



Optimizing Reaction Conditions for Silylations of Imines

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Introduction

Silylamines are useful intermediate functional groups because they are mildly reactive and functional group tolerant.¹ One use for silylamines is as umpolung substrates in which the reactivity has been reversed. Imines typically act as electrophiles; however silylamines exhibit nucleophilic behavior at the carbonyl carbon. This change in reactivity is valuable because silylamines can now participate in reactions that they could not prior to silylation. Current methods in the literature use copper catalysts with silylboranes to synthesize silanes.² However, silylboranes are air/water sensitive and expensive. This research uses disilanes as the silicon source and an economical copper catalyst to synthesize silylamines.

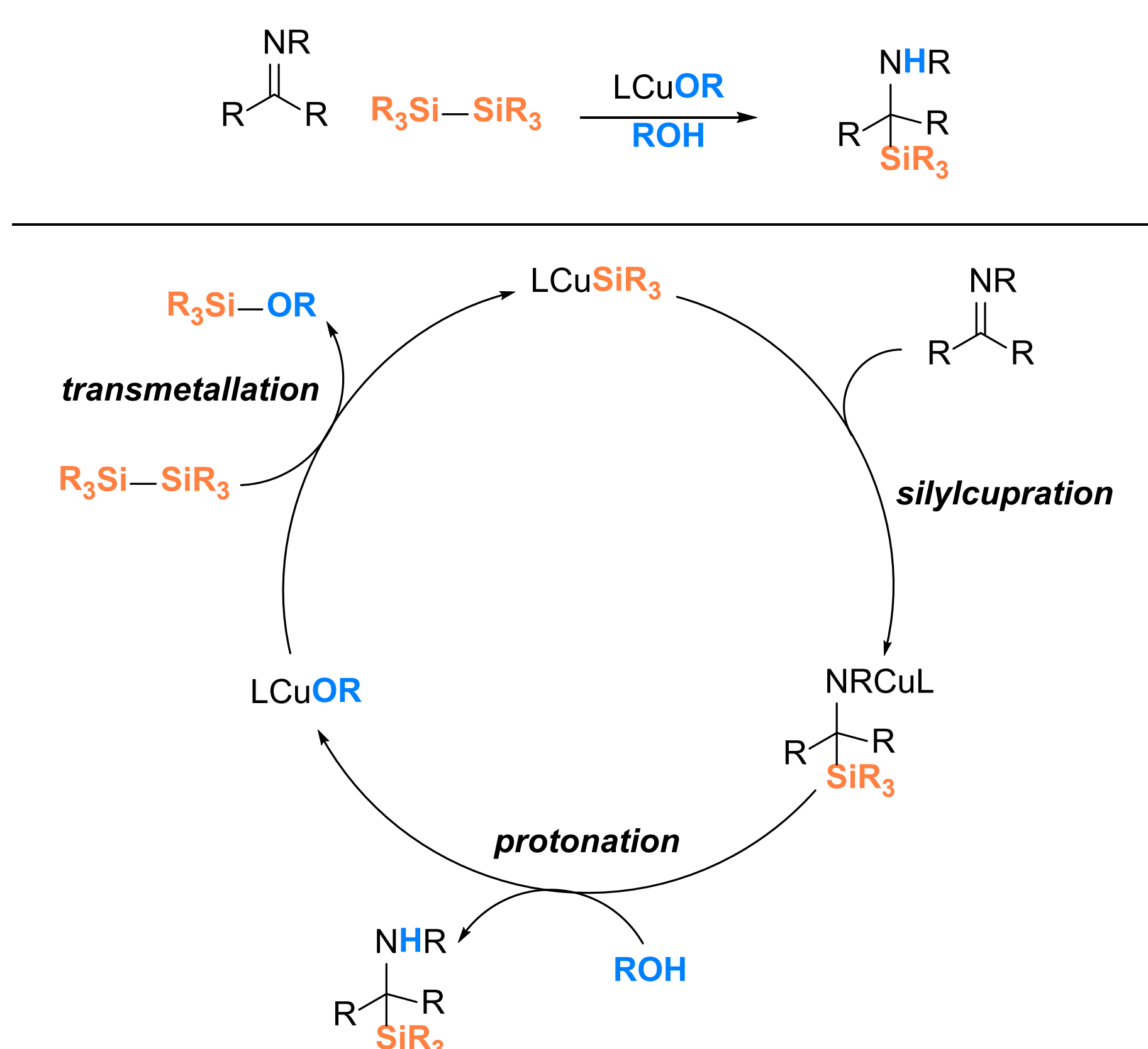
Hypotheses

1. A copper silyl species made from a disilane can attack an imine.
2. An alcohol additive can turn over the catalyst and allow the regeneration of the copper silyl species.
3. The result is that an α -silylamine can be synthesized catalytically from a disilane with a copper catalyst.

