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Design and Application of Intramolecular Vinylogous Michael Reaction for the Construction of 2-Alkenyl Indoles

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Battu Harish,[a,b] Sanjay Yadav,[a,b] and Surisetti Suresh*,[a,b]

A base-mediated transformation planned on a designed intramolecular vinylogous Michael addition (intra-VMA) is presented to access 3-substituted 2-alkenyl indole derivatives. The reaction represents the first example of the intra-VMA for the construction of indoles. One-pot *N*-allylation of *ortho*-tosylamidocinnamates/congeners with γ-bromocrotonates followed by intra-VMA has been described to provide access to a diverse range of 2-alkenyl indole derivatives in high yields. The synthetic value of the developed intra-VMA has been demonstrated by gram-scale synthesis of a representative indole derivative and also in the formal synthesis of MK-7246: a Merck's clinical CRTH2 antagonist.

The indole core has been inspiring organic chemists and drug discovery research teams from the academia and industry.[1] This is due to the reasons that indole framework is of paramount importance owing to its ubiquitous presence in the natural products, the molecules essential for life-processes and life-saving drugs.[2] Probably, the construction of the indole nucleus has ranked as the highly attracted problems and resulted in the development of several 'named' reactions.[3] The development of new methods to construct 2,3-disubstituted indoles has received significant attention from the synthetic community.[4] Among them, in particular, 2-alkenyl substituted ones have received considerable attraction due their interesting chemistry and potential biological profiles (Figure 1).[5] The methods to access 2-alkenyl-3-substituted indoles include transition metal-mediated C–H functionalization of indoles at C2-position with alkenyl partners.[6] The groups of Fukuyama and Chatani, independently, reported palladium-catalyzed cross coupling of C2 pre-functionalized indole and alkenyl partners to access 2-alkenyl indoles.[7] Gevorgyan and co-workers reported an intramolecular palladium-catalyzed oxidative amination of furans to produce 2-alkenyl indoles.[8] Seo and Cheon reported a cyanide-catalyzed intramolecular imino-Stetter reaction for the synthesis of 2-alkenyl indoles.[9] Recently, we disclosed an NHC-catalyzed imine umpolung strategy for the synthesis of 2-alkenyl indoles.[10] On the other hand, the vinylogous principle has emerged as one of the important reaction strategies to construct C–C bonds and the resulted structural motifs are embedded with an additional alkenyl functionality.[11] Although the vinylogous variant of the Michael (conjugate) addition reaction has been well-explored, most of the reported methods describe the intermolecular versions (**Scheme 1a**).[12] The intra-VMA is still an underexplored reaction in spite of its potential to access useful carbo- and heterocyclic systems comprising an intact double bond that can be applicable to further organic transformations.[13] We have previously shown that intra-VMA followed by aromatization of *ortho*-O-allyl cinnamates resulted in the generation of substituted benzofurans involving the migration of the *exo*-double bond (**Scheme 1b**).[14]

We became interested to explore the intra-VMA chemistry to construct indole core (**Scheme 1c**). The indole nucleus has earned "privileged structure" status in medicinal chemistry/drug discovery processes.[15] We envisaged and designed the precursor **3a** possessing essential elements for the intra-VMA and **3a** can in turn be accessed from the reaction of *o*-tosylamidocinnamate **1a** and γ-bromocrotonate **2a**.

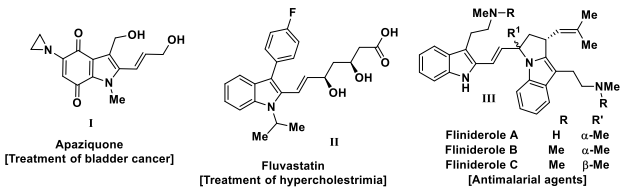

Fig 1 Representative biologically/therapeutically important 2-alkenyl-3-substituted indoles.

