Literature Report V

Enantioselective Three-Component Fluoroalkylarylation of Unactivated Olefins

Reporter: Yi-Xuan Ding
Checker: Zhou-Hao Zhu
Date: 2020-7-6

Chu, L. *et al. J. Am. Chem. Soc*. **2020**, *142*, 9604

CV of Prof. Lingling Chu

Education and Employment:

- **2003–2007** B.S., Hefei University of Technology
- **2007–2012** Ph.D., SIOC.
- **2012–2013** Assistant Professor, SIOC.
- **2013–2016** Postdoc., Princeton University
- **2016–Now** Professor, Donghua University

Research Interests:

- Develop novel and efficient catalytic systems by using clean and renewable energy
- Develop synthetic methodologies for fluorinated organic compounds

Contents

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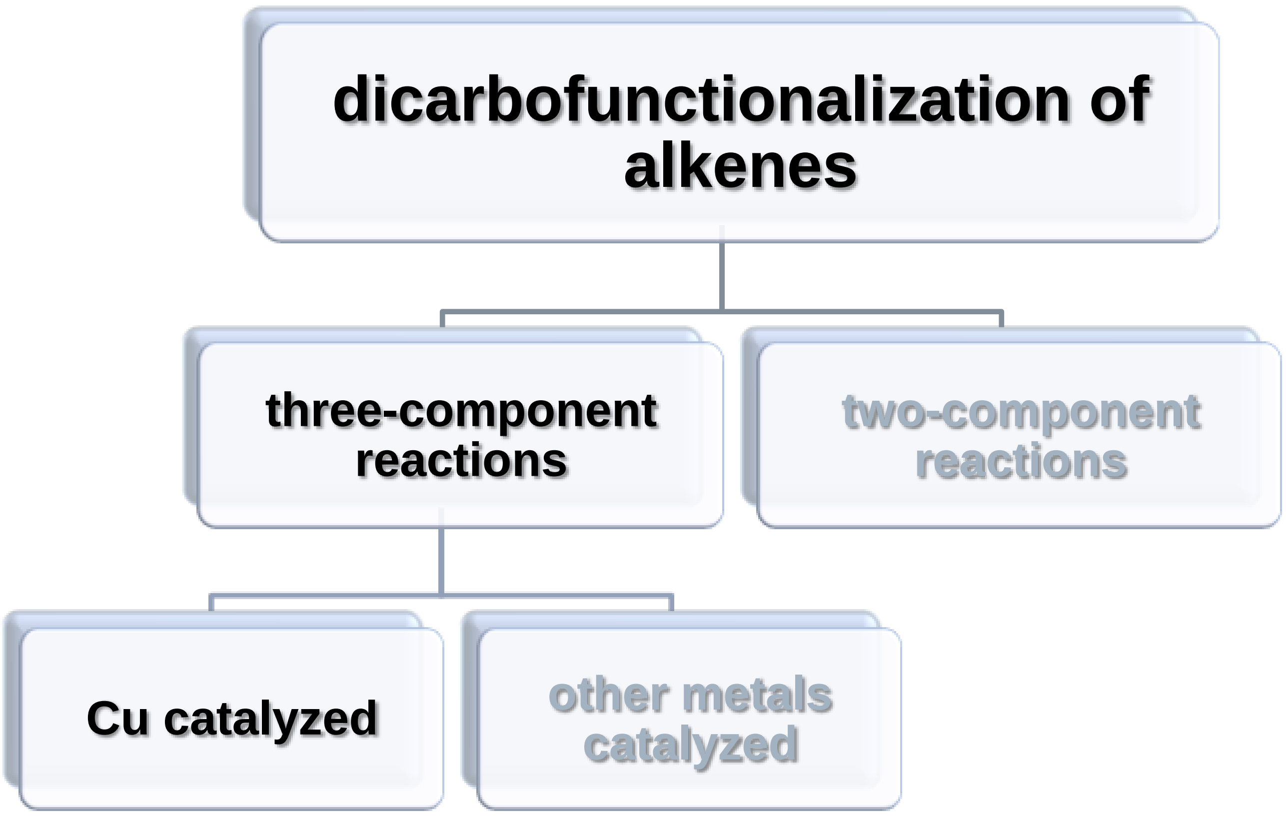
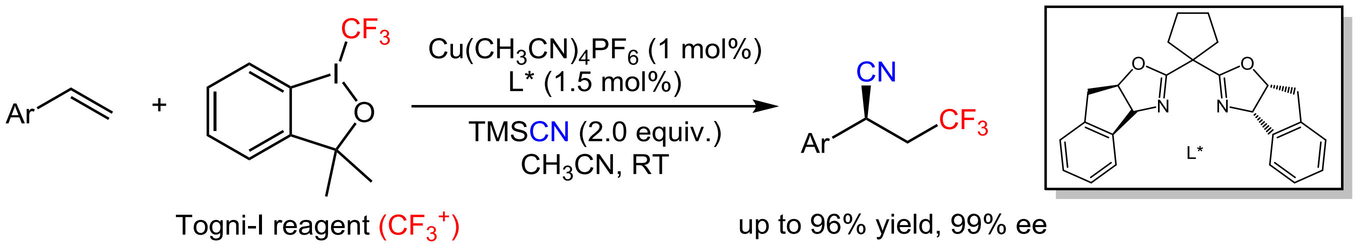
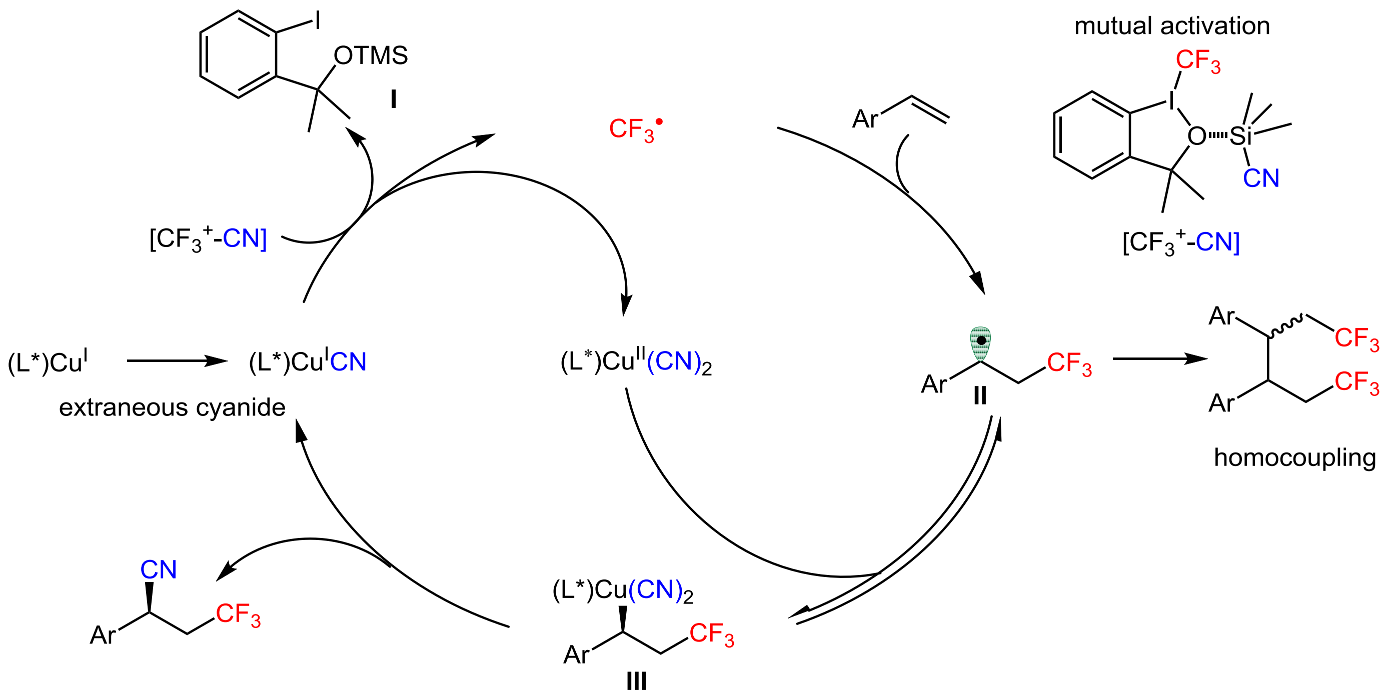


Introduction





Liu, G. *et al. J. Am. Chem. Soc.* **2016**, *138*, 15547.

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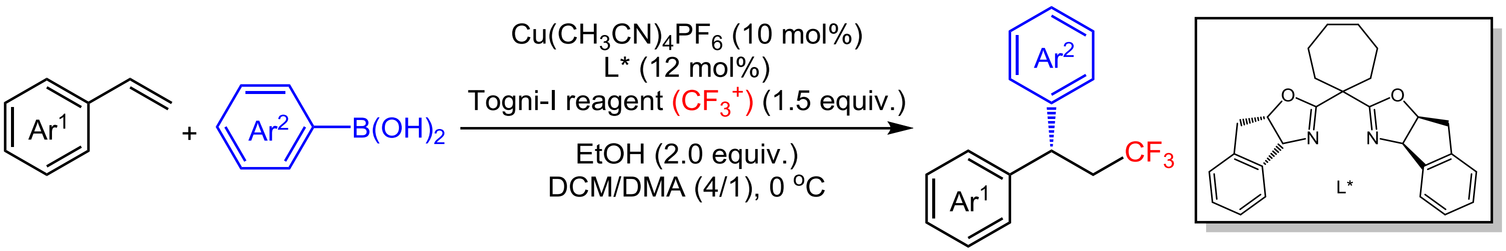
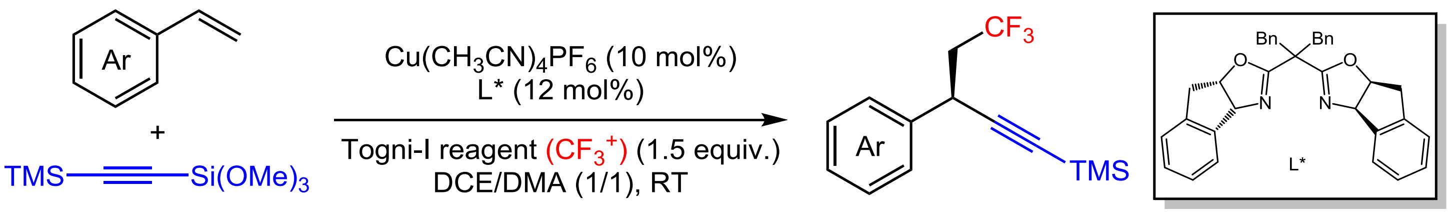


up to 89% yield, 94% ee

Liu, G. *et al. J. Am. Chem. Soc.* **2017**, *139,* 2904.



up to 88% yield, 97% ee

Liu, G. *et al. J. Am. Chem. Soc.* **2018**, *140,* 10965.

