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Trifluoromethylation of Model Aryl Halides (toward bistrifluoromethylquinazolinespirohexadienone)

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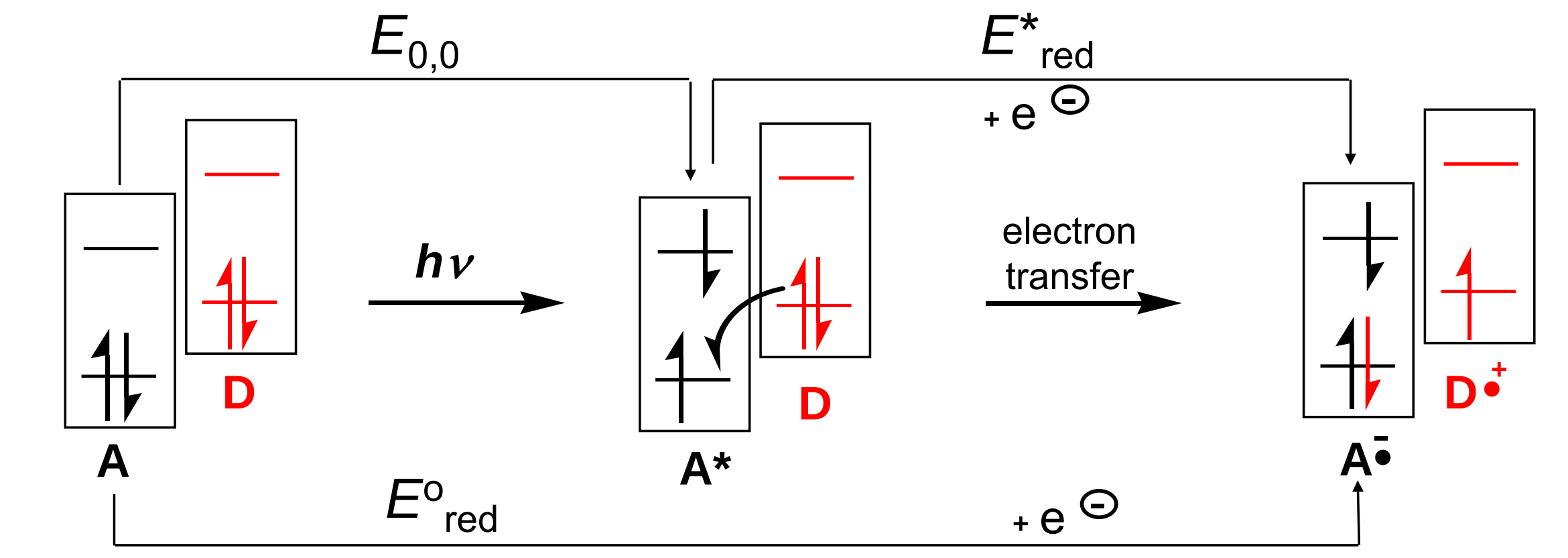
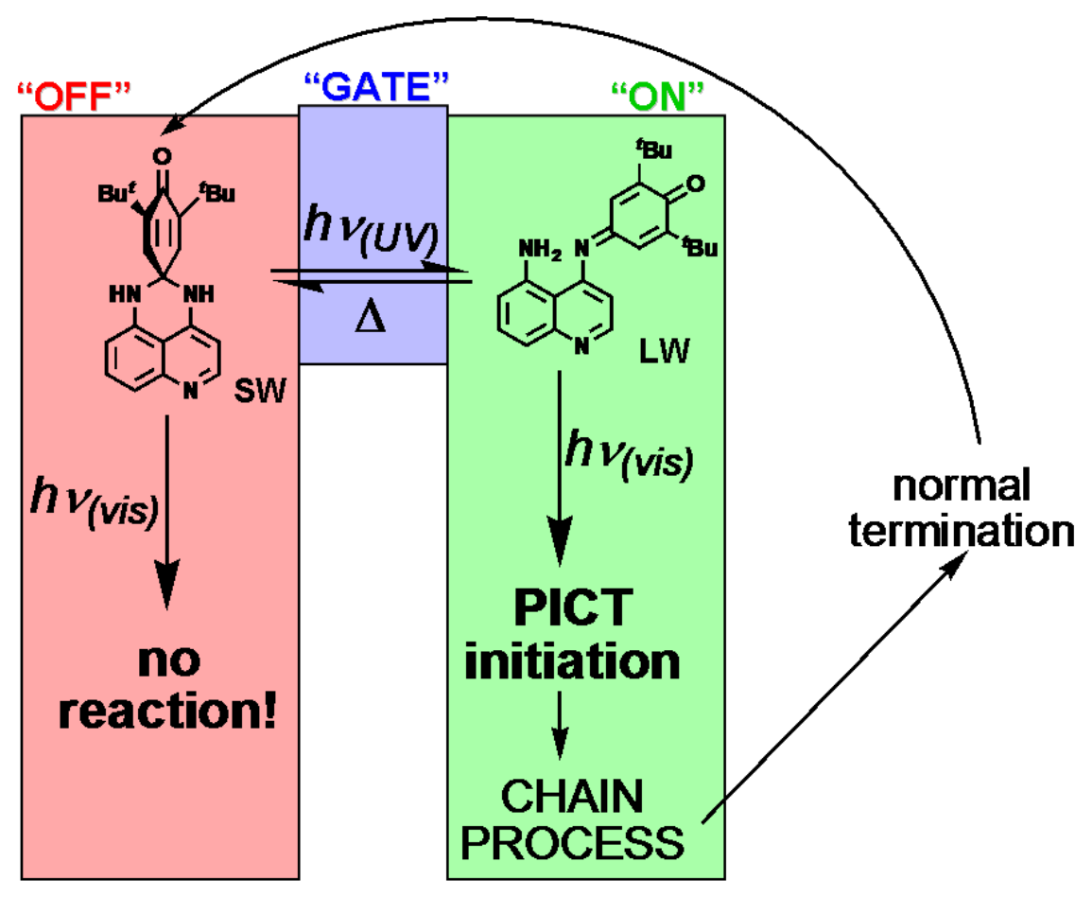
Photoinduced Charge Transfer (PICT)