[a] *Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad 500 007, India. E-mail: surisetti@iict.res.in; suresh.surisetti@yahoo.in.*
[b] *Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India.*
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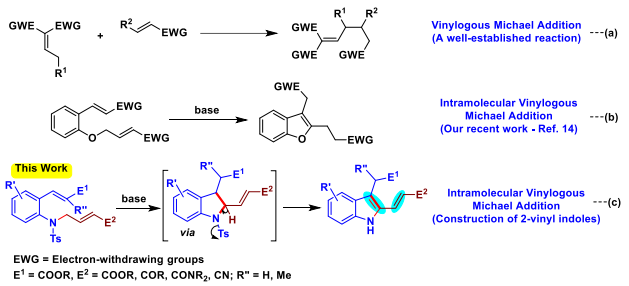
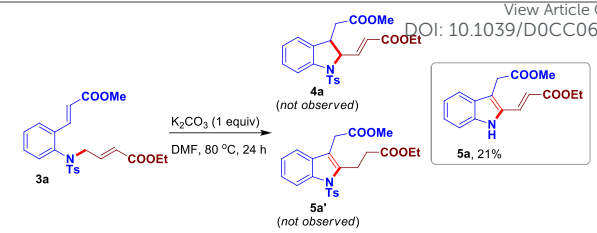


Scheme 1 Intermolecular- and intramolecular-vinylogous Michael addition reactions

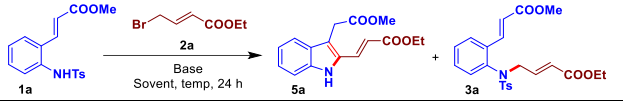
According to our hypothesis, treatment of **3a** with a base would generate a carbanion on the active methylene adjacent to nitrogen, which can be stabilized by the double bond of the α,β-unsaturated ester moiety. Intramolecular addition of the carbanion to the other conjugate acceptor in **3a** would produce dihydroindole **4a**. Thus generated dihydroindole **4a** (i) would undergo a base-mediated elimination of tosyl group followed by aromatization to lead to 3-subsituted 2-alkenyl indole derivative **5a** (or) (ii) 2-*exo*-double bond migration of **4a** involving aromatization would provide 2,3-disubstituted indole **5a'**, akin to the reported synthesis of 2,3-disubstituted benzofurans[14] involving intra-VMA. We commenced our study by treating **3a** with K_2CO_3 base in DMF at 80 °C. The reaction resulted in the formation of 2-acryl substituted indole-3-acetate **5a** in 21% yield with the retention of the (*E*)-geometry of the *exo*-double bond. However, the other products **4a**/**5a'** were not observed (**Scheme 2**). Probably, under the basic conditions aromatization involving tosyl group elimination is more feasible.

We next conducted a sequential transformation involving *N*-allylation—intra-VMA by using *o*-tosylamidocinnamate **1a** and γ-bromocrotonate **2a** in one-pot. The reaction of **1a** and **2a** in the presence of K_2CO_3 provided the desired product **5a** in 30% yield along with *N*-allylated intermediate **3a** in 42% yield (**Table 1**, entry 1). Note that the one-pot approach is more efficient than the step-wise process to produce 2-alkenyl substituted indole-3-acetate **5a** with complete control of the stereochemistry of the *exo*-double bond. Invigorated by the one-pot transformation, we carried out an optimization assay, using **1a** and **2a**, with an objective to improve the yield of **5a** and mitigate the formation of the *N*-allylated intermediate **3a** (**Table 1**). Accordingly, we screened different bases, solvents and reaction conditions. The use of bases like K_3PO_4, NaH, and DBU did not provide better results (**Table 1**, entries 2-4). The reaction of **1a** and **2a** in NMP or DMSO afforded slightly better results (**Table 1**, entries 5 and 6). An increase in the temperature from 80 °C to 120 °C in the one-pot reaction of **1a** and **2a**, in the presence of K_2CO_3 in DMSO, resulted in drastic improvement in the yield of **5a** while diminishing the formation of **3a** (**Table 1**, entries 7 and 8). Further increase in the temperature was not found to be useful (**Table 1**, entry 9). As it was expected this reaction failed in the absence of base (**Table 1**, entry 10) (see SI for an extensive optimization study).



