ChemComm

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C7CC00323D

Journal Name

COMMUNICATION

Metal-free benzannulation of 1,7-diynes toward unexpected 1-aroyl-2-naphthaldehydes and their application in fused aza-heterocyclic synthesis

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

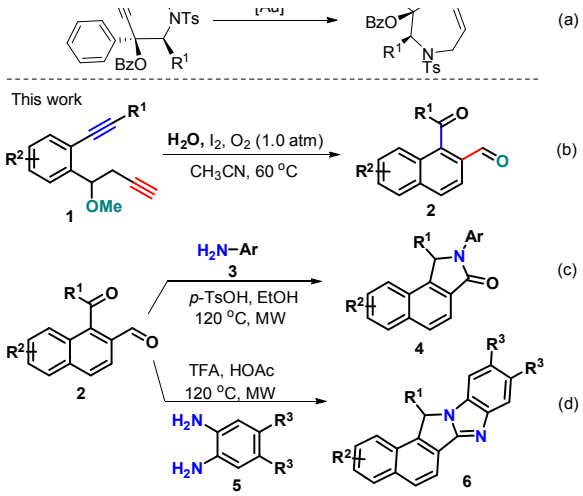
DOI: 10.1039/x0xx00000x

www.rsc.org/

Ai-Fang Wang,[a] Peng Zhou,[a] Yi-Long Zhu,[a] Wen-Juan Hao,*[,a] Guigen Li,[b] Shu-Jiang Tu,*[,a] and Bo Jiang*[,a]

A novel I_2-mediated benzannulation of 1,7-diynes involved 1,4-oxo-migration has been established, providing a range of unexpected 1-aroyl-2-naphthaldehydes with a 1,4-dicarbonyl unit. The resulting 1-aroyl-2-naphthaldehydes have been successfully applied in the synthesis of benzo[*e*]isoindol-3-ones and benzo[*e*]benzo[4,5]imidazo[2,1-*a*]isoindoles using aromatic amines and benzene-1,2-diamines as nucleophiles, respectively. The mechanisms for forming these compounds were proposed.

1,4-Dicarbonyl compounds as key core components are prevalent in a multitude of biological molecules of pharmaceutical and material interest.[1] Specifically, 1,4-dicarbonyls are types of competent reactants endowed with two electrophilic sites, which could be served as versatile and synthetically useful feedstocks for the preparation of various carbocyclic and heterocyclic compounds.[2] To date, significant efforts have been directed to develop efficient protocols toward 1,4-dicarbonyl synthesis. Generally, the vast majority of well-established synthetic strategies for the construction of 1,4-dicarbonyls include conjugate addition of acyl anions to Michael acceptors,[3] nucleophilic substitution of α-haloketones,[4] chain extension of 1,3-dicarbonyls,[5] oxidative coupling of enolates[6] or alkenes,[7] the addition of homoenolate equivalents to acid derivatives,[8] and enolate heterocoupling.[9] Despite these significant advances achieved in this field, current 1,4-dicarbonyl synthesis has mainly relied on the use of carbonyl precursor. To the best of our knowledge, the utilization of 1,7-diynes without any carbonyl unit as starting materials *via* domino benzannulation for the creation of conjugate 1,4-dicarbonyls has not yet been documented.



Scheme 1. Profile application of 1,7-diynes

Metal-catalyzed cycloisomerizations of 1,n-diynes have proven to be exceptionally efficient methods to construct synthetically significant poly-cyclic molecules in an atom-economical manner.[10] For instance, Chan and co-workers reported Au(I)-catalyzed cycloisomerization reactions of 1,7-diyne benzoates to selectively generate indeno[1,2-*c*]azepines (Scheme 1a).[10g] Recently, our group has established a series of domino cyclization reactions for multiple ring formations.[11] For this purpose, we planned the preparation of diyne-anchored starting materials by taking advantage of a methodology in which tandem cycloisomerization across its C≡C π system results in functionalized polycyclic products.[10] Surprisingly, we found I_2-mediated reaction of the preformed 1,7-diynes **1** underwent unexpected oxygen migration and benzannulation process in the presence of H_2O, providing functionalized 1-aroyl-2-naphthaldehydes **2** with conjugate 1,4-dicarbonyl unit (Scheme 1b). The resulting 1-aroyl-2-naphthaldehydes have been subjected with the reactions of aryl amines **3**, enabling

