Science

AAAS

Ligand-Controlled C(sp^3)–H Arylation and Olefination in Synthesis of Unnatural Chiral α–Amino Acids

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Dr. Hong Mei

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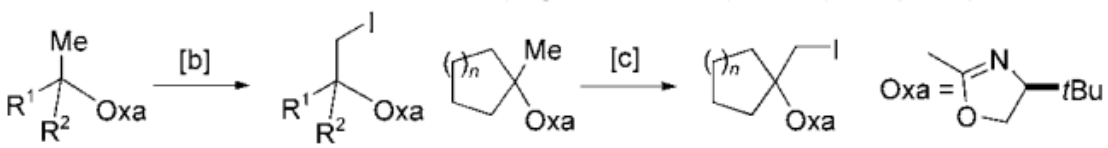
Palladium-catalyzed Activation of The Inert β-C(sp^3)–H Bonds of Aliphatic Carboxylic Acid Derivatives

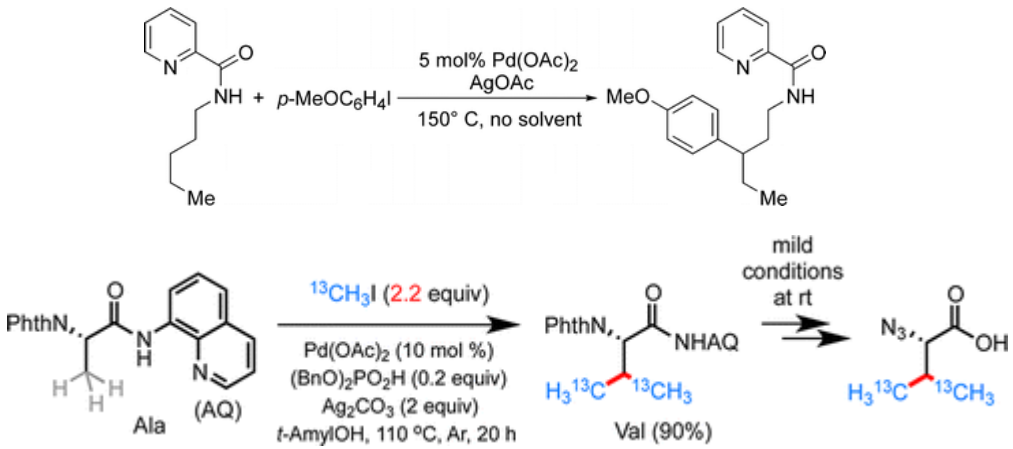
- **chiral oxazolines**



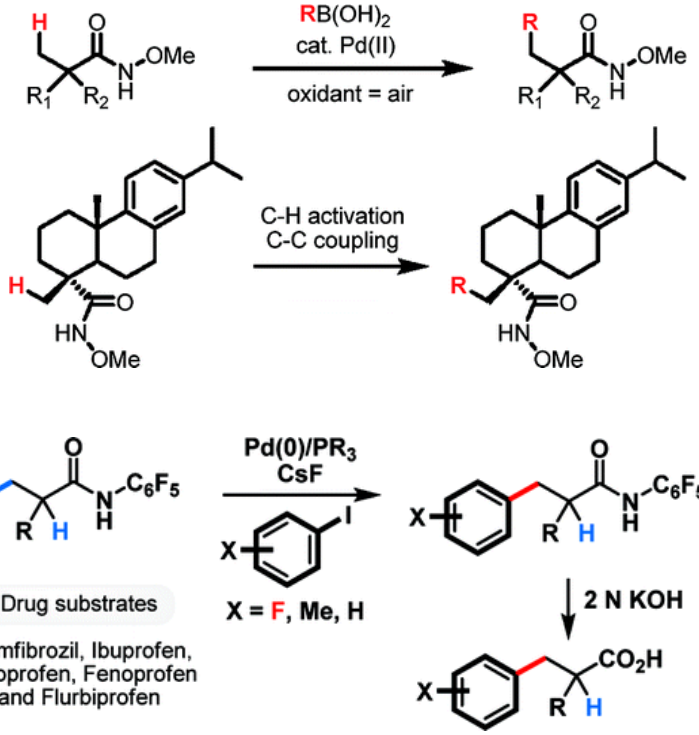
$Pd(OAc)_2$ (10 mol%), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2 , 24°C

