

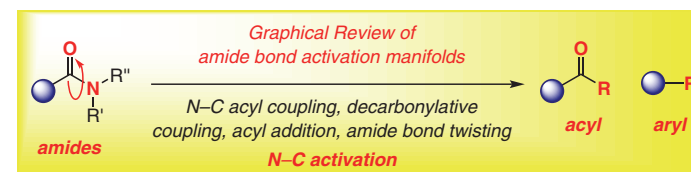
# Amide N–C Bond Activation: A Graphical Overview of Acyl and Decarbonylative Coupling

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**Abstract** This Graphical Review provides an overview of amide bond activation achieved by selective oxidative addition of the N–C(O) acyl bond to transition metals and nucleophilic acyl addition, resulting in acyl and decarbonylative coupling, together with key mechanistic details pertaining to amide bond distortion underlying this reactivity manifold.

**Key words** C–N activation, amide bond activation, acyl coupling, decarbonylative coupling, acyl addition, catalysis

The importance of amide bonds is undeniable. The amide bond is the fundamental linkage of life in peptides and proteins. Due to its special dipolar character, amides are indispensable in pharmaceuticals, pesticides, and polymers. At present, more than 50% of drug candidates contain amide bonds. Remarkably, reactions of amides are the most common type of reactions used in current medicinal chemistry.

Typical planar amides feature strong amidic resonance,  $n_N \rightarrow \pi^*_{C=O}$  conjugation (15–20 kcal/mol), which renders amide bond cleavage extremely difficult. However, the amide bond can be sterically twisted or electronically activated by functionalizing the nitrogen atom of the amide bond. In this way, the amide bond resonance can be significantly decreased or diverted onto the activating group, thus enabling highly selective activation of N–C(O) amide bonds.

Recent years have seen an explosion of amide bond activation methods. Although the concept of amide bond twisting and the concurrent decrease of amidic resonance in bridged lactams was proposed as early as the 1930s, it was not until 2015 that generic acyclic twisted amides

were used for the first time as cross-coupling partners in selective N–C(O) bond activation, thus effectively serving as surrogates for acyl and aryl halides and pseudohalides in transition-metal catalysis.

Amide bond activation can be categorized as acyl coupling and decarbonylative coupling. This reactivity is triggered by selective oxidative addition of the N–C(O) acyl bond to a transition metal, leading to either direct transmetalation or CO de-insertion. Furthermore, the successful use of amides as acyl halide equivalents in transition-metal catalysis spearheaded the development of an array of highly selective methods for nucleophilic acyl addition to amide bonds, resulting in an alternative disconnection to acyl products. In many cases, the direct nucleophilic acyl addition shows advantages over transition-metal-catalyzed variants; however, it should be noted that these manifolds are broadly complementary.

This Graphical Review provides an overview of the key studies in amide bond activation covering the period of 2015 to 2022. The goal of this Graphical Review is to provide a summary of the reactions developed and the manifolds established in the main areas of amide bond activation, including acyl and decarbonylative coupling as well as acyl nucleophilic addition, while highlighting the underlying mechanisms and amides that are critical to this reactivity manifold. Throughout the review we have attempted to cite the seminal reports and precedents. However, the reader should note that due to the format of this review and the large number of contributions, the review is not comprehensive.

Throughout the review, the reactions are categorized by the type of mechanism. An important aspect that the reader should pay special attention to is the role of specific amides that participate in each reaction manifold. In general, sterically twisted or electronically activated amides can be prepared (1) from carboxylic acids or their derivatives, or (2) from generic 1° or 2° amides. Both methods are valuable in terms of the synthetic advantages of amide bonds in cross-coupling and acyl addition chemistry. However, for derivatization of biomolecules and late-stage functionalization of pharmaceuticals, only amides that can be generically prepared from 1° or 2° amides are useful. We hope that this Graphical Review will stimulate further progress in this tremendously important field of chemistry.

