https://doi.org/10.1595/205651321X16221259093681 *Johnson Matthey Technol. Rev.*, 2021, **65**, (3), 496–501

JOHNSON MATTHEY
TECHNOLOGY REVIEW
www.technology.matthey.com

"Palladium Assisted Synthesis of Heterocycles"

By Navjeet Kaur (Banasthali University, Rajastan, India), Taylor & Francis Group LLC, Boca Raton, USA, 2019, 444 pages, ISBN: 978-0-815-37425-1, £180.00, US$240.00

Reviewed by Fedor Romanov Michailidis
Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse, Belgium

Email: fedorromanov87@gmail.com

1. Introduction

The title of the book is "Palladium Assisted Synthesis of Heterocycles". The book covers literature extensively for the last two decades of research in the field of palladium-catalysed synthetic methodologies for accessing heterocycles of various nature and size. The book is written by Navjeet Kaur, an Assistant Professor in the Department of Chemistry at Banasthali University, India, whose research focuses on the synthesis of 1,4-benzodiazepine-based heterocyclic compounds which find widespread use in organic synthetic and medicinal chemistries.

In recent decades, numerous reports aimed at synthesising *N*–, *O*–, and *S*–containing heterocyclic compounds have appeared in scientific literature owing to their wide variety of biological activity. Indeed, heterocyclic compounds are prevalent in many natural products and pharmaceutically active compounds. Therefore, the development of newer approaches that employ efficient and atom-economical routes is an area of active research. Metal-catalysed syntheses of heterocyclic compounds are established and rewarding methods in organic synthesis. Palladium is one of the most commonly used transition metals in catalysis as it enables a wide number of versatile organic transformations, including reactions that form valuable C–C, C–O, C–N and C–S bonds. Palladium tolerates many functional groups and thus circumvents a lot of protecting group chemistry. Moreover, most palladium-based transformations proceeded in high yields and with exquisite stereo- and regioselectivity. These advantages have led to a significant growth in organopalladium chemistry over the last two decades, making palladium catalysts extremely active and reliable reagents for the syntheses of heterocycles.

2. Saturated Nitrogen Heterocycles

To highlight the importance of the topics discussed in the book, I will focus my review on the syntheses of saturated nitrogen heterocycles of various ring sizes. For many decades, saturated *N*-heterocycles were utilised as medicinal compounds, and they are key structural components of various therapeutic drugs, such as captopril (hypertension), morphine (analgesic) and vincristine (cancer chemotherapy).

The book is exhaustive and very detailed, so instead of reviewing it chapter-by-chapter, I have grouped my comments by subject matter. In what follows, the discussion will focus on the syntheses of some of the most medicinally relevant saturated nitrogen heterocycles, grouped by their respective ring sizes: (a) five-membered heterocycles, (b) six-membered heterocycles, and (c) seven-membered heterocycles.

2.1 Five-Membered Saturated Nitrogen Heterocycles

Five-membered saturated nitrogenous heterocycles such as pyrrolidines are present in numerous biologically active compounds. Therefore, synthetic chemists are continuously interested in preparing and functionalising these heterocyclic compounds. Saturated five-membered *N*–heterocycles are significant not only for the preparation of pigments,

drugs and pharmaceuticals, but also for the development of organic functional materials.

Palladium-catalysed carboamination of alkenes has become a useful and reliable method for the synthesis of a broad array of saturated nitrogen heterocycles (1). For example, *N*-acyl-protected pyrrolidines are synthesised stereoselectively from *γ*-(*N*-acylamino)alkenes by reacting them with aryl bromides under palladium catalysis. Moreover, the reaction occurs with high levels of enantioselectivity when the chiral ligand (*S*)-NMDPP is employed (**Scheme I**, Equation (i)) (2–4).

In 2004, Wolfe and coworkers reported a palladium-catalysed coupling of *γ*-aminoalkenes with aryl bromides to yield 2-benzylpyrrolidines (**Scheme I**, Equation (ii)) (5). In addition to pyrrolidines being an interesting class of medicinally-relevant compounds (6), this carboamination method was demonstrated to involve a novel, intramolecular *syn*-aminopalladation step (3, 4).