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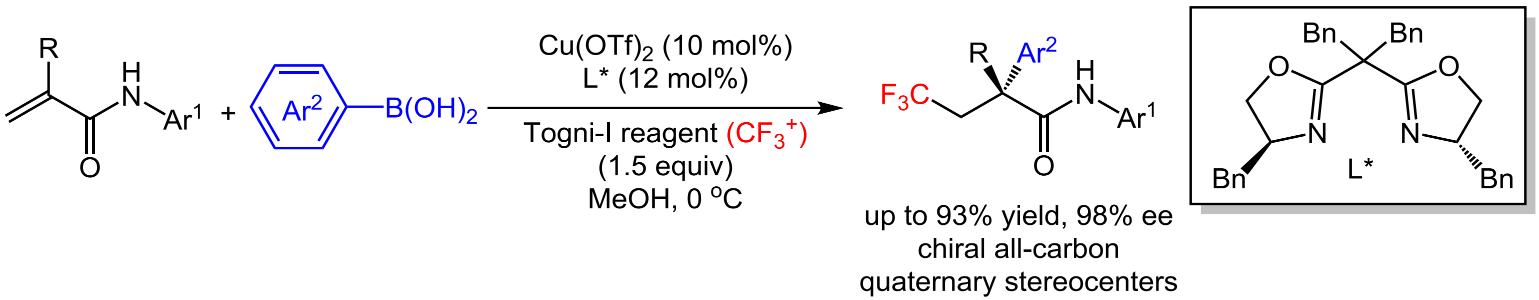
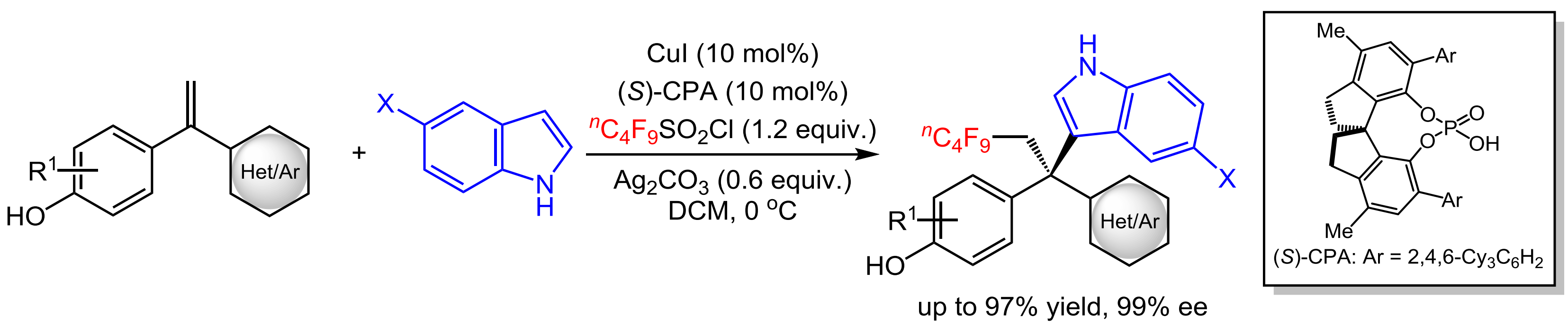


Liu, G. *et al. J. Am. Chem. Soc.* **2019**, *141*, 1887.



Liu, X.-Y. *et al. J. Am. Chem. Soc.* **2019**, *141*, 1074.

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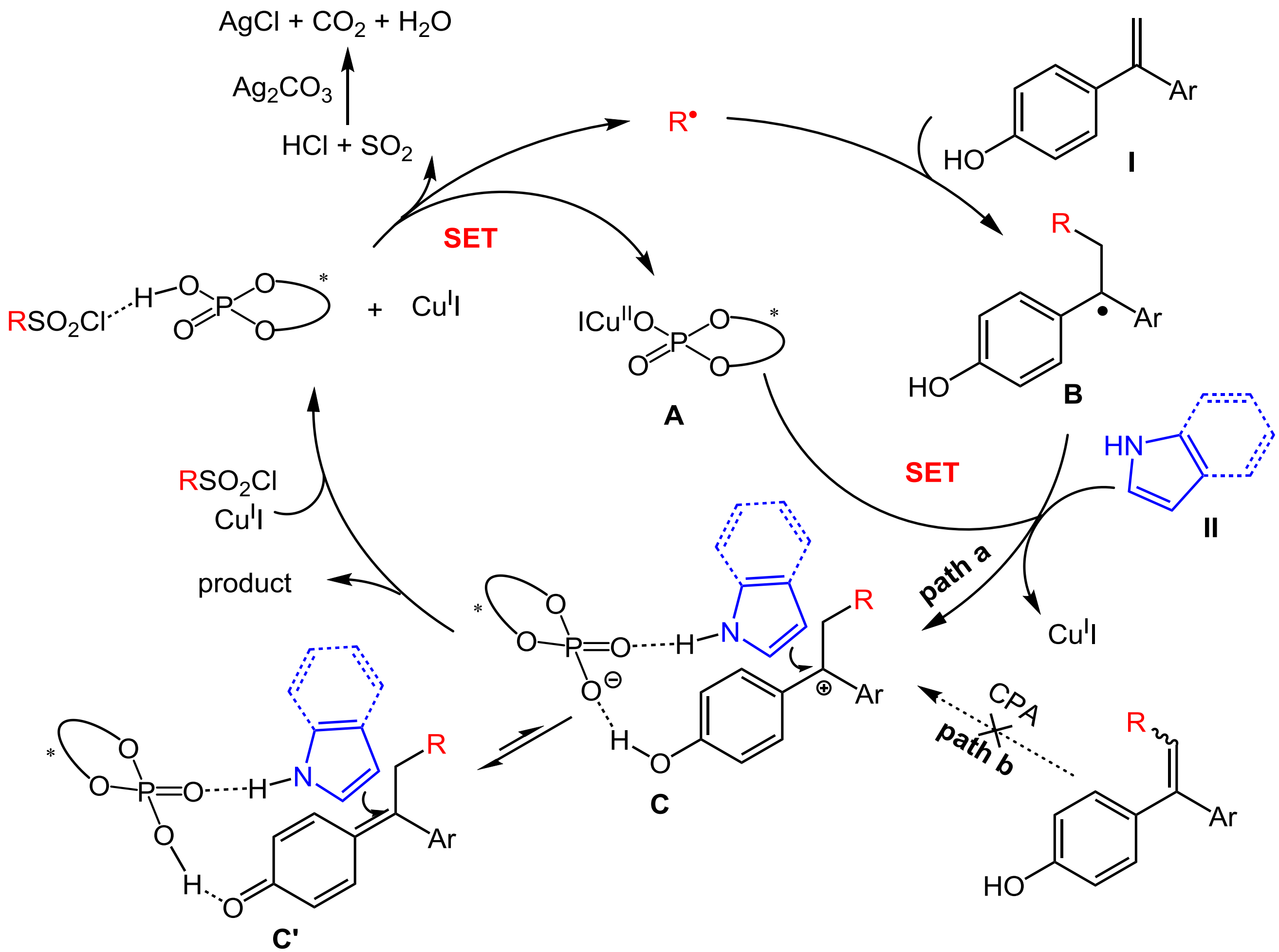

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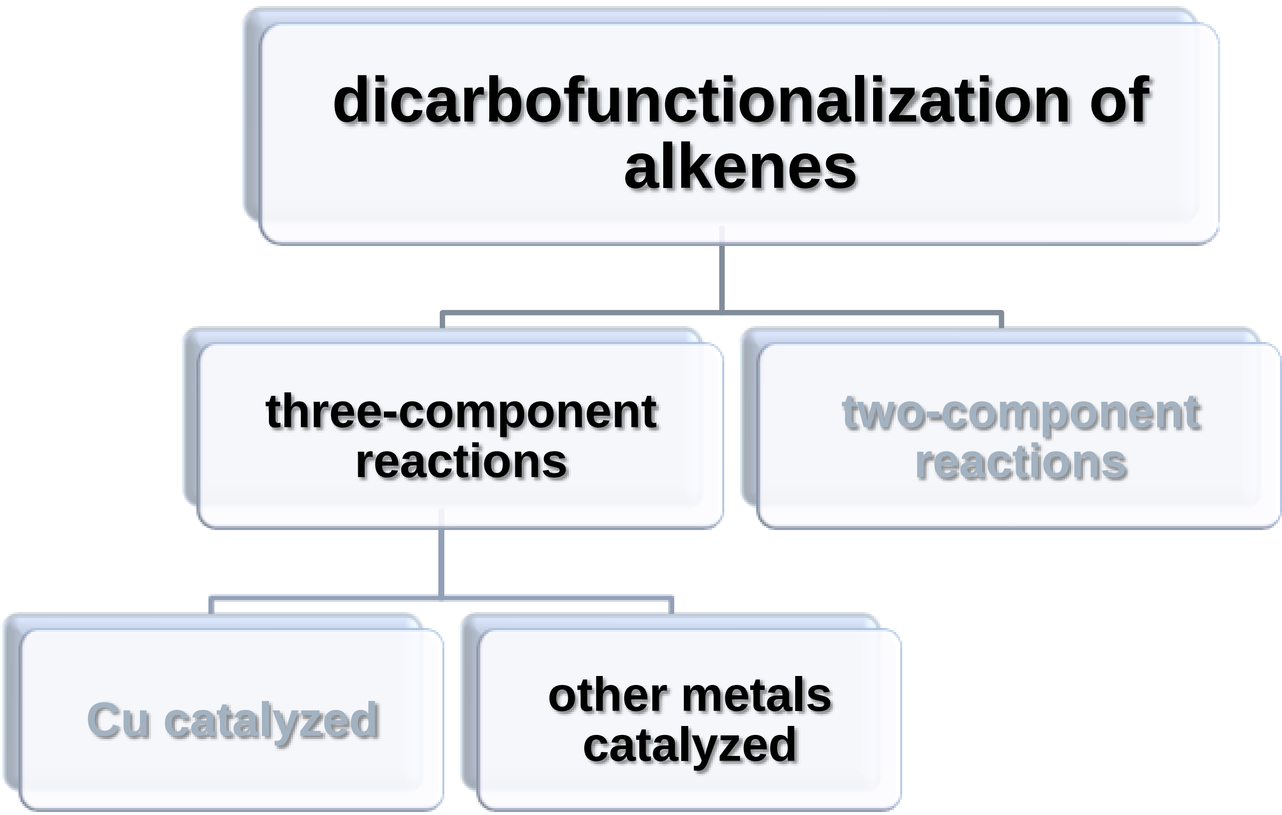