R. Giri, X. Chen, J.-Q. Yu, Angew. Chem. Int. Ed. 44, 2112–2115 (2005)

- **8-aminoquinoline auxiliary**



- **a variety of weakly coordinating amide directing groups**



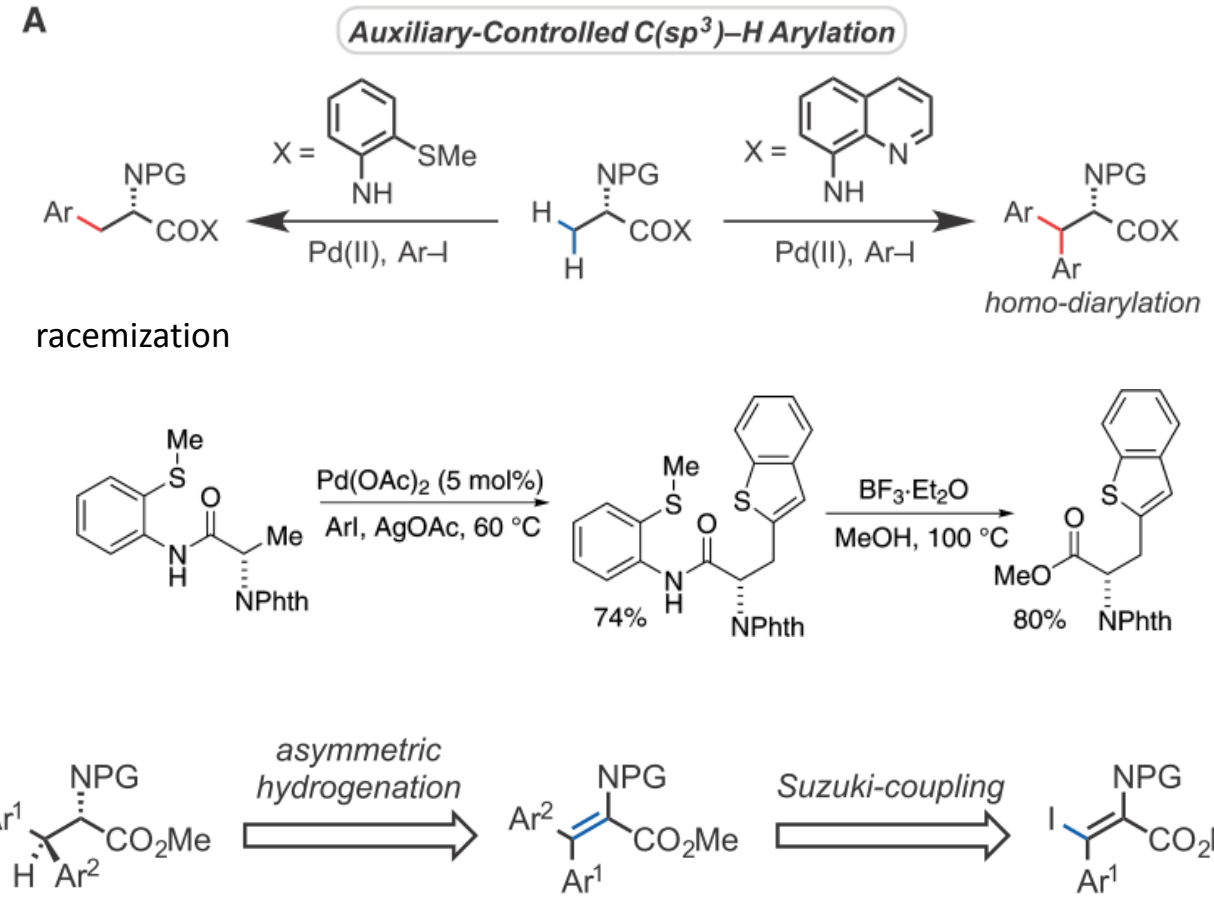
V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.

S.-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135–12141.

D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191.

M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886–9887.

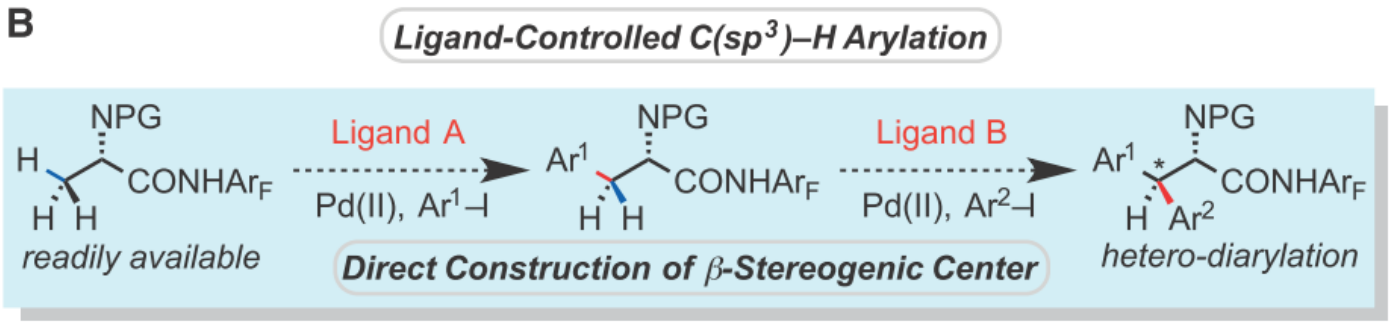
Methods for Synthesizing Chiral β -Ar-β-Ar'-α–amino Acids