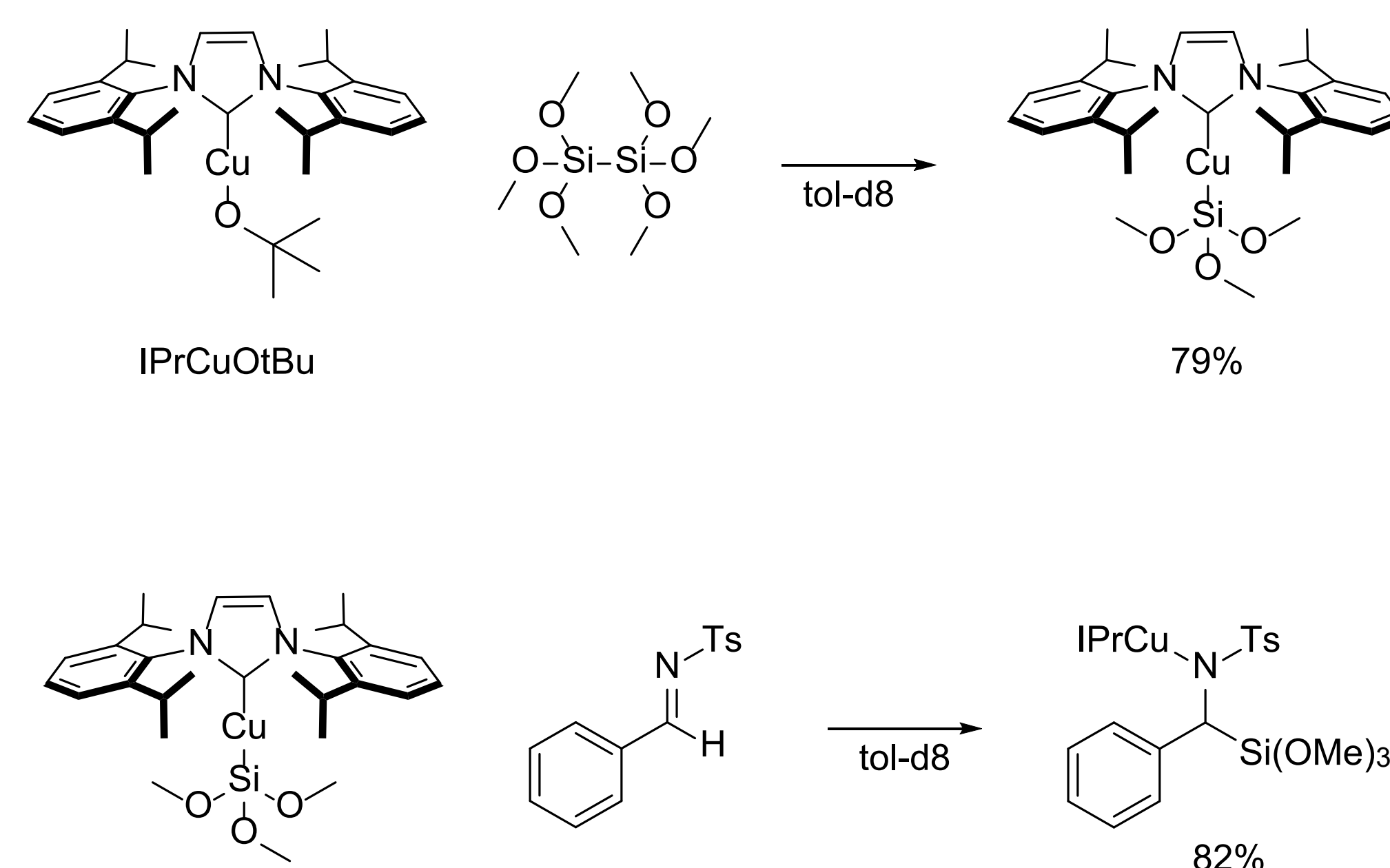
Objectives

1. Optimize the silylation of imines by altering reaction conditions such as the ligand, solvent, alcohol additive, temperature, and disilane.
2. Establish a substrate scope for the addition of disilanes to imines.
