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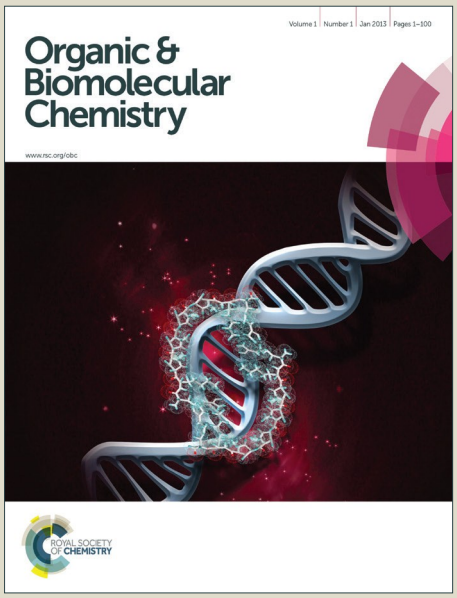

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Diversity-Oriented Approach to Indolocarbazoles *via* Fischer Indolization and Olefin Metathesis: Total Synthesis of Tjipanazole D and I

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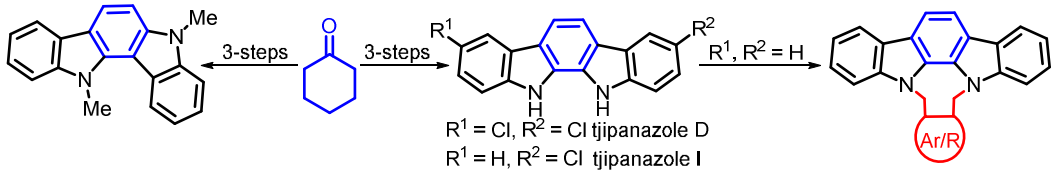

ABSTRACT: New synthetic strategies to indolocarbazoles have been reported via a two-fold Fischer indolization under green conditions using L-(+)-tartaric acid and N,N-dimethyl urea. Starting with cyclohexanone, a bench-top starting material, this methodology has been extended to the total synthesis of natural products such as tjipanazoles **D** and **I** as well as core structure of asteropusazole and racemosin **B**. Here, an atom economic reactions like ring-closing metathesis, enyne-metathesis, and Diels–Alder reaction have been used as key steps. Diverse strategies demonstrated here are useful in medicinal chemistry and material science to design a library of decorated indoles.

INTRODUCTION

Indoles are considered as privileged structures because of their unique role in various biochemical processes. They are extensively used as critical building blocks in developing new drugs which are suitable for the treatment of cancer, circulatory disease, Alzheimer's, and other neurological disorders (Figure 1).[1] Recently, there has been growing interest in using indole motifs as the starting materials for library design[2] and such activity leads to the identification of high-affinity ligands.[3] Here, various indolocarbazole scaffolds have been assembled by judicious selection of well-known reactions in an orchestrated sequence.

Among indole-based heterocycles, carbazoles and indolocarbazoles are found in a number of natural products and as an important drugs (**1-11**).[4] The chemistry of indolo[2,3-a]carbazoles has been widely studied because of their promising antifungal, antimicrobial, anticancer and antihypertensive activities.[5] Now, several indolocarbazole alkaloids are in the clinical trials due

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to their potential use in cancer therapy.[6] Additionally, they were also used for optical and solar cell applications, *viz* organic field-effect transistors (OFET), organic thin film transistors (OTFT) and organic light-emitting diodes (OLEDs).[7]

In view of our interest to design diverse polycycles using Fischer indolization (FI),[8] ring-closing metathesis (RCM),[9] enyne metathesis (EM),[10] Diels–Alder (DA)[11] reaction and Suzuki–Miyaura (SM) cross-coupling[12] as key steps, here we conceived various strategies to indolocarbazoles based on these key reactions and our efforts in this direction are described here.

