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Shanghai Institute of Organic Chemistry, CAS

KO*t*Bu: A single electron  
donor?

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June 21, 2016

**Introduction**

**Transition metal-free cross coupling reactions**

**Reductive fragmentation of dithianes**

**S<sub>RN</sub>1 reactions in DMF**

**Summary**

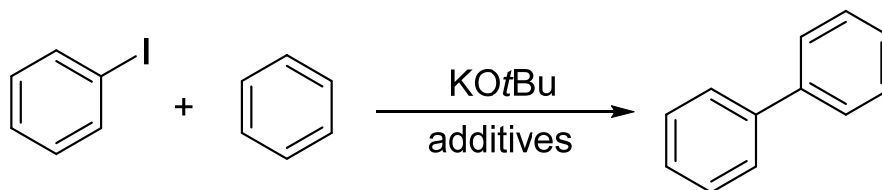
**References**



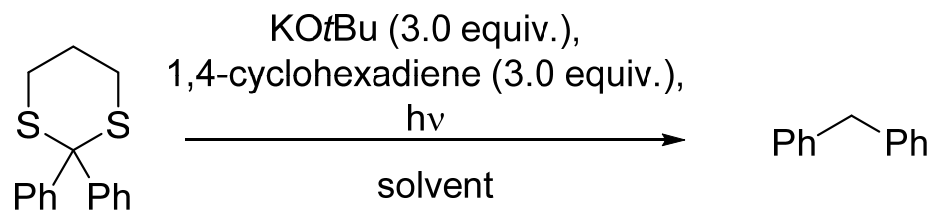
# Introduction

Alkali metal tert-butoxides ( $\text{KO}t\text{Bu}$ ,  $\text{NaO}t\text{Bu}$ ) play key roles in organic chemistry, acting as powerful bases. But recently, many studies have used  $\text{KO}t\text{Bu}$  in organic reactions that involve single electron transfer.

1) transition metal-free cross coupling reactions



2) reductive fragmentation of dithianes



3)  $\text{S}_{\text{RN}}1$  reactions in DMF

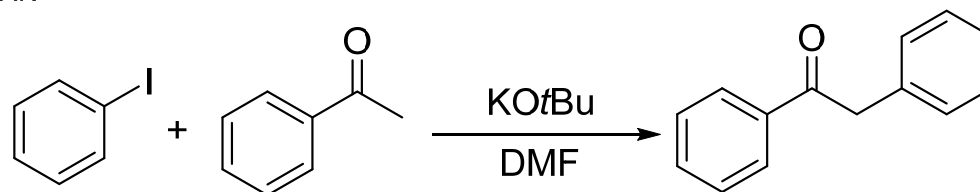
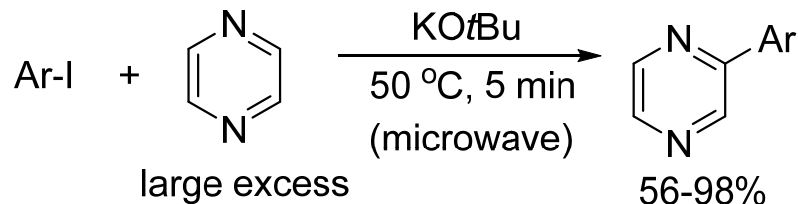


Figure 1.  $\text{KO}t\text{Bu}$  participated SET reactions

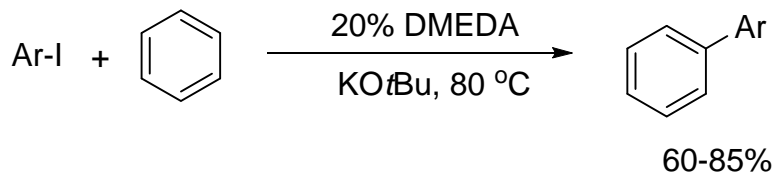
# Transition metal-free cross coupling reactions

KOtBu promoted biaryl coupling of electron deficient Nitrogen heterocycles and haloarenes

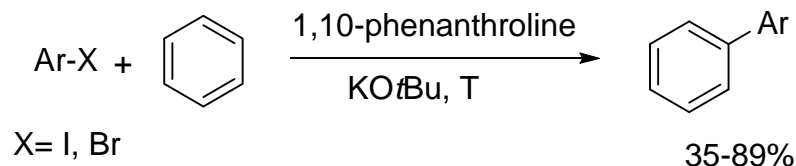


Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673.

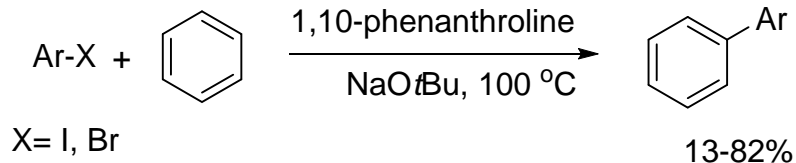
Lei, Kwong and coworkers:



Shi and coworkers:



Hayashi and coworkers:

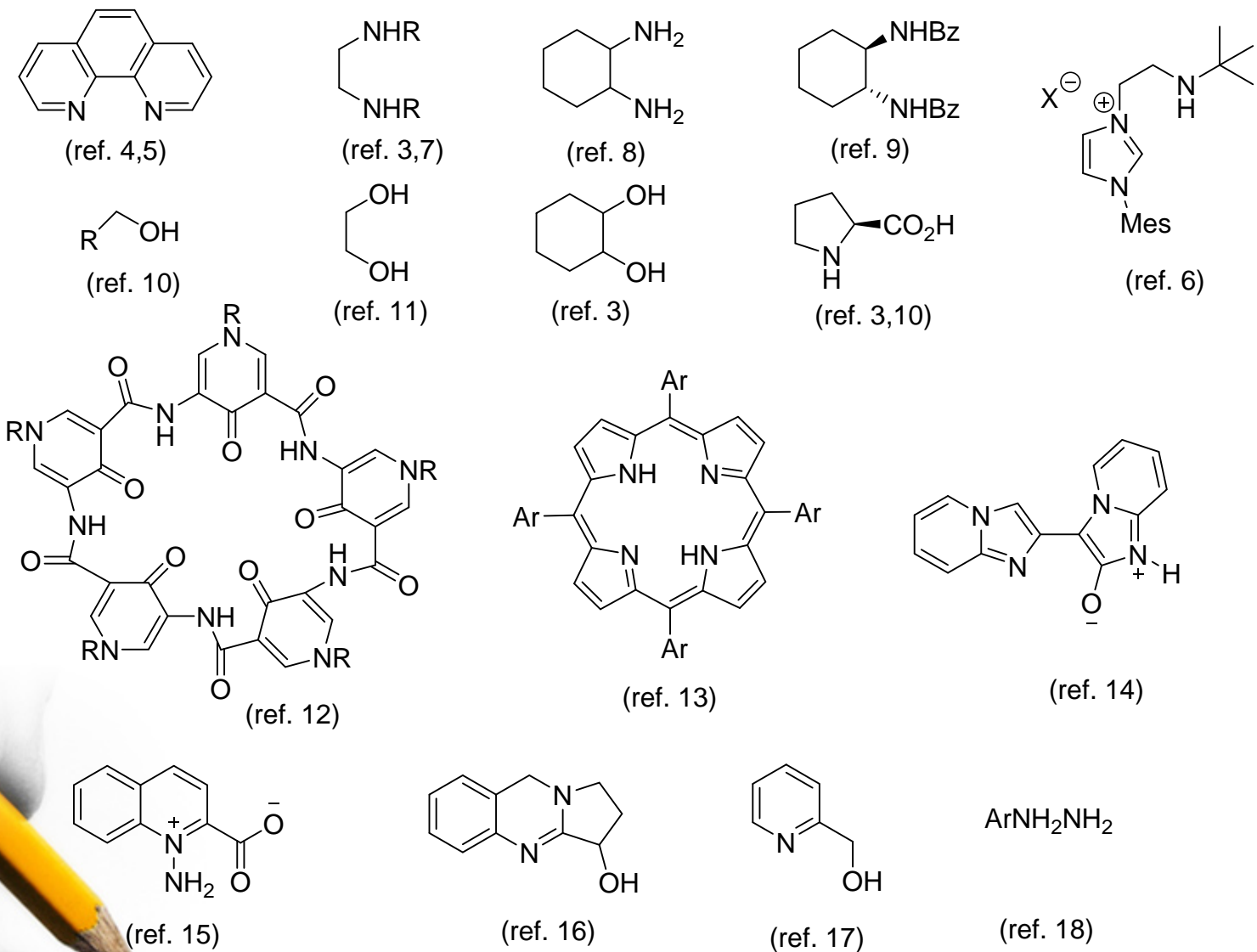


Lei, A. et.al. *J. Am. Chem. Soc.* **2010**, *132*, 16737.

Hayashi, T. et. al. *J. Am. Chem. Soc.* **2010**, *132*, 15537.

Shi, Z. J. et. al. *Nat. Chem.* **2010**, *2*, 1044.

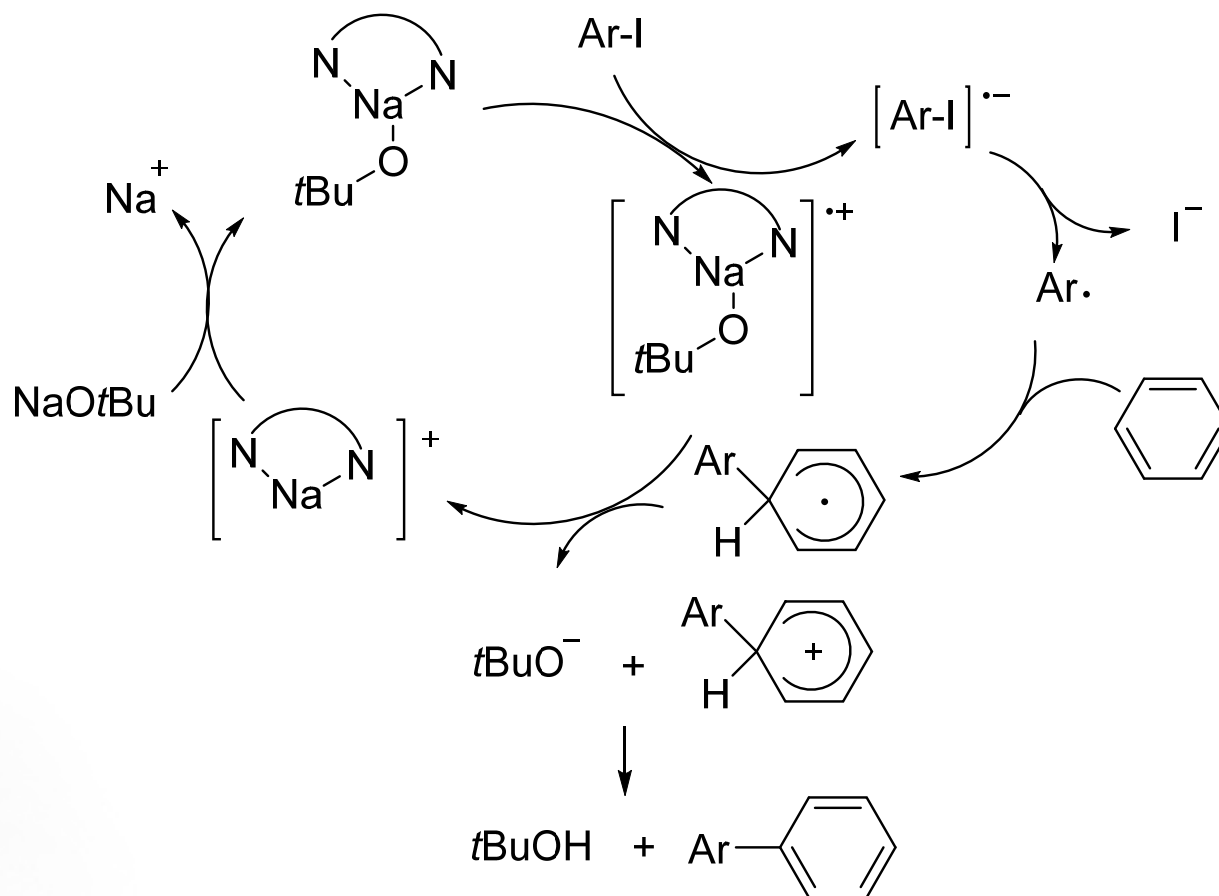
# Transition metal-free cross coupling reactions