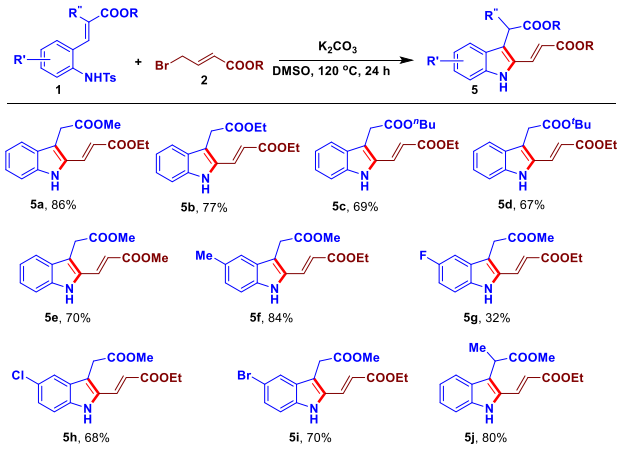
Scheme 2 The base-mediated intra-VMA.

Table 1 Optimization study[a]



Entry	Base	Solvent	Temp (°C)	%yield of 5a[b]	%yield of 3a[b]
1	K_2CO_3	DMF	80	30	42
2	K_3PO_4	DMF	80	10	28
3	NaH	DMF	80	12	32
4	DBU	DMF	80	24	30
5	K_2CO_3	NMP	80	34	28
6	K_2CO_3	DMSO	80	40	32
7	K_2CO_3	DMSO	100	72	14
8	***K_2CO_3***	***DMSO***	***120***	***86***	***10***
9	K_2CO_3	DMSO	150	80	08
10	—	DMSO	120	—	—

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), base (1.50 mmol), solvent (3 mL); [b]Isolated yields



Scheme 3 Synthesis of 2-alkenyl-3-indole acetate derivatives.

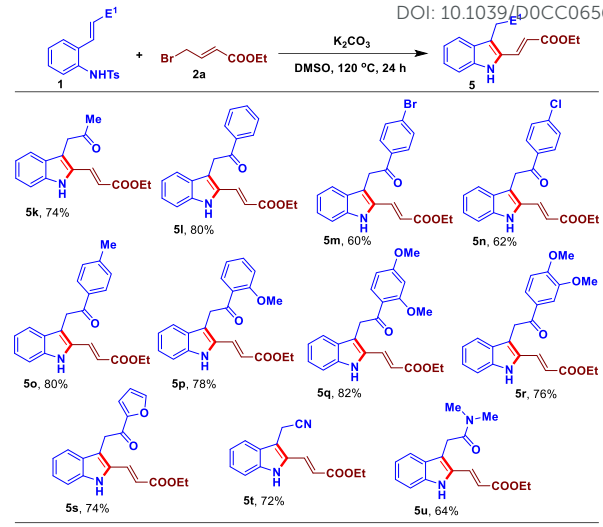
Later, we tested this transformation by using different departing groups on the nitrogen atom in place of tosyl (Ts) group in **1a**. It turned out that the tosyl group stood out to be the best among the groups tested including acetyl (Ac),

benzenesulfonyl (Bs), *p*-nitrobenzenesulfonyl (Ns), mesitylenylsulfony (Mts) and methanesulfonyl (Ms) (see, SI for more details).

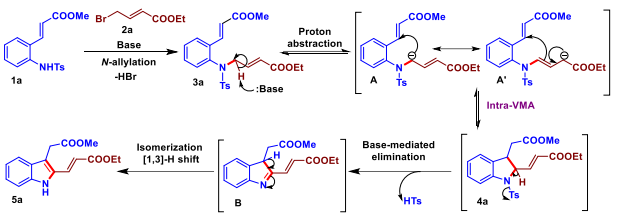
By applying the suitable conditions from the optimization assay (**Table 1**, entry 8); we intended to evaluate the scope of the one-pot transformation involving sequential *N*-allylation followed by intra-VMA–elimination–aromatization to generate diverse 2-alkenyl indole derivatives (**Scheme 3**). Initially, *o*-tosylamidocinnamates and γ-bromocrotonates bearing different alkyl groups present on their ester parts were examined in the one-pot process. Despite the corresponding 2-alkenyl indole derivatives **5a-e** were obtained in high yields, the combination of methyl ester **1a** and ethyl ester **2a** proved to give better results. We then employed precursors bearing different substitutions on the benzene ring of the methyl *o*-tosylamidocinnamates **1** and ethyl 4-bromocrotonate **2a** in this one-pot sequential transformation. The reaction of **2a** and *o*-tosylamidocinnamate having methyl group on the benzene ring provided the corresponding 2-alkenyl indole derivative **5f** in high yield. *o*-Tosylamidocinnamates bearing halogen groups on the benzene ring were also employed. Although the substrate containing fluoro-substituent returned a low yield of the corresponding 2-alkenyl indole derivative **5g**, the chloro- and bromo-substituents tolerated well to furnish the respective 2-alkenyl indole derivatives **5h-i** in good yields. Having an α-methyl substituent on the conjugate ester part of **1** also successfully delivered the respective 2-alkenyl indole product **5j** in 80% yield.

