ORGANIC CHEMISTRY FRONTIERS

CCS 中国化学会 CHINESE CHEMICAL SOCIETY

SIOC

ROYAL SOCIETY OF CHEMISTRY

A metal-free aromative cascade for the synthesis of diverse heterocycles

Journal:	*Organic Chemistry Frontiers*
Manuscript ID	QO-RES-11-2019-001336.R1
Article Type:	Research Article
Date Submitted by the Author:	24-Dec-2019
Complete List of Authors:	Schlitzer, Steven; University of Oklahoma, Chemistry and Biochemistry Arunprasath, Dhanarajan; University of Oklahoma, Chemistry and Biochemistry Stevens, Katelyn; University of Oklahoma Sharma, Indrajeet; University of Oklahoma, Chemistry and Biochemistry;

Journal Name

COMMUNICATION

A metal-free aromative cascade for the synthesis of diverse heterocycles

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

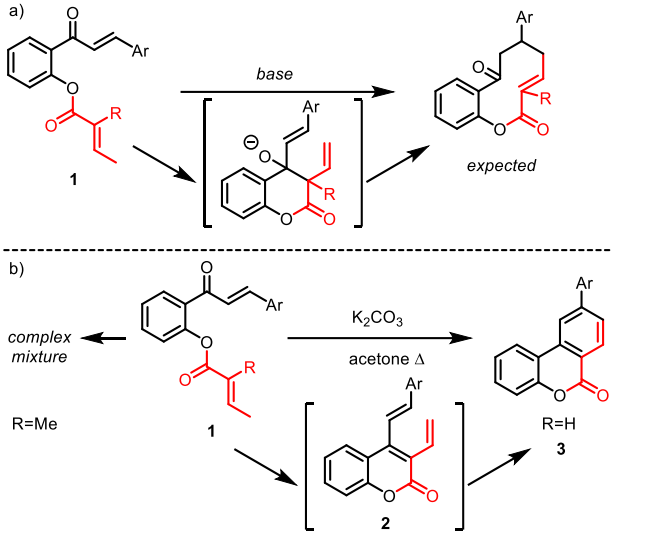
Steven C. Schlitzer,[a] Dhanarajan Arunprasath,[a] Katelyn G. Stevens[a] and Indrajeet Sharma*[a]

A metal-free aromative cascade has been developed for the synthesis of diverse heterocycles from readily accessible hydroxy/aminochalcones and acid/alkyl halides. The cascade beings by a base-mediated intramolecular aldol cyclization/dehydration sequence to provide a triene, which sets the stage for a 6π-electrocyclization/oxidative aromatization to access diverse heterocyclic scaffolds.

Cascade reactions are an elegant strategy for assembling molecular complexity in organic synthesis.[1] Furnishing high efficiency and atom economy, cascade reactions use multiple transformations in a one-pot fashion.[2] Employing cascade reactions as an approach eases reaction workup, purification, time, and waste management.[3] These advantages altogether make cascade reactions ideal for green chemical synthesis.[4]

In continuing our work on cascade approaches to medium-sized scaffolds,[5] we designed a metal-free cascade comprised of an intramolecular aldol reaction/anionic oxy-Cope rearrangement to furnish 10-membered lactones (Scheme 1a). The cascade precursor is readily accessible through the standard coupling of hydroxychalcones to unsaturated acids. However, when we exposed precursor **1** (R=Me) to basic conditions, we recovered a complex mixture of products. We suspected that the additional methyl group was dissuading the desired enolization, leading to ketene formation and subsequent fragmentation of the hydroxychalcone component.[6] When the methyl group was removed (R=H), we did not observe any trace of desired macrolactone, but small quantities of the aromatized benzo[*c*]coumarin **3**, which presumably formed via an intramolecular 6π-electrocyclization of 1,3,5-triene **2** (Scheme 1b).[7]

Although there are examples in literature of 6π-electrocyclization employed in the synthesis biologically relevant natural products,[8] this serendipitous cascade represents a unique approach for the construction of functionalized benzo[*c*]coumarins that does not rely on modification of a pre-formed coumarin scaffold.[9]



Scheme 1 a) Anionic oxy-Cope approach to 10-membered macrolactones. b) Serendipitous approach to benzo[*c*]coumarins.