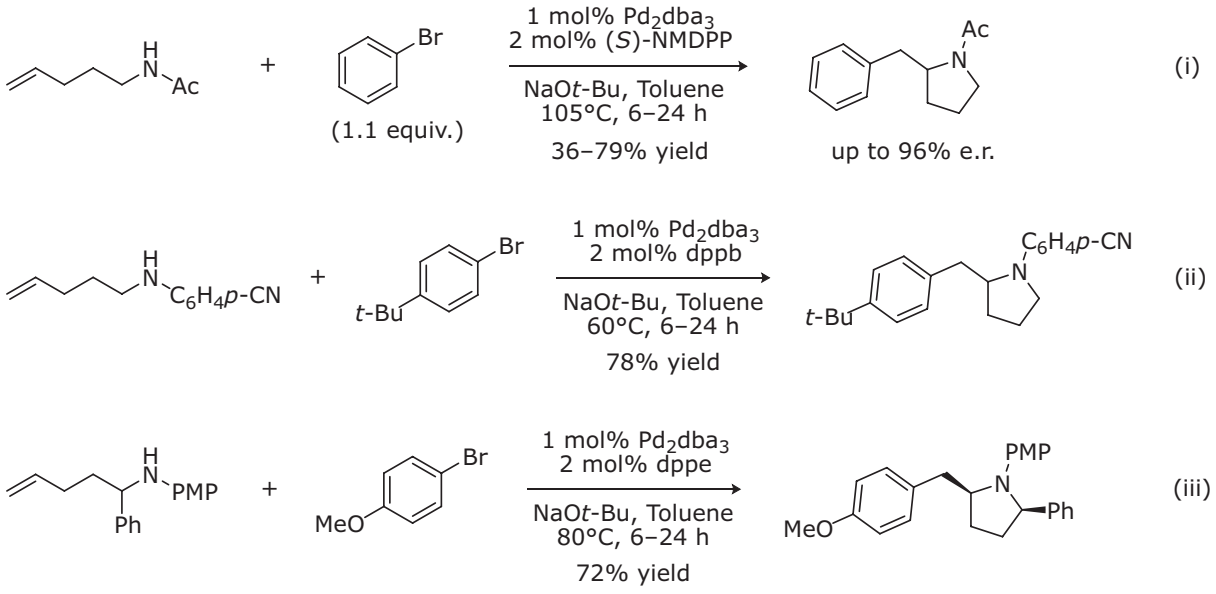
In a related reaction, carboamination of aminoolefins with 4-bromoanisole proceeds with high diastereoselectivity leading to formation of valuable 2,5-*cis*-disubstituted pyrrolidines (**Scheme I**, Equation (iii)) (3, 4).

2.2 Six-Membered Saturated Nitrogen Heterocycles

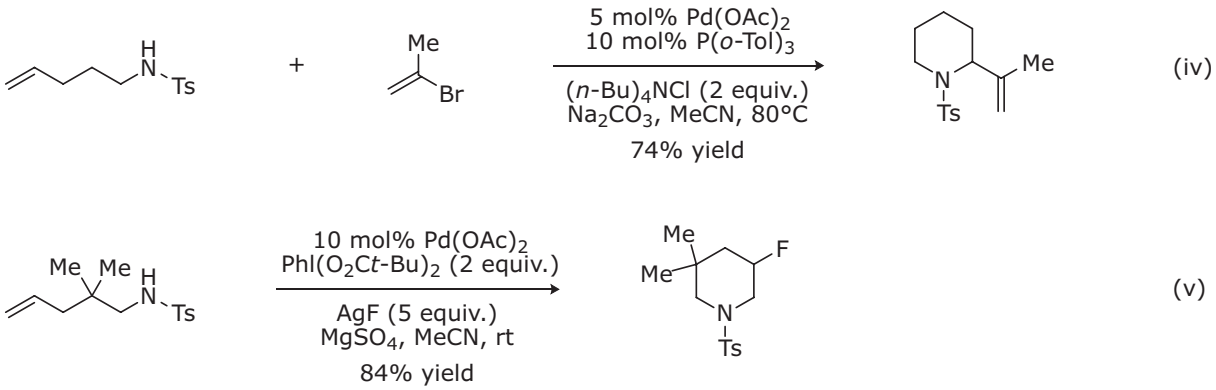
Six-membered heterocyclic compounds are widely abundant in pharmaceutical actives. Drugs containing saturated heterocycles such as substituted piperidines possess a wide range of pharmacological activities. For example, they are utilised to modulate angina pectoris, hypertension, diabetes, act as Ca^{2+} channel blockers, antitumour agents, and possess hepatoprotective properties. In addition, piperidine derivatives are frequently used as organocatalysts and organic bases in organic synthesis. In this section, the discussion will focus on applications of palladium catalysts to form substituted piperidines.