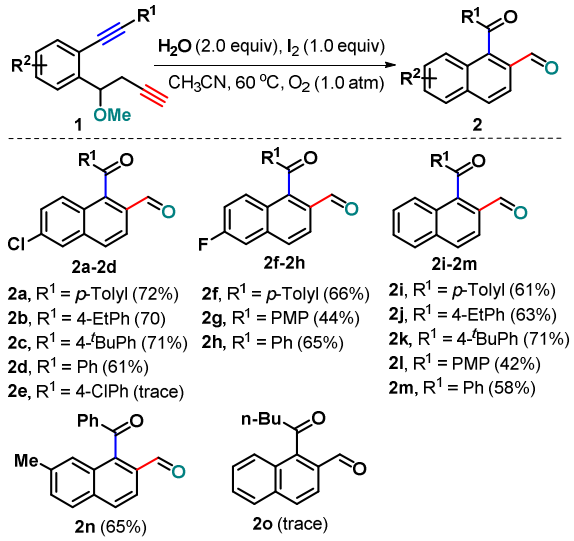
[a] *School of Chemistry and Materials Science, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou 221116, P. R. China. Email: wjhaol@jsnu.edu.cn (WJH); laotu@jsnu.edu.cn (SJT); jiangchem@jsnu.edu.cn (BJ) Fax: +8651683500065; Tel: +8651683500065*
[b] *Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, United States.*

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available. CCDC 1526668 (**2a**), 1526669 (**4h**), 1526670 (**4l**): [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C7CC00323D

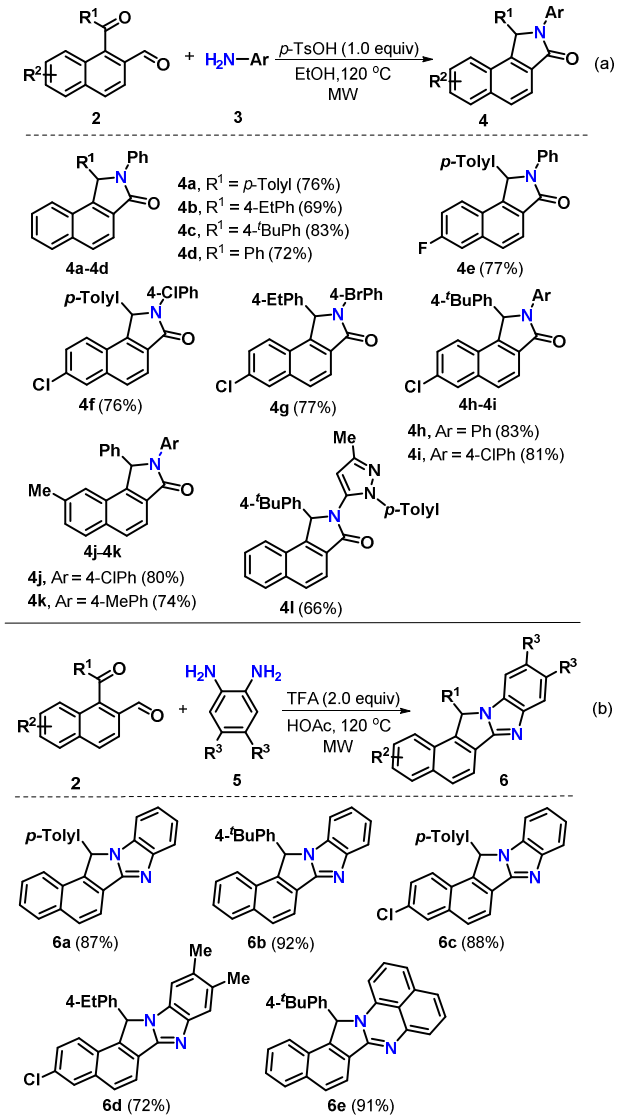
microwave-assisted (MW) domino [4 + 1] cyclization to give tricyclic benzo[*e*]isoindol-3-ones **4** with good yields (Scheme 1c). Using benzene-1,2-diamines **5** as replacement for aryl amines **3**, the reaction afforded high yields of pentacyclic benzo[*e*]benzo [4,5]imidazo[2,1-*a*]isoindoles **6** *via* double [4 + 1] cyclization cascades (Scheme 1d). Herein, we would like to report these interesting transformations.