## Biographical Sketches



**Chengwei Liu** received his Ph.D. from Rutgers University with Prof. Michal Szostak in 2020. He conducted his postdoctoral research at the University of Oxford with Prof. Stephen P. Fletcher from 2020 to 2021. He was subsequently

an assistant professor at Nanjing University of Information Science and Technology from 2021 to 2022. In the summer of 2022, he joined the faculty at Shanghai University, where he started his independent career and was promot-

ed to full professor in 2022. His research group is focused on amide bond activation, C–O bond activation, C–S bond activation, and lanthanide organometallic chemistry.



**Michal Szostak** received his Ph.D. from the University of Kansas in 2009. He carried out postdoctoral research at Princeton University and the University of Manchester. In 2014, he joined the faculty at Rutgers University, where he is currently Professor of Chemistry. His research group de-

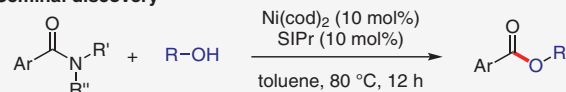
veloped the concept of acyclic twisted amide bond activation. In 2022, he edited the book '*Amide Bond Activation: Concepts and Reactions*'. His current research is focused on the development of new synthetic methodology based on transition-metal catalysis, amide bond activation, NHC

ligands, inert bond activation, and applications to the synthesis of biologically active molecules. He is the author of over 240 publications.

- New concept
- Bench-stable electrophiles
- Non-toxic

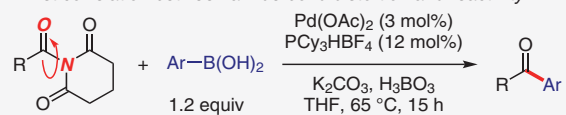
(1a) Szostak, *Amide Bond Activation: Concepts and Reactions*, 2022.

#### Seminal discovery

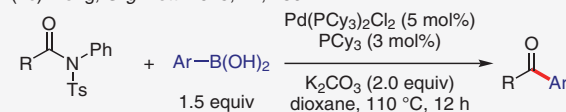


(1b) Hie, *Nature* **2015**, 524, 79.

- First correlation between amide bond distortion and reactivity



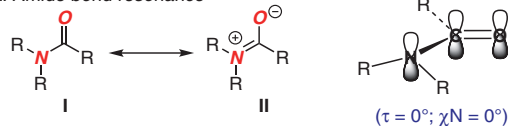
(1c) Meng, *Org. Lett.* **2015**, 17, 4364.



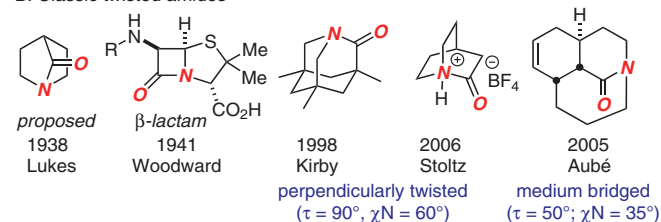
(1d) Li, *Chem. Commun.* **2015**, 51, 5089.

#### Concept was first introduced: C–N bond activation of twisted amides

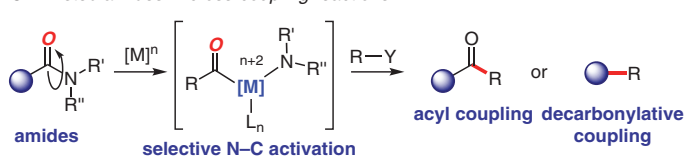
##### A. Amide bond resonance



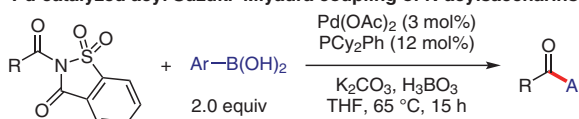
##### B. Classic twisted amides



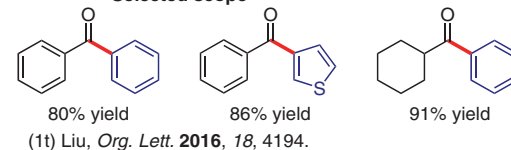
##### C. Twisted amides in cross-coupling reactions



