

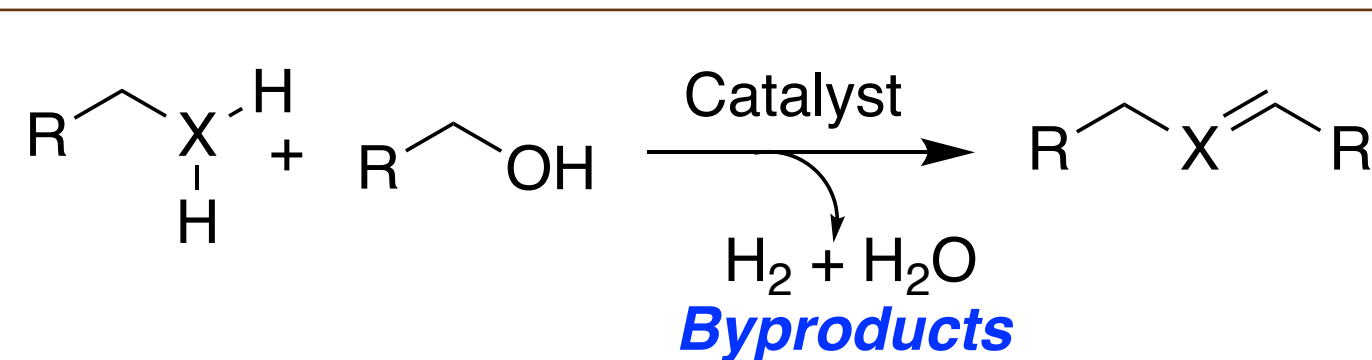
# Novel catalyst for cost-effective and green acceptor-less dehydrogenation



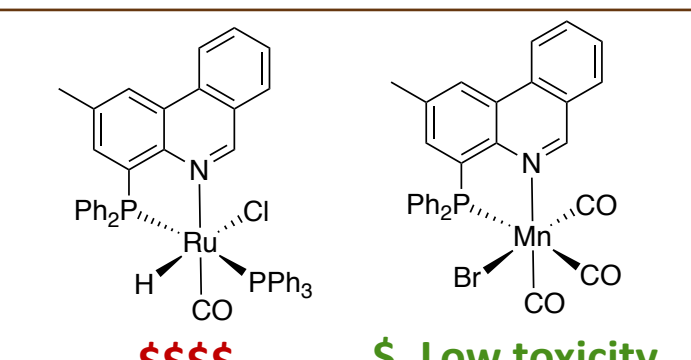
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## Introduction

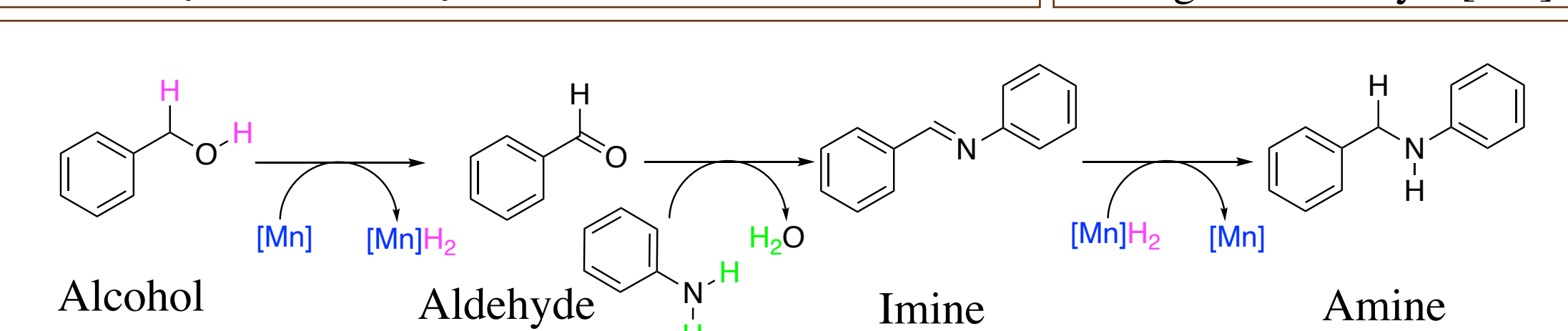
- Catalyst** A chemical reaction has an associated activation energy, the minimum amount of energy reactant molecules must possess for conversion into products. A catalyst lowers this activation energy by providing an alternate pathway or mechanism for the reaction to proceed, allowing faster reaction times and higher product yields!
- Acceptor-less dehydrogenation (ADH)** (Figure 1) is the reaction motif whereby a reactant is **dehydrogenated** (i.e.: **hydrogen atoms removed**) to produce an intermediate (aldehyde) that further reacts to form product, **without** the need for an “acceptor” molecule for the removed hydrogen atoms. Reactions that require a hydrogen acceptor produce potentially toxic and environmentally harmful waste; hence, ADH is a highly sought-after method for synthesis. [1]
- Cost-effective.** Several ruthenium (Ru)-based catalysts can mediate acceptor less dehydrogenation reactions, but the low earth abundance of Ru makes them quite expensive. [1] There is interest in finding earth abundant replacements for the Ru atom, such as the novel Mn catalyst explored in this study (Figure 2).
- Green:** The mechanism (Figure 3) allows the use of alcohols instead of aldehydes as starting materials, which is favored because the synthesis of aldehydes is relatively expensive and harmful to the environment. The necessary aldehyde is generated *in situ* (i.e.: in the reaction mixture) and consumed in the next step, providing a greener mechanism for the reaction. [2]
- Objective:** optimizing ADH reaction & applying it to various substrates to gauge generalizability.



