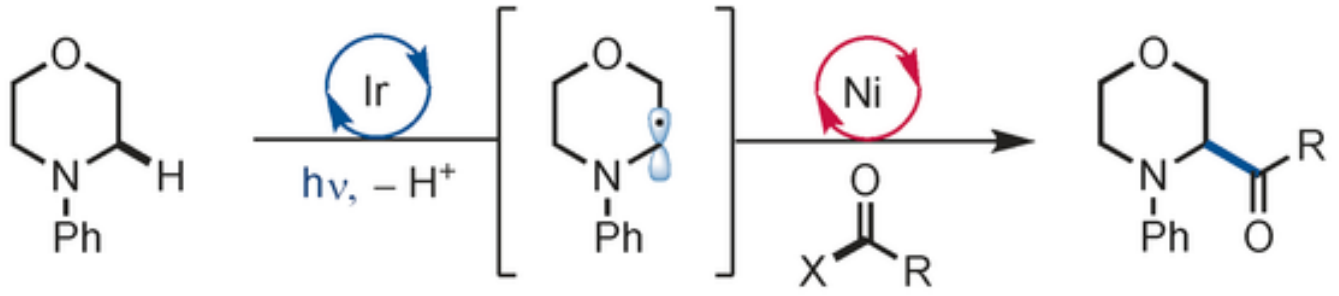
Direct Acylation of C(sp^3)-H Bonds Enabled by Nickel and Photoredox Catalysis

Candice L. Joe and Abigail G. Doyle

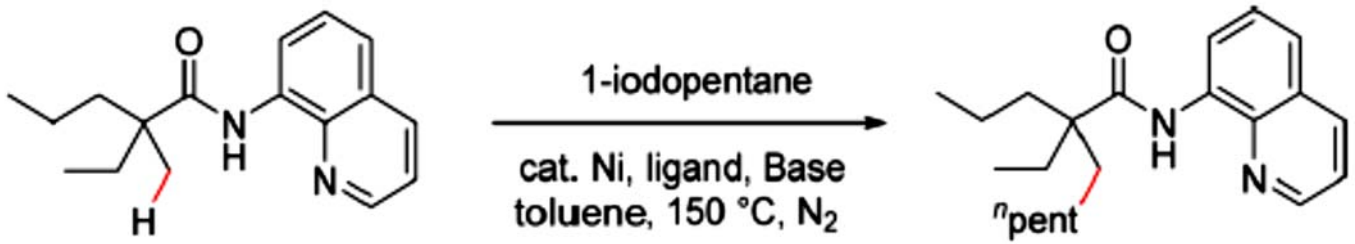
Angew. Chem. Int. Ed., **2016**, 55, 4040



- formal C(sp^3)–H bond activation
- C(sp^3)–C(sp^2)$_{acyl}$ cross-coupling

28 examples
up to 86% yield

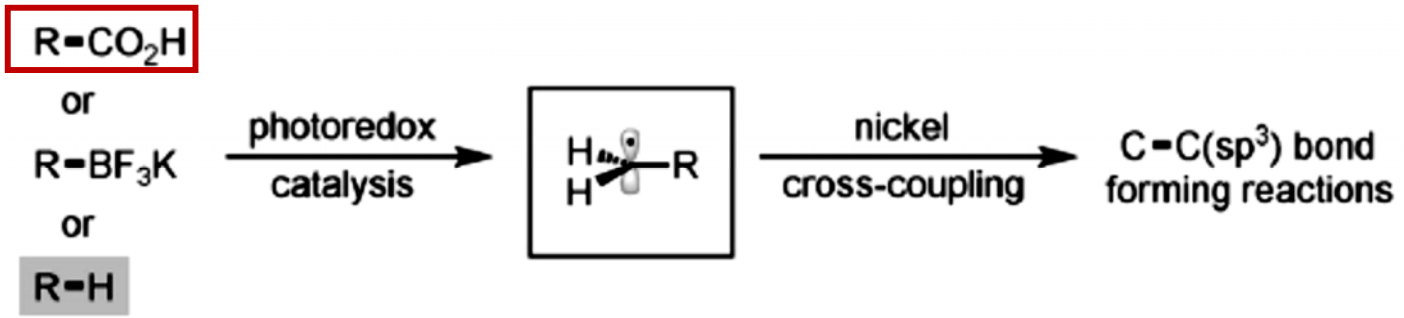
Nickel-Catalyzed Site-Selective Alkylation of Unactivated C(sp^3)–H Bonds