**Figure 2. Selected ligand that facilitate coupling of haloarenes with arenes in the presence of KO<sup>t</sup>Bu**

# Transition metal-free cross coupling reactions

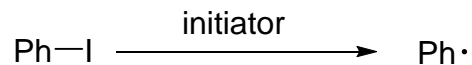
## Mechanistic insights:



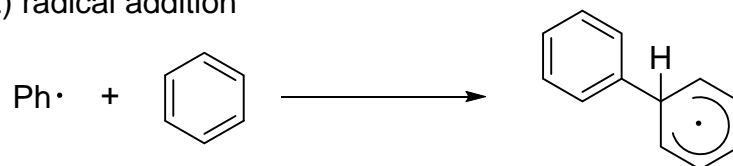
**Figure 3. Proposed mechanism of biaryl coupling by Hayashi**

# Transition metal-free cross coupling reactions

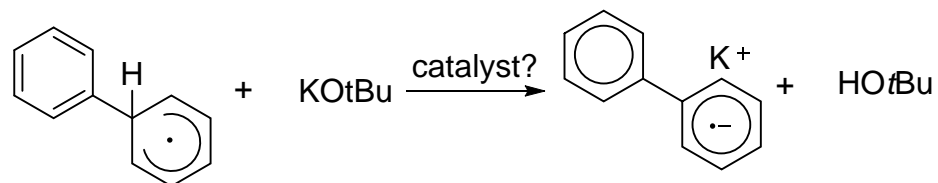
1) initiation



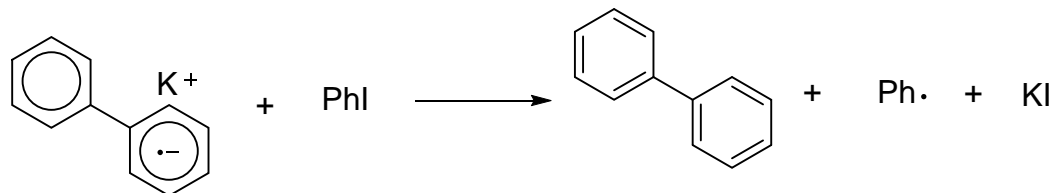
2) radical addition



3) deprotonation



4) dissociative electron transfer

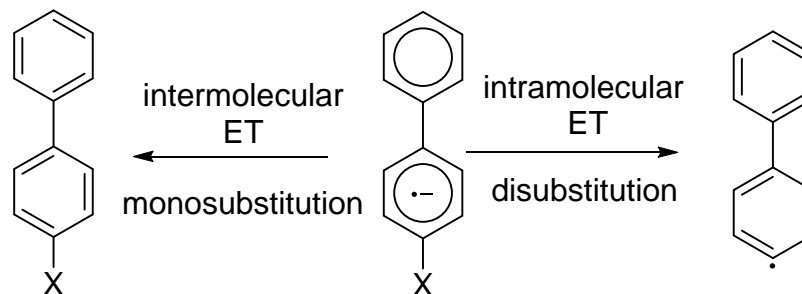
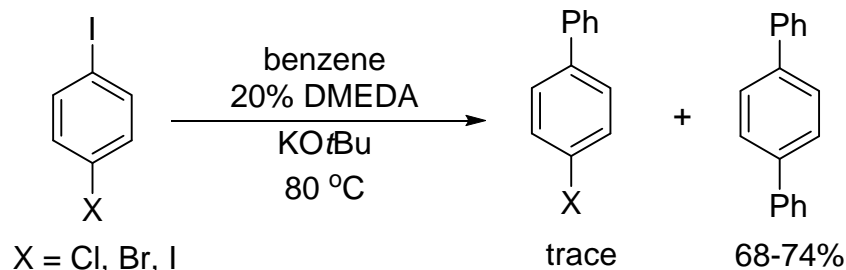


**Figure 4. Base-promoted homolytic aromatic substitution: A radical chain mechanism**

# Transition metal-free cross coupling reactions

Several evidences support the radical anion intermediate:

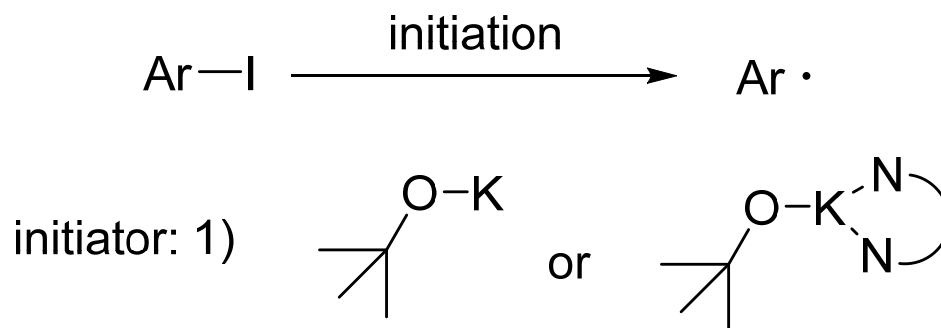
1. In all these reports, strong bases, usually KO<sup>t</sup>Bu was needed.
2. Ketyl and related radical anions readily transfer electrons to halides, including aryl halides.
3. Aromatic radical anions generated electrochemically had been show to reduce alkyl halides.
4. In Lei, Kwong and coworkers' work, when using Bunnett and Creary's dihalide as substrates, disubstituted products were formed. These observations can readily be accommodated by a base-promoted HAS mechanism.





# Transition metal-free cross coupling reactions

The most controversial point is the initial step.



2) in situ generated super electron donor (SED)

Shirakawa, E.; Itch, K.-i.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537.

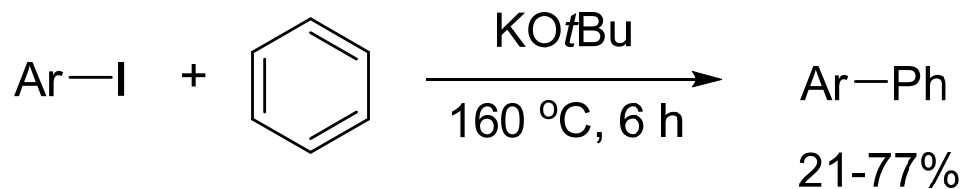
Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2014**, *5*, 476.

# Transition metal-free cross coupling reactions

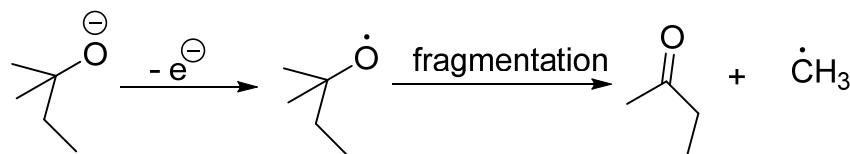
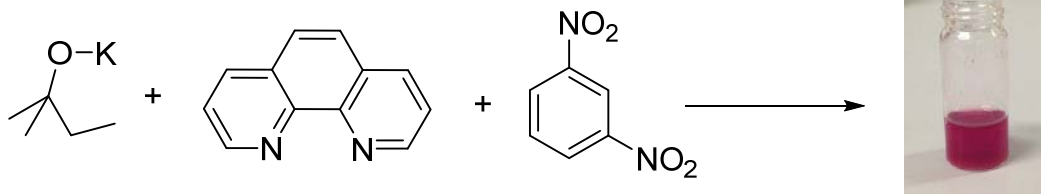
The most representative works to support KO<sup>t</sup>Bu as initiator are reported by Wilden, Lei and Jutand.

## In Wilden's work:

1) Biaryl coupling can proceed in the absence of organic additives.



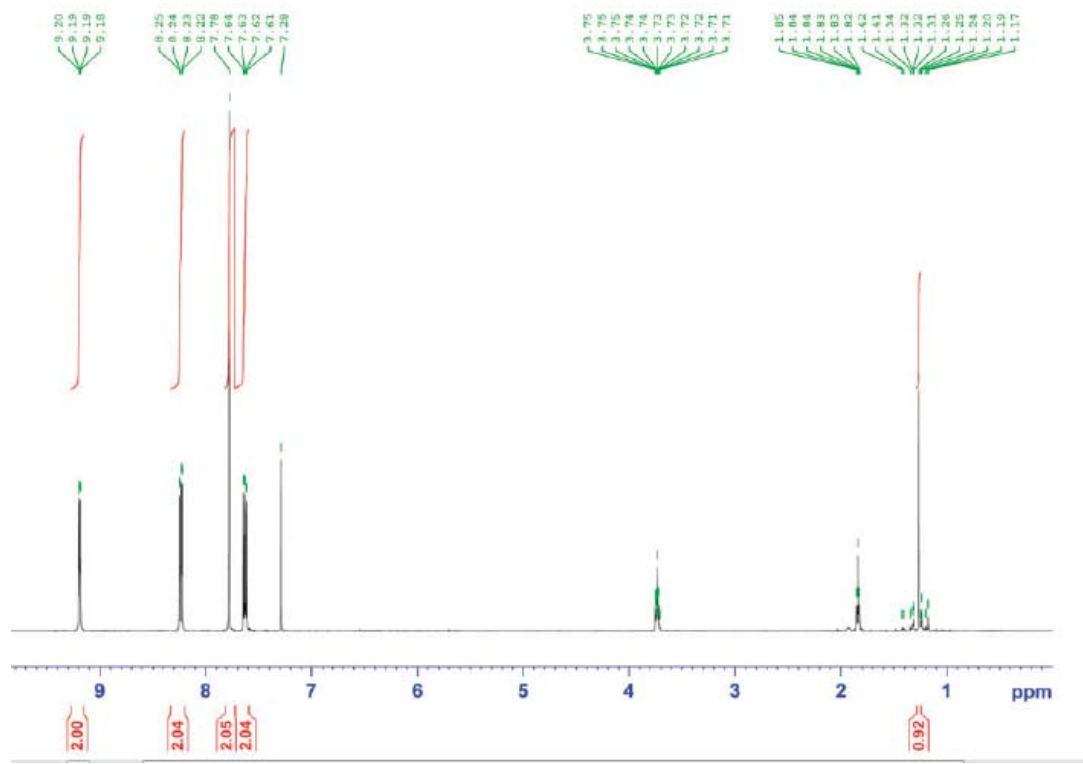
2) Janovsky test for enolizable ketones showed positive effect.