Larock, Weinreb and coworkers reported the synthesis of vinyl piperidines from *N*-tosyl aminoolefins and vinyl halides in the presence of a palladium catalyst (7). Nucleophilic attack of the allylpalladium intermediate affords *N*-sulfonamide–protected vinyl piperidines (**Scheme II**, Equation (iv)). These compounds could be used as building blocks and incorporated into lead molecules.

Fluorinative cyclisation of aminoalkenes was carried out with palladium catalysis. Liu *et al*. reported an oxidative fluorocyclisation protocol of alkenes with a palladium catalyst (8, 9). As a result, various fluorinated piperidine derivatives are formed with high regioselectivity. Mechanistically, the reaction is very interesting and involves: (a) *trans*-aminopalladation of the alkene; (b) oxidation of the C(sp^3)–palladium(II) intermediate to C(sp^3)–palladium(IV); and (c) reductive elimination of C(sp^3)–palladium(IV) intermediate. The final C–F bond is formed by reductive elimination following oxidative fluorination of the C–Pd bond by a combination of inorganic fluoride salt and oxidant (**Scheme II**, Equation (v)). Therefore, both the hypervalent iodine reagent and silver(I) fluoride



Scheme I. Synthesis of substituted pyrrolidines



Scheme II. Synthesis of substituted piperidines

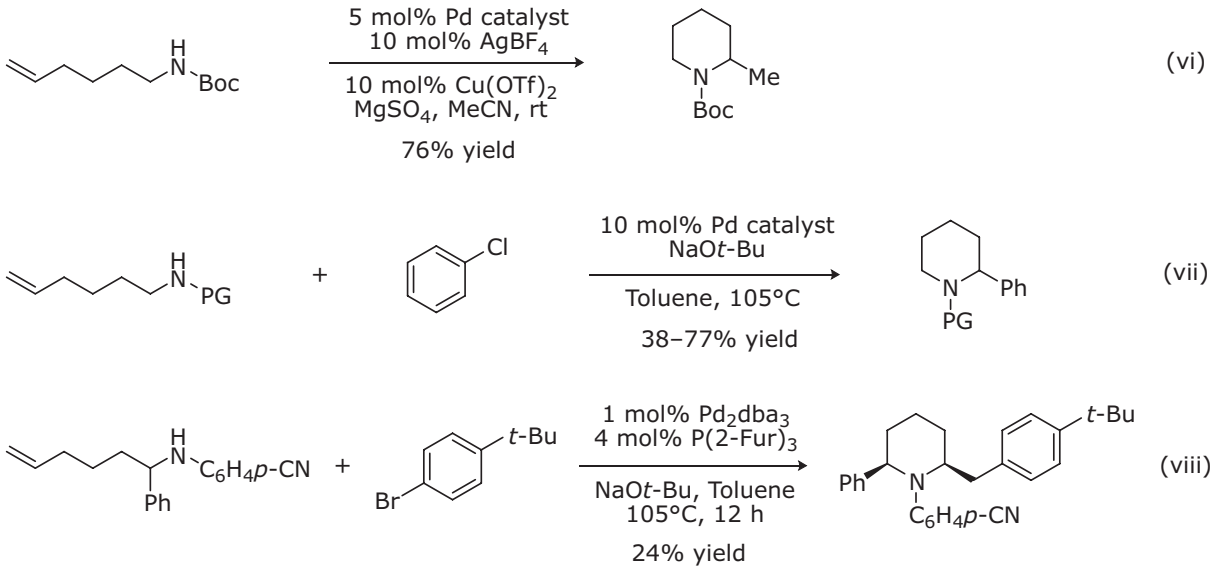
are crucial for this transformation. Interestingly, the fluoropiperidine product is not observed when an *N*-aryl acrylamide is reacted under the AgF/PhI(OPiv)$_2$ catalytic system. Instead, C–H bond activation of the solvent (acetonitrile) is seen, silver(I) fluoride acting as both a Lewis acid and a Brønsted base (10).