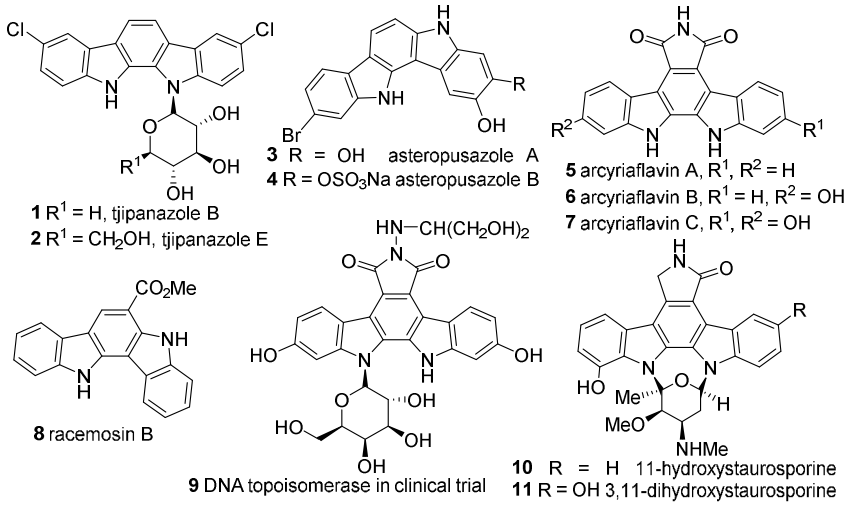
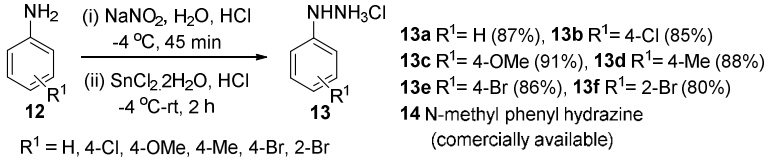


FIGURE 1.Various naturally and biologically active compounds

RESULTS AND DISCUSSION

The required phenylhydrazine hydrochloride derivatives **13a-f** were prepared by using the literature procedure starting with commercially available aniline derivatives (Scheme 1).[13]



Scheme 1: Synthesis of various phenyl hydrazine hydrochloride derivatives **13**

Our journey towards indolocarbazoles commenced with the synthesis of the substrates **17a-c** (Scheme 2), as key intermediates, was accomplished *via* FI between cyclohexanone **15** and phenylhydrazine hydrochlorides **13a-f**, **14** followed by regioselective oxidation sequence using periodic acid (Scheme 2).[14] Besides, the other two keto derivatives **18a** and **18b** were prepared by FI/DDQ oxidation protocol.[15]

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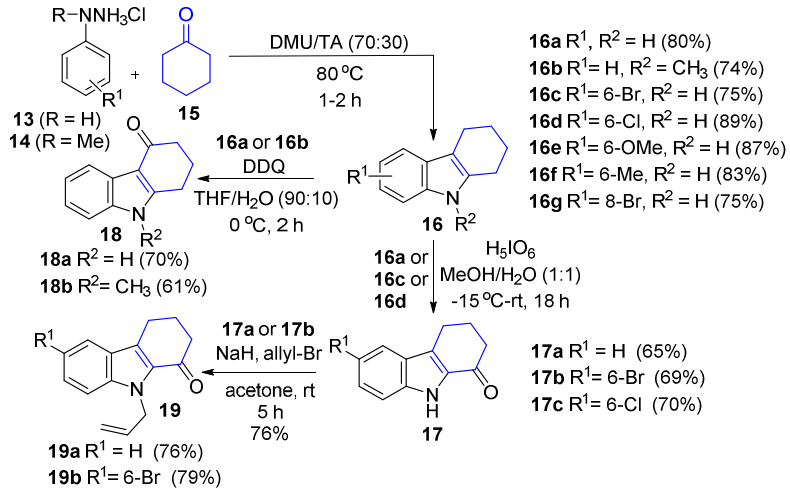
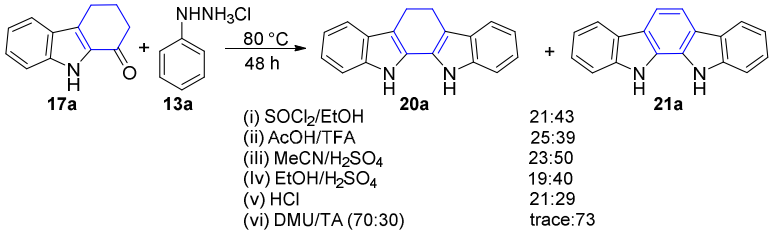


