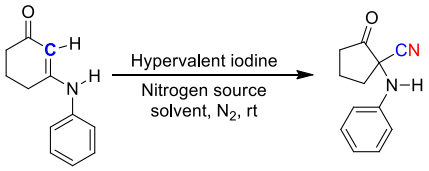
Recently, hypervalent iodine compounds have been widely used in different organic transformations owing to their mild oxidizing nature, excellent leaving tendency and ability to initiate free radical.[12] Moreover, hypervalent iodine mediated ring contraction reactions are limited to glycals,[13] cyclic ketones and olefins.[12b] To the best of our knowledge,

there is no available report for the RCC reaction of exocyclic β-enaminones using hypervalentiodine (III) (Kosers reagent) in combination with inorganic azide as the nitrogen source.

Over the last few years, we have been working to develop methodology for new and known classes of substituted cyclohexane-1,3-dione synthesis and their applications.[14] In context of our investigation, herein we report synthesis of different cyanocyclopentanones (CCP) from exocyclic β-enaminones *via* ring contractive cyanation (RCC) reaction using hydroxy(tosyloxy)iodobenzene (HTIB) and NaN_3 at ambient temperature. A very interesting and unusual role of sequential addition of substrates on the course of reaction mechanism for the final product formation was critically investigated.

In a trial reaction, we observed a very unusual ring contraction of exocyclic β-enaminones. With this lead, we began our optimization studies choosing 3-(phenylamino)cyclohex-2-enone **1a** as a bench stable model substrate using HTIB and sodium azide.

Table 1: Optimization studies of RCC reaction for CCP synthesis[a]



1a **2a**

Entry	Hypervalent iodine	Azide	Solvent	Yield [%][b]
1	HTIB	NaN_3	DCE	37
2[c]	HTIB	NaN_3	DCM	61
3	HTIB	NaN_3	$CHCl_3$	54
4	HTIB	$TMSN_3$	DCM	Trace
5	HTIB	NaN_3	Toluene	n.r.
6	HTIB	NaN_3	Benzene	n.r.
7	HTIB	NaN_3	CH_3OH	n.d.
8	HTIB	NaN_3	AcOH	n.r.
9	HTIB	NaN_3	HFIP	n.d.
10	HTIB	NaN_3	TFE	n.d.
11	HTIB	NaN_3	AcOEt	n.d.
12	DIB	NaN_3	DCM	n.r.
13	PIFA	NaN_3	DCM	n.r.
14[d]	HTIB	NaN_3	DCM	22
15[e]	HTIB	NaN_3	DCM	30
16[f]	HTIB	NaN_3	DCM	Trace
17	**HTIB**	**NaN_3**	**DCM**	**70**
18	HTIB	-	DCM	n.r.
19	-	NaN_3	DCM	n.r.

[a] Reaction conditions: **1a** (0.5347 mmol), hypervalent iodine(III) (0.6417 mmol), NaN_3 (2.673 mmol) in dichloromethane (2 mL) for 12 h.; n.d. = not detected, n.r. = no reaction, HTIB = [hydroxy(tosyloxy)iodo]benzene].

[b] Isolated yield.

[c] NaN_3 (1.2 equiv.) was used.

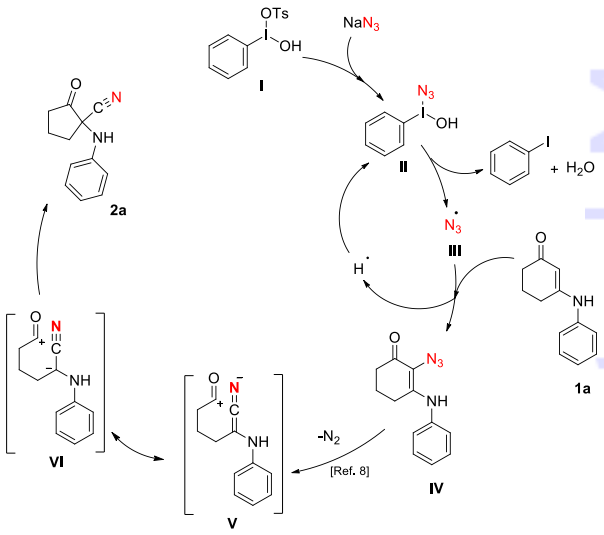
[d] HTIB (0.8 equiv).