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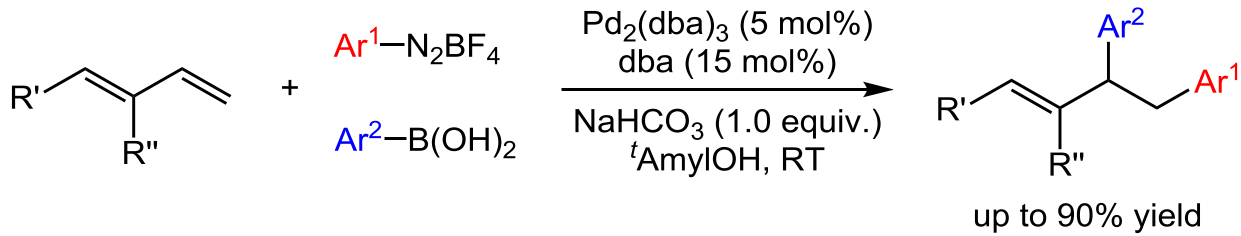

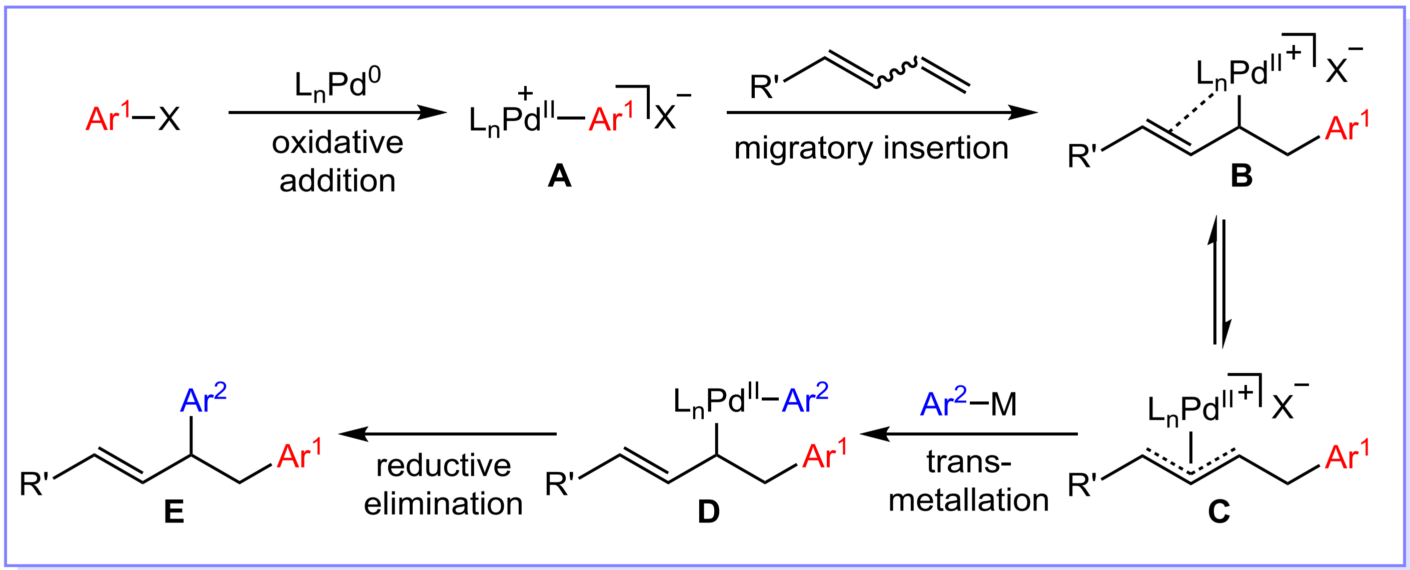

Sigman, M. S. *et al. Org. Lett.* **2014**, *16*, 4666.

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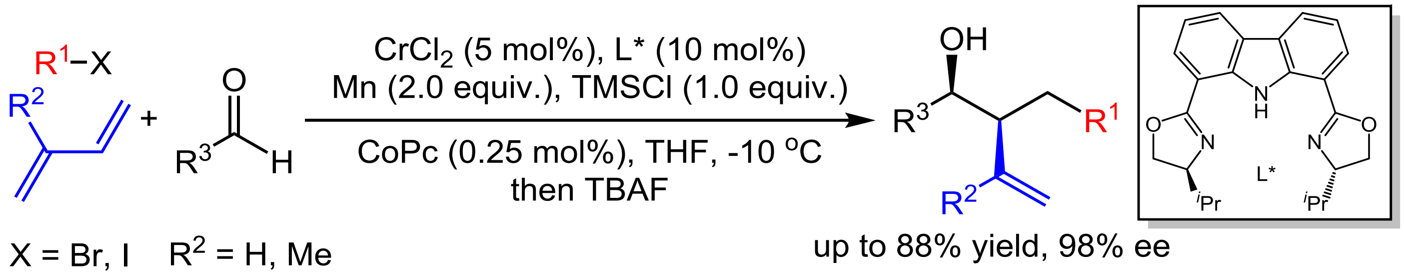

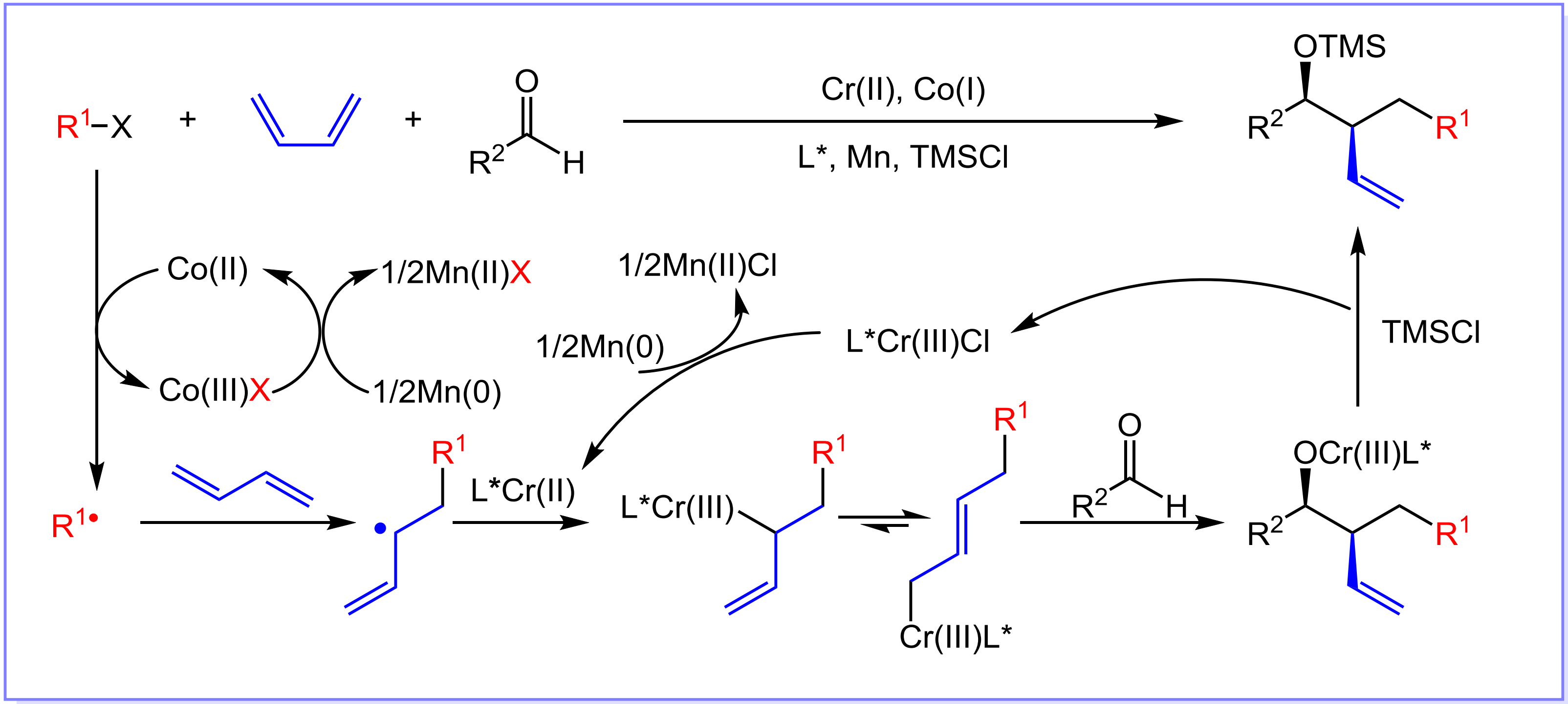

Zhang, G. *et al. J. Am. Chem. Soc.* **2018**, *140*, 2735.