3. Study the copper catalyzed mechanism of disilane addition to imines.

Proposed Reactivity For Silylation of Imines

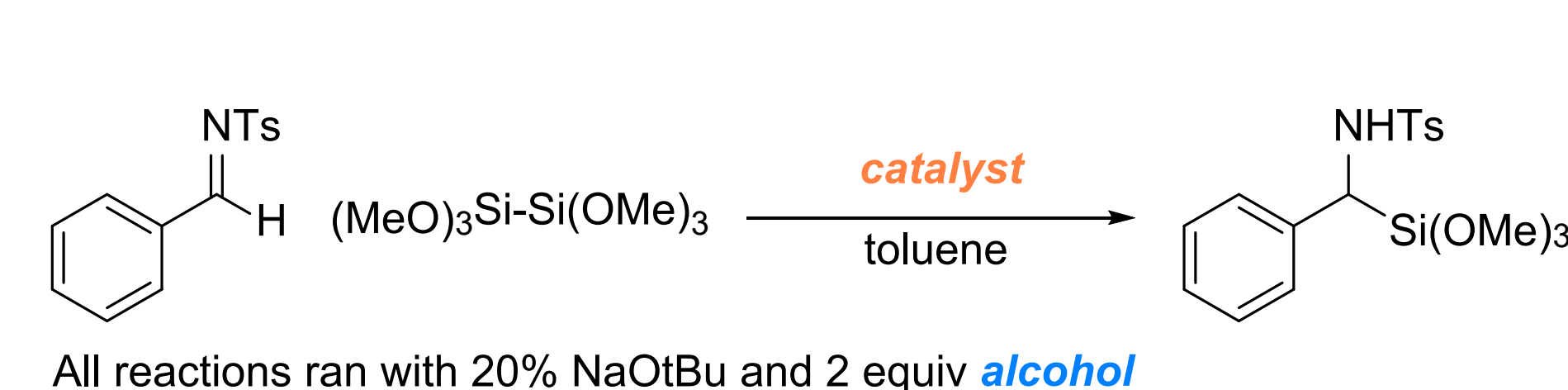


Stoichiometric NMR Studies of Independent Steps (Addn.)