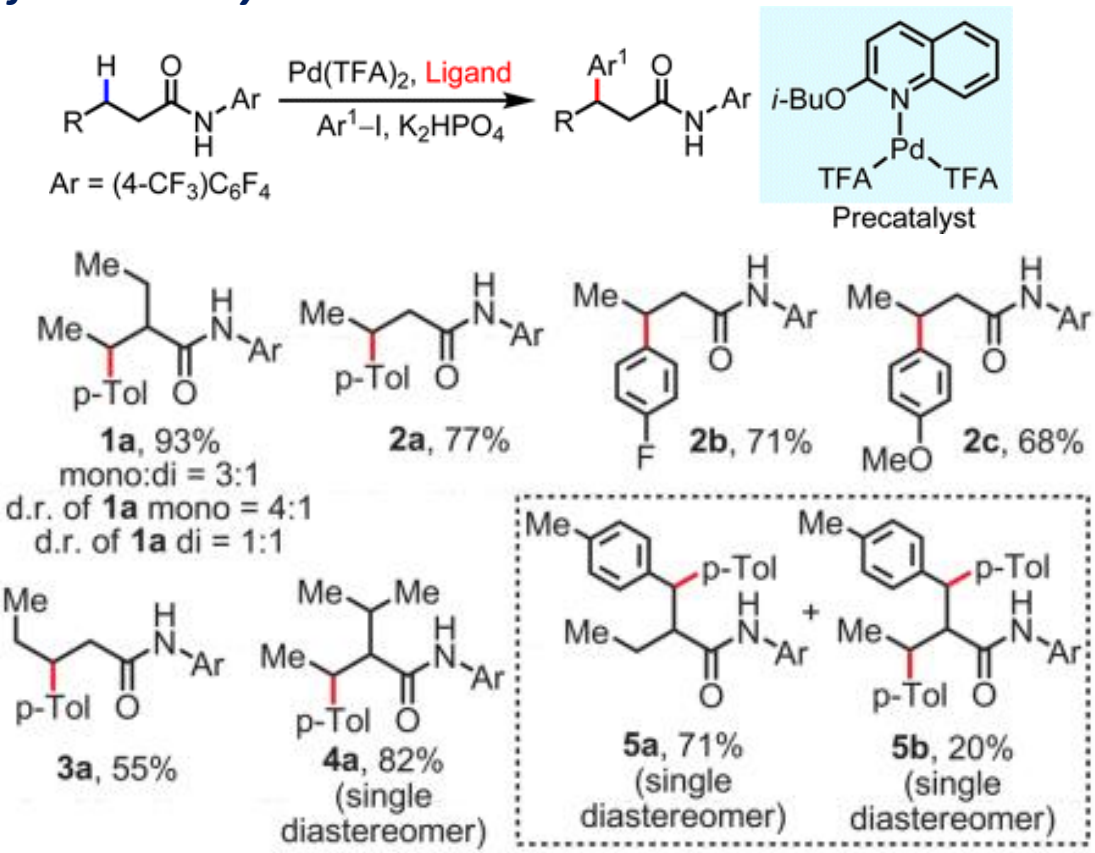
L. D. Tran, O. Daugulis, *Angew. Chem. Int. Ed.* **2012**, *51*, 5188–5191.