Inspired by these results, we envision applying this approach to the synthesis of heterocyclic scaffolds, which are found in numerous natural products and drug molecules. In particular, the benzo[*c*]coumarin core can be found in several natural products, and was recently used as a precursor to access the cannabinoid receptor agonist cannabinol.[10d] In addition, the related heterocycles such as phenanthridin-6(5*H*)-ones, dibenzofurans, and carbazoles are also commonly found in nature and medicinally relevant compounds (Fig. 1).[10]

Although there are multiple methods currently available in literature for the synthesis of these heterocycles, most rely on the use of transition metal catalysts.[11] With high cost and difficult purification, reducing the use of expensive transition metal catalysts in chemical reactions is a unifying goal in the

[a] *Department of Chemistry and Biochemistry, and Institute of Natural Products Applications and Research Technologies, University of Oklahoma, 101 Stephenson Parkway, Norman, OK-73071, USA, E-mail: isharma@ou.edu*

†Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

synthetic community.[12] Keeping these advantages in mind, our serendipitous cascade is attractive and provides an alternative metal-free method for the synthesis of aromatic heterocycles.

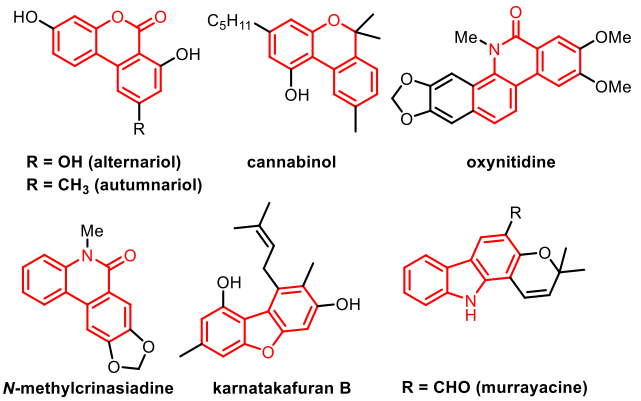
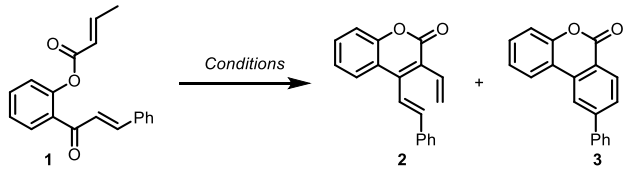


Fig. 1 Aromatic heterocycles in natural products.

We commenced our reaction optimization for the formation of benzo[*c*]coumarin **3**. When precursor **1** was exposed to K_2CO_3 in refluxing acetone for 16 hours, we observed complete conversion of **1** to triene **2**, with further conversion to **3** (Table 1, entry 1). These reaction conditions however resulted in a low overall yield of **3**. We then attempted the reaction utilizing organic bases, beginning with Et_3N. After 16 hours of stirring at reflux temperature in dichloromethane, we observed no conversion to triene **2** and pure **1** was recovered (entry 2). When a stronger base (DBU) was utilized, we then observed full conversion of **1** to furnish a mixture of **2** and **3** (entry 3). Inspired by recent reports into the 6π-electrocyclization of 1,3,5-triene systems,[9] DMSO was employed as the reaction solvent, and improved conversion of **2** to **3** was observed (entry 4). When the reaction was heated to 80 °C in DMSO, full conversion of **2** to **3** was observed, with an isolated yield of 82% (entry 5).

Table 1 Reaction optimization for aldol elimination/ electrocyclization sequence.



Entry	Base (equiv.)	Solvent	Temp.	**2/3**[b]
1	K_2CO_3 (3.0)	Acetone	reflux	1:2 (23)[c]
2	Et_3N (3.0)	DCM	reflux	N.R.
3	DBU (3.0)	DCM	rt	95:5
4	DBU (3.0)	DMSO	rt	90:10
5	**DBU (3.0)**	**DMSO**	**rt → 80 °C**	**0:100 (82)[c]**
6	DBU (2.0)	DMSO	rt → 80 °C	0:100 (64)[c]
7	DBU (1.0)	DMSO	rt → 80 °C	0:100 (45)[c]
8	DBU (0.1)	DMSO	rt → 80 °C	trace

[a]All optimization reactions were performed by adding base at room temperature to a solution of **1** in DMSO (0.15 M). The reaction vessel was sealed and heated at the indicated temperature for 16 hours. [b]The percent ratio of **2** and **3** was determined by crude ^{1}H NMR integration. [c]Isolated yield of **3** obtained after column chromatography. N.R. = No reaction

The reaction was also successful using lower quantities of base, however a notable decrease in the isolated yield was observed (entries 6 and 7) with a longer reaction time. When 0.1 equivalents of base was utilized, incomplete conversion of 1 was observed, and 3 was obtained in trace quantity (entry 8).