Our initial investigation was started with the treatment of benzene-tethered 1,7-diyne **1a** by water and 2.0 equivalents of I_2[12] under air conditions in acetonitrile at 50 °C, and the unexpected 2-naphthaldehyde **2a** was generated in a low 27% yield (Table 1, entry S1, See Supporting Information). After careful screening of the reaction conditions, we found that the reaction in the presence of I_2 (1.0 equiv) and H_2O (2.0 equiv) in acetonitrile at 60 °C under O_2 conditions afforded product **2a** in 72% yield (entry S15).



Scheme 2 Substrate scope for forming products **2**. Yields of isolated products based on 1,7-diynes **1**.

Under the above optimal conditions, we explored the reaction scope by using a variety of the preformed benzene-tethered 1,7-diynes **1** (Scheme 2). Chloro substituent at C4-positions of the internal arene rings of 1,7-diynes **1** was proven not to hamper this benzannulation reaction. Both electron-donating (methyl **1a**, ethyl **1b** and *t*-butyl **1c**) and electron-neutral (H **1d**) groups at para-positions of arylalkynyl motifs can all tolerate the reaction conditions well, delivering the corresponding substituted 1-aroyl-2-naphthaldehydes **2a**-**d** in good yields (61%-72%). However, the presence of electron-withdrawing chloro group (**1e**) at this position failed to provide the desired product **2e**, indicating electronic effect of substituents on the arylalkynyl moiety showed a critical influence on the success of this transformation. Afterward, 4-fluoro-substituted counterparts **1f**-**h** with various functional groups attached with the arylalkynyl moiety were found to be adaptable to this reaction, giving access to the corresponding products **2f**-**h** in 44%-66% yields. Among them, a significant drop in the yields was obtained (**2g**, 44%) as the *p*-methoxyphenyl (PMP) counterpart (**1g**) was employed as a reaction partner. This similar inferior outcome was observed in the reaction of 1,7-diynes **1l** (product **2l**, 42% yield). These results revealed that both electron-withdrawing and strong electron-donating groups at the arylalkynyl moiety are not beneficial to the reaction process. Alternatively, substrates **1i-1m** without substituent on the internal arene ring were successfully converted to the corresponding products **2i-2m** with yields ranging from 42% to 71%. Similarly, 1,7-diyne **1n** bearing a methyl group resided at C5-position of the internal arene ring still showed high reactivity, furnishing product **2n** in 65% yield. Unfortunately, 1,7-diyne **1o** carrying an *n*-butyl group was an ineffective substrate.



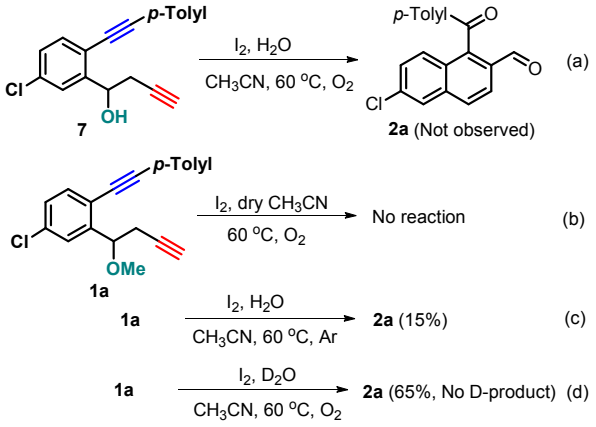
Scheme 3 Synthesis of polycyclic products **4** and **6**. Yields of isolated products based on compounds **2**.