**Figure 1.** General scheme of acceptor-less dehydrogenation. Note that no hydrogen acceptors are required, resulting in an improved atom efficiency and economy.



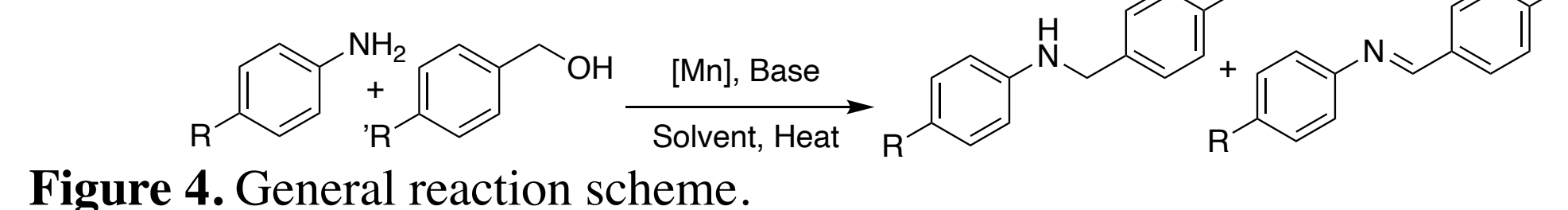
**Figure 2.** Comparison of ruthenium catalyst [Ru] vs. manganese catalyst [Mn].



**Figure 3.** Mechanism of acceptor-less dehydrogenation (ADH).

## Procedure

### Reaction



**Figure 4.** General reaction scheme.

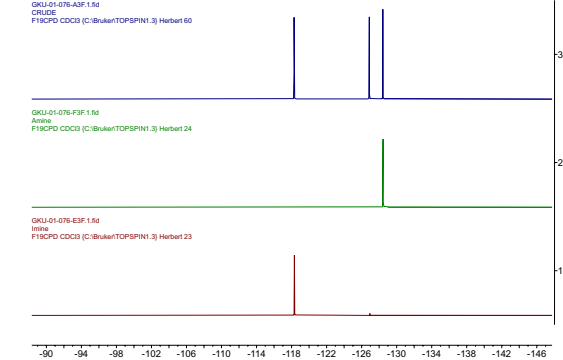
### Purification of product

Remove base by vacuum filtration  
Remove solvent by rotary evaporation

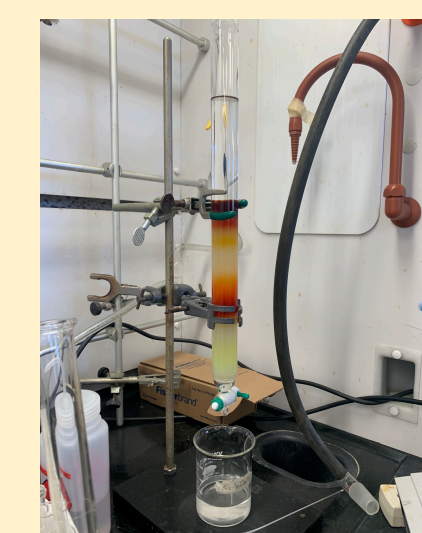
Thin layer chromatography (TLC) & crude NMR to determine product formation

Column chromatography to isolate final product(s). Mixture components separated based on the relative polarity as they pass down the silica column.

