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Silver-Mediated Oxidative Decarboxylative Intramolecular Asymmetric Radical Cyclization (C_{sp3}−C_{sp2}) via Memory of Chirality: Access to Circumdatin Alkaloids

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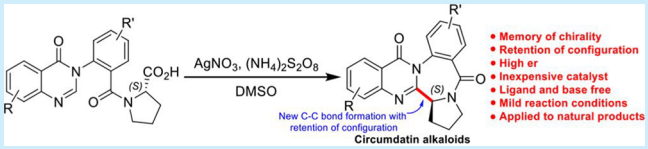
Supporting Information

ABSTRACT: A novel silver-mediated oxidative decarboxylative intramolecular asymmetric radical cyclization has been developed to form a C_{sp3}−C_{sp2} bond via memory of chirality. The application of the process has been demonstrated for the synthesis of the circumdatin class of alkaloids in high enantiopurity with retention of the configuration. The developed protocol is mild and works with an inexpensive silver catalyst in the absence of ligand, base, or additives. The involvement of a monoradical in the reaction has been established by trapping the radical intermediate.

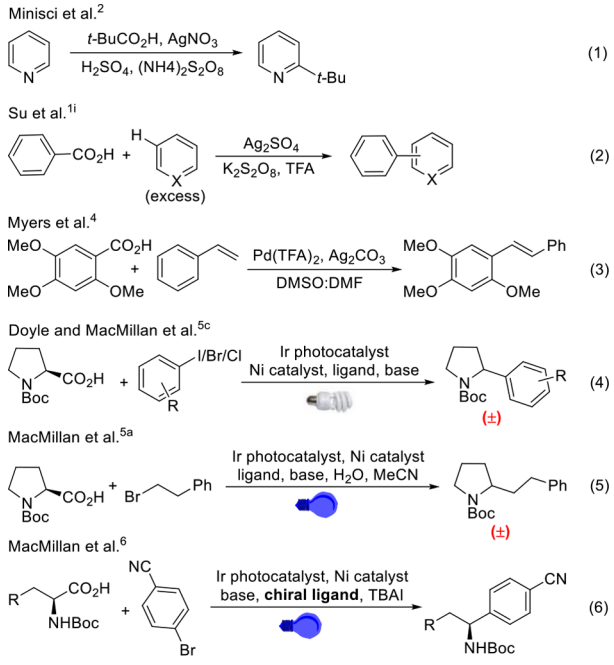


Oxidative decarboxylative coupling (ODC) reactions are the subject of enormous contemporary interest, because of their versatility, leading to a vast array of scaffolds via regioselective formation of a new C−C or C−heteroatom bonds, utilizing carboxylic acid group as a handle.[1] The work in this area, which started in the late 1960s, came to the limelight after the classical Minisci reaction,[2] which has been now largely explored with several different variants (see eqs 1 and 2 in Scheme 1).[1i,3] The discovery of the Heck-type oxidative decarboxylative coupling by Myers truly commenced the research activities in this area (eq 3 in Scheme 1).[4] Lately, the pioneering work by MacMillan in the area of photocatalyzed decarboxylative radical C−C coupling reactions led to novel transformations and useful scaffolds (eqs 4−6 in Scheme 1), which caught immense attention from organic chemists.[5] The amino acid substrates, upon decarboxylation by a photocatalyst, generate achiral radical intermediates, which provide racemic compounds. However, MacMillan et al. recently demonstrated that intervention of chiral ligands could provide enantioenriched products (eq 6 in Scheme 1).[6]

The formation of an enantioenriched product via a conformationally labile stereogenic center of an enantiopure substrate was first reported by Seebach et al.[7] Later, Fuji et al. demonstrated the concept on naphthalenyl substrate and coined the term "memory of chirality (MOC)".[8] The area of MOC is not fully explored, compared to the other areas of synthetic organic chemistry.[9]

Examples of MOC via decarboxylative intermolecular radical coupling are rare,[9] and there are only two examples in the literature, wherein MOC has been reported in the decarboxylative intramolecular radical coupling. The first example, reported by Rychnovsky, utilized transannular radical cyclization via photodecarboxylative coupling (eq 1 in Scheme 2),[10] and the second example reported by Griesbeck utilized intramolecular photodecarboxylative 1,7-diradical coupling, which provided a product with complete inversion of the configuration (see eq 2 in Scheme 2).[11] Interestingly, until now, oxidative decarboxylative intramolecular radical coupling with MOC has not been reported in the literature.