After our successful achievement with 1-aroyl-2-naphthaldehydes **2** having conjugate 1,4-dicarbonyl moiety, we decided to employ them as starting materials to react with aryl amines **3** to investigate the feasibility of [4 + 1] cyclization toward the expected tricyclic benzo[*e*]isoindol-3-ones **4**, due

View Article Online
DOI: 10.1039/C7CC00323D

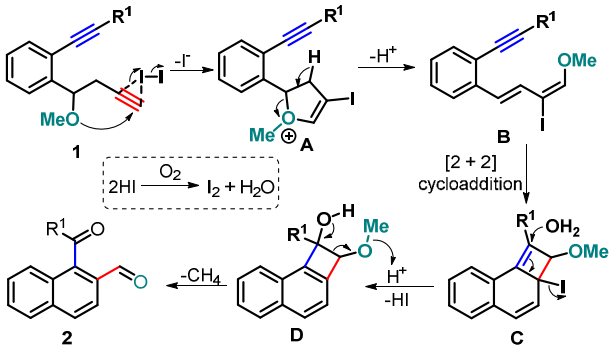
to the isoindol-3-one framework extensively exists in natural products and shows a broad spectrum of biological activities.[13] As expected, the reaction of **2** with **3** was conducted in EtOH at 120 °C under microwave heating using *p*-TsOH as a Brønsted acid promoter (1.0 equiv), leading to the corresponding benzo[*e*]isoindol-3-ones **4** (Scheme 3a). Next, the scope of this [4 + 1] cyclization was evaluated by treating the preformed substrates **2** with a variety of aryl amines **3** (Scheme 3). The results from Scheme 3 revealed that 1-aroyl-2-naphthaldehydes **2** carrying electron-neutral and donating groups at the para-position of aroyl ring all readily participated in this transformation. The variety of substituents located on naphthalene ring of **2**, including fluoro, chloro and methyl, would be compatible under the present reaction conditions. Similarly, the reaction proceeded smoothly with various functional groups (H **3a**, chloro **3b**, bromo **3c**, and methyl **3d**) on the phenyl ring of **3**, delivering the collection of tricyclic benzo[*e*]isoindol-3-ones **4a-4k** with yields ranging from 69% to 83%. Heteroarylated amine **3e** could also be accommodated, thus confirming the reaction efficiency, as pyrazol-5-yl product **4l** was obtained in 66% yield.

To further expand the synthetic application of this methodology, upon treatment of benzene-1,2-diamine **5a** with 1-aroyl-2-naphthaldehydes **2** in the presence of trifluoroacetic acid (TFA, 2.0 equiv) and HOAc allowed microwave-assisted double [4 + 1] cyclization cascades to afford pentacyclic benzo[*e*]benzo[4,5] imidazo[2,1-*a*]isoindoles **6a-c** in 87%-92% yields (Scheme 3b). Alternatively, 4,5-dimethylbenzene-1,2-diamine **5b** was proved to be a suitable diamine precursor (**6d**, 72%). Notably, naphthalene-1,8-diamine **5c** could be successfully engaged in the current bicyclization, providing the corresponding hexacyclic benzo[4,5]isoindolo[2,1-*a*]perimidine **6e** in 91% yield. The structures of products **2**, **4** and **6** have been determined by NMR and HR-MS spectral analysis. In the cases of products **2a**, **4h**, and **4l**, their structures have been further confirmed by X-ray diffractional analysis.



Scheme 4 Control experiments

To gain mechanistic insight into this reaction, several control experiments were carried out. The reaction of *O*-unprotected 1,7-diyne **7** was performed under the standard conditions, but no expected product **2a** was observed with the starting material **7** remaining (Scheme 4a), indicating that the methyl protection of hydroxyl group is necessary for this transformation. Without H_2O, the reaction of **1a** did not proceed, confirming that H_2O plays a key role in the success of this cyclization (Scheme 4b). The same reaction under Ar conditions only gave 15% yield of **2a** with the starting material **1a** remaining (Scheme 4c), suggesting that oxygen atom of aroyl group may come from H_2O rather than molecular O_2 and molecular O_2 may facilitate the regeneration of I_2 from iodine anion during the reaction process.[14] The reaction in D_2O gave the desired product **2a** without D-content (Scheme 4d).