Scheme 2: Synthesis of keto derivatives **17**, **18** and **19**

Having the desired substrates **17a-c** and **19a-b** in hand, we next investigated the feasibility of FI sequence with suitable phenylhydrazines. Initially, carbazole derivative **17a** was subjected to FI by treating with phenylhydrazine hydrochloride **13a** using conventional methods (e.g. $SOCl_2$/EtOH, AcOH/TFA, MeCN/H_2SO_4, EtOH/H_2SO_4 and HCl system) to deliver a mixture of non-aromatized **20a** and aromatized **21a** compounds with different ratios (Scheme 3). Interestingly, reaction of **17a** with phenylhydrazine hydrochloride **13a** in the presence of *N*,*N*-dimethyl urea (DMU)/L-(+)-tartaric acid (TA) conditions,[8f] delivered a fully aromatized indolocarbazole **21a** in 73% yield along with the trace amounts of **20a**. To expand the diversity of carbazole derivatives, the indolocarbazoles **17b-c** and **19a-b** were subjected to FI with other hydrazine derivatives **13b-f** and **14** to generate the corresponding indolocarbazole derivatives **21b-o** in 46-78% yield (Scheme 4). Surprisingly, when the indole derivative **17a** was treated with 4-bromo phenylhydrazine **13e** aromatized indolocarbazole **21e** was obtained along with de-brominated carbazole **21a**.



Scheme 3: Optimization of indolocarbazole **21** *via* conventional methods

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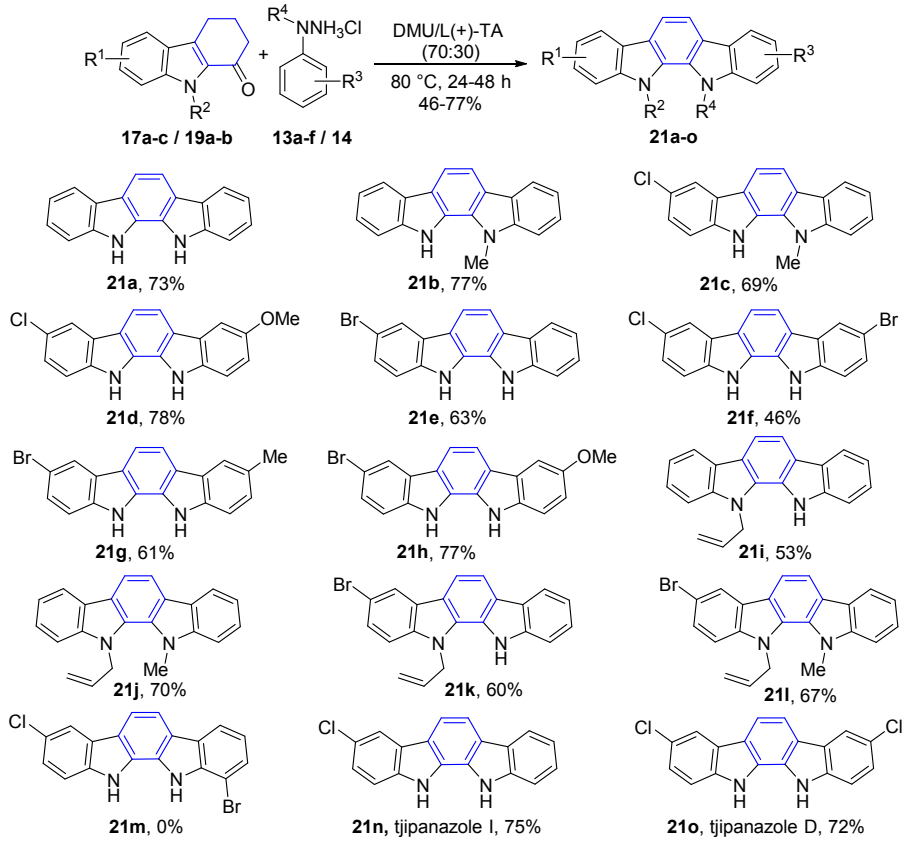
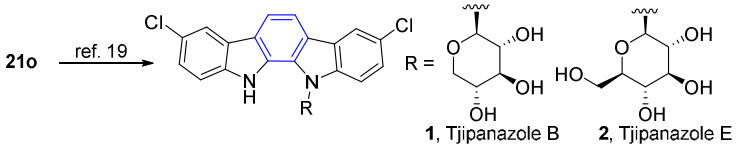