With optimized conditions in hand, we then turned our attention towards the substrate scope for this cascade (Fig. 2). The reaction was amenable to substituents on the pre-existing aromatic ring, resulting in good yields for compounds **3b** and **3c**. Next, we explored the electronic influence of the triene on the overall reaction cascade. Electron- neutral and electron-donating substituents were well-tolerated and resulted in good to excellent yields (**3d-3f**). The reaction though was low-yielding with trifluoromethyl substituted compound **3g**. Reaction conditions were also tolerant of other heterocycles comprising the chalcone component, and furan-substituted **3h** was synthesized in good yields. Finally, A lower yield was observed for methyl-substituted compound **3i**, and in this instance we observed byproducts arising from incomplete electrocyclization in the crude NMR.

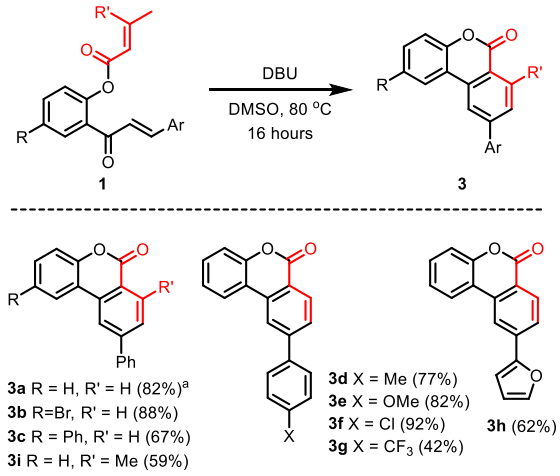


Fig. 2 Scope of benzo[*c*]coumarin substrate examples; all reactions were performed by adding DBU (3.0 equiv) to a 0.15 M solution of **1** (1.0 equiv) in DMSO at room temperature. After stirring for 90 minutes at room temperature, the reaction was heated to 80 °C for 16 hours. [a]Reaction was also performed at 1-gram scale with an isolated yield of 76%.

Addressing a limitation in some of the current electrocyclization-based methods for benzo[*c*]coumarin formation, we wondered if our method was suitable for synthesizing their nitrogen analogues, phenanthridin-6(5*H*)-ones (Fig. 3).[9a] By coupling *N*-alkylaminochalcones to crotonyl chloride, we were able to access precursors **4** in a three-step sequence. Parent compound **5a** was synthesized in excellent yields, and notably, was suitable to a 1-gram scale-up, with only a slight decrease in overall yield (89%). The reaction also tolerated other *N*-protecting groups well, with benzyl-protected **5b** synthesized in comparable yields. Alkyl protection of the amide was crucial to the success of this reaction however; when the free N-H amide was exposed to the optimized DBU heating conditions, a complex mixture of products was recovered. Similarly, the reaction conditions were not suitable for the common nitrogen protecting groups *tert*-butylcarbamate (boc)

and tosyl group.[13] In both cases, cleavage of the crotonylamide bond was observed at room temperature, resulting in recovery of the corresponding aminochalcone precursor.

Like their oxygen-containing counterparts, the cascade was tolerant of electron-neutral and electron-donating substituents (**5f-5h**). Again, we observed diminished yields with electron-withdrawing substituents, with cyano-substituted **5i** synthesized in only moderate yields. We observed higher yields overall for the synthesis of these phenanthridin-6(5*H*)-ones, presumably due to the disfavoured ketene-mediated fragmentation of **4**, relative to **1**, in the presence of a strong base.[6]

