ChemComm

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

ROYAL SOCIETY OF CHEMISTRY
View Article Online
DOI: 10.1039/C6CC10292A

Journal Name

COMMUNICATION

N-Heterocyclic Carbene (NHC) Catalyzed Atom Economical Construction of 2,3-Disubstituted Indoles

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Battu Harish,[ab] Manyam Subbireddy,[a] and Surisetti Suresh*[ab]

A novel organocatalytic approach harnessing the unique reactivities of *N*-hererocyclic carbenes (NHCs) has been revealed for the construction of indoles. The NHC catalysed atom economic synthesis of a wide range of 2-substituted indole-3-acetic acid derivatives is displayed. Strategic application of the developed method was demonstrated for a short synthesis of cyclin-dependent kinase (CDK) inhibitor, paullone.

Historically, the construction of indole nucleus is one of the most sought after challenges that has received a great deal of attention from chemistry community over several decades.[1] There have been excellent methods developed for the construction of indole framework ranging from the classical Möhlau and Fischer indole syntheses to the modern Larock indole synthesis.[2] Many of these syntheses suffer from strong acidic/basic conditions, use of toxic metal catalysts, low yields, less stable or expensive starting materials, atom economy issues and generation of by-products. Considering these concerns, metal-free approaches utilizing readily available precursors for the construction of indoles are very much required and such routes would definitely complement the hitherto known strategies. Despite the concept of organocatalysis has marked the significant breakthroughs in the plethora of organic transformations,[3] its application in the construction of indole nucleus has been very scarcely realized.

2-Substituted indole-3-acetic acid derivatives have gained considerable attention because they have shown a wide range of potential biological activity profiles (Figure 1).[4] Though there have been several syntheses reported for these class of compounds, the methods involve the use of unfriendly reagents, toxic metals and harsh reaction conditions.[5] Recently, Opatz *et al.* and Lee *et al.* have reported sodium cyanide mediated and catalysed reactions, respectively.[5i,j]

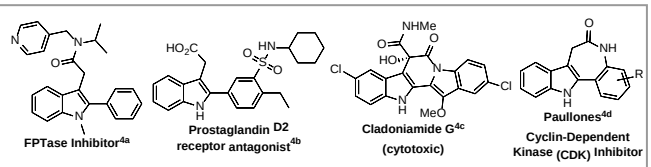
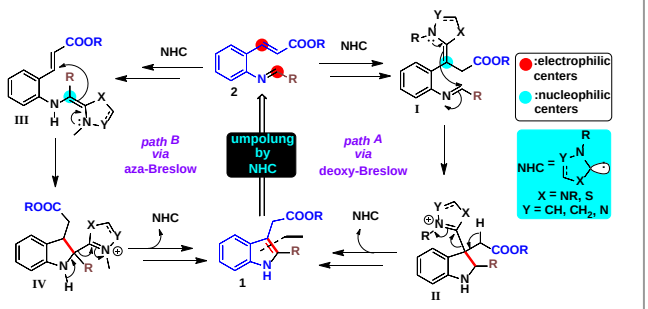


Fig 1 Biologically active 2-substitute indole-3-acetic acid derivatives.



Scheme 1 Strategy for NHC catalysed construction of substituted indoles.

Organocatalytic approaches underpinning atom-economics would provide alternative route and complement the existing routes for the construction of these important entities. However, very few reports are available on the organocatalytic routes for indole construction in general[6] and such routes are elusive for the synthesis of 2-substituted indole-3-acetic acid derivatives. For more than a decade, *N*-heterocyclic carbenes (NHCs) have emerged as powerful organocatalysts by their unique reactivities towards electrophiles to reverse their polarities known as umpolung.[7]

Sheidt and co-workers[8] have developed the synthesis of 2-arylindoles by the addition of acyl anion equivalents, generated through NHC, to the transient aza-*ortho* quinine methides. We envisioned the synthesis of 2-substituted indole-3-acetic acid derivatives from *ortho*-imino cinnamate **2** using the disconnection approach as shown in the Scheme 1.

[a] B. Harish, M. Subbireddy, Dr. S. Suresh
Organic and Biomolecular Chemistry Division
CSIR-Indian Institute of Chemical Technology (CSIR-IICT)
Hyderabad 500 007, India
E-mail: surisetti@iict.res.in; suresh.surisetti@yahoo.in.
[b] B. Harish, Dr. S. Suresh
Academy of Scientific and Innovative Research (AcSIR)
CSIR-Indian Institute of Chemical Technology (CSIR-IICT)
Hyderabad 500 007, India.