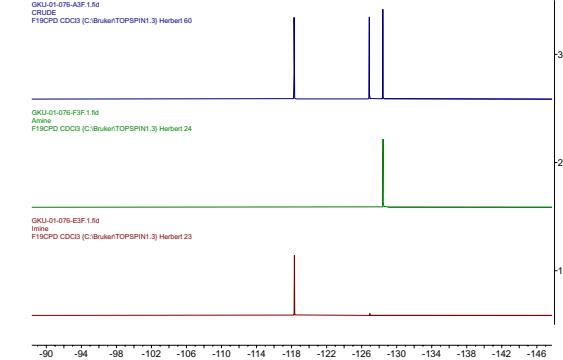
Nuclear magnetic resonance (NMR) to confirm product purity



**Figure 5.** TLC: left two lanes for starting materials, then reaction mixture & known product.



**Figure 6.** Column chromatography (CC) of a reaction mixture to isolate pure product.



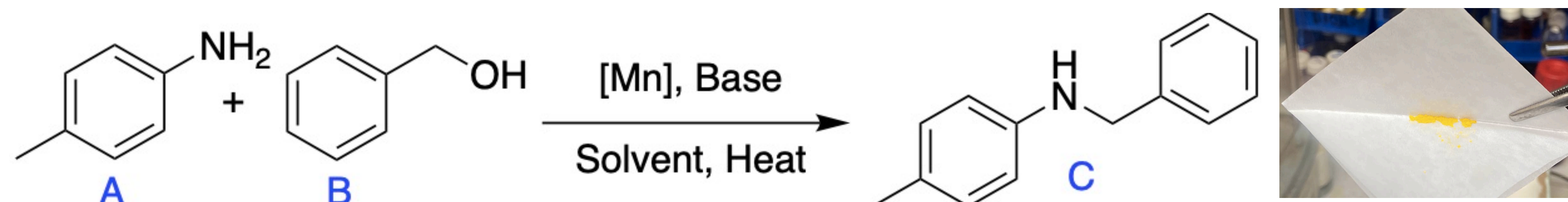
**Figure 7.** Fluorine NMR of 2k (left). The crude mixture (top) shows 3 signals, representing the starting material, amine and imine products. The lower two panels show the purified amine and imine (one signal each) after CC.

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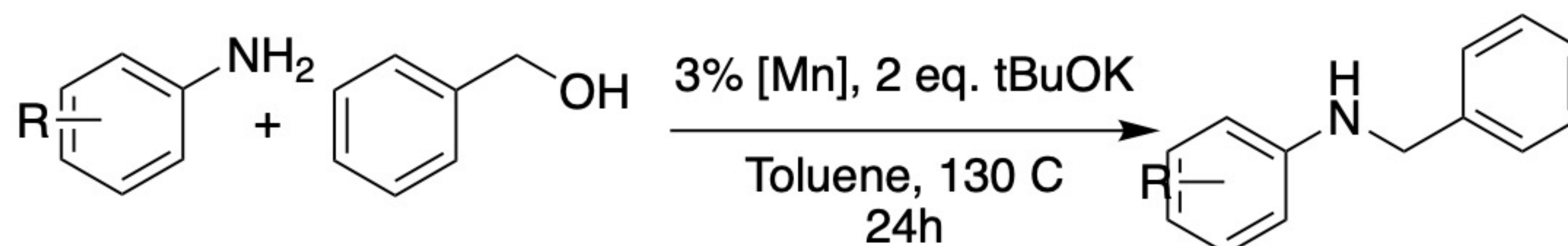
## Results and Discussion