[e] Reaction temperature was 40 °C.

[f] HTIB (2 equiv.).

Among the different solvents, only chlorinated solvents were found to be active for the RCC reaction (Table 1, entries 1-3, 17). Replacement of NaN_3 by $TMSN_3$ did not lead to the formation of desired RCC product (Table 1, entry 4). Then, various hypervalent iodine compounds were also screened but no product formation was observed (Table 1, entry 12-13). Further changing the reaction temperature or stoichiometry of the HTIB, no significant changes were observed in product yields (Table 1, entry 14-16). The highest yield of the product was obtained by using 1 equiv. of 1a, 1.2 equiv. of HTIB and 5 equiv. of NaN_3 in 2 mL CH_2Cl_2 solvent at ambient temperature under nitrogen atmosphere (Table 1, entry 17). During optimization we noticed very interesting role of sequential addition of substrates (NaN_3, HTIB and exocyclic β-enaminones) on their reactivity. The mechanism of the present reaction could probably follow two different routes depending on the mode of addition of sodium azide.

On the basis of the above observations and the precedent literature,[8-9],[15],[17] we propose a plausible mechanistic pathway for the ring contraction and concurrent cyanation reaction (Scheme 2). Initially, the ligand exchange reaction occurs between HTIB (**I**) and sodium azide leading to the formation of intermediate **II**. Thermal homolytic cleavage of **II**

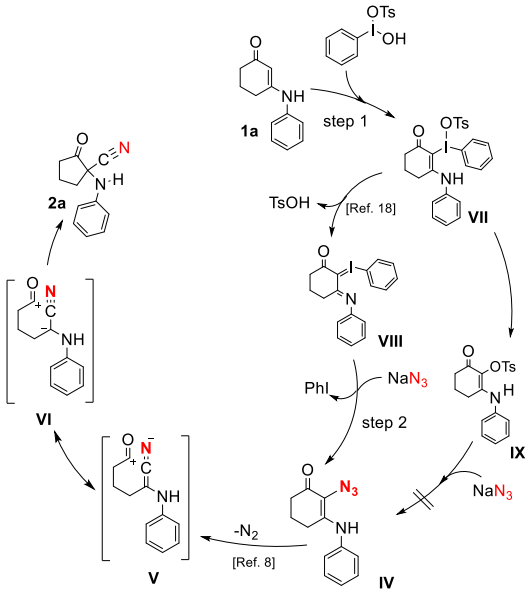


Scheme 2: Proposed mechanism for RCC reaction of exocyclic β-enaminone on one pot addition of sodium azide.

may generate the azide radical **III** which further trapped by the β-enaminone **1a** forming intermediate **IV**.[9],[17] The proposal subsequently supported by separate treatment with (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) and O_2 as radical scavenger which substantially decreased the product formation, could be an evidence that the reaction may be following radical pathway (supporting information). Recently, Hu *et al.* described the reactivity of vinyl azide and their participation in carbocyclic rearrangement reactions.[17a] They suggested that the

10.1002/adsc.201601208

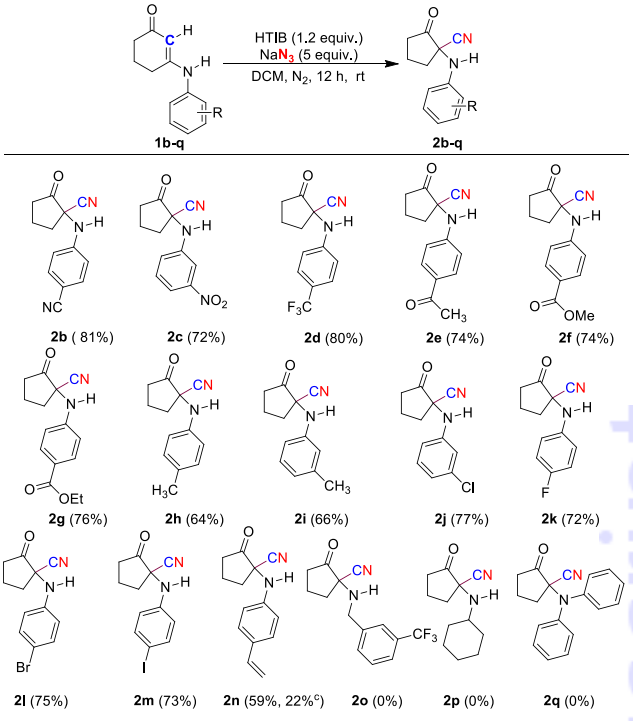
intermediate **IV** was similar to a cyclic vinyl azide and the ring strain usually inhibited the formation of bicyclic fused azirine and led to the formation of zwitterionic intermediate **V**. Intermediate **V** favored the formation of **2a** *via* an electrocyclic ring closing reaction of **VI**.[17b] [8b]



