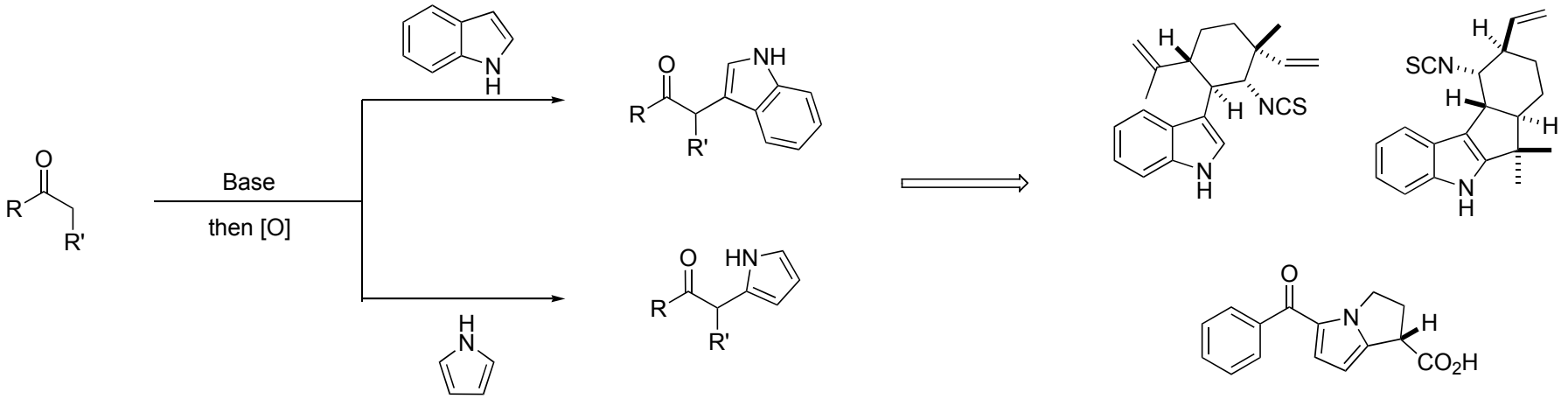
The Direct Coupling Of Carbonyl Compounds With Indoles And Pyrroles