N. Rodríguez, J. A. Romero-Revilla, M. Á. Fernández-Ibáñez, J. C. Carretero, *Chem. Sci.* **2013**, *4*, 175–179.

Methods for Synthesizing Chiral β -Ar-β-Ar′-α–amino Acids

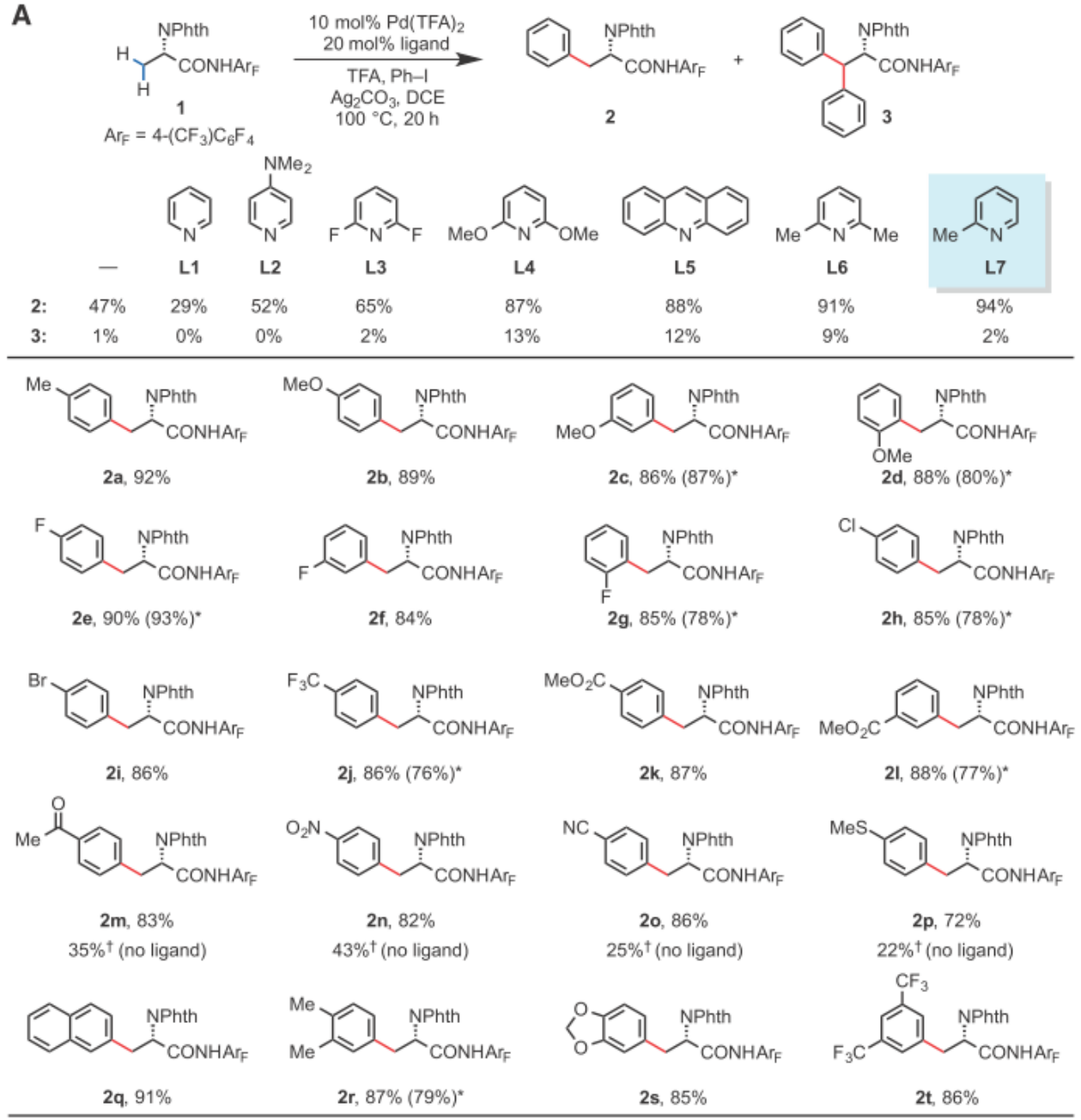


A Ligand for Monoarylation

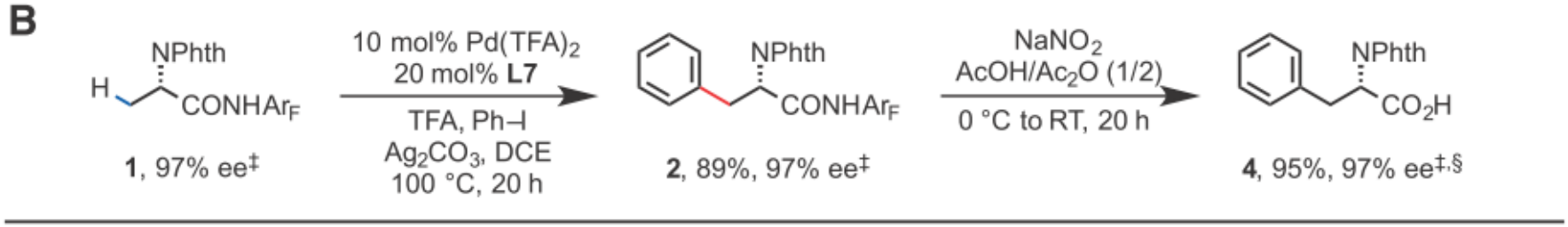


M. Wasa *et al., J. Am. Chem. Soc.* **2012**, *134*, 18570–18572.

A Diverse Array Of Monodentate Pyridine-derived Ligands