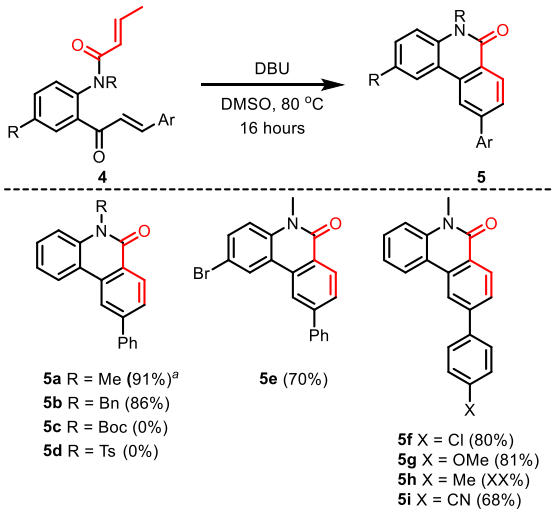
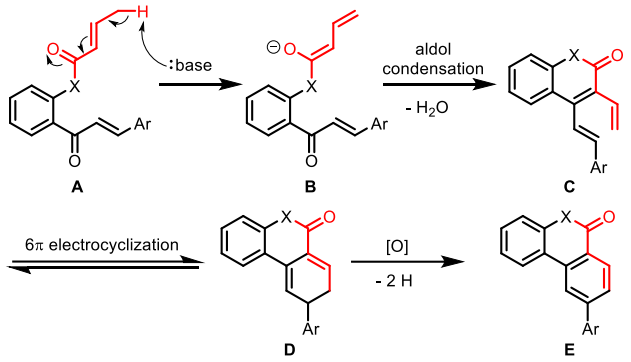


Fig. 3 Scope of phenanthridin-6(5*H*)-one substrate examples; all reactions were performed by adding DBU (3.0 equiv) to a 0.15 M solution of **1** (1.0 equiv) in DMSO at room temperature. After stirring for 90 minutes at room temperature, the reaction was heated to 80 °C for 16 hours. [a]Reaction was also performed at 1-gram scale with an isolated yield of 89%.

A plausible reaction mechanism for this cascade is depicted in scheme 2. First, γ-deprotonation of crotonate **A** generates enolate **B** which undergoes *α*-enolate attack onto the ketone followed by the loss of water to generate 1,3,5-triene **C**. Under heating conditions, triene **C** can perform a 6π-electrocyclization forming **D**, which is capable of aromatization via an aerial oxidation,[14] generating benzocoumarin or phenanthradinone **E**.



Scheme 2. Proposed mechanism for the formation of Benzo[*c*]coumarins.

Several experiments were performed to validate the proposed reaction mechanism. We were able to isolate triene **C** after 90 minutes of stirring at room temperature in the presence of DBU. When triene **C** is exposed to the same DBU conditions while heating to 80 °C for 16 hours, **E** is obtained in good yields supporting our proposal that it is an intermediate in this process. It was also found that the addition of the single electron oxidant DDQ can promote the oxidation of **D** to **E**. We then probed whether the reaction cascade could be accomplished via direct α-enolization of esters **1**, instead of indirect γ-enolization. When hydroxychalcone was coupled to vinylacetic acid, we observed complete olefin isomerization to give exclusively α,β-unsaturated product **1a**.

Fortunately, when hydroxychalcone was coupled to various arylacetic acids, we were able is isolate esters **6** in good yields. (Fig. 4). These substrates tolerated α-enolization well and underwent the desired aldol elimination/6π-electrocyclization cascade at 120 °C to provide heterocycles **7a**-**7d** in yields ranging from good to excellent. The reaction conditions were also suitable for the formation of phenanthradinones **7e** and **7f**. Unfortunately, phenyl- and pyridine- substituted **6g** and **6h** respectively did not undergo electrocyclization after triene formation, even when the reaction temperature was elevated to 180 °C.

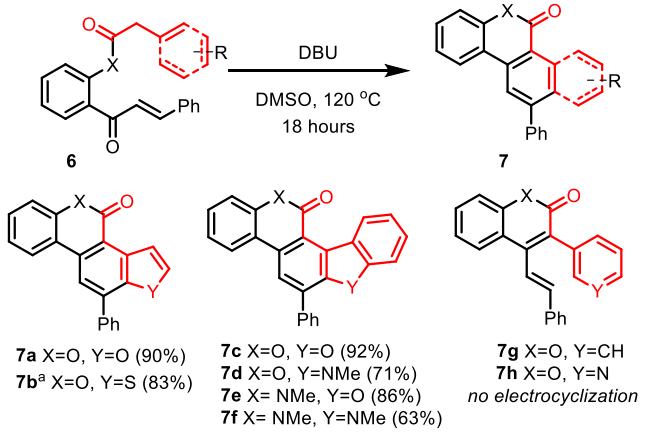


Fig. 4 Scope of electrocyclization cascade incorporating an aryl component; all reactions were performed by adding DBU (3.0 equiv) to a 0.15 M solution of **1** (1.0 equiv) in DMSO at room temperature. After stirring for 90 minutes at room temperature, the reaction was heated to 120 °C for 16 hours. [a]Compound was prone to intramolecular aldol elimination under coupling conditions and reaction was performed using the corresponding triene.

