Asymmetric Synthesis

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Enantioselective Synthesis of Carbocycles and Heterocycles by Radical/Polar and Polar/Radical Cascades**

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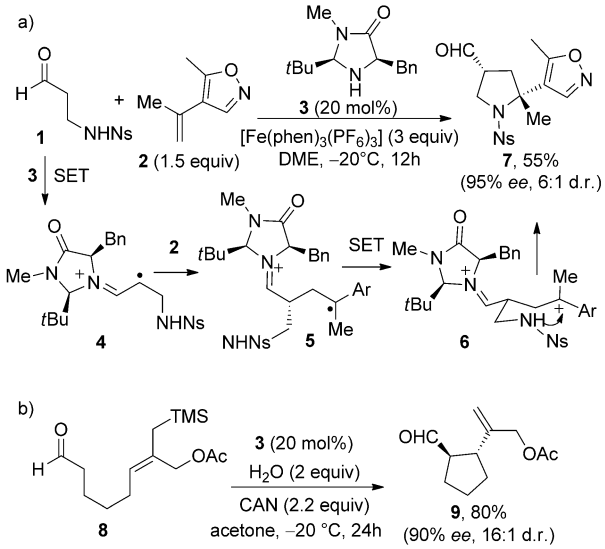
asymmetric synthesis · carbocycles · cyclization · heterocycles · radicals

Only twenty years ago, enantioselective synthesis, involving radical intermediates, was still regarded as rather limited. However, the knowledge of the parameters essential for stereocontrol and the use of chiral auxiliaries in radical reactions had already reached a very high level of development. Another breakthrough came from the work of Porter, Sibi, and co-workers with the introduction of chiral Lewis acids.[1] All necessary tools were then available for additional applications. To go deeper into the understanding of the control of stereoselectivity in radical reactions, the reader is invited to refer to the series of excellent chapters and reviews devoted to this topic.[2] Recent studies have put to rest any remaining misconceptions by demonstrating the usefulness and the potential of free radicals in enantioselective synthesis.[3] Complex radical/polar crossover reactions have achieved remarkable success in the preparation of a wide range of enantiopure, functionalized cyclic compounds. Different approaches have been exploited to control enantioselectivity, including the use of organocatalysts, chiral Lewis acids, chiral reducing agents, chirality transfer, or the memory-of-chirality phenomenon.[2c,d]

A comprehensive chapter by Yang and Sibi accounts for state of the art in the field up to 2010.[4] The present highlight aims to report a selection of the most appealing recent enantioselective processes involving radical/polar or polar/radical cascades leading to carbocycles and heterocycles. These reactions illustrate several possible approaches.

Outstanding contributions, from Bach and co-workers[5] and MacMillan and co-workers,[6] have resulted from the combined use of organocatalysts and either photoinduced electron transfer or redox systems.

In 2007, Hasegawa and Sibi, and MacMillan and co-workers simultaneously reported the organo-SOMO-catalyzed C–O and C–C bond formation, respectively.[6a,7] In the continuation of their early work, MacMillan et al. have expanded this strategy to target enantioenriched cyclic compounds.[8] Very recently, they succeeded in synthesizing enantioenriched pyrrolidines through a tandem radical/polar strategy.[8d] As exemplified in Scheme 1 a, the formation of



Scheme 1. Organo-SOMO-catalyzed pyrrolidine formation. CAN = ceric ammonium nitrate, DME = dimethoxyethane, Ns = 2-nitrobenzenesulfonyl, phen = 1,10-phenanthroline, TMS = trimethylsilyl.

tetrasubstituted pyrrolidines involves the activation of β-amino aldehyde **1** with the imidazolidinone catalyst in the presence of iron(III) to form the radical cation **4**. The latter adds to olefin **2** to give rise to **5**. After a second single-electron transfer (SET), the resulting carbenium ion **6** undergoes the polar ring closure leading to **7**. The high level of enantiocontrol (up to three stereogenic centers can be controlled) relies on the geometry of the three-π-electron system of intermediate **4** and on the selective shielding of its Si face by the benzyl group.[8c]

The intramolecular radical allylation shown in Scheme 1b offers new routes to five-, six-, and seven-membered rings.[8d] In this case the α-iminium radical intermediate undergoes 5-

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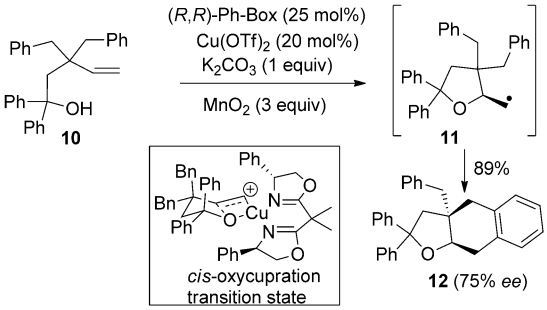
exo-trig cyclization onto the double bond of an allylsilane. Subsequent oxidation triggers Me_3Si^+ elimination.