Phil S. Baran and Co-workers

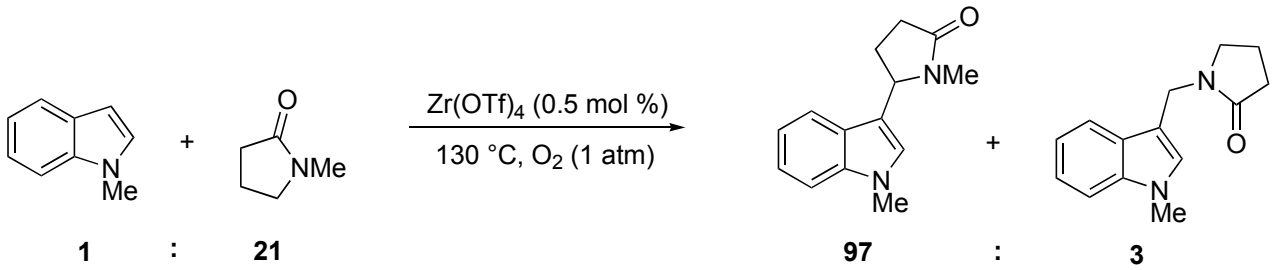
J. Am. Chem. Soc. **2004**, *126*, 7450

Angew. Chem. Int. Ed. **2005**, *44*, 609

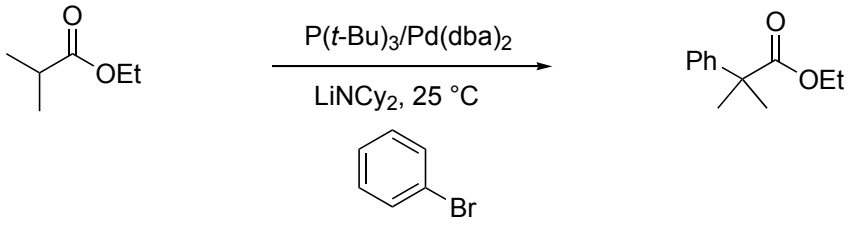


David L. Waller
Current Literature
2 April 2005

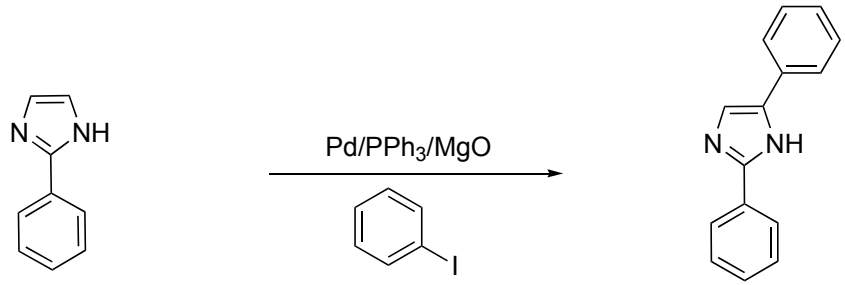
Examples of Some Oxidative Couplings to Arenes



Angew. Chem. Int. Ed. **2004**, *43*, 4231



Acc. Chem. Res. **2003**, *36*, 234



75-85%

J. Am. Chem. Soc. **2003**, *125*, 10580

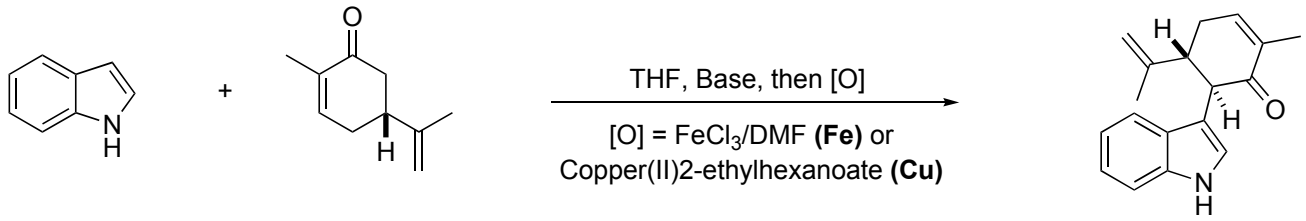
Retrosynthetic Analysis Presents Need For New Method

-Disconnection at C-3 leads to two hypothetical synthons.

-Actual coupling could be realized through the corresponding radical coupling (2· and 3·).

-Radicals could be derived from the corresponding anions (2▬ and 3▬) by oxidation.

Experimental Optimization and Development

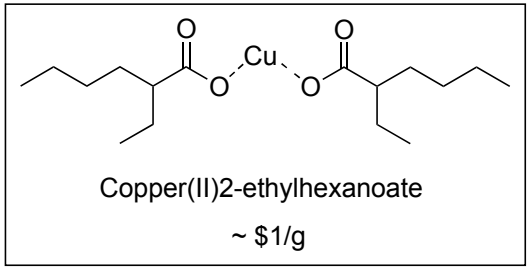


-Product isolated as single diastereomer.

-Cu oxidant gave higher yields and eliminated need for DMF cosolvent.

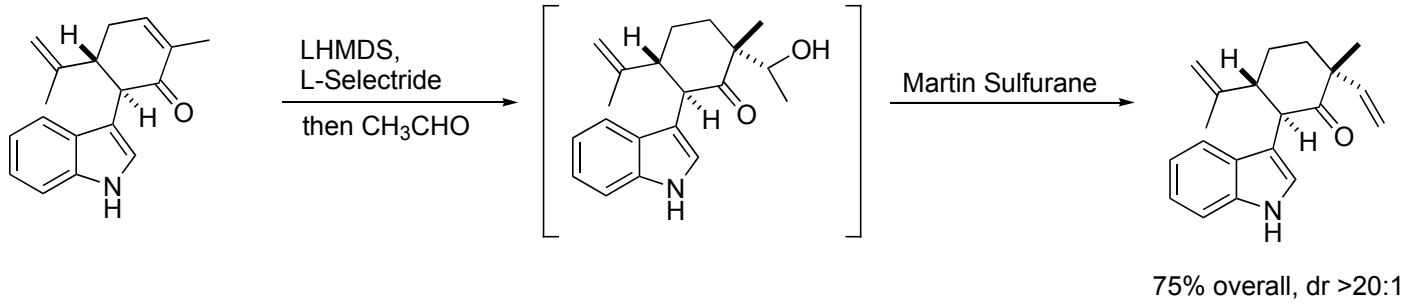
-Starting materials recovered along with small amount of dimerized carvone.