† Electronic Supplementary Information (ESI) available: Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data, copies of NMR spectra for products. See DOI: 10.1039/x0xx00000x

We hypothesized that NHC can inverse the polarity of electrophilic centers of either β-carbon of the α,β-unsaturated ester (*via* deoxy-Breslow intermediate I)[7d,9] or imine carbon (*via* aza-Breslow intermediate III)[10] of the precursor **2** that would provide a neucleophilic center (through umpolung) and subsequently add on to the remaining electrophilic center. This course would eventually lead to cyclization-aromatization cascade to provide 2-substituted indole-3-acetic acid derivatives.

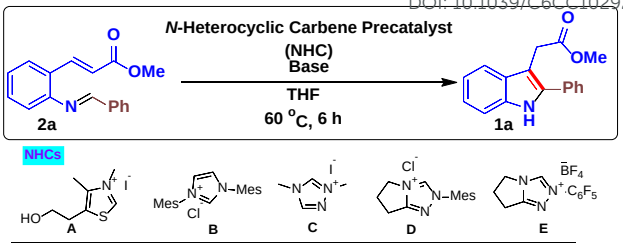
Accordingly, we have started our investigations using the precursor **2a** under NHC catalysis settings. Initially, we have performed the reaction of **2a** with the NHC precursors such as thiazolium (**A**), imidazolium (**B**) salts and a base like DBU (Table 1, entries 1-2). However, these reactions were not successful to provide the desired product. Much to our delight, triazolium NHC precatalyst **C** in the presence of DBU has furnished the desired product **1a** in high yield (Table 1, entry 3). It is interesting to note that while bicyclic triazolium NHC precatalyst **D** bearing *N*-mesityl group has afforded the product **1a** in good yield (Table 1, entry 4), triazolium NHC precatalyst **E** containing *N*-pentafluorophenyl group has failed to give the product (Table 1, entry 5). DBU was found to give better yields among the bases screened (Table 1, entries 3 and 6-7). It should be noted that this transformation did not work with either base or NHC alone.

With the suitable NHC and base in hand, we turned to perform this transformation sequentially—starting from *ortho*-aminocinnamate **3a**. Accordingly, **3a** and benzaldehyde **4a** were reacted to give the imine **2a**. Subsequently, the crude **2a** was subjected to NHC catalysis conditions to obtain the product **1a** in 90% yield (Scheme 2). Later several bases, solvents and reaction conditions were screened for this sequential transformation (see supporting information for a detailed optimization study). It turned out that NHC precatalyst **C** in the presence of DBU in THF solvent stands out the best combination amongst the conditions tested.

We then studied the scope of this NHC-catalyzed transformation. Initially, the scope of the ester group on the acrylate part has been studied (Scheme 3). All the tested esters gave comparable yields of the corresponding indole derivatives **1a-c** while methyl ester stands out the best. This transformation was well tolerated with the cinnamide precursor as the corresponding 2-phenyl substituted indole-3-acetamide derivative **1d** was synthesised in 66% yield. *ortho*-Imino cinnamonitrile has also been converted to the corresponding 2-phenyl 3-indole acetonitrile derivative **1e** under the NHC catalysis settings. Later we turned our attention to rework on the aniline part—as expected we have isolated the differently substitued indoles **1f-h** in moderate to good yields. Next the generality of the benzaldehyde part has been tested using different electron withdrawing groups like NO_2, CN, CF_3—all gave high yields of the corresponding indole derivatives **1i-k**. Halogen substituted benzaldehydes have been used in this sequential transformation—*ortho*-imino cinnamates derived from *o*-, *m*- and *p*-substituted chloro benzaldehydes have provided the corresponding indloles **1l-n** in very good yields under the NHC catalysis conditions. Indoles **1o-r** bearing fluoro and bromo substitutions on the 2-aryl group have also been synthesized in high yields. Comparatively, *ortho*-imino cinnamates primed from benzaldehydes having electron donating substituents have resulted in slightly lower yields of the corresponding 2-aryl-indol-3-acetic esters **1s-w**. *ortho*-imino cinnamates derived from multisubstituted benzaldehydes bearing halogen and electron donating groups furnished the corresponding substituted indole derivatives **1x-y** in 69-75% yields. Biphenyl-4-carboxaldehyde- and 1-naphthaldehyde-derived *ortho*-imino cinnamates have also been tested in this transformation to afford the corresponding indole derivatives **1z** and **1aa** in 80% and 62% yields, respectively.