Removal of Amide Auxiliary and Determination of Enantiomeric Purity



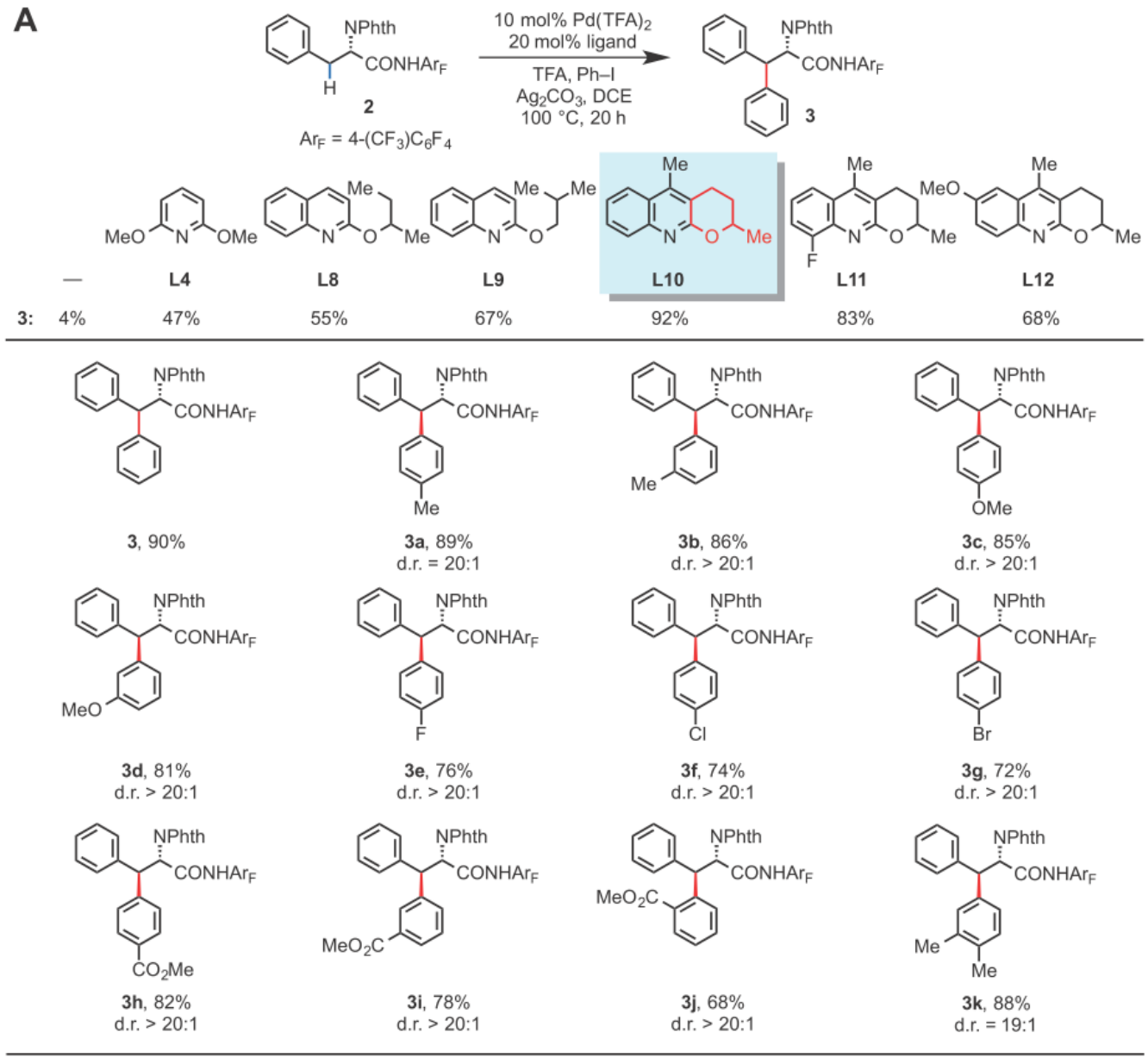
when conducted at 100°C, these reactions are typically complete within 20 hours, and no racemization of the α-chiral center is observed.

Subsequent removal of the auxiliary can be accomplished under mild conditions without loss of enantiomeric purity.