Scheme 4: Synthesis of indolocarbazoles **21a-o** *via* Fischer indolization

The target molecules tjipanazoles **B** and **E** can be synthesized by known *N*-substitution reaction condition from tjipanazole **D** (Scheme 5).[16]



Scheme 5: Formal synthesis of tjipanzoles **B** and **E**

The core structure of asteropusazole was also synthesized by using this methodology. In this regard, the indole derivatives **18a** and **18b** containing keto group were subjected to FI with phenylhydrazine hydrochloride **13a**. Unfortunately, the desired indolocarbazoles **22** and **23** were not obtained. However, *N*-protected indole derivative **18b** was reacted with *N*-methylphenylhydrazine **14** to deliver the fully aromatized product **24** in 51% yield, whose carbon framework is similar to that of indole natural products asteropusazole[16-17] and racemosin B[18] (Figure 1, Scheme 6).

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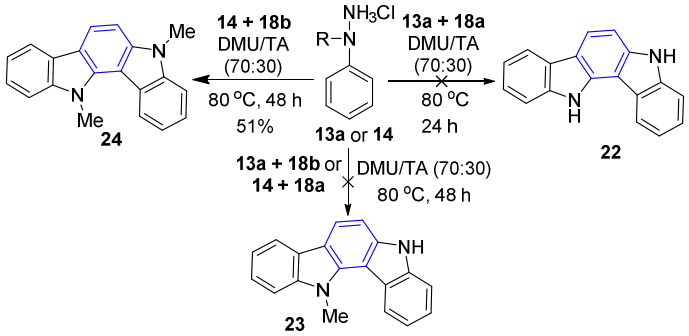
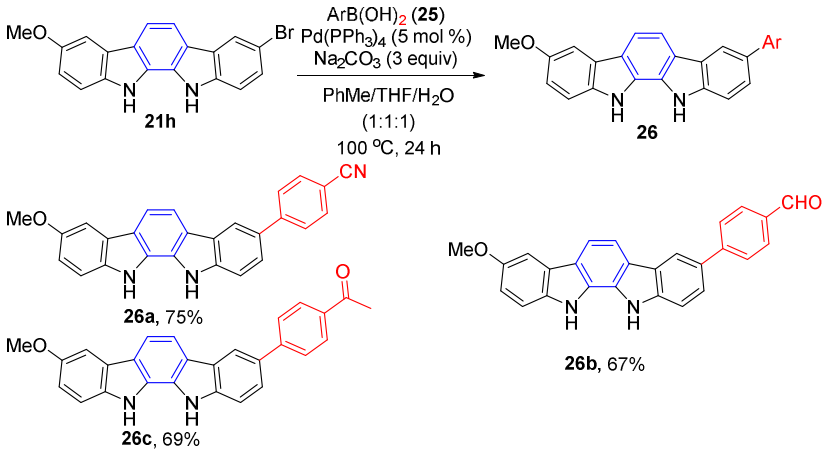


Scheme 6: Synthesis of core structure of asteropusazoles and racemosin **B** *via* Fischer indolization

To expand the carbazole chemical space, SM cross-coupling reaction of **21h** was studied with 4-substituted phenylboronic acids **25**. In this regard, functionalized indolocarbazoles **26a-c** were obtained in 67-75% yield (Scheme 7).



Scheme 7: Synthesis of carbazole derivatives **26** *via* SM cross-coupling reaction

Since many natural products (Figure 1) are *N*-protected indolocarbazoles, our strategies were directed to assemble *N*-annulated or *N*-allylated indolocarbazoles. To this end, we synthesized various *N*-annulated indolocarbazoles using RCM, EM and DA reaction as key steps. The di-allyl compound **27** was prepared starting with *N*-allylation of the keto derivative **17a** followed by FI/*N*-allylation sequence. Alternatively, **27** was also synthesized from **21a** using *N*-allylation, whereas **21a** was synthesized by FI of the keto derivative **17a** (Scheme 8).

