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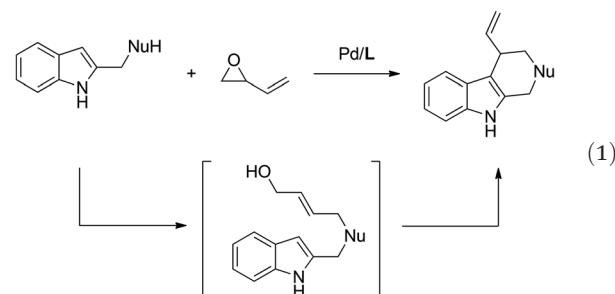
We have developed Pd-catalyzed intermolecular Friedel-Crafts-type allylic alkylation and allylic dearomatization reactions of substituted indoles bearing a nucleophilic group with vinyloxirane, providing an efficient method to synthesize structurally diverse tetrahydrocarboline and spiroindolenine derivatives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

Substituted indole nucleus and polycyclic skeletons embedded with indoline moieties represent important structural motifs in numerous natural products and pharmaceuticals.¹ Meanwhile, transition-metal catalyzed Friedel-Crafts-type allylic alkylation² and allylic dearomatization³ 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.⁴ The Tamura group⁵ and Trost group⁶ respectively reported Pd-catalyzed allylic dearomatization of indoles with allylic alcohols in the presence of trialkylborane. After that, Bandini and coworkers⁷ 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 Carreira⁸ group disclosed that branch allylic alcohols were suitable allylic precursors under acidic conditions. Recently, we have developed a Ru-catalyzed⁹ intermolecular dearomatization of indoles with allylic alcohols *via* a cascade sequence including the allylic dearomatization/cyclization/allylic amination reaction. In addition, we realized an iridium-catalyzed¹⁰ intermolecular allylic dearomatization reaction of substituted indoles using the Carreira ligand and Fe(OTf)₂ as an additive.

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† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, and copies of ¹H and ¹³C NMR spectra. See DOI: [10.1039/c6ob01523a](https://doi.org/10.1039/c6ob01523a)

In addition to these reports on employing allylic alcohols as suitable electrophiles in allylic substitution reactions, vinyloxirane under palladium catalysis could *in situ* generate an allylic alcohol upon the attack by a suitable nucleophile.¹¹ Inspired by these elegant reports, we envisioned the utilization of vinyloxirane might enable a cascade reaction with indole bearing a nucleophile (eqn (1)). Herein, we describe such a Pd-catalyzed cascade allylic alkylation reaction of dimethyl malonate tethered indoles with vinyloxirane, including the intermolecular nucleophilic ring-open reaction of vinyloxirane and the subsequent intramolecular allylic alkylation and dearomatization reactions.



We initiated our investigation with the optimization of the reaction of dimethyl 2-((1*H*-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



Table 1 Optimization of the reaction conditions^a

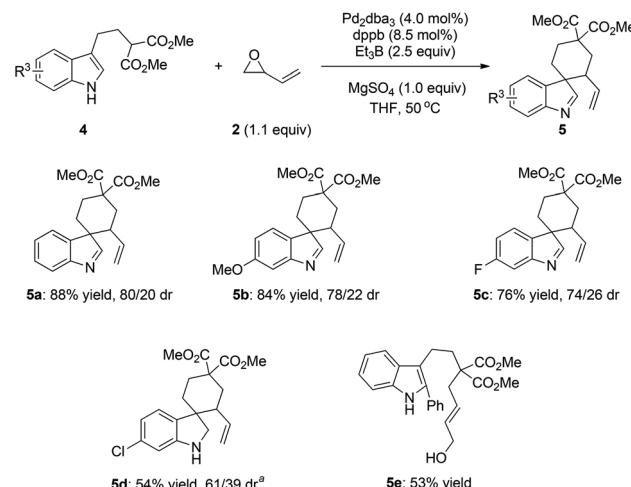
Entry	Ligand	X	Y	Additive	Yield ^b (%)
1	PPh_3	1.3	11	—	Trace
2	$\text{P}(\text{OPh})_3$	1.3	11	—	Trace
3	dppe	1.3	5.5	—	79 ^c
4	dppp	1.3	5.5	—	79 ^c (64)
5	dppb	1.3	5.5	—	71 ^c
6	dppf	1.3	5.5	—	19 ^c
7	dppp	1.1	5.5	—	69
8	dppp	2.0	5.5	—	32
9 ^d	dppp	1.1	5.5	Na_2SO_4	79
10 ^d	dppp	1.1	5.5	CaCl_2	20
11 ^d	dppp	1.1	5.5	MgSO_4	83
12 ^e	dppp	1.1	5.5	MgSO_4	82

^a Reaction conditions: 0.2 mmol of 1a, 2.5 mol% Pd_2dba_3 , 0.5 mL Et_3B (1 M in THF) in THF (2.0 mL) at 50 °C. ^b Isolated yield. ^c Determined by GC-MS (normal dodecane as the internal standard). ^d 5.0 equiv. additive was used. ^e 1.0 equiv. additive was used.

tested the effects of various additives such as Na_2SO_4 , CaCl_2 and MgSO_4 (entries 9–12, Table 1). The reaction with MgSO_4 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%).

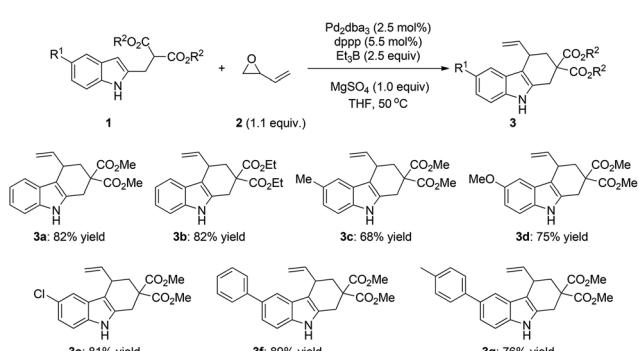
By taking advantage of the nucleophilicity of the C-3 position of indoles, we have developed an allylic dearomatization



Scheme 2 The substrate scope for intermolecular allylic dearomatization reaction. Reaction conditions: 0.2 mmol of 4, 0.22 mmol of 2, 4.0 mol% Pd_2dba_3 , 8.5 mol% dppb, 0.5 mL Et_3B (1 M in THF) and 0.2 mmol of MgSO_4 in THF (2.0 mL) at 50 °C. ^a Reaction conditions: 7.5 mol% Pd_2dba_3 , 16 mol% dppb, 0.5 mL Et_3B (1 M in THF) and 0.2 mmol of MgSO_4 in THF (2.0 mL) at 50 °C, and then reduced by NaBH_3CN .

reaction of indoles with an intramolecular design. The Pd-catalyzed allylic cascade reaction of C-3 substituted indoles with vinyloxirane 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% yields) 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 vinyloxirane through a cascade sequence. These protocols provide a rapid construction of structurally diverse tetrahydrocarboline and spiroindolene derivatives under mild conditions.



Scheme 1 The substrate scope for intermolecular Friedel–Crafts-type allylic alkylation reaction. Reaction conditions: 0.2 mmol of 1, 0.22 mol of 2, 2.5 mol% Pd_2dba_3 , 5.5 mol% dpp, 0.5 mL Et_3B (1 M in THF) and 0.2 mmol of MgSO_4 in THF (2.0 mL) at 50 °C.

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