- In the presence of light, an electron in a photooxidant (acceptor, **A**) is promoted from the HOMO to the LUMO.
- Creates a "hole" in the former HOMO that can be filled by an electron from a donor molecule (**D**) that you want to oxidize.
- Excited state reduction potential (E^*_{red}) is a measure of how good this "hole" is at accepting an electron from a donor.
- Cannot directly measure E^*_{red} but can calculate from ground state reduction potential (E^o_{red}) and excitation energy ($E_{0,0}$).

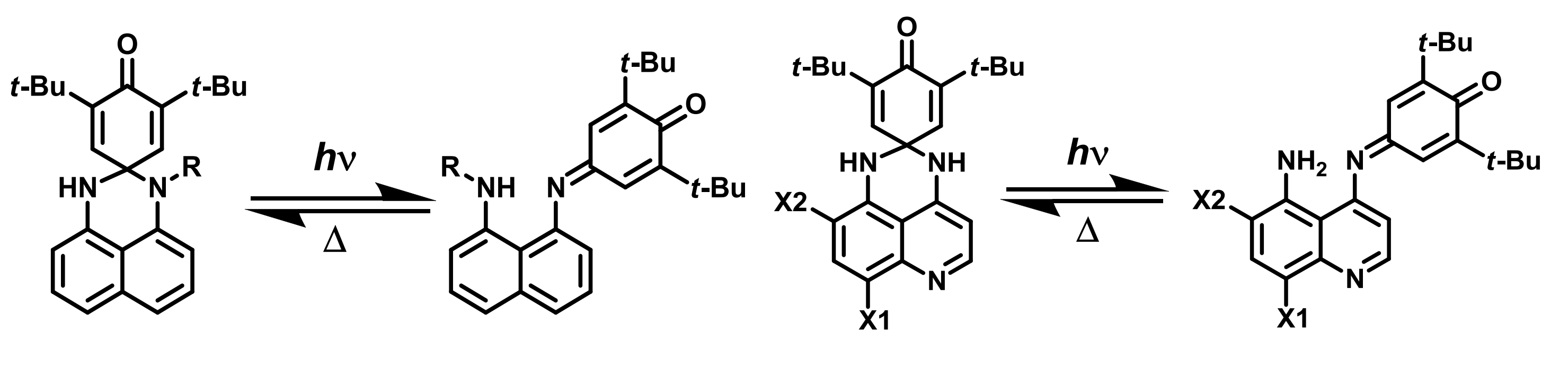
Photoinduced Charge Transfer (PICT)



- Photochromes can be used to gate PICT when:
  - Photochrome in short-wavelength (SW) form does not initiate PICT
  - Irradiation with UV light causes isomerization to long-wavelength (LW) form
  - LW form initiates PICT
- Requires a photochrome with:
  - Large gap between E^*_{red}(SW) and E^*_{red}(LW) to allow gating
  - Large positive E^*_{red}(LW) to allow initiation of PICT
  - Thermal (not photochemical) fade from LW to SW

Computed E^o_{red} (vs. SCE in CH_3CN)