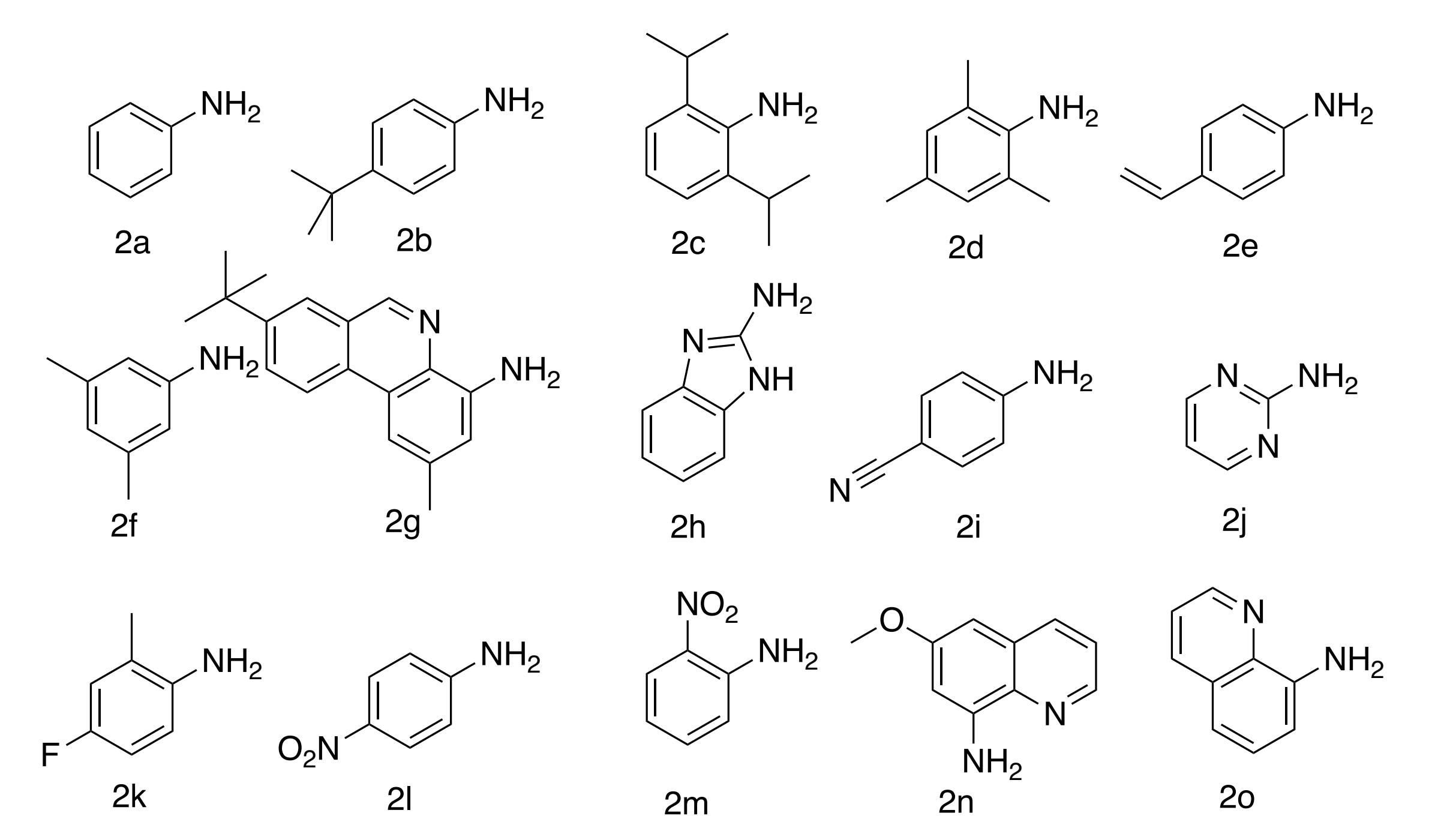
**Figure 8.** [Left] Scheme for [Mn] optimization runs. As detailed in Table 1, the above reaction was conducted under different conditions by varying base and solvent identity, stoichiometric ratios of A, B and [Mn], reaction temperature, and state of the system – open vs. closed. All reactions were conducted under inert conditions (Argon or nitrogen) to overcome the limitation of catalyst instability in the air. [Right] Mn catalyst.

**Table 1.** Conditions and percent yields for various runs. Run #4 conditions chosen were optimal for subsequent substrate reactions. Although Run 6 provides slightly higher yield, the increases is not sufficiently high to justify running the reaction for twice as long.