Scheme 3: Proposed mechanism for ring contraction and concurrent cyanation of exocyclic β-enaminone on sequential addition of sodium azide.

Interestingly, the reaction probably followed another route when HTIB was added into a solution of β-enaminone **1a** (step 1) and stirred for 1 h in DCM at ambient temperature followed by the addition of NaN_3 in step 2 (Scheme 3). In step 1, HTIB undergoes ligand exchange reaction with β-enaminone **1a** to form intermediate **VII,** which participated in conjugation through elimination of TsOH to give **VIII** as stable intermediate.[18] The intermediate **VIII** was purified, determined by mass and NMR spectroscopy (supporting information). Upon prolonged stirring at room temperature, intermediate **VII** slowly converted into intermediate **IX**, which was also confirmed by mass and NMR (supporting information). When **IX** was isolated and further treated with sodium azide, no conversion to product was observed, which indicated that the reaction does not react through intermediate **IX**. In step 2, when **VIII** was treated separately with sodium azide, the desired CCP product **2a** was obtained in comparable yield, which probably follow the similar path as that proposed in Scheme 2. Addition of TEMPO didn't show significant effect on the reactivity in this step-wise reaction, which could indicate the possible non radical pathway (Scheme 3).

Table 2: Electronic effect at the aromatic ring of exocyclic β-enaminones in RCC reaction.[a][b]

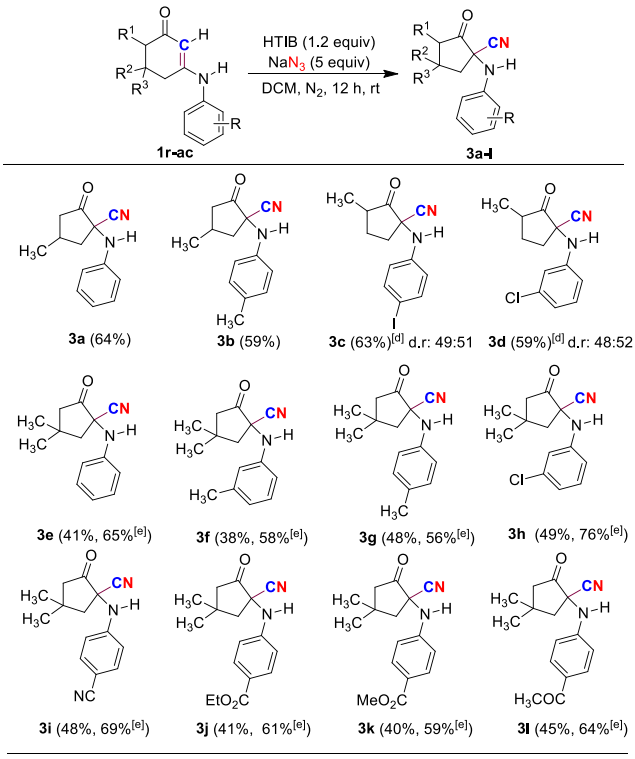


[a] Reaction conditions: 1a (1 mmol.), HTIB (1.2 mmol.) and sodium azide (5 mmol.) in dichloromethane solvent (2 mL) for 12 h at room temperature (rt).
[b] Isolated yield.
[c] Reaction carried out at 0 °C.