# Transition metal-free cross coupling reactions

3) Mass spectroscopy showed that butanone is the major component by mixing phenanthroline and potassium pentoxide .

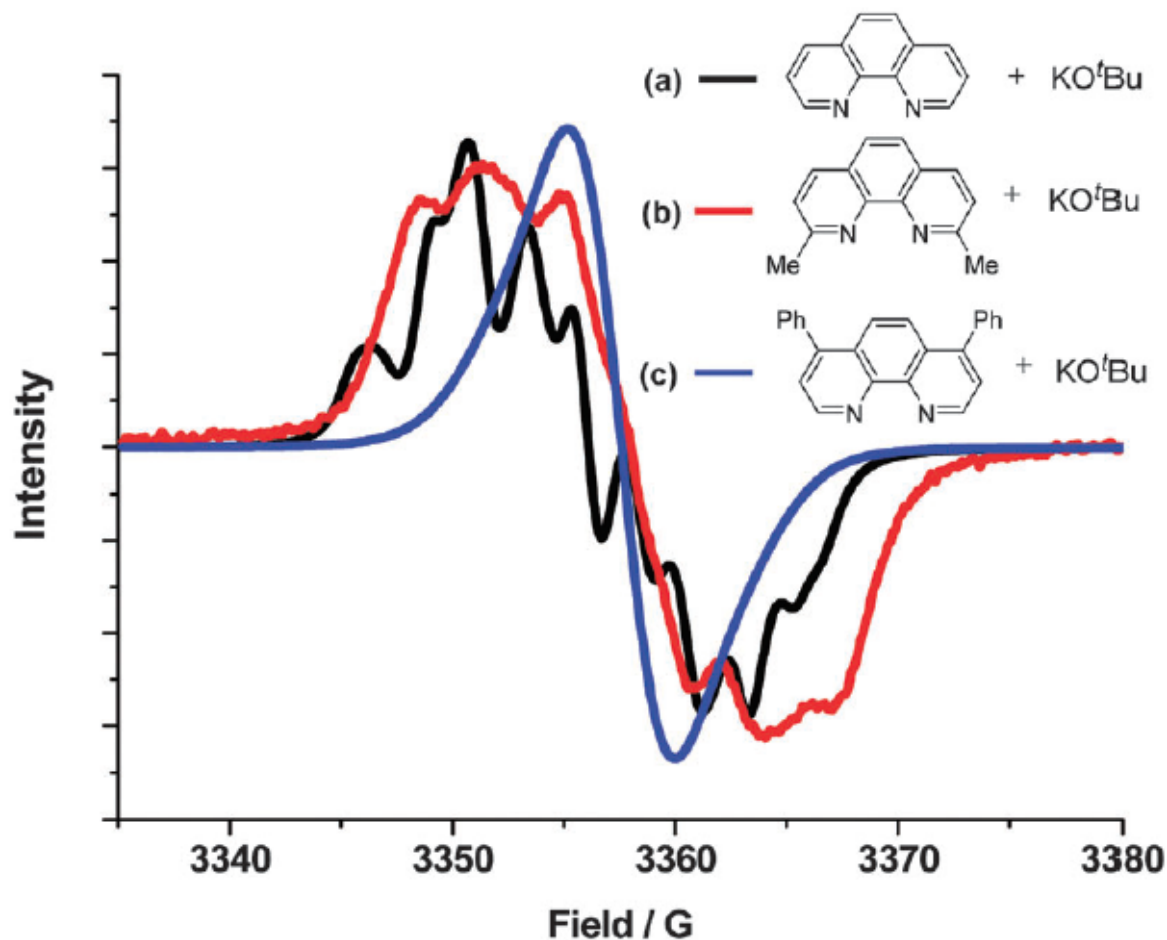
4) A mixture of equimolar phenanthroline and  $\text{KO}^t\text{Bu}$  was prepared and observed by NMR, the intensity of the  $t\text{Bu}$  dramatically decreased almost immediately, and the phenanthroline are left untouched.



# Transition metal-free cross coupling reactions

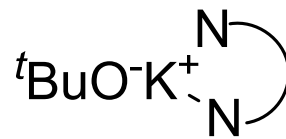
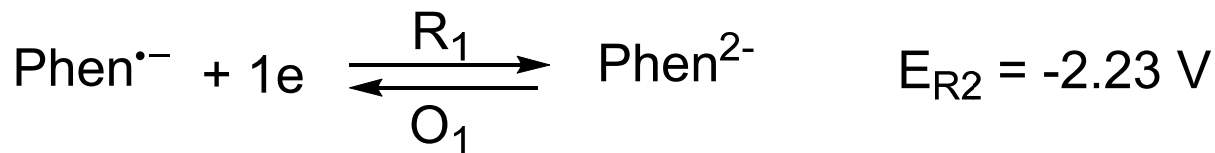
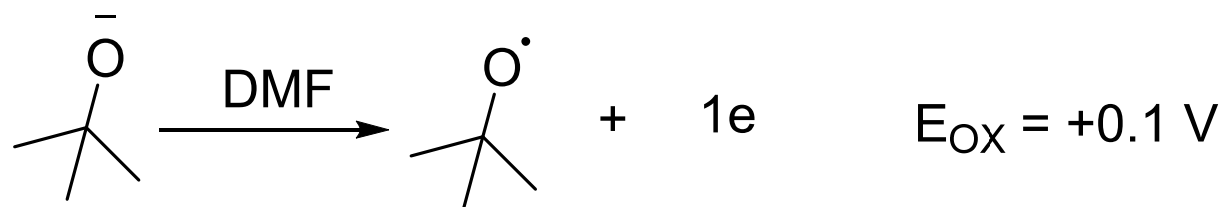
According to Lei and Jutand's work:

1) When mixing phenanthroline and KO<sup>t</sup>Bu in DMF, a strong EPR signal was observed, this provided direct proof for the presence of phenanthroline radical anion.



# Transition metal-free cross coupling reactions

2) Cyclic voltammetry experiments showed that:

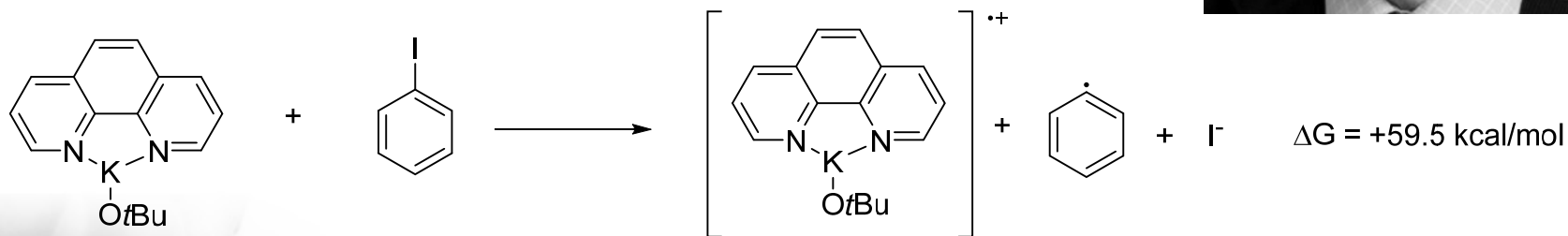


Inner-sphere ET



# Transition metal-free cross coupling reactions

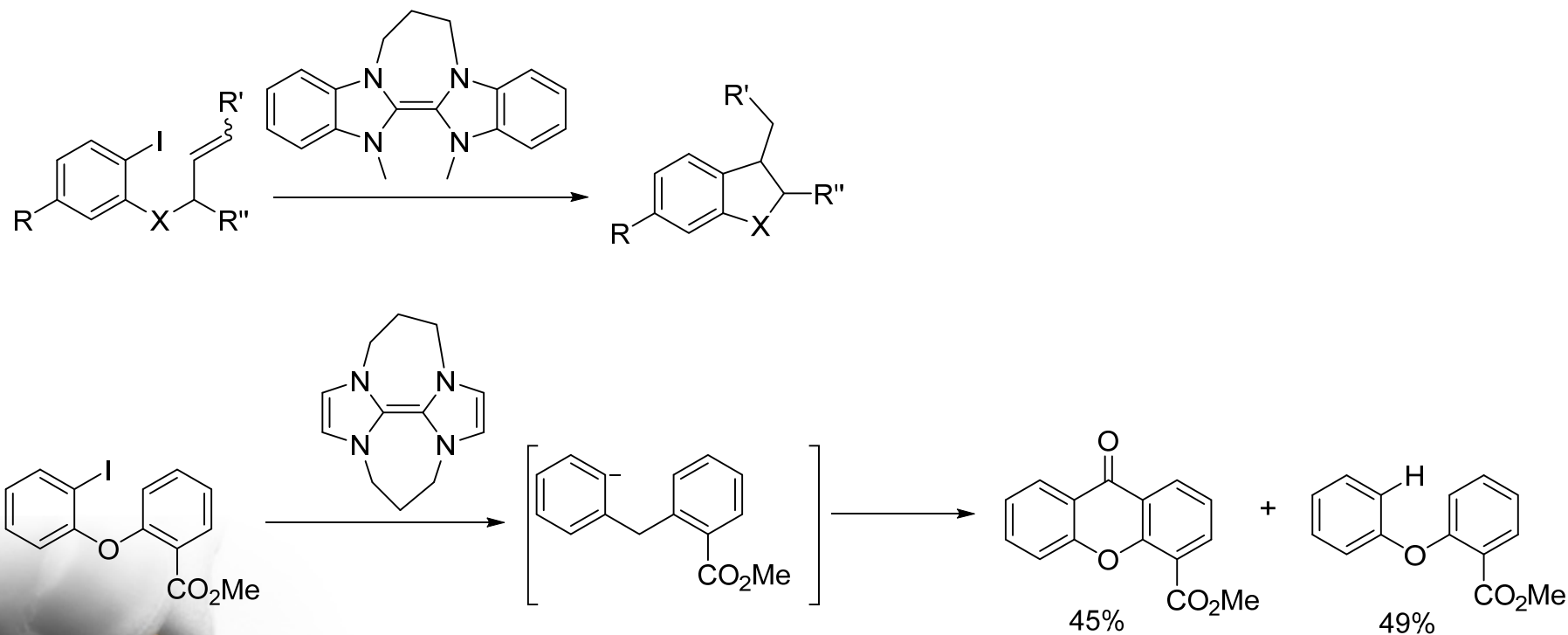
Murphy made the greatest contribution to super electron donor as initiator.