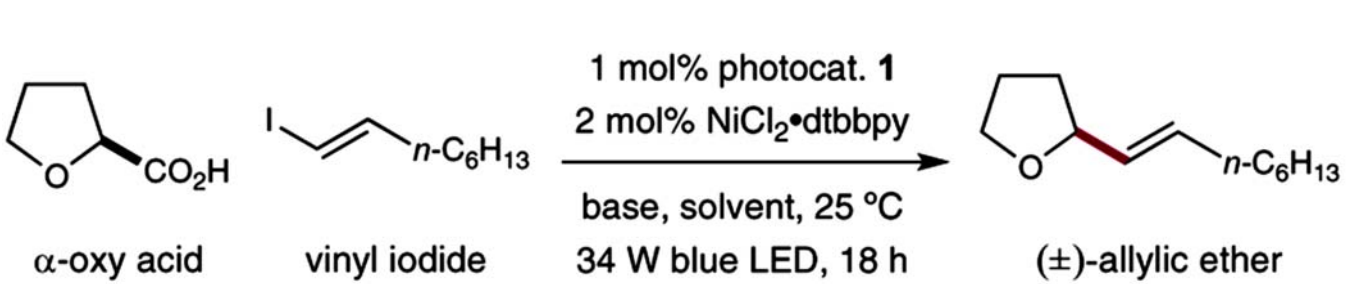


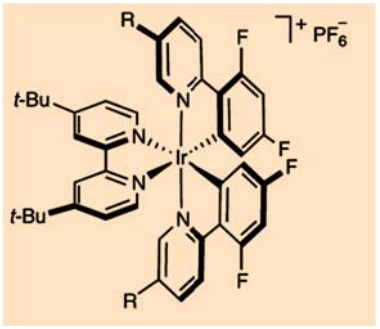
N. Chatanis, *J. Am. Chem. Soc.* , **2014**, 136, 898.

- ✓ Coordinating directing groups
- ✓ High reaction temperatures
- ✓ Limited scope

Previous work: Photogeneration of alkyl radicals for nickel-catalyzed cross-coupling







D. W. C. McMillan, *J. Am. Chem. Soc.* , **2015**, 137, 624.

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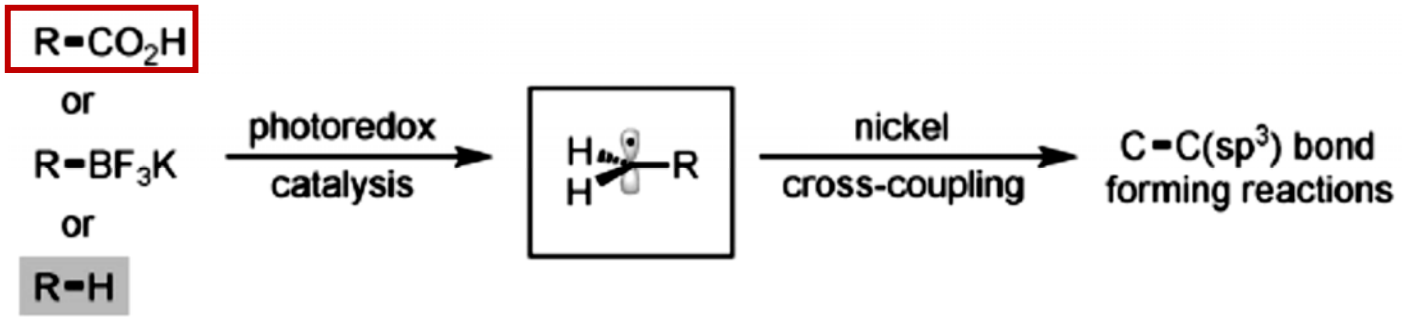
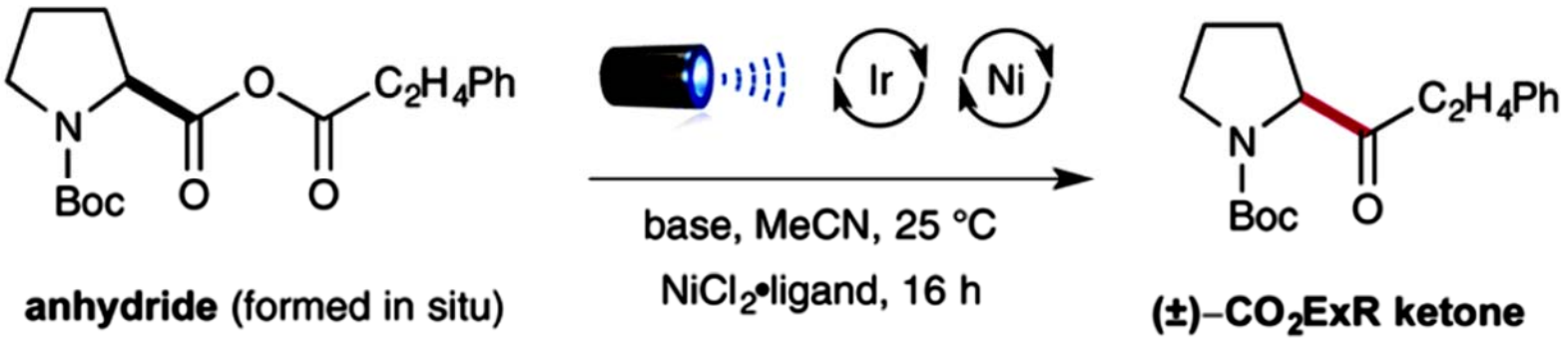


