Ligand-accelerated enantioselective methylene C(sp^3)-H bond activation

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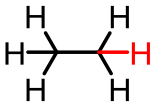
Joseph Salamoun
Current Literature 09/10/16
Wipf Group

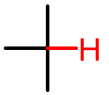
C(sp^3)-H Functionalization

- Challenges:
  - Reaction efficiency
  - Functional group compatibility/reaction scope
  - Regio- and stereo-selectivity
  - Atom economy (directing groups are very large and add linear steps)
- Not all C(sp^3)-H are created equally!

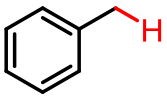
Variable BDEs



ca. 98 kcal/mol

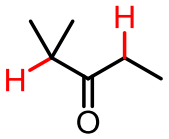


ca. 93 kcal/mol

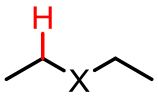


ca. 88 kcal/mol

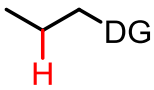
ca. 86 kcal/mol



pKa selectivity
kinetic v. thermodynamic control

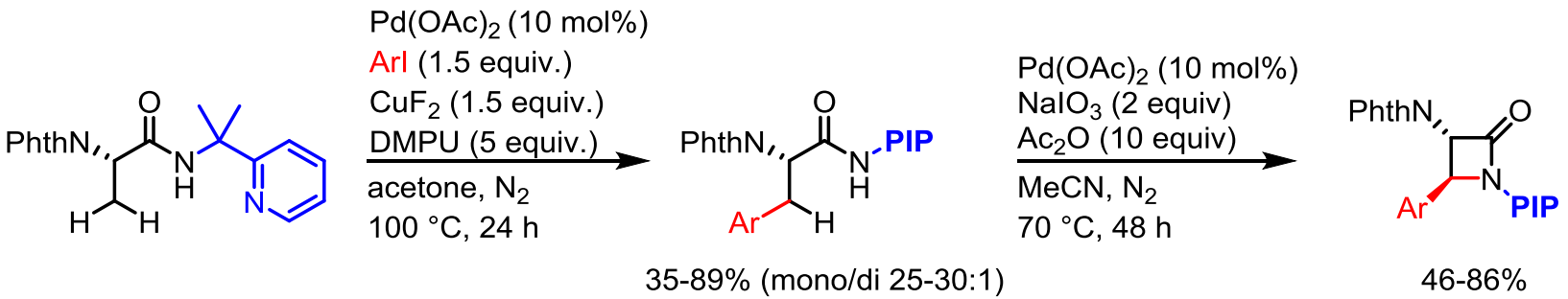


proximity to heteroatoms

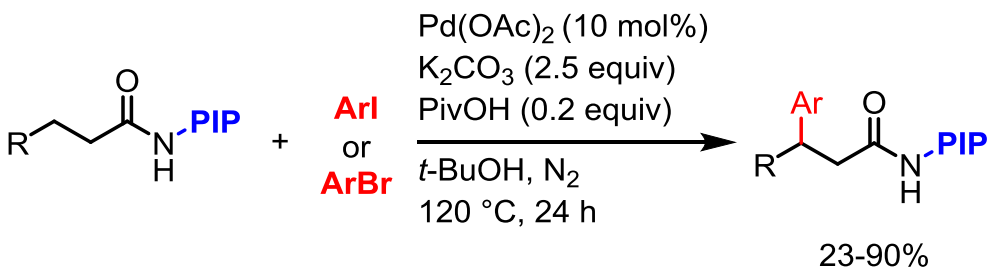


proximity to directing group

C(sp^3)-H Functionalization by the Shi Group

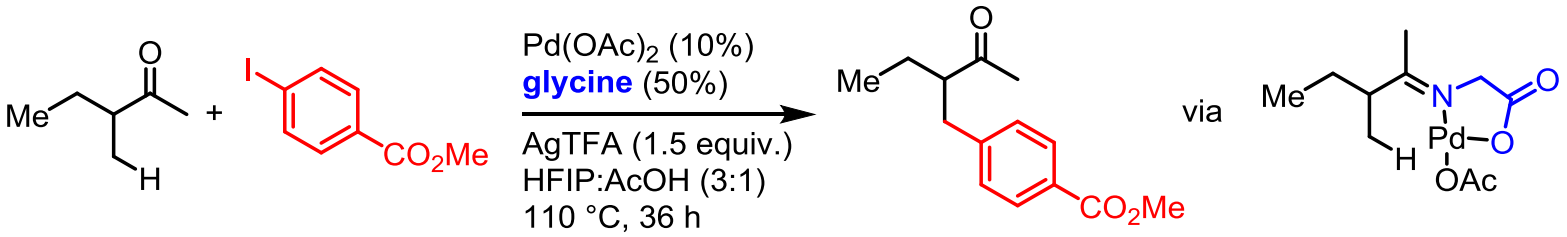


Angew. Chem. Int. Ed. **2013**, *52*, 13588.



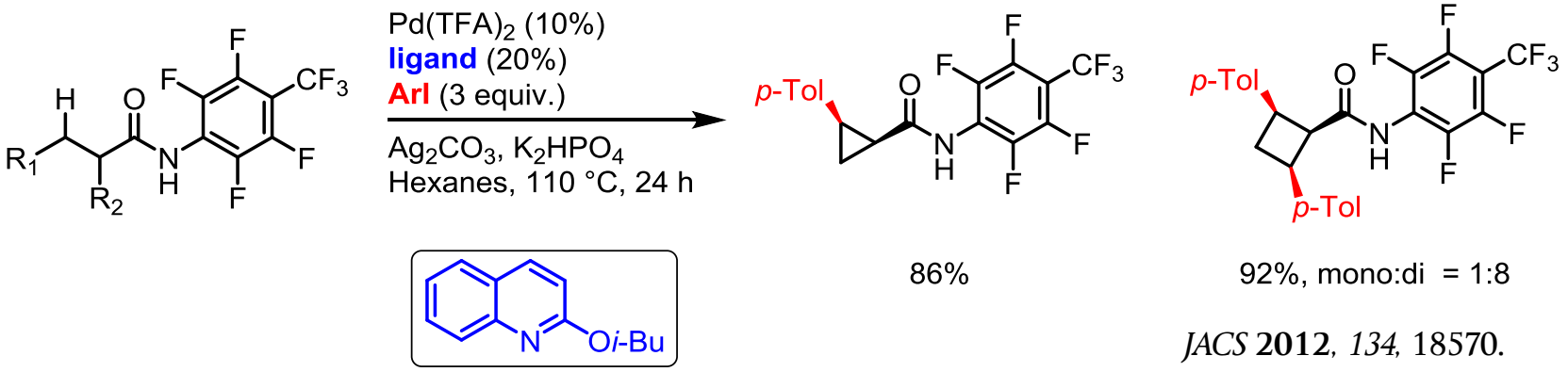
Chem. Commun. **2014**, *50*, 8353.

C(sp^3)-H Functionalization by the Yu Group



71%

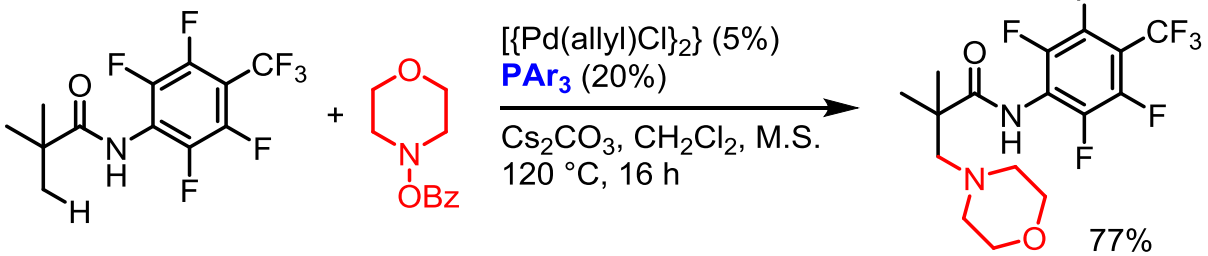
Science **2016**, *351*, 252.