*t*BuOK as an electron donor is less likely because the free energy is +59.5 kcal/mol, which is too large for *t*BuOK to give an electron to iodobenzene.

# Transition metal-free cross coupling reactions

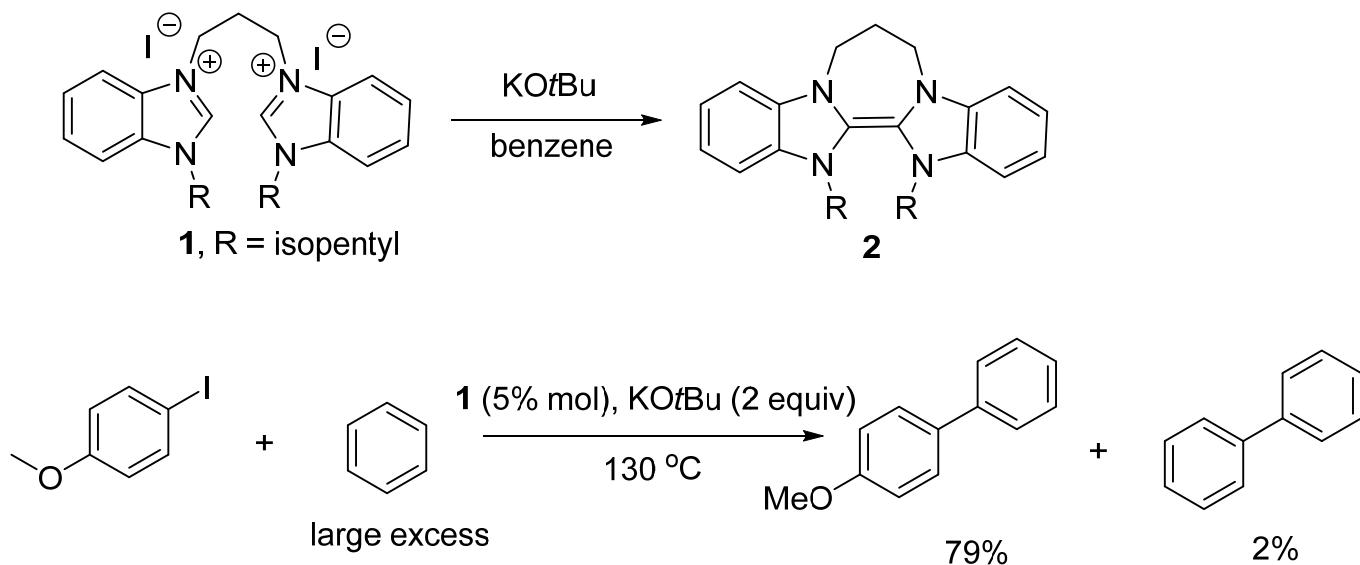
## Previous work of Murphy:



J. A. Murphy, T. A. Khan, S.-Z. Zhou, D. W. Thomson and M. Mahesh, *Angew. Chem., Int. Ed.*, **2005**, *44*, 1356–1360;  
 J. A. Murphy, S.-Z. Zhou, D. W. Thomson, F. Schoenebeck, M. Mohan, S. R. Park, T. Tuttle and L. E. A. Berlouis, *Angew. Chem., Int. Ed.*, **2007**, *46*, 5178–5183.

# Transition metal-free cross coupling reactions

## Super electron donors as initiator:



This provided direct proof for super electron donor as initiator.

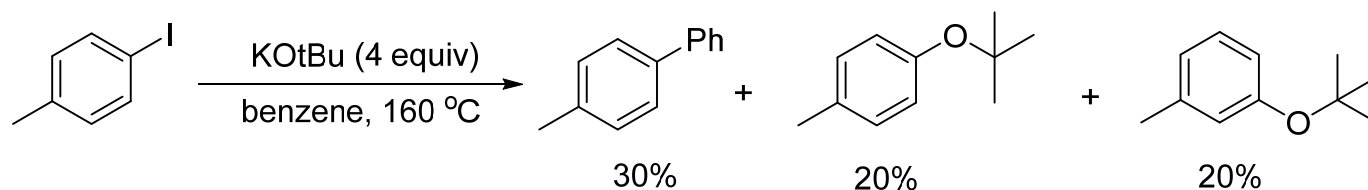
Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2014**, 5, 476.



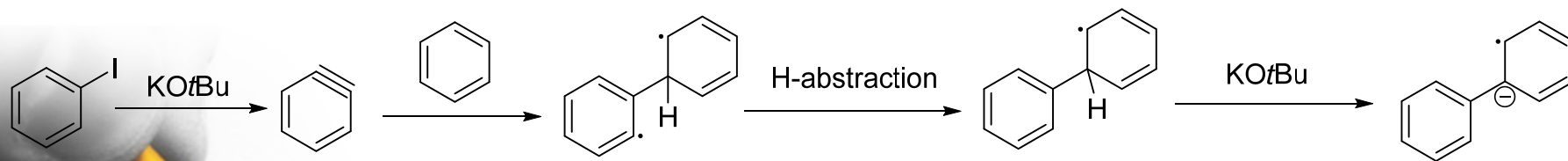
# Transition metal-free cross coupling reactions

## Initiation with KOtBu only:

Given the large thermodynamic barrier for electron transfer mentioned before, buoxide cannot be the direct initiator of the radical chemistry, so the radical must be formed in another way.



## A benzyne mechanism was proposed:

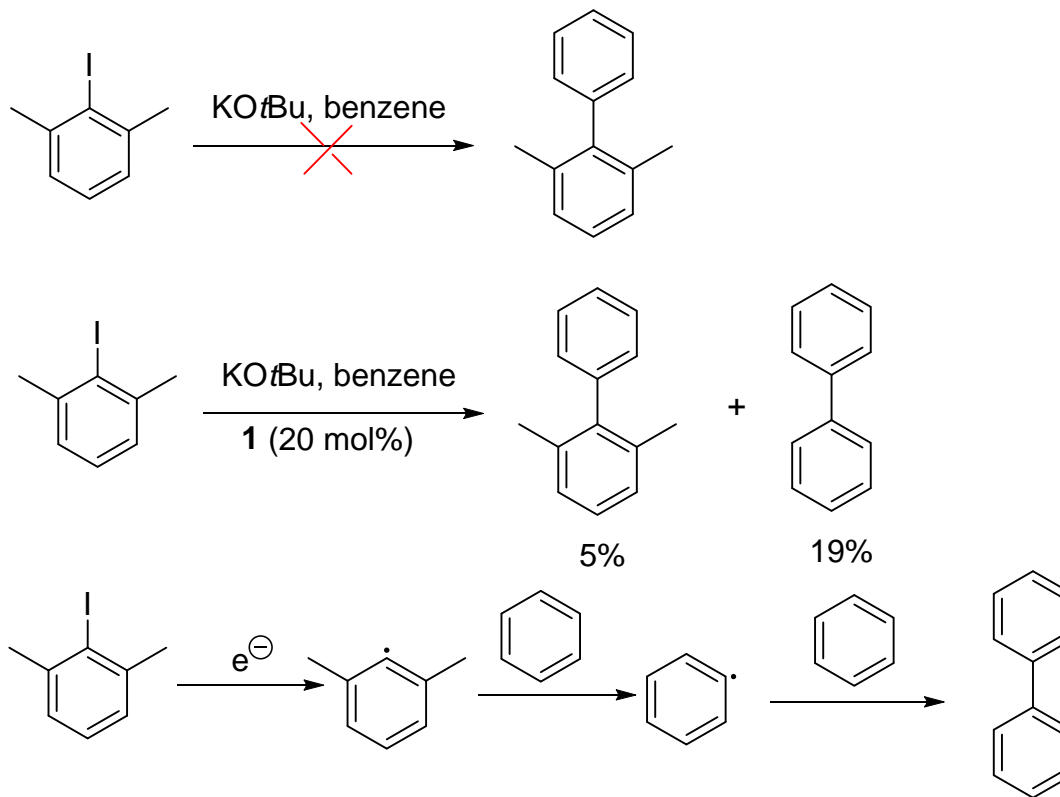


**Figure 5: Proposed pathway from benzyne to an electron donor in the absence of “additive”**

Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2014**, 5, 476.

