

Cluster Preface: Stereoselective Synthesis of Stereogenic Quaternary Carbons: A Formidable Challenge and Remarkable Recent Progress

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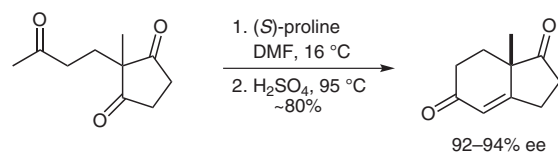
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Abstract: The stereoselective synthesis of stereogenic quaternary carbons is a challenging task, with significant progress being registered only in the last few years. In this *Synlett* Cluster, the most recent developments are presented by experts in this field.

Key words: stereoselective synthesis, quaternary carbons, stereocenters

When the target of a chemical synthesis endeavor contains one or more stereogenic quaternary carbons, how to assemble these quaternary stereocenters becomes a central component of synthesis planning and execution. Many factors contribute to this challenge: steric hindrance, the need generally to forge such carbon centers by C–C bond formation, and the inability in most situations to invert quaternary stereocenters. That the chemical synthesis of such carbons is particularly challenging can be seen in the structures of existing pharmaceutical agents. Of the 150 top-selling brand-name drugs in 2008, the only ones that contain stereogenic quaternary carbons are steroid (e.g., Advair Diskus) or opioid derivatives (e.g., OxyContin), which undoubtedly are prepared by semisynthesis.¹

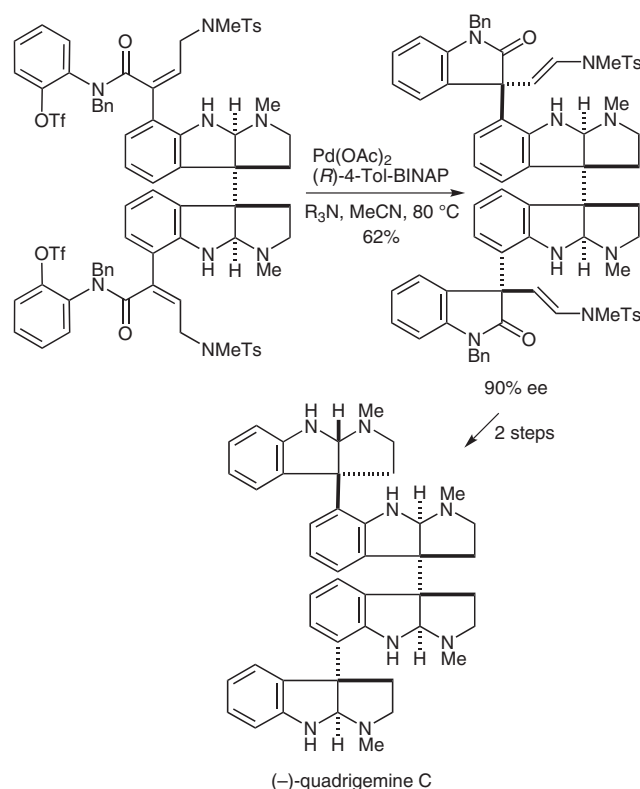
Although chemical reactions that form quaternary carbons have been known for well over 100 years, it is only in the last 20 years that a variety of reactions that allow enantioselective construction of stereogenic quaternary carbons have become available.² Many of these are catalytic enantioselective processes. The outstanding early example is the remarkable desymmetrizing Hajos–Parish–Wiechardt–Eder–Sauer reaction (Scheme 1),³ which presaged by many years the recent spectacular developments in the field of organocatalysis.



Scheme 1

When we surveyed the field of catalytic enantioselective synthesis of quaternary stereocenters in 2004, we found that only four catalytic asymmetric transformations – Diels–Alder reactions, intramolecular Heck reactions,

reactions of allylmethyl intermediates with carbon nucleophiles, and reactions of chiral carbon nucleophiles with carbon electrophiles – were documented to give high enantioselectivities in the construction of a range of products.^{2f} At that time, only the intramolecular catalytic asymmetric Heck reaction⁴ had been demonstrated to be useful in the construction of a diverse array of structurally complex molecules, as, for example, its use in my laboratory to prepare (–)-quadrigemine C.⁵



Scheme 2

Recent progress in this area has been striking, with many of the gaps in existing methods that we pointed out in 2004 now filled, and numerous methods beyond our vision at the time now introduced. The papers in this *Synlett* Cluster, all by leaders in this field, describe some of the most recent developments in the enantioselective synthesis of stereogenic quaternary carbons. Enjoy!

References and Notes

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