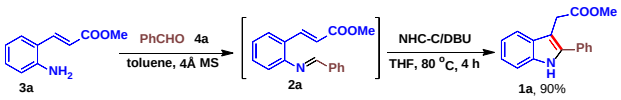
It is interesting to note that different heteroaromatic aldehydes including pyridyl, quinolinyl, thiophenyl, pyrrolyl and pyrazolyl aldehyes have proven to be successful to afford the corresponding variously substituted 2-heteroaryl indol-3-acetic esters **1ab-af** in very good yields (Scheme 4).

Table 1 Optimization study[a]

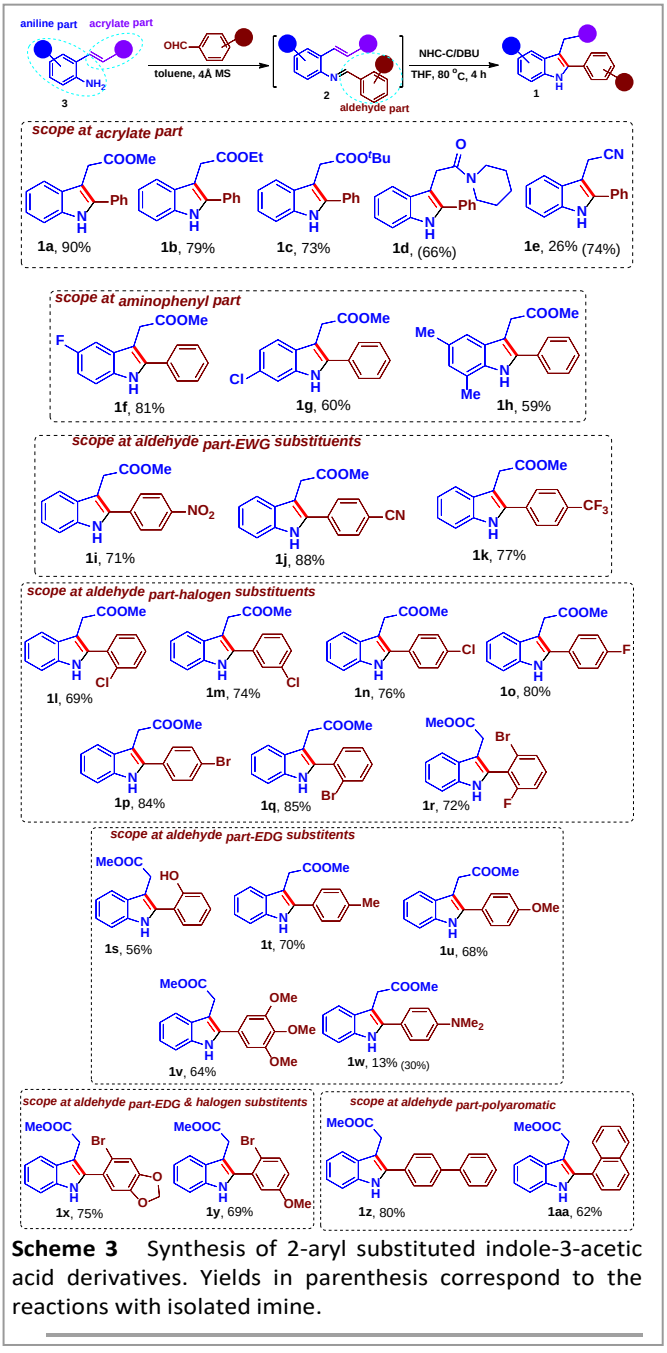


Entry	NHC	Base	%yield of 1a[b]
1	**A**	DBU	—
2	**B**	DBU	—
3	***C***	***DBU***	***85 (90)[c]***
4	**D**	DBU	82
5	**E**	DBU	—
6	**C**	TBD	65
7	**C**	Cs_2CO_3	68

[a]Reaction conditions: **2a** (0.5 mmol), NHC (30 mol%), base (1.2 equiv), THF (4 mL); [b]Yields are for isolated products; [c]Reaction was performed at 80 °C for 4 h; Mes: 2,4,6-trimethylphenyl



Scheme 2 Sequential imine formation—NHC catalysed construction of methyl 2-(2-phenyl-1*H*-indol-3-yl)acetate **1a**; MS: Molecular Sieves

