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Metal-Free Formal Oxidative C–C Coupling by In Situ Generation of an Enolonium Species
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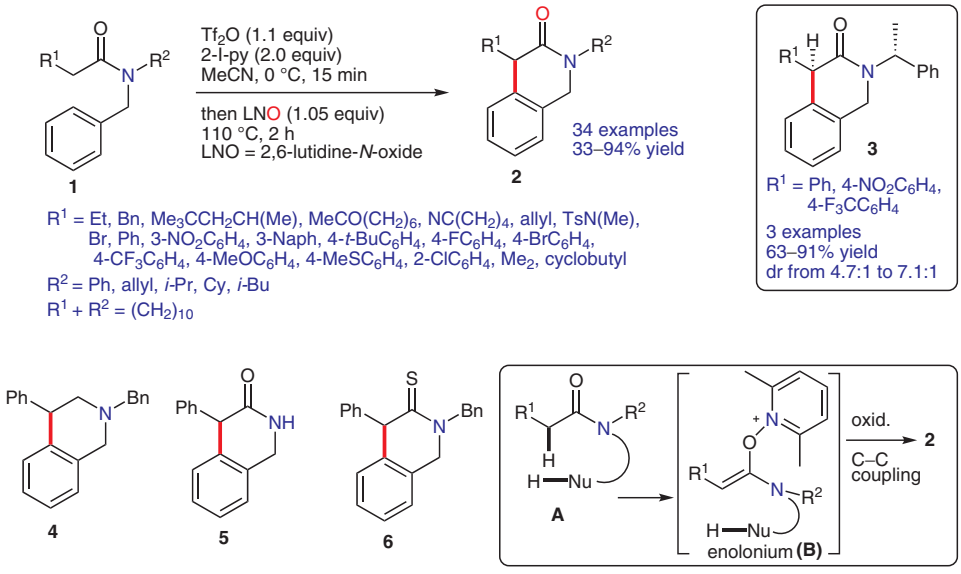
Synthesis of Isoquinolinones by Amide Umpolung



Significance: Reported is a method for synthesizing isoquinolinones **2** by intramolecular cyclization of benzylamides **1** by treatment with 2,6-lutidine *N*-oxide and 2-iodopyridine in acetonitrile. Various linear and branched amides **1** containing EDGs and EWGs with various substitution patterns provided the desired C–C coupling products **2** in moderate to good yields. These reactions are formal C–H ene and C–H Sakurai processes. Chiral amides **1** [R^1 = Ph, 4-$O_2NC_6H_4$, 4-$F_3CC_6H_4$; R^2 = CH(Me)Ph] underwent diastereoselective cyclization to give **3** in good to excellent yields and moderate to good diastereoselectivities. A gram-scale reaction of **1a** (R^1 = Ph; R^2 = Bn) afforded the corresponding product **2a** in 99% yield. X-ray crystal analysis of a product **2** confirmed the assigned structures.

Comment: Isoquinolines represent an important class of heterocycles found in many biologically active natural products, and they are useful intermediates in the synthesis of pharmaceuticals (see, for example: S. Dhanasekaran , A. Suneja, V. Bisai, V. K. Singh *Org. Lett.***2016**, *18*, 634). The reported method is a derivative of previous work (A. B. Charette, M. Grenon *Can. J. Chem*. **2001**, *79*, 1694). Compound **2a** was transformed into **4**, **5**, and **6** (49–99% yield). A synthesis of the drug McN-5652 was also achieved. A mechanism is proposed involving an electrophilic enolonium intermediate **B**, obtained by polarity reversal at the α-center of carboxamide **A**. An experiment with the ^{18}O-labeled amide **1b** (R^1 = 4-BrC_6H_4, R^2 = Bn; 93% ^{18}O) led to product **2b** with complete loss of the ^{18}O label, supporting the proposed mechanism.

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Synthesis of Heterocycles

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