86%

92%, mono:di = 1:8

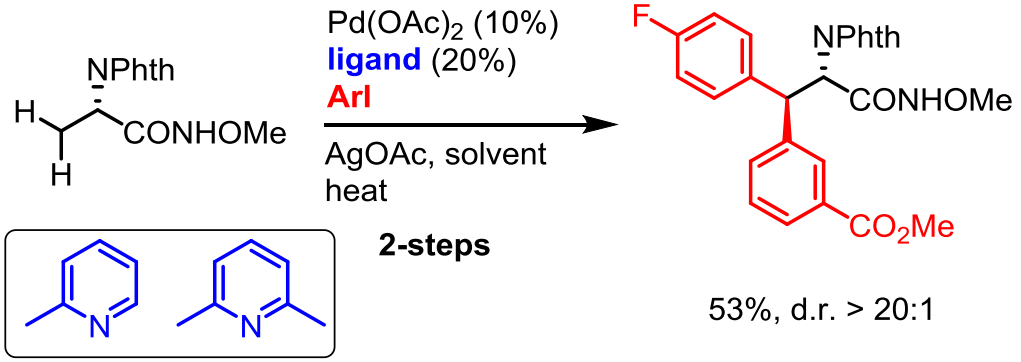
JACS **2012**, *134*, 18570.



77%

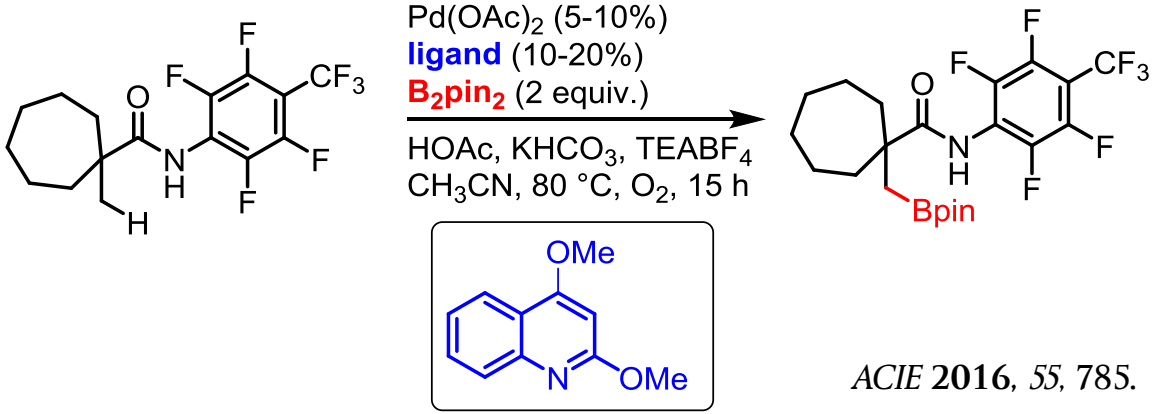
ACIE **2015**, *54*, 6545.

