Photoredox/Nickel Dual Catalyzed Enantioselective Radical Coupling Reactions

报告人: 王华南

导　师: 麻生明 教授

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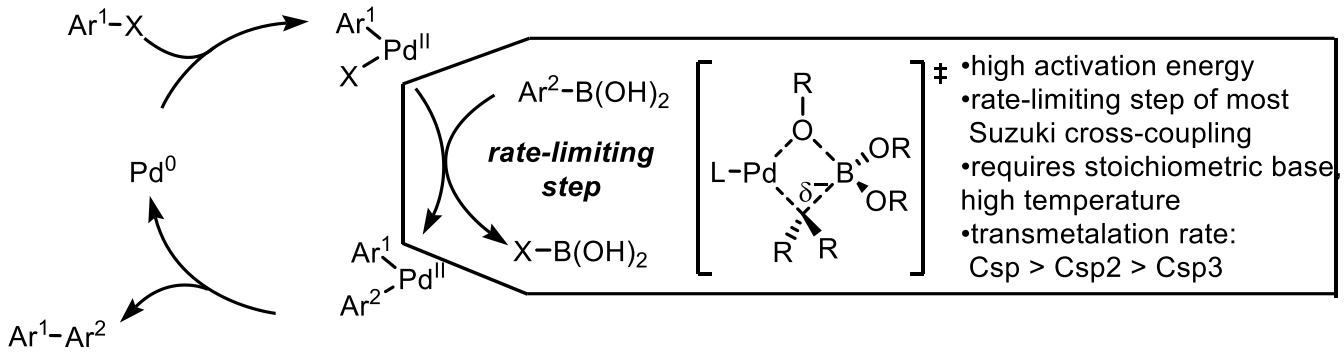
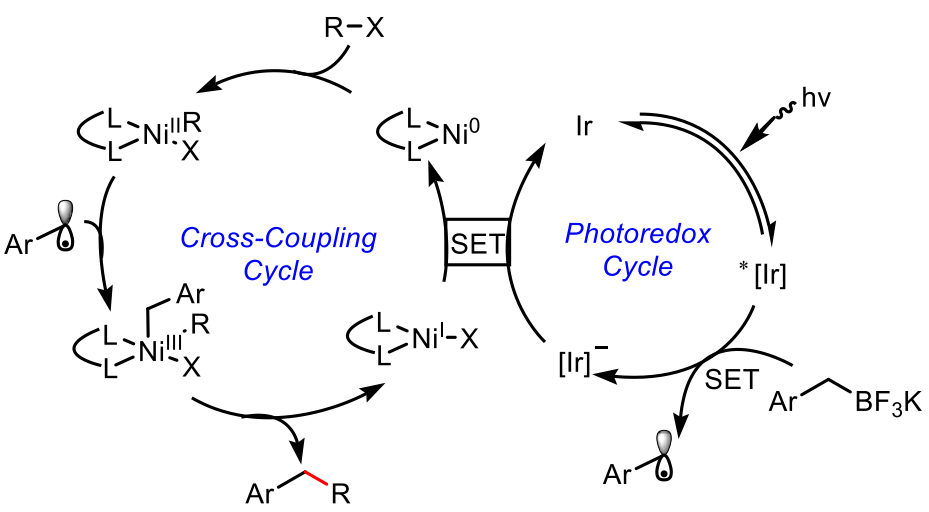
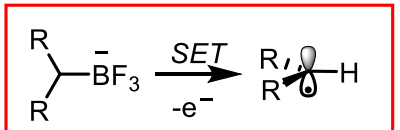


Photoredox Cross-Coupling: Single-Electron Transmetalation





Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433.

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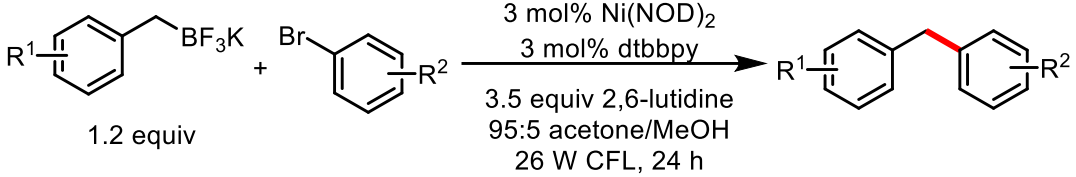
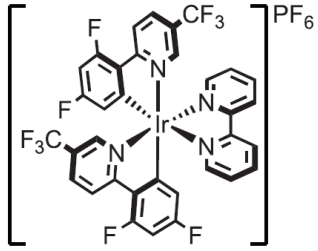
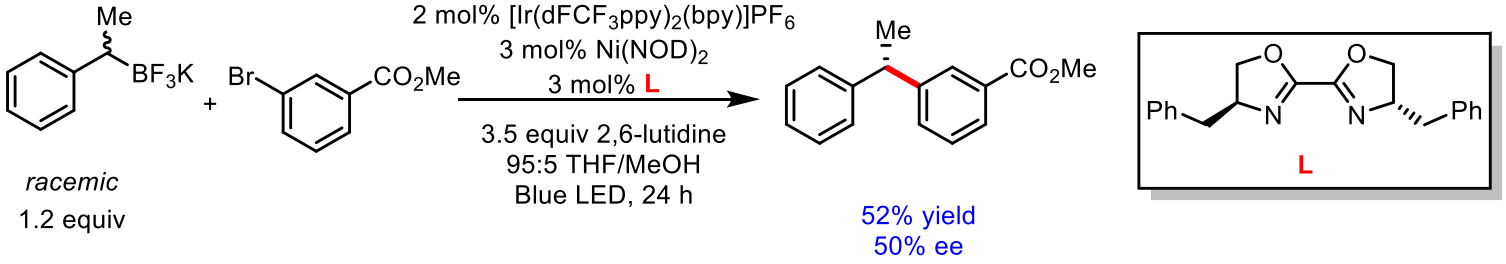
2.1. Generate radicals through C-B bond cleavage







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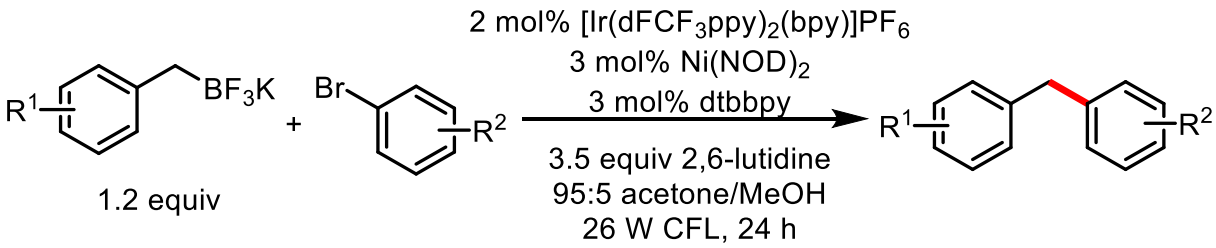

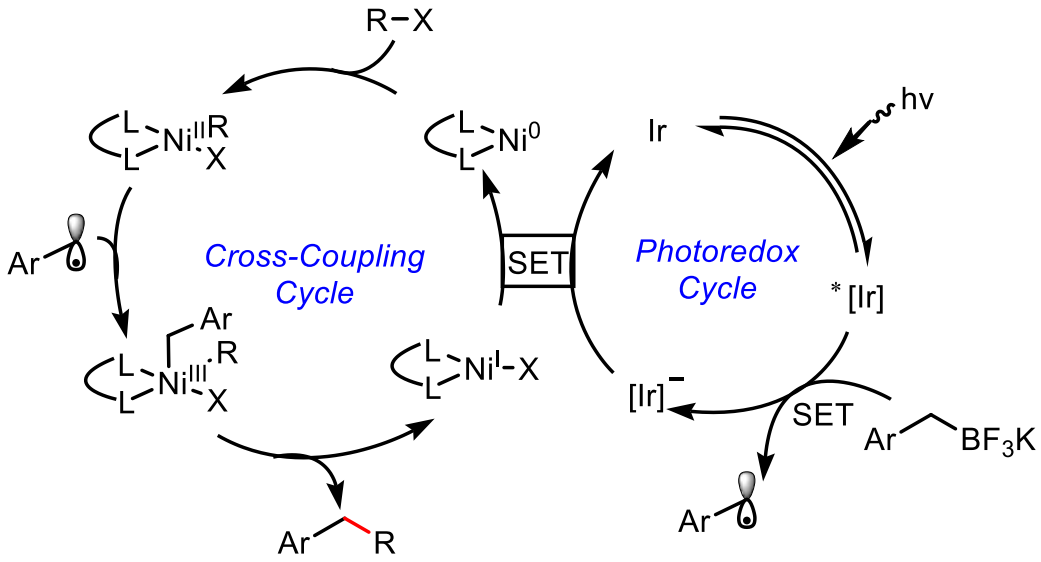

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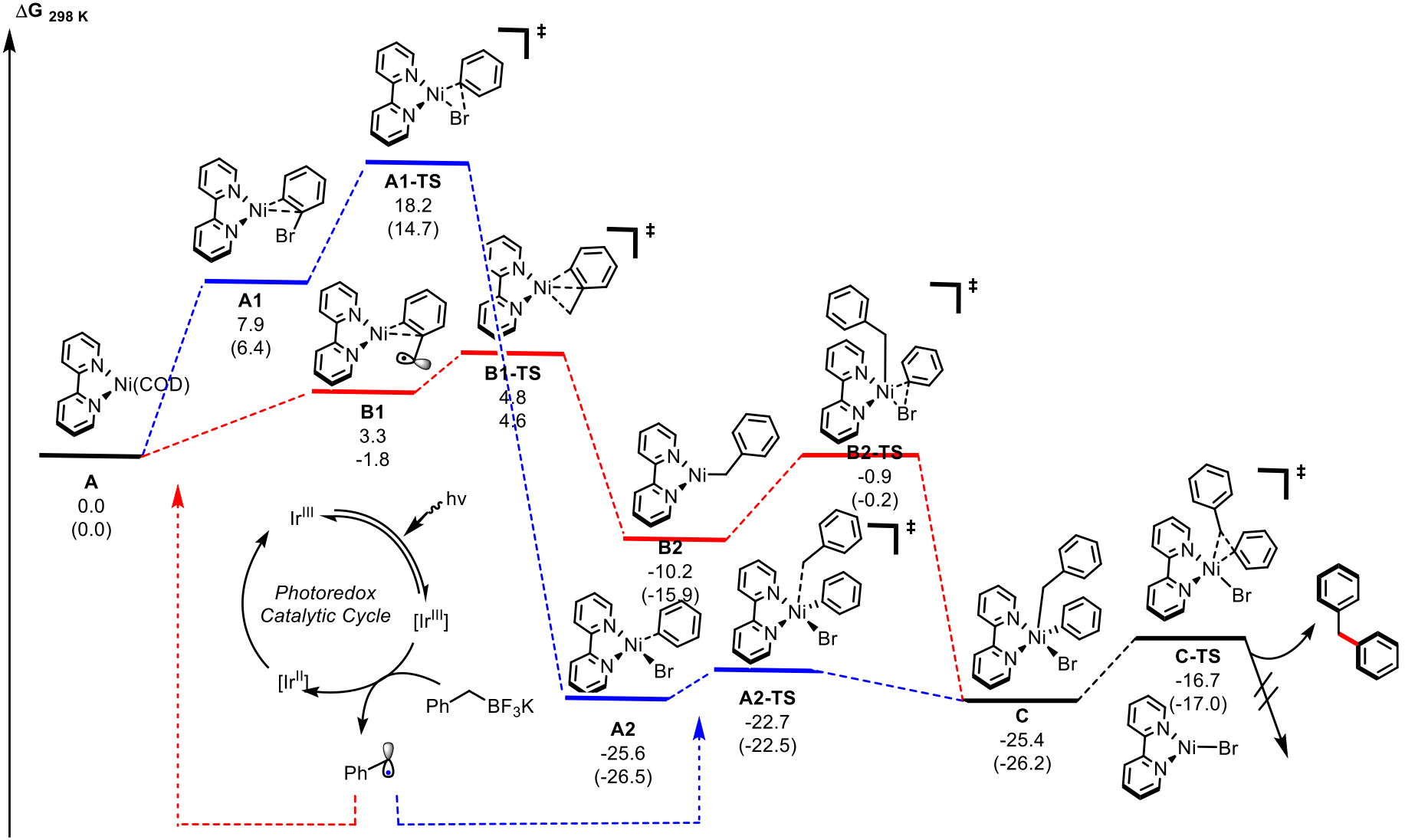

Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896.