We then examined the scope of the substrates containing other electron-withdrawing groups (EWGs) in the place of the ester group in **1a**. Accordingly, we performed the sequential *N*-allylation followed by intra-VMA–elimination–aromatization cascade using different *o*-tosylamidochalcones and **2a** (**Scheme 4**). The reaction of **2a** and *o*-tosylamidophenyl substituted α,β-unsaturated ketone, having an enolizable methyl group, afforded the corresponding 2-alkenyl indole derivative **5k** in 74% yield. *o*-Tosylamidochalcones comprising different substitutions on the carbonyl side were employed in the present one-pot sequential transformation. The corresponding 2-alkenyl indole derivatives **5l-r** were obtained in high yields. The treatment of **2a** and α,β-unsaturated ketone having heteroaryl group such as 2-furyl group on the carbonyl side afforded the corresponding 2-alkenyl indole derivative **5s** in good yield. We also examined nitrile as an EWG on the Michael acceptor part as the reaction of *o*-tosylamidocinnamonitrile and **2a** provided the respective indole derivative **5t** in 72% yield. Having amide moiety as an EWG on the alkene part of **1** also tolerated to furnish the respective 2-alkenyl-3-indole acetamide **5u** in 64% yield. However, having nitro group as an EWG on the Michael acceptor part of **1** proved to be unsuccessful starting material, which got decomposed.

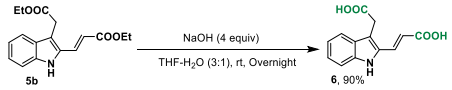
Considering the literature reports[13-14] and above experiments, we proposed a plausible reaction mechanism (**Scheme 5**) for the present one-pot sequential *N*-allylation followed by intra-VMA–elimination–aromatization cascade. Base-mediated reaction of **1a** and **2a** provides the *N*-allylation intermediate



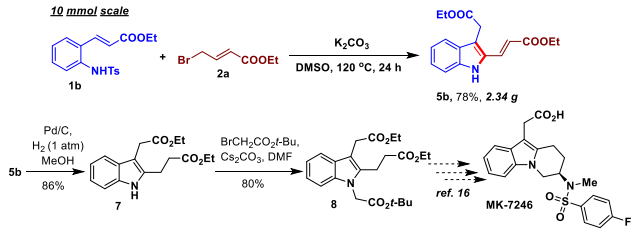
Scheme 4 Synthesis of 3-substituted 2-alkenyl indole derivatives



Scheme 5 Plausible mechanism



Scheme 6 Hydrolysis of ester groups of **5b**



Scheme 7 Gram-scale synthesis of **5b** and Formal synthesis of MK-7246

3a. Base would abstract a proton on the active methylene group, next to the conjugate ester moiety, to give a carbanion intermediate **A**. Note that the intermediate **A** can also exist in the form of its resonance structure **A'**. The intermediate **A'** could act as a vinylogous Michael donor. The thus generated carbanion of **3a** would add to the other electrophilic β-carbon of the Michael acceptor in the same molecule *via* an intra-VMA process to provide intermediate **4a**. Base-mediated elimination of the tosyl group from **4a** would give intermediate **B**, which upon isomerization could provide the 2-alkenyl-3-indole acetate **5a**.

The diester **5b** was subjected to base-mediated hydrolysis to obtain the corresponding 4,5-indole-fused (*E*)-hept-2-enedioic acid **6** in 90% yield (**Scheme 6**).