C(sp^3)-H Functionalization by the Yu Group

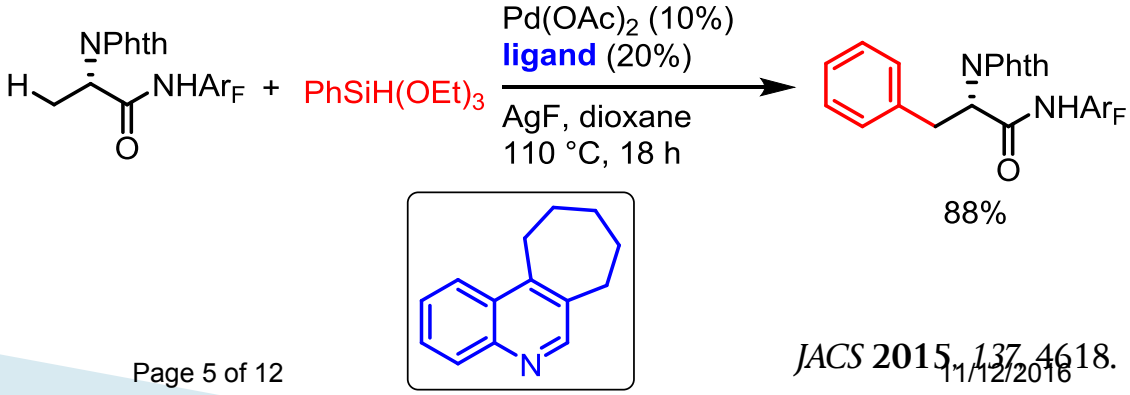


53%, d.r. > 20:1

JACS **2012**, *134*, 18570.



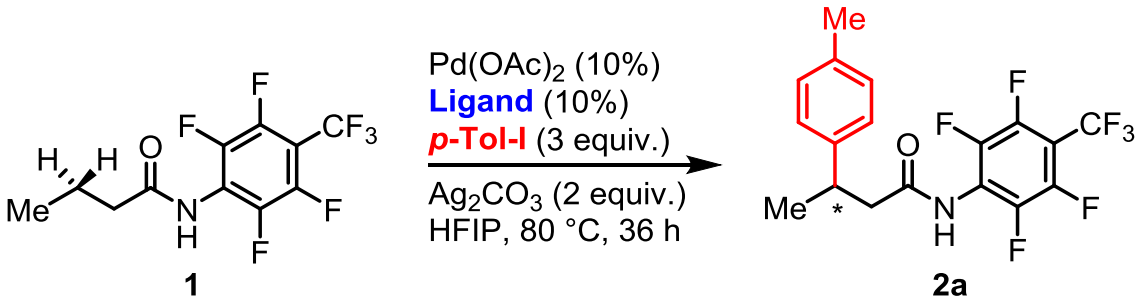
ACIE **2016**, *55*, 785.

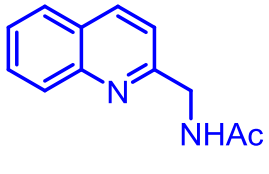


88%

JACS **2015**, *137*, 4618.

Ligand Optimization



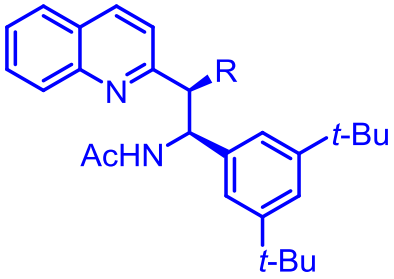


L6, N.R.

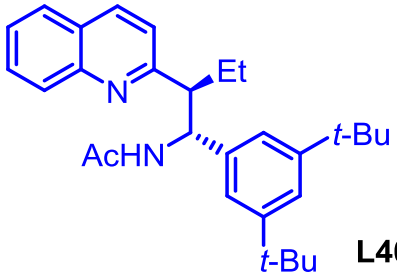
L9, 46%

L10, 58%

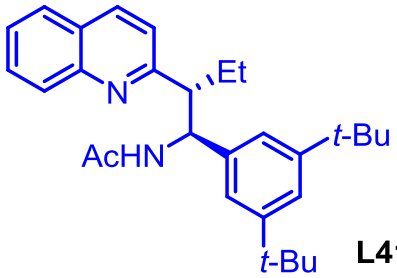
L17, 76%, 29:71 er



R = Me	**L34**, 86%, 90:10 er
Et	**L35**, 82%, 92.5:7.5 er
n-Pr	**L36**, 71%, 90.5:9.5 er
i-Pr	**L37**, 48%, 78:22 er
OMe	**L38**, 69%, 84:16 er
Bn	**L39**, 75%, 88:12 er