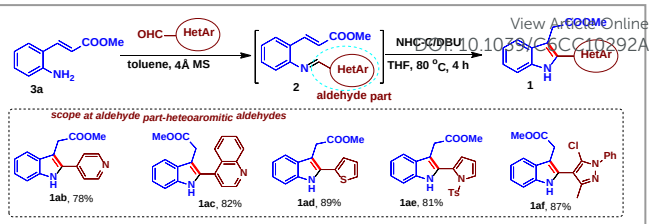


Scheme 3 Synthesis of 2-aryl substituted indole-3-acetic acid derivatives. Yields in parenthesis correspond to the reactions with isolated imine.

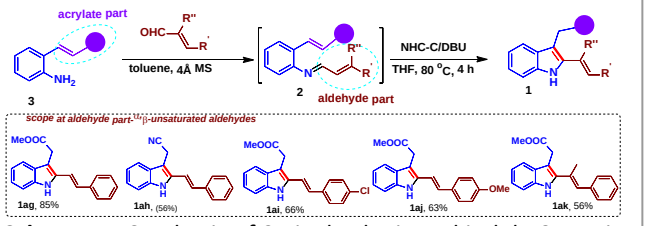
Further, this transformation is not limited to only aromatic aldehydes as α,β-unsaturated aldehydes have also furnished the corresponding 2-vinyl substituted indol-3-acetic esters **1ag-ak** in moderate to good yields (Scheme 5). With the aliphatic subtituents like $(CH_2)_2Ph$ on the aldehyde part, the desired indole derivative was not obtained under the reaction conditions.

It is worth noting that the presented method has enabled to scale up the reaction to a gram scale for the synthesis of methyl 2-(2-(2-bromophenyl)-1*H*-indol-3-yl)acetate **1q** while maintaining the high yield (Scheme 6).

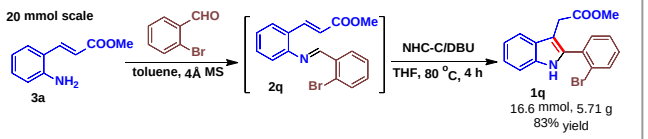
The synthetic utility of the present transformation has been demonstrated with the synthesis of a cyclin-dependent kinase (CDK) inhibitor, paullone.[4d] In continuation of our interest in the development of copper catalysed tandem reactions,[11] we



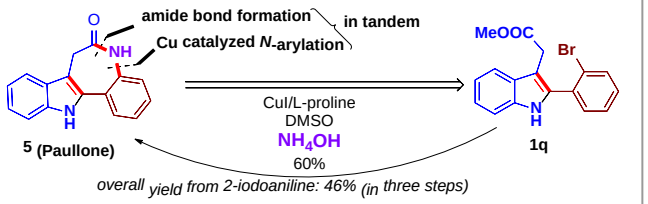
Scheme 4 Synthesis of 2-heteroaryl substituted indole-3-acetic acid derivatives.



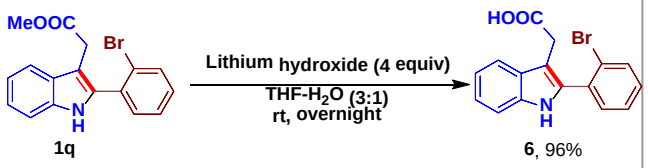
Scheme 5 Synthesis of 2-vinyl substituted indole-3-acetic acid derivatives.



Scheme 6 Gram scale synthesis of **1q**.



Scheme 7 Retro-synthetic analysis and synthesis of paullone by tandem reaction triggered by copper catalysis.



Scheme 8 Synthesis of 2-(2-(2-bromophenyl)-1*H*-indol-3-yl)acetic acid. Yields in parenthesis correspond to the reactions with isolated imine.

became interested to exploit the strategy to the synthesis of paullone. It is worth mentioning that a tandem copper catalyzed *N*-arylation followed by amidation of the methyl 2-(2-(2-bromophenyl)-1*H*-indol-3-yl)acetate **1q** gave the desired paullone **5** in a single step (Scheme 7). The overall yield for the synthesis of paullone is 46% starting from 2-iodoaniline in three simple steps. It should be mentioned that while the same has been synthesized in 12% overall yield starting from 2-iodoaniline in eight steps besides the use of special precursors.[5e]

We have also synthesized the indole-3-acetic acid **6** of methyl 2-(2-(2-bromophenyl)-1*H*-indol-3-yl)acetate by simple hydrolysis (Scheme 8).