To demonstrate the synthetic power of the present protocol, we embarked on to apply it in the formal synthesis of an intermediate of Merck's clinical agent MK-7246 (**Scheme 7**), which is a potent and selective CRTH2 [chemo-attractant receptor expressed on T helper type 2 (Th2) cells] antagonist, for the treatment of respiratory diseases.[16] Initially, to prove the practicality of the present one-pot sequential method, we carried out a multi-gram scale reaction of **1b** and **2a** to afford the representative 2-alkenyl-3-indole acetate **5b** in high yield (**Scheme 7**). The indole **5b** was subjected to palladium-catalyzed hydrogenation to effect the reduction of the *exo*-alkenyl moiety of **5b** to give **7**. The compound **7** was treated with *t*-butyl bromoacetate to give the corresponding *N*-alkylated intermediate **8** (**Scheme 7**). The agent MK-7246 can formally be synthesized from **8** using the literature reports.[16]

In summary, we have presented an unprecedented strategy involving intra-VMA–elimination–aromatization cascade for the construction of indoles. The one-pot sequential transformation based on the base-mediated *N*-allylation followed by intra-VMA–elimination–aromatization cascade using *o*-tosylamidocinnamates/congeners and γ-bromocrotonates has been described for the synthesis of 2-alkenyl indole derivatives in reasonable to high yields. The synthesis of 2-alkenyl indole derivatives has been accomplished using a one-pot, transition metal-free process. The present one-pot protocol has been demonstrated in the formal synthesis of selective CRTH2 antagonist MK-7246, a Merck's clinical agent. Further explorations on the intra-VMA chemistry and its applications are in progress in our laboratory.

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Notes and references

1 (a) R. J. Sundberg, *Indoles*; Academic Press: San Diego, 1996; (b) J. A. Joule and K. Mills, *Heterocyclic Chemistry*; Blackwell Science: Oxford, UK, 2000; (c) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.* 2006, **106**, 2875 and references cited therein; (d) G. W. Gribble, *Indole Ring Synthesis: From Natural Products to Drug Discovery*; John Wiley: West Sussex, 2016.

2 (a) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489; (b) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules*, **2013**, *18*, 6620 and references cited therein; (c) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257; (d) N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2017, **134**, 159 and references cited therein.

3 (a) L. Kürti and B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: London, 2005; (b) J. J. Li, *Named Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*; Springer: Berlin, 2006; (c) M. Inman and C. J. Moody, *Chem. Sci.*, 2013, **4**, 29.

4 For selected reviews on 2,3-disubstituted indoles, see: (a) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2011, **111**, PR215; (b) Y. Kobayashi and T. Fukuyama, *J. Heterocyclic Chem.*, 1998, **35**, 1043; For selected important papers, see: (c) R. C. Larock, E. K. Yum and M. D. Refvik, *J. Org. Chem.*, 1998, **63**, 7652; (d) Y. Chen, X. Xie and D. Ma, *J. Org. Chem.*, 2007, **72**, 9329.

5 For selected papers on the chemistry and biology 2-vinyl substituted indoles, see: (a) K. Bera and C. Schneider, *Chem. Eur. J.*, 2016, **22**, 7074; (b) J.-J. Zhao, S.-B. Sun, S.-H. He, Q. Wu and F. Shi, *Angew. Chem. Int. Ed.*, 2015, **54**, 5460; (c) J.-J. Zhao, M. Tang, H.-H. Zhang, M.-M. Xu and F. Shi, *Chem. Commun.*, 2016, **52**, 5953; (d) T. J. H. Arends and J. A. Witjes *Urol. Clin. North Am.*, 2020, **47**, 73; (e) G. L. Plosker and A. J. Wagstaff, *Drugs* 1996, **51**, 433; (f) D. H. Dethe, R. D. Erande and A. Ranjan, *J. Am. Chem. Soc.* 2011, **133**, 2864.