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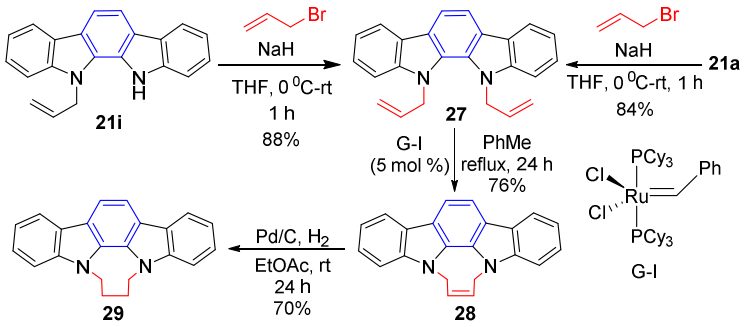
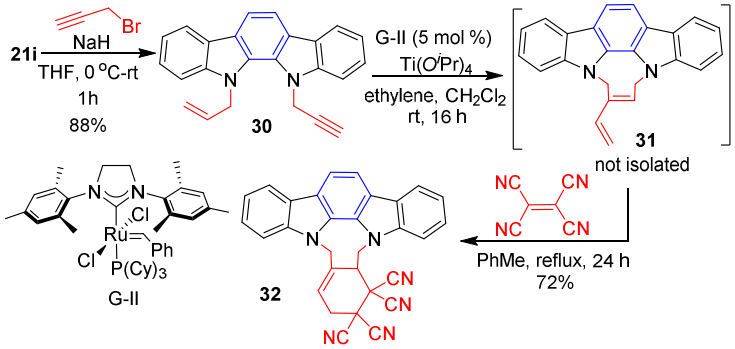


Scheme 8: Synthesis of indolocyclophane **29** *via* RCM and hydrogenation sequence

Subsequently, the di-allyl indolocarbazole **27** was subjected to the RCM sequence with the aid of Grubbs first generation (G-I) catalyst in refluxing toluene produced the desired macrocyclic compound **28** in 76% yield. Finally, hydrogenation of double bond present in **28** delivered the cyclophane **29** in 70% yield (Scheme 8).[19]

To expand the substrate scope, the mono-allyl compound **21i** was successfully converted into an enyne building block **30** by treatment with propargyl bromide using NaH in dry THF. The diene building block **31** was generated *via* metathesis protocol and different reaction conditions were screened in the presence of G-I and Grubb's second generation (G-II) catalysts. However, these attempts were unsuccessful and ultimately, we found that the presence of the titanium isopropoxide and ethylene[20] atmosphere facilitate the metathesis protocol.[21] Under these conditions, enyne building block **30** was reacted with G-II catalyst in dry CH_2Cl_2 to furnish the diene **31**.



Scheme 9: Synthesis of indolocarbazole **32** *via* enyne metathesis and DA reaction

Later, without isolating the intermediate **31**, it was subjected to DA sequence with tetracyanoethylene as a dienophile in refluxing toluene to deliver a novel heptacyclic compound **32** in 72% yield (Scheme 9).

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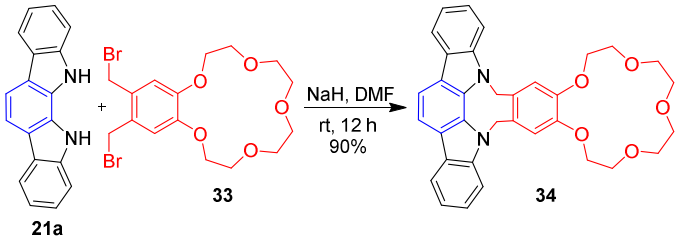

Scheme 10: Synthesis of octacyclic indolocarbazole **34** *via N*-alkylation

Creation of molecular complexity and variety from simple precursors is the major objective of the diversity-oriented synthesis (DOS).[22] To this end, we wish to synthesize the crownophane derivative,[23] **34** which is a hybrid of crown ether and indolocyclophane. For this purpose, the required dibromo derivative **33** was prepared using the literature procedure.[24] In this regard, the indolocarbazole moiety **21a** was subjected to bis-*N*-alkylation in dry DMF using NaH conditions to deliver the desired indolocrownophane derivative **34** in 90% yield (Scheme 10).