Scheme 5. Plausible mechanism for forming **2**

On the basis of the above analysis, a reasonable mechanism for forming products **2** was proposed in Scheme 5. In the first stage, in the presence of I_2, intramolecular 5-*endo-dig oxo*-cyclization occurs to give dihydrofuran cation, followed by ring opening of dihydrofuran ring (1,4-oxo-migration) to yield diene intermediates **B** detected by LC-MS (See Supporting Information). Subsequent [2+2] cycloaddition of dienes **B**[15] generates cyclobutene intermediates **C**, which undergo allylic nucleophilic substitution and ring opening of cyclobutenes to access products **2**.[16] I_2 is believed to be regenerated by reaction with iodine anion and molecular O_2.[14] The formation of products **4** involved *in situ* formation of imines (**2** to **E**), 5-*exo-trig* cyclization (**E** to **F**), nucleophilic addition of H_2O (**F** to **G**), dehydration and tautomerization (**G** to **4**) sequence (Scheme S1, see Supporting Information). Similar to the above, the synthesis of products **6** is expected to consist of nucleophilic additions-dehydration (**2** to **I**), intramolecular cyclization (**I** to **K**), second dehydration and tautomerization (**K** to **6**) sequence (Scheme S1).

In conclusion, we have discovered a new I_2-mediated synthesis of unexpected 1-aroyl-2-naphthaldehydes through metal-free benzannulation of 1,7-diynes involved 1,4-oxo-migration process. The resulting 1-aroyl-2-naphthaldehydes as an alternative 1,4-dielectrophilic reagent have been successfully applied in fused aza-heterocyclic synthesis. The microwave-assisted [4 + 1] cyclization of 1-aroyl-2-naphthaldehydes with aromatic amines gave tricyclic benzo[*e*]isoindol-3-ones with good yields whereas pentacyclic benzo[*e*]benzo[4,5]imidazo[2,1-*a*]isoindoles with high yields were obtained through double [4 + 1] cyclization cascades using benzene-1,2-diamines as a reaction partner. A further investigation on

View Article Online
DOI: 10.1039/C7CC00323D

reaction mechanism and assessing biological activity of these resultant compounds is currently underway in our laboratory.

We are grateful for financial support from the NSFC (No. 21232004, 21472071 and 21602087), PAPD of Jiangsu Higher Education Institutions, the Outstanding Youth Fund of JSNU (YQ2015003), NSF of Jiangsu Province (BK20151163 and BK20160212), the Qing Lan Project and NSF of Jiangsu Education Committee (15KJB150006).

Notes and references

1 (a) P. Gull, O. A. Dar, M. A. Malik and A. A. Hashmi, *Microb. Pathog.*, 2016, **100**, 237. (b) S. Kumar, S. Chatterjee, J. Tripathi and S. Gautam, *J. Agri. Food Chem.*, 2016, **64**, 8773. (c) S. P. Devi, S. Kumaria, S. R. Rao and P. Tandon, *Trop. Plant Biol.,* 2016, **9**, 267. (d) T. Sreelatha, S. Kandhasamy, R. Dinesh, S. Shruthy, S. Shweta, D. Mukesh, D. Karunagaran, R. Balaji, N. Mathivanan and P. T. Perumal, *Bioorg. Med. Chem. Lett.,* 2014, **24**, 3647.

2 For representative examples, see: (a) D. C. Gerbino, D. Augner, N. Slavov and H.-G. Schmalz, *Org. Lett.,* 2012, **14**, 2338. (b) Z. Shen, P. K. Dornan, H. A. Khan, T. K. Woo and V. M. Dong, *J. Am. Chem. Soc.,* 2009, **131**, 1077. (c) B. Jiang, B.-M. Feng, S.-L. Wang, S.-J. Tu and G. Li, *Chem.-Eur. J.*, 2012, **18**, 9823. (d) Y. Cheng, J.-H. Peng, Y.-J. Li, X.-Y. Shi, M.-S. Tang and T.-Y. Tan, *J. Org. Chem.*, 2011, **76**, 1844. (e) B. Jiang, R. Fu, J.-K. Qiu, Y. Yu, S.-L. Wang and S.-J. Tu, *RSC Adv.*, 2016, **6**, 74372.