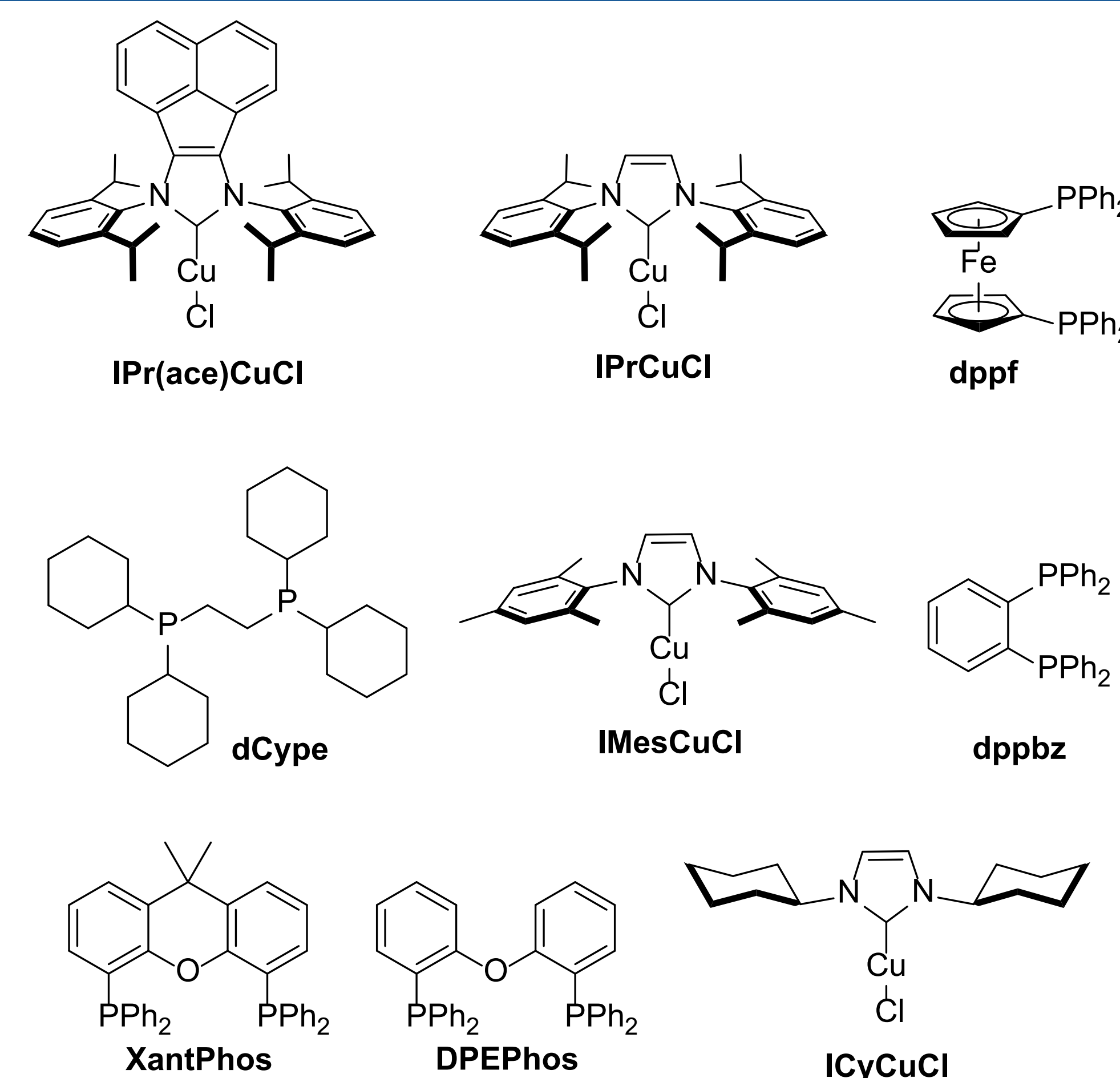
These stoichiometric reactions suggested that a catalytic reaction was possible.