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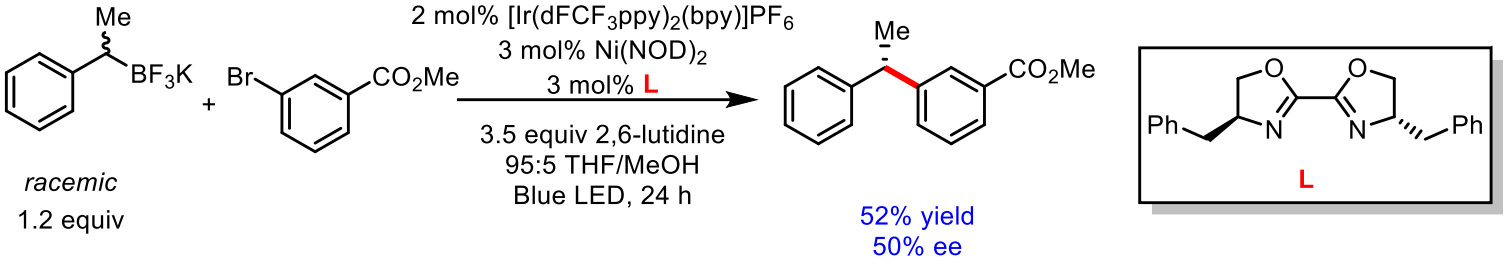

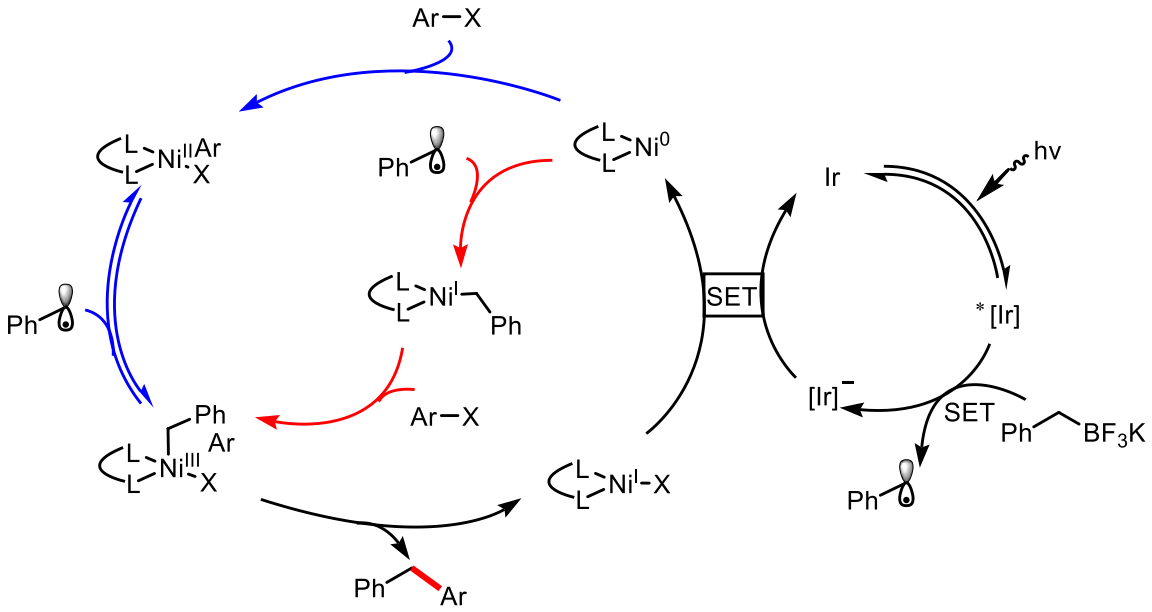

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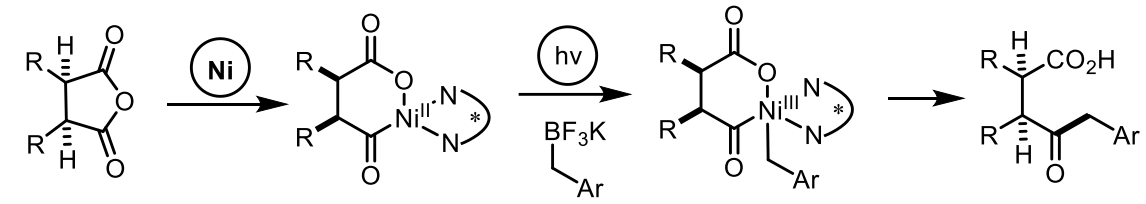
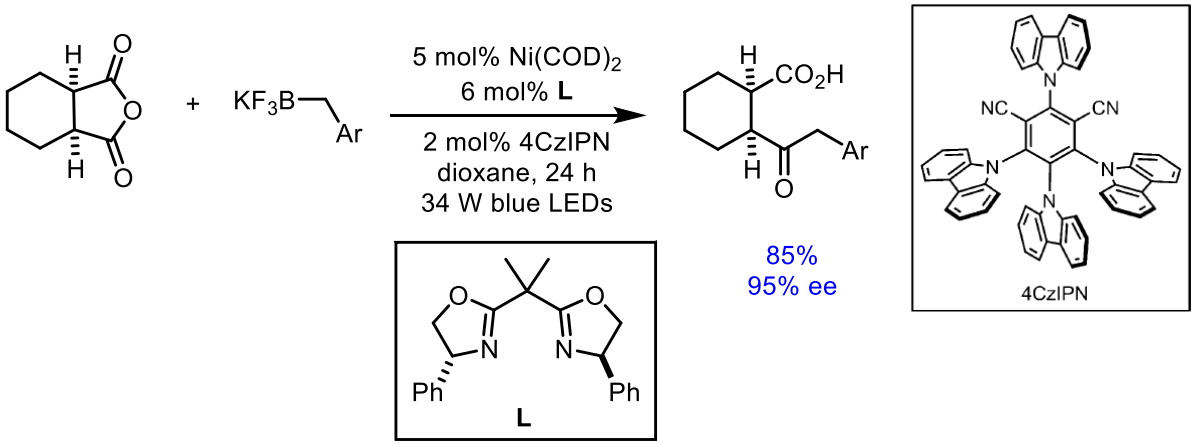
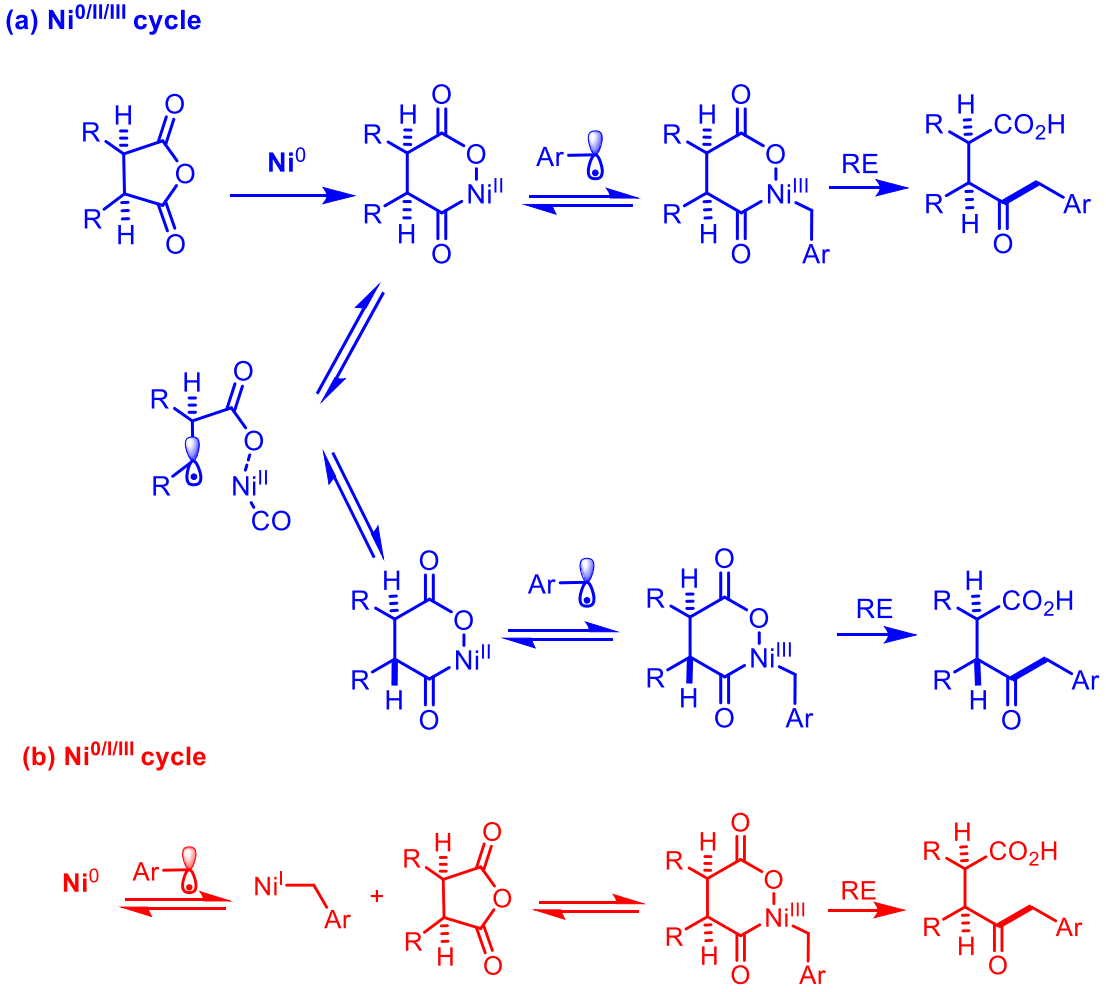




Stache, E. E.; Rovis, T.; Doyle, A. G. *Angew. Chem. Int. Ed*. **2017**, *56*, 3679.

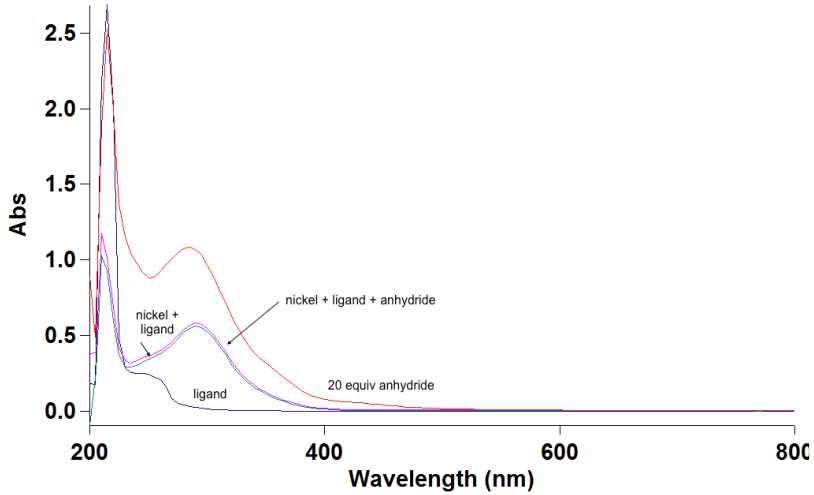
2.1. Generate radicals through C-B bond cleavage

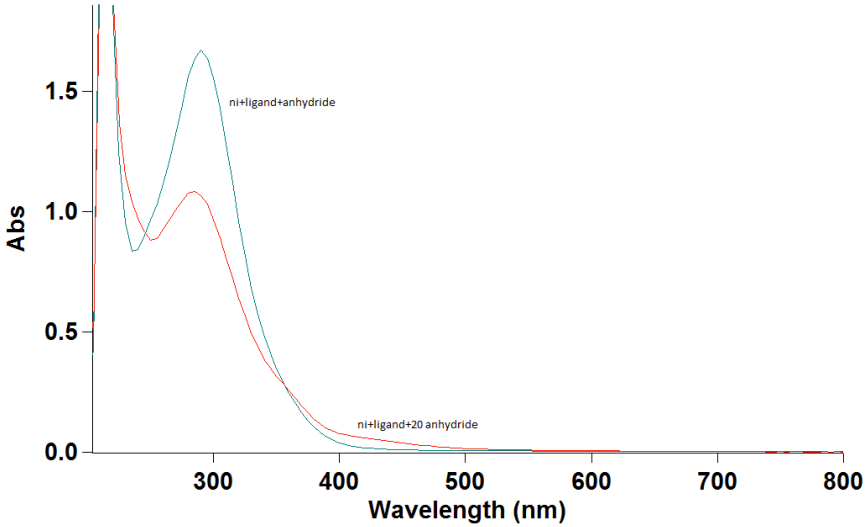


Stache, E. E.; Rovis, T.; Doyle, A. G. *Angew. Chem. Int. Ed*. **2017**, *56*, 3679.

2.1. Generate radicals through C-B bond cleavage

(*S*,*S*)-PhBox (L1):





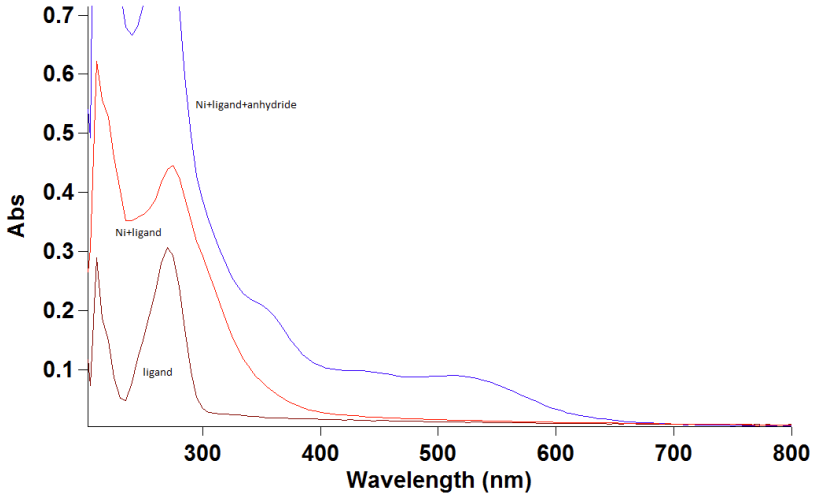
The initial mixture of **Ni + L** and Anhydride shows no indication of oxidative addition, by color change or the development of changes in the visible region. However, after the addition of more anhydride and longer stir time, a slight change in color and change in spectrum were observed. These data suggest that oxidative addition, under stoichiometric conditions, is slow.

Anhydride was used stoichiometrically and in excess (20 equiv). A stir time of 10 minutes was used for mixing **Ni + L** and Anhydride according to the general procedure. With an excess of anhydride, mimicking reaction conditions, oxidative addition is observed after only 10 min.

Stache, E. E.; Rovis, T.; Doyle, A. G. *Angew. Chem. Int. Ed*. **2017**, *56*, 3679.

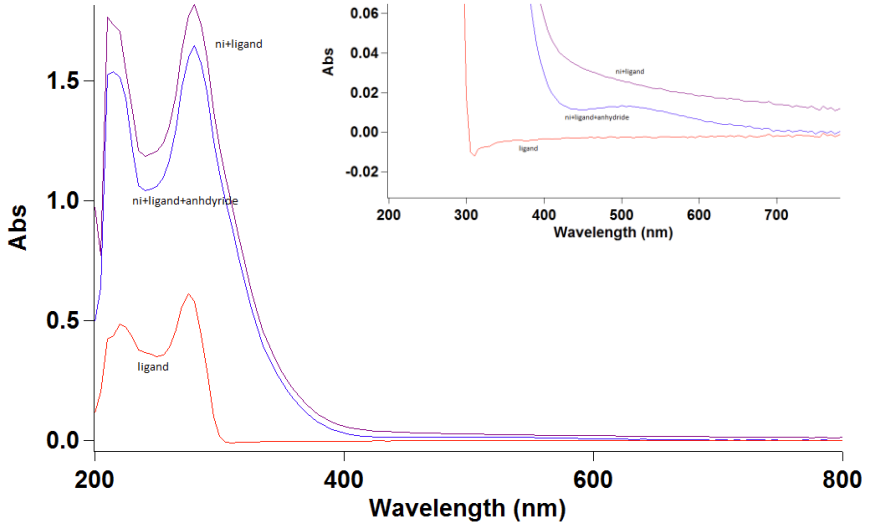
2.1. Generate radicals through C-B bond cleavage

(*S*)-*t*BuPyrOx:



A significant change,consistent with the color change and probable oxidative addition, is observed in the spectrum, developing features in the 350-500 nm range. These data suggest that oxidative addition is occurring (within 10 min) under these catalyst conditions.