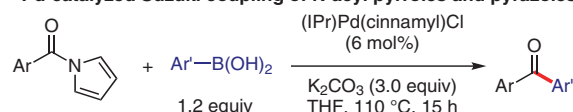
#### Pd-catalyzed acyl Suzuki–Miyaura coupling of *N*-acylsaccharins



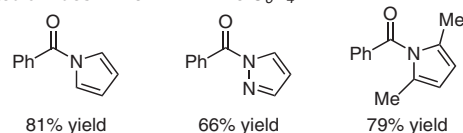
#### Selected scope



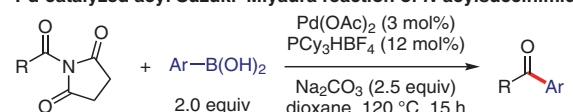
#### Pd-catalyzed Suzuki coupling of *N*-acyl pyrroles and pyrazoles



#### Selected amides when $\text{Ar}' = 4\text{-Me-C}_6\text{H}_4$



#### Pd-catalyzed acyl Suzuki–Miyaura reaction of *N*-acylsuccinimides

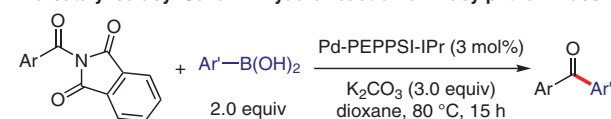


(1v) Osumi, *Org. Biomol. Chem.* **2017**, 15, 8867.

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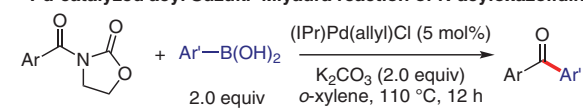
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- (1f) Meng, *Chem. Rev.* **2021**, 121, 12746.
- (1g) Meng, *Synlett* **2016**, 27, 2530.
- (1h) Liu, *Chem. Eur. J.* **2017**, 23, 7157.
- (1i) Meng, *Eur. J. Org. Chem.* **2018**, 2352.
- (1j) Takise, *Chem. Soc. Rev.* **2017**, 46, 5864.
- (1k) Kaiser, *Chem. Soc. Rev.* **2018**, 47, 7899.
- (1l) Dander, *ACS Catal.* **2017**, 7, 1413.
- (1m) Adachi, *Tetrahedron Lett.* **2018**, 59, 1147.
- (1n) Guo, *Chem. Eur. J.* **2018**, 24, 7794.
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- (1q) Li, *Trends Chem.* **2020**, 2, 914.
- (1r) Gao, *J. Org. Chem.* **2022**, in press, DOI: 10.1021/acs.joc.2c01094.
- (1s) Feng, *Angew. Chem. Int. Ed.* **2022**, 61, e202212213.

#### Pd-catalyzed acyl Suzuki–Miyaura reaction of *N*-acylphthalimides



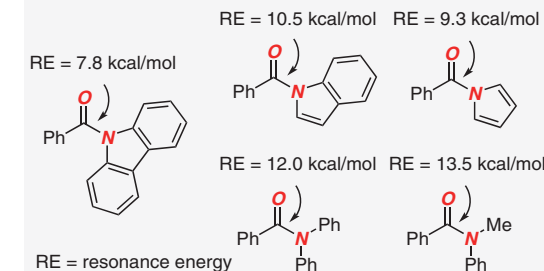
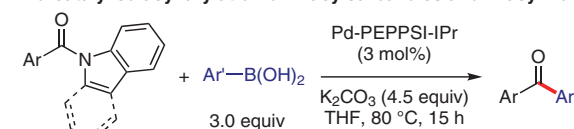
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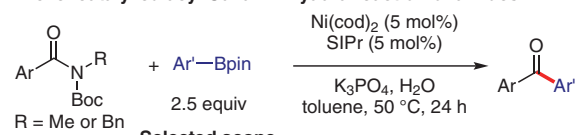