CONCLUSIONS

In summary, we have developed a diversity oriented approach to indolocarbazoles *via* deep eutectic solvents.[8f, 25] Also, twenty five indolocarbazoles with additional functionalities have been generated using a variety of reactions such as RCM, EM, DA reaction and SM cross-coupling as key steps. These strategies have been extended for the synthesis of natural products tjipanazole **D** and **I** as well as core structure of asteropusazole and racemosin **B**. Various methodologies demonstrated to deliver multitude of compounds for biological as well as material science applications. The hybrid molecule containing indolocyclophane derivative **34** with crown ether moiety is useful in host-guest chemistry for metal ion binding studies. The tactics used here to deliver distinct indole building blocks demonstrate the power of synthetic convergence of well-known reactions.

SUPPORTING INFORMATION

The copies of ^{1}H and ^{13}C NMR for all the new compounds associated with this article can be found at http://dx.doi.org/

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DOI: 10.1039/C6OB01679K

REFERENCES

1. (a) Z. Bian, C. C. Marvin, M. Pettersson and S. F. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 14184; (b) E. V. Mercado-Marin, P. Garcia-Reynaga, S. Romminger, E. F. Pimenta, D. K. Romney, M. W. Lodewyk, D. E. Williams, R. J. Andersen, S. J. Miller, D. J. Tantillo, R. G. S. Berlinck and R. Sarpong, *Nature*, 2014, **509**, 318; (c) K. Higuchi and T. Kawasaki, *Nat. Prod. Rep.*, 2007, **24**, 843; (d) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875; (e) T. Heinrich and H. Böttcher, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2681; (f) H. Takayama, S.-i. Tsutsumi, M. Kitajima, D. Santiarworn, B. Liawruangrath and N. Aimi, *Chem. Pharm. Bull.*, 2003, **51**, 232; (g) S. Hibino and T. Choshi, *Nat. Prod. Rep.*, 2001, **18**, 66; (h) A. R. Katritzky and A. F. Pozharskii, *In Handbook of Heterocyclic Chemistry*, Oxford, Pergamon, 2000.

2. (a) K. Bondensgaard, M. Ankersen, H. Thøgersen, B. S. Hansen, B. S. Wulff and R. P. Bywater, *J. Med. Chem.*, 2004, **47**, 888; (b) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga and H. J. Mitchell, *J. Am. Chem. Soc.*, 2000, **122**, 9939; (c) J. S. Mason, I. Morize, P. R. Menard, D. L. Cheney, C. Hulme and R. F. Labaudiniere, *J. Med. Chem.*, 1999, **42**, 3251; (d) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber and P. S. Anderson, *J. Med. Chem.*, 1988, **31**, 2235.

3. O. Prien, *ChemBioChem*, 2005, **6**, 500.

4. (a) S. B. Markad and N. P. Argade, *J. Org. Chem.*, 2016, **81**, 5222; (b) S. Samala, G. Singh, R. Kumar, R. S. Ampapathi and B. Kundu, *Angew. Chem. Int. Ed.*, 2015, **54**, 9564; (c) P. Raju, G. Gobi Rajeshwaran and A. K. Mohanakrishnan, *Eur. J. Org. Chem.*, 2015, 7131; (d) S. B. Markad and N. P. Argade, *Org. Lett.*, 2014, **16**, 5470; (e) M. Inman and C. J. Moody, *Chem. Sci.*, 2013, **4**, 29; (f) S. Samala, A. K. Mandadapu, M. Saifuddin and B. Kundu, *J. Org. Chem.*, 2013, **78**, 6769; (g) J. J. Li, *Heterocyclic Chemistry in Drug Discovery*, John Wiley & sons, New Jersey, 2013; (h) T. Janosik, N. Wahlström and J. Bergman, *Tetrahedron*, 2008, **64**, 9159; (i) S. Roy, A. Eastman and G. W. Gribble, *Tetrahedron*, 2006, **62**, 7838; (j) Y.-Z. Hu and Y.-Q. Chen, *Synlett*, 2005, **2005**, 42; (k) H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303; (l) C. A. Merlic, Y. You, D. M. McInnes, A. L. Zechman, M. M. Miller and Q. Deng, *Tetrahedron*, 2001, **57**,

View Article Online
DOI: 10.1039/C6OB01679K

5199; (m) T. J. Hagen, K. Narayanan, J. Names and J. M. Cook, *J. Org. Chem.*, 1989, **54**, 2170.