Scheme 1. Intermolecular Decarboxylative Coupling Reactions



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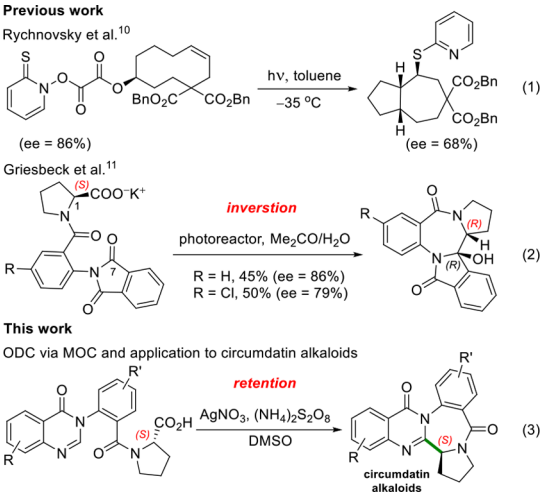
Scheme 2. Intramolecular Decarboxylative Coupling Reactions via MOC and This Work



We envisioned that MOC would be possible to achieve with an intramolecular ODC of an amino acid substrate to form a new asymmetric C−C bond if the chiral radical intermediate could be trapped before racemization. For this purpose, a rigid circumdatin alkaloid scaffold was selected to study our hypothesis (see eq 3 in Scheme 2). Circumdatin class of quinazolinone alkaloids have a wide range of biological properties.[12] They have been synthesized using C−N bond coupling/forming reactions; however, C−C bond coupling has never been utilized for their synthesis (see Figure 1).[12,13]

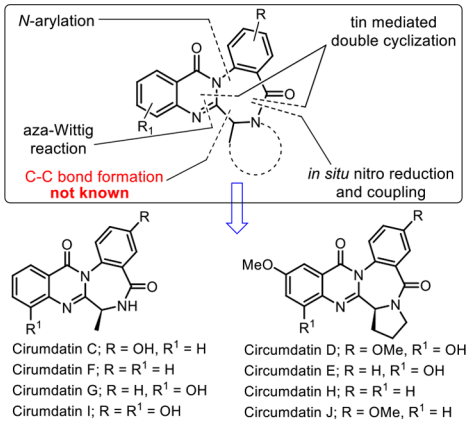
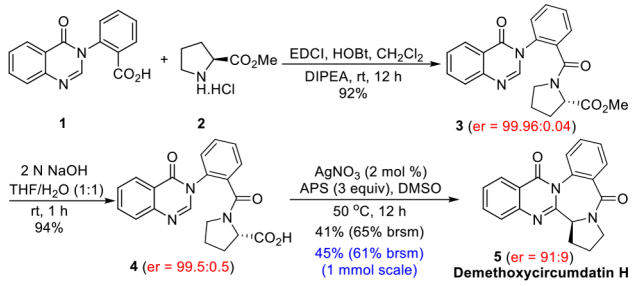


Figure 1. Circumdatin alkaloids and known strategies for their synthesis.

The proline substrate **4** was designed for the implementation of our postulate (see Scheme 3). It was synthesized starting from quinazolinone **1**, which was obtained from anthranilic acid in a single step.[14] Coupling of quinazolinone **1** with enantiomerically pure proline methyl ester **2** provided the product **3**, which, upon hydrolysis, furnished proline substrate **4** in excellent yields and enaniomeric ratio (er). The substrate **4** was treated with silver carbonate and ammonium persulfate (APS) in dimethylformamide/dimethyl sulfoxide (DMF/DMSO) (95:5) at 110 °C. To our delight, the expected product, demethoxycircumdatin H **5**, was obtained in 14% yield with 90:10 er [see the Supporting Information (SI)]. The spectral and analytical data, as well as the specific rotation, is in