3 For representative examples, see: (a) K. Miura, M. Tojino, N. Fujisawa, A. Hosomi and I. Ryu, *Angew. Chem., Int. Ed.,* 2004, **43**, 2423. (b) H. Nemoto, T. Kawamura and N. Miyoshi, *J. Am. Chem. Soc.,* 2005, **127**, 14546. (c) M. C. Myers, A. R. Bharadwaj, B. C. Milgram and K. A. Scheidt, *J. Am. Chem. Soc.,* 2005, **127**, 14675. (d) D. Enders, J. Han and A. Henseler, *Chem. Commun.* 2008, **34**, 3989. (e) D. A. Dirocco, K. M. Oberg, D. M. Dalton and T. Rovis, *J. Am. Chem. Soc.,* 2009, **131**, 10872. (f) A. T. Biju, N. E. Wurz and F. Glorius, *J. Am. Chem. Soc.,* 2010, **132**, 5970. (g) J. M. Um, D. A. DiRocco, E. L. Noey, T. Rovis and K. N. Houk, *J. Am. Chem. Soc.,* 2011, **133**, 11249. (h) T. Jousseaume, N. E. Wurz and F. Glorius, *Angew. Chem., Int. Ed.,* 2011, **50**, 1410. (i) J. Zhang, C. Xing, B. Tiwari and Y. R. Chi, *J. Am. Chem. Soc.,* 2013, **135**, 8113. (j) M. M. D. Wilde and M. Gravel, *Angew. Chem., Int. Ed.,* 2013, **52**, 12651.

4 For representative examples, see: (a) M. Yasuda, S. Tsuji, Y. Shigeyoshi and A. Baba, *J. Am. Chem. Soc.,* 2002, **124**, 7440. (b) J. Kondo, H. Shinokubo and K. Oshima, *Angew. Chem., Int. Ed.,* 2003, **42**, 825. (c) C. Liu, Y. Deng, J. Wang, Y. Yang, S. Tang and A. Lei, *Angew. Chem., Int. Ed.,* 2011, **50**, 7337. (d) N. Esumi, K. Suzuki, Y. Nishimoto and M. Yasuda, *Org. Lett.,* 2016, **18**, 5704.

5 (a) S. Lai, C. K. Zercher, J. P. Jasinski, S. N. Reid and R. J. Staples, *Org. Lett.,* 2001, **3**, 4169. (b) S. Xue, Y. K. Liu, L. Z. Li and Q. X. Guo, *J. Org. Chem.,* 2005, **70**, 8245. (c) A. Voituriez, L. E. Zimmer and A. B. Charette, *J. Org. Chem.,* 2010, **75**, 1244.

6 (a) K. Ryter and T. Livinghouse, *J. Am. Chem. Soc.,* 1998, **120**, 2658. (b) C. T. Avetta, L. C. Konkol, C. N. Taylor, K. C. Dugan, C. L. Stern and R. J. Thomson, *Org. Lett.,* 2008, **10**, 5621. (c) M. D. Clift and R. J. Thomson, *J. Am. Chem. Soc.,* 2009, **131**, 14579.

7 (a) M. Rössle, T. Werner, A. Baro, W. Frey and J. Christoffers, *Angew. Chem., Int. Ed.,* 2004, **43**, 6547. (b) M. Rössle, T. Werner, W. Frey and J. Christoffers, *Eur. J. Org. Chem.,* 2005, **23**, 5031. (c) J. Xie and Z. Z. Huang, *Chem. Commun.,* 2010, **46**, 1947. (d) F. Zhang, P. Du, J. Chen, H. Wang, Q. Luo and X. Wan, *Org. Lett.,* 2014, **16**, 1932.

8 (a) P. Setzer, A. Beauseigneur, M. S. M. Pearson-Long and P. Bertus, *Angew. Chem., Int. Ed.,* 2010, **49**, 8691. (b) Z. L. Shen, K. K. K. Goh, H. L. Cheong, C. H. A. Wong, Y. C. Lai, Y. S. Yang and T. P. Loh, *J. Am. Chem. Soc.,* 2010, **132**, 15852. (c) B. B. Parida, P. P. Das, M. Niocel and J. K. Cha, *Org. Lett.* 2013, **15**, 1780.

9 (a) P. S. Baran and M. P. DeMartino, *Angew. Chem., Int. Ed.,* 2006, **45**, 7083. (b) M. P. DeMartino, K. Chen and P. S. Baran, *J. Am. Chem. Soc.,* 2008, **130**, 11546. (c) B. M. Casey and R. A. Flowers II, *J. Am. Chem. Soc.,* 2011, **133**, 11492.