The optimized reaction conditions were further applied to explore the substrate diversity of various β-enaminones by assessing the electronic effect on amino substituted aryl groups (Table 2). Both the sequences as stated in Scheme 2 and 3 were followed to see any effect on the product yield, but no significant influence was observed for the selected substrates. Therefore, one pot addition of substrates was followed for simple and easy access of the reactions (Scheme 2). Electron deficient groups such as *p*-CN, *m*-NO_2, *p*-CF_3, *p*-$COCH_3$, *p*-CO_2CH_3 and *p*-$CO_2CH_2CH_3$ aryl amine substituted β-enaminones **1b-g** performed excellently and delivered the corresponding CCP products **2b-g** in 72-81% yields. Electron rich aryl amine substituted β-enaminones **1h-i** gave 64-66% yield of the desired product **2h-i**. Electron pulling effect may stabilized the zwitterionic intermediate **VI** and facilitate the formation of final product. Interestingly, the haloaryl amino substituted β-enaminones **1j-m** participated well in the reaction and delivered the anticipated cyclopentanones **2j-m** in 72-77% yields. In such cases, electronegativity of halogen atom might influence the facile transformation into the product. In addition, 4-vinyl substituted β-enaminone **1n** gave the desired cyclopentanone **2n** in 59% yield. We next targeted β-enaminones **1o-q** for RCC reaction, but unfortunately no product was detected, possibly due to either electronic or steric effect which hinders the formation

Table 3: Effect of substitution at cyclohexenyl moiety of exocyclic β-enaminones in RCC reaction.[a][b]

10.1002/adsc.201601208



[a] Reaction conditions: 1r-ac (1 equiv.), HTIB (1.2 equiv.) and NaN_3 (5 equiv.) in dichloromethane solvent (2 mL) for 12 h at room temperature (rt).
[b] Isolated yield.
[c] NaN_3 was added in one pot manner.
[d] Diastereomeric mixture was isolated.
[e] NaN_3 was added sequentially after 1 h.

of intermediates (IV, V and VI; Scheme 2) without aryl substitution at *N*-atom of β-enaminone. Moreover, *β*-enaminones derived from cyclopentane-1,3-dione and aryl amine did not lead to the formation of ring contraction product might be due to its high strain and instability in the reaction media (Scheme 4, Supporting information).

Next, we evaluated the substitution effect on cyclohexenone moiety of β-enaminones under standard reaction conditions. A series of β-enaminones with methyl substitution at various positions remarkably affect the yield of the corresponding CCP products (Table 3). Methyl substitution at C-5 and C-6 position of β-enaminones afforded desired CCP products **3a-d** in 59-64% yields. It is noteworthy that the compounds **3c** and **3d** were isolated as diastereomeric mixture (Table 3). This result suggests that β-enaminones of electron rich methyl substituted cyclohexane-1,3-diones may have largely destabilized transition states **V** to **VI** (Scheme 2) and therefore decrease the product yield. Further, this concept was supported by taking 5,5-dimethyl substituted β-enaminones **1v-1ac** under the standard reaction condition (Scheme 2) delivered the expected CCP products, **3e-l** only in 38-49% yields. Surprisingly, we found that the change in the mode of addition of sodium azide (Scheme 3) highly influenced the yields of **3e-l** to 56-76%. The reason may be in case of highly substituted electron rich β-enaminones **1v-1ac**, C-2 carbon behaving as good nucleophile and participated in the reaction with HTIB faster and favoured similar intermediates **XI** and **XII**, which afforded high yield of the products (Scheme 3).

The structure of the products was further confirmed by single crystal XRD study of compound **2a** and **3a** (Figure 1) (detailed provided in supporting information).

