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Enantioselective Atom Transfer Radical Additions to Olefins

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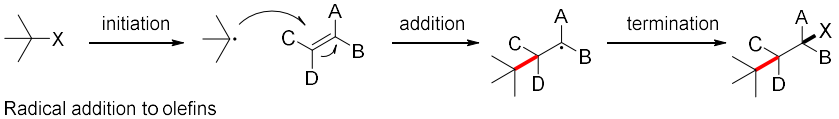
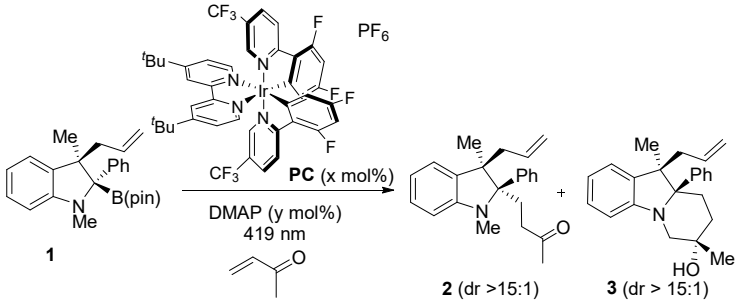
Carbon-centered radicals are highly reactive species that readily add to olefins. This process generates at least one new carbon-carbon bond and frequently generates new stereogenic centers. As shown in the figure below, initiation of the radical addition is frequently accomplished through hemolysis of a C-X bond (X is halide, BR2, carboxylic acid). Addition to an olefin generates a new radical, which can be quenched in a variety of ways, including abstraction of the original X group. In light of their ability to form multiple new bonds and stereocenters, radical additions to olefins represent attractive synthetic methods to build complex small molecules in a rapid and efficient manner.



Radical addition to olefins

The challenges associated with developing radical additions to olefins relate to controlling the high reactivity of radical species. In particular, the addition step can generate a mixture of regioisomers and/or stereoisomers arising from addition to either terminus of the olefin or either face of the olefin, respectively. Next, the addition product is a radical, so it can add to another olefin leading to polymerization, or it can be quenched, frequently forming a new C-X bond or C-H bond.

Our studies over the previous funding period have focused on the radical addition of indoline-based radicals. Indoles and indolines are prized substructures in drug discovery and natural products research. A Reaxys search revealed over 6500 naturally occurring indoles and 143 indoline natural products. Likewise, a DrugBank search revealed 270 indoles in pre-clinical development and 69 approved drugs. We previously described an enantioselective synthesis of indoline boronic esters that involved a Pd-catalyzed allylation of indole-boronates. Allylation at carbon 3 induces a 1,2-boronate rearrangement to form the boronic esters **1**. To develop the synthetic utility of these products, we have explored their participation in radical additions to olefins.