Optimization of Silylation of Imines



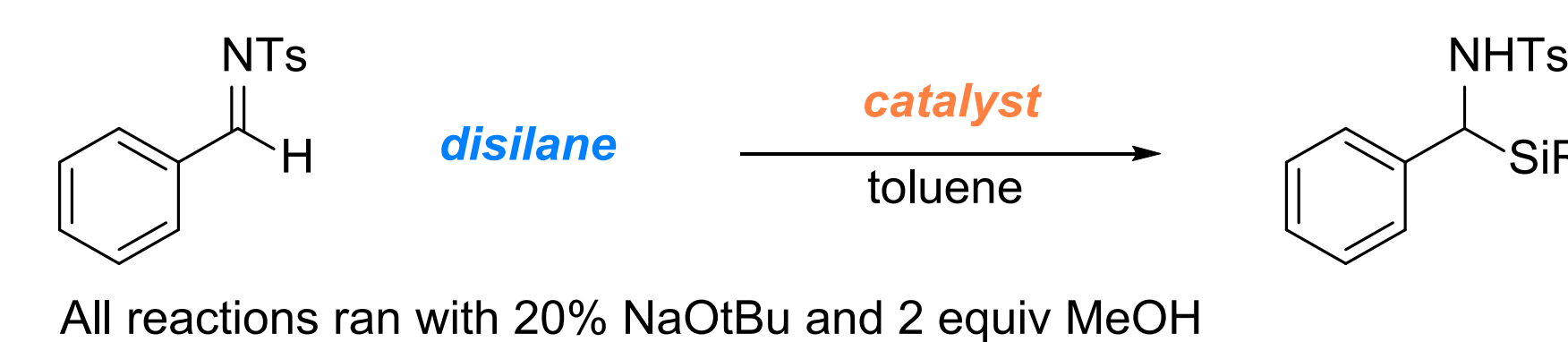
entry	catalyst	alcohol	SM	reduction	yield
1	IPrCuCl	MeOH	24%	23%	0%
2	IPr(ace)CuCl	MeOH	20%	55%	2%
3	IMesCuCl	MeOH	3%	24%	0%
4	dppbz/CuCl	MeOH	72%	2%	17%
5	XantPhos/CuCl	MeOH	47%	2%	12%
6	DPEPhos/CuCl	MeOH	46%	17%	0%
7	IPrCuCl	EtOH	81%	1%	0%
8	IPrCuCl	iPrOH	10%	66%	0%
9	IPrCuCl	tBuOH	41%	5%	0%
10	IPr(ace)CuCl	EtOH	16%	52%	0%
11	IPr(ace)CuCl	tBuOH	65%	3%	0%
12	IPrCuCl*	MeOH	16%	37%	0%
13	IPr(ace)CuCl*	MeOH	22%	38%	2%
14	dppf/CuCl	MeOH	9%	11%	3%
15	dCype/CuCl	MeOH	55%	0%	16%
16	ICyCuCl	MeOH	17%	77%	0%

*the order of addition was switched from imine then disilane to disilane then imine