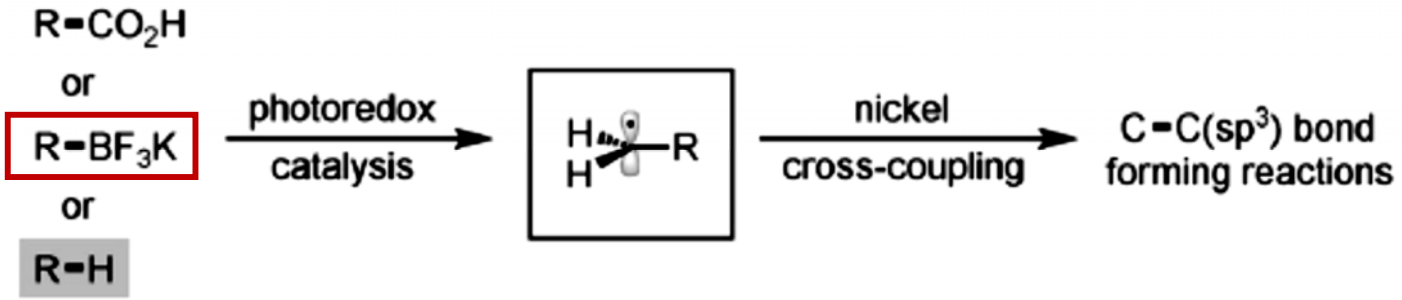


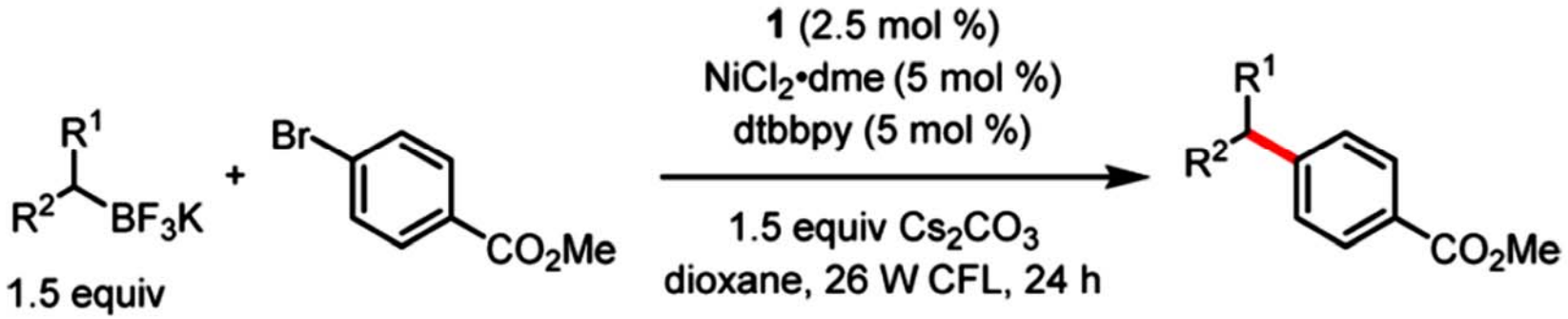
anhydride (formed in situ)

(±)–CO_2ExR ketone

D. W. C. McMillan, *J. Am. Chem. Soc.* , **2015**, 137, 11938.

Previous work: Photogeneration of alkyl radicals for nickel-catalyzed cross-coupling