Lastly, we turned our attention towards accessing other benzannulated heterocyclic scaffolds, namely dibenzofurans and carbazoles (Fig. 5). By changing the chalcone coupling partner to ethyl 4-bromocrotonate, compounds **8** and **9** were prepared. We envision that when exposing to base, they could undergo enolization via γ-deprotonation, and unlike their **1** and **4** counterparts, act as nucleophiles from the γ-position as opposed to the *α*-position, setting the stage for the 6π-electrocyclization step. Indeed, when **8** and **9** were exposed to the optimized DBU heating conditions, **10** and **11** could be isolated in good yields. Notably, this reaction required heating to 120 °C, as evidence of incomplete electrocyclization was observed after heating to 80 °C for 16 hours.[15]

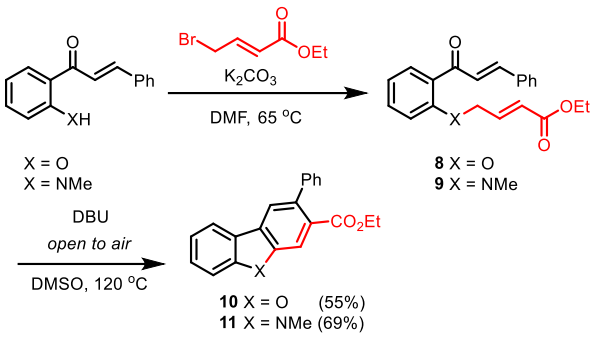


Fig. 5 Aldol/electrocyclization route to carbazoles and dibenzofurans; all reactions were performed by adding DBU (3.0 equiv) to a 0.15 M solution of **1** (1.0 equiv) in DMSO at room temperature. After stirring for 90 minutes at room temperature, the reaction was heated to 120 °C for 16 hours.

In conclusion, we have disclosed a new method for the preparation of benzo[*c*]coumarin and phenanthradin-6(5*H*)-one scaffolds via a one-pot aldol elimination/6π-electrocyclization/oxidative aromatization reaction cascade. This new metal-free method benefits from high atom economy, straightforward starting material synthesis, and moderate to high yields. By altering the chalcone coupling partner, dibenzofurans and carbazoles can also be prepared in moderate yields using the method described herein. Application of this cascade to other scaffolds is currently underway and will be reported in due course.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

We thank Dr. Susan Nimmo, Dr. Steven Foster, and Dr. Douglas R. Powell from the Research Support Services, University of Oklahoma, for expert NMR, mass spectral, and X-ray crystallographic analyses, respectively. The work was supported by the NSF CHE-1753187, and the American Chemical Society Petroleum Research Fund (ACS-PRF) Doctoral New Investigator grant (PRF no. 58487-DNI1). Additional funding was provided by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institute of Health under grant number P20GM103640.

Notes and references

1 For reviews on cascade reactions, see: (a) R. Ardkhean, D. F. J. Caputo, S. M. Morrow, H. Shi, Y. Xiong and E. A. Anderson, Cascade Polycyclizations in Natural Product Synthesis, *Chem. Soc. Rev*. 2016, **45**, 1557–1569; (b) A. C. Jones; J. A. May, R. Sarpong and B. M. Stoltz, Cascade Polycyclizations in Natural Product Synthesis, *Angew. Chem., Int. Ed.* 2014, **53**, 2556–2591; (c) K. C. Nicolaou and J. S. Chen, The Art of Total Synthesis through Cascade Reactions, *Chem. Soc. Rev*. 2009, **38**, 2993–3009; (d) I. Vilotijevic and T. F. Jamison, Epoxide-Opening Cascades in the Synthesis of Polycyclic Polyether Natural Products, *Angew. Chem., Int. Ed.* 2009, **48**, 5250–5281; (e) A. Padwa, A Chemistry Cascade: From Physical Organic Studies of Alkoxy Radicals to Alkaloid Synthesis, *J. Org. Chem.* 2009, **74**, 6421–6441; (f) A. Padwa, Chapter 2: Cascade Reactions of Carbonyl Ylides for Heterocyclic Synthesis, *Prog. Heterocycl. Chem.* 2009, **20**, 20–46; (g) V. F. Ferreira, Synthesis of Heterocyclic Compounds by Carbenoid Transfer Reactions, *Curr. Org. Chem.* 2007, **11**, 177–193; (h) G. H. P. Roos and C. E. S. Raab, Dirhodium(II) Carbenes: A Rich Source of Chiral Products, *Afr. J. Chem.* 2001, **54**, 1–40; (i) A. Padwa, Tandem Processes of Metallo Carbenoids for the Synthesis of Azapolycycles, *Top. Curr. Chem.* 1997, **189**, 121–158.