(*S*)-6-Me-*t*BuPyrOx (L4):



A small but significant change, consistent with the color change and probable oxidative addition, is observed in the spectrum, developing a feature at 500 nm. These data suggest that oxidative addition is occurring (within 10 min) under these catalyst conditions.

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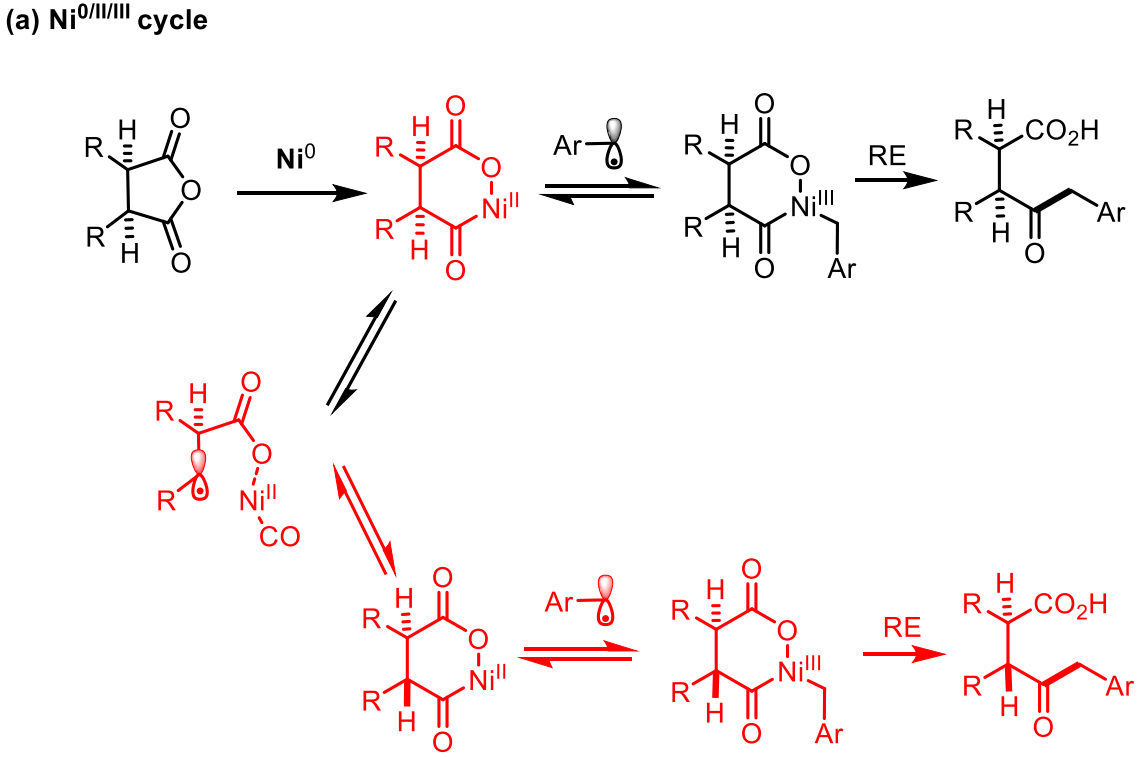
2.1. Generate radicals through C-B bond cleavage



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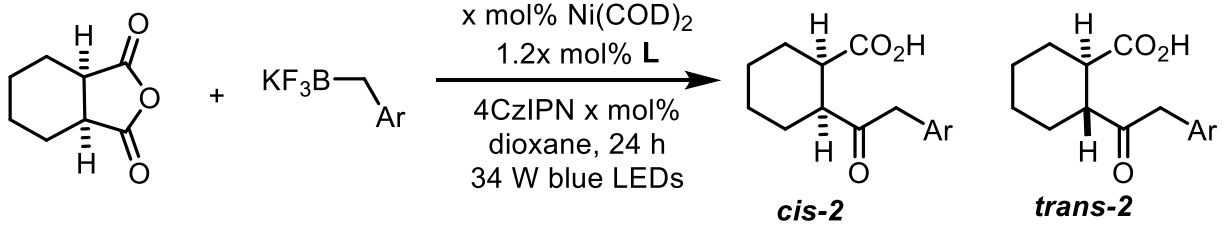
2.1. Generate radicals through C-B bond cleavage

Epimerization investigation



Entry	Nickel (mol%)	4CzIPN (mol%)	Yield[a] [%]	d.r.[b]	*ee cis*[c] [%]	*ee trans*[d] [%]
1	2.5	2	91	99:1	79	nd
2	5	2	72	24:1	87	nd
3	10	2	62	3.8:1	90	83
4	15	2	56	1.4:1	81	88
5	15	4	78	2.1:1	90	85
6	15	1	49	1:1.2	86	82

[a] Yield determined by ^{1}HNMR on 0.1 mmol scale using benzoic acid as a standard. [b] d.r. determined by HPLC on the acid on a chiral stationary phase. [c] ee of ***cis-2*** determined by HPLC on the methyl ester on a chiral stationary phase. [d] ee of ***trans-2*** determined by HPLC on the acid on a chiral stationary phase. [e] Performed on 0.25 mmol scale using benzoic acid as a standard.

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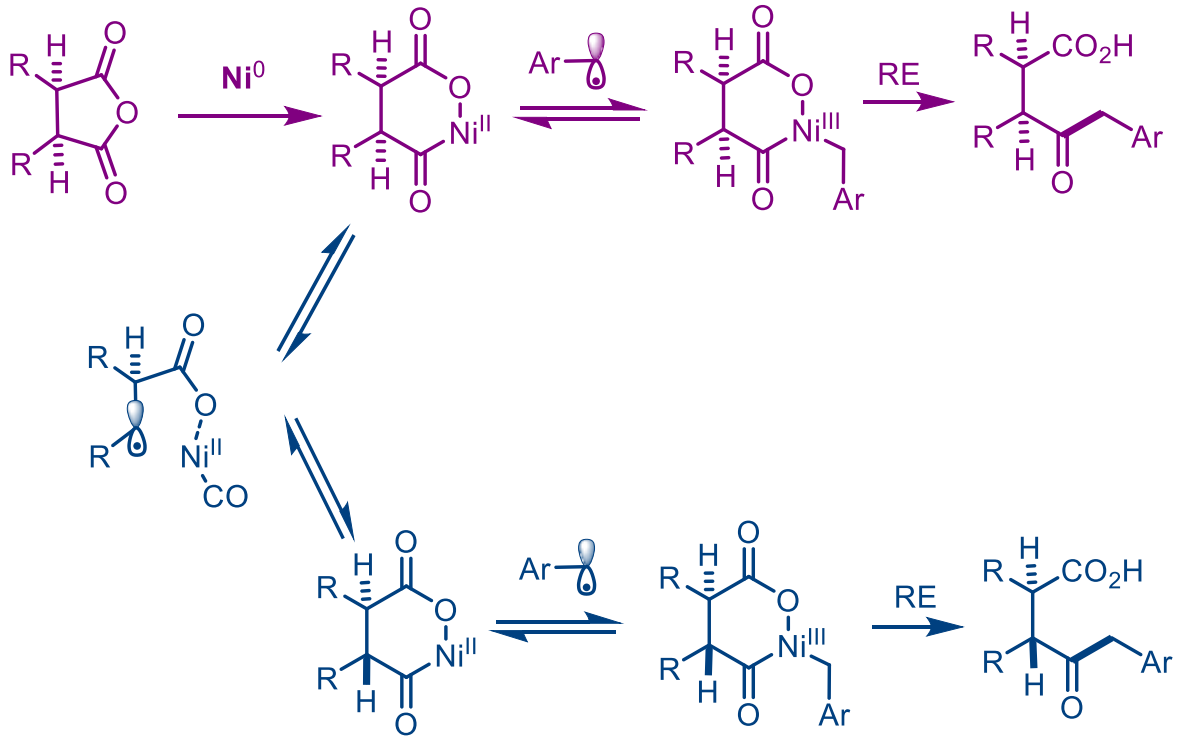
2.1. Generate radicals through C-B bond cleavage

(a) $Ni^{0/II/III}$ cycle



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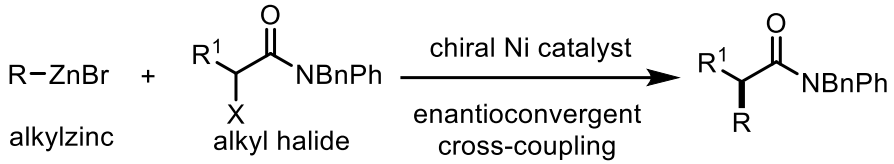
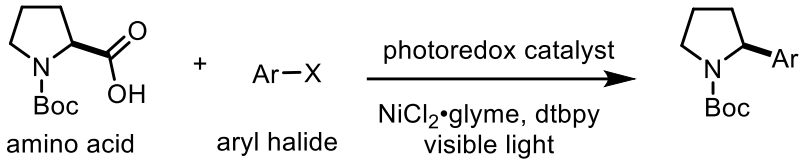
2.2. Generate radicals through C-C bond cleavage

Enantioselective Nickle-Catalyzed Cross-Coupling



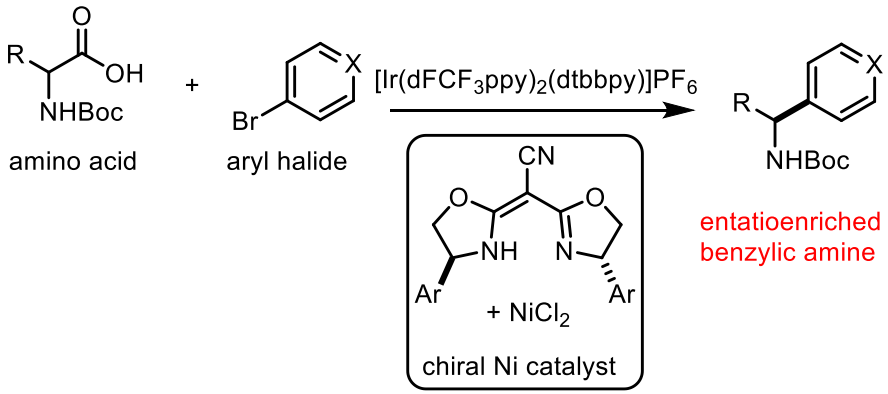
Fu, 2005

Photoredox-Nickle Decarboxylative Arylation



Doyle , Maclillan, 2014

Asymmetric Decarboxylative C_{sp3}-C_{sp2} Cross-Coupling

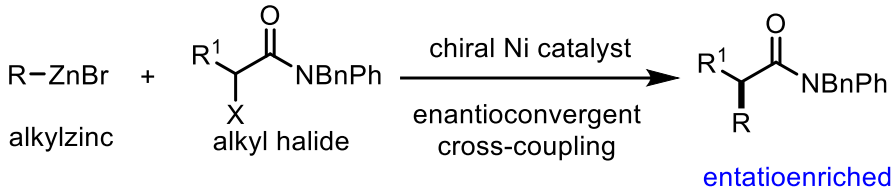


Fu + Maclillan, 2016

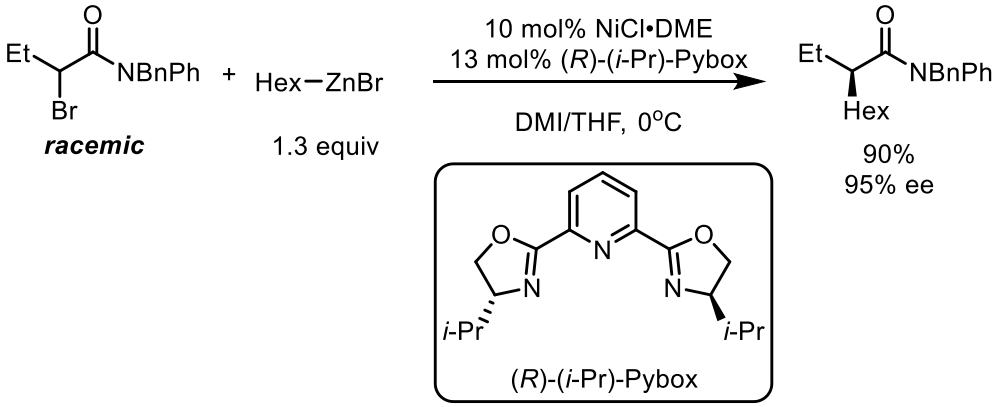
Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832.

2.2. Generate radicals through C-C bond cleavage

Enantioselective Nickle-Catalyzed Cross-Coupling



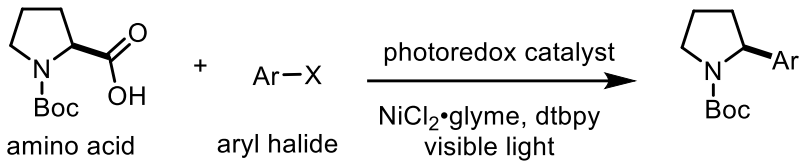
Fu, 2005



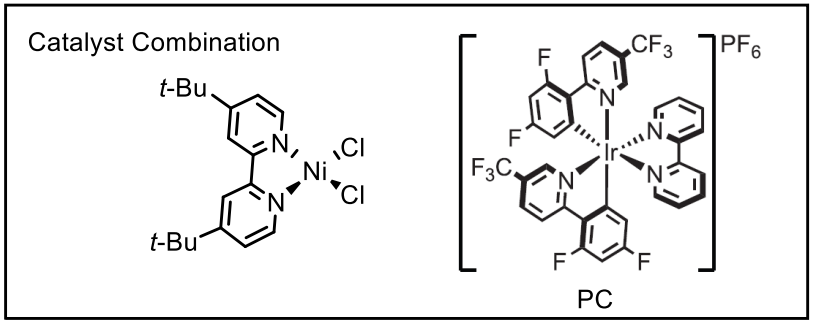
Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.