G. A. Molander, *J. Am. Chem. Soc.* , **2015**, 137, 2195.

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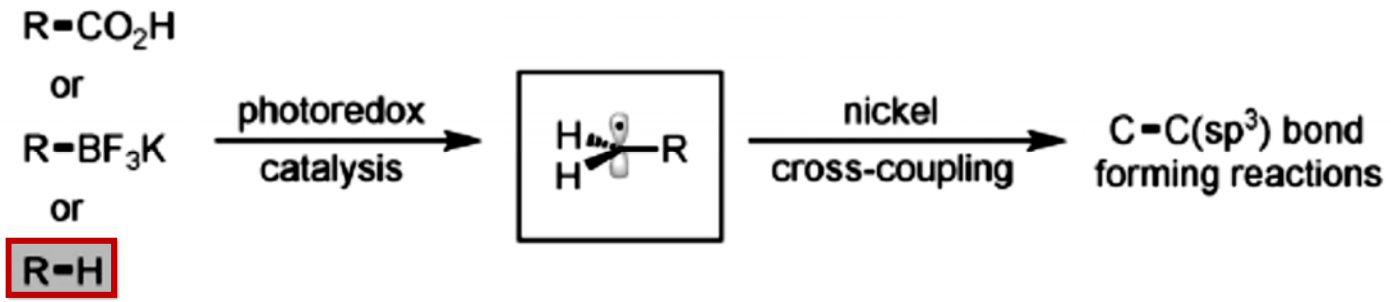
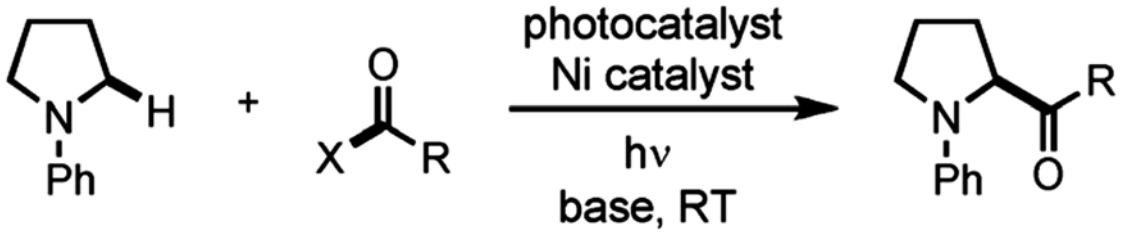
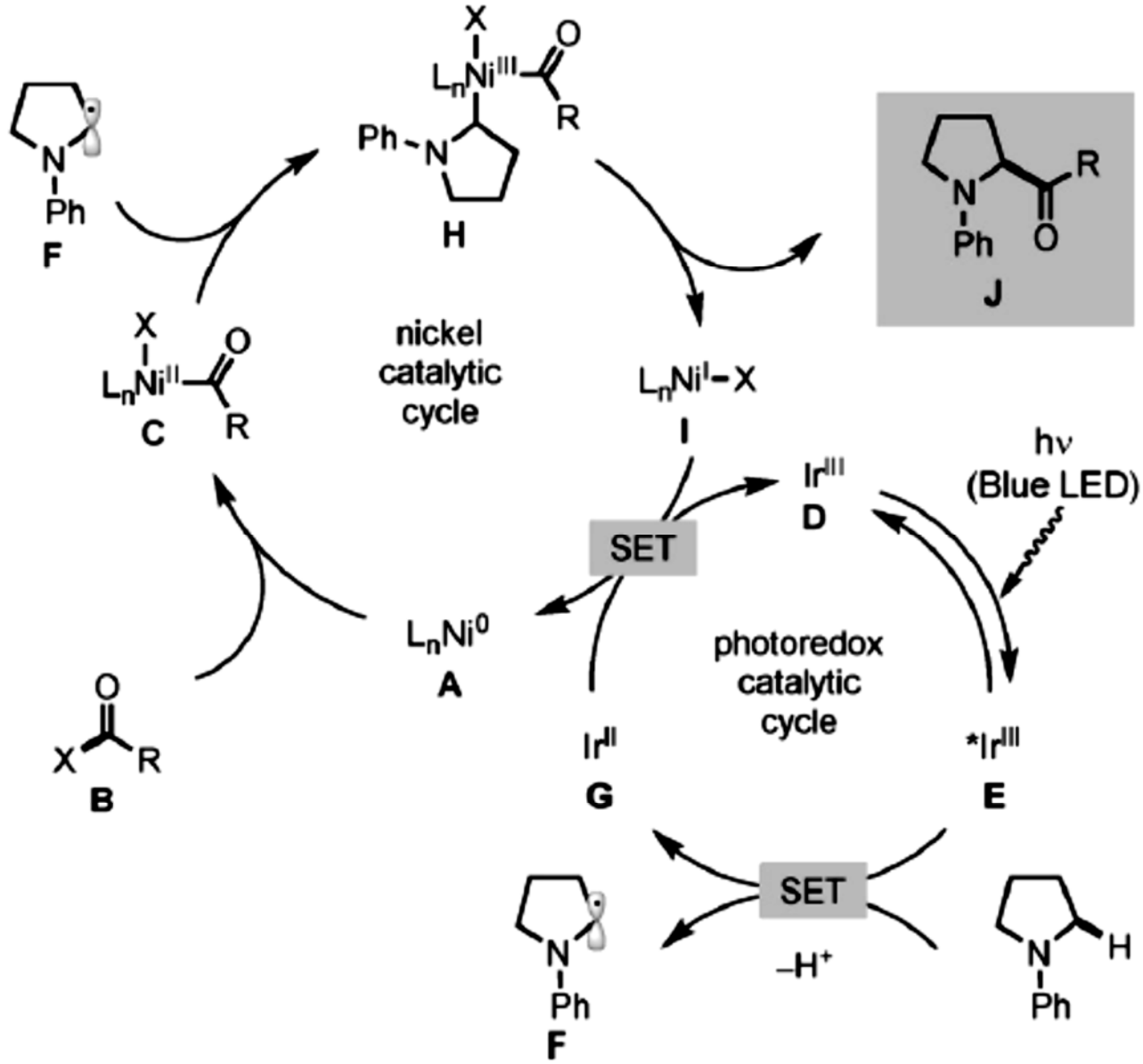