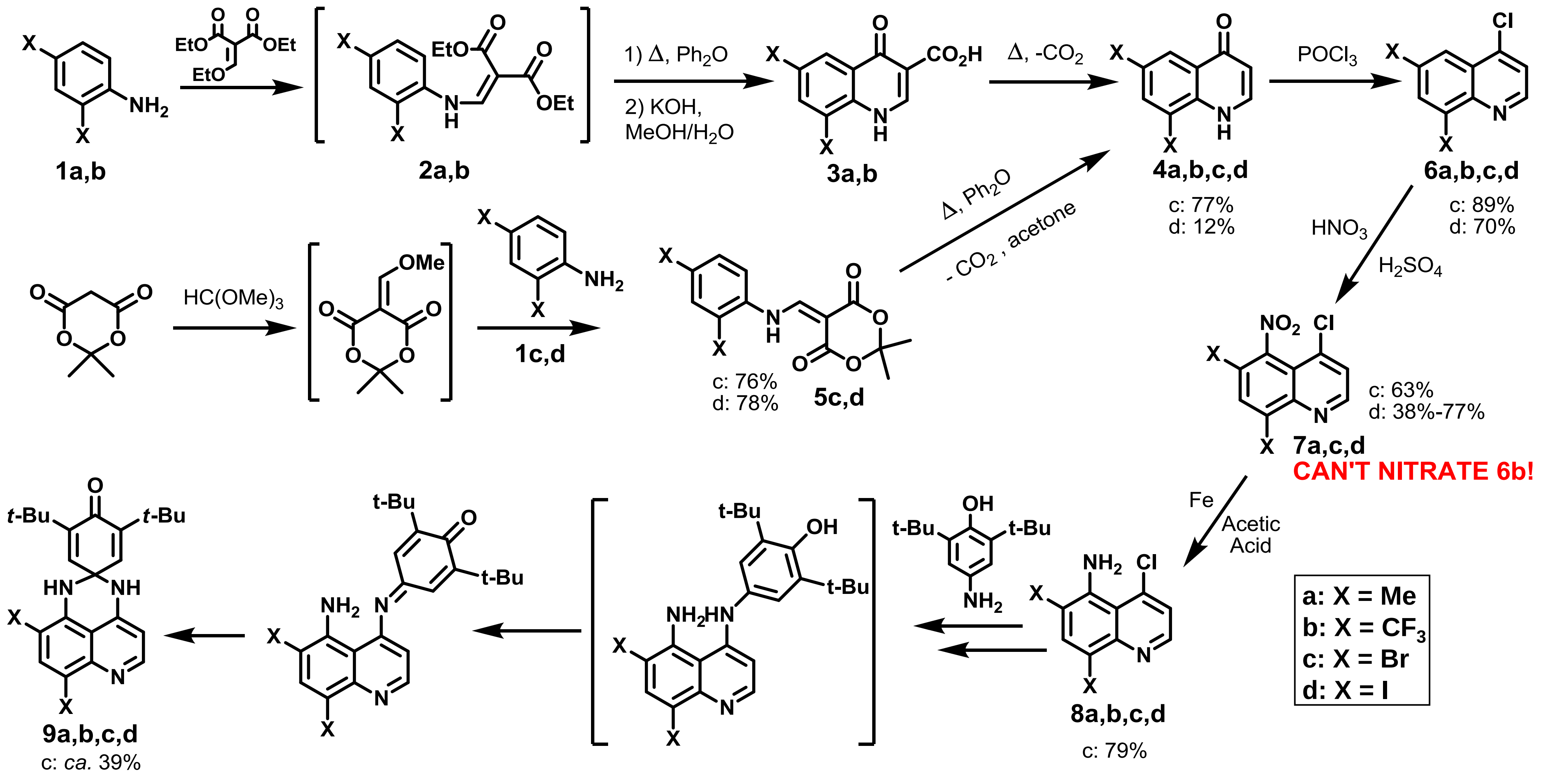
PSHDs (Perimidinespirohexadienones)[1] **QSHDs (Quinazolinespirohexadienones)[2]**



SW		LW
-1.698 V	R=H	-0.897 V
-1.665 ± 0.020 V		-0.860 ± 0.028 V
-1.560 V	R=Me	-0.886 V
- 1.610 ± 0.013 V		-0.840 ± 0.028 V
-1.626 V	X1=Me, X2=H	-0.721 V
-1.618 ± 0.009 V		-0.723 ± 0.018 V
-1.612 V	X1=X2=Me	-0.724 V
-1.611 ± 0.043 V		-0.733 ± 0.007 V
-1.432 V	$X1=X2=CF_3$	-0.502 V