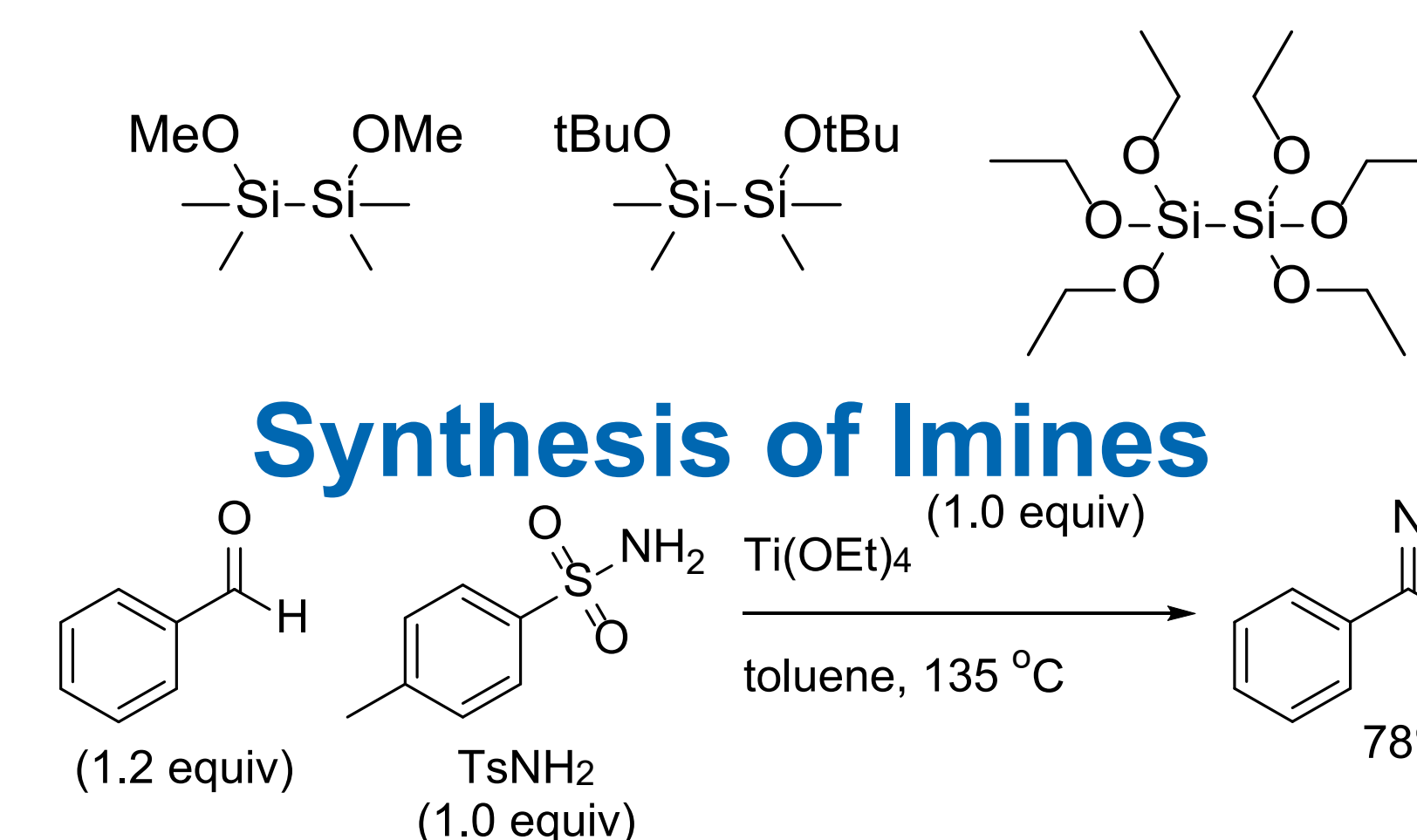


Different Disilanes

Reactions ran using hexamethoxydisilane resulted in poor yields. We decided to try using different disilanes in hopes of increasing the yield. We used 1,2-dimethoxytetramethyldisilane, ditertbutoxytetramethyldisilane, and hexaethoxydisilane.



entry	catalyst	disilane	SM	reduction	yield
1	IPrCuCl	Me ₂ MeOSi-SiOMeMe ₂	68%	0%	20%
2	IPrCuCl	Me ₂ tBuOSi-SiOtBuMe ₂	44%	0%	16%
3	IPrCuCl	(EtO) ₃ Si-Si(OEt) ₃	67%	0%	11%
4	IPr(ace)CuCl	Me ₂ MeOSi-SiOMeMe ₂	58%	0%	17%
5	IPr(ace)CuCl	Me ₂ tBuOSi-SiOtBuMe ₂	56%	0%	18%
6	IPr(ace)CuCl	(EtO) ₃ Si-Si(OEt) ₃	83%	0%	19%



The amide was difficult to remove from the reaction mixture, so an excess of the aldehyde was used to ensure that all of the amide was consumed. Attack of the copper silyl species required an electron deficient imine, however, this means that the imine is subject to rapid hydrolysis and could not be exposed to water.

Future Directions

We will continue optimizing the reaction conditions to improve the yield of the α -silyl amine by changing the ligand and the identity of the disilane. Once optimization is complete, the substrate scope will be explored using a variety of different imines. The mechanism of silylation will also be explored.

Conclusions

We have found that copper catalyzed addition to imines with disilanes is not as straight-forward as initially envisioned. This is likely due the formation of a copper hydride that reduces the imine, which results in an amine without silane incorporation. It seems that other disilanes and ligand choice can control the distribution of reduction and silylation. Future work will focus on using different ligands and disilanes to promote the silylation product.

Acknowledgements

We would like to thank Prof. Rick Fitch for many helpful conversations and 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

References

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2. (a) Hensel, A.; Nagura, K.; Delvos, L. B.; Oestreich, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 4964-4967. (b) Chen, Z.; Huo, Y.; An, P.; Wang, X.; Song, C.; Ma, Y. *Org. Chem. Front* **2016**, *3*, 1725. (c) Vyas, D. J.; Fröhlich, R.; Oestreich, M. *Org. Lett.* **2011**, *13*, 2094-2097.