Michael *et al.* reported a hydroamination reaction of tethered aminoolefin substrates to access substituted piperidines (11). For example, an aminoolefin is converted to a methyl-substituted piperidine in the presence of a tridentate-ligated palladium catalyst and silver tetrafluoroborate (**Scheme III**, Equation (vi)). Presumably, this reaction proceeds through a nucleophilic attack of the amine on the palladium-activated olefin. The piperidine product is then released by protodemetalation.

Next, the synthesis of piperidines *via* palladium-catalysed carboamination was carried out to: (a) examine and identify suitable reaction conditions for the transformation by screening various ligands on palladium; and (b) examine the diastereoselectivity of reactions that provide disubstituted piperidines (**Scheme III**, Equation (vii)) (11). Gratifyingly, the palladium-catalysed carboamination turned out to be successful when preparing 2,6-disubstituted piperidines. However, in most cases, only modest yields are obtained due to competing side reactions (**Scheme III**, Equation (viii)) (12).

2.3 Seven-Membered Saturated Nitrogen Heterocycles

Seven-membered heterocyclic compounds are important structural components found in numerous



Scheme III. More syntheses of substituted piperidines

medicinal compounds. Because of their importance in pharmaceutical chemistry, seven-membered nitrogen-containing heterocycles are important molecules to consider. They are inherently non-aromatic and, therefore, embody useful non-flat scaffolds for drug discovery. For these reasons, many seven-membered nitrogen heterocycles are referred to as 'privileged scaffolds' in medicinal chemistry. In particular, azepanes and benzazepines have attracted much of chemists' attention and their preparation is a topic of extensive studies.

However, seven-membered nitrogen heterocycles are relatively underexplored in medicinal chemistry, in particular when compared to their four-, five- and six-membered congeners. For example, it has been reported that among all US Food and Drug Administration (FDA) approved drugs only 33 of them possess seven- or eight-membered *N*–heterocycles. In contrast, the number of drugs which contain five- or six-membered rings are 250 and 379, respectively (13). The main reason for this is the scarcity of general and convenient synthetic protocols for the preparation of seven-membered nitrogen heterocycles. Most of the methods that have been developed for the construction of *N*–heterocycles lead mostly to five- or six-membered ring systems, while the synthesis of seven-membered and larger heterocyclic compounds still lags behind. Nevertheless, some efficient ring-forming protocols have been tailored for the construction of seven-membered rings. Many of these protocols are based on palladium-catalysed reactions.

For example, Nakamura and coworkers disclosed that an *exo*-methylene azepane derivative is formed in 84% yield by an intramolecular palladium-catalysed hydroamination of an amino-tethered methylenecyclopropane (**Scheme IV**, Equation (ix)) (14). Here, the key allylpalladium intermediate is produced *via* distal bond cleavage of the cyclopropane ring. Reductive elimination then furnishes the observed azepane derivative (15).

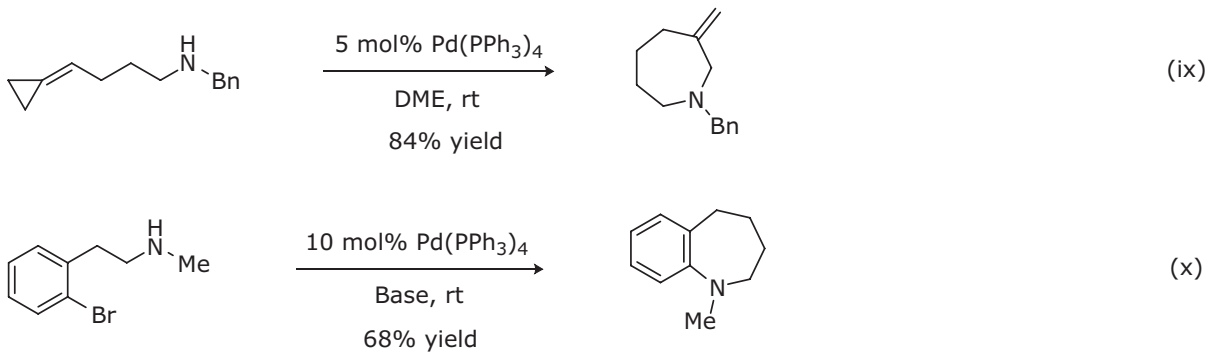
Buchwald *et al.* developed a palladium-catalysed C–N coupling reaction between aryl halides and amines. This reaction was extended to an intramolecular version which affords interesting benzazepine derivatives (**Scheme IV**, Equation (x)) (16).