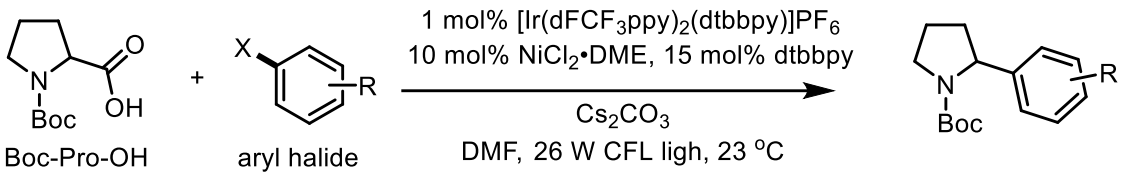
2.2. Generate radicals through C-C bond cleavage

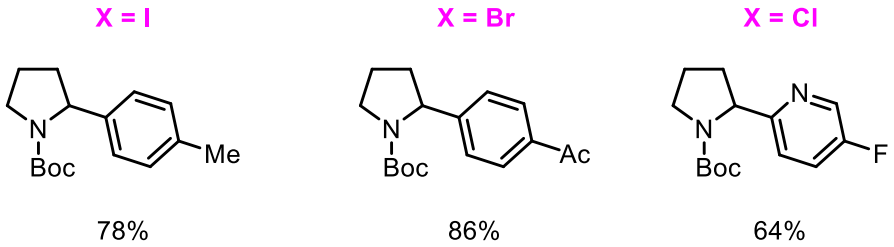
Photoredox-Nickle Decarboxylative Arylation



Doyle , Maclillan, 2014



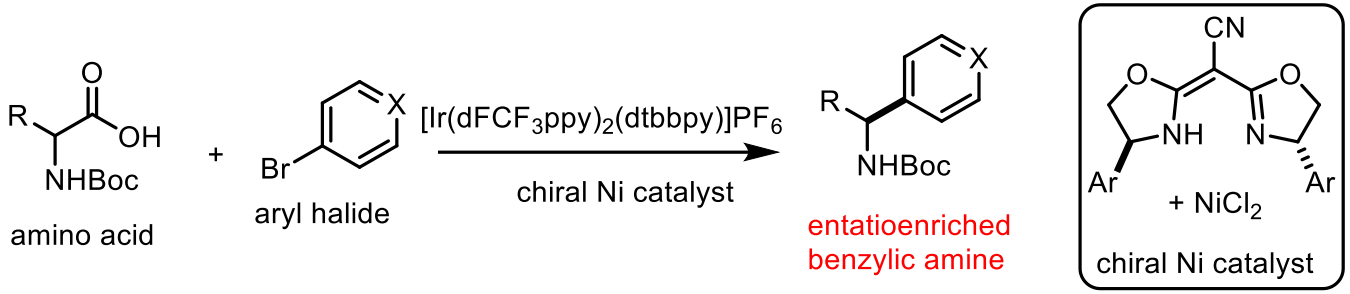


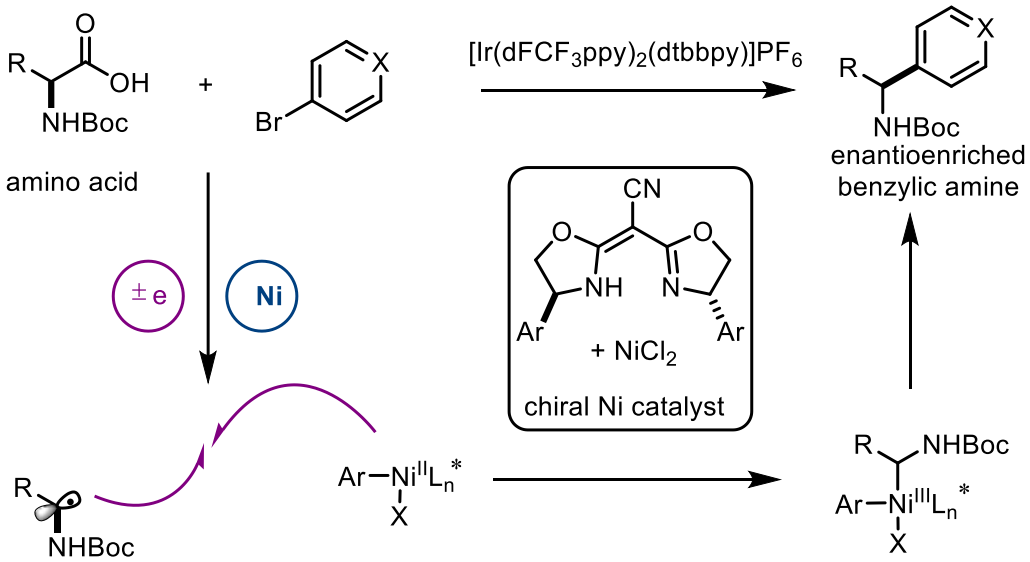


Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437.

2.2. Generate radicals through C-C bond cleavage

Asymmetric Decarboxylative C_{sp3}-C_{sp2} Cross-Coupling





Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832.

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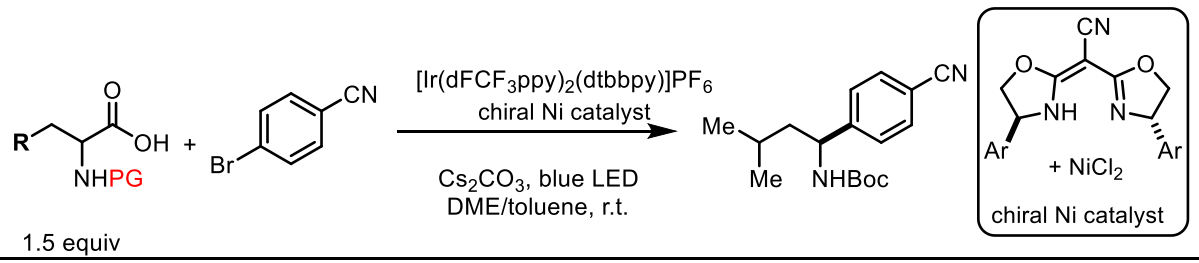
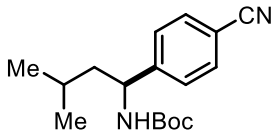
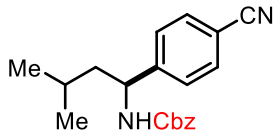
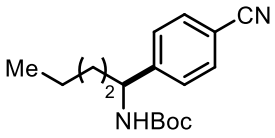




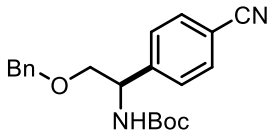
1
71%, 92% ee



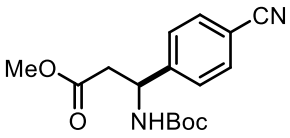
2
45%, 88% ee



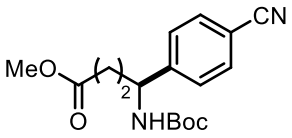
3
84%, 90% ee



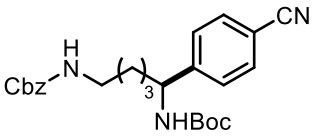
4
84%, 84% ee



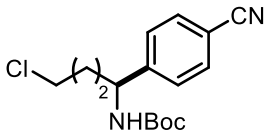
5
80%, 82% ee



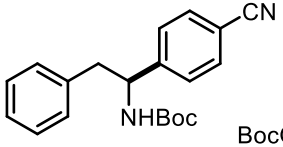
6
84%, 82% ee



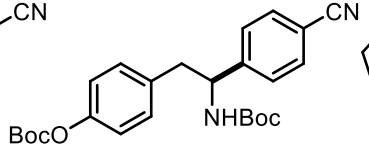
7
74%, 85% ee



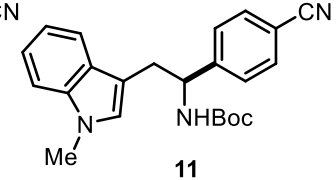
8
71%, 85% ee



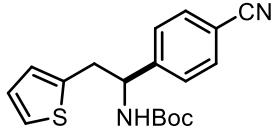
9
67%, 90% ee



10
76%, 85% ee



11
51%, 84% ee

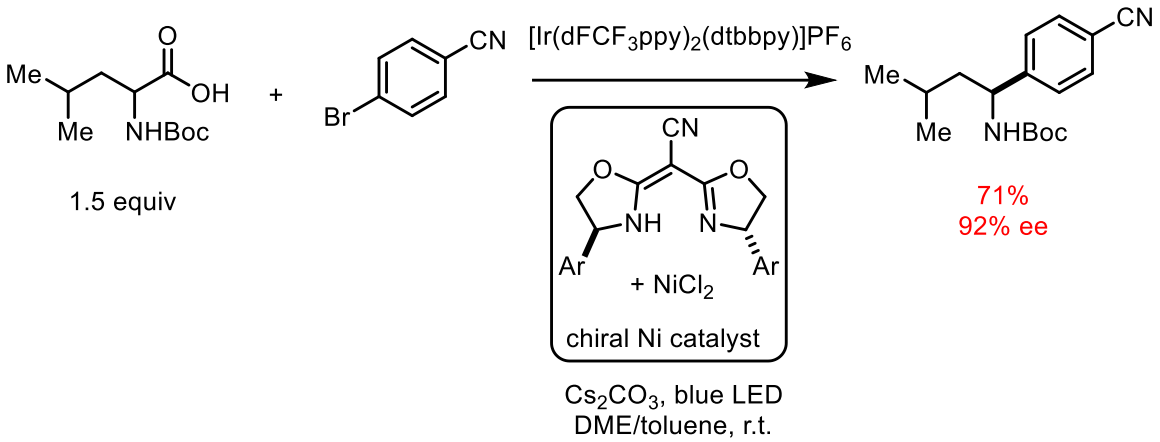


12
72%, 91% ee

Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832.

2.2. Generate radicals through C-C bond cleavage

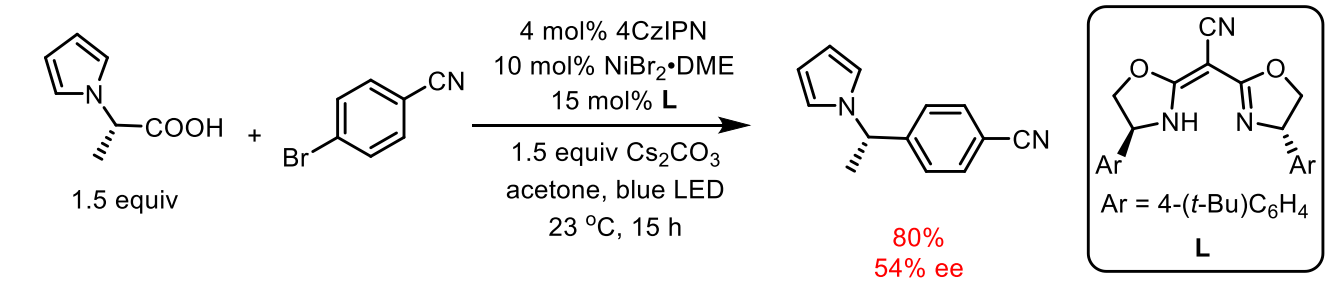
Asymmetric Decarboxylative C_{sp3}-C_{sp2} Cross-Coupling

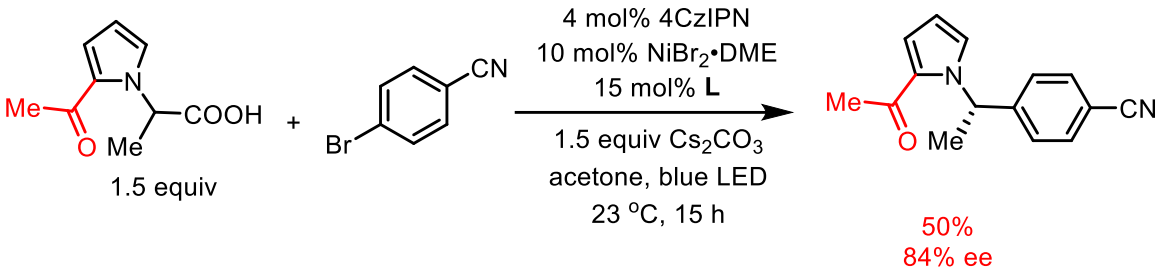


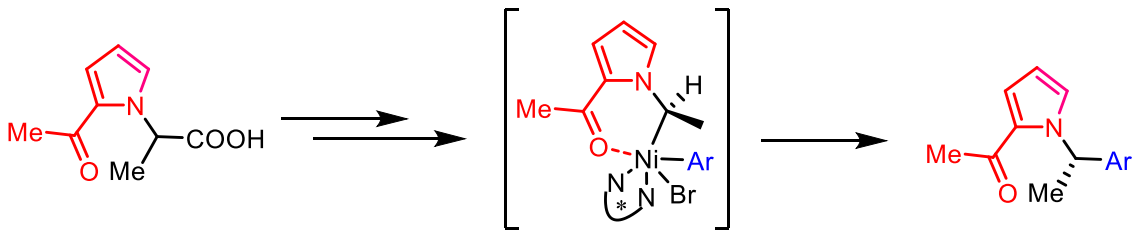
Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832.

Pezzetta, C.; Bonifazi, D.; Davidson, R. W. M. *Org. Lett.* **2019**, *21*, 8957.