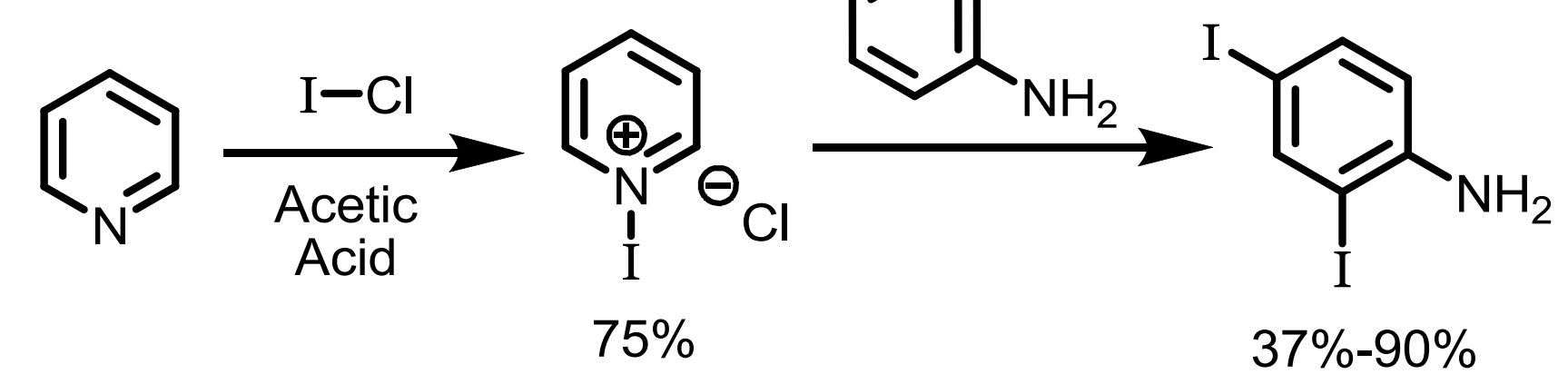
- Using our published method,[3] we can accurately and efficiently **predict E^o_{red}** for new targets with good agreement to experimental potentials (vs. SCE in acetonitrile with Bu_4NPF_6) for compounds we have in hand.
- Replacing X1 and X2 with electron withdrawing groups (EWG) in the QSHD creates a much more positive E^o_{red} in the LW form (making it more reducible, and a stronger photooxidant from its excited state), while preserving the difference in E^o_{red} between SW and LW necessary for gating.
- We are currently attempting synthesis of $X=CF_3$, but it is complicated due to the inability to nitrate intermediate while $X=CF_3$

Synthetic Route



- **9a** has previously been prepared and studied in our group.[2]
- This route cannot be used for **9b**, as nitration of **6b** fails!
- A group member has found a reported synthesis of **4c,d**[4] that works better from **1c,d** than the method for **4a,b**[2] and is one step shorter!
- **1d** is not commercially available but readily prepared by a literature route.[5]
- I am working to find a route to prepare **9b** by trifluoromethylating **7c,d** or **8c,d** or similar analogs by introducing CF_3 after the problematic nitration of **6c,d.**

1d not commercially available:

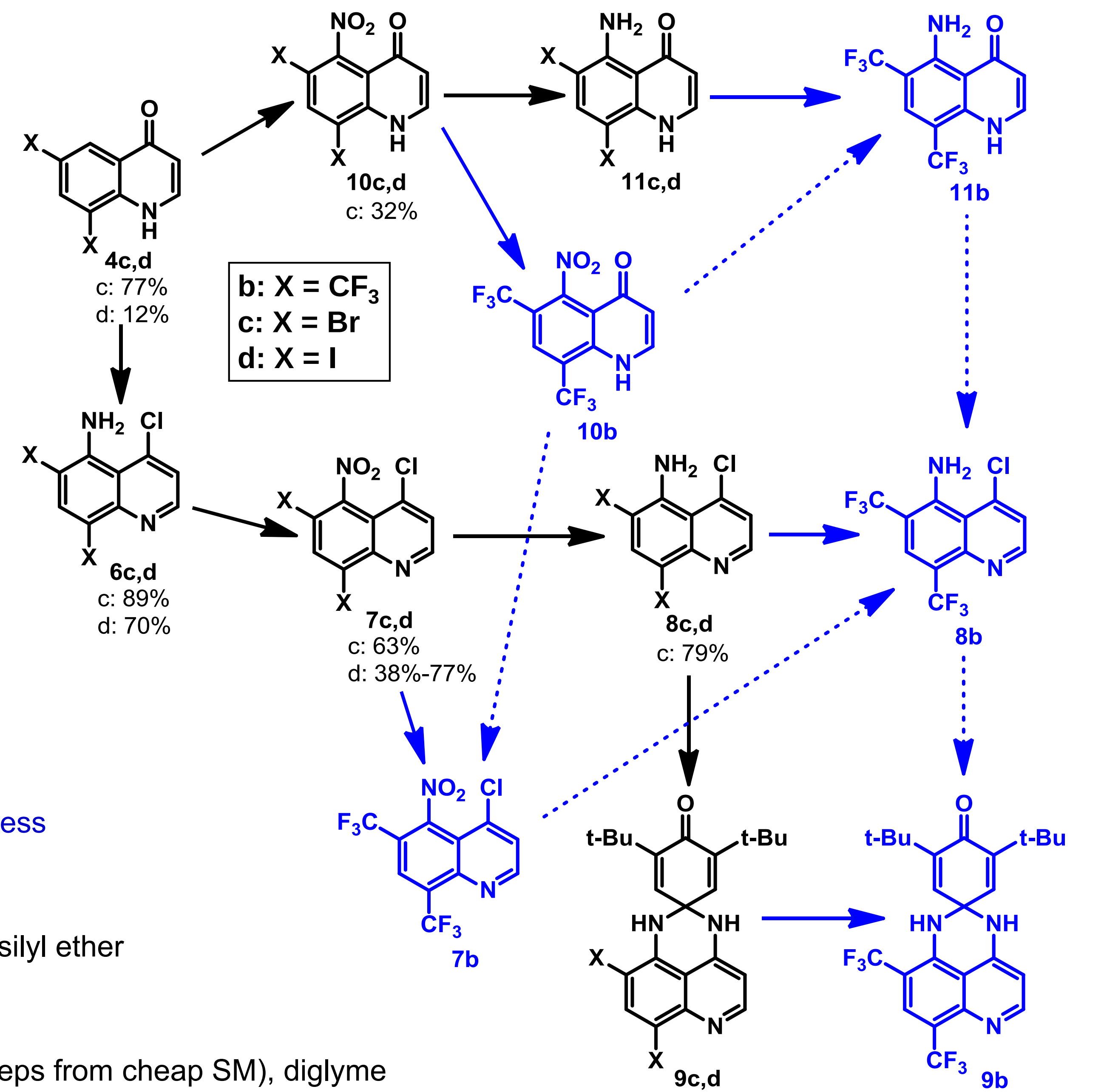


Installation of Trifluoromethyl Groups

There are <u>many</u> ways to trifluoromethylate, but none yet proven completely general. There are various catalysts, ligands, and CF_3 sources (many are expensive, and not necessarily commercially available), as well as a range of substrates (ArCl, ArBr, ArI, boronic acid/esters, etc.).