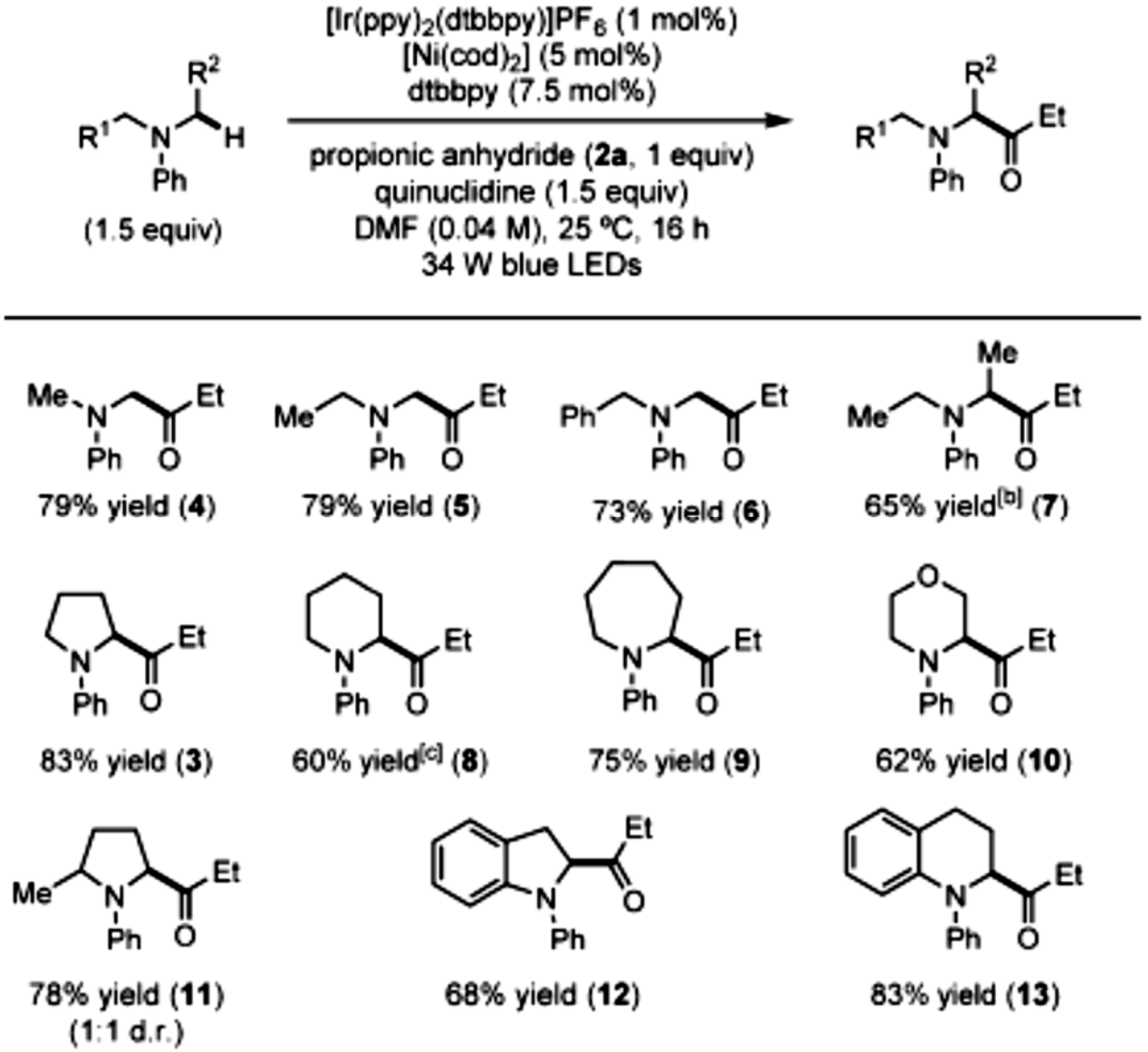
- ✓ Direct, modular
- ✓ Mild conditions
- ✓ Simple starting materials