2.2. Generate radicals through C-C bond cleavage





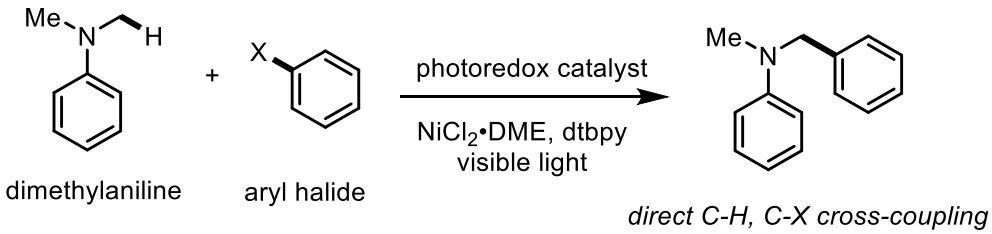


Hypothetical chelation of the alkyl radical to Ni thanks to a directing group on the Heterocyclic moiety

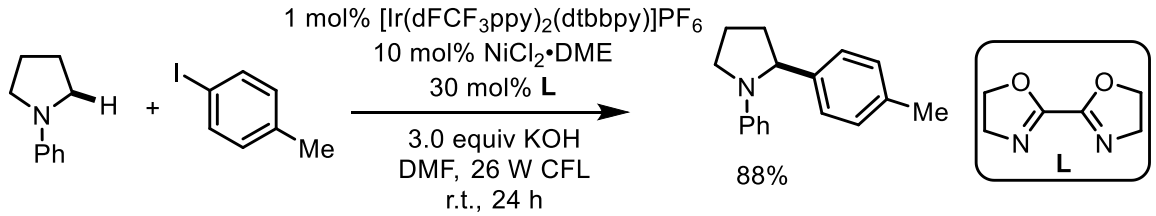
Pezzetta, C.; Bonifazi, D.; Davidson, R. W. M. *Org. Lett.* **2019**, *21*, 8957.

Contents

2.3. Generate radicals through C-H bond cleavage

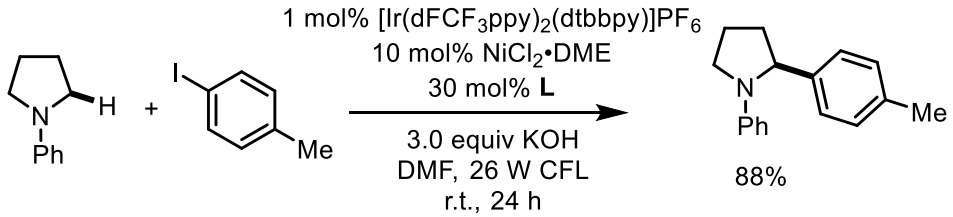


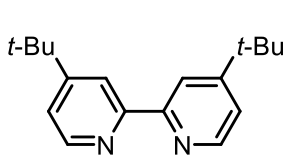
Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science 2014*, **345**, 437.

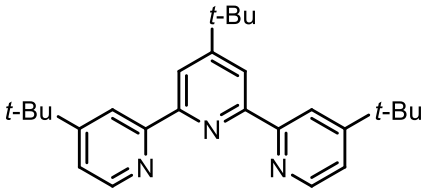


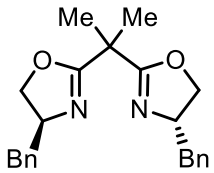
Ahneman, D. T.; Doyle, A. G. *Chem. Sci.* **2016**, *7*, 7002.

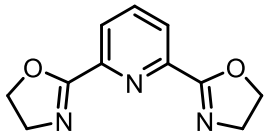
2.3. Generate radicals through C-H bond cleavage

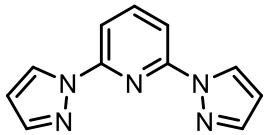


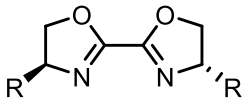

dtbbpy, 0 yield

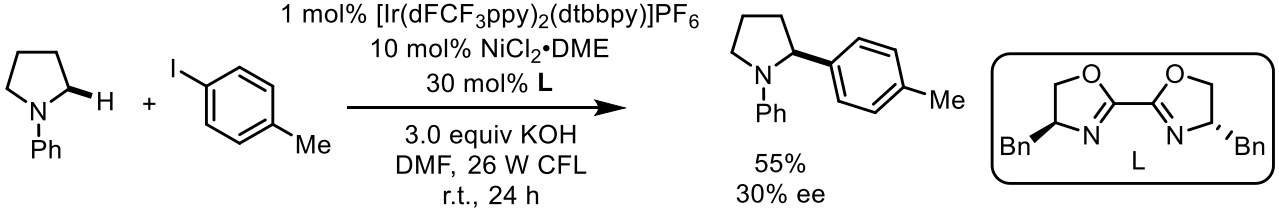

terpy', 0 yield


Bn-Box, 0 yield


PyBox, 0 yield

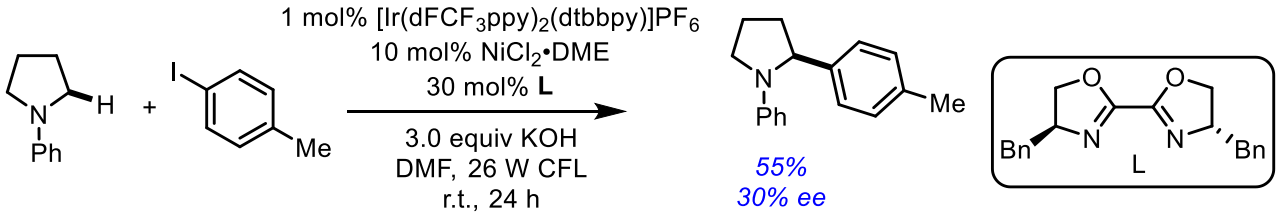

bpp, 10 % yield


R = H BiOx, 88 % yield
R = Bn Bn-BiOx, 54 % yield
R = *i*-Pr *i*-Pr-BiOx, 0 yield

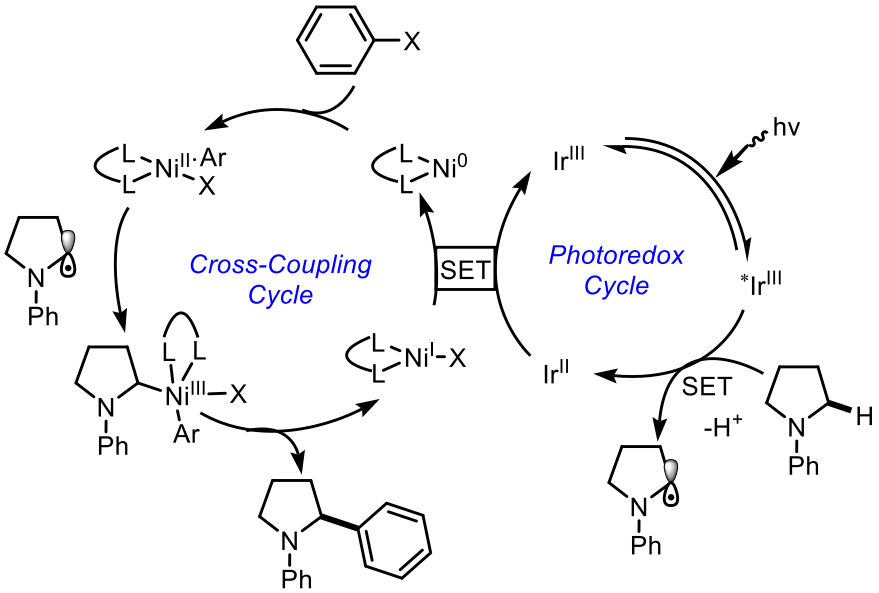


Ahneman, D. T.; Doyle, A. G. *Chem. Sci.* **2016**, *7*, 7002.

2.3. Generate radicals through C-H bond cleavage

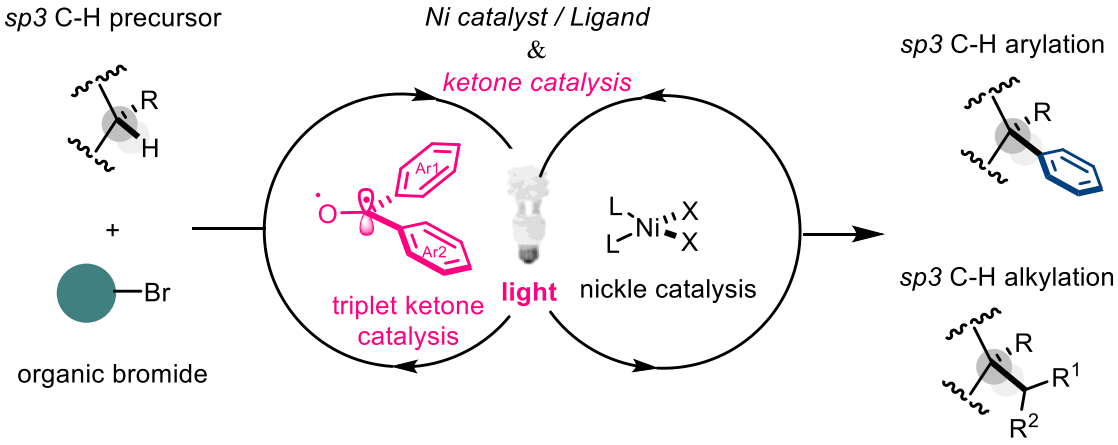


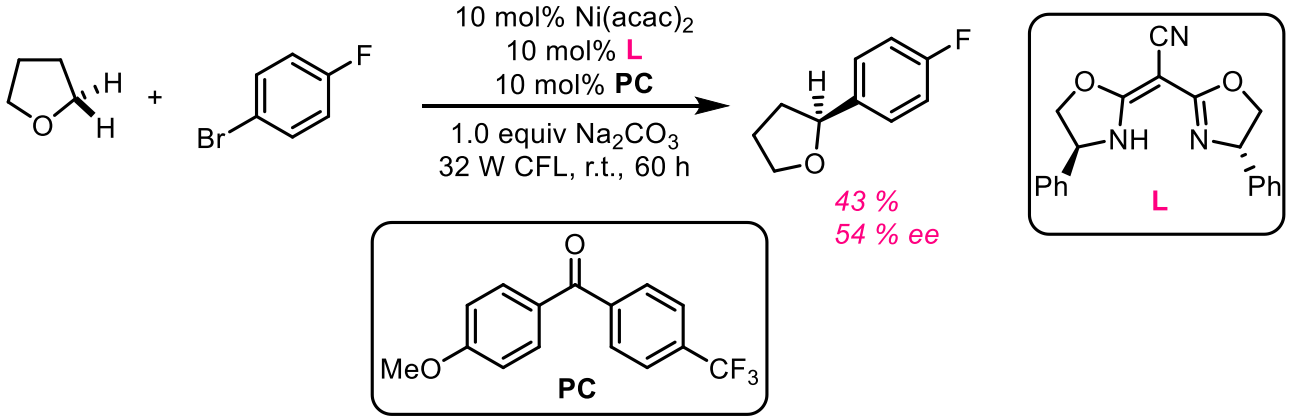
Proposed mechanism



Ahneman, D. T.; Doyle, A. G. *Chem. Sci.* **2016**, *7*, 7002.

2.3. Generate radicals through C-H bond cleavage

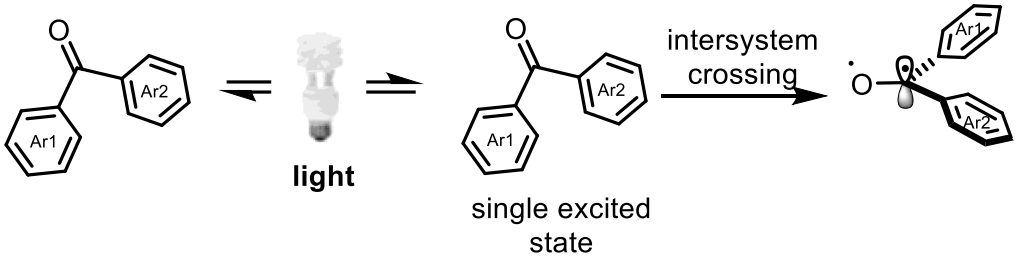




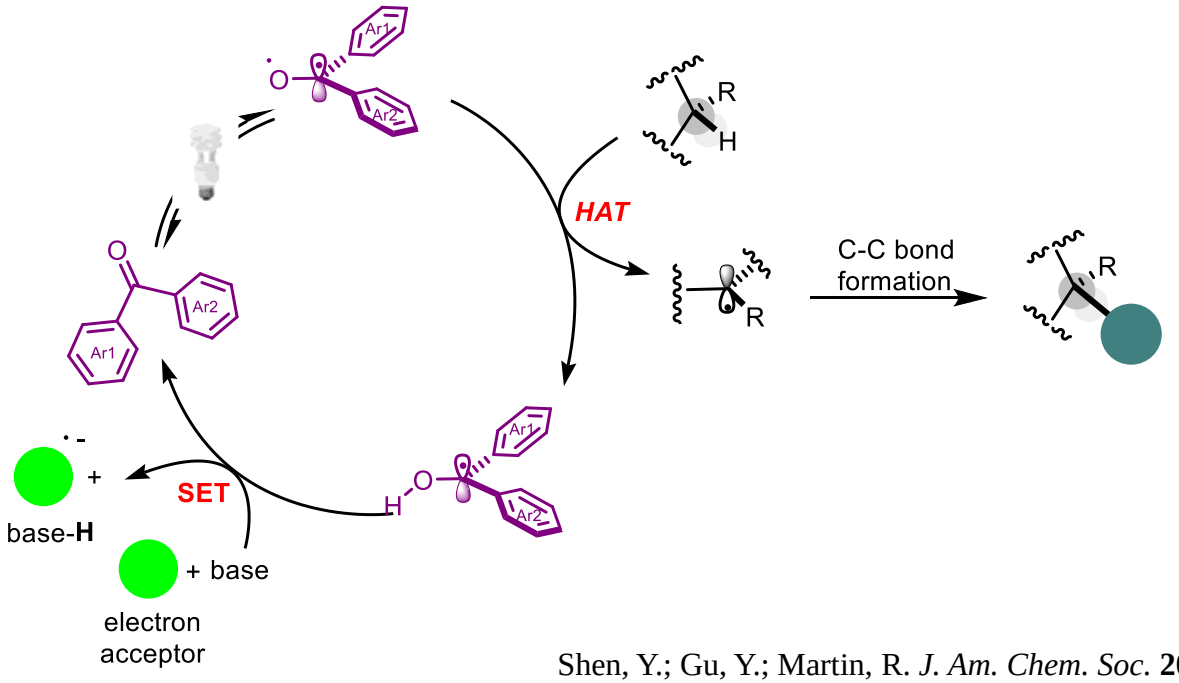
Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.

