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*Editorial*

# Asymmetric Catalysis in Organic Synthesis

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Received: 6 September 2019; Accepted: 11 September 2019; Published: 15 September 2019

Biological systems, in most cases, recognize a pair of enantiomers as different substances eliciting different responses. Therefore, one enantiomer may act as a very effective therapeutic agent whereas the other enantiomer, at worst, interacts with a totally different target resulting in undesired side effects. Thalidomide offers a tragic example that led to the death of approximately 2000 children and serious malformation of arms and legs in 10,000 babies born around the world [1]. This disaster emphasized the need for a greater regulation governing the use of drugs, particularly enantiomers. The impetus is on synthetic chemists to provide highly efficient and reliable methods to access the desired compounds in an enantiomerically pure format, avoiding underside effects of unwanted enantiomers. Regulatory guidance was published, firstly in the US followed by the EU [2,3], reflecting rigorous steps required to follow before an approval of racemates is granted. The Australian and Canadian guidance are also based on similar principles [4,5]. As chiral drugs comprise more than half the drugs approved worldwide, including many of the top-selling drugs [6], these regulations create a chronic problem for the pharmaceutical industry. In particular, the costs associated with chiral separation of racemates.

Among the different approaches used to access enantiomerically pure compounds, chiral transition metal complexes [7,8] and organocatalysts [9,10] evolved as essential instruments in the toolbox of organic chemists. Their use has become a truly indispensable technology for industrial scale production of active pharmaceutical ingredients [10,11]. This power emerges from their high efficiency to catalyze a broad range of chemical transformations with high tolerance of numerous functional groups and impressive levels of chemo-, regio-, diastereo-, and enantioselectivities. They have also facilitated the discovery of new patterns of reactivity that by far opened the door to the creation of bonds forming strategies that never existed previously.

This Special Issue includes four articles and one review.

The article by Qin et al. [12] provides computational DFT investigations on the bisphospholanoethane (BPE)-ligated Cu-catalyzed enantioselective addition of enynes to ketones. Two BPE-mesitylcopper (CuMes) catalysts, namely BPE-CuMes and (*S*,*S*)-Ph-BPE–CuMes, were employed to probe the reaction mechanism with the emphasis on stereoselectivity. The calculations on the BPE-CuMes system indicated that the active metallized enyne intermediate acts as the catalyst for the catalytic cycle.

The article by Adly, Ghanem and co-workers [13] contributes to the understanding of the stereoselectivity of chiral dirhodium(II) carboxylate catalysts carrying *N*-protected *tert*-leucine ligand through investigating the possible effect of ligand stereo-purity on catalyst structure and enantioselectivity. This was also justified through a new X-ray crystal structure for the $Rh_2$(*S*,*S*,*S*,*R*-PTTL)$_4$ catalyst.

The article by Liu et al. [14] provides a concise method for the preparation of new $C_2$-symmetric six-membered NHCs and their application for the asymmetric diethylzinc addition of arylaldehydes.

The article by Rafiński [15] provides a highly efficient and enantioselective approach to the synthesis of functionalized benzofuran-3(2H)-ones which proceeds via an intramolecular Stetter reaction using *β*,*β*-disubstituted Michael acceptors in the construction of five-membered rings with fully-substituted quaternary stereogenic centers. As a result, a series of chiral 2,2-disubstituted benzofuran-3(2H)-one derivatives with linear, branched, and cyclic aliphatic substitutions on the quaternary stereogenic center were obtained in high yields and with excellent enantioselectivities of up to 99% *ee*.

The review by Adly [16] provides an update on how the knowledge around the structure of dirhodium(II) carboxylate catalysts has evolved over the years with a particular emphasis on the impact of this knowledge on enantioselectivity prediction and catalyst design.

In conclusion, these five publications give an overview of the possibilities of different catalysts to be used in different asymmetric transformations, in particular in synthetic reactions at very mild reaction conditions. Finally, we sincerely thank all authors for their enthusiastic support and contributions towards the success of this Special Issue.

**Author Contributions:** FGA and AG prepared the article.

**Funding:** This research received no external funding

**Conflicts of Interest:** The authors declare no conflict of interest

## References

1. Anonymous. Medicine: The Thalidomide Disaster. *Time Mag.* **1962**, *LXXX*, 6. 10 August 1962.
2. FDA's Policy statement for the development of new stereoisomeric drugs. *Chirality* **1992**, *4*, 338–340.
3. Branch, S. International regulation of chiral drugs, in Chiral Separation Techniques. In *A Practical Approach*, 2nd ed.; Subramanian, G., Ed.; Wiley-VCH: Weinheim, Germany, 2001; pp. 319–342.
4. Rauws, A.G.; Groen, K. Current regulatory (draft) guidance on chiral medicinal products: Canada, EEC, Japan, United States. *Chirality* **1994**, *6*, 72–75.
5. Investigation of Chiral Active Substances—3CC29a. Quality Guidelines, Standards and Guidelines, Theraputic Drug Adminstration (TGA) 2002. Available online: https://www.tga.gov.au/quality-guidelines (accessed on 22 January 2019).
6. Van Arnum, P. Single-enantiomer drugs drive advances in asymmetric synthesis (Cover story). *Pharm. Technol.* **2006**, *30*, 58–66.
7. Bolm, C.; Beller, M. Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals. In *Second Revised and Enlarged Edition*; Wiley-VCH: Weinheim, Germany, 2008.
8. Bates, R. *Organic Synthesis Using Transition Metals*; John Wiley & Sons: Chickester, UK, 2012.
9. Oliveira, V.; Cardoso, M.; Forezi, L. Organocatalysis: A Brief Overview on Its Evolution and Applications. *Catalysts* **2018**, *8*, 605.
10. Berkessel, A.; Gröger, H. Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis; John Wiley & Sons: Weinheim, Germany, 2006.
11. Crawley, M.L.; Trost, B.M. Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective; John Wiley & Sons: Hoboken, NJ, USA, 2012.
12. Li, H.; Luo, M.; Tao, G.; Qin, S. Theoretical Calculations on the Mechanism of Enantioselective Copper (I)-Catalyzed Addition of Enynes to Ketones. *Catalysts* **2018**, *8*, 359.
13. Adly, F.G.; Bollard, H.; Gardiner, M.G.; Ghanem, A. Chiral dirhodium (II) carboxylates: New insights into the effect of ligand stereo-purity on catalyst structure and enantioselectivity. *Catalysts* **2018**, *8*, 268.
14. Li, J.; Zhou, B.; Jiang, Y.; Liu, X. Synthesis of New C2-Symmetric Six-Membered NHCs and Their Application for the Asymmetric Diethylzinc Addition of Arylaldehydes. *Catalysts* **2018**, *8*, 46.
15. Rafiński, Z. NHC-Catalyzed Organocatalytic Asymmetric Approach to 2, 2-Disubstituted Benzofuran-3 (2H)-ones Containing Fully Substituted Quaternary Stereogenic Center. *Catalysts* **2019**, *9*, 192.
16. Adly, F.G. On the structure of chiral dirhodium (II) carboxylate catalysts: Stereoselectivity relevance and insights. *Catalysts* **2017**, *7*, 347.

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