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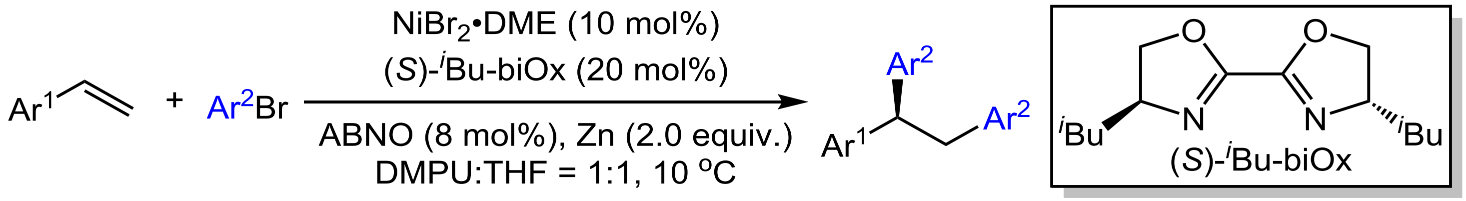

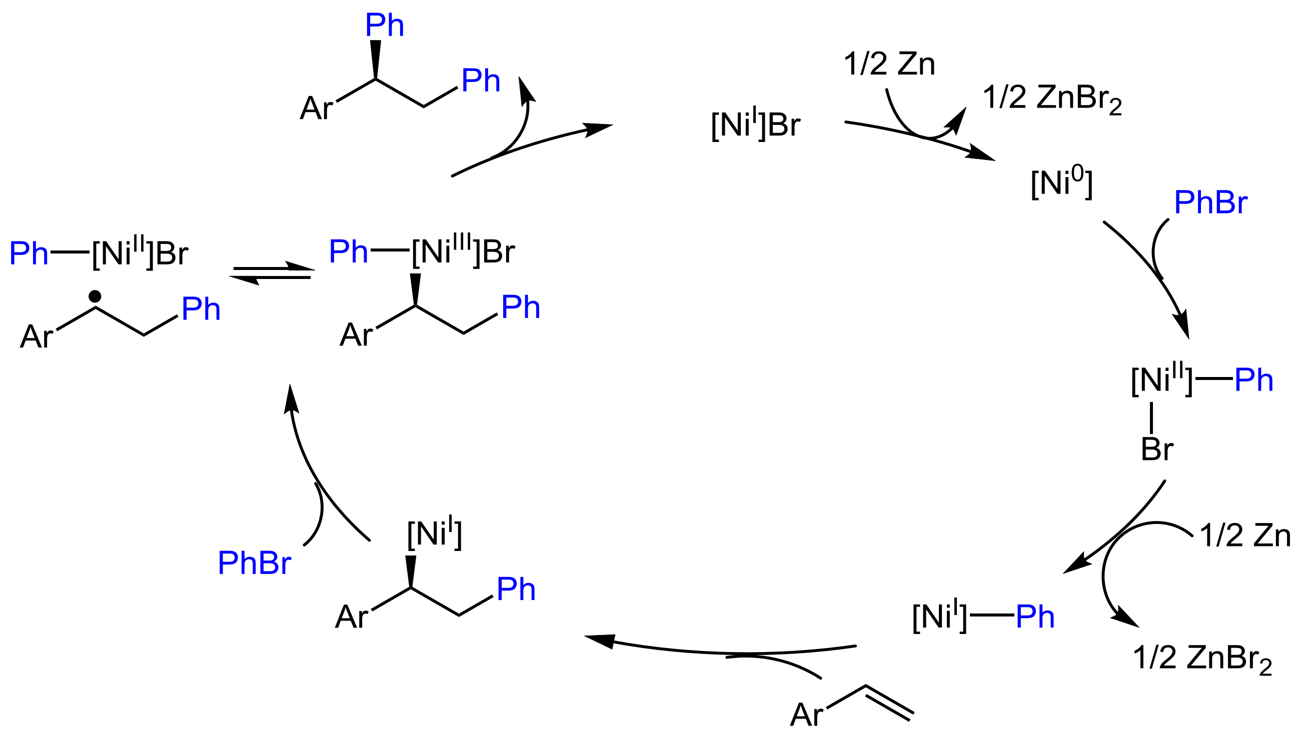

Diao, T. *et al. Angew. Chem. Int. Ed.* **2019**, *58,* 3198.

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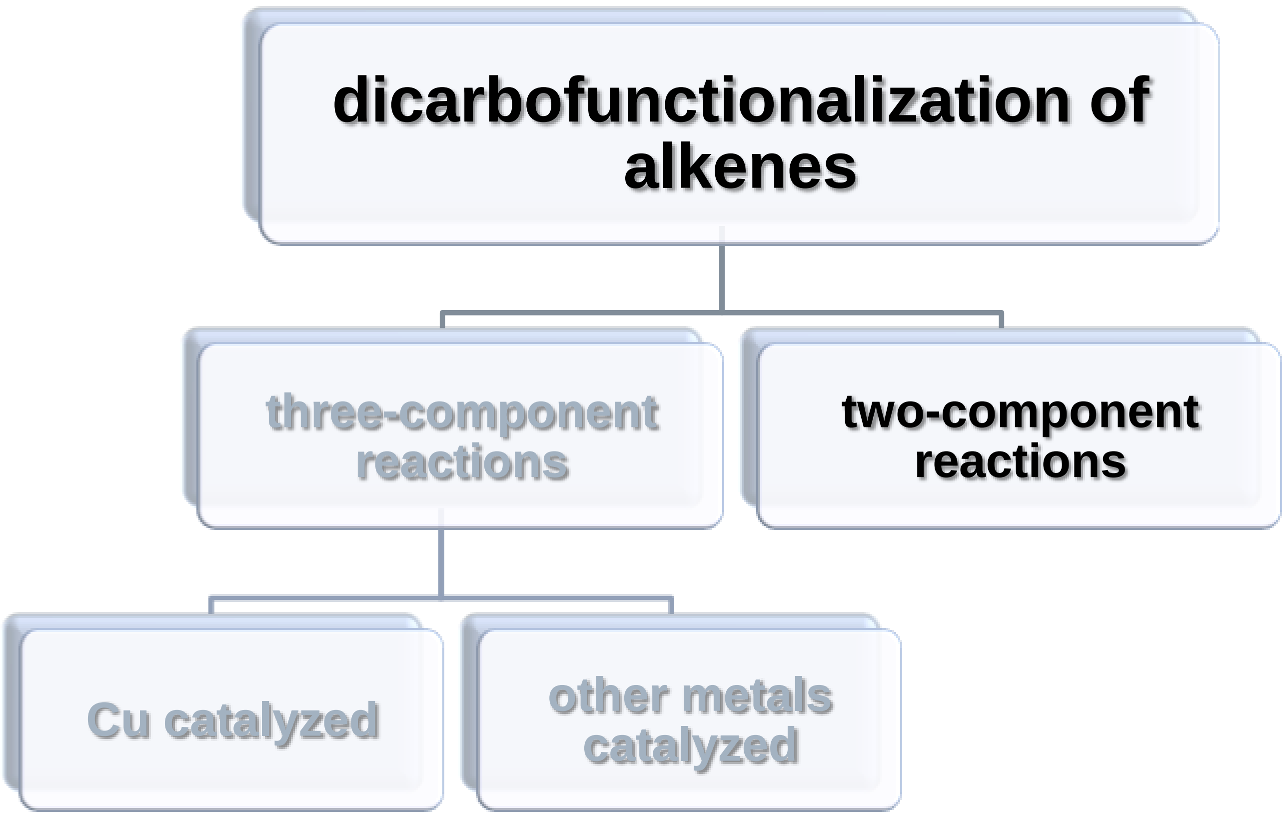

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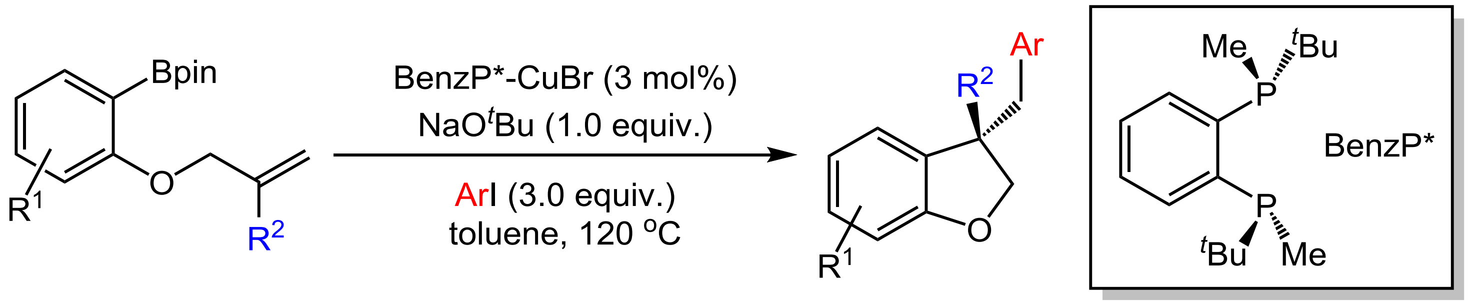
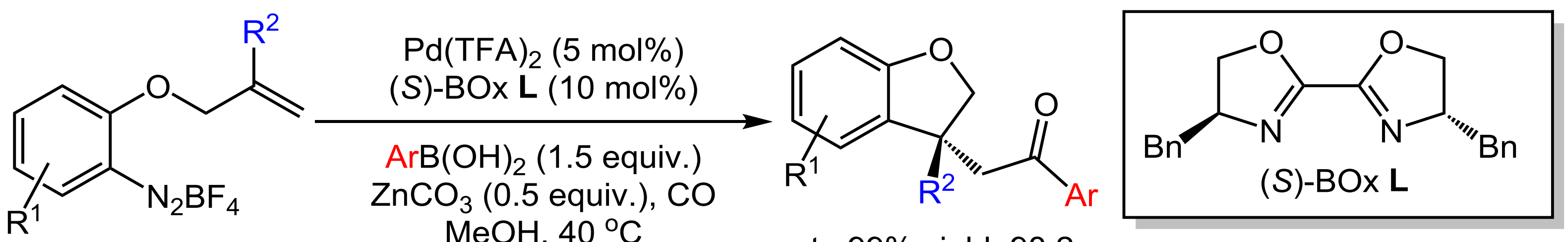


up to 77% yield, 98:2 er

Brown, M. K. *et al. J. Am. Chem. Soc.* **2015**, *137,* 14578.



up to 99% yield, 98:2 er

Correia, C. R. D. *et al. Angew. Chem. Int. Ed.* **2018**, *57,* 12067.