# Transition metal-free cross coupling reactions

## Confirmation experiments:

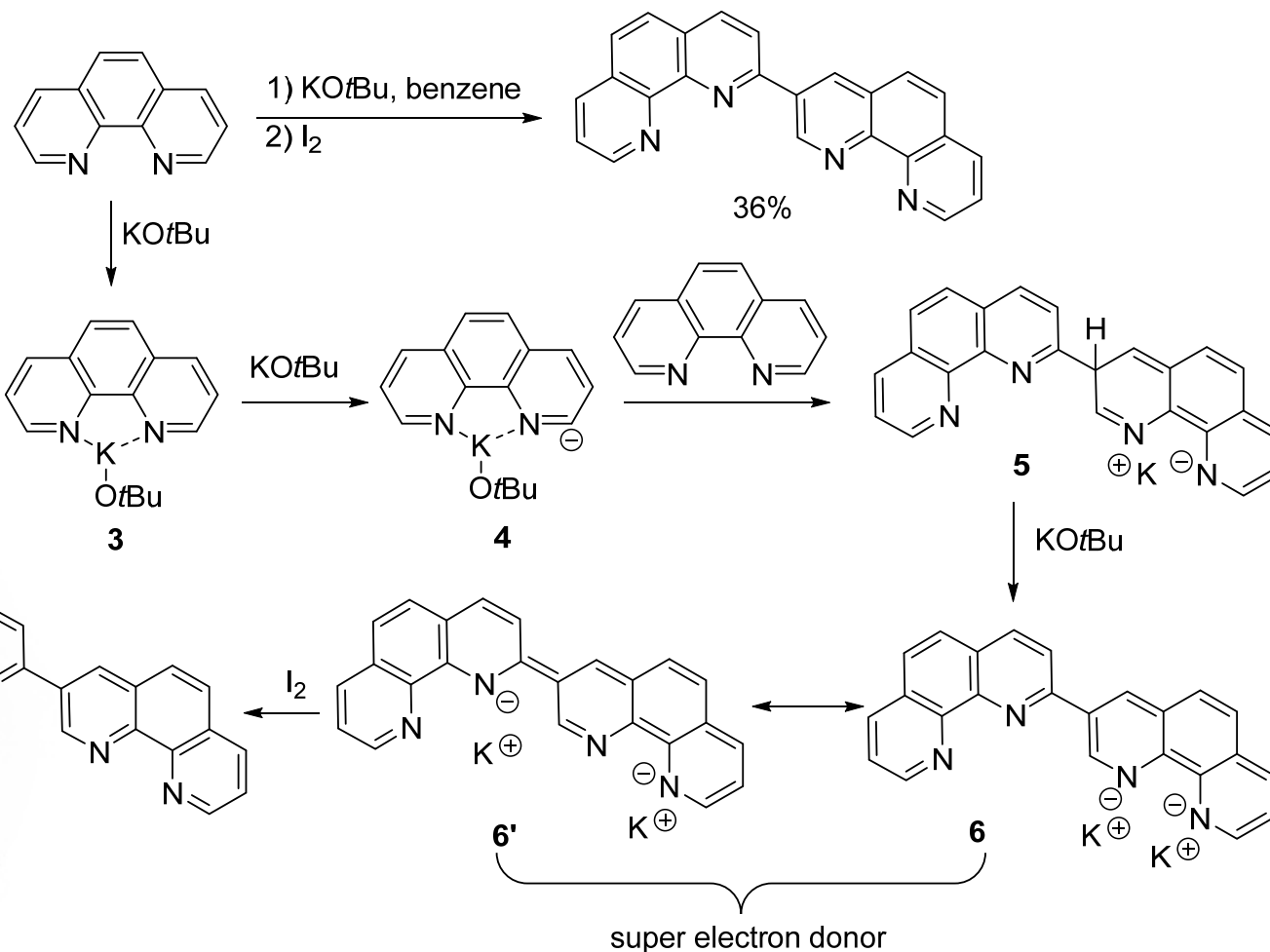
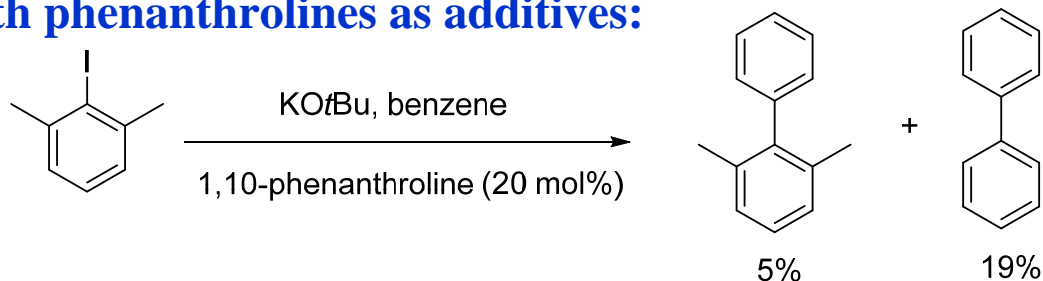


All these information confirm that benzyne is the intermediate in additive free coupling reactions.

Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2014**, 5, 476.

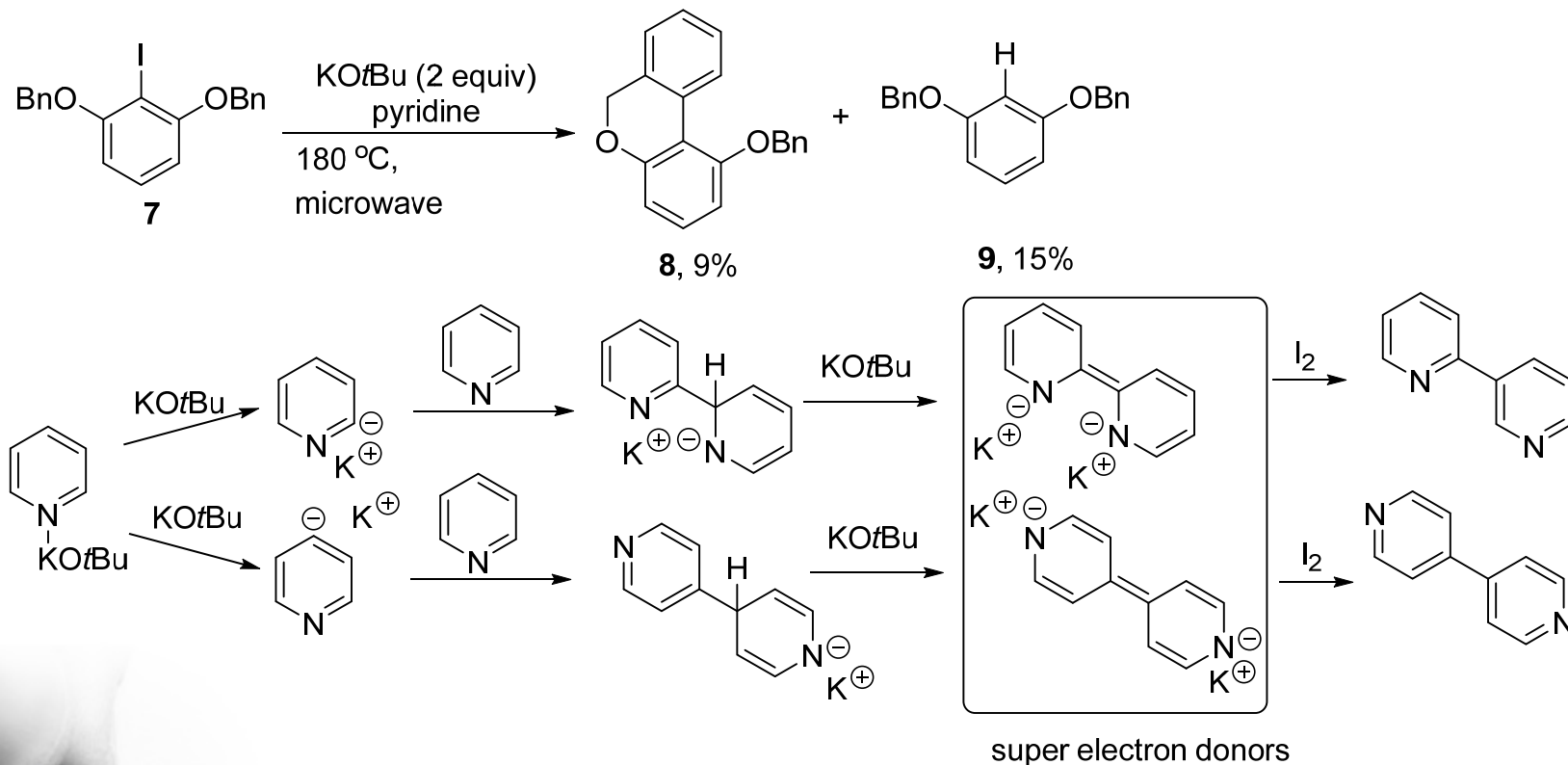
# Transition metal-free cross coupling reactions

## Initiation with phenanthrolines as additives:



# Transition metal-free cross coupling reactions

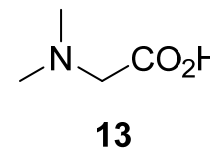
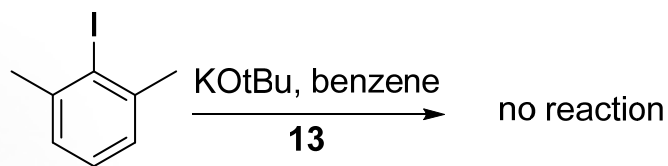
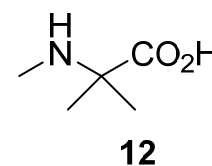
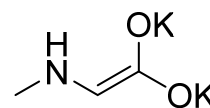
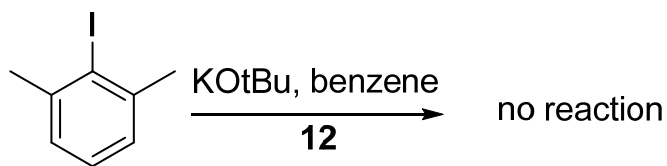
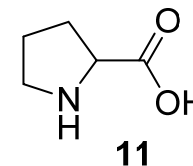
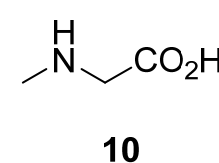
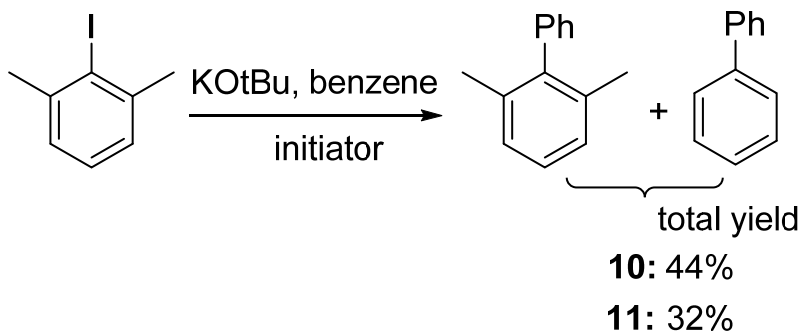
## Initiation with pyridine as solvent:



Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2014**, 5, 476.

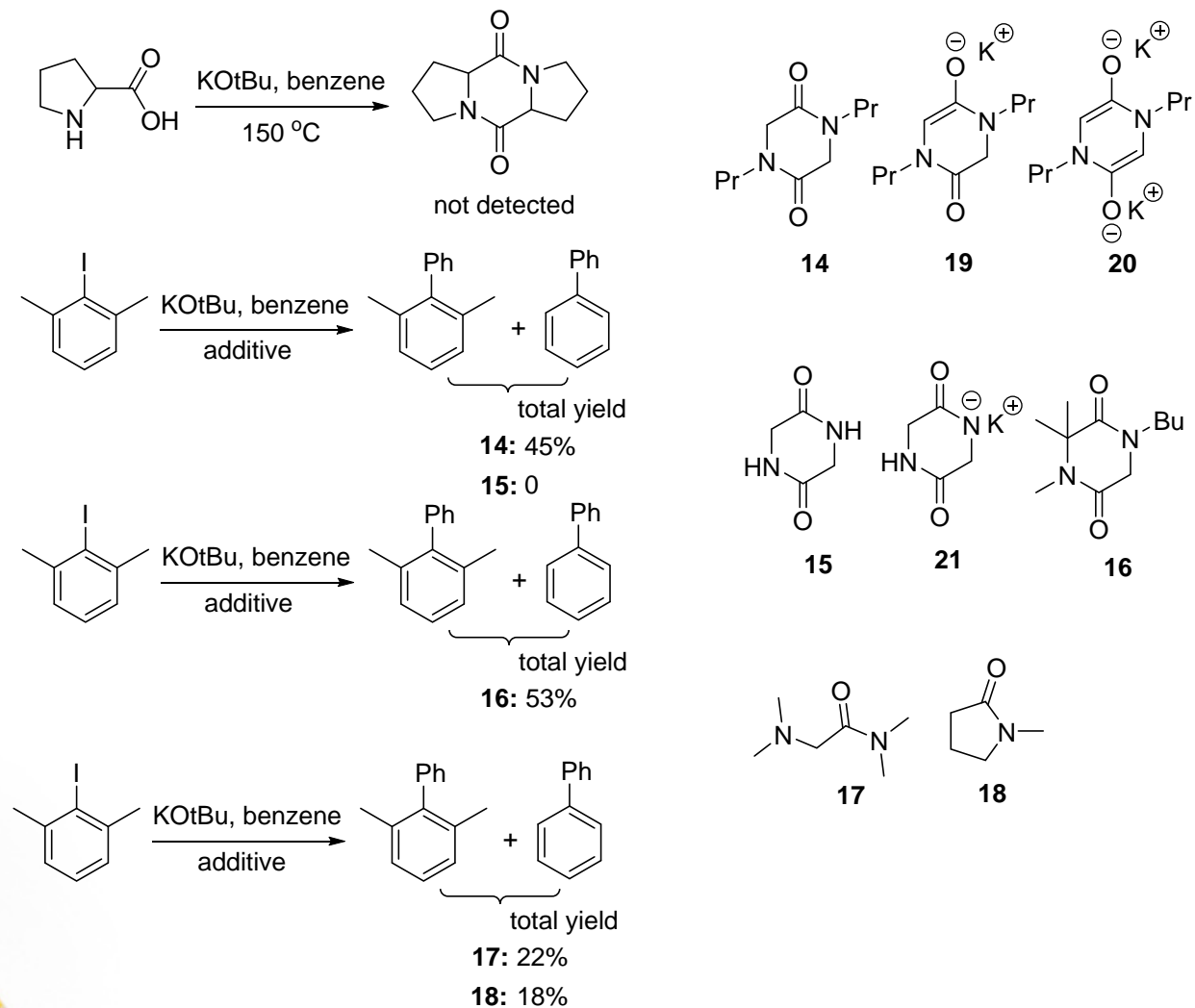
# Transition metal-free cross coupling reactions