A. G. Doyle, *Angew. Chem. Int. Ed.* **2016**, 55, 4040

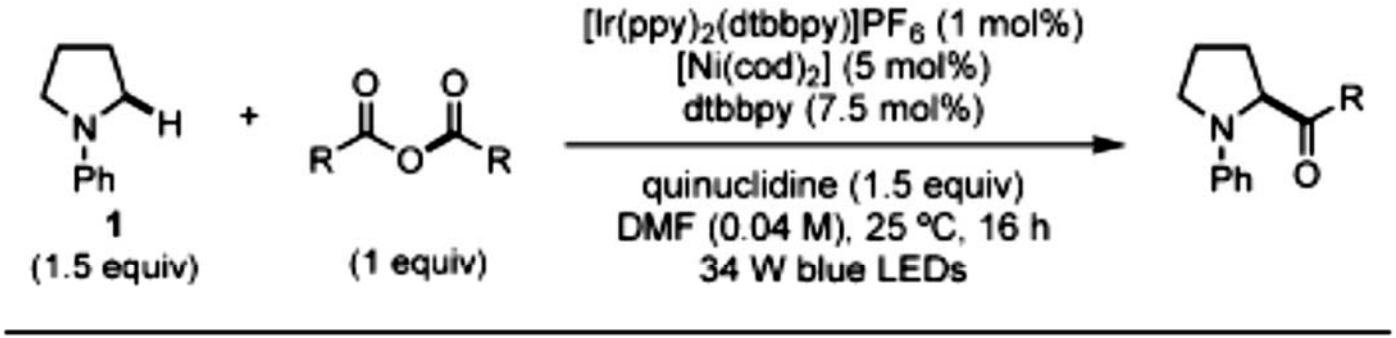
Proposed catalytic cycle for metallaphotoredox C-H acylation

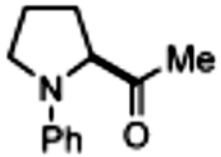


Amine and symetric anhydride scope

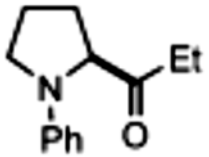


Amine and symetric anhydride scope

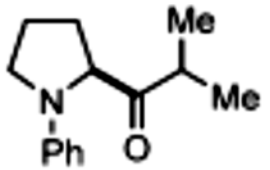




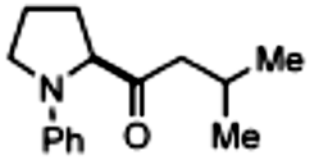
57% yield (**18**)



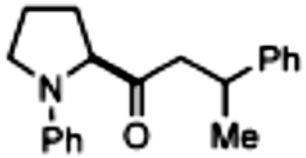
83% yield (**3**)



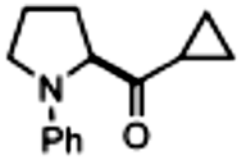
69% yield (**19**)



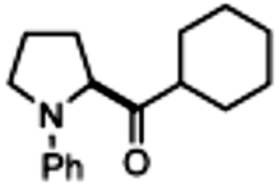
74% yield (**20**)