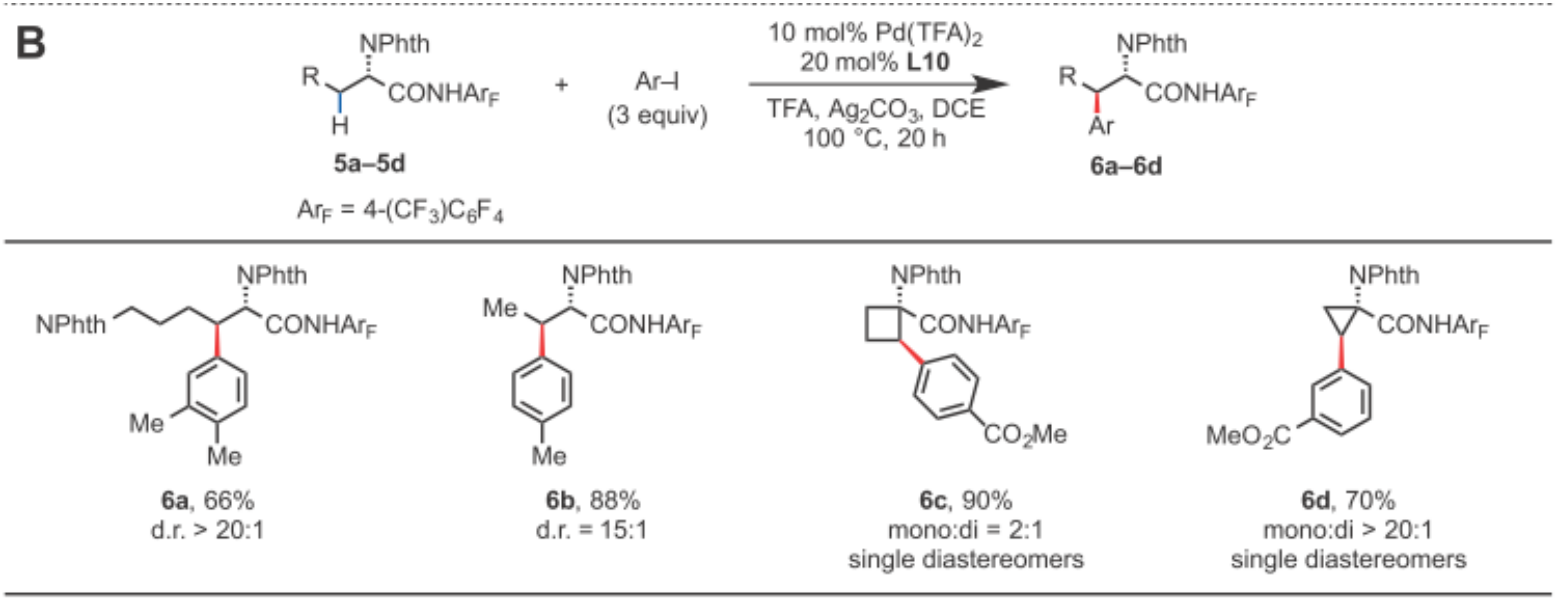
the monoarylated products are readily converted to the corresponding N-fluorenylmethyloxycarbonyl–protected unnatural amino acids