Seven-membered ring-annulated indoles were also synthesised through palladium catalysis (17, 18). Lautens *et al.* reported a highly modular one-pot tandem reaction involving direct arylation of indoles (19). Interesting fused tricyclic indole derivatives were synthesised by reacting (bromoalkyl)indoles with phenyl iodide in the presence of a palladium catalyst and norbornene (**Scheme V**, Equation (xi)) (20–22). Importantly, different substituents such as amine, ester, OMe, Me, Cl, or NO_2 are tolerated under the reaction conditions without affecting its yield. However, only 38% yield was observed when a *N*-methyl tosyl substituent is present at the *meta* position of phenyl iodide, presumably due to unfavourable steric interactions.

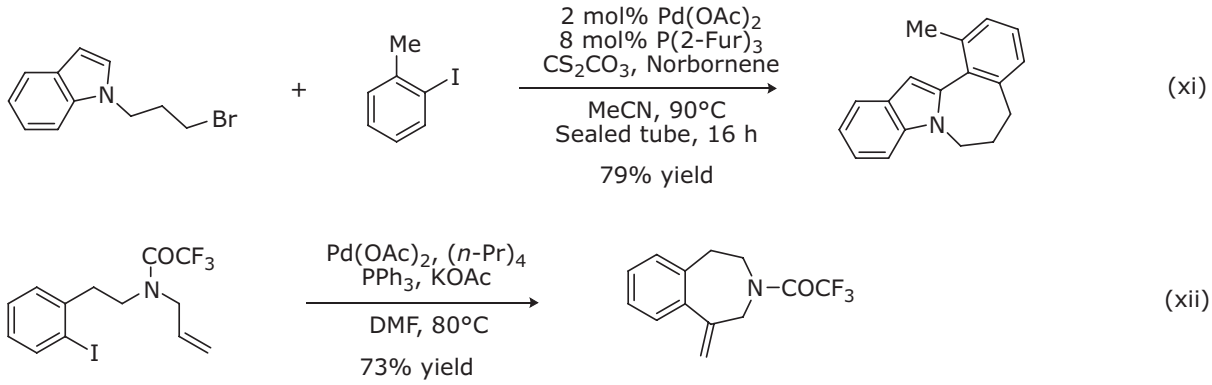
Stewart and coworkers synthesised a seven-membered benzazepine derivative with an exocyclic double bond by cyclising an allylamine-tethered aryl iodide through a palladium-catalysed 8-*endo*-*trig* process (**Scheme V**, Equation (xii)) (23).

3. Conclusions

In summary, the book "Palladium Assisted Synthesis of Heterocycles" presents a thorough compilation of modern palladium-catalysed synthetic methodologies aimed at accessing heterocycles of various nature and size. It is well-structured and written and covers literature extensively for the last two decades of research



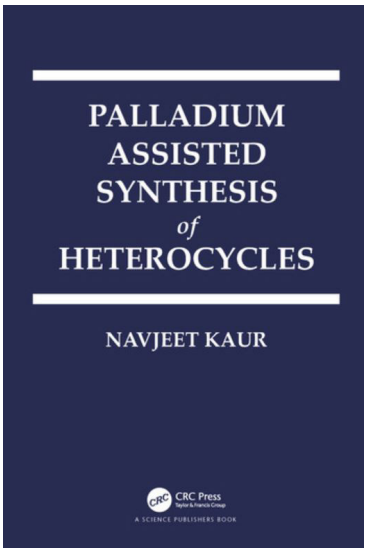
Scheme IV. Synthesis of substituted azepanes and benzoazepanes



Scheme V. More syntheses of seven-membered nitrogen heterocycles

in the field. The book is highly recommended to all medicinal chemists who are interested in incorporating heterocycles into their lead molecules and are looking for a concise synthetic approach to making them. It is also recommended to all process chemists who are developing expedient and reliable methods aimed at accessing heterocyclic molecules.