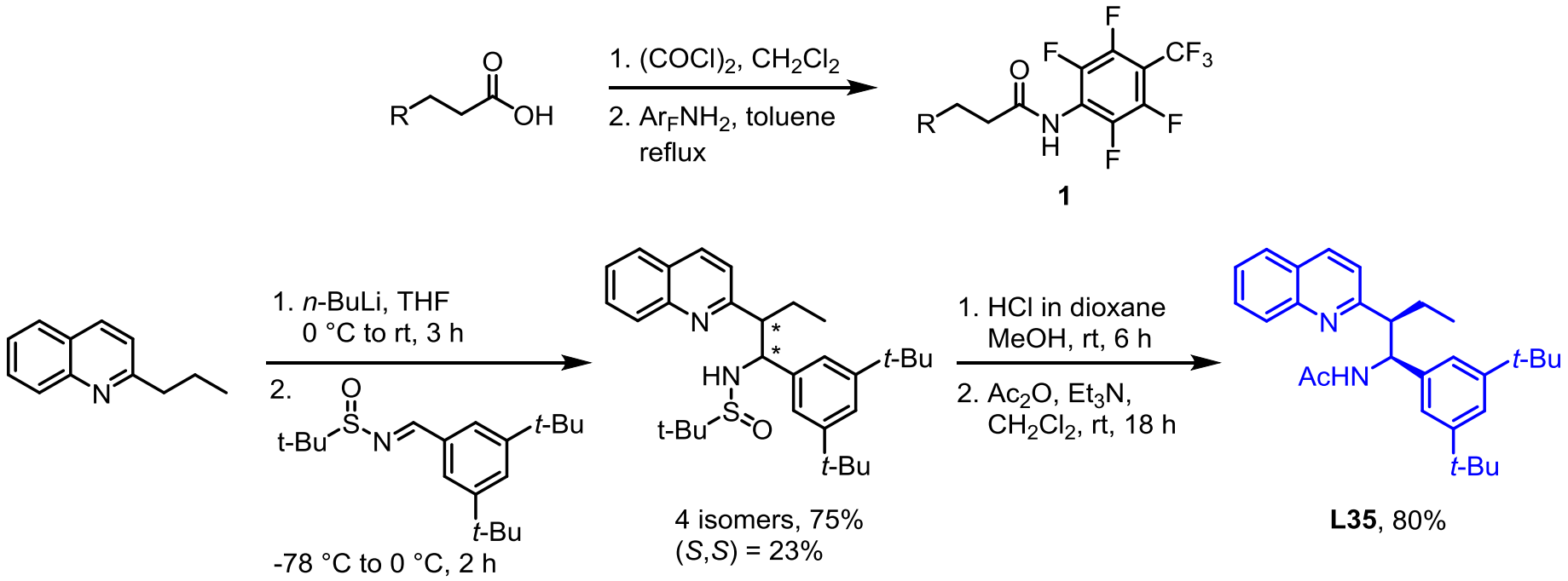
L40, 13%, 31:69 er



L41, 15%, 68:32 er

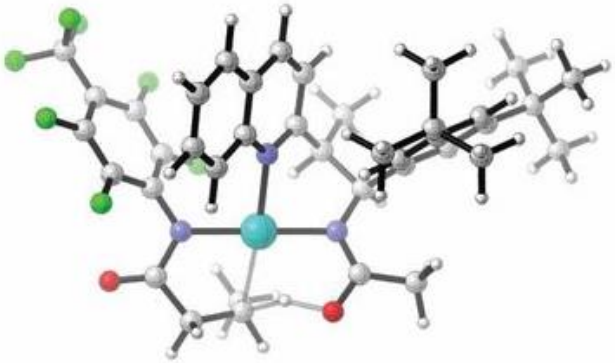
Science **2016**, *352*, 1023.