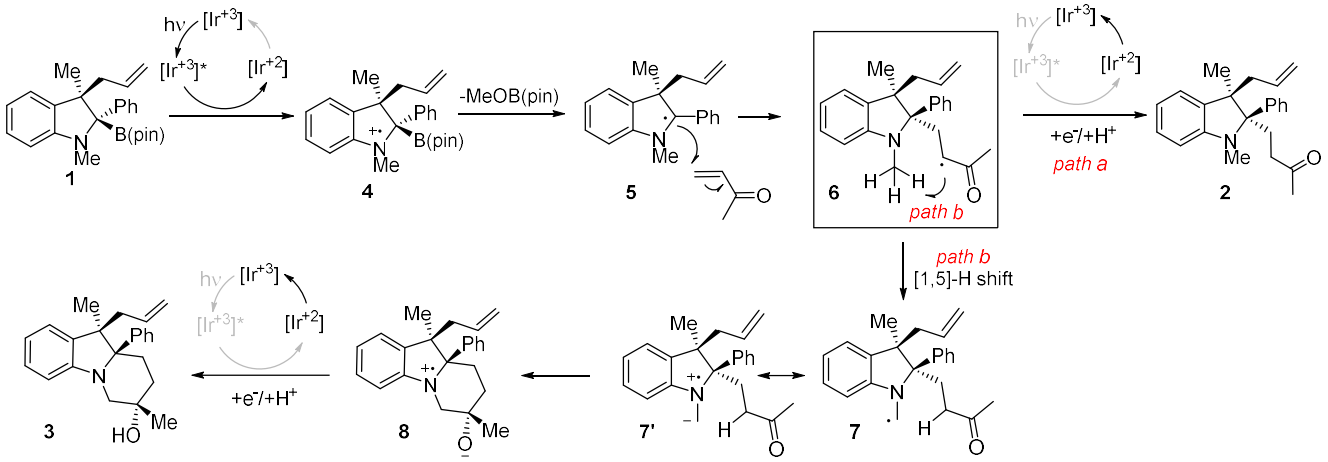


entry	**PC** (mol%)	DMAP (mol%)	solvent	yield (%)[b]	**2**:**3**
1	2	20	acetone/MeOH	72	2:1
2	1	20	acetone/MeOH	65	2:1
3	**1**	**20**	**acetone**	**62**	**>20:1**
4	1	20	MeOH	66	2:1
5	1	100	acetone/MeOH	52	5:1
6	**2**	**0**	**acetone/MeOH**	**64**	**>1:20**

Boronic ester **1** underwent 1,4-addition to methyl vinyl ketone to form **2** with unexpectedly high diastereoselectivity when irradiated in the presence of photocatalyst **PC**. More surprising was the formation of a new product with the same molecular weight as **2**, but in which the N-methyl singlet had apparently changed to a diastereotopic methylene. The ^{1}H and ^{13}C NMR data supported assignment as the tricyclic structure **3**, which would formally arise from addition of a C-H from the N-methyl across the ketone carbonyl of **2**. This product was also generated in high diastereoselectivity.

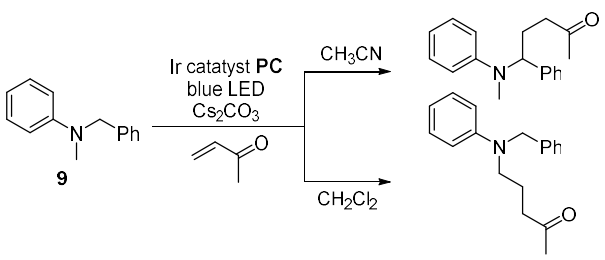
X-ray crystal structures indicated that both **2** and **3** were formed with apparent inversion of stereochemistry at the indoline C2 position. The product distribution between the 1,4-addition adduct **2** and annulation product **3** was found to markedly depend on reaction conditions. For example, only the 1,4-addition product was formed when the reaction was conducted in acetone that had been stored on the benchtop. Alternatively, the annulated product **3** was formed exclusively when DMAP was omitted from the reaction. Control experiments indicated that **2** was not converted to **3** under the reaction conditions.

Several experiments were performed to explore the substrate scope of this reaction and to better understand the reaction. First, essentially identical results were obtained with a variety of substituted aryl rings at C2 of the indoline. Aliphatic groups in this position were not tolerated (no reaction). Separately, cyanoacrylate and methyl acrylate gave only the 1,4 addition product. Second, deuterium and stereochemical probe experiments are most consistent with the mechanism shown below.



Single electron transfer from the indoline nitrogen of **1** to a photo-excited Ir^{+3} complex would generate the radical cation **4**. Loss of the boryl group would lead to tertiary radical **5**. Subsequent addition to methyl vinyl ketone would generate the α-keto radical **6**, which sits at a branch point between the 1,4-addition product and the annulation. In path a, the reduced Ir^{+2} photocatalyst transfers an electron to the α-keto radical to form an enolate, which can be protonated to form **2**.

Alternatively, α-keto radical intermediate **6** could undergo 1,5-hydrogen atom transfer from the N-methyl group to result in radical **7**. Addition of this radical to the ketone would form the observed piperidine ring. Finally, reduction of the radical cation by Ir+2 would close the photocatalytic cycle, and protonation of the alcohol would provide the observed product **3**.



Ongoing work seeks to extend these concepts to acyclic systems. The Ir photocatalyst shown above can directly oxidize certain amines to form α-amino radicals. In a remarkable case of selectivity, we find that a simple switch in solvent completely alters the regioselectivity of a photocatalytic radical addition of *N*-methyl, benzyl aniline **9** to an olefin. In a polar solvent, we observe addition from the most stable radical; in methylene chloride we observe only addition at the least hindered position. Efforts are underway to explain and exploit this observation.