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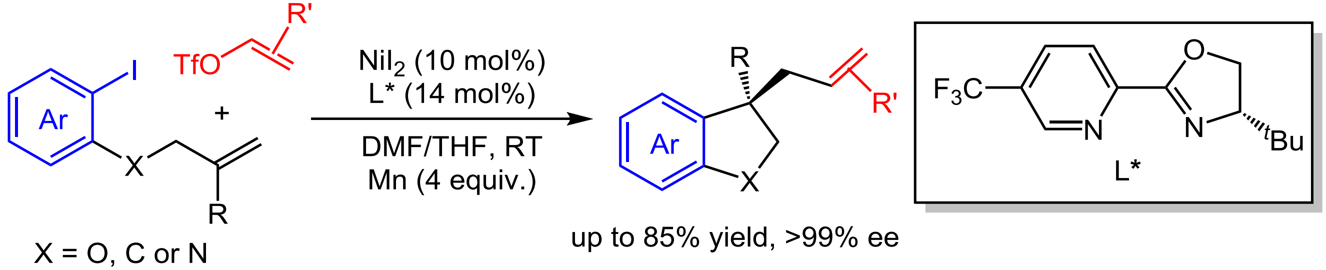
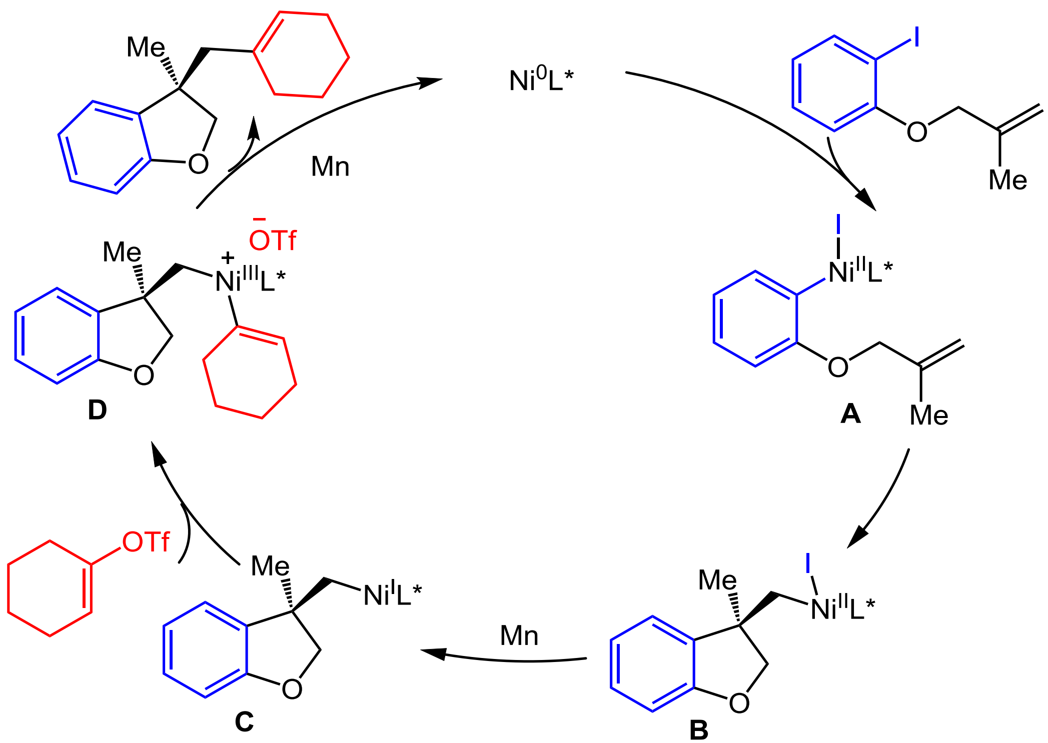
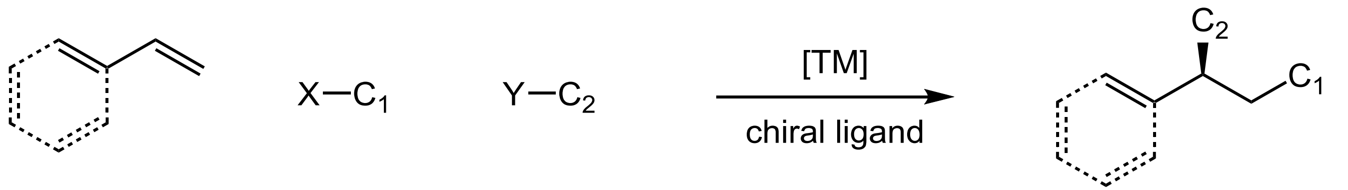




Shu, X.-Z. *et al. J. Am. Chem. Soc.* **2019**, *141,* 7637.

Background and project synopsis

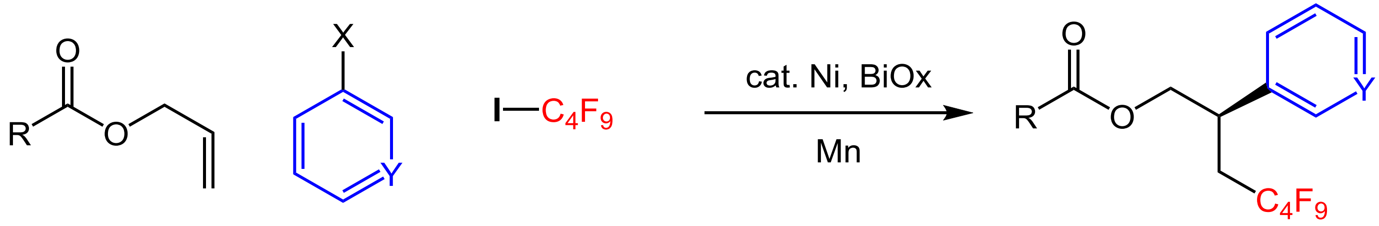
Previous work



vinylarenes
or 1,3-dienes

no examples of
unactivated alkenes

This work



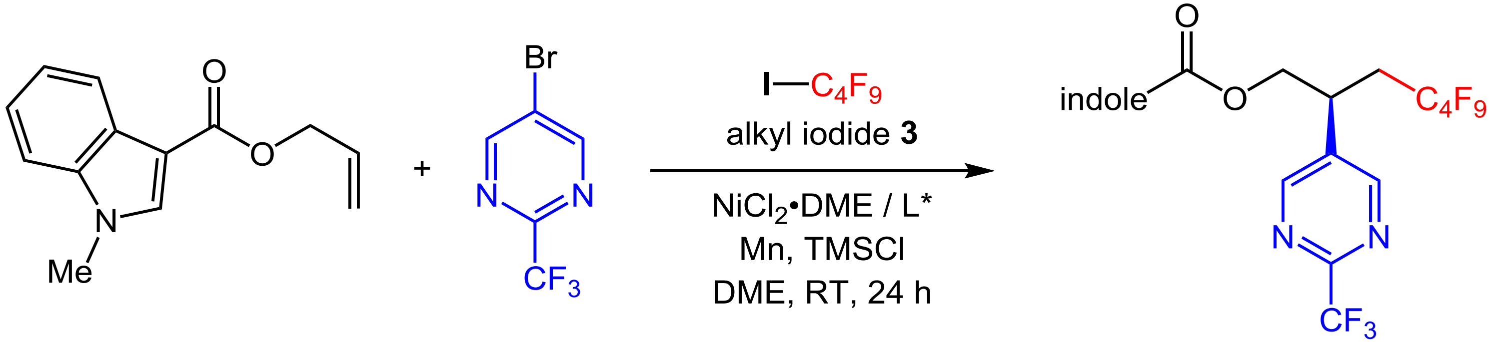
nonactivated alkene

aryl bromide

perfluoro iodide

enantioenriched product

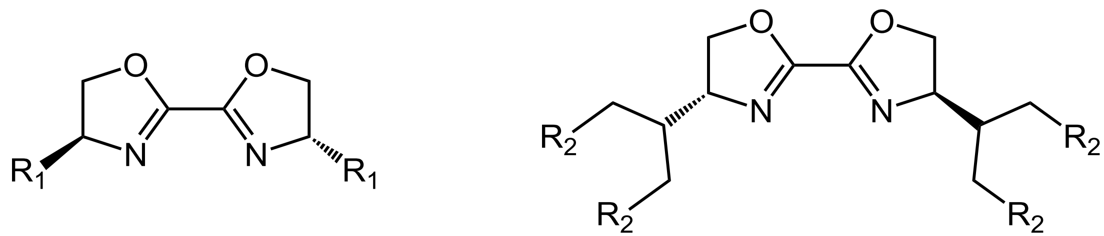
Optimization of reaction conditions



1
nonactivated alkene

2
aryl bromide

4
enantioenriched product



(S,S)

L1: R_1 = Bn; **L2**: R_1 = ^{i}Pr

L3: R_1 = ^{i}Bu; **L4**: R_1 = Cy

(R,R)

L5: R_2 = Et;

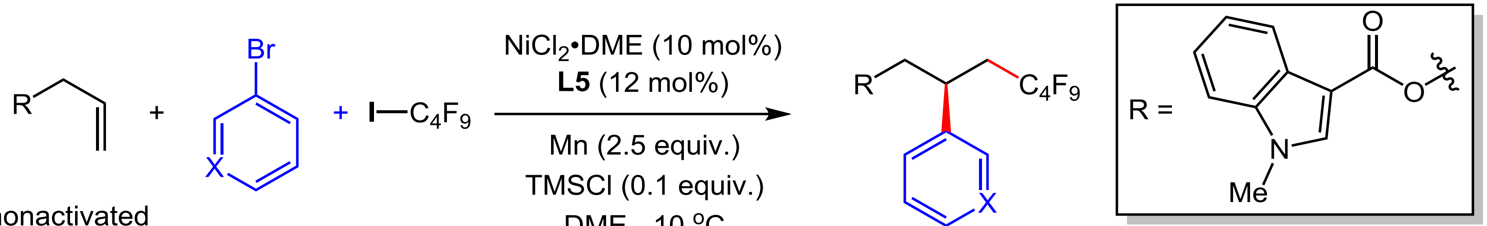
L6: R_2 = ^{n}Pr (new ligand)

Optimization of reaction conditions

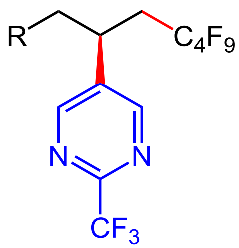
Entry[a]	Variations from standard conditions	Yield	Er
1	**L1**	21%	20:80
2	**L2**	55%	12:88
3	**L3**	24%	10:90
4	**L4**	75%	9:91
5	**L5**	87%	94:6
6	**L6**	81%	94:6
7	-10 ^{o}C, instead of RT	76%	95:5
8	Zn or TDAE, instead of Mn	Trace	
9	w/o nickel, **L5**, or Mn	0%	

[a]Reactions were carried out with alkene **1** (0.2 mmol), aryl bromide **2** (0.1 mmol), C_4F_9I (0.2 mmol), $NiCl_2$·glyme (10 mol%), chiral ligand (12 mol%), TMSCl (0.01 mmol), Mn (0.25 mmol), DME [0.5 M], RT, 24 h. Yields were determined by GC using an internal standard. The er values were determined by HPLC on a chiral stationary phase.