2 B. M. Trost, The Atom Economy—A Search for Synthetic Efficiency, *Science* 1991, *254*, 1471–1477.

3 K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, Cascade Reactions in Total Synthesis, *Angew. Chem., Int. Ed*. 2006, **45**, 7134–7186.

4 (a) P. T. Anastas and J. C. Warner, *Green Chemistry; Theory and Practice*, Oxford University Press: Oxford, 2000; p 135; (b) A. S. Matlack, *Introduction to Green Chemistry*; Marcel Dekker: New York, 2001; p 570.

5 (a) K. Chinthapally, N. P. Massaro and I. Sharma, Rhodium Carbenoid Initiated O-H Insertion/Aldol/Oxy-Cope Cascade for the Stereoselective Synthesis of Functionalized Oxacycles, *Org. Lett*., 2016, **18**, 6340–6343; (b) K. Chinthapally, N. P. Massaro, H. L. Padgett and I. Sharma, Serendipitous Cascade of Rhodium Vinylcarbenoids with Aminochalcones for the Synthesis of Functionalized Quinolines, *Chem. Comm.* 2017, **53**, 12205–12208; (c) N. P. Massaro, J. C. Stevens, A. Chatterji and I. Sharma, Stereoselective Synthesis of Diverse Lactones through a Cascade Reaction of Rhodium Carbenoids with Ketoacids, *Org. Lett*. 2018, **20**, 7585–7589.

6 (a) B. R. Cho, Y. K. Kim, Y. J. Seung, J. C. Kim and S. Y. Pyun, Elimination Reactions of Aryl Phenylacetates Promoted by $R_2NH/R_2NH_2^+$ in 70 mol MeCN(aq). Effect of the β-Phenyl Group on the Ketene-Forming Transition State, *J. Org. Chem*. 2000, **65**, 1239–1242; (b) W. You, Y. Li and M. K. Brown, Stereoselective Synthesis of All-Carbon Tetrasubstituted Alkenes from In Situ Generated Ketenes and Organometallic Reagents, *Org. Lett.* 2013, **15**, 1610–1613; (c) R. F. Pratt and T. C. Bruice, The Carbanion Mechanism (E1cB) of Ester Hydrolysis. III. Some Structure-Reactivity Studies and the Ketene Intermediate, *J. Am. Chem. Soc.* 1970, **92**, `5956–6964; (d) A. D. Allen and T. T. Tidwell, Ketenes and Other Cumulenes as Reactive Intermediates, *Chem. Rev.* 2013, **113**, 7287–7342; (e) D. H. Paull, A. Weatherwax and T. Lectka, Catalytic, Asymmetric Reactions of Ketenes and Ketene Enolates, *Tetrahedron* 2009, **65**, 6771–6803.

7 (a) W. H. Okamura and A. R. De Lera, *In Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming and L. A. Paquette, Eds.; Pergamon Press: New York, 1991; Vol. 5, p 699; (b) R. V. Essen, D. Frank, H. W. Sunnemann, D. Vidovic, J. Magull and A. de Meijere, Domino 6π-Electrocyclization/Diels-Alder Reactions on 1,6-Disubstituted (*E*,*Z*,*E*)-1,3,5-Hexatrienes: Versatile Access to Highly Substituted Tri- and Tetracyclic Systems, *Chem. Eur. J.* 2005, **11**, 6583–6592; (c) K. Voigt, P. von Zezschwitz, K. Rosauer, A. Lanksy, A. Adams, O. Reiser and A. de Meijere, The Twofold Heck Reaction on 1,2-Dihalocycles and Subsequent 6π-Electroclyzation of the Resulting (*E*, *Z*, *E*,)-1,3,5-Hexatrienes: A New Formal [2+2+2]-Assembly of Six-Membered Rings, *Eur. J. Org. Chem.* 1998, 1521–1534; (d) P. von Zezschwitz, F. Petry and A. de Meijere, A One-Pot Sequence of Stille and Heck Couplings: Synthesis of Various 1,3,5-Hexatrienes and their Subsequent 6π-Electrocyclizations, *Chem. Eur. J.* 2001, **7**, 4035–4046; (e) H. W. Sunnemann and A. de Meijere, Steroids and Steroid Analogues from Stille-Heck Coupling Sequences, *Angew. Chem. Int. Ed*. 2004, **43**, 895–897; (f) R. von Essen, P. von Zezschwitz, D. Vidovic, A and de Meijere, A New Phototransformation of Methoxycarbonyl-Substitutes (*E*, *Z*,

E)-1,3,5-Hexatrienes: Easy Access to Ring-Annelated 8-Oxabicyclo[3.2.1]octa-2,6-diene Derivatives, *Chem. Eur. J.* 2004, **10**, 4341−4352.

