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SYNFACTS Highlights in Current Synthetic Organic Chemistry

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Category

Synthesis of Heterocycles

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Coupling Radical Homoallylic Expansions with C–C Fragmentations for the Synthesis of Heteroaromatics: Quinolines from Reactions of *o*-Alkenylarylisonitriles with Aryl, Alkyl, and Perfluoroalkyl Radicals

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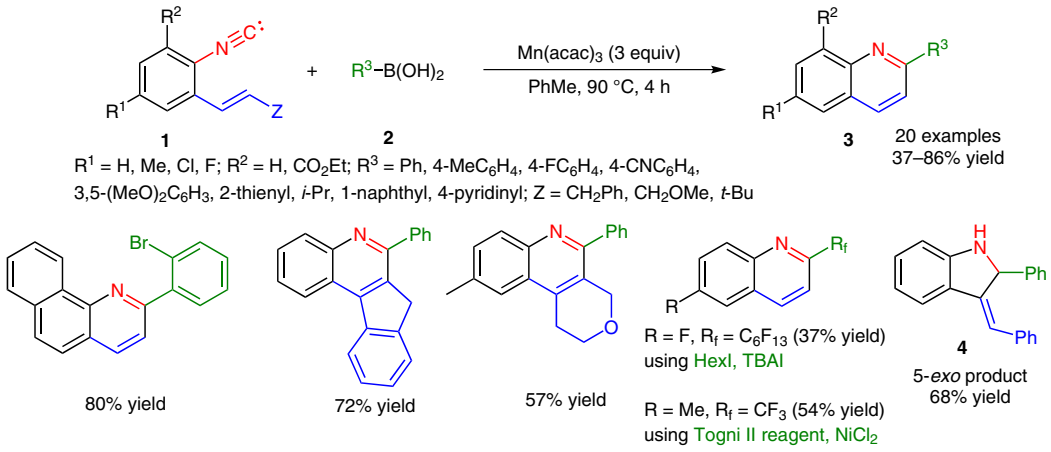
Synthesis of Quinolines From *o*-Alkenylaryl Isonitriles



Significance: Quinoline natural products and synthetic quinoline derivatives show a wide range of biological activities, and the latter play a pivotal role in drug development. A vast number of synthetic methods for preparing this class of heterocycles have been reported (G. A. Ramann, B. J. Cowen *Molecules* **2016**, *21*, 986). Particularly interesting methods involve radical-mediated cyclization of iminyl radicals generated from oxime derivatives (J. C. Walton *Molecules* **2016**, 21, 660). Cyclization of imidoyl radicals generated from *o*-alkynyl isonitriles in the presence of boronic acids leads to the formation of quinolines. Competition between 5-*exo* and 6-*endo* products occurs when the alkyne is substituted with alkyl, phenyl, or benzyl groups. The present work describes the use of alkene-substituted aryl isonitriles to produce alkyl radicals, which are more efficient than vinyl radicals in homoallylic radical expansion, thereby circumventing the selectivity problem in the formation of six-membered rings through 6-*endo*-dig cyclization of the correspondent alkyne precursors.

Comment: Oxidative activation of boronic acid **2** generates a radical that adds to *o*-alkenylaryl isonitrile **1**, initiating a radical cyclization–homoallylic expansion–fragmentation reaction to produce quinoline **3**. The scope of the reaction in terms of **1** and **2** was quite broad, and donor and acceptor substituents on the aryl ring gave products in good yields. Alkylboronic acids underwent reaction, whereas alkenyl derivatives failed to give the corresponding products **3**. Besides boronic acids, iodoperfluorocarbons were also successfully used as radical precursors, furnishing compounds **3** in moderate yields. The presence of an *o*-alkenyl substituent on **1** is crucial for selectivity in the reaction. Compounds **3** are produced with good efficiency, following the trend in radical stability (Z = Bn > CH_2OMe > *t*-Bu). However, **1** (Z = Ph) gave the 5-*exo* product **4** exclusively. Constrained bicyclic alkenes gave 6-*endo*-quinoline products, without the alkyl-radical C–C bond fragmentation. Control experiments involving trapping of the benzylic cation or radical support the proposed radical pathway instead of a cationic one. Calculations support a radical-mediated cyclization–expansion–fragmentation pathway over the direct formation of a 6-*endo* product.

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