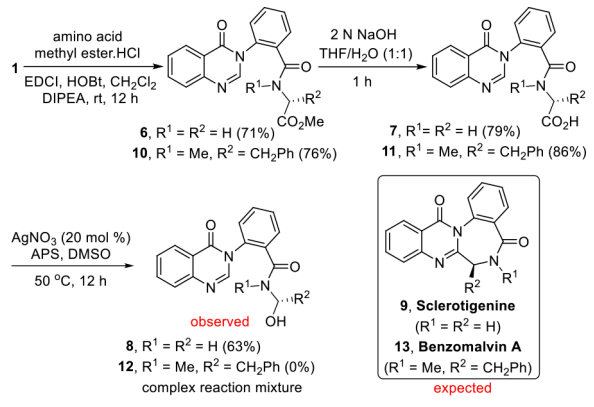
Scheme 3. Synthesis of Demethoxycircumdatin H



agreement with the literature,[13c] which confirms that the reaction proceeded via MOC with retention of the configuration. This result encouraged us to optimize the protocol further for better yields and enantiopurity. The same reaction was attempted with silver nitrate, and we observed improved yields. Several permutations and combinations of solvents, equivalent of silver nitrate and oxidants at various temperatures were studied (see the SI). The optimum condition found for this transformation is silver nitrate (2 mol %), APS (3 equiv) in DMSO at 50 °C for 12 h to obtain the best possible yield 41% (65% brsm) with 91:9 er. The reaction also worked very well on 1 mmol scale to furnish 45% (61% brsm, 91:9 er) yield. The recovered starting material **4** obtained from 1 mmol scale reaction was utilized to reproduce the protocol without loss of yield or enantiopurity (Scheme 3).

Once the protocol is set, our curiosity was to see whether it can be applied on acyclic N−H-free amino-acid-containing substrates. The natural product sclerotigenine (**9**) was chosen for this purpose (see Scheme 4). The developed sequence of

Scheme 4. Application of the Protocol on Acyclic N−H-Free/N-Me Amino Acid Substrates



reactions provided the glycine derivative **7** with good yields. Application of the above developed protocol on substrate **7** did not show the formation of sclerotigenine (**9**). Most of the starting material **7** remained unchanged. Hence, the reaction was attempted with various equivalents of $AgNO_3$, and, interestingly, we observed the alcohol product **8** at 20 mol % in good yield by decarboxylative hydroxylation. This protocol represents an alternative method to Barton's photodecarboxylative hydroxylation and its variations,[15] which will be explored in due course of time (Scheme 4). We reasoned that the free amide N−H of the amino acid might be responsible for the formation of alcohol **8**. Therefore, the natural product benzomalvin A (**13**) having the acyclic amino acid phenyl-

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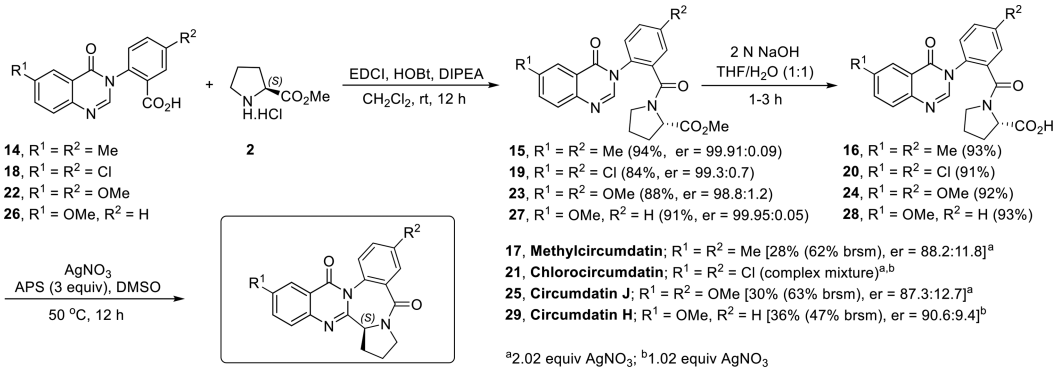
Scheme 5. Synthesis of Circumdatin Alkaloids