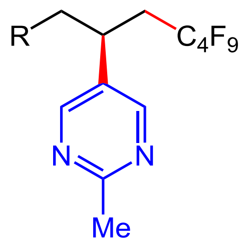
Scope of aryl halides



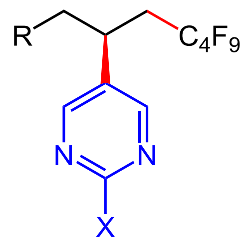
nonactivated alkene — aryl halide — **enantioenriched product**



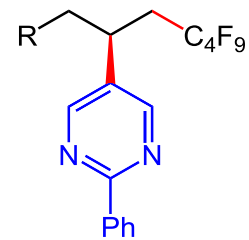
4 76%, 95:5 er



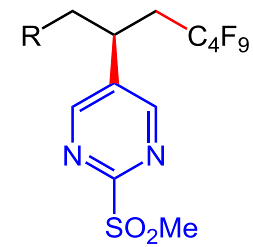
5 62%, 93:7 er



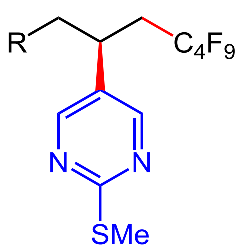
6 X = F, 96%, 95:5 er
7 X = Cl, 85%, 95:5 er



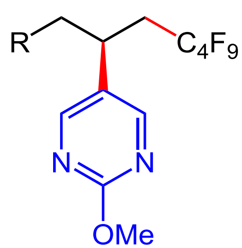
8 87%, 93:7 er



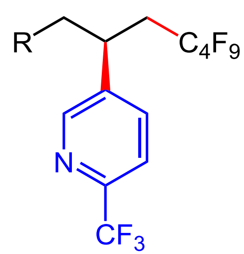
9 47%, 90:10 er



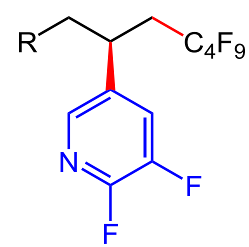
10 49%, 91:9 er



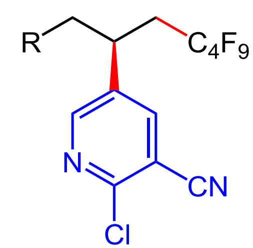
11 59%, 88:12 er



12 89%, 97:3 er

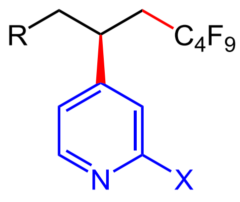


13 68%, 95:5 er

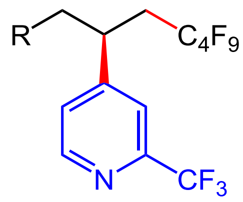


14 75%, 95:5 er

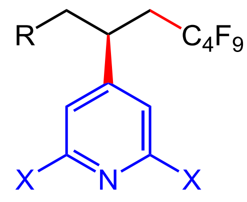
Scope of aryl halides



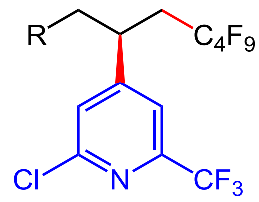
15 X = F, 77%, 94:6 er
16 X = Cl, 90%, 95:5 er



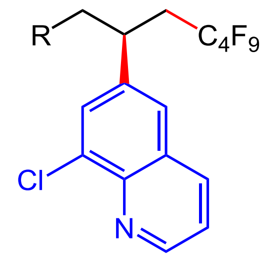
17 91%, 94:6 er



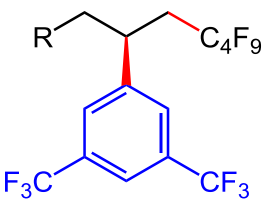
18 X = F, 55%, 96:4 er
19 X = Cl, 55%, 95:5 er



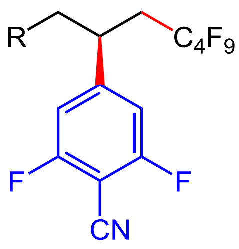
20 50%, 95:5 er



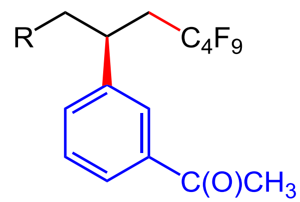
21 70%, 96:4 er



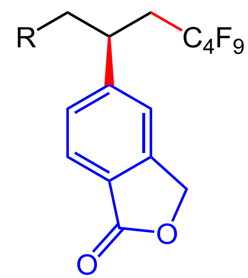
22 70%, 94:6 er



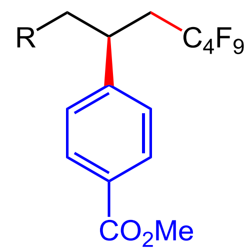
23 90%, 96:4 er



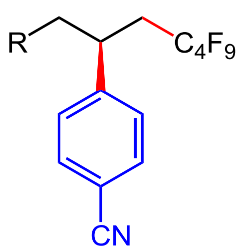
24 76%, 92:8 er



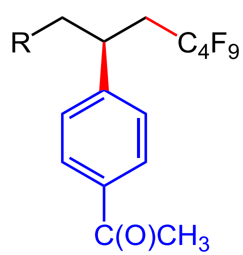
25 64%, 93:7 er



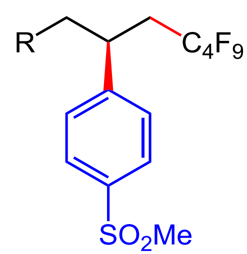
26 88%, 92:8 er



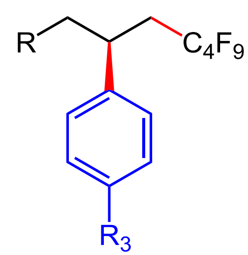
27 80%, 93:7 er



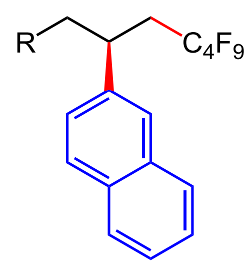
28 84%, 92:8 er



29 72%, 93:7 er
recrystallization: 98:2 er

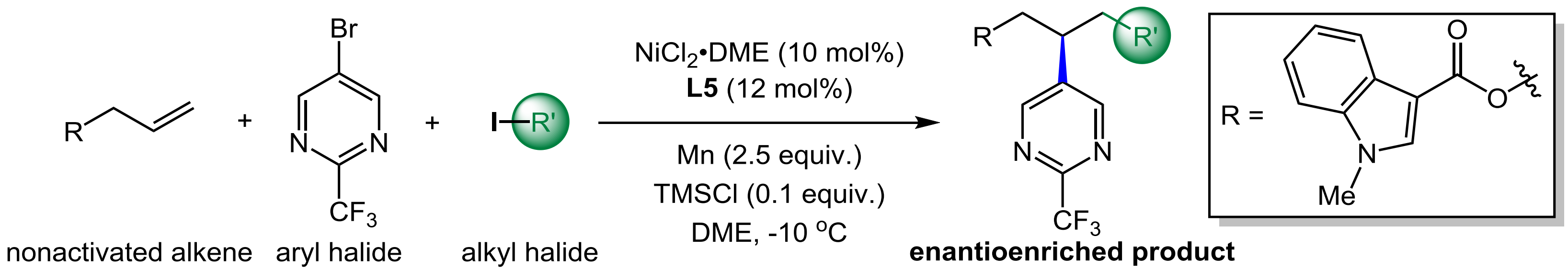


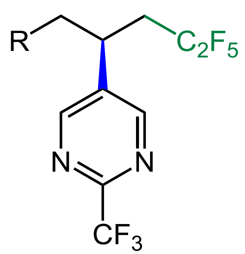
30 R_3 = Me, 80%, 89:11 er
31 R_3 = OMe, 75%, 89:11 er