5. M. Prudhomme, *Eur. J. Med. Chem.*, 2003, **38**, 123.
6. S. Akinga, K. Sugiyama and T. Akiyama, *Anti-Cancer Drug Des.*, 2000, **15**, 43.
7. (a) P. Gong, J. Sun, P. Xue, C. Qian, Z. Zhang, J. Sun and R. Lu, *Dyes Pigm.*, 2015, **118**, 27; (b) P. Gong, P. Xue, C. Qian, Z. Zhang and R. Lu, *Org. Biomol. Chem.*, 2014, **12**, 6134; (c) H. Sasabe and J. Kido, *Eur. J. Org. Chem.*, 2013, 7653; (d) K. S. Park, S. M. Salunkhe, I. Lim, C. G. Cho, S. H. Han and M. M. Sung, *Adv. Mater.*, 2013, **25**, 3351; (e) N. Blouin and M. Leclerc, *Acc. Chem. Res.*, 2008, **41**, 1110; (f) J.-F. Morin and M. Leclerc, *Macromolecules*, 2001, **34**, 4680.
8. (a) S. Kotha, R. Ali, V. Srinivas and N. G. Krishna, *Tetrahedron*, 2015, **71**, 129; (b) S. Kotha and O. Ravikumar, *Eur. J. Org. Chem.*, 2014, 5582; (c) S. Kotha and A. K. Chinnam, *Synthesis*, 2014, **46**, 301; (d) A. S. K. Hashmi, W. B. Yang and F. Rominger, *Chem. - Eur. J.*, 2012, **18**, 6576; (e) D. McAusland, S. Seo, D. G. Pintori, J. Finlayson and M. F. Greaney, *Org. Lett.*, 2011, **13**, 3667; (f) S. Gore, S. Baskaran and B. König, *Org. Lett.*, 2012, **14**, 4568.
9. (a) S. Kotha and V. R. Aswar, *Org. Lett.*, 2016, **18**, 1808; (b) K. Kashinath, S. Dhara and D. S. Reddy, *Org. Lett.*, 2015, **17**, 2090; (c) S. Kotha, A. S. Chavan and M. Shaikh, *J. Org. Chem.*, 2012, **77**, 482; (d) J. Cossy, S. Arseniyadis and M. Chiristophe, *Metathesis in Natural Product Synthesis*, Wiley -VCH, Weinheim, 2010; (e) C. K. Malik, R. N. Yadav, M. G. B. Drew and S. Ghosh, *J. Org. Chem.*, 2009, **74**, 1957; (f) S. Kotha and M. K. Dipak, *Chem. - Eur. J.*, 2006, **12**, 4446; (g) S. Kotha, K. Mandal, K. K. Arora and V. R. Pedireddi, *Adv. Synth. Catal.*, 2005, **347**, 1215; (h) S. Kotha, A. C. Deb and R. V. Kumar, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1039; (i) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem. Int. Ed.*, 2005, **44**, 4490.
10. (a) R. H. Grubbs and D. J. O'Leary, *Handbook of Metathesis, Application in Organic Synthesis*, Wiely-VCH:Weinheim, Germany, 2nd edn., 2015; (b) S. Kotha, D. Goyal, N. Thota and V. Srinivas, *Eur. J. Org. Chem.*, 2012, 1843; (c) S. Kotha and A. S. Chavan, *J. Org. Chem.*, 2010, **75**, 4319; (d) S. Kotha, M. Meshram and A. Tiwari, *Chem. Soc. Rev.*, 2009, **38**, 2065; (e) S. Kotha and P. Khedkar, *Eur. J. Org. Chem.*, 2009, 730; (f) O. Debleds and J.-M. Campagne, *J. Am. Chem. Soc.*, 2008, **130**, 1562; (g) D. A. Clark, A. A.