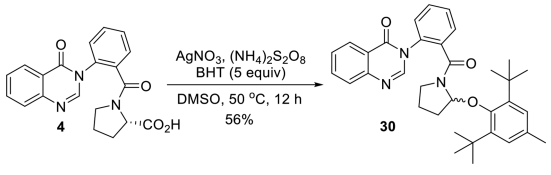
alanine was targeted, wherein the nitrogen is fully substituted. The required benzomalivin A precursor **11** was prepared and subjected to the developed protocol (2−20 mol % of $AgNO_3$). However, a complex reaction mixture was observed, along with some unconsumed starting material. These experiments prove that the developed protocol could be applied to only cyclic amino acid substrates, probably because of the stability of cyclic radical intermediate. Therefore, we focused on proline-based circumdatin alkaloids and their analogues.

The dimethyl-substituted analogue methylcircumdatin **17** was synthesized from the corresponding substrate **16** in 28% (62% brsm) yield with 88.2:11.8 er, using 2.02 equiv of $AgNO_3$ (Scheme 5). The protocol was also applied for the synthesis of the dichloro-substituted analogue chlorocircimdatin **21**; however, the desired product could not be observed, plausibly because of the presence of a chloro substituent in a silver-catalyzed decarboxylative radical reaction.[16] The protocol worked well on the dimethoxy-substituted precursor **24** and afforded the natural product circumdatin J (**25**) in 30% (63% brsm) yield with 87.3:12.7 er (Scheme 5). For the synthesis of natural product circumdatin H (**29**), the monomethoxy-substituted acid **26** was synthesized by a different route (see the SI) and transformed to the proline derivative **28**. The protocol worked well on the substrate **28** and furnished circumdatin H (**29**) in 36% (47% brsm) yield with 90.6:9.4 er, using 1.02 equiv of $AgNO_3$ (Scheme 5). The quinazolinone substrates **4**, **16**, **24**, and **28** required variable amounts of $AgNO_3$, probably because of the difference in the extent of silver interaction with the substrates, depending on the presence of substituents.[16]

The presence of a monoradical intermediate in our oxidative decarboxylative intramolecular radical cyclization protocol was confirmed by the trapping experiment with BHT to obtain the radical trapped product **30** in 56% crude yield (see Scheme 6).

Based on this observation and the literature precedents,[11,17−19] a plausible mechanism for the developed oxidative decarboxylative intramolecular asymmetric radical cyclization via MOC is depicted in Figure 2. The proline derivative **4** on oxidative decarboxylation generates a chiral

Scheme 6. Radical Trapping Experiment



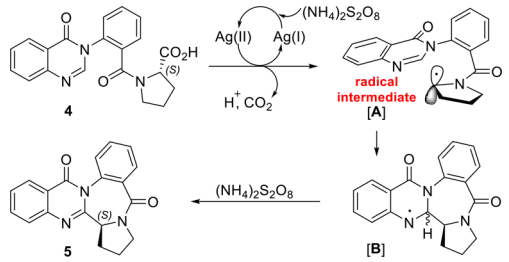


Figure 2. Plausible mechanism for the developed protocol.

radical intermediate[17] **A**, which attacks the internal electrophilic position of the quinazolinone[18] and delivers demethoxycircumdatin H **5** via intermediate **B**. We believe that the atropisomerism[19] present in this system plays an important role in MOC.[11]

In conclusion, a novel oxidative decarboxylative intramolecular asymmetric radical cyclization via MOC using inexpensive $AgNO_3$, and APS to construct circumdatin natural products and their congeners has been demonstrated. To the best of our knowledge, this is the first report involving a monoradical in an intramolecular ODC of C_{sp3}−C_{sp2} via MOC with retention of the configuration. The involvement of a monoradical was confirmed by mechanistic studies. The developed method is operationally simple and has a synthetic potential, which can be explored to construct various chiral heterocyclic scaffolds, biologically active molecules, and natural products. Further improvement of the protocol and finding its new applications is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental details, analytical data and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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