Palladium-catalyzed Arylation of Secondary C(sp^3)–H Bonds

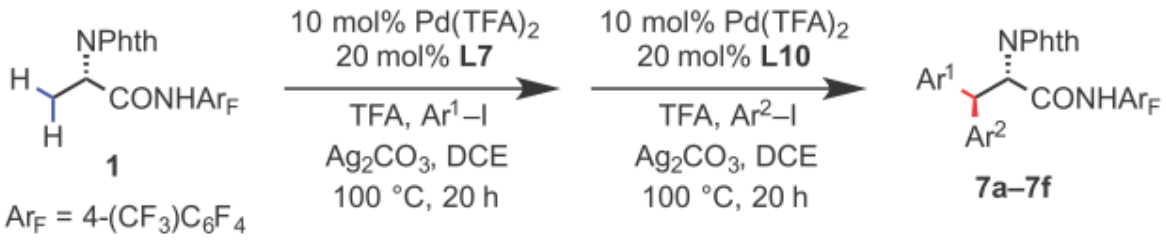
A Ligand for Diarylation

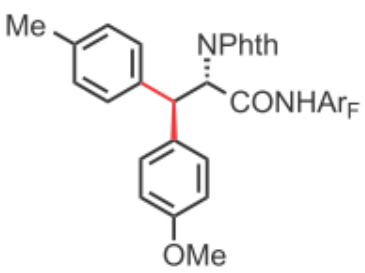


Arylation of Alkyl Amino Acid Derivatives

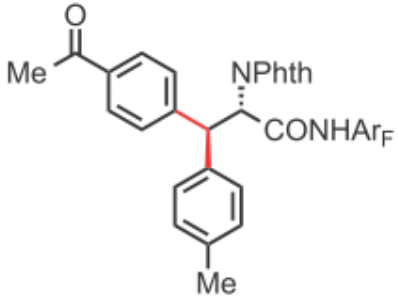


One-Pot Diarylation

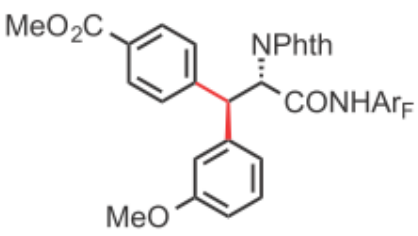




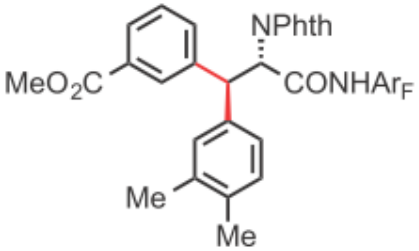
7a, 68%
d.r. = 19:1



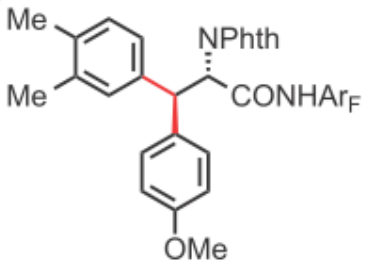
7b, 62% (60%)*
d.r. = 19:1



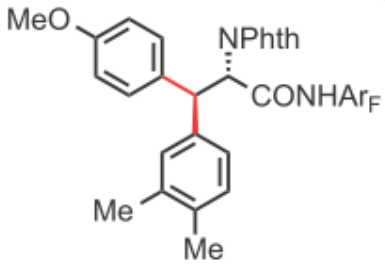
7c, 65%
d.r. > 20:1



7d, 66%
d.r. > 20:1



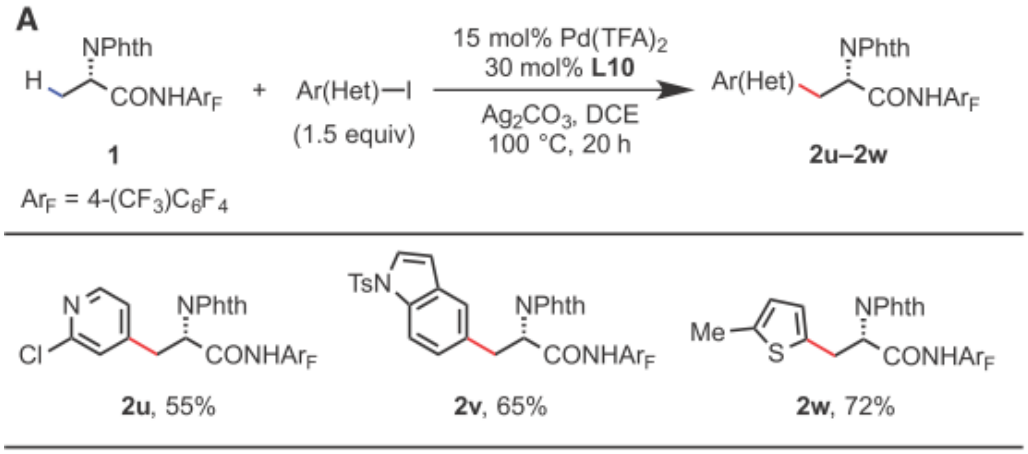
7e, 59%
d.r. > 20:1