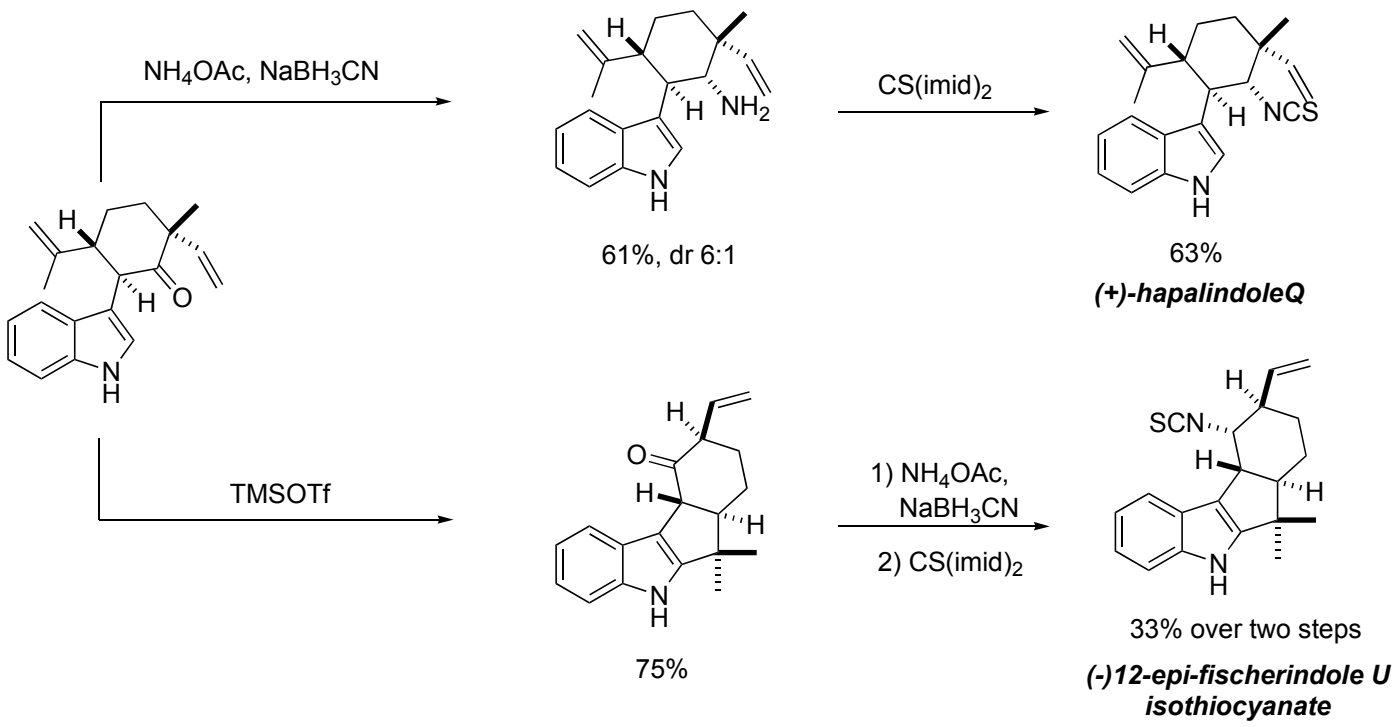
-Yield not diminished on >100 mmol scale.