In conclusion, an NHC catalyzed novel approach has been established for the construction of variously substituted 2-aryl/heteroaryl/vinyl indole-3-acetic acid derivatives. Gram

scale synthesis of a representative example, methyl 2-(2-(2-bromophenyl)-1*H*-indol-3-yl)acetate has been presented. A short two-step synthesis of cyclin-dependent kinase (CDK) inhibitor, paullone has been accomplished from *N*-heterocyclic carbene catalysed reaction of methyl (*E*)-3-(2-(((*E*)-2-bromobenzylidene)amino)phenyl)acrylate followed by copper catalysed *N*-arylation-amidation. Efforts are underway to investigate the mechanism of the present NHC catalysed indole construction. Further studies are in progress on exploring the utilization of the presented concept for suitable organic synthesis.

We thank the Department of Science and Technology (DST), India for Fast track grant (SB/FT/CS-055/2012) and CSIR, New Delhi for financial support as part of XII Five Year plan the under title ORIGIN (CSC-0108). BH thanks CSIR, MS thanks DST for financial support.

Notes and references

1 (a) A. Baeyer, *Justus Liebigs Ann. Chem.,* 1866, **140**, 295; (b) A. Baeyer and A. Emmerling, *Ber. Dtsch. Chem. Ges.,* 1869, **2**, 679; (c) R. B. Van Order and H. G. Lindwall, *Chem. Rev.,* 1942, **30**, 69.

2 (a) R. Möhlau, *Ber. Dtsch. Chem. Ges.,* 1881, **14**, 171; (b) E. Fischer and F. Jourdan, *Ber. Dtsch. Chem. Ges.,* 1883, **16**, 2241; (c) E. Fischer and O. Hess, *Ber. Dtsch. Chem. Ges.,* 1884, **17**, 559; (d) B. Robinson, *Chem. Rev.,* 1969, **69**, 227; (e) R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.,* 1991, **113**, 6689; (f) S. Cacchi and G. Fabrizi, *Chem. Rev.,* 2005, **105**, 2873; (g) M. Platon, R. Amardeil, L. Djakovitch and J.-C. Hierso, *Chem. Soc. Rev.,* 2012, **41**, 3929.

3 (a) D. W. C. MacMillan, *Nature,* 2008, **455**, 304; (b) H. Pellissier, *Recent Developments in Asymmetric Organocatalysis*, Royal Society of Chemistry, Cambridge, 2010; for a review on non-asymmetric organocatalysis, see: (c) P. Renzi and M. Bella, *Chem. Commun.,* 2012, **48**, 6881.

4 (a) B. W. Trotter, A. G. Quigley, W. C. Lumma, J. T. Sisko, E. S. Walsh, C. S. Hamann, R. G. Robinson, H. Bhimnathwala, D. G. Kolodin, W. Zheng, C. A. Buser, H. E. Huber, R. B. Lobell, N. E. Kohl, T. M. Williams, S. L. Graham and C. J. Dinsmore, *Bioorg. Med. Chem. Lett.,* 2001, **11**, 865; (b) Z. Yang, S. Reiling, T. R. Nieduzak, R. M. Mathew, S. Jackson and K. J. Harris, PCT Int. Appl. WO 2008014186 *Chem. Abstr.,* 2008, **148**, 214951; (c) D. E. Williams, J. Davies, B. O. Patrick, H. Bottriell, T. Tarling, M. Roberge and R. J. Andersen, *Org. Lett.,* 2008, **10**, 3501; (d) C. Schultz, A. Link, M. Leost, D. W. Zaharevitz, R. Gussio, E. A. Sausville, L. Meijer and C. Kunick, *J. Med. Chem.,* 1999, **42**, 2909.