Run	System	A:B	Base	Base Eq.	[Mn] (mol %)	Solvent	Time (hours)	Temp. (°C)	Isolated Yield (C)
1	Closed	1:1.3	KOH	2	3	THF	24	80	0%
2	Closed	1:1.3	KOH	2	3	Toluene	24	130	0%
3	Open	1:1.3	tBuONa	2	3	Toluene	24	130	0%
4	Open	1:1.3	tBuOK	2	3	Toluene	24	130	49.1%
5	Closed	1:1.3	tBuOK	2	3	Toluene	24	130	14.3%
6	Open	1:1.3	tBuOK	2	3	Toluene	48	130	52.4%
7	Open	1:1.3	tBuOK	2	1	Toluene	24	130	31.6%
8	Open	1:1.3	tBuOK	2	5	Toluene	24	130	24.5%
9	Open	2:1	tBuOK	2	3	Toluene	24	130	15.7% (+ 11.3 % imine)
10	Open	1:2	tBuOK	2	3	Toluene	24	130	31.3%



**Figure 9.** Optimized conditions from Table 1. These conditions were used to conduct the substrate scope reactions reported in Table 2.



**Figure 10.** Substrate scope. The amine (NH<sub>2</sub>) substrates above were used as starting materials and reacted with benzyl alcohol as shown in Figure 9 above. The associated yields of the products are reported in Table 2. Similar reaction substrate scope was also compiled for various substituted benzyl alcohols, reacted with aniline (2a).

	Amine Isolated Yield	Imine Isolated Yield
2a	31%	0%
2b	36%	0%
2c	0%	0%
2d	0%	2.3%
2e	22%	11%
2f	21.8%	15.5%
2g	33%	0%
2h	0%	0%
2i	0%	0%
2j	0%	0%
2k	21.6%	20.9%
2l	0%	14%
2m	0%	10%
2n	33.4%	0%
2o	0%	38%

**Table 2.** Percent yield for amine substrates in Figure 10. Occasionally the imine intermediate (see Figure 3) was isolated.