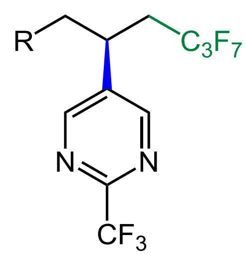
32 79%, 87:13 er

Scope of alkyl halides

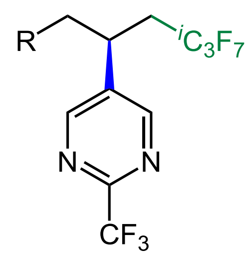




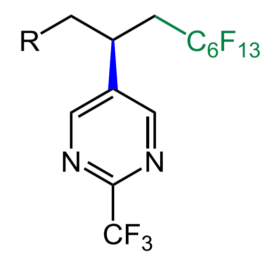
33 88%, 96:4 er



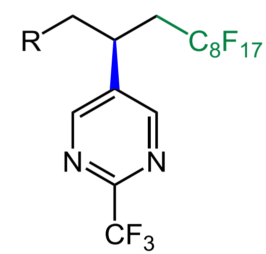
34 86%, 95:5 er



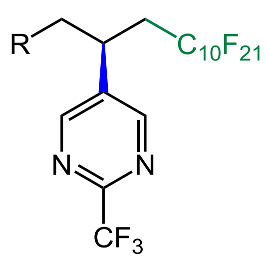
35 83%, 96:4 er



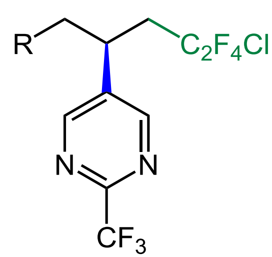
36 78%, 95:5 er



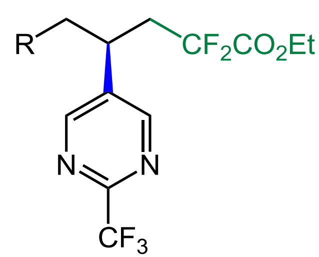
37 62%, 93:7 er



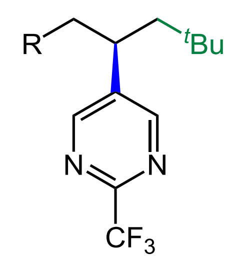
38 50%, 94:6 er



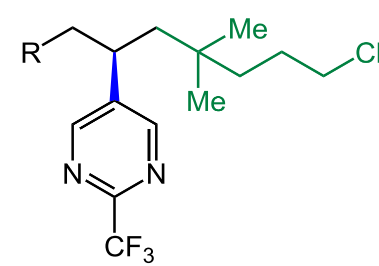
39 66%, 93:7 er



40 77%, 90:10 er

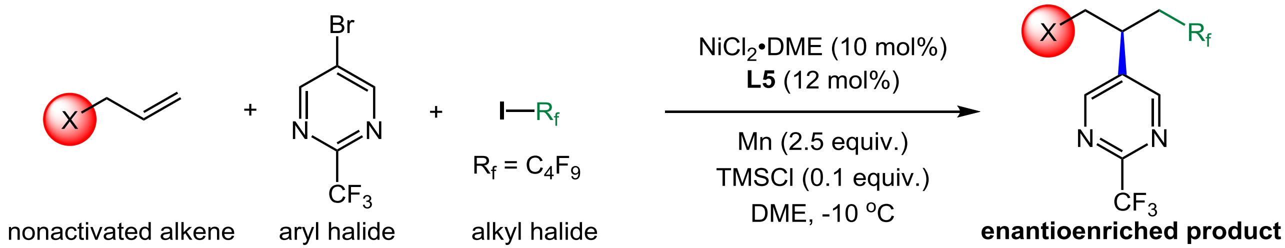


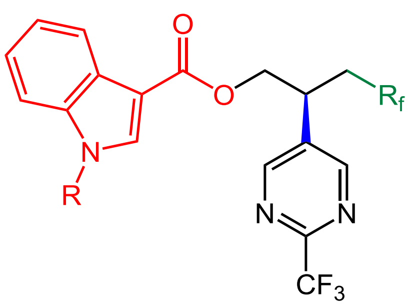
41 45%, 96:4 er



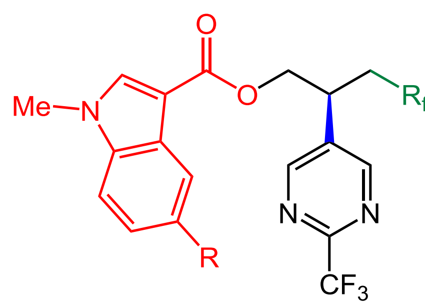
42 47%, 96:4 er

Scope of alkenes

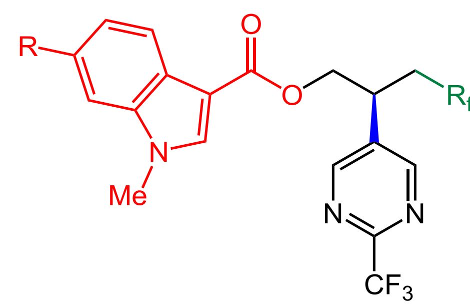




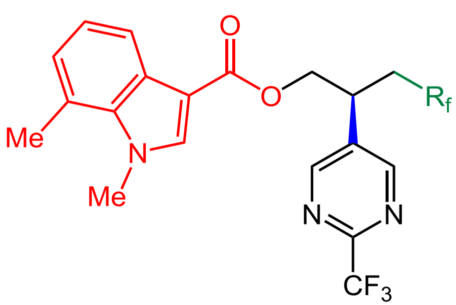
43 R = H, 63%, 95:5 er
44 R = Bn, 67%, 93:7 er
45 R = C_5H_{11}, 81%, 95:5 er



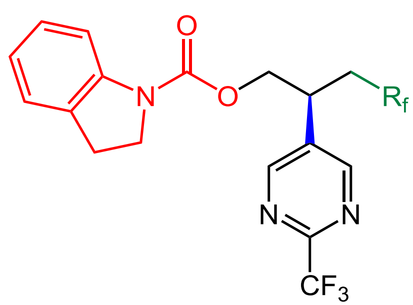
46 R = Me, 74%, 95:5 er
47 R = F, 74%, 94:6 er



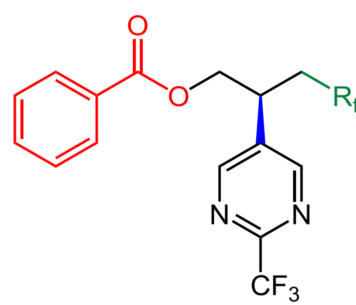
48 R = Me, 76%, 96:4 er
49 R = Cl, 81%, 94:6 er