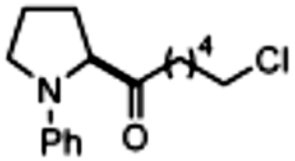
65% yield (1:1 dr) (**21**)



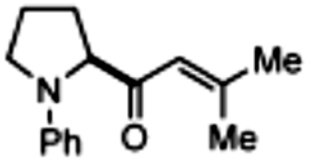
73% yield (**22**)



74% yield (**23**)

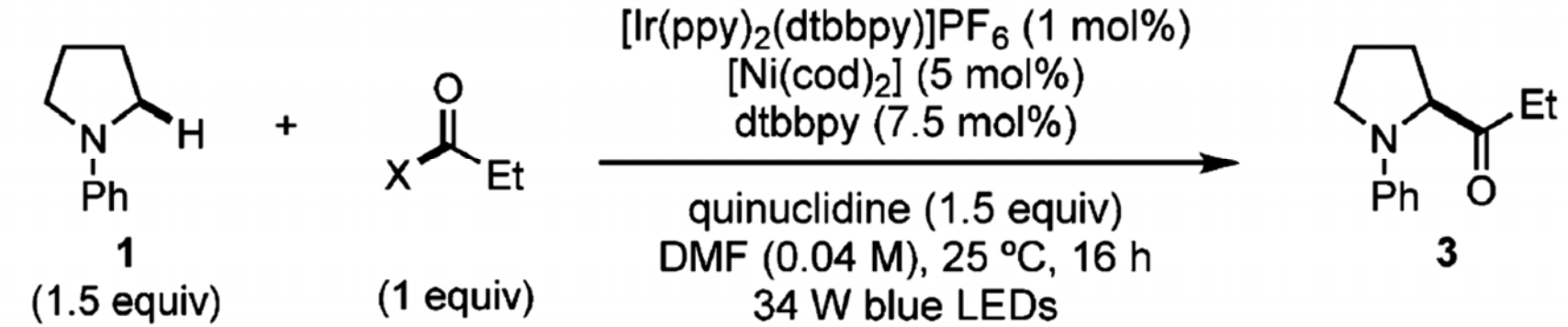


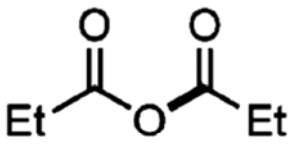
64% yield[b] (**24**)



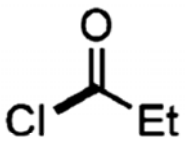
65% yield[b] (**25**)

Acyl cross-copupling partners

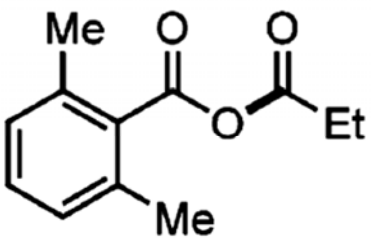




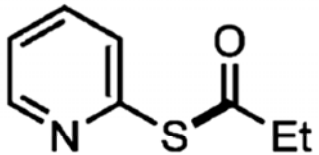
83% yield (**2a**)



<5% yield[b] (**2b**)