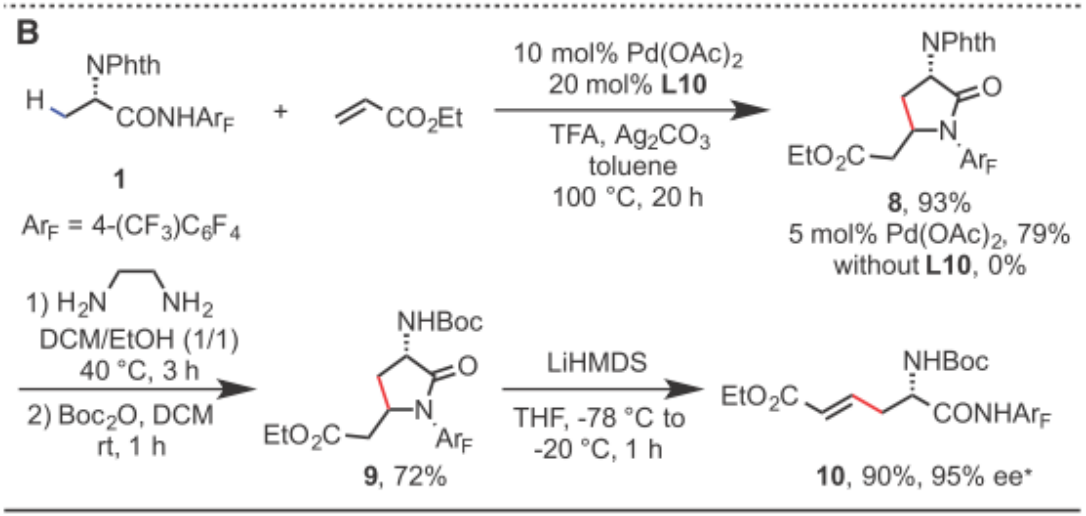
7f, 60%
d.r. = 16:1

Further Applications of Pd Catalysis with L10

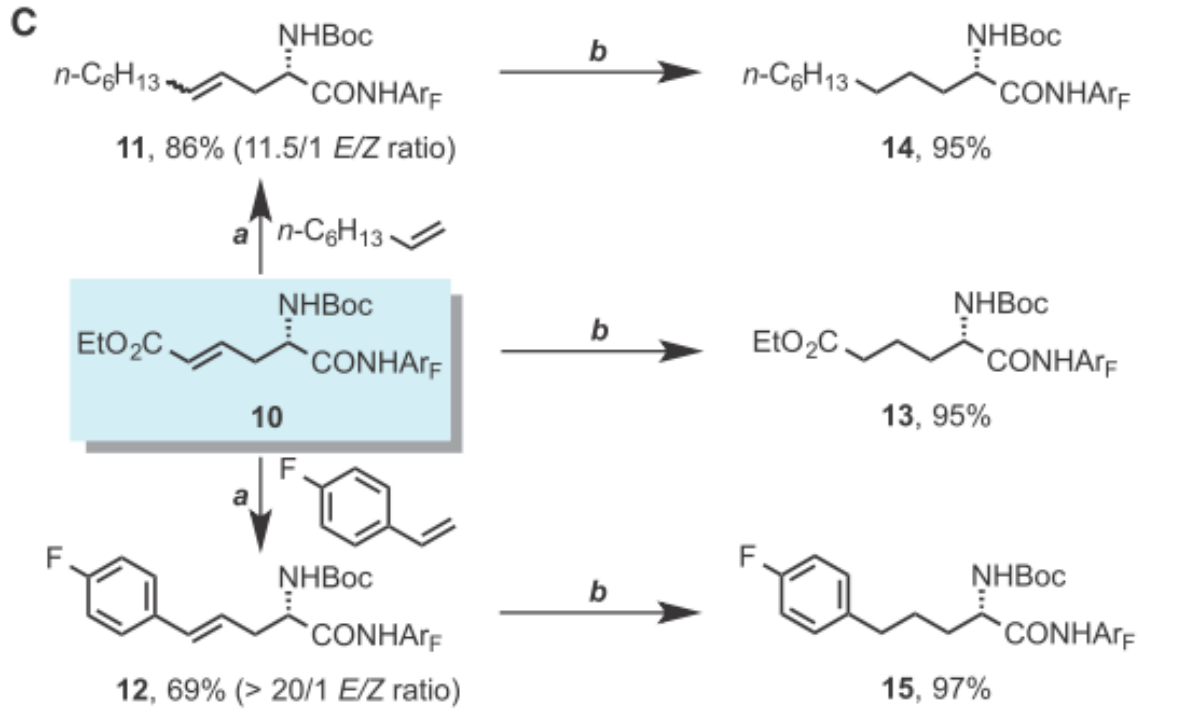
Ligand-enabled C(sp³)–H arylation with heteroaryl iodides



C(sp³)–H olefination of alanine derivatives



Further Applications of Pd Catalysis with L10



Reagents and conditions: (a) 5 mol% Grubbs Catalyst 2nd Generation, DCM, 50 °C, 16–19 h.(b) Pd/C, H_2, rt, EtOAc, 40 min–24 h.

Mechanistic Studies

C(sp 3)–H arylation with aryl iodides likely proceeds via a Pd(II)/Pd(IV) catalytic cycle, olefination probably proceeds via a Pd(II)/Pd(0) redox manifold