Enantio- and chemoselective copper-catalyzed reduction of ketones using a disilane as the reductant

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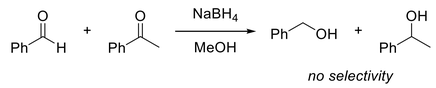
Introduction

Reduction reactions are currently hindered by a lack of functional group tolerance when using traditional reducing agents like boron and aluminum hydrides and catalytic hydrogenations. As a result, reactions such as the Luche reduction, and more recently hydrosilylations, have been developed.[1] However, these reactions do not allow for selective reduction of ketones when similar carbonyl functional groups are present, although there have been reports of aldehydes being selectively reduced by iron-imine catalyzed hydroboration and iron-complex catalyzed hydrogenation.[2]

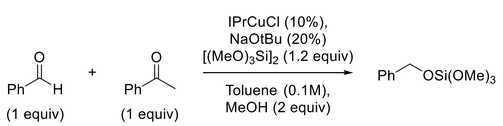


We hope to develop a reaction that enantioselectively reduces ketones in the presence of other readily reducible functional groups by using a copper catalyst and disilane as a terminal reductant. The mechanism likely proceeds through a a 1,2-Brook Rearrangement.[3]

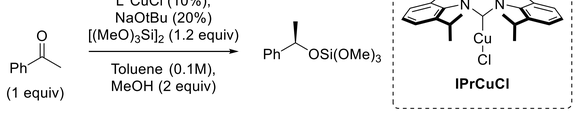
Previous and Current Work

Previous work demonstrated copper alkoxides can activate a disilane and can catalytically reduce an aldehyde in the presence of ketone.[4] This reaction showed remarkable functional group tolerance and we hope to expand the work to be enantioselective. This presents a significant challenge as this reaction works best with NHC ligands, which are notoriously difficult to work with in enantioselective reactions.

previous work:



current work

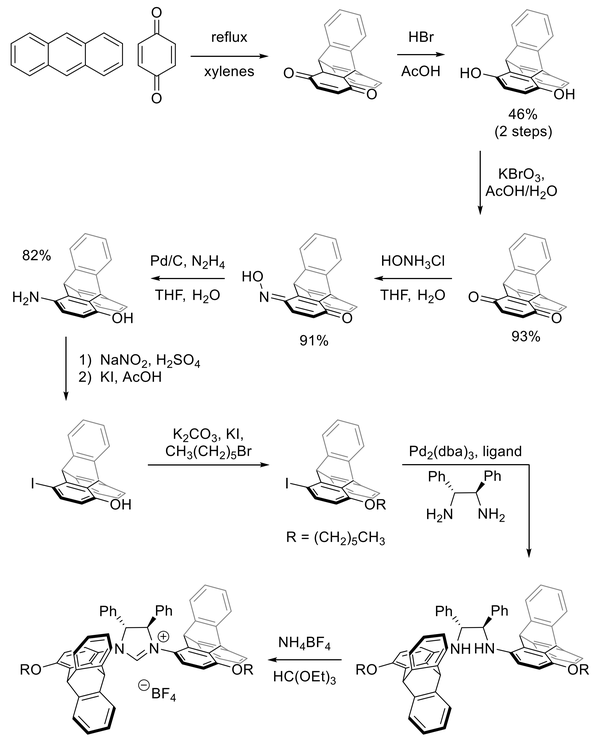


Hypotheses

1. A new design of chiral NHC ligand will allow for a faster synthesis as well as better enantioinduction.
2. Chiral NHC ligands are the best choice to render the reduction reaction enantioselective.

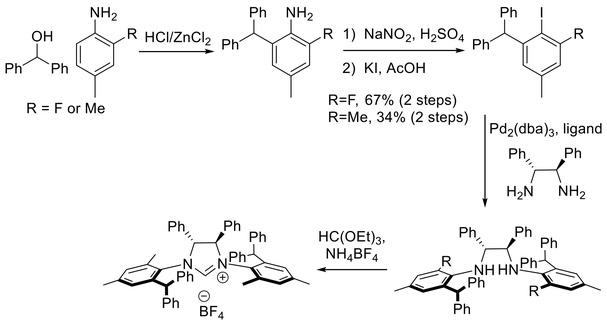
Traditional Synthesis of Chiral NHC Ligands

One of the significant challenges of chiral NHC ligands is that they lack the appropriate geometry to create a chiral environment around the metal. As such, significant amounts of steric bulk must be added to the NHC to enforce chirality around the metal. This usually results in rather long syntheses for the ligand. An example of this can be seen below, which was reported a few years ago.[5] A couple of steps have foiled our attempts to synthesize this ligand.



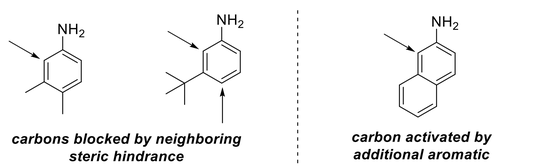
New Synthesis of Chiral NHC Ligands

Clearly, a better synthesis could be envisioned and, if successful, would provide significant value by allowing new asymmetric reaction with NHC ligands to be developed. Below is our proposed synthesis, which is notably shorter than previously reported syntheses.



While the R group on the aniline is necessary to block one of the *ortho* positions so that double addition does not occur, two *ortho* groups all but ensures that the Buchwald-Hartwig coupling will fail. Since directly blocking one *ortho* carbon is problematic, indirectly blocking it may allow the Buchwald-Hartwig coupling to proceed.

Alternative Anilines Which May Prove to Be Better Starting Materials



carbons blocked by neighboring steric hindrance

carbon activated by additional aromatic

Each of the above aniline bias addition to one of the *ortho* carbons and not the other. These may prove to be better substrates for the above synthesis.

Future Directions

1. Complete synthesis of chiral NHC ligands.
2. Perform an asymmetric reduction using chiral ligands.

Conclusions

We have shown that the synthesis of chiral NHC ligands remains significantly challenging. Literature methods for their synthesis are highly problematic while new syntheses present unique steric challenges. However, once we perform the reduction, we expect it to be highly selective for ketones over several other easily reducible functional groups as well as highly enantioselective.

Acknowledgements

We would like to thank the Department of Chemistry and Physics for their generous support.

Funding

NSF grant CHE-0521075 (MRI 400 MHz NMR)
Start-up funds provided Indiana State University
Center for Student Research and Creativity at ISU
Joseph R. Siefker Memorial Scholarship

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