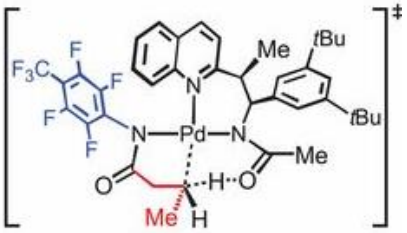
Starting Material and Ligand Synthesis



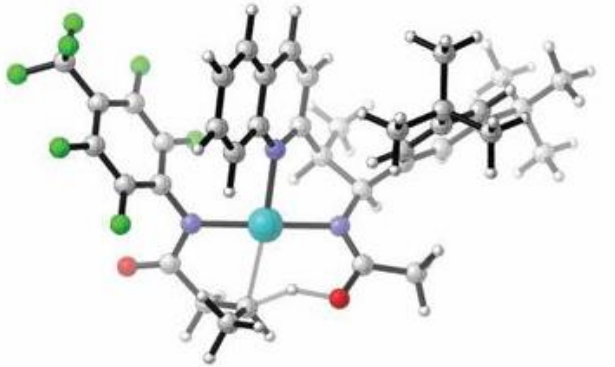
Science **2016**, *353*, 1023.

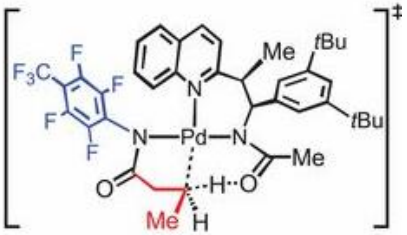
DFT Derived Transition State Structures





TS_R
$\Delta\Delta G$ = 0.0 kcal/mol





TS_S
$\Delta\Delta G$ = 1.2 kcal/mol

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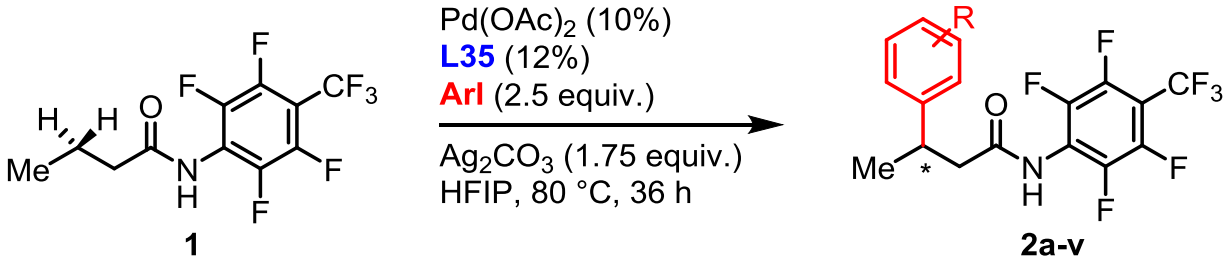
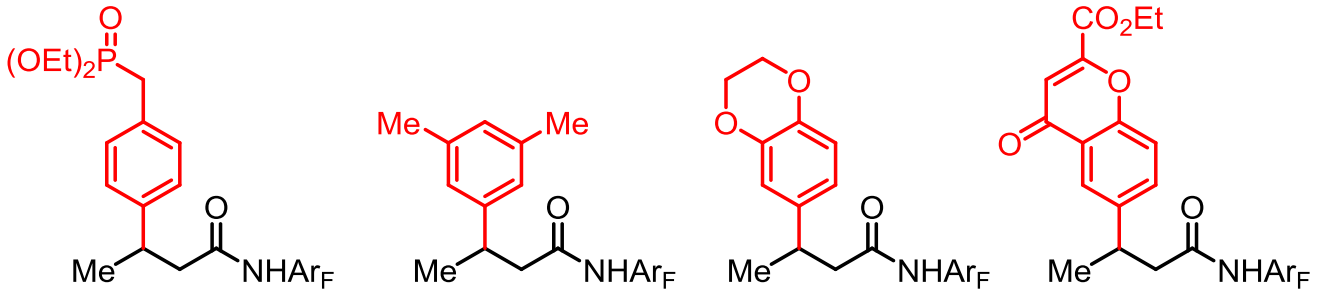
Aryl Iodide Scope