## Amino acids and their derivatives as additives:



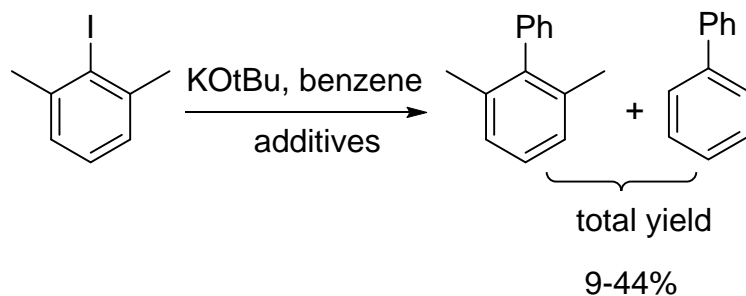
Zhou, S.; Doni, E.; Anderson, G. M.; Kane, R. G.; MacDougall, S. W.; Ironmonger, V. M.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 17818.

# Transition metal-free cross coupling reactions

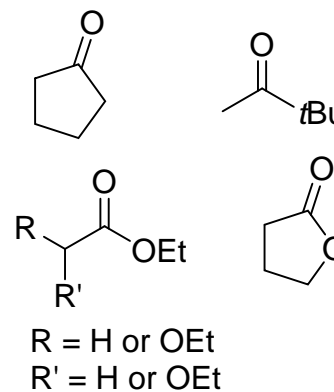


Zhou, S.; Doni, E.; Anderson, G. M.; Kane, R. G.; MacDougall, S. W.; Ironmonger, V. M.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 17818.

# Transition metal-free cross coupling reactions



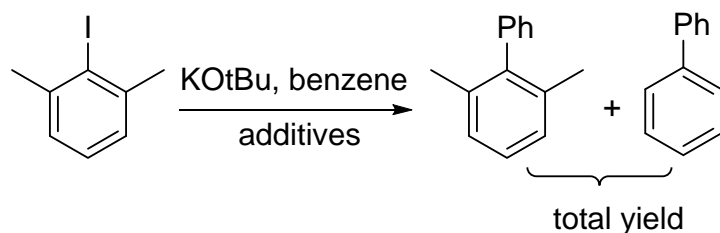
additives



All in all, electron-rich alkenes are good electron donors to trigger the biaryl coupling reactions.

# Transition metal-free cross coupling reactions

## Alcohols and 1, 2-diols as additives:



total yield

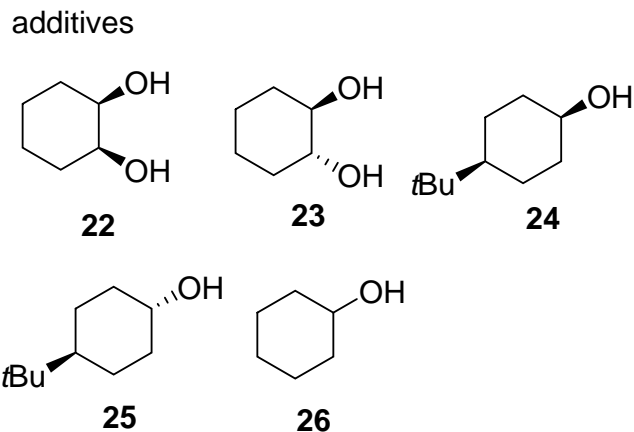
**22:** 32%

**23:** 44%

**24:** 10%

**25:** 5%

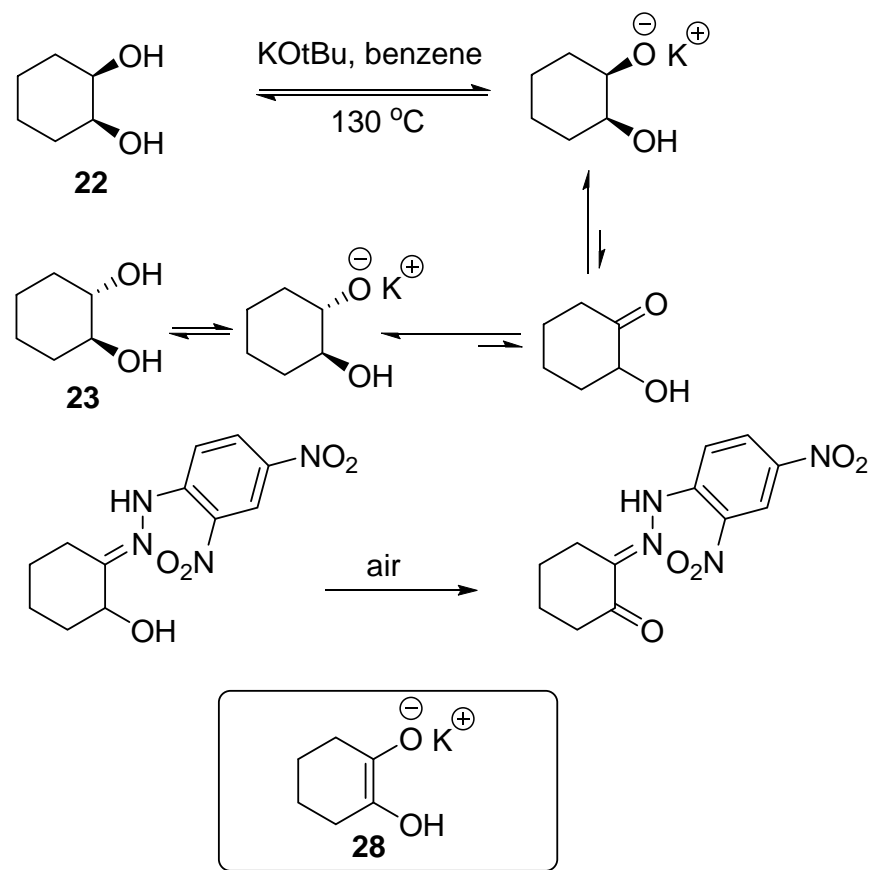
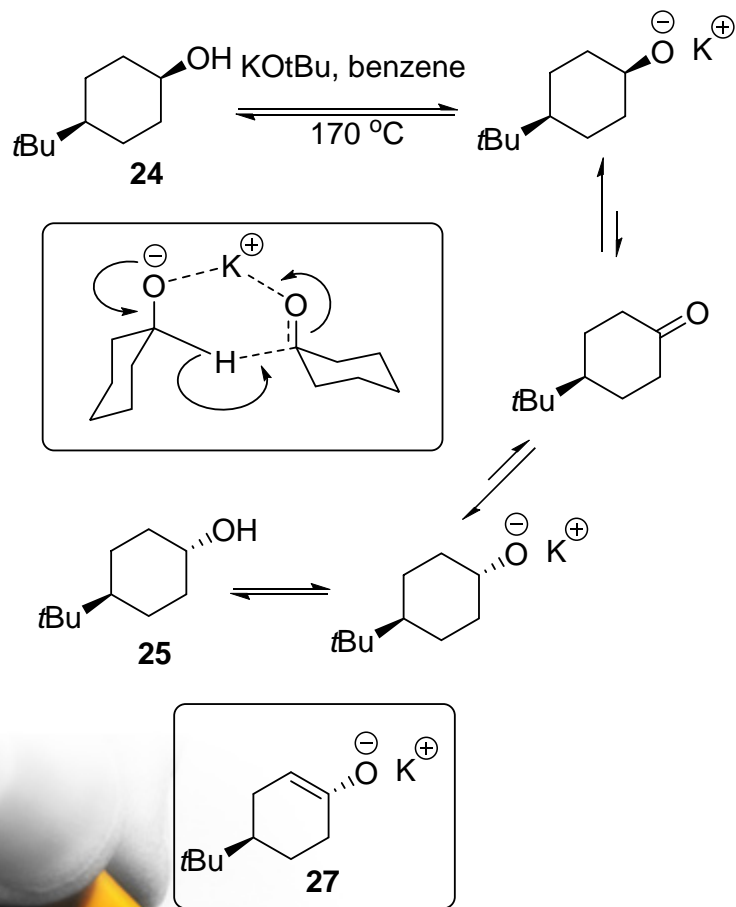
**26:** 7%



Zhou, S.; Doni, E.; Anderson, G. M.; Kane, R. G.; MacDougall, S. W.; Ironmonger, V. M.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 17818.