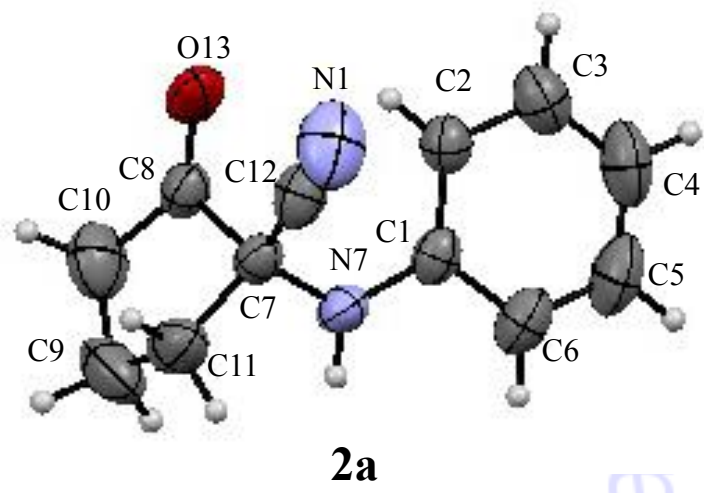


Figure 1: X-ray single crystal structures of **2a** and **3a**.[16]

In conclusion, we have demonstrated a general method for ring contractive cyanation (RCC) reaction of exocyclic β-enaminones to produce CCP products following a one-pot consecutive approach. The significant role of HTIB and sodium azide for product formation and the critical involvement in mechanistic steps were investigated. Several new classes of cyclopentanones were synthesized under this method with wide substrate scope in good yields.

Experimental Section

To an oven dried screw cap reaction vial 3-(phenylamino)cyclohex-2-enone **1a** (100 mg, 0.5347 mmol), HTIB (251.5 mg, 0.6417 mmol), sodium azide (179 mg, 2.6735 mmol) and dichloromethane (DCM, 2 mL) were added under N_2 atmosphere. The reaction mixture was allowed to stir for 12 h at room temperature under N_2 atmosphere and the progress of reaction was monitored by TLC. On completion of the reaction, the reaction mixture was concentrated under reduced pressure and the crude residue was subjected to column chromatography on silica gel (mesh 60-120) using hexane:EtOAc gradient to get the product **2a** (74.8 mg, 70%) as white solid; mp: 90.7-92.2 ^oC. ^1H, ^{13}C NMR, GC-MS, HRMS and FTIR data are provided in supporting information.

Acknowledgements

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References

[1] A. Grudniewska, S. Hayashi, M. Shimizu, M. Kato, M. Suenaga, H. Imagawa, T. Ito, Y. Asakawa, S. Ban, T. Kumada, T. Hashimoto, A. Umeyama, *Org. Lett.*, **2014**, *16*, 4695−4697.

[2] a) M. Mandal, H. Yun, G. B. Dudley, S. Lin, D. S. Tan, S. J. Danishefsky, *J. Org. Chem.*, **2005**, *70*, 10619-10637; b) S. Iimura, L. E. Overman, R. Paulini, A. Zakarian, *J. Am. Chem. Soc.*, **2006,** *128*, 13095-13101; c) K. Michalak, M. Michalak, J. Wicha, *J. Org. Chem.*, **2010**, *75*, 8337–8350.

[3] a) S. Prevost, N. Dupre, M. Leutzsch, Q. Wang, V. Wakchaure, B. List, *Angew. Chem. Int. Ed.*, **2014**, *53*, 8770 –8773; b) Y-P Xue, W-D Z. Li, *J. Org. Chem.*, **2011**, *76*, 57–64; c) R. Betík, P. Herrmann, M. Kotora, *Eur. J. Org. Chem.*, **2010**, *2010*, 646–655.

[4] J. Guo, G. Xu, Z. Han, Y. Zhang, Y. Fu, Q. Guo, *ACS Sustainable Chem. Eng.*, **2014**, *2*, 2259−2266.

[5] a) J. Gui, D. Liu, C. Zhuang, L. Yang, Y. Li, X. Zhang, 103664557, **2014**; b) Y. Feng, J. Hao, Y. Wang, C. Liu, L. Mao, P. Wang, 103349990, **2013**.

[6] J. W. Seo, H. J. Kim, B. S. Lee, J. A. Katzenellenbogen, D. Y. Chi, *J. Org. Chem.*, **2008**, *73*, 715-718.