8 (a) E. L. Myers, and D. Trauner (2012). 2.19 *Selected Diastereoselective Reactions: Electrocyclizations. Comprehensive Chirality.* E. M. Carreira and H. Yamamoto. Amsterdam, Elsevier: 563–606; (b) M. Bian, L. Li and H. Ding, Recent Advances on the Application of Electrocyclic Reactions in Complex Natural Product Synthesis, *Synthesis*, 2017, **49**, 4383–4413; (c) T. Choshi and S. Hibino, Synthetic Studies on Nitrogen-Containing Fused-Heterocyclic Compounds Based on Thermal Electrocyclic Reactions of 6π-Electron and Aza-6π Electron Systems, *Heterocycles*, 2011, **6**, 1205−1240; (d) H. W. Sunnemann, M. G. Banwell and A. de Meijere, Synthesis and Use of New Substituted 1,3,5-Hexatrienes in Studying Thermally Induced 6π-Electrocyclizations, *Eur. J. Org. Chem*. 2007, 3879−3893; (e) T. Itoh, T. Abe, T. Choshi, T. Nishiyama, R. Yanada and M. Ishikura, Concise Total Synthesis of Pyrido[4,3-*b*]carbazole Alkaloids using Copper-Mediated 6π-Electrocyclization, *Eur. J. Org. Chem*. 2016, 2290−2299.

9 (a) C. Mou, T. Zhu, P. Zheng, S. Yang, B. A. Song and Y. R. Chi, Green and Rapid Access to Benzocoumarins via Direct Benzene Construction through Base-Mediated Formal [4+2] Reaction and Air Oxidation, *Adv. Synth. Catal*. 2016, **358**, 707−712; (b) T. N. Poudel and Y. R. Lee, An Advanced and Novel One-Pot Synthetic Method for Diverse Benzo[c]chromen-6-ones by Transition-Metal Free Mild Base-Promoted Domino Reaction of Substituted 2-HydroxyChalcones with β-Ketoesters and its Application to Polysubstituted Terphenyls, *Org. Biomol. Chem*. 2014, **12**, 919−930.

10 (a) C. E. Turner, M. A. Elsohla and E. G. J. Boeren, Constituents of Cannabis Sativa L. XVII. A Review of the Natural Constituents, *Nat. Prod*. 1980, **43**, 169−234; (b) M. A. ElSohly and D. Slade, Chemical Constituents of Marijuana: The Complex Mixture of Natural Cannabinoids, *Life Sci.* 2005, **79**, 539−548; (c) H. Raistrick, C. E. Stickings and R. Thomas, Studies in the Biochemistry of Micro-organisms: Alternariol and Alternariol Monomethyl Ether, Metabolic Products of *Alternaria Tenuis, Biochemical Journal*, 1953, *55*, 421−433; (d) Y. Li, Y. Ding, J. Wang, Y. Su, and X. Wang, Pd-Catalyzed C-H Lactonization for Expedient Synthesis of Biaryl Lactones and Total Synthesis of Cannabinol, *Org. Lett.* 2013, **15**, 2574-2577; (e) W. R. L. Sidwell, H. Fritz and Ch. Tamm, Autumnariol and Autumnariniol, Two New Dibenzo-a-pyrons from *Eucomis Autumnalis Graeb*. Demonstration of a Remote Coupling Over Six Bonds in the Magnetic Proton Resonance Spectra, *Helv. Chem. Act.* 1971, *54*, 207−215; (f) M. Nakamura, A. Aoyama, M. T. A. Salim, M. Okamoto, M. Baba, H. Miyachi, Y. Hashimoto and H. Aoyama, Structural Development Studies of Anti-Hepatitis C Virus Agents with a Phenanthradinone Skeleton, *Bioorg. & Med. Chem*. 2010, **18**, 2402−2411; (g) S. Patil, S. Kamath, T. Sanchez, N. Neamati, R. F. Schinazi and J. K. Buolamwini, Synthesis and Biological Evaluation of Novel 5(*H*)-phenanthradin-6-ones, 5(*H*)-phenanthradin-6-one diketo Acid, and Polycyclic Aromatic Diketo Acid Analogues as New HIV-1 Integrase Inhibitors, *Bioorg. & Med. Chem*. 2007, **15**, 1212−1228; (h) S. Manniche, K Sprogoe, P. W. Dalsgaard, C. Christophersen and T. O. Larsen, Karnatakafurans A and B: Two Dibenzofurans Isolated from the Fungus *Aspergillus Karnatakaensis, J. Nat. Prod.* 2004, **67**, 2111−2112; (i) A. W. Schmidt, K. R. Reddy and H. Knoller, Occurrence, Biogenesis, and Synthesis of Biologically Active Carbazole Alkaloids, *Chem. Rev*. 2012, **112**, 3193−3328.