6 For selected examples on C-2 functionalization of indoles to 2-vinyl indoles, see: (a) V. Lanke and K. R. Prabhu, *Org. Lett.* 2013, **15**, 2818; (b) S. Sharma, S. Han, M. Kim, N. K. Mishra, J. Park, Y. Shin, J. Ha, J. H. Kwak, Y. H. Junga and I. S. Kim, *Org. Biomol. Chem.* 2014, **12**, 1703; (c) A. García-Rubia, R. G. Arrayás and J. C. Carretero, *Angew. Chem. Int. Ed.* 2009, **48**, 6511.

7 For cross-coupling of indoles and alkenyl partners, see: (a) T. Fukuyama, X. Chen and G. Peng, *J. Am. Chem. Soc.* 1994, **116**, 3127; (b) H. Tokuyama, Y. Kaburagi, X. Chen and T. Fukuyama, *Synthesis* 2000, **3**, 429; (c) M. Tobisu, H. Fujihara, K. Koh and N. Chatani, *J. Org. Chem*. 2010, **75**, 4841.

8 A. S. Makarov, M. G. Uchuskin and V. Gevorgyan, *J. Org. Chem.* 2018, **83**, 14010.

9 H.-A. Seo and C.-H. Cheon, *J. Org. Chem.* 2016, **81**, 7917.

10 B. Harish, M. Subbireddy and S. Suresh, *Chem. Commun.* 2017, **53**, 3338.

11 For an excellent recent review on vinylogous concept, see: (a) C. Curti, L. Battistini, A. Sartori and F. Zanardi, *Chem. Rev.* 2020, **120**, 5, 2448 and references cited therein; (b) O. Obulesu, J. B. Nanubolu and S. Suresh, *Org. Biomol. Chem.* 2015, **13**, 8232; (c) O. Obulesu, V. Murugesh, B. Harish and S. Suresh, *J. Org. Chem.* 2018, **83**, 6454.

12 (a) I. D. Jurberg, I. Chatterjee, R. Tannert and P. Melchiorre, *Chem. Commun.* 2013, **49**, 4869; (b) X. Jusseau, L. Chabaud and C. Guillou, *Tetrahedron* 2014, **70**, 2595; (c) C. Schneider and F. Abels, *Org. Biomol. Chem.* 2014, **12**, 3531; (d) H. B. Hepburn, L. Dell'Amico and P. Melchiorre, *Chem. Rec.* 2016, **16**, 1787; (e) Y. Yin and Z. Jiang, *ChemCatChem* 2017, **9**, 4306.

13 (a) K. Clinch, C. J. Marquez, M. J. Parrotta and R. Ramage, *Tetrahedron* 1989, **45**, 239; (b) S. Nara, H. Toshlma and A. Ichihara, *Tetrahedron Lett.* 1996, **37**, 6745; (c) D. Gray and T. Gallagher, *Angew. Chem. Int. Ed.* 2006, **45**, 2419; (d) T. Gallagher, I. Derrick, P. M. Durkin, C. A. Haseler, C. Hirschhauser and P. Magrone, *J. Org. Chem.* 2010, **75**, 3766; (e) K. Lee, H. Kim and J. Hong, *Angew. Chem. Int. Ed.* 2012, **51**, 5735; (f) R. M. de Figueiredo, R. Fröhlich and M. Christmann, *Angew. Chem. Int. Ed.* 2008, **47**, 1450; (g) Z.-Y. Wang, W.-T. Wong and D. Yang, *Org. Lett.* 2013, **15**, 4980; For a very recent example, see: (h) D. Li, Y. Yang, M. Zhang, L. Wang, Y. Xu, D. Yang and R. Wang, *Nat. Commun.* 2020, **11**, Article number: 2559.

14 B. Harish, M. Subbireddy, O. Obulesu and S. Suresh, *Org. Lett.* 2019, **21**, 1823.

15 (a) R. W. D. Simone, K. S. Currie, S. A. Mitchell, J. W. Darrow and D. A. Pippin, *Comb. Chem. High Throughput Screen.* 2004, **7**, 473; (b) L. Yet, *Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis*; Willey: Hoboken, 2018.

16 C. Molinaro, P. G. Bulger, E. E. Lee, B. Kosjek, S. Lau, D. Gauvreau, M. E. Howard, D. J. Wallace and P. D. O'Shea, *J. Org. Chem.* 2012, 77, 2299 and references cited therein.