10 For representative examples, see: (a) L. Ye, Y. Wang, D. H. Aue and L. Zhang, *J. Am. Chem. Soc.,* 2012, **134**, 31. (b) H. Shi, L. Fang, C. Tan, L. Shi, W. Zhang, C. Li, T. Luo and Z. Yang, *J. Am. Chem. Soc.,* 2011, **133**, 14944. (c) C. A. Sperger and A. Fiksdahl, *J. Org. Chem.,* 2010, **75**, 4542. (d) A. Das, H. K. Chang, C. H. Yang and R. S. Liu, *Org. Lett.,* 2008, **10**, 4061. (e) J. J. Lian, P. C. Chen, Y. P. Lin, H. C. Ting and R. S. Liu, *J. Am. Chem. Soc.,* 2006, **128**, 11372. (f) D. H. Zhang, L. F. Yao, Y. Wei and M. Shi, *Angew. Chem., Int. Ed.,* 2011, **50**, 2583. (g) W. Rao, M. J. Koh, P. Kothandaraman and P. W. H. Chan, *J. Am. Chem. Soc.,* 2012, **134**, 10811.

11 (a) J. K. Qiu, B. Jiang, Y. L. Zhu, W. J. Hao, D. C. Wang, J. Sun, P. Wei, S. J. Tu and G. Li, *J. Am. Chem. Soc.,* 2015, **137**, 8928. (b) Z. Z. Chen, S. Liu, W. J. Hao, G. Xu, S. Wu, J. N. Miao, B. Jiang, S. L. Wang, S. J. Tu and G. Li, *Chem. Sci.,* 2015, **6**, 6654. (c) Y. L.Zhu, B. Jiang, W. J. Hao, J. K. Qiu, J. Sun, D. C. Wang, P. Wei, A. F. Wang, G. Li and S. J. Tu, *Org. Lett.,* 2015, **17**, 6078. (d) Y. L. Zhu, B. Jiang, W. J. Hao, A. F. Wang, J. K. Qiu, P. Wei, D. C. Wang, G. Li and S. J. Tu, *Chem. Commun.,* 2016, **52**, 1907.

12 For selected I_2-meidated reactions, see: (a) X. Du, H. Chen, Y. Chen, J. Chen and Y. Liu, *Synlett,* **2011**, 1010. (b) M. S. Yusubov and V. V. Zhdankin, *Resource-Efficient Technol.*, 2015, **1**, 49. (c) P. Finkbeiner and B. J. Nachtsheim, *Synthesis,* 2013, **45**, 979.

13 (a) Y. Nozawa, K. Yamamoto, M. Ito, N. Sakai, K. Mizoue, F. Mizobe and K. Hanada, *J. Antibiot.,* 1997, **50**, 635. (b) Y. Nozawa, M. Ito, K. Sugawara, K. Hanada and K. Mizoue, *J. Antibiot*., 1997, **50**, 641. (c) D. Comins, S. Schilling and Y. Zhang, *Org. Lett.*, 2005, **7**, 95. (d) D. Augner, D. C. Gerbino, N. Slavov, J.-M. Neudörfl and H.-G. Schmalz, *Org. Lett.*, 2011, **13**, 5374.

14 (a) W.-J. Hao, J.-Q. Wang, X.-P. Xu, S.-L. Zhang, S.-Y. Wang and S.-J. Ji, *J. Org. Chem.,* 2013, **78**, 12362. (b) T. B. Nguyen, M. Corbin, P. Retailleau, L. Ermolenko and A. Al-Mourabit, *Org. Lett.* 2015, **17**, 4956. (c) W. Fan, Q. Li, Y. Li, H. Sun, B. Jiang and G. Li, *Org. Lett.*, 2016, **18**, 1258.

15 (a) M. R. Siebert, J. M. Osbourn, K. M. Brummond and D. J. Tantillo, *J. Am. Chem. Soc.,* 2010, **132**, 11952. (b) B.-L. Lu and M. Shi, *Angew. Chem., Int. Ed.,* 2011, **50**, 12027. (c) K. M. Brummond and D. Chen, *Org. Lett.,* 2005, **7**, 3473. (d) S. Yang, Q. Xu and M. Shi, *Tetrahedron,* 2016, **72**, 584. (e) H. Ohno, T. Mizutani, Y. Kadoh, A. Aso, K. Miyamura, N. Fujii and T. Tanaka, *J. Org. Chem.*, 2007, **72**, 4378.

16 (a) M. E. Jung and P. Davidov, *Org. Lett.,* 2001, **3**, 3025.