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Enantioselective Atom Transfer Radical Additions to Olefins

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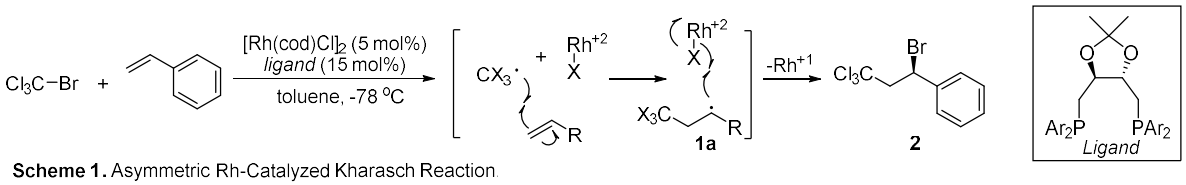
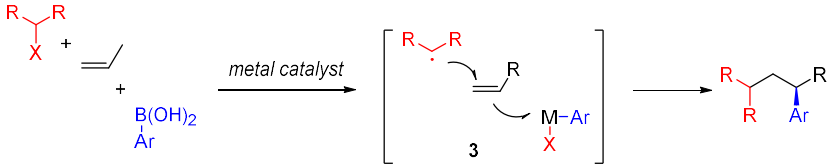
Carbon-centered radicals are valuable reactive intermediates for organic synthesis. They can be generated reductively, oxidatively, or thermally. In most synthetic applications, carbon-centered radicals add to olefins. These reactions are frequently highly efficient, in part due to the large enthalpic driving force associated with formally exchanging a C-C double bond for a C-C single bond. Moreover, the high reactivity of radicals leads to early transition states. In turn, the early transition state often renders radical reactions less sensitive to steric constraints than related polar transformations. However, a major limitation of radical reactions has been the difficulty with which stereochemistry can be controlled. The high reactivity of radical intermediates can be associated with poor control of relative and/or absolute stereochemistry.

We initiated a program to develop enantioselective, catalytic reactions involving radical intermediates. Much prior work in this area focused on the use of chiral Lewis acids or enamines. Our interest was in developing an asymmetric Kharasch reaction (Scheme 1). Synthetically, this reaction is useful because it forms a new C-C bond, introduces a trihalogenated carbon, and forms a new, reactive alkyl halide stereocenter. Mechanistically, this transformation provided an opportunity to control the stereochemistry of C-Br bond formation by using optically active metal-bromide complex (see transition structure **1a**). Ultimately, Rh(I)(DIOP) complexes were identified as superior catalysts for these reactions, providing 10:1 – 20:1 er's for a range of aryl olefins.



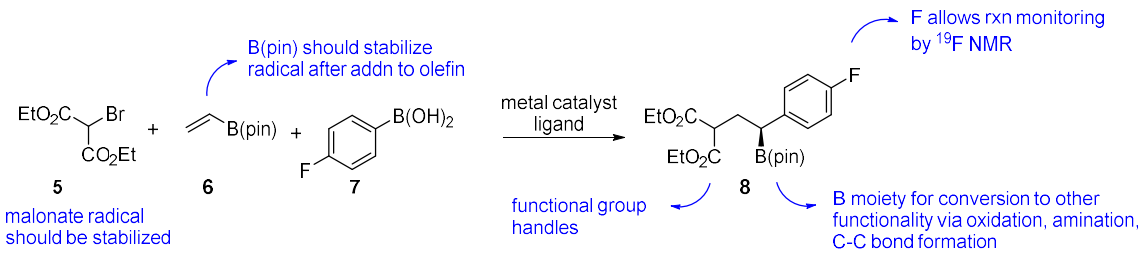
Scheme 1. Asymmetric Rh-Catalyzed Kharasch Reaction.

To extend this reaction concept, we considered an enantioselective three component coupling reaction which would involve the same initial steps as the Krarasch reaction, but diverge later in the mechanism (Scheme 2). Specifically, we envisioned radical addition to an olefin as in the Kharasch addition. The resulting secondary radical could be trapped with an M(Ar) species (see transition structure **3**), which would then lead to reductive elimination to form the coupled product (**4**).



Scheme 2. Metal-catalyzed, asymmetric three-component coupling reaction.

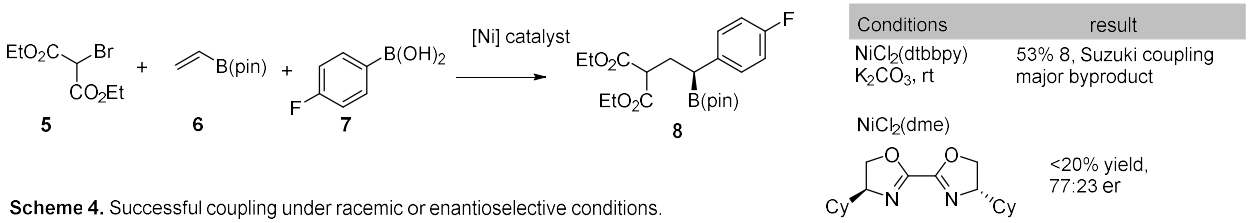
As an experimental test of this idea, we designed the screening platform outlined in Scheme 3. The overall reaction is a three component coupling between radical precursor **5**, vinyl boronate **6**, and aryl boronic acid **7**. The logic behind these substrates was as follows. First, the malonate radical is stabilized, and therefore accessible under standard reaction conditions. The vinyl boronate should lead to a stabilized radical after addition of the malonate,



Scheme 3. Reaction design for catalyst screening.