[7] a) D. S. Reddy, W. R. Judd, J. Aube, *Org. Lett.*, **2003**, *21*, 3899-3902; b) M-C P. Yeh, M-N Lin, C-H Hsu, C-J Liang, *J. Org. Chem.*, **2013**, *78*, 12381−12396; c) L. Zhao, J. Wang, H. Zheng, Y. Li, K. Yang, B. Cheng, X. Jin, X. Yao, H. Zhai, *Org. Lett.*, **2014**, *16*, 6378-6381; d) R. Castillo, J. Andres, L. R. Domingo, *Eur. J. Org. Chem.*, **2005**, *2005*, 4705-4709.

[8] a) H. W. Moore, L. Hernandez, Jr., D. M. Kunert, F. Mercer, A. Sing, *J. Am. Chem. Soc.*, **1981**, *103*, 1769-1777. b) H. W Moore, *Acc. Chem. Res.* **1979**, *12*, 125. c) W. Weyler, Jr., D. S. Pearce, H. W. Moore, *J. Am. Chem. Soc.*, **1973**, *95*, 2603-2610.

[9] a) D. Kvaskoff, H. Luerssen, P. Bednarek, C. Wentrup, *J. Am. Chem. Soc.*, **2014**, *136*, 15203−15214. b) C. Wentrup, *Chem. Rev.*, **2017**, DOI: 10.1021/acs.chemrev.6b00738.

[10] S. E. Tichy, B. T. Hill, J. L. Campbell, H. I. Kenttamaa, *J. Am. Chem. Soc.*, **2001**, 123, 7923-7924.

[11] R. A. Abramovitch, B. W. Cue, Jr., *J. Am. Chem. Soc.*, **1976**, *98*, 1478-1486.

[12] a) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.*, **2016**, *116*, 3328−3435; b) L. F. Silva, Jr, *Molecules* **2006**, 11, 421-434; c) Yusubov, M. S., Chi, K-W., Park, J. Y., Karimov, R., Zhdankin, V. V., *Tetrahedron Letters.*, **2006**, *47*, 6305-6308.

[13] a) A. Kirschning, *Eur. J. Org. Chem.*, **1998**, *11*, 2267–2274. b) K. M. Engstrom, M. R. Mendoza, M. Navarro-Villalobos, D. Y. Gin, *Angew. Chem., Int. Ed. Engl.*, **2001**, *40*, 1128–1130.

[14] a) D. Sharma, Bandna, A. K. Shil, B. Singh, P. Das, *Synlett*, **2012**, *23*, 1199-1204; b) P. Das, D. Sharma, B. Singh, WO/2011/117881, **2011**; c) D. Sharma C. B. Reddy A. K. Shil, R. P. Saroach, P. Das, *Mol Divers*, **2013**, *17*, 651–659; d) V. Thakur, D. Sharma, P. Das, *Mol Divers*, **2016**, *20*, 29–40; e) D. Sharma, Bandna, C. B. Reddy, S. Kumar, A. K. Shil, N. R. Guha, P. Das, *RSC Adv.*, **2013**, *3*, 10335-10340.

[15] a) F. Xie, Z. Qi, X. Li, *Angew. Chem. Int. Ed.*, **2013**, *52*, 11862 –11866; b) K. Matcha, A. P. Antonchick, *Angew. Chem. Int. Ed.*, **2013**, *52*, 2082 –2086; c) R. Narayan, A. P. Antonchick, *Chem. Eur. J.*, **2014**, *20*, 1 – 6; d) X-Q. Li, W-K. Wang, Y-X. Han, C. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 2588-2598. (e) C. Thétaz, C. Wentrup, *J. Am. Chem. Soc.*, **1976**, 98, 1258-1259.

[16] CCDC number for compound **2a**: 1485839 and **3a**: CCDC 1485838, detailed provided in the Supporting information).

[17] a) B. Hu and S. G. DiMagno, *Org. Biomol. Chem.*, **2015**, *13*, 3844–3855. b) A. Hassner, N. H. Wiegand, H. E. Gottlieb, *J. Org. Chem.*, **1986**, *51*, 3176-3180.

[18] a) l. Papoutsis, S. Spyroudis, A. Varvoglis, *Tetrahedron Letters*, **1996**, *37*, 913-916; b) I. Papoutsis, S. Spyroudis, A. Varvoglis, C. P. Raptopoulou, *Tetrahedron*, **1997**, *53*, 6097-6112.

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