2.3. Generate radicals through C-H bond cleavage

Triplet photoexcited Diaryl ketones



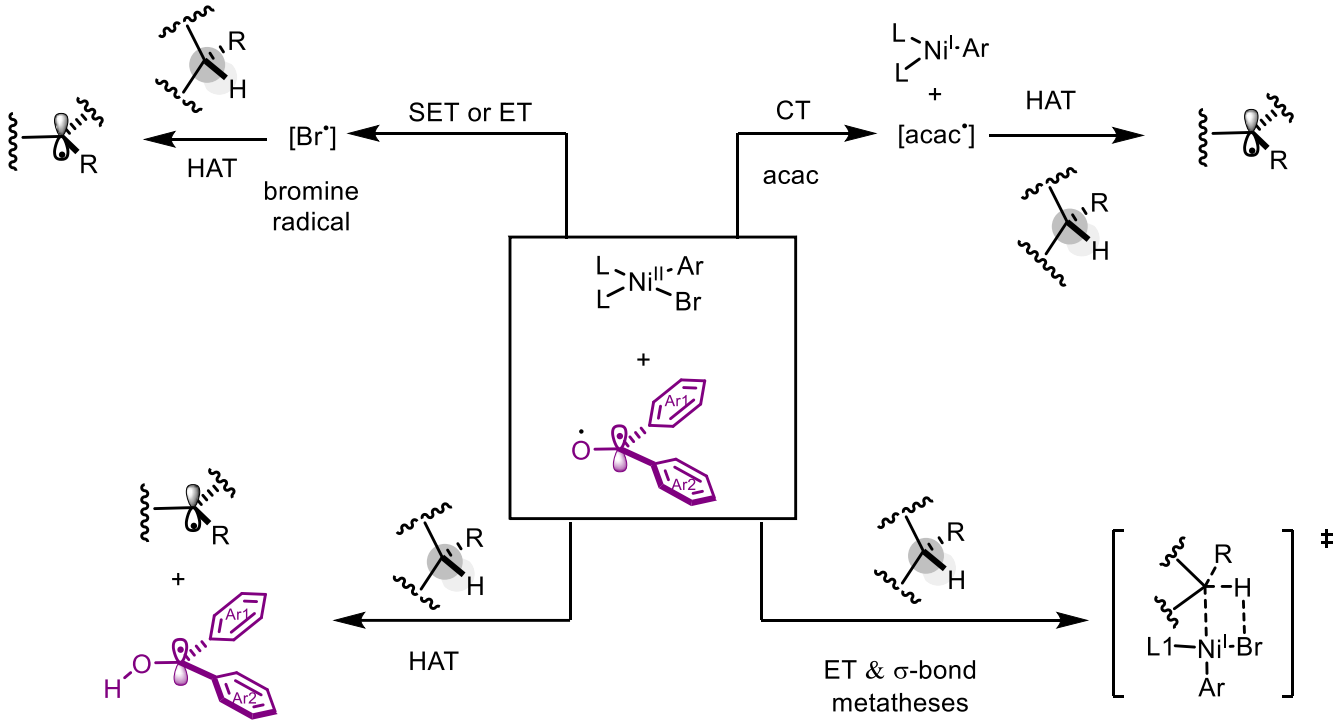
Triplet ketones as HAT and SET catalysts



Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.

2.3. Generate radicals through C-H bond cleavage

Proposed Pathways for sp3 C.H Cleavage

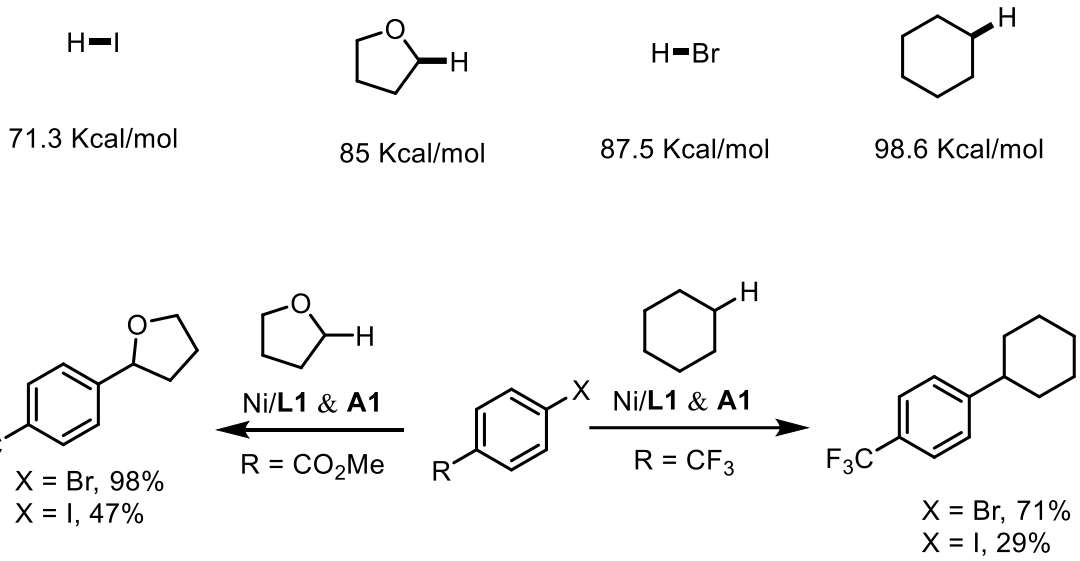


Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.

2.3. Generate radicals through C-H bond cleavage

Ruling Out the Intermediacy of Br Radicals

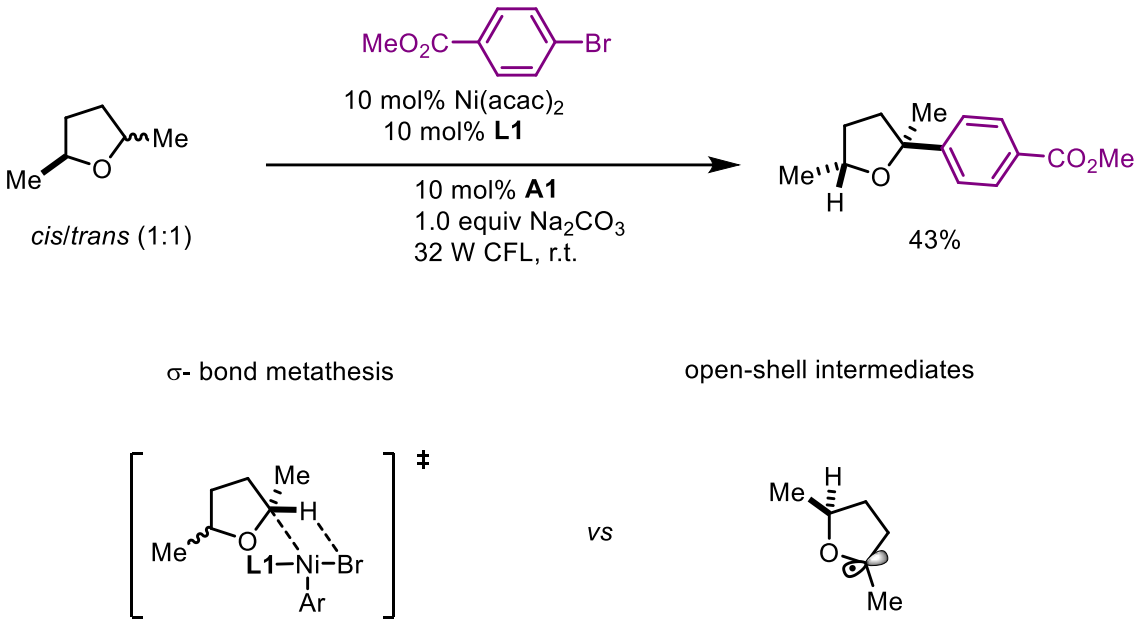
BDE mismatch



Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.

2.3. Generate radicals through C-H bond cleavage

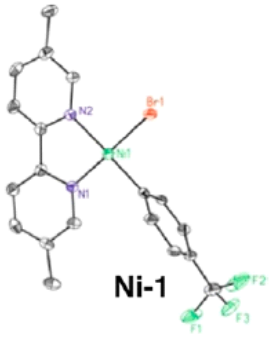
Assessing Intramolecular σ-Bond Metathesis

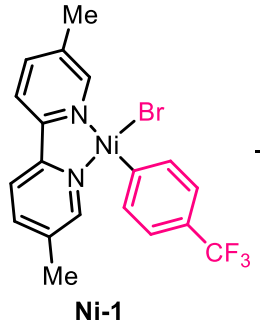


Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.

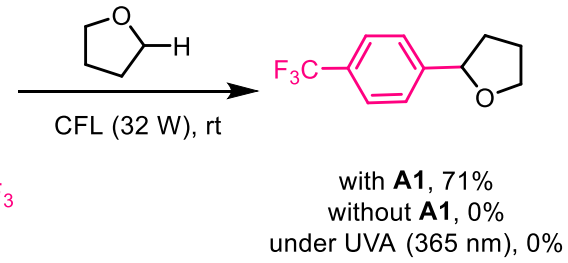
2.3. Generate radicals through C-H bond cleavage

Stoichiometric experiments with Ni-1



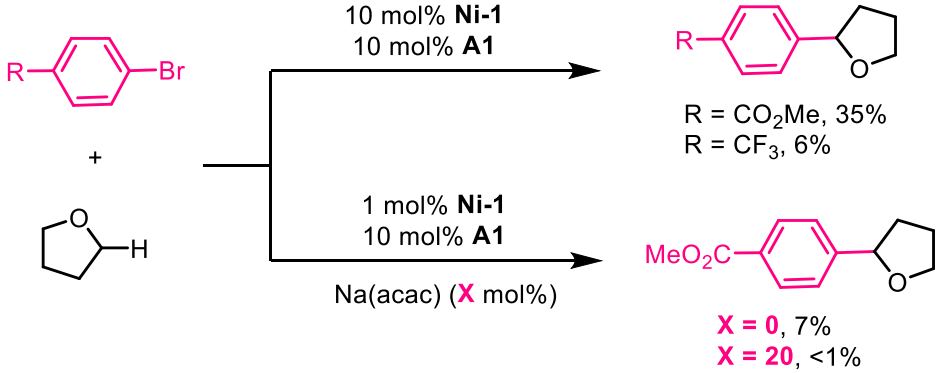


Ni-1



with **A1**, 71%
without **A1**, 0%
under UVA (365 nm), 0%

Catalytic competence of Ni-1

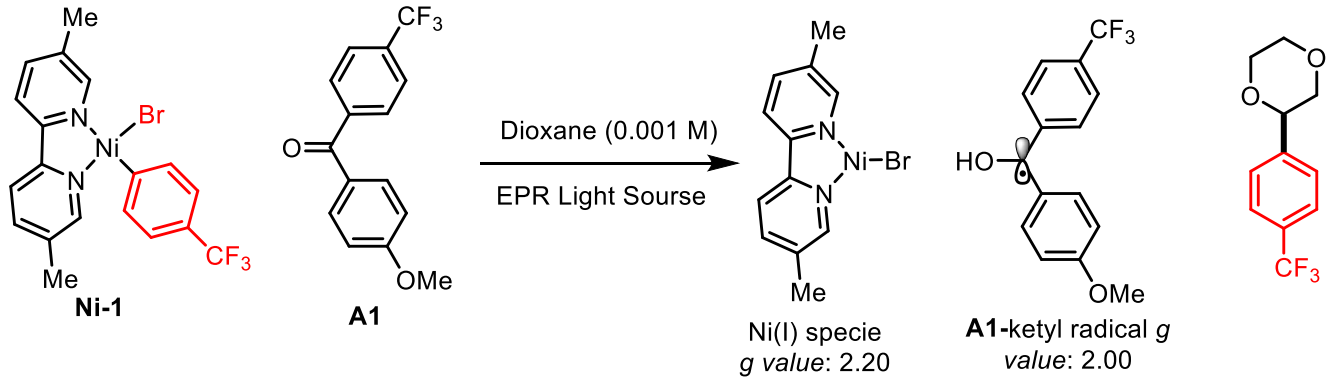


R = CO_2Me, 35%
R = CF_3, 6%

X = 0, 7%
X = 20, <1%

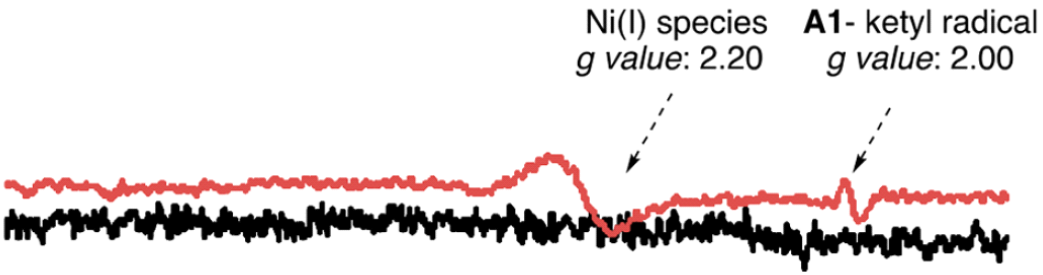
Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.