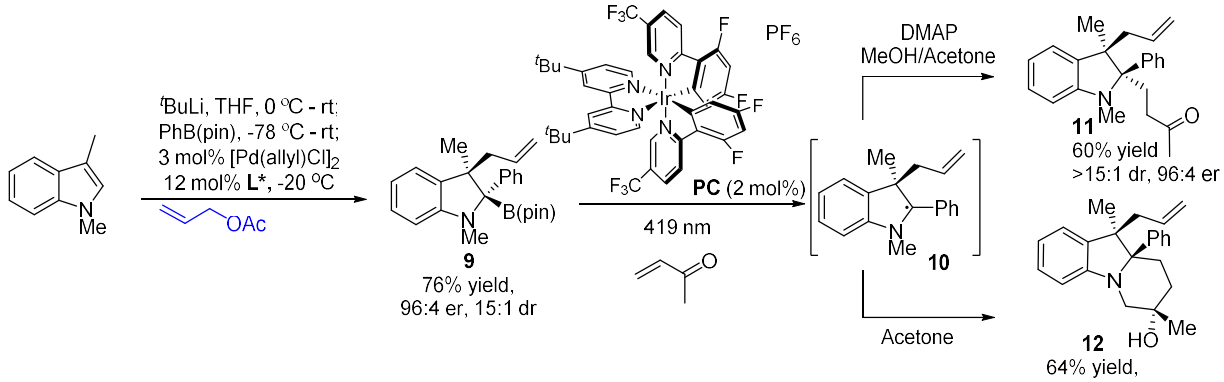
and after 3-component coupling would provide a synthetic handle for additional functionalization. Finally, the fluoro-phenyl group should provide clearly resolvable ^{19}F NMR signals for rapid analysis. Using this reaction for optimization, we evaluated a range of metal/ligand combinations. No product was observed with Pd, Mn, Co, Ir or Cu catalysts. However, Ni complexes showed some promise. The major determinant seems to be the ligand. Currently, we have promising leads with regard to conversion and with regard to enantioselectivity.

In the racemic reaction, the major side product is the direct cross-coupling between the malonate and the aryl boronic acid (Scheme 4). Conversions are high, but selectivity is around 2:1 favoring the desired product. Substituted bipyridyl ligands appear optimal. One unanticipated complexity of the reaction relates to the equilibrium between the boronic acid (shown) and the boroxine $[ArBO]_3$, which appear to be present in different ratios in different samples, and which appear to give different selectivities. In terms of an enantioselective version, encouraging enantioselectivity is observed with c-Hex bisoxazoline ligands, although conversion remains very low. Ongoing efforts seek to build on these initial discoveries.



Scheme 4. Successful coupling under racemic or enantioselective conditions.

In parallel to the studies on 3-component couplings, we have explored an unrelated asymmetric radical reaction. We recently developed a method to access tertiary boronic esters through an asymmetric 3-component allylation reaction. In an effort to exploit these products, we developed a photocatalytic radical functionalization of the C-2 position of the indoline (Scheme 5). For example, boronic ester **9** was formed in good yield as a single diastereomer in 92% ee in the presence of a Pd(phosphoramidite) catalyst. Exposure to an Ir photocatalyst (**PC**) likely formed the radical **10**. In the presence of DMAP, this radical undergoes 1,2 addition to electron deficient olefins to form products such as ketone **11** in high yield and stereoselectivity. Interestingly, in the absence of DMAP, an annulation to tricycle **12** is observed, presumably involving C-H abstraction from the N-Me group. In this reaction, the stereoselectivity of the radical addition was unanticipated. The high reactivity of radicals often results in low stereocontrol. Moreover, the difference between a methyl and an allyl group is relatively modest. Nonetheless, control reactions indeed implicated the free radical **10**, and suggest that the reaction outcome is dictated by the methyl/allyl stereocenter.



Scheme 5. Asymmetric 3-component coupling and radical funtionalization of tertiary boronates.

Ongoing efforts will seek to enhance the yield of the racemic three component coupling shown in Scheme 4 with bipyridyl ligands. Here, we need to limit the direct cross coupling through either electronic or steric manipulation of the ligand. In regards to the enantioselective coupling, we will explore other ligand designs and reaction conditions to improve both turnover and selectivity. With optimized reaction conditions we will examine the scope and limitations. Finally, in regard to the boronate functionalization, our highest priority is to determine if this unique annulation reaction is limited to indolines. A more general transformation could be broadly useful in the asymmetric synthesis of piperdines.