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Digest Paper

Catalytic asymmetric synthesis of 3,3-disubstituted oxindoles: diazooxindole joins the field

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ABSTRACT

The catalytic asymmetric synthesis of 3,3-disubstituted oxindoles, a big family of privileged scaffolds in natural products and drugs, is of current interest. Recently, the catalytic asymmetric functionalization of diazooxindoles emerges as a potentially general and flexible strategy for this purpose, with several notable examples coming out in 2013. In this digest, synthetic applications of diazooxindoles have been summarized and discussed, which might be helpful for readers to understand the special properties of this type of donor/acceptor cyclic diazo reagent and to develop new catalytic asymmetric reactions.

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Introduction

Recently, the need for privileged scaffolds in the development of new biological probes and drugs gives an incentive for the catalytic asymmetric construction of 3,3-disubstituted oxindoles,[1] a family of prominent structural motifs that are wildly present in natural products, drugs, and pharmaceutically active compounds.[2] Intensive studies in the past several years resulted in a number of elegant catalytic protocols for the asymmetric synthesis of 3-substituted 3-hydroxyoxindoles[3] or 3-aminooxindoles,[4] other heteroatom substituted quaternary oxindoles,[5] all-carbon quaternary oxindoles,[6] and spirocyclic oxindoles.[7] The driving force for these studies is largely related to the fact that both the substituent and absolute configuration at C3 position of oxindoles greatly influence the biological activity of the compounds,[8] which justifies the enthusiasm in the catalytic asymmetric synthesis of 3,3-disubstituted oxindoles in sufficient structural diversity.

In 2010, we made the first comprehensive review to summarize the known six catalytic asymmetric synthetic strategies to 3,3-disubstituted oxindoles (routes a–g, Scheme 1).[1a] The past three years have witnessed tremendous achievements of these strategies.[3–7] Noticeably, the catalytic enantioselective construction of this privileged framework has become an ideal platform to develop and testify new chiral catalysts and new synthetic strategies. For example, the asymmetric desymmetrization of

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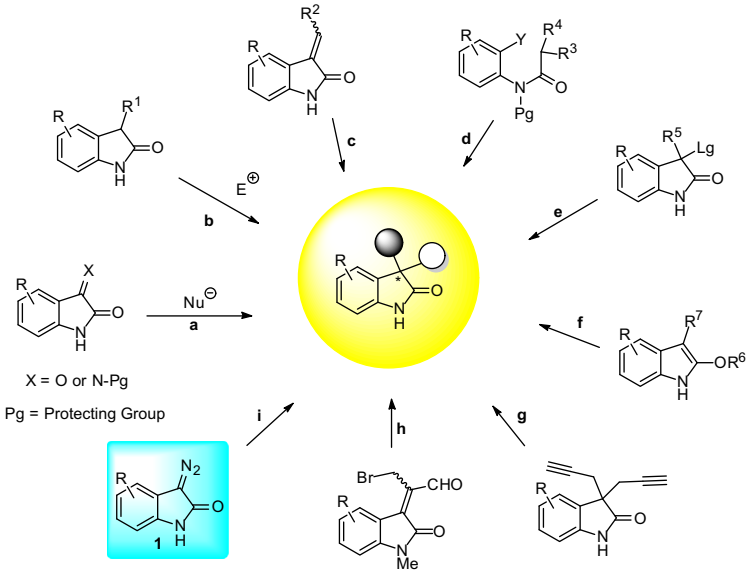


Scheme 1. Known strategies used for synthesizing 3,3-disubstituted oxindoles.

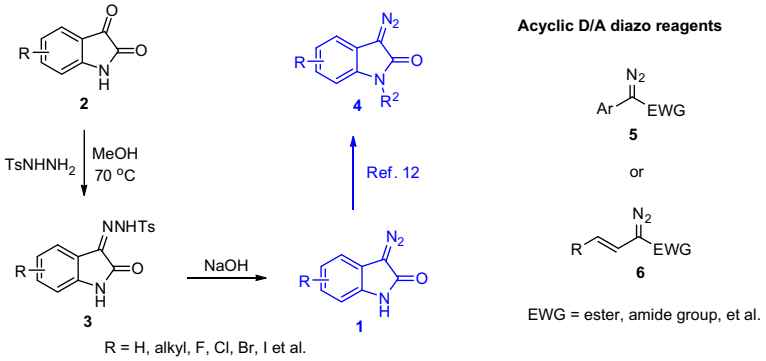
oxindole based 1,6-heptadiyne emerged as a new strategy for the construction of quaternary oxindoles, which contributed to the first highly enantioselective Cu-catalyzed azide–alkyne cycloaddition (route g);[9] a novel [3+2] annulation of dipoles with a tetrasubstituted alkene functionality proved to be fruitful for constructing spirocyclic oxindoles featuring two adjacent spiro carbons (route h).[10] In this digest, we would like to highlight another promising strategy based on the elaboration of diazooxindoles (route i), which might be potentially a general strategy for the synthesis of 3,3-disubstituted oxindoles but not introduced in previous reviews, as catalytic asymmetric versions just came out this year.

Diazooxindole **1** is a kind of cyclic donor/acceptor (D/A) diazo reagents[11] readily accessed from isatin **2** in a large scale without purification by silica gel column chromatography (Scheme 2). [12] The corresponding N-substituted analogues **4** can also be prepared conveniently according to literature reports.[12b–d] The electronic and steric properties of diazooxindoles can be readily tuned by using an appropriate substituent, either on the aromatic ring or on the nitrogen atom. Comparing with other commonly used acyclic donor–acceptor diazo compounds, the stability of 3-diazooxindoles can be attributed to the amide group and resonance delocalization due to its cyclic structure, which is enhanced by the electron-withdrawing substituents on the oxindole framework.[13] Accordingly, diazooxindoles are found to be less reactive in some reactions than the corresponding acyclic diazo reagents such as aryldiazoacetates **5** and vinyldiazoacetates **6**,[14] which might reasonably explain why the corresponding catalytic asymmetric studies are in the infancy.

Although cyclic, diazooxindoles could undergo typical reactions of a diazo reagent, including O–H, C–H, and N–H insertion, cyclopropanation, and cycloaddition reactions. Therefore, the asymmetric functionalization of diazooxindoles constitutes a general strategy for the enantioselective construction of various types of 3,3-disubstituted oxindoles featuring a C3 heteroatom-containing or all-carbon quaternary stereogenic center, spirocyclic or not. In the following, protocols based on the transformation of diazooxindoles are classified into two parts: (i) racemic or achiral versions and (ii) catalytic asymmetric versions. Special attention is paid to those reactions that are potentially applicable for the design of catalytic enantioselective reactions.

Diazooxindole related racemic or achiral reactions

Early attempts to explore the reactivity patterns of diazooxindoles date back to the sealed-tube pyrolysis of diazooxindole to afford isoindigo at 200 °C by Staudinger and Goldstein in 1916.[15] Since then, the decomposition of diazooxindoles to react with different reaction partners was fragmentarily examined in the following century, which was accelerated in recent years due to the hunt for new oxindole based heterocyclic compounds for biological evaluation.



Scheme 2. The synthesis of diazooxindoles **1** or **4**.