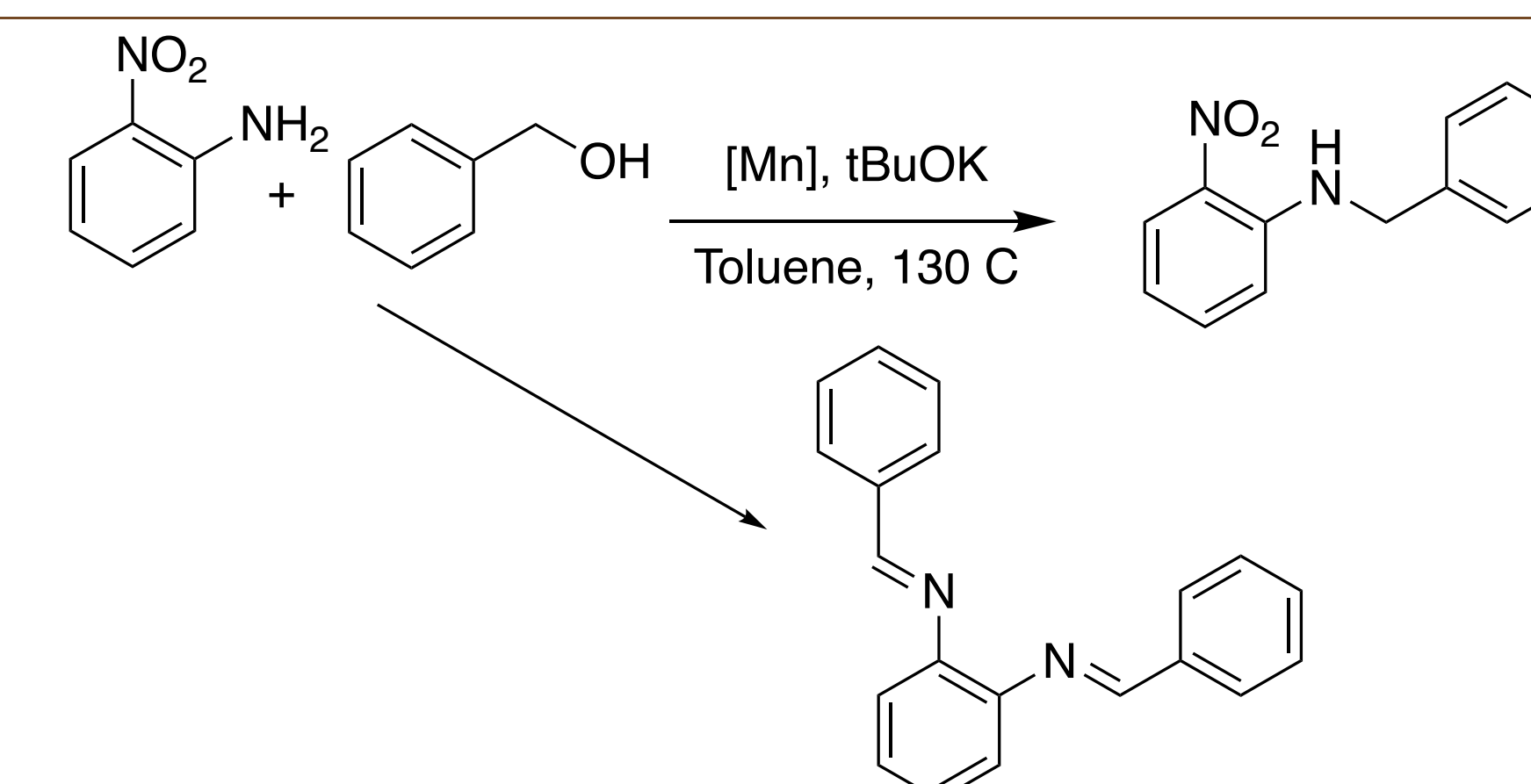


## Discussion

- Optimized product yield was around 50%. Even the optimized procedure, when applied to substituted amines, provided lower yields that varied from 10 to 40%. The varied yields can be explained by the amines' steric and electronic structure.
- Sterics.** The negligible yields of reactions of 2c and 2d are explained based on the steric restraints imposed by the bulky groups of the 2 and 6 position of the aniline (the positions adjacent to the amine group) which prevent nucleophilic attack by the amine to aldehyde formed *in situ* as shown in Figure 3.
- Electronics.** Lower yields of aniline (2a) reaction versus toluidine (A) reaction is explained by the electronic induction that enhances nucleophilicity of the amine in toluidine because of the electron-donating methyl group.
- Amine, imine or both products were isolated from the reactions, which is consistent with the ADH mechanism (Figure 3), which involves formation of an imine intermediate which is then hydrogenated to form the amine.

## Conclusions

- The isolation of the imine product shows that in some runs, the hydrogenation did not occur as efficiently and both imine and amine products were obtained. Factors affecting the efficiency of hydrogenation are being explored further.
- Some reaction runs yielded surprising products, such as the scenario shown in Figure 11. When 2-nitroaniline was reacted with benzyl alcohol, instead of the expected product, a trimer-like structure was obtained. This is because the nitro group of the starting material was reduced to an amino group, yielding a molecule with 2 amino groups which then reacted with 2 equivalents of benzyl alcohol to yield the product shown below.



**Figure 11.** The unexpected product from the 2-nitroaniline + benzyl alcohol reaction. Its identity was determined based on HRMS (high resolution mass spectroscopy) data which measures the exact mass of a molecule.

## Future Directions

- Substituted benzyl alcohol starting material.** The reaction will be performed by varying the substituents (R groups) on the benzyl alcohol reactant shown in Figure 9. Current trials are underway which involve reacting such substituted benzyl alcohols with aniline, with successful product formation with yields of above 30.
- Investigating utility of new product in Figure 11.** This product can be a useful ligand for organometallic compounds, so refining this synthesis to obtain better yields and selectivity would provide a new avenue for synthesis using [Mn]. This will be explored by varying substituents to produce ligands known to be utilized in organometallic compounds.
- Further optimization runs to obtain greater selectivity for imine product over the amine to determine variables impacting selectivity.

## Acknowledgements & References

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- Mondal, R.; Lozada, I. B.; Stotska, O.; Herbert, D. E. Catalytic Synthesis of Luminescent Pyrimidines via Acceptor-Less Dehydrogenative Coupling. *J. Org. Chem.* **2020**, *85* (21), 13747–13756.