11 (a) R. Bates, *Organic Synthesis Using Transition Metals,* 2nd ed.; John Wiley & Sons, Ltd. 2012; p 462; (b) M. Beller and C. Bolm, *Transition Metals for Organic Synthesis*, Vol. 1, 2nd ed; Wiley−VCH Verlag GmbH & Co. KgaA, Weinheim 2004; p 662; (c) Tsuji, J. *Transition Metal Reagents and Catalysts*; John Wiley & Sons, Ltd 2000; p 477.

12 (a) P. R. Schreiner, Metal-Free Organocatalysis through Explicit Hydrogen Bonding Interactions, *Chem. Soc. Rev.,* 2003, **32**, 289−296; (b) S. D. Su, J. Zhang, B. Frank, A. Thomas, X. Wang, J. Paraknowitsch and R. Schlogl, Metal-Free Heterogenous Catalysis for Sustainable Chemistry, *ChemSusChem,* 2010, **3**, 169−180; (c) J. D. Hayler, D. K. Leahy, E. M. Simmons, A Pharmaceutical Industry Perspective on Sustainable Metal Catalysis, *Organometallics*, 2018, **38**, 36−46.

13 For some examples of DBU mediated boc deprotection, see: (a) M.C. Yang, C. Peng, H. Huang, L. Yang, X. H. He, W. Huang, H. L. Cui, G. He and B. Han, Organocatalytic Asymmetric Synthesis of Spiro-oxindole Piperidine Derivatives that Reduce Cancel Cell Proliferation by Inhibiting MDM2-p53 Interaction, *Org. Lett*. 2017, **19**, 6752−6755. (b) E. L. Millington, H. A. Dondas, C. W. G. Fishwick, C. Kilner and R. Grigg, Catalytic bimetallic [Pd(0)/Ag(I) Heck-1,3-dipolar Cycloaddition Cascade Reactions Accessing Spiro-oxindoles. Concomitant In Situ Generation of Azomethine Ylides and Dipolarophile, *Tetrahedron* 2018, **74**, 3564−3577; (c) B. M. Trost, D. A. Bringley, T. Zhang and N. Cramer, Rapid Access to Spirocyclic Oxindole Alkaloids: Application of the Asymmetric Palladium-Catalyzed [3+2] Trimethylenemethane Cycloaddition, *J. Am. Chem. Soc*. 2013, **135**, 16720−16735; (d) B. M. Trost, N. Cramer, and H. Bernsmann, Concise Total Synthesis of (±)-Marcofortine B. *J. Am. Chem. Soc*. 2007, **129**, 3086−3087.

14 (a) M. Miao, M. Jin, H. Xu, P. Chen, S. Zhang and H. Ren, Synthesis of 5*H*-dibenzo[*c,g*]chromen-5-ones via $FeCl_3$-Mediated Tandem C-O Bond Cleavage/6π Electrocyclization/Oxidative Aromatization, *Org. Lett.* 2018, **20**, 5718−5722; (b) B. E. Moulton, H. Dong, C. T. O'Brien, S. B. Duckett, Z. Lin and I. J. S. Fairlamb, A Natural Light Induced Regioselective 6π-Electrocyclization-Oxiative Aromatization Reaction: Experimental and Theoretical Insights, *Org. Biomol. Chem*., 2008, **6**, 4523−4532.

15 S. Saha, A. Banerjee and M. S. Maji, Transition-Metal-Free Redox-Neutral One-Pot C3-Alkenylation of Indoles Using Aldehydes, *Org. Lett.* 2018, **20**, 6920−6924.