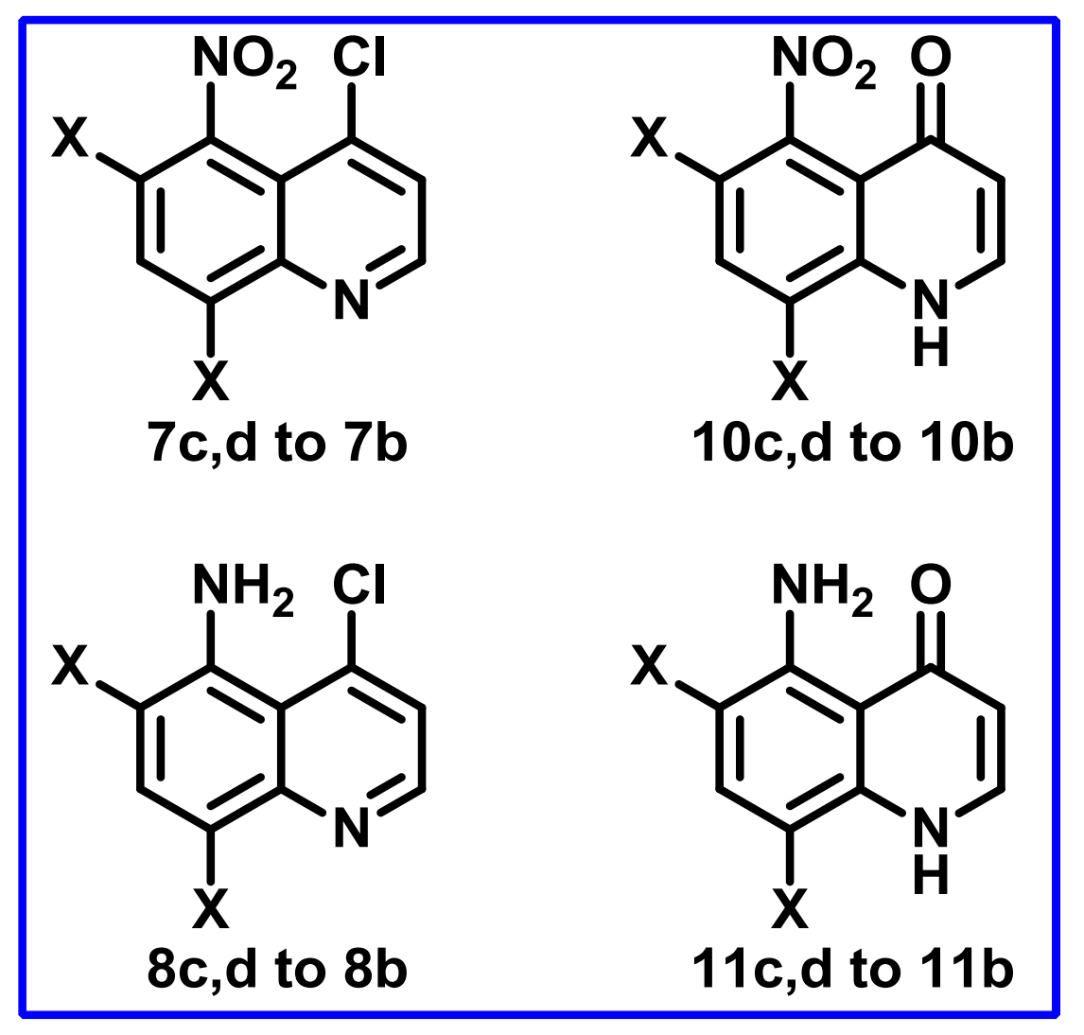
- We prefer aryl halides if possible, due to our work to date.
- Attempted trifluoromethylations thus far:
  - Chen & Buchwald[6]
    - stoichiometric flow process, broader scope, many ArI, some ArBr (private communication)
    - CuI, CF_3CO_2K, NMP (inexpensive!)
    - attempted by Chen & Buchwald on our compounds (**7c**,**d**) without success – *o*-nitro problematic (proven by model compounds); free amine also likely problematic
  - Odom[7]
    - stoichiometric batch process, limited scope described in lit
    - but ArBr substrates definitely feasible
    - CuI, CF_3CO_2K, NMP (similar conditions for cyanation too)
    - Attempted on **7c** and **10c**, both of which were unsuccessful
- Other trifluoromethylations to try:
  - Hartwig[8]
    - stoichiometric [(phen)$CuCF_3$] from CuO*t*-Bu tetramer, batch process
    - **our current method of choice!**
  - Amii[9]
    - CF_3 transfer from trifluoroacetaldehyde morpholine heminaminal silyl ether
    - <u>catalytic</u> batch process, compatible with *o*-NO_2
    - works for ArI, not ArCl (ArBr?)
    - CuI (cat), phen (cat), CsF (2 eq), 2 eq CF_3 reagent (make in 2 steps from cheap SM), diglyme
    - considered comparable to, more difficult than Hartwig[8], but catalytic! (Future option to explore?)