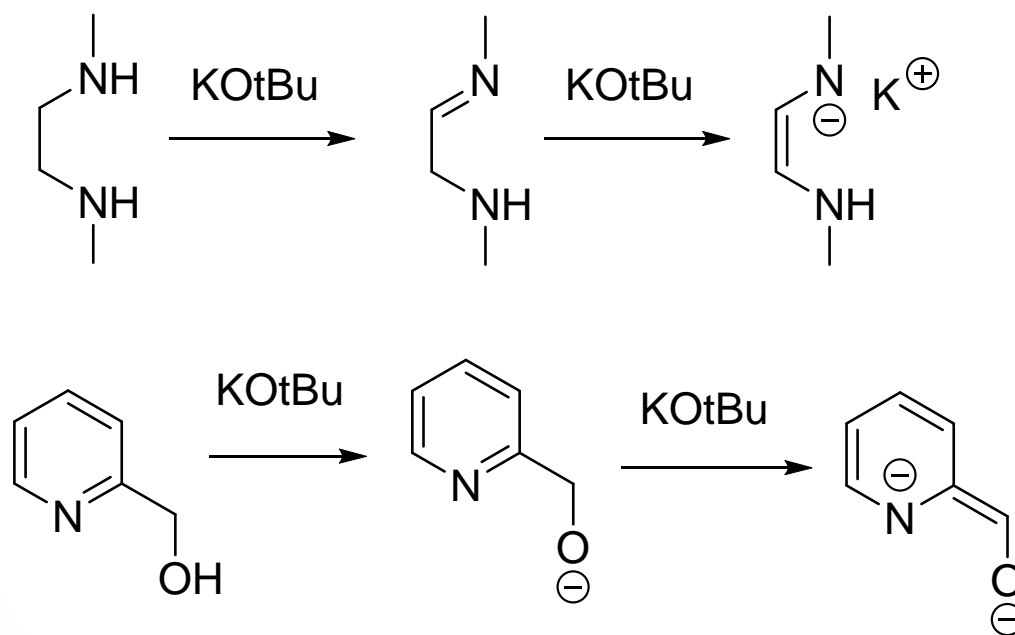
# Transition metal-free cross coupling reactions



Zhou, S.; Doni, E.; Anderson, G. M.; Kane, R. G.; MacDougall, S. W.; Ironmonger, V. M.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 17818.

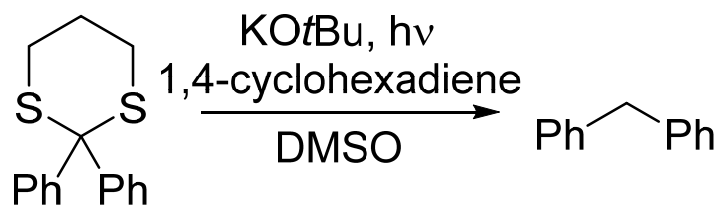
# Transition metal-free cross coupling reactions

Other additives as initiators:



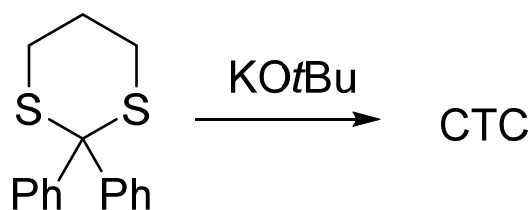
Zhou, S.; Doni, E.; Anderson, G. M.; Kane, R. G.; MacDougall, S. W.; Ironmonger, V. M.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 17818.

# Reductive fragmentation of dithianes

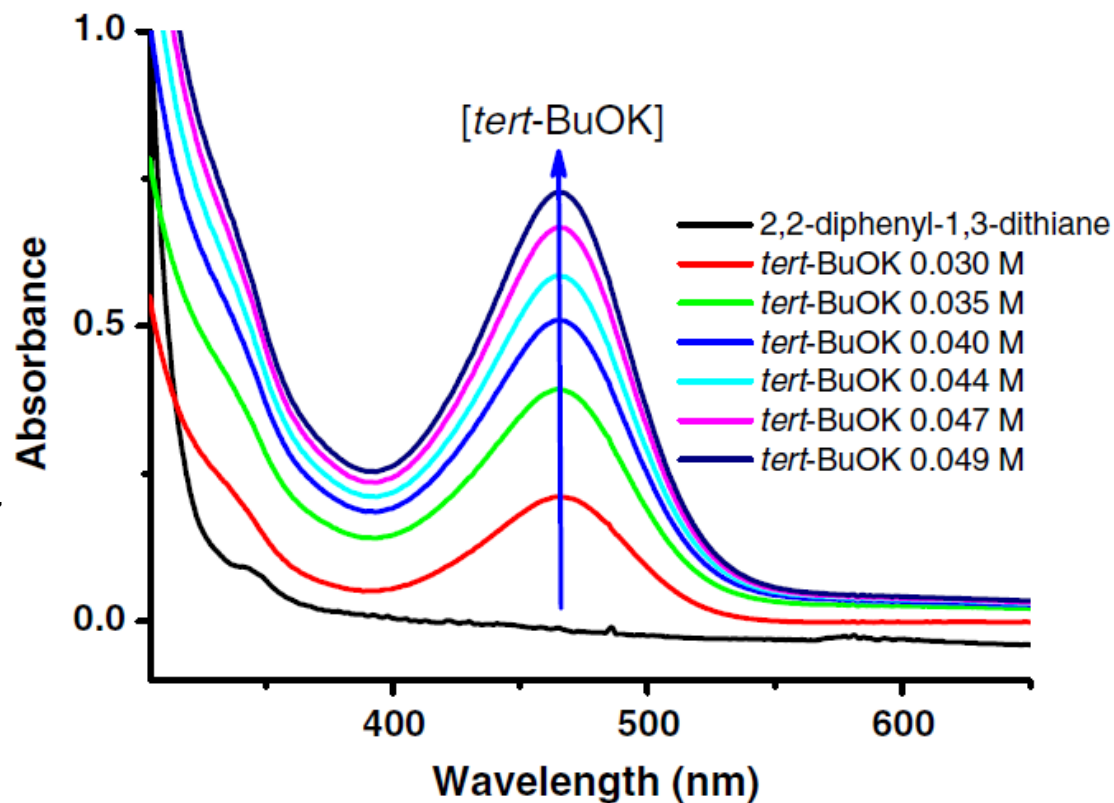


92%

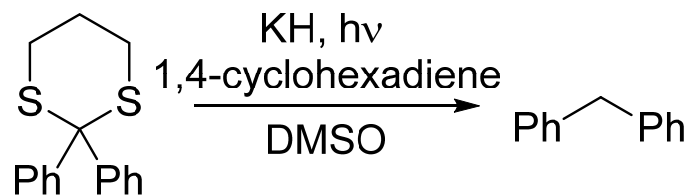
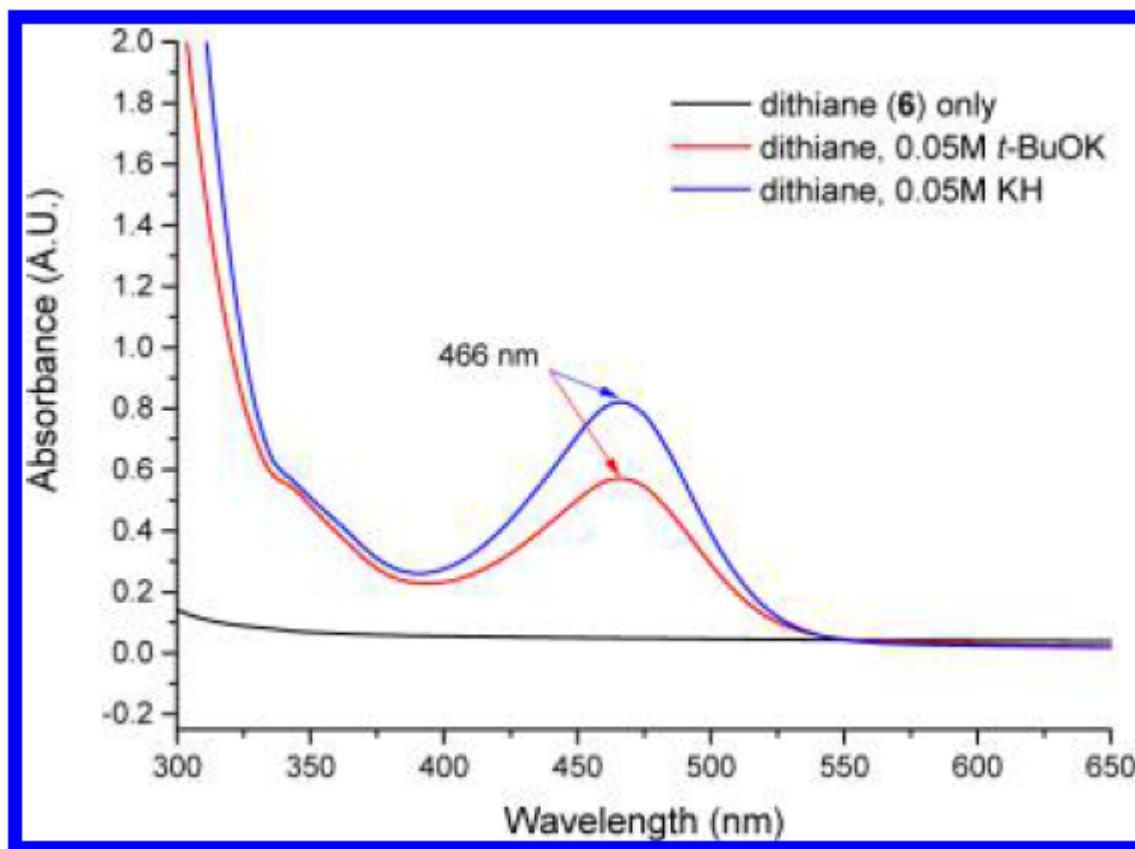
## Evidence for the CTC formation