para R = Me	**2a**, 78%, 95:5 er		*para* R = Cl	**2g**, 67%, 95:5 er	
H	**2b**, 89%, 95:5 er		Br	**2h**, 56%, 95:5 er	
CH_2OMe	**2c**, 64%, 95.5:4.5 er		CF_3	**2i**, 45%, 94:6 er	
OMe	**2d**, 83%, 95:5 er		COMe	**2j**, 64%, 96:4 er	
OCF_3	**2e**, 57%, 94:6 er		CO_2Me	**2k**, 78%, 95.5:4.5 er	
F	**2f**, 84%, 94:6 er				
meta R = Me	**2l**, 71%, 96:4 er		*ortho* R = OMe	**2q**, 57%, 89:11 er	
OMe	**2m**, 78%, 96:4 er		CO_2Me	**2r**, 79%, 90:10 er	
F	**2n**, 58%, 95:5 er				
I	**2o**, 50%, 96:4 er				
CO_2Me	**2p**, 62%, 96:4 er				



2s, 60%, 93.5:6.5 er **2t**, 61%, 94:6 er **2u**, 58%, 94:6 er **2v**, 56%, 92:8 er

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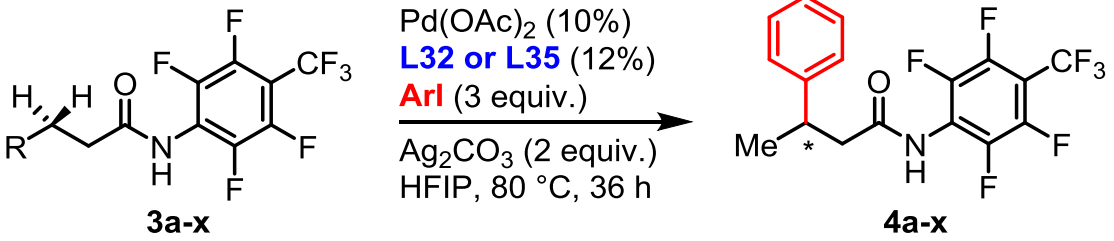
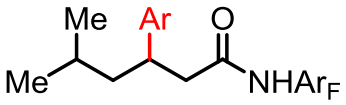
Scope of Amides and Acids



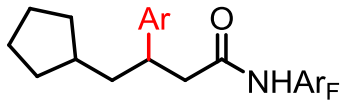
3a-x **4a-x**

R = Et **4a**, 78%, 93.5:6.5 er
n-Pr **4b**, 83%, 95:5 er
n-amyl **4c**, 80%, 94:6 er
-$(CH_2)_{10}$Me **4d**, 79%, 94:6 er
cyclopentyl **4e**, 48%, 89.5:10.5 er
cyclohexyl **4f**, 56%, 93.5:6.5 er

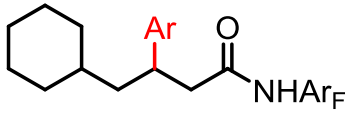
R = -$(CH_2)_2$Ph **4k**, 72%, 90:10 er
-$(CH_2)_4CO_2$Me **4l**, 60%, 95:5 er
-$(CH_2)_5CO_2$Me **4m**, 68%, 95:5 er
-$(CH_2)_3$NPhth **4n**, 50%, 93.5:6.5 er
-$(CH_2)_3$OMe **4o**, 40%, 95.5:4.5 er