Trifluoromethylation Options in our Synthetic Scheme

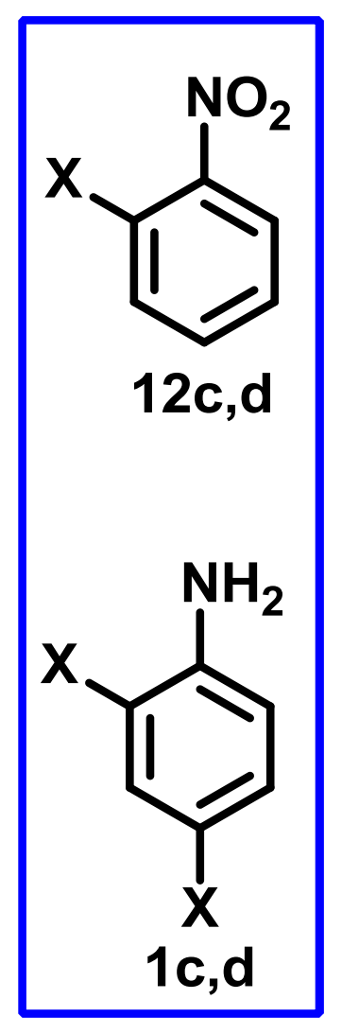


Trifluoromethylation of Model Compounds

Goals



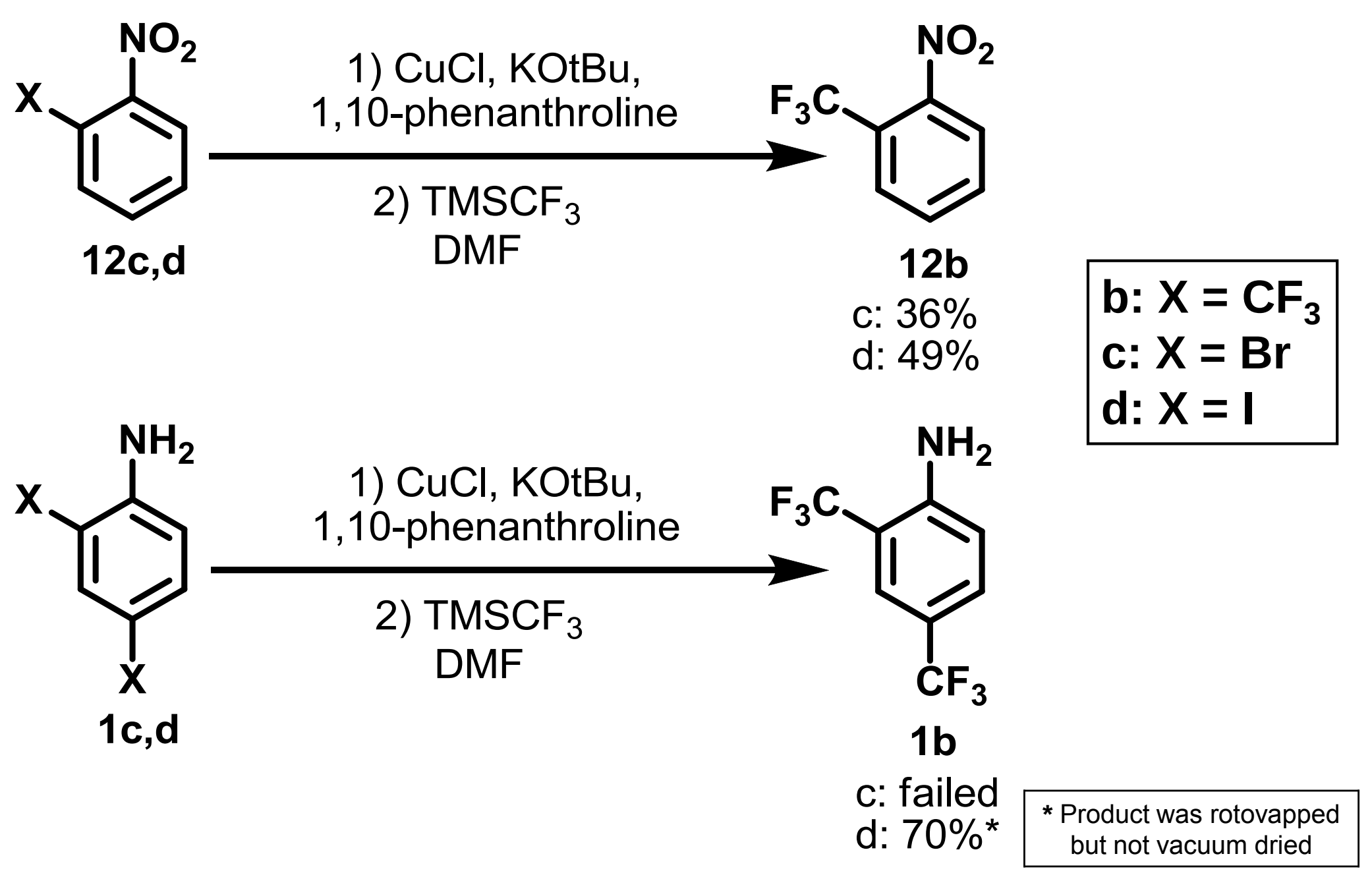
Models



- Ideas from our syntheses to date:
  - We have a precedent method for the conversion of **4a** to **10a** to **11a** with (**a**: X1=X2=Me) and we have successfully converted **4c** to **10c**.
  - There is currently not a precedent for the conversion of **11** to **8** or **10** to **7**. While the transformations seem reasonable, we have not attempted them yet.
  - Thus if possible we would prefer to trifluoromethylate at **7** or **8** (or **9**) rather than at **10** or **11**.
  - Due to ease of synthesis, we would prefer to move forward with compounds **c** (X=Br) rather than **d** (X=I), if possible.