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DOI: 10.1039/C6OB01679K

Kulkarni, K. Kalbarczyk, B. Schertzer and S. T. Diver, *J. Am. Chem. Soc.*, 2006, **128**, 15632; (h) S. Kotha and N. Sreenivasachary, *Chem. Commun.*, 2000, 503.

11. (a) S. Kotha, V. R. Aswar and A. Manchoju, *Tetrahedron*, 2016, **72**, 2306; (b) S. Kotha and P. Khedkar, *J. Org. Chem.*, 2009, **74**, 5667; (c) S. Kotha, T. Ganesh and A. K. Ghosh, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1755.
12. (a) S. Kotha and K. Lahiri, *Eur. J. Org. Chem.*, 2007, 1221; (b) R. Lepine and J. P. Zhu, *Org. Lett.*, 2005, **7**, 2981; (c) H. Maeda, M. Suzuki, H. Sugano, M. Mayamura and R. Ishida, *Chem. Pharm. Bull.*, 1988, **36**, 190.
13. D. B. Zhao, Z. Z. Shi and F. Glorius, *Angew. Chem. Int. Ed.*, 2013, **52**, 12426.
14. V. T. Humne, M. S. Naykode, M. H. Ghom and P. D. Lokhande, *Tetrahedron Lett.*, 2016, **57**, 688.
15. D. Sissouma, S. C. Collet and A. Y. Guingant, *Synlett*, 2004, **2004**, 2612.
16. J. T. Kuethe, A. Wong and I. W. Davies, *Org. Lett.*, 2003, **5**, 3721.
17. X. Zheng, L. Lv, S. Lu, W. Wang and Z. Li, *Org. Lett.*, 2014, **16**, 5156.
18. L.-n. Liang, T.-y. Fan, T. Huang, C. Yan, M. Xu and S. Liu, *Tetrahedron Lett.*, 2015, **56**, 434.
19. (a) S. Kotha, A. K. Chinnam and M. E. Shirbhate, *J. Org. Chem.*, 2015, **80**, 9141; (b) S. Kotha, M. E. Shirbhate and G. T. Waghule, *Beilstein J. Org. Chem.*, 2015, **11**, 1274; (c) R. Gibe, J. R. Green and G. Davidson, *Org. Lett.*, 2003, **5**, 1003.
20. M. Mori, N. Sakakibara and A. Kinoshita, *J. Org. Chem.*, 1998, **63**, 6082.
21. A. Fürstner and K. Langemann, *J. Am. Chem. Soc.*, 1997, **119**, 9130.
22. (a) M. D. Burke and S. L. Schreiber, *Angew. Chem. Int. Ed.*, 2004, **43**, 46; (b) S. Samala, R. K. Arigela, R. Kant and B. Kundu, *J. Org. Chem.*, 2014, **79**, 2491; (c) S. Kotha, D. Goyal and A. S. Chavan, *J. Org. Chem.*, 2013, **78**, 12288; (d) A. Trabocchi, *Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology*, John Wiley & Sons, New Jersey, 2013.
23. (a) S. Kotha and G. T. Waghule, *J. Org. Chem.*, 2012, **77**, 6314; (b) S. Kotha, D. Kashinath and P. Khedkar, *Synthesis*, 2007, 3357; (c) J. Xu, Y. H. Lai and W. Wang, *Org. Lett.*, 2003, **5**, 2781.
24. S. Kotha and E. Brahmachary, *Indian J. Chem., Sect B*, 2001, **40**, 1.

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25. (a) D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor and D. J. Ramon, *Eur. J. Org. Chem.*, 2016, 612; (b) P. Liu, J.-W. Hao, L.-P. Mo and Z.-H. Zhang, *RSC Adv.*, 2015, **5**, 48675; (c) Q. Zhang, K. De Oliveira Vigier, S. Royer and F. Jerome, *Chem. Soc. Rev.*, 2012, **41**, 7108; (d) Ru and B. Konig, *Green Chem.*, 2012, **14**, 2969.