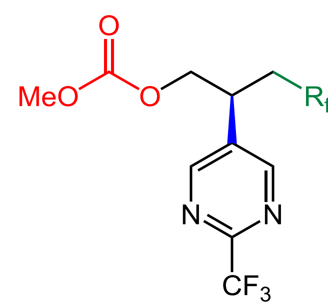
50 79%, 96:4 er



51 64%, 91:9 er

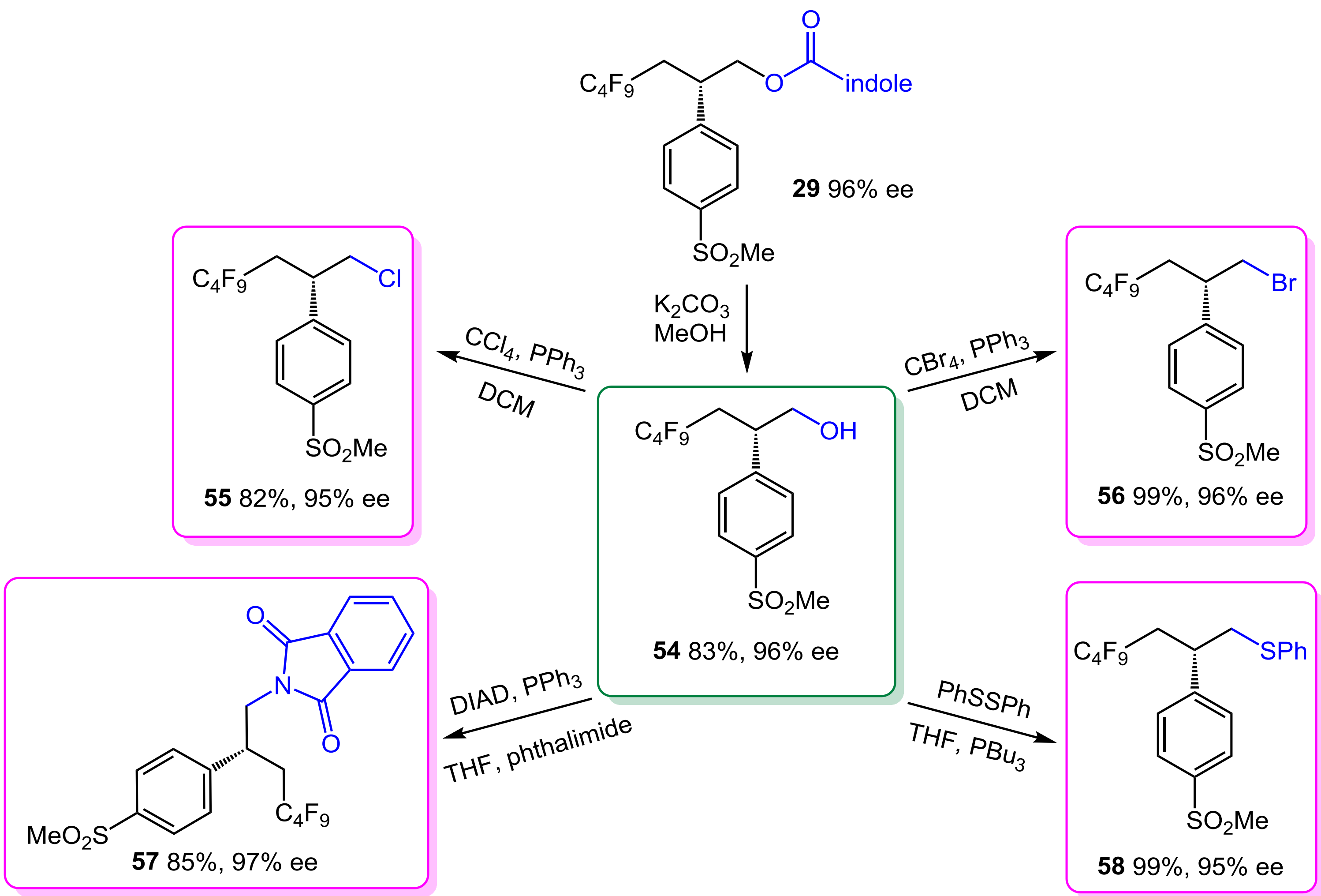


52 83%, 89:11 er

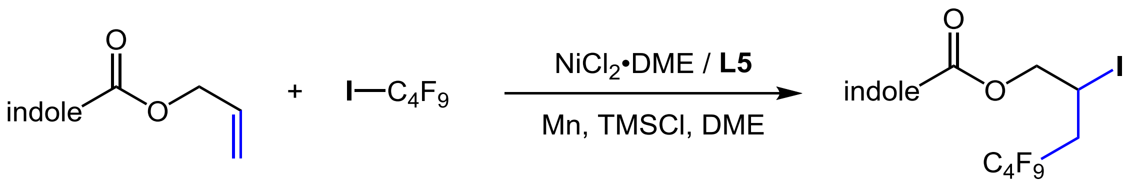


53 78%, 91:9 er

Product transformations

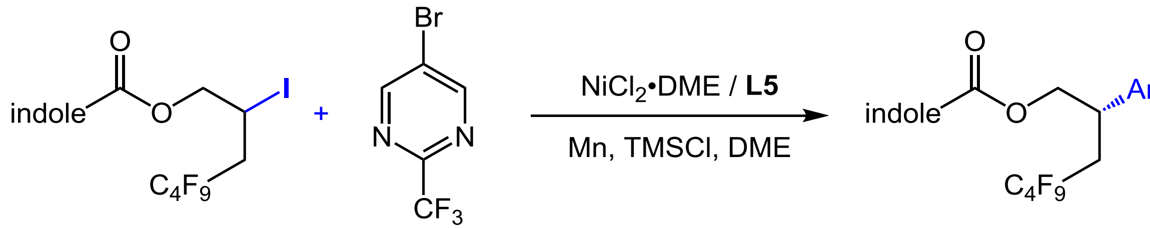


Preliminary mechanistic studies



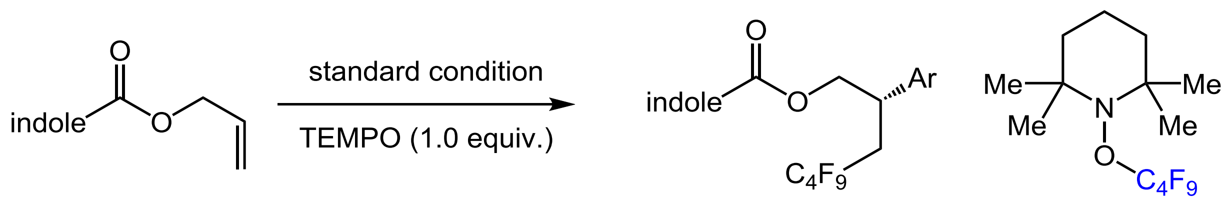
1

59, 44%, 50:50 er



59, racemic

4, 95%, 95:5 er

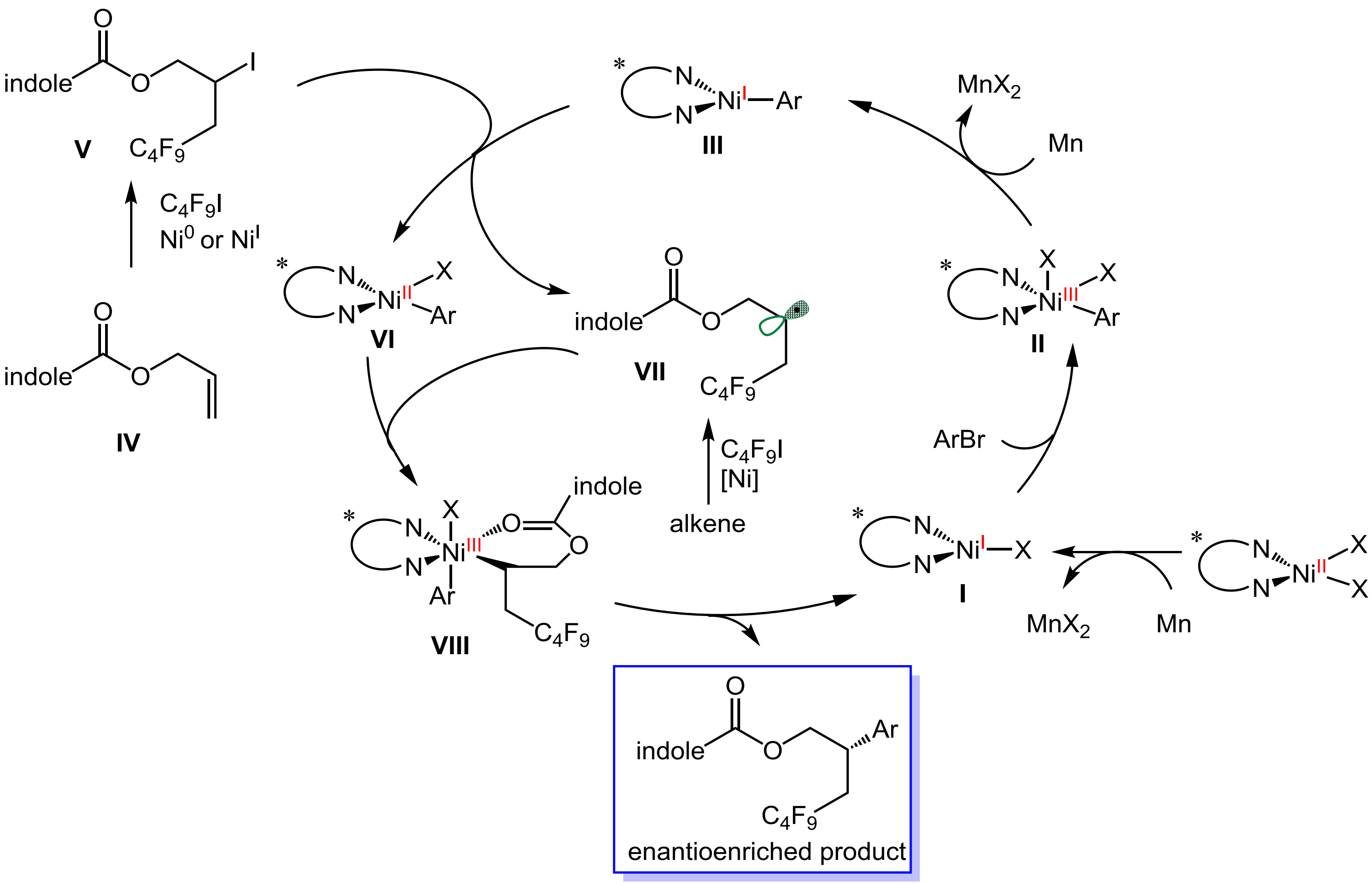


1

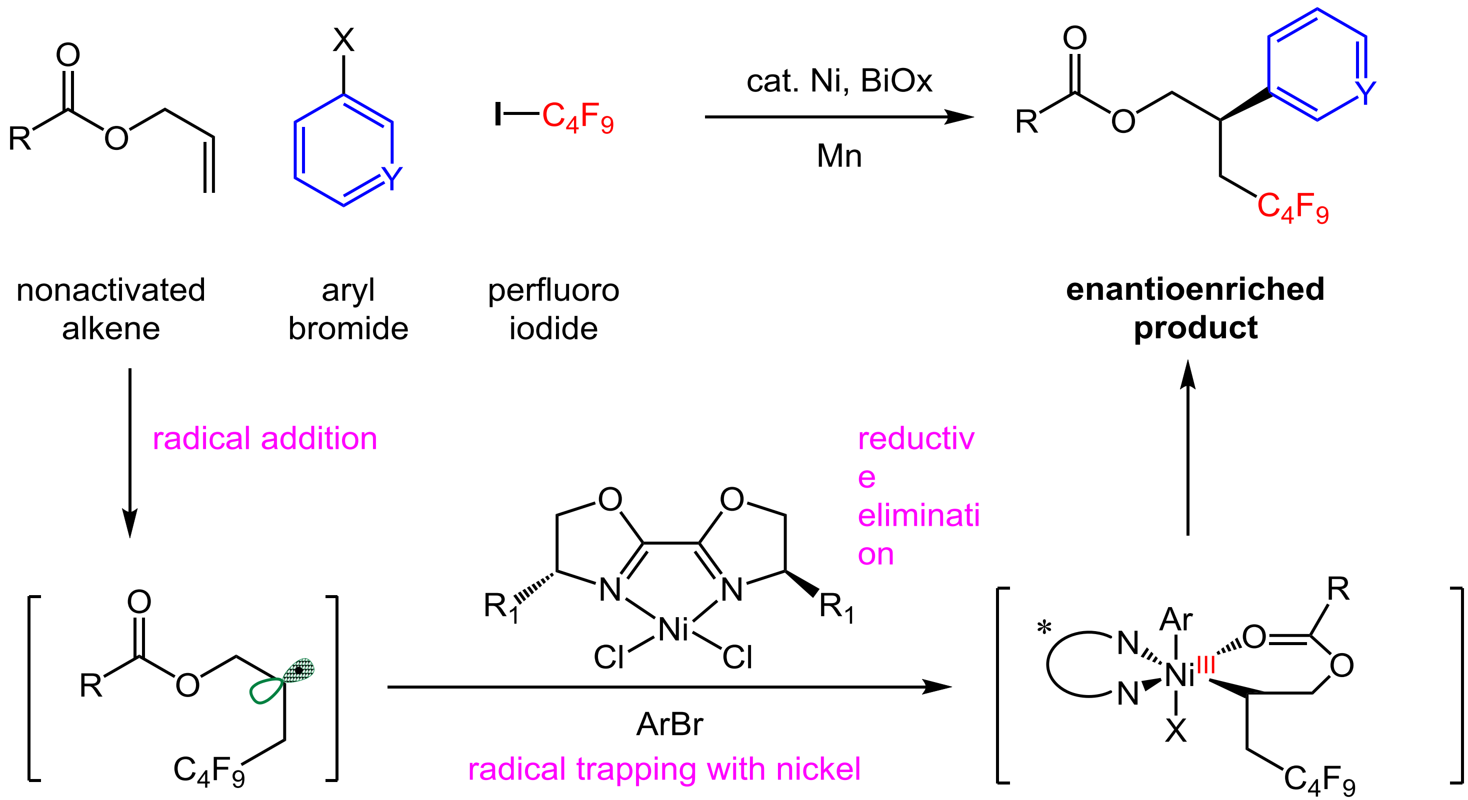
4, not observed

60, 44%

Proposed mechanism



Summary



■ Three-Component ■ Regio- & Enantio-selectivity ■ Broad substrate scope

Writing strategy

Importance of dicarbofunctionalization of alkenes

↓

Challenge of three-component reactions

↓

The known examples of dicarbofunctionalization of alkenes

↓

Consideration of three-component dicarbofunctionalization of unactivated alkenes

The first paragraph

Transition-metal-catalyzed dicarbofunctionalization of alkenes has been proven as a powerful strategy to the rapid generation of molecular complexity by simultaneously forging two vicinal sp^3 C−C bonds from abundant building blocks in one single operation; however, enantio-selective control of the newly formed stereogenic centers, particularly in three-component assembly mode, remains a formidable challenge. The known examples of three-component reactions strongly rely on the asymmetric functionalization of vinylarenes via a radical relay strategy, wherein intercepting the putative benzylic radicals by chiral transition metal catalysts is key. Nevertheless, unactivated alkenes were not applicable in this asymmetric radical protocol, presumably because of lacking resonance stabilization for the in situ generated highly reactive alkyl radical species.

The first paragraph

Indeed, asymmetric dicarbofunctionalization of unactivated alkenes has been primarily restricted to intramolecular, two-component assembly modes. To the best of our knowledge, catalytic, enantioselective, three-component difunctionalization of unactivated alkenes has not been reported. Herein, we report an enantioselective 1,2-fluoroalkylarylation of unactivated alkenes with aryl halides and perfluoroalkyl iodides through a chelation-assisted nickel-catalyzed cross-electrophile coupling which demonstrates an example of the integration of three-component dicarbofunctionalization of unactivated alkenes with a high level of enantioselectivity for the first time.

Writing strategy

Summary of this work

↓

Explain the reasons for high enantioselectivity and efficiency

↓

Application of products

The last paragraph

In conclusion, we have developed the first enantioselective, three-component 1,2-fluoroalkylarylation of unactivated alkenes with aryl halides and fluoroalkyl iodides via a chelation-assisted Ni-catalyzed multicomponent cross-electrophile coupling. The benign protocol allows for the facile construction of a wide range of functionalized chiral β-fluoroalkyl arylalkanes with high efficiency and excellent enantioselectivity from readily available starting materials. The pendant ester group plays a crucial role in achieving high levels of enantioselectivity and efficiency in this three-component, asymmetric difunctionalization of unactivated alkenes. Moreover, the chelating group could be readily cleaved to give enantioenriched alcohols, further transformations of which generate a series of chiral fluoroalkyl-containing motifs that could be useful in the areas of pharmaceuticals and agrochemicals.

Representative examples

With a particular interest in the introduction of fluoroalkyl groups because of their increasing importance in medicinal agents, **as well as** the high reactivity of perfluoroalkyl radicals, **our group** previously developed… **(由于……，并且……，我们……)**.

This asymmetric, three-component difunctionalization protocol could be feasibly scaled up, **yield and enantioselectivity of product 4 on a gram scale were comparable to a smaller scale. (……与……可以相媲美)**.

To shed some light on the plausible mechanism of this novel nickel-catalyzed enantioselective three-component fluoroalkylarylation reaction… (阐明，弄清楚).

Thanks
for your attention