The memory of chirality is an alternative approach to enantiocontrol. It is based on the preservation of the chiral information contained within the substrate in the radical reaction intermediate located at the initial stereocenter.[9] This approach was recently applied to the construction of β-lactams as well as to the radical cascade cyclization of enediynes.[10]

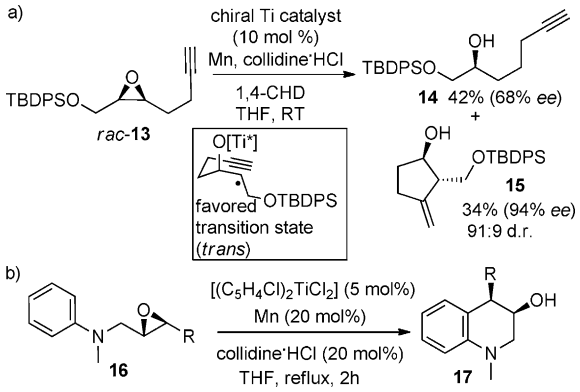
Chemler and co-workers have made a major contribution to the design of new tandem reactions by opting for the reverse strategy, that is the polar/radical strategy.[11] They have developed a copper(II)-catalyzed intramolecular *cis* aminocupration of alkenes. This methodology affords a ready access to an impressive variety of enantioenriched heterocycles, through haloamination[11a] and carboamination.[11b] It has recently been extended to carboetherification.[11c] As exemplified in Scheme 2, a chairlike transition state controlled by the Ph-Box ligand explains the total control of the stereocenter created in intermediate **11**. In these reactions, enantioselectivity does not result from the radical step, but the stereogenic center is preserved during the latter. A promising enantioselectivity (75% *ee*) was reached in the desymmetrizing cascade rearrangement of the pentenol derivative **10**.[11c]



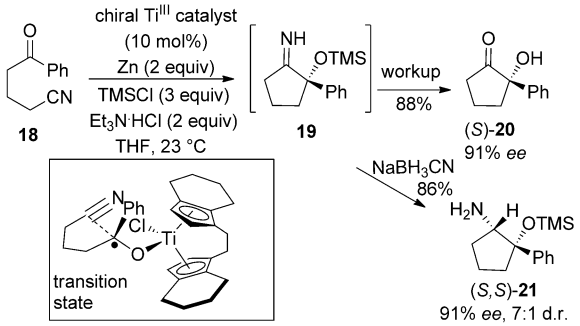
Scheme 2. Enantioselective copper-catalyzed heterocyclization. Tf = trifluoromethanesulfonyl.

In the last decade, Gansäuer et al. have largely contributed to the development of titanocene-based electron-transfer reducing agents. The catalytic enantioselective regiodivergent opening of the racemic epoxide (REO) **13** has found a key application in the achievement of enantioselective and diastereoselective 5-*exo*-dig radical cyclizations (Scheme 3 a).[12] Application of the REO strategy to the recently disclosed intramolecular arylation of epoxides might offer (by selecting appropriate R groups) an elegant route to enantioenriched tetrahydroquinolines **17** (Scheme 3 b).[12c]

Enantioselective titanium(III)-catalyzed cyclization of ketyl radicals was investigated by Streuff et al. As illustrated in Scheme 4, when the ketonitrile **18** was treated with triethylamine hydrochloride, zinc dust, and chlorotrimethylsilane in the presence of Brintzinger's ansa-titanocene catalyst, the α-hydroxyketone **20** was isolated in 88% yield and 91% *ee*, after hydrolysis. When the imine intermediate was reduced with $NaBH_3CN$, the vicinal amino alcohol **21** was



Scheme 3. Titanocene-catalyzed regiodivergent epoxide opening. CHD = cyclohexadiene, TBDPS = *tert*-butyldiphenylsilyl, THF = tetrahydrofuran.



Scheme 4. Enantioselective reductive cyclization of ketonitrile.

formed. The plausible transition state framed in Scheme 4, could explain the enantioselectivity of the cyclization. The opposite enantiomer is disfavored because its formation would induce strong repulsive steric interactions between the phenyl group and the ligand.[13]

Strategies based on enantioselective radical/polar or polar/radical crossover processes designed for the synthesis of carbocycles and heterocycles have reached an impressive level of achievement. Because of the ever improving understanding of the factors governing stereoselectivity, one can anticipate that new artful and mild methodologies should appear in the near future.

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