Model Compounds to address Halogen choice and Nitro v. Amino:

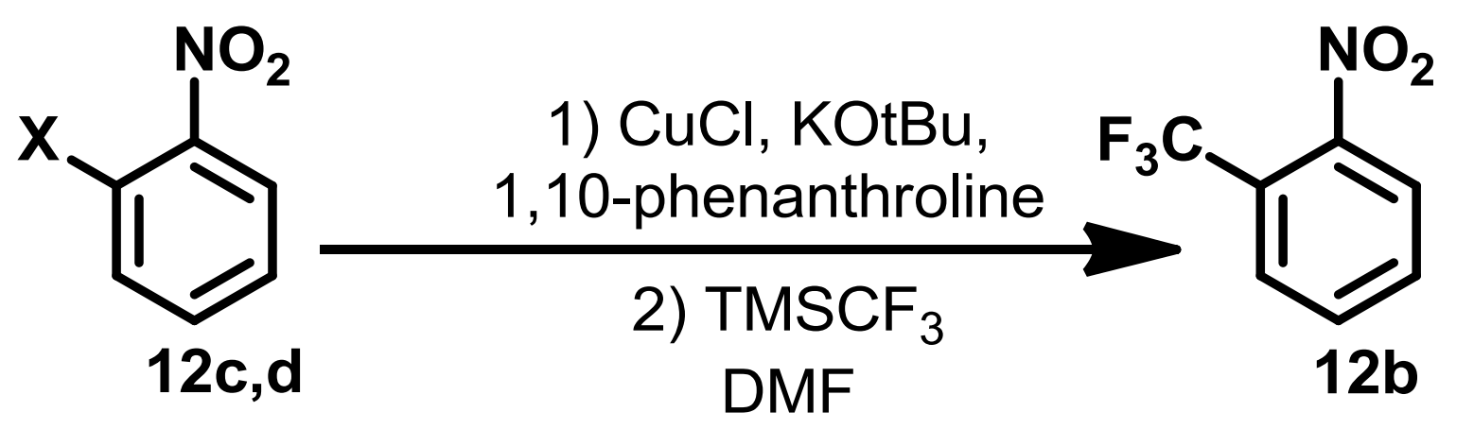
- Actual yields were determined by $\frac{\text{EXPERIMENTAL}}{\text{THEORETICAL}} \times$ GC Purity.
- **12c,d** and **1c** are all commercially available and relatively inexpensive.
- **1d** is not commercially available but easily prepared.[5]

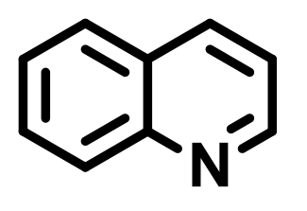
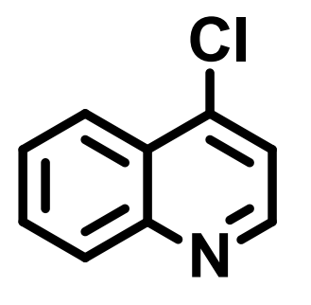
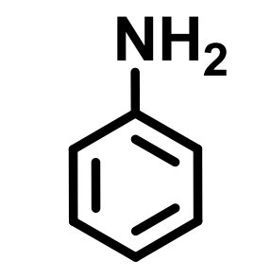


- The model compounds **12c,d** and **1d** can all be trifluoromethylated fairly cleanly, in reasonable yields and purity, as assessed by GC/MS, by our optimized version of Hartwig's method.[7]
- Unable to convert **1c** to **1b** under same conditions – mostly recovered 1c, but did find several other peaks including some mono-trifluoromethylated intermediate but no bis-trifluoromethylated product was observed.
- The reactions of **12c,d** commonly yielded minor amounts of homo-coupled 2,2'-dinitrobiphenyl.

Model Studies to address Complications in the Real System:

- Will quinoline interfere with the reaction (*e.g.*, displacing phenanthroline ligand)?
  - We determined that it does not interfere with trifluoromethylation of **12c,d.**
  - Still need to test with **1d**.
- Will the less active halogen (Cl) on the more reactive ring (quinoline) also be replaced?
  - We determined that it will not reactive competitively with either **12c,d**.
  - Still need to test with **1d**.
- Is trifluoromethylation of the amino intermediate inherently impossible?
  - No. We successfully trifluoromethylated **1d** to **1b**.
  - No. Added aniline does not inhibit trifluoromethylation of **12c,d** to **12b**.



with no additive		c: 36% d: 49%
with 1 equiv. quinoline		c: 69% d: 67%
with 1 equiv. 4-cholorquinoline		c: 58% d: 73%
with 1 equiv. aniline		c: 63% d: 27%

Future Work

- Model compound studies will be finished by running the interference reactions (quinoline and 4-chloroquinoline) with **1d**.
- Then attempt trifluoromethylation of the real systems starting with **7c** (then **7d** or **8d**, preferred, or **10c**, **10d**, **11d**, or **9d**, as needed.
- Complete the synthesis of **9b** and study its electrochemistry, photochemistry, and photophysics.

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