2.3. Generate radicals through C-H bond cleavage



EPR experiments with Ni-1

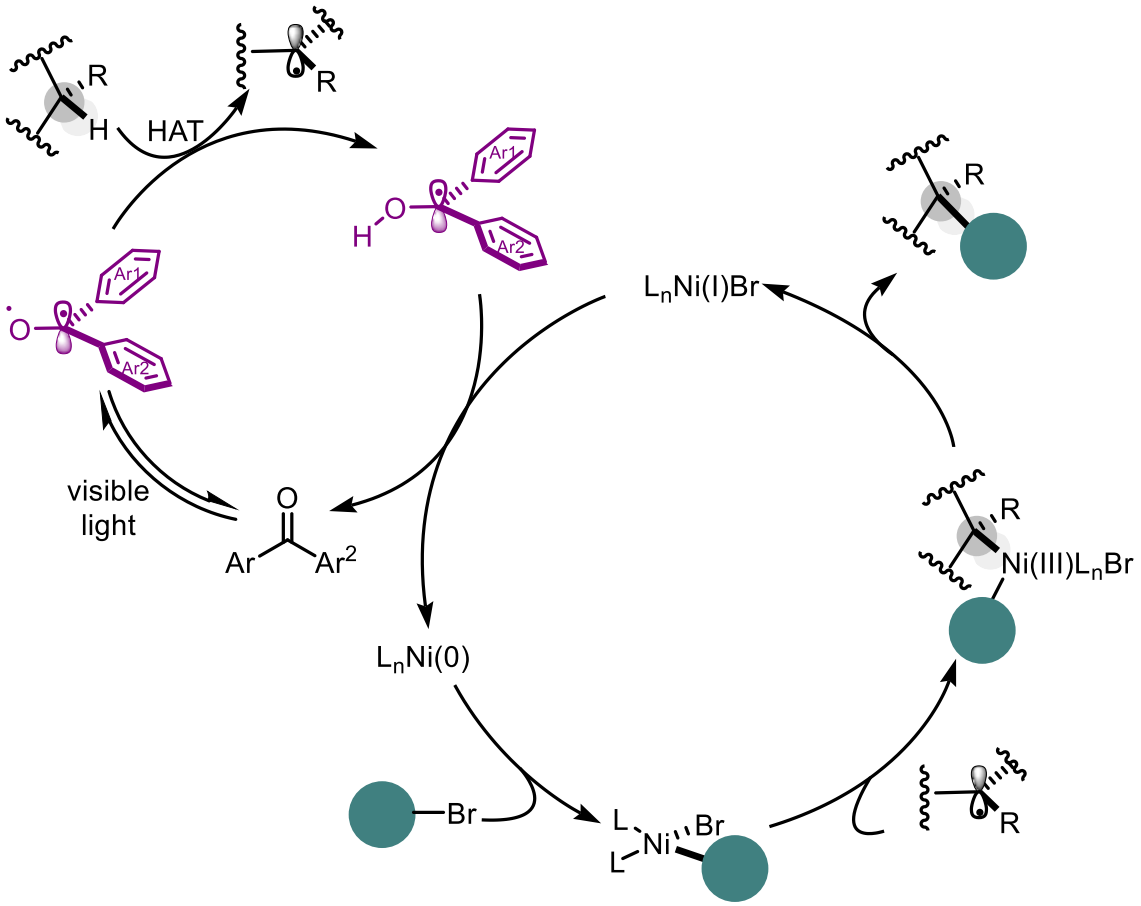
--- **Ni-1** + **A1** Irradiation (0 min)
--- **Ni-1** + **A1** Irradiation (30 min)
g value 2.20: g value 2.00



Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.

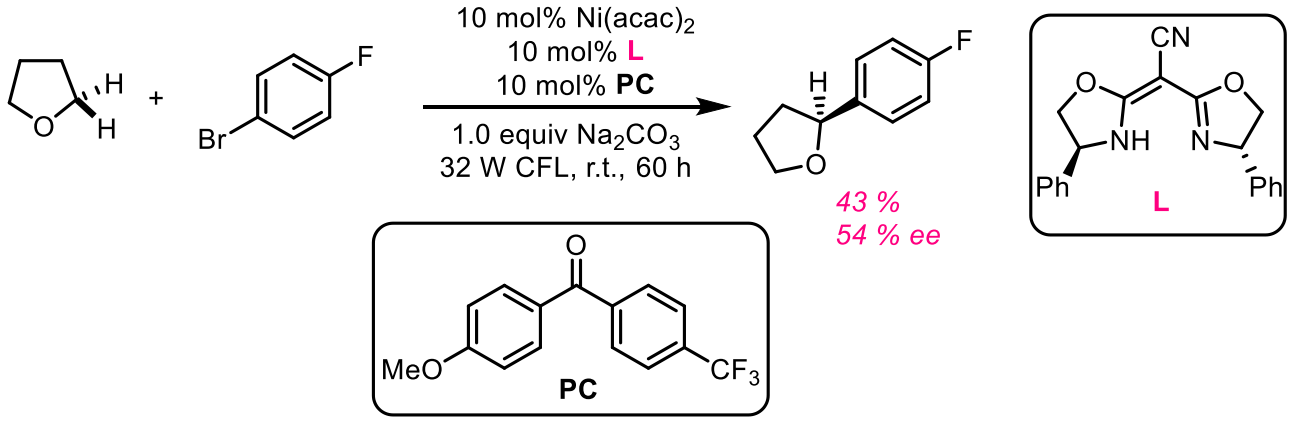
2.3. Generate radicals through C-H bond cleavage

Mechanistic Hypothesis



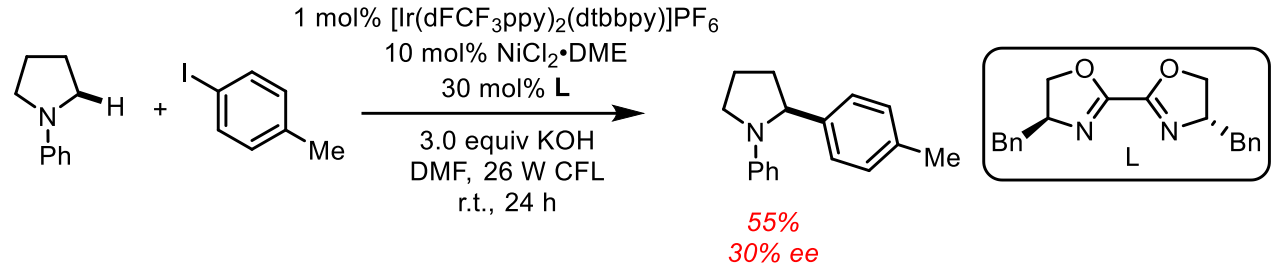
Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.

2.3. Generate radicals through C-H bond cleavage

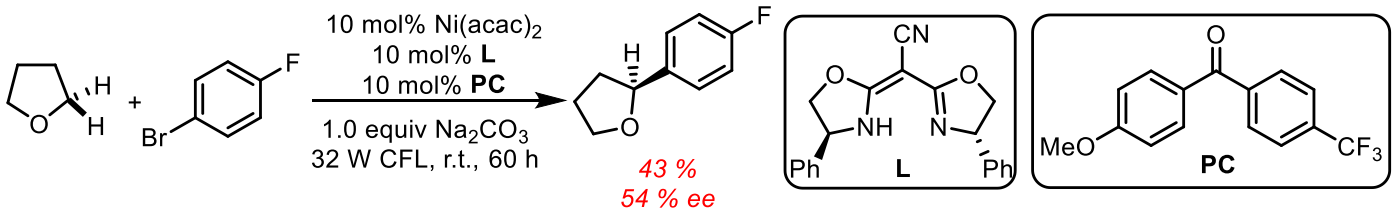


Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.

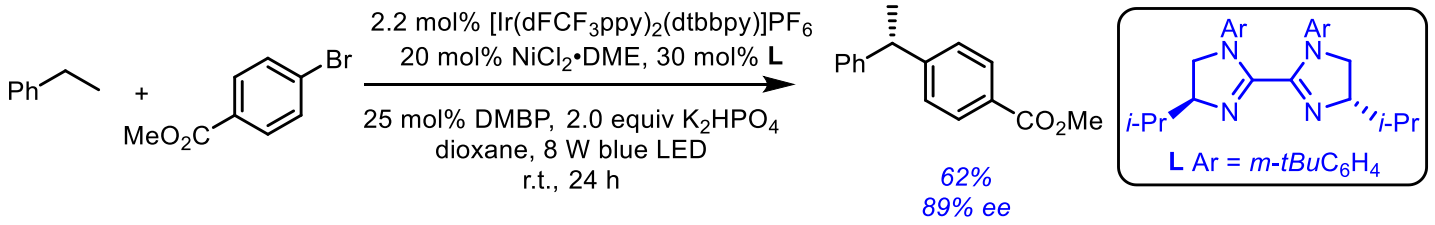
2.3. Generate radicals through C-H bond cleavage



Derek T. Ahneman, Abigail G. Doyle *Chem. Sci.* **2016**, *7*, 7002.

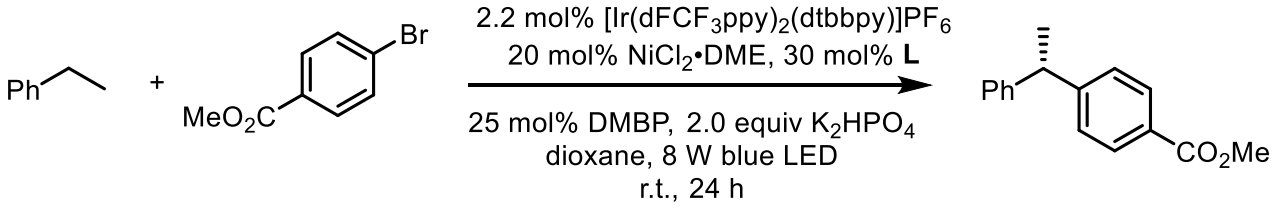


Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.

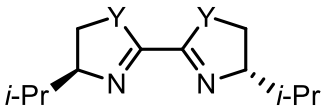


Cheng, X.; Lu, H.; Lu, Z. *Nature Commun.* **2019**,*10*, 3549.

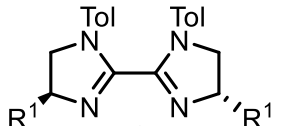
2.3. Generate radicals through C-H bond cleavage



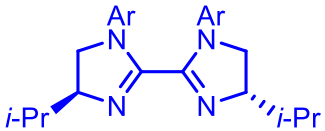
Entry	L	yield (%)	ee
1	**LS1**	79	38
2	**LS2**	33	25
3	**L1a**	44	85
4	**L1b**	62	72
5	**L1c**	35	84
6	**L1d**	44	85
7	**L1e**	44	90
8[b]	**L1e**	62	89
9[c]	**L1e**	62	85



LS1 Y = O
LS2 Y = N*i*Pr



L1a R^1 = *i*Pr
L1b R^1 = *s*Bu
L1c R^1 = Cy

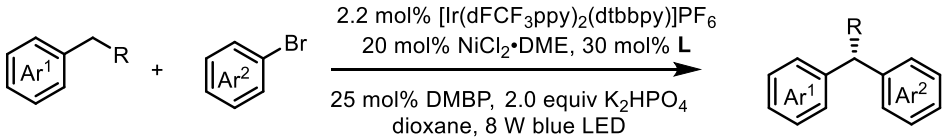


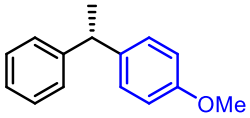
L1d Ar = *m*-*i*PrC$_6$H$_4$
L1e Ar = *m*-*tBu*C$_6$H$_4$

[a]General reaction conditions: 1a (1.0 mL), 2a (0.2 mmol), Ir(dFCF$_3$ppy)$_2$(dtbbpy)Cl (2.2 mol%), NiCl$_2$•DME (20 mol%), **L** (20 mol%), DMBP (25 mol%), and K$_2$HPO$_4$ (2.0 equiv.) in dioxane (3 mL) under the irradiation of 8W blue LEDs for 24 h. Yields determined by 1H-NMR using TMSPh as an internal standard. Enantiometric ratio (ee) determined by chiral HPLC. [b]Run for 34 h. [c]Using 1a (0.8 mmol) for 96 h

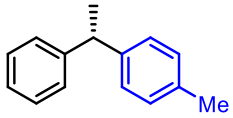
Cheng, X.; Lu, H.; Lu, Z. *Nature Commun.* **2019**,*10*, 3549.