CTC absorption at 467 nm in the UV-vis spectrum

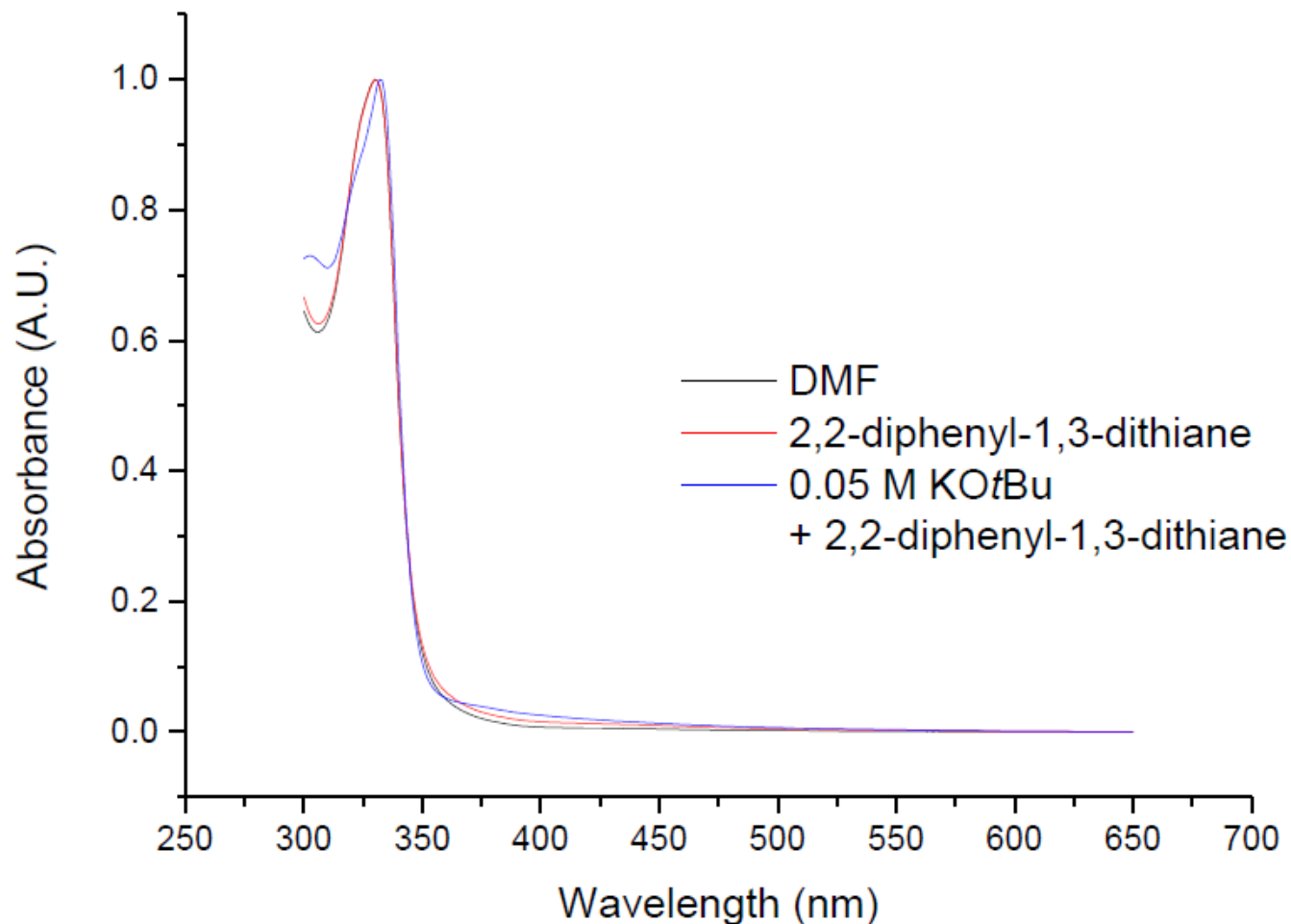


# Reductive fragmentation of dithianes



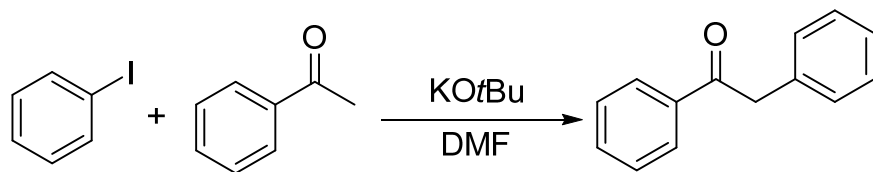
13%

# Reductive fragmentation of dithianes

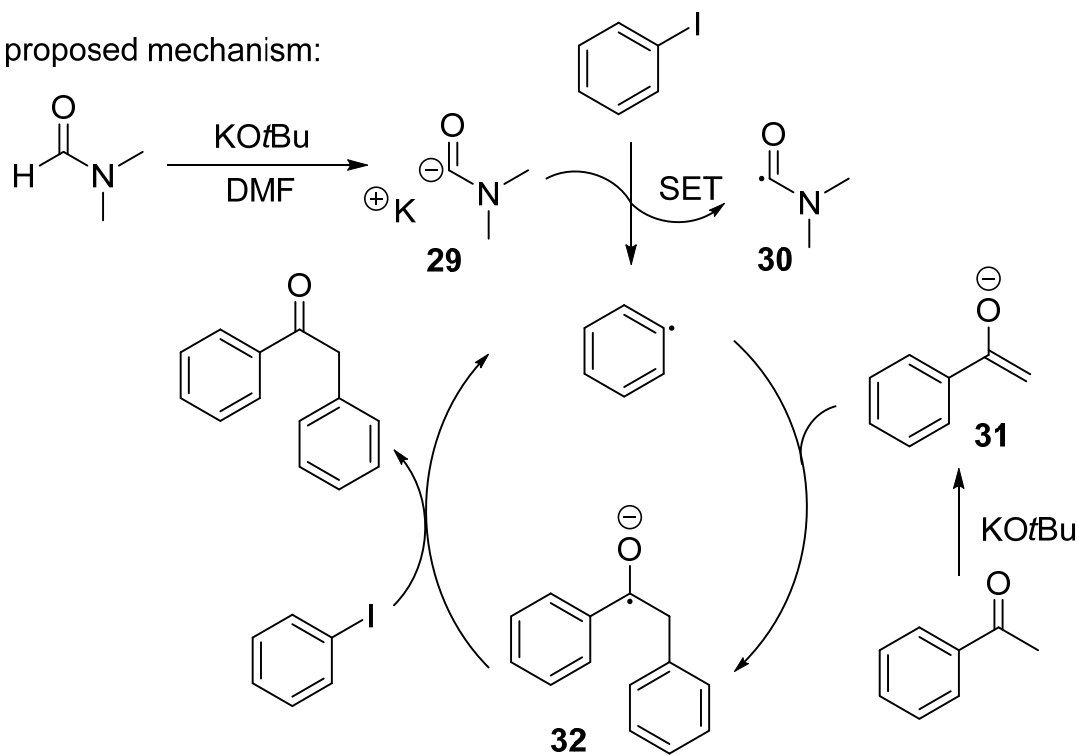


**DMF as solvent:** No UV-visible absorption observed at 466 nm. This shows that no charge transfer complex was formed between dithiane and KOtBu and that in the cases with DMSO as solvent **it is deprotonation of DMSO that leads to the dimsyl anion which forms a charge transfer complex with the dithiane.**

# $S_{RN}1$ reactions in DMF



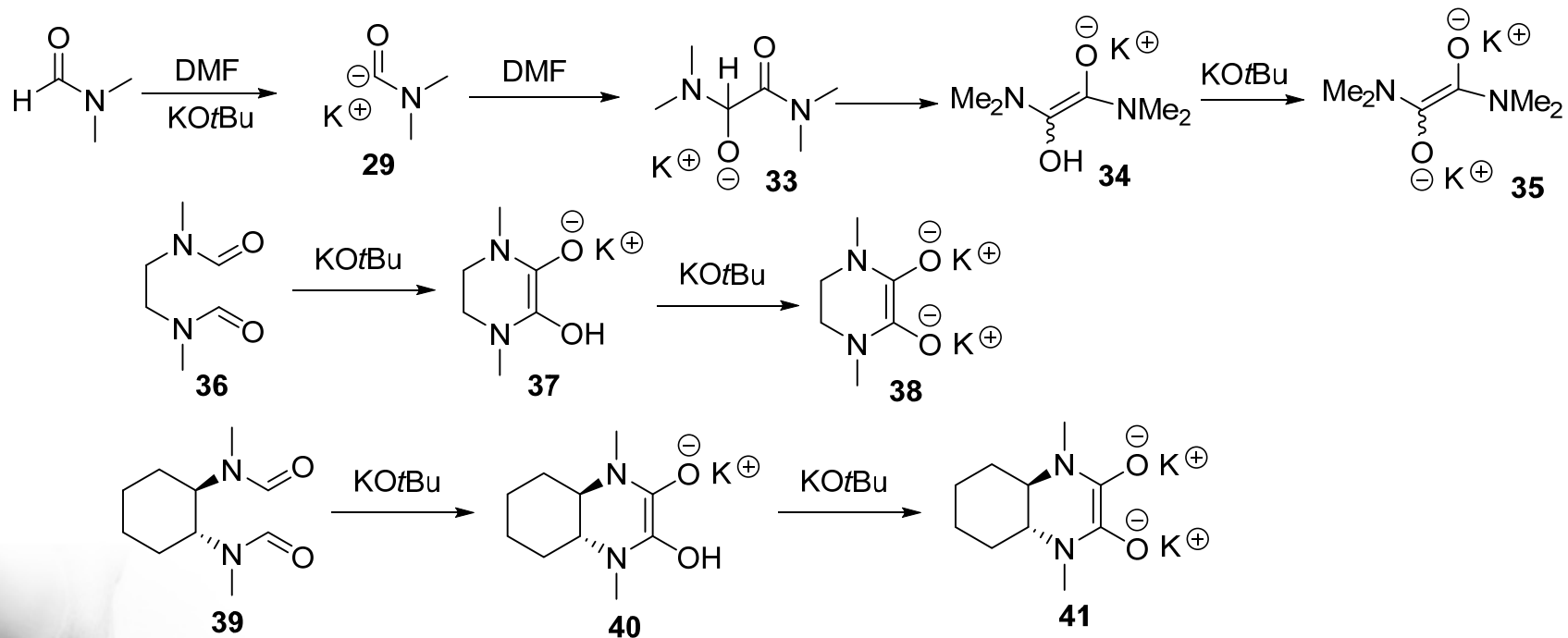
proposed mechanism:

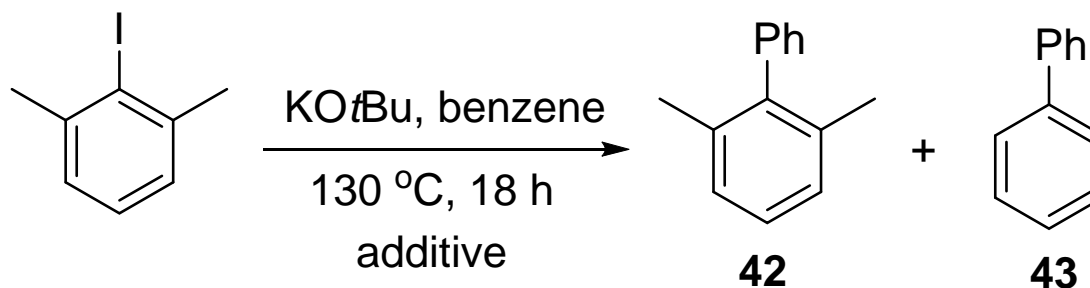


Pichette Drapeau, M.; Fabre, I.; Grimaud, L.; Ciofini, I.; Ollevier, T.; Taillefer, M.  
*Angew. Chem., Int. Ed.* **2015**, *54*, 10587.

# $S_{RN}1$ reactions in DMF

Murphy and coworkers proposed an alternative mechanism :





entry	additive	yield (%) ( <b>42</b> + <b>43</b> )
1	DMF (0.2 equiv)	0.6
2	<b>36</b> (0.1 equiv)	8
3	<b>39</b> (0.1 equiv)	16

**Figure 6: comparison of reactivity of DMF and diformamide in coupling reactions that use KOtBu as a base**

These experiments showed the ability of formamides to dimerize in the presence of KOtBu to form electron donors.



# Summary

- 1. The role of KO $t$ Bu in single electron transfer reactions is discussed.**
- 2. Although in transition metal-free reactions, KO $t$ Bu as a single electron donor is proposed by many workers, considering the large energy barrier, the direct electron transfer from KO $t$ Bu seems impossible.**
- 3. KO $t$ Bu maybe only act as a base in these SET reactions.**
- 4. Further studies are needed to have more accurate understanding of KO $t$ Bu involved single electron transfer reactions and the role KO $t$ Bu played.**



# References

- (1) Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E.; McGuire, T.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2016**, ASAP.
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