"The use of substoichiometric quantities of oxidant (relative to all anionic species) in an enolate coupling is without precedent"

Indole Alkaloid Synthesis Utilizing Indole Coupling Methodology





The Scope of the Indole Coupling Process

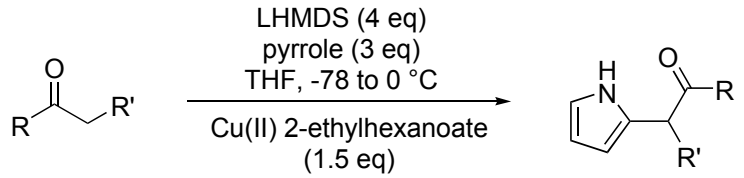
-Brief survey of the scope of the process was conducted.

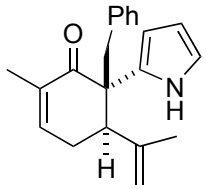
-Note tolerance of free alcohols, amides and steric encumberance.

-Compound 13 bears a quaternary carbon center.

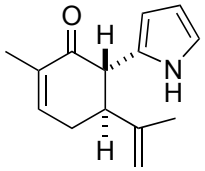
-Yields are modest. Diastereoselectivity is good to excellent.

Extending the Oxidative Coupling to Pyrroles

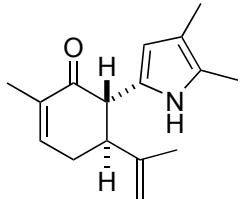




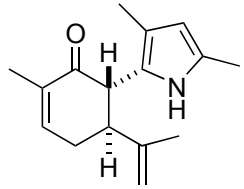
54%, dr >20:1



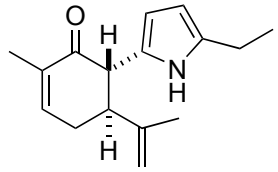
53%, dr >20:1



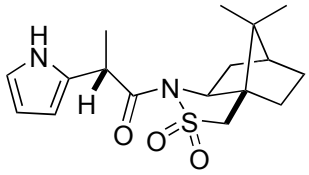
67%, dr >20:1



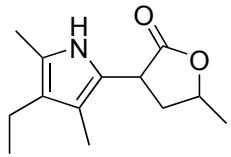
54%, dr >20:1



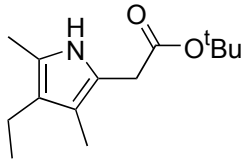
42%, dr >20:1



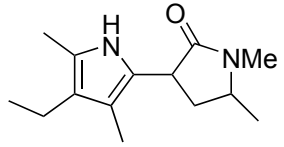
42%, dr 14:1



57%, dr 1:1

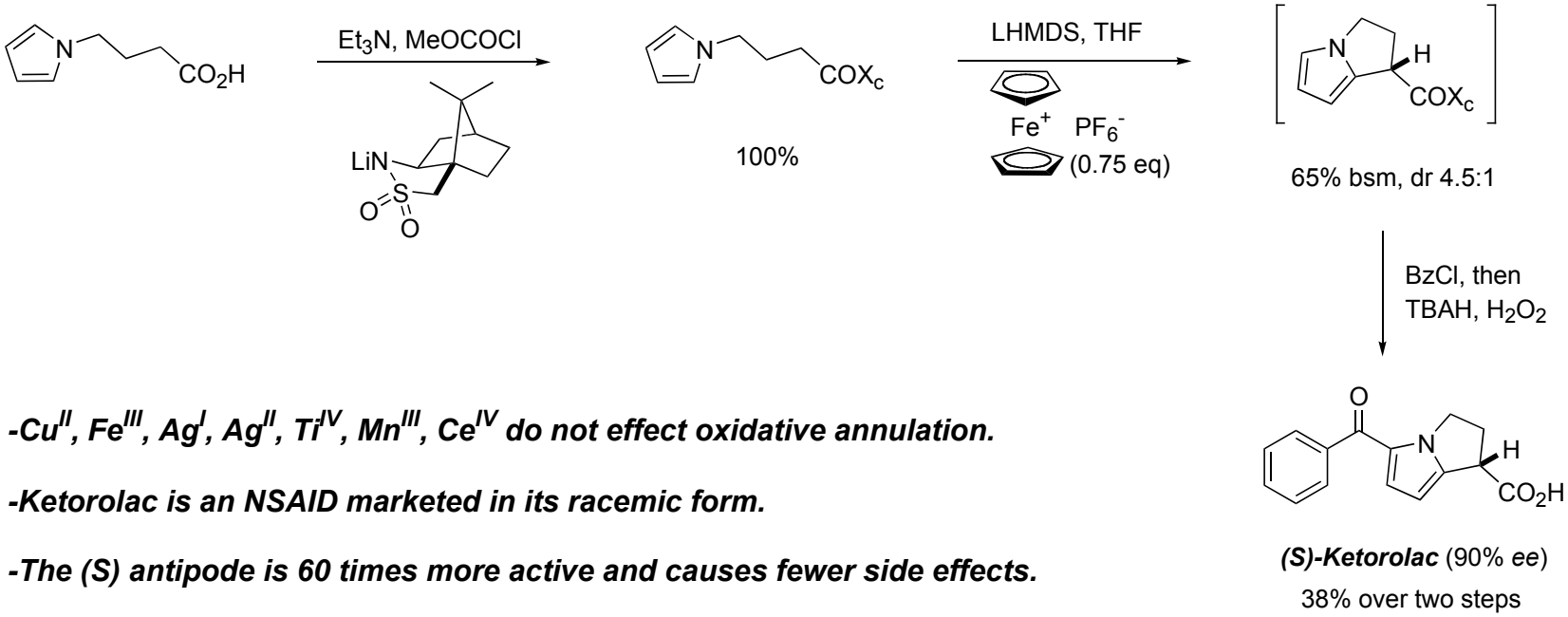


41%



42%, dr 1:1

Synthesis of (*S*)-Ketorolac



-Cu^{II}, Fe^{III}, Ag^{I}, Ag^{II}, Ti^{IV}, Mn^{III}, Ce^{IV} do not effect oxidative annulation.

-Ketorolac is an NSAID marketed in its racemic form.