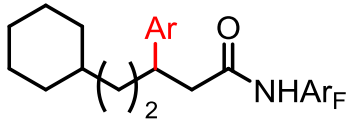
4g, 71%, 95:5 er



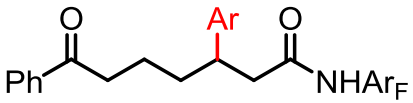
4h, 72%, 94:6 er



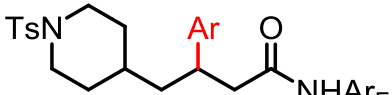
4i, 74%, 95:5 er



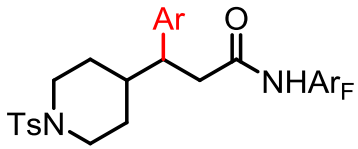
4j, 81%, 95:5 er



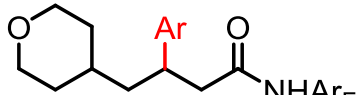
4p, 35%, 94:6 er



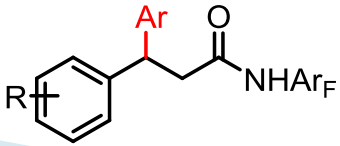
4q, 68%, 95:5 er



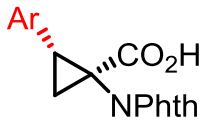
4r, 37%, 96:4 er



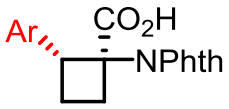
4s, 57%, 93:7 er



R = H **4t**, 85%, 87:13 er
4-CO_2Me **4u**, 87%, 92.5:7.5 er
3-MeI **4v**, 85%, 90:10 er



4w, 56%, 92:8 er



4x, 42%, 80:20 er

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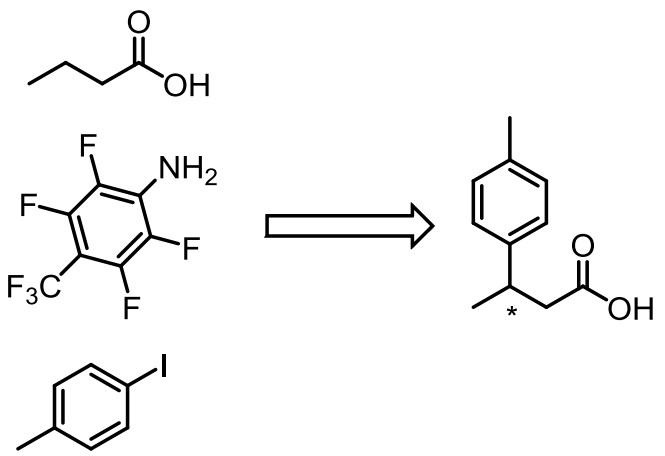
Poor Atom/Step Economy with DG Chemistry Remains a Major Challenge



Combined MW: 539.2323 MW: 178.2310

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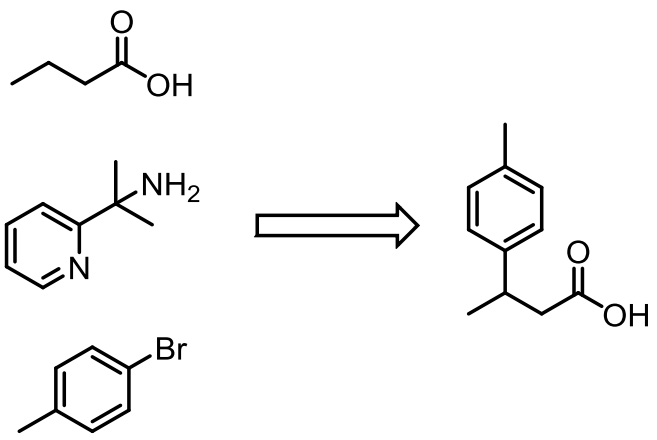

Combined MW: 395.3410 MW: 178.2310

Chem. Commun. **2014**, *50*, 8353.

Conclusions

Highlights:

- Useful methodology when conjugate addition is difficult.
- Excellent enantioselectivity.
- Ligands are accessible and tunable.

Room for Improvement:

- Are non-aromatic pi bonds (alkenes, alkynes) tolerated?
- . . . and heterocycles?
- Reaction times are long and catalyst loading is higher than typical cross-couplings.
- DG accounts for significant loss of atom economy.