2.3. Generate radicals through C-H bond cleavage

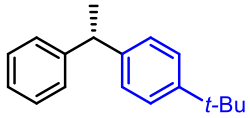




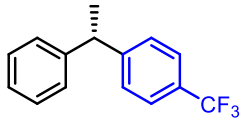
58%, 90% ee



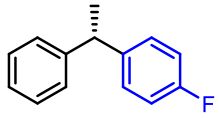
61%, 90% ee



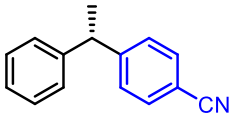
84%, 91% ee



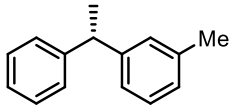
45%, 89% ee



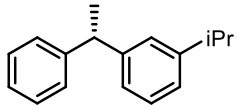
71%, 87% ee



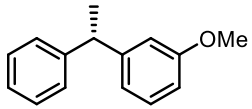
50%, 86% ee



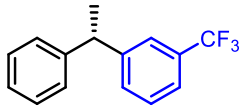
82%, 91% ee



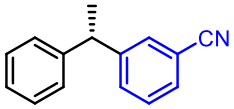
87%, 88% ee



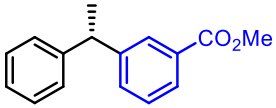
67%, 89% ee



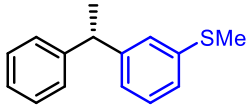
63%, 90% ee



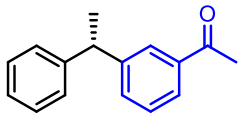
59%, 80% ee



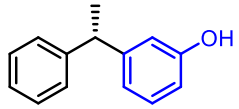
59%, 87% ee



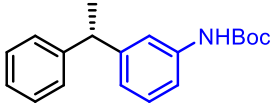
34%, 91% ee



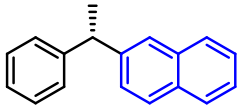
66%, 85% ee



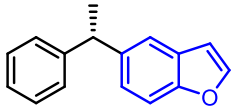
46%, 90% ee



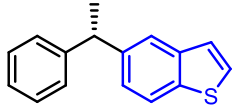
73%, 80% ee



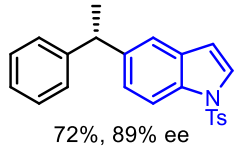
48%, 91% ee



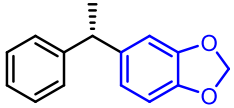
66%, 88% ee



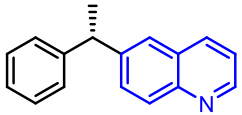
56%, 88% ee



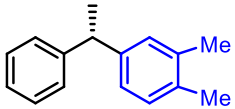
72%, 89% ee



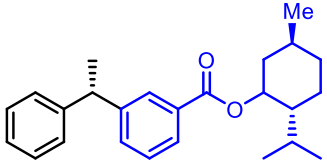
50%, 89% ee



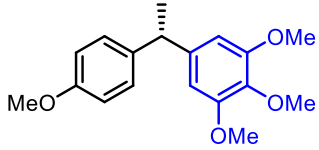
79%, 70% ee



68%, 92% ee



61%, 87% ee

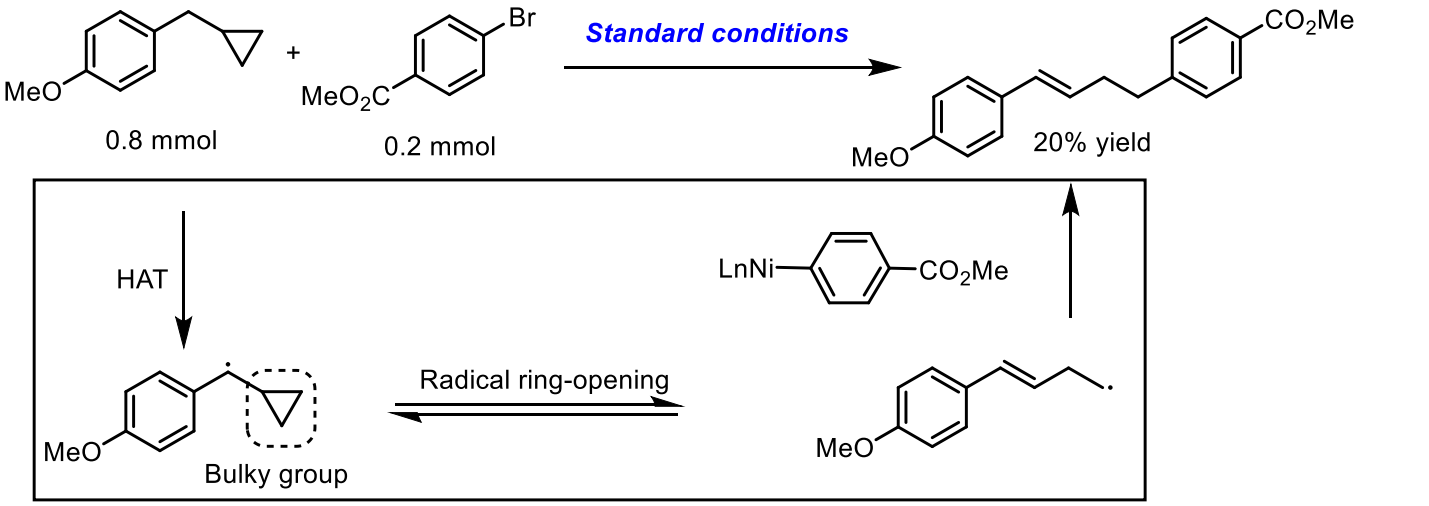


23%, 85% ee

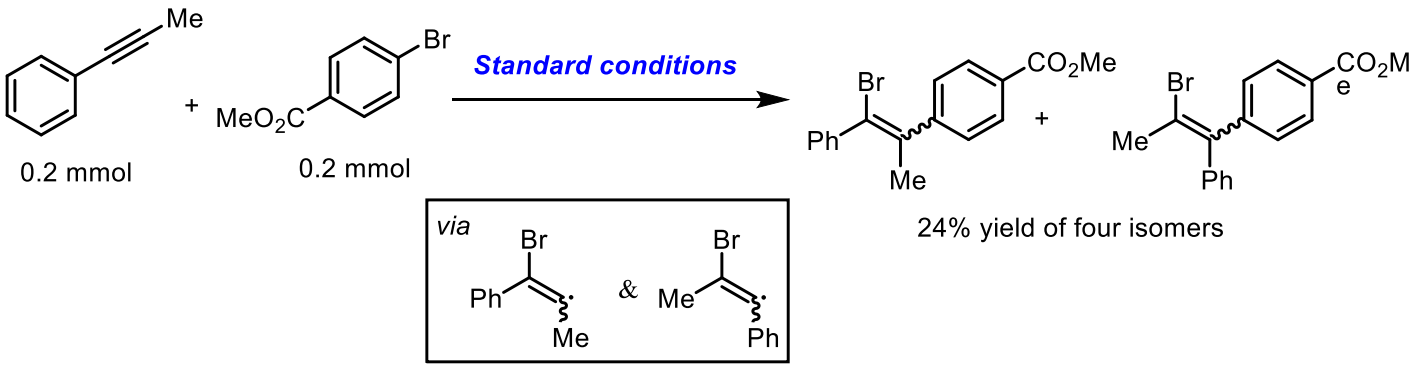
Cheng, X.; Lu, H.; Lu, Z. *Nature Commun.* **2019**,*10*, 3549.

2.3. Generate radicals through C-H bond cleavage

Radical-clock experiments



Bromine radical trapping experiments



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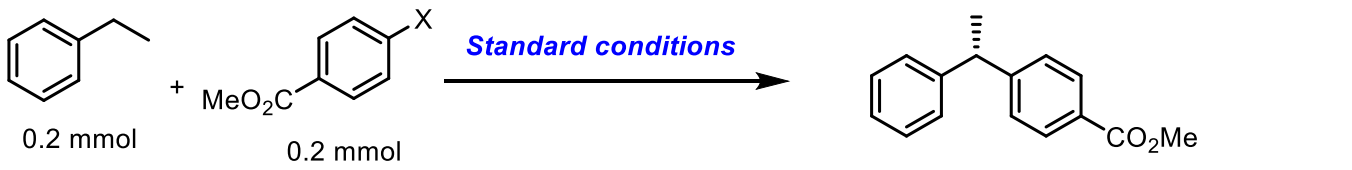
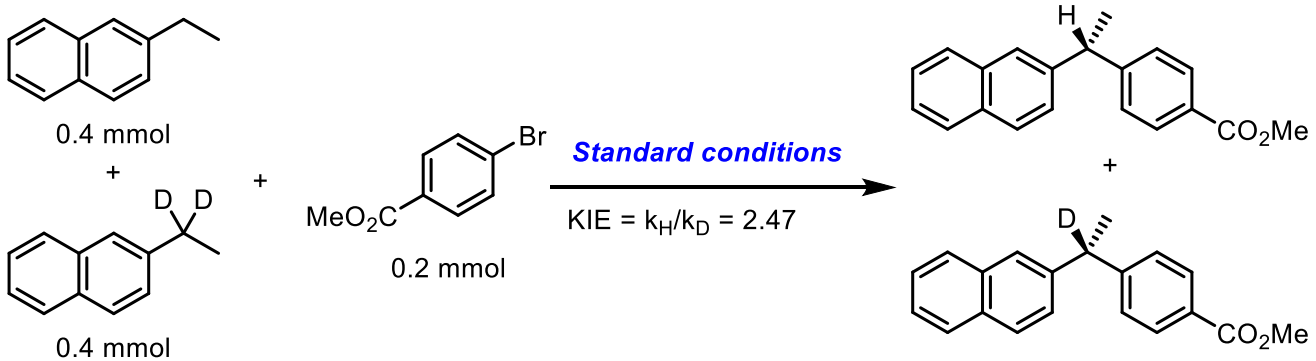
2.3. Generate radicals through C-H bond cleavage

Halide additive studies



X= Cl, 0% yield
X= Br, 62% yield
X= I, 0% yield
X= Cl, with 1.0 equiv. of KBr, 58% yield

Kinetic isotopic effect experiments



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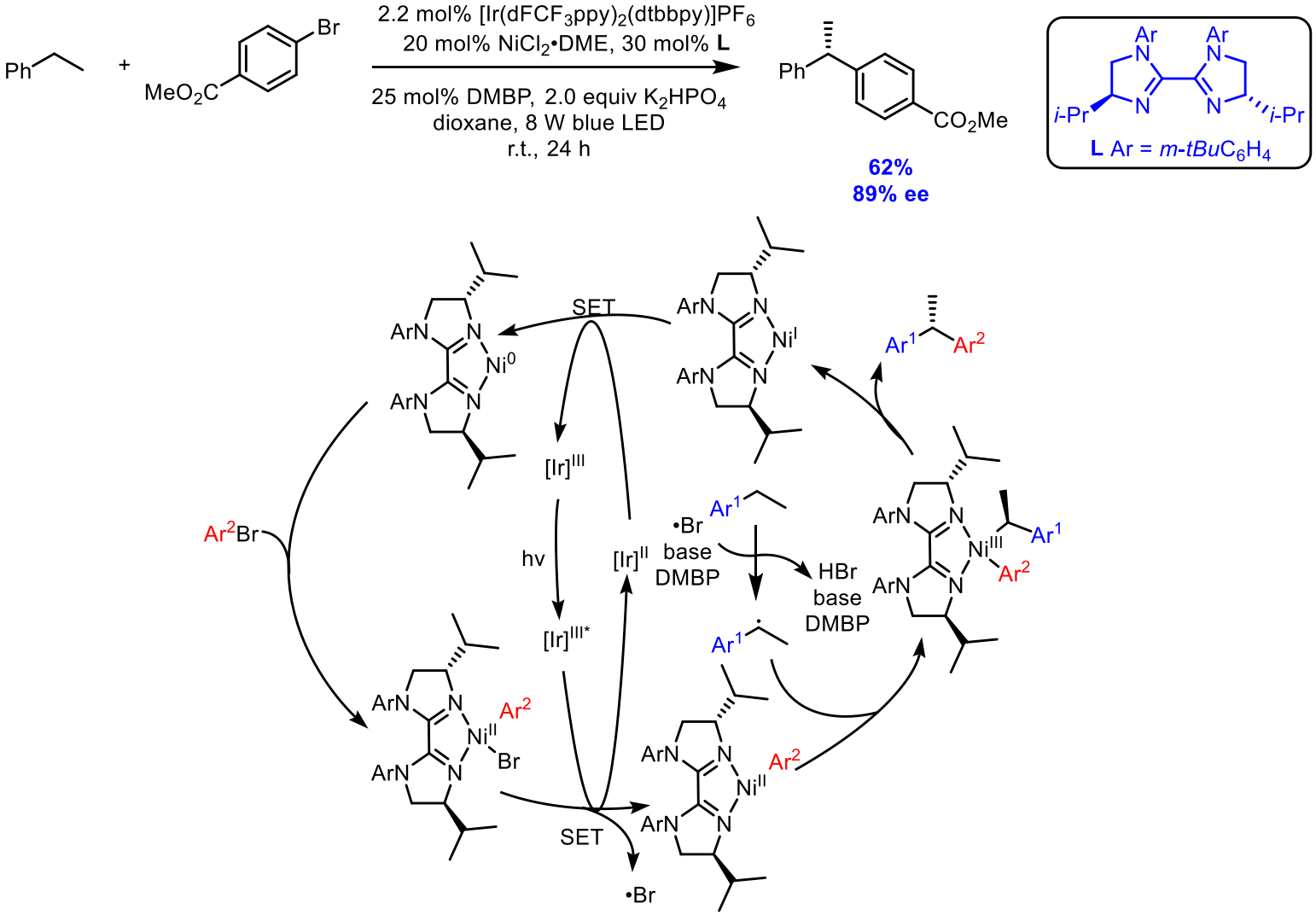
2.3. Generate radicals through C-H bond cleavage



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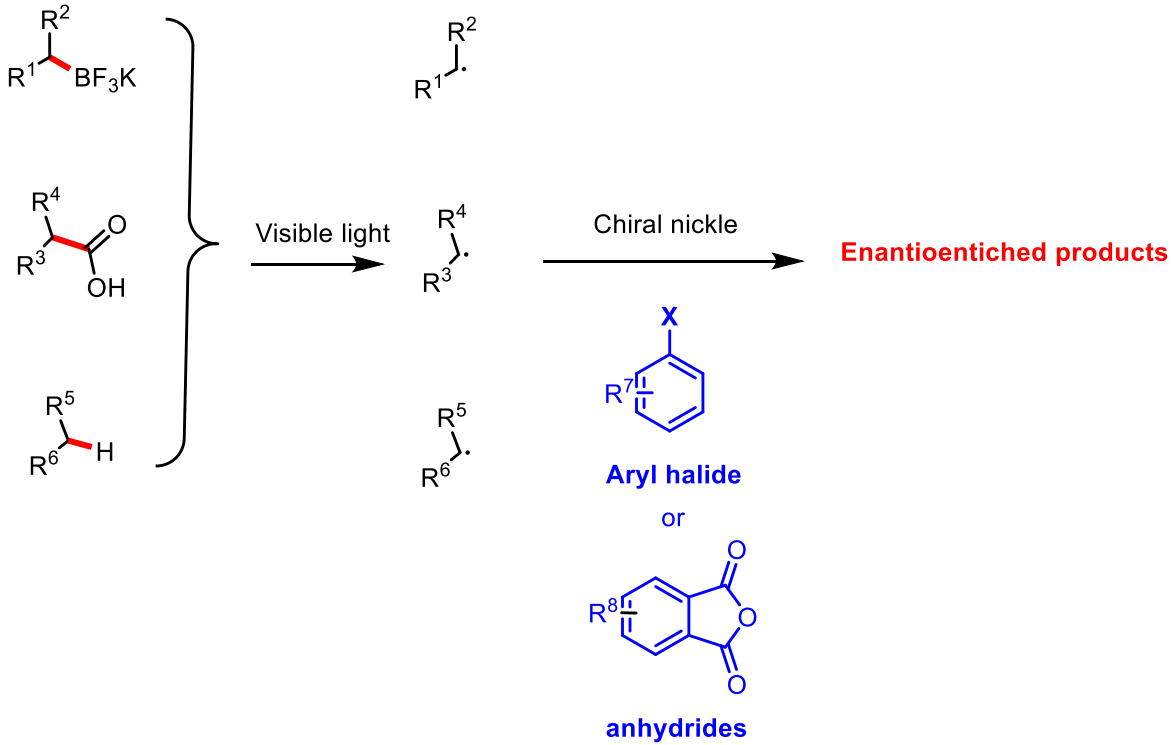
Contents

3. Summary



Chanllenges and chances

1. **Different reaction substrates (now the reaction substrates limited in aryl halides and anhydrides)**
2. **Complex structure latestage functionallization (for medicines and natural products)**
3. **Limited construction C-C BOND (still many chemical bond should be explore, C-N, C-O, C-S, C-P et.al)**
4. **C-H/C-H bond radical coupling**

Thanks for your attention!