From my personal perspective, the book is clearly written, concise and easy to read. It might be a little too detailed and monotonous for the unprepared reader, but the information presented inside is well structured and the table of contents allows facile navigation through the text in order to find the specific information suited for each reader.



"Palladium Assisted Synthesis of Heterocycles"

References

1. M. Eggersdorfer, D. Laudert, U. Létinois, T. McClymont, J. Medlock, T. Netscher and W. Bonrath, *Angew. Chem. Int. Ed.*, 2012, **51**, (52), 12960
2. Q. Yang, J. E. Ney and J. P. Wolfe, *Org. Lett.*, 2005, **7**, (13), 2575
3. J. E. Ney and J. P. Wolfe, *Angew. Chem. Int. Ed.*, 2004, **43**, (27), 3605
4. J. S. Nakhla, J. W. Kampf and J. P. Wolfe, *J. Am. Chem. Soc.*, 2006, **128**, (9), 2893
5. J. P. Wolfe, *Synlett*, 2008, (19), 2913
6. D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, (5), 435
7. R. C. Larock, H. Yang, S. M. Weinreb and R. J. Herr, *J. Org. Chem.*, 1994, **59**, (15), 4172
8. T. Wu, G. Yin and G. Liu, *J. Am. Chem. Soc.*, 2009, **131**, (45), 16354
9. G. Yin and G. Liu, *Angew. Chem. Int. Ed.*, 2008, **47**, (29), 5442
10. G. Liu, *Org. Biomol. Chem.*, 2012, **10**, (31), 6243
11. F. E. Michael and B. M. Cochran, *J. Am. Chem. Soc.*, 2006, **128**, (13), 4246
12. M. Mouhtaram, L. Jung and J. F. Stambach, *Tetrahedron*, 1993, **49**, (7), 1391
13. E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, (24), 10257
14. I. Nakamura, H. Itagaki, and Y. Yamamoto, *Chem. Heterocycl. Compd.*, 2001, **37**, (12), 1532
15. I. Nakamura, T. Sato, M. Terada and Y. Yamamoto, *Org. Lett.*, 2008, **10**, (13), 2649
16. J. P. Wolfe, R. A. Rennels and S. L. Buchwald, *Tetrahedron*, 1996, **52**, (21), 7525
17. G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, (7), 2875
18. S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, (7), 2873
19. C. Bressy, D. Alberico and M. Lautens, *J. Am. Chem. Soc.*, 2005, **127**, (38), 13148
20. G. Dyker, *J. Org. Chem.*, 1993, **58**, (23), 6426
21. G. Dyker, *Angew. Chem. Int. Ed.*, 1992, **31**, (8), 1023
22. C. Blaszykowski, E. Aktoudianakis, D. Alberico, C. Bressy, D. G. Hulcoop, F. Jafarpour, A. Joushaghani, B. Laleu and M. Lautens, *J. Org. Chem.*, 2008, **73**, (5), 1888
23. S. G. Stewart, C. H. Heath and E. L. Ghisalberti, *Eur. J. Org. Chem.*, 2009, (12), 1934

The Reviewer

Fedor Romanov Michailidis defended his PhD dissertation in 2014 at the University of Geneva, Switzerland, under the supervision of Professor Alexakis, working on the development of new organocatalytic methodologies. Romanov Michailidis won the competitive Postdoc. Mobility grant from the Swiss National Science Foundation (SNF) which he used to travel abroad for a postdoctoral fellowship with Professor Rovis at Colorado State University, Fort-Collins and Columbia University, New York in the USA. Since 2017, Romanov Michailidis was a researcher in Medicinal Chemistry at Celgene Corporation (now Bristol-Myers Squibb) in Cambridge, Massachusetts, USA. Since summer 2020, he relocated back to Europe where he occupies an identical role at Janssen Pharmaceutica in Beerse, Belgium. Romanov Michailidis' research interests extend beyond drug discovery and he made important contributions to the fields of C–H activation, photoredox catalysis and electrochemistry.