5 For the transition metal catalysed synthesis of 2-substituted indole-3-acetic acid derivatives, see: (a) T. Fukuyama, X. Chen and G. Peng, *J. Am. Chem. Soc.,* 1994, **116**, 3127; (b) O. Baudoin, M. Cesario, D. Guénard and F. Guéritte, *J. Org. Chem.,* 2002, **67**, 1199; (c) Y. Kasaya, K. Hoshi, Y. Terada, A. Nishida, S. Shuto and M. Arisawa, *Eur. J. Org. Chem.,* 2009, 4606; (d) M. Tobisu, H. Fujihara, K. Koh and N. Chatani, *J. Org. Chem.,* 2010, **75**, 4841; (e) D. R. Stuart, P. Alsabeh, M. Kuhn and K. Fagnou, *J. Am. Chem. Soc.,* 2010, **132**, 18326; (f) D. Takeda, M. Yamashita, K. Hirano, T. Satoh and M. Miura, *Chem. Lett.,* 2011, **40**, 1015; (g) S. Soto, E. Vaz, C. Dell'Aversana, R. Álvarez, L. Altucci and Á. R. de Lera, *Org. Biomol. Chem.,* 2012, **10**, 2101; (h) Z. Hu, S. Luo and Q. Zhu, *Adv. Synth. Catal.,* 2015, **357**, 1060; for sodium cyanide mediated and catalysed reactions, see: (i) T. Opatz and D. Ferenc, *Org. Lett.,* 2006, **8**, 4473; (j) S. J. Lee, H.-A. Seo and C.-H. Cheon, *Adv. Synth. Catal.,* 2016, **358**, 1566.

6 S. Müller, M. J. Webber and B. List, *J. Am. Chem. Soc.,* 2011, **133**, 18534.

7 For excellent reviews on NHC catalyses, see: (a) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.,* 2007, **107**, 5606; (b) N. Marion, S. Díez-González and S. P. Nolan, *Angew. Chem. Int. Ed.,* 2007, **46**, 2988; (c) E. M. Phillips, A. Chan and K. A. Scheidt, *Aldrichimica Acta,* 2009, **42**, 55; (d) S. J. Ryan, L. Candish and D. W. Lupton, *Chem. Soc. Rev.,* 2013, **42**, 4906; (e) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature,* 2014, **510**, 485; (f) R. S. Menon, A. T. Biju and V. Nair, *Chem. Soc. Rev.,* 2015, **44**, 5040; (g) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.,* 2015, **115**, 9307.

8 M. T. Hovey, C. T. Check, A. F. Sipher and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2014, **53**, 9603.

9 For reports on NHC catalysis involving deoxy-Breslow intermediate prior to 2013, see ref. 7d and references cited therein; (a) D. Enders, K. Breuer, U. Kallfass and T. Balensiefer, *Synthesis,* 2003, 1292; (b) C. E. I. Knappke, A. J. Arduengo III, H. Jiao, J.-M. Neudörfl and A. J. von Wangelin, *Synthesis,* 2011, 3784; (c) H. Mayr, S. Lakhdar, B. Maji and A. R. Ofial, *Beilstein J. Org. Chem.,* 2012, **8**, 1458; (d) S.-i. Matsuoka, Y. Tochigi, K. Takagi and M. Suzuki, *Tetrahedron,* 2012, **68**, 9836; (e) B. Maji, M. Horn and H. Mayr, *Angew. Chem. Int. Ed.,* 2012, **51**, 6231; (f) S.-i. Matsuoka, S. Namera, A. Washio, K. Takagi and M. Suzuki, *Org. Lett.,* 2013, **15**, 5916; (g) T. Kato, Y. Ota, S.-i. Matsuoka, K. Takagi and M. Suzuki, *J. Org. Chem.,* 2013, **78**, 8739; (h) M. Schedler, N. E. Wurz, C. G. Daniliuc and F. Glorius, *Org. Lett.,* 2014, **16**, 3134; (i) T. Kato, S.-i. Matsuoka and M. Suzuki, *J. Org. Chem.,* 2014, **79**, 4484; (k) A. Bhunia, S. Thorat, R. G. Gonnade and A. T. Biju, *Chem. Commun.,* 2015, **51**, 13690.

10 For reports on aza-Breslow intermediates, see: (a) S. Simonovic, J.-C. Frison, H. Koyuncu, A. C. Whitwood and R. E. Douthwaite, *Org. Lett.,* 2009, **11**, 245; (b) D. A. DiRocco and T. Rovis, *Angew. Chem. Int. Ed.,* 2012, **51**, 5904; (c) D. A. DiRocco, K. M. Oberg and T. Rovis, *J. Am. Chem. Soc.,* 2012, **134**, 6143.

11 (a) O. Obulesu, J. B. Nanubolu and S. Suresh, *Org. Biomol. Chem.,* 2015, **13**, 8232; (b) V. Murugesh, B. Harish, M. Adiseshu, J. B. Nanubolu and S. Suresh, *Adv. Synth. Catal.,* 2016, **358**, 1309.