Synthesis of natural products and strategies to develop analogous molecules

Some recent works

**Ti(III)-Mediated Stereoselective Radical Reactions: Application in the Synthesis of Natural Products**

An efficient method for stereoselective synthesis of 1,3-diols, especially with 2-substitution, was developed in our lab using Ti(III)-mediated radical ring opening of various substituted 2,3-epoxy alcohols. The general strategy is depicted above.


**In fact, in any synthesis of natural products in our laboratory the Ti(III)-mediated epoxide opening is always used as one of the key steps.**
Some of the natural products synthesized in our laboratory using Ti(III)-mediated epoxide opening reaction as one of the key steps


Stereoselective syntheses of highly substituted carbo-, oxa-, and azacycles using Ti(III)-mediated opening of 2,3-epoxy alcohols.
Stereoselective construction of quaternary chiral centres remains a challenging task. A novel method for the same was developed by us using a Ti(III)-mediated opening of chiral 2,3-epoxy alcohols regioselectively at the 2-position followed by trapping of the intermediate radical with methyl acrylate or acrylonitrile to lead to the stereoselective formation of tetrasubstituted chiral centers.


In a subsequent study on stereoselective construction of quaternary chiral centres, a trisubstituted α,β-unsaturated ester moiety was suitably placed in a molecule also bearing an epoxy alcohol moiety at its other end to intramolecularly trap the intermediate radical, which was formed when the molecule was treated with Cp₂Ti(III)Cl to regio- and stereoselectively open its epoxy ring, giving rise to a quaternary chiral center.


A method that was originally developed by us for the synthesis of polyketide based natural products is found today equally effective in the synthesis of structurally complex terpenes.

An architecturally challenging sesquiterpenoid penifulvin A having a highly complex dioxa[5.5.5.6]fenestrane skeleton has recently been synthesized in our laboratory using a Ti(III)-mediated epoxide opening followed by a concomitant radical cyclization reaction to stereoselectively construct the most important central quaternary centre of the molecule.

After successful completion of the synthesis of penifulvin A, synthesis of another marine-derived sesquiterpenoid fungal metabolite, asperaculin A, a novel dioxa[5.5.5.6]fenestrane, was undertaken. Two distinct lactonization sequences from a common intermediate led to the first synthesis of 9-deoxyasperaculin A in 14 steps (16% overall yield) and 16 steps (18% overall yield), respectively. [2,3]-Wittig-Still rearrangement and Ti(III)-mediated epoxide opening-cyclization were employed as some of the key steps for the stereoselective generation of the vicinal all-carbon quaternary centers of the target molecule.


An expedient approach toward the unified total syntheses of (+)-iridomyrmecin, (−)-isoiridomyrmecin, (+)-7-epiboschnialactone, (+)-teucriumlactone, and (−)-dolichodial in chirally pure forms starting from readily available (+)-β-citronellene has been developed using a Ti(III)-mediated reductive epoxide opening-cyclization for the construction of the core cyclopenta[c]pyran skeleton of the iridoid lactones with complete diastereoselectivity for the newly created bridgehead stereogenic centers. Subsequent transformations gave a short access to (+)-teucriumlactone and (−)-dolichodial and formal access to potentially other iridoids.


An isatin-derived and 3,3-disubstituted oxindole-appended epoxy-acrylate underwent Cp2Ti(III)Cl-mediated reductive oxirane-ring opening with concomitant intramolecular 5-exo-trig radical cyclization leading to tetrahydrofuran based oxa-spirooxindole systems.
An efficient and novel route for assembling pyrrolo/piperidino[1,2-a]indoles has been developed involving a Ti(III)-mediated reductive epoxide opening reaction of N-tethered epoxy-indoles that triggered facile intramolecular cyclization followed by an oxidative quenching step.
