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We have developed Pd-catalyzed intermolecular Friedel–Crafts-type allylic alkylation and allylic dearmatization reactions of substituted indoles bearing a nucleophilic group with vinyloxirane, providing an efficient method to synthesize structurally diverse tetrahydrocarboline and spiroindolenine derivatives under mild conditions.

Substituted indole nucleus and polycyclic skeletons embedded with indoline moieties represent important structural motifs in numerous natural products and pharmaceuticals. Meanwhile, transition-metal catalyzed Friedel–Crafts-type allylic alkylation and allylic dearmatization reactions of indoles have proved to be efficient and successful strategies for the synthesis of structurally diverse indolines in good yields with high diastereoselectivity and enantioselectivity. However, most of the successful examples to date have employed allyl carbonates as electrophiles. Allylic alcohols as electrophiles in allylic substitution reactions in the presence of suitable promoters were reported in the last decade. The Tamaru group and Trost group respectively reported Pd-catalyzed allylic dearmatization of indoles with allylic alcohols in the presence of trialkylborane. After that, Bandini and coworkers elegantly described the use of allylic alcohols in the catalytic and enantioselective Friedel–Crafts alkylation reaction in the presence of chiral gold complexes. Moreover, the Carreira group disclosed that branch allylic alcohols were suitable allylic precursors under acidic conditions. Recently, we have developed a Ru-catalyzed intermolecular dearmatization of indoles with allylic alcohols via a cascade sequence including the allylic dearmatization/cyclization/allylic amination reaction. In addition, we realized an iridium-catalyzed intermolecular allylic dearmatization reaction of substituted indoles using the Carreira ligand and Fe(OTf)2 as an additive.

We initiated our investigation with the optimization of the reaction of dimethyl 2-((1H-indol-2-yl)methyl) malonate 1a and vinyloxirane 2. First, various ligands were examined in the presence of Pd2dba3 with Et3B as a promoter in THF at 50 °C. As shown in Table 1, when the monodentate ligand Ph3P or P(OPh)3 was used, no reaction was observed (entries 1 and 2, Table 1). Notably, bidentate ligands such as dppe and dppp could afford the product 3a in the same yield (entries 3 and 4, Table 1, 79% yield as determined by GC-MS). However, the desired product 3a and substrate 1a have a similar polarity and therefore cause the difficulty in separation in the case of incomplete conversion. Dppp was used as a preferred ligand because substrate 1a could not be consumed completely using dppe as the ligand. By reducing the loading of vinyloxirane, better yield could be obtained (entry 7, Table 1). In the presence of 2.5 mol% of Pd2dba3 and 5.5 mol% of dppp, we then...
tested the effects of various additives such as Na₂SO₄, CaCl₂, and MgSO₄ (entries 9–12, Table 1). The reaction with MgSO₄ proceeded smoothly, providing the desired product 3a with the best result (82% yield, entry 12, Table 1).

Under the optimized reaction conditions (entry 12, Table 1), we next turned our attention to explore the substrate scope of the reaction. As summarized in Scheme 1, substrates bearing different ester groups could be tolerated, giving the corresponding products in 82% yield in both cases (3a, 3b, Scheme 1). The reactions of 5-substituted indole substrates with either an electron-donating group (Me, OMe, Ph) or an electron-withdrawing group (Cl) proceeded smoothly under the optimal conditions, affording the desired products in good yields (68–89%).

By taking advantage of the nucleophilicity of the C-3 position of indoles, we have developed an allylic dearomatization reaction of indoles with an intramolecular design. The Pd-catalyzed allylic cascade reaction of C-3 substituted indoles with vinylloxirane has also been successful in a dearomatization fashion. The results are summarized in Scheme 2. With dppb as the ligand, the reactions of substrates 4a and 4b, bearing an electron-donating group on the indole core, could give the desired products with satisfactory yields (84–88%) and moderate diastereoselectivity (5a: 80/20, 5b: 78/22, Scheme 2). For the 6-F substituted indole 4c, moderate yield and diastereoselectivity could also be achieved (76% yield, 74/26 dr). Notably, substrate 4d and its dearomatized product have a similar polarity, which led to the difficulty in product separation. To address this problem, a one-pot reaction including an in situ reduction was carried out to convert the indolenine to the corresponding indoline (54% yield with 61/39 dr). Interestingly, for the more bulky substrate 4e, allylic alcohol 5e was obtained in 53% yield under the same reaction conditions. These results indicated that the current Pd-catalyzed cascade reaction firstly generates the corresponding allylic alcohol.

In conclusion, we have developed Pd-catalyzed intermolecular Friedel–Crafts-type allylic alkylation and allylic dearomatization of indoles with vinylloxirane through a cascade sequence. These protocols provide a rapid construction of structurally diverse tetrahydrocarboline and spiroindolenine derivatives under mild conditions.

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Notes and references


11 For recent review on vinyl epoxides, see: J. He, J. Ling and P. Chiu, Chem. Rev., 2014, 114, 8037.