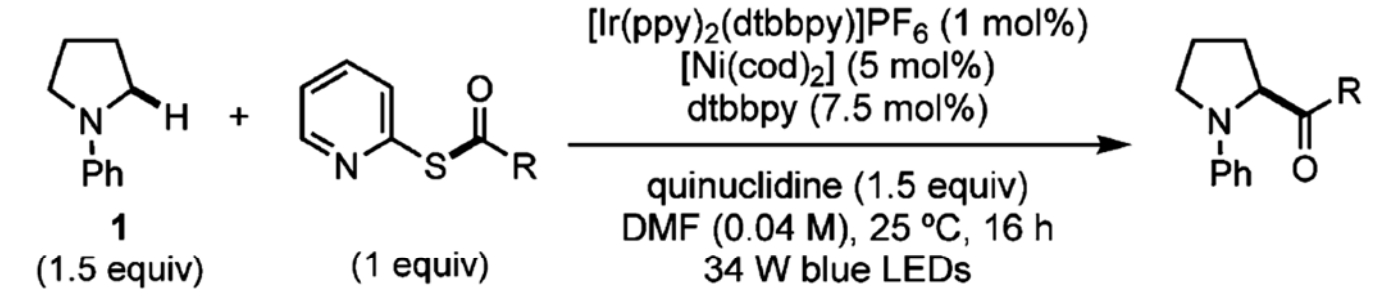


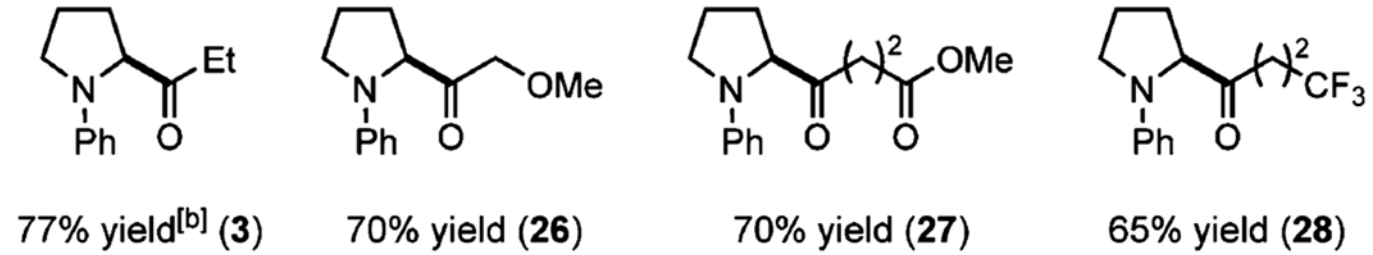
64% yield (**2c**)



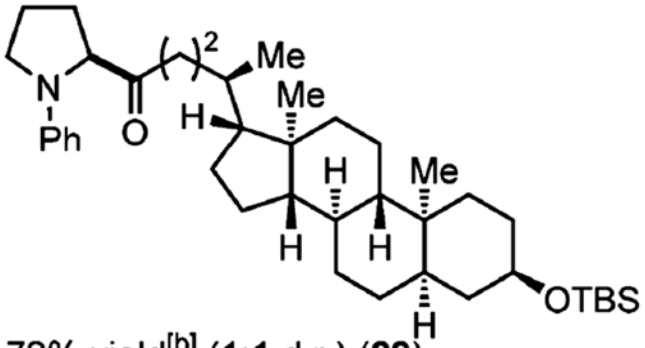
77% yield (**2d**)

Thioester scope

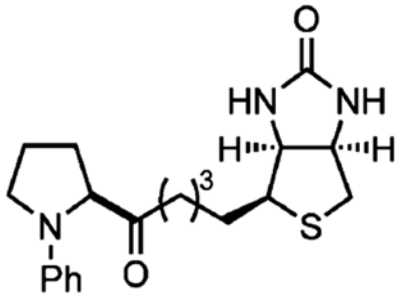




77% yield[b] (**3**) 70% yield (**26**) 70% yield (**27**) 65% yield (**28**)



72% yield[b] (1:1 d.r.) (**29**)

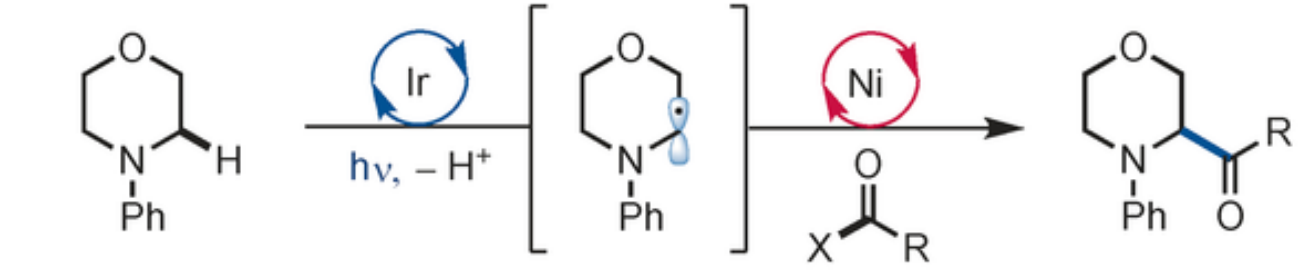


76% yield[b] (**30**)

Conclusion

A novel method for C(sp^3)-H activation by nickel and photoredox catalysis was developed.

- ✓ Direct synthesis of α-amino-ketones from N-aryl amines and acyl donors.
- ✓ Metallaphotoredox catalysis can afford a strategic alternative for C(sp^3)-H funcionalization.
- ✓ This method can be extended to late-stage coupling of complex and biologically relevant partners.



- formal C(sp^3)–H bond activation
- C(sp^3)–C(sp^2)$_{acyl}$ cross-coupling

28 examples
up to 86% yield

THANK YOU FOR YOUR ATTENTION!