-The (S) antipode is 60 times more active and causes fewer side effects.

-Commerical route is 5 steps, 45% from pyrrole and racemic.

-Baran's route is 5 steps, 25% and enantioselective.

Proposed Mechanism of the Direct Oxidative Coupling

-Proposed mechanism for direct intermolecular coupling only.

-"Intramolecular cyclization probably differs"

-Observations supporting this mechanism:

-dimerization of pyrrole never observed

-*N*-protected pyrroles do not react

-only 1 eq of oxidant is required

-characteristic red color of Cu(I) salts observed at end of reaction

-same trends are noted for the coupling of indoles

-Ferrocenium oxidant ineffective for direct intramolecular couplings, as Cu^{II} is ineffective for cyclization.

A Summary

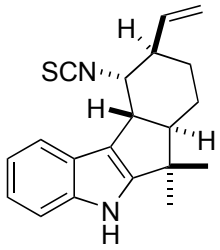
-Method developed for the oxidative coupling of indoles and pyrroles to carbonyl compouds.

-Method is simple and straightforward in its disconnections.

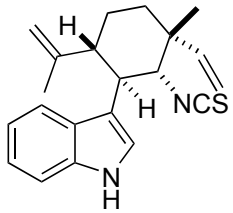
-Method utilizes enolates, and metalloenamines along with a stoichiometric oxidant.

-Negates need for pre-functionalization of arenes for coupling (i.e. halogenation) and protection.

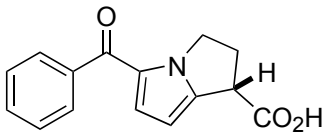
-Utility demonstrated in the synthesis of three natural products.



(-)12-epi-fischerindole U isothiocyanate



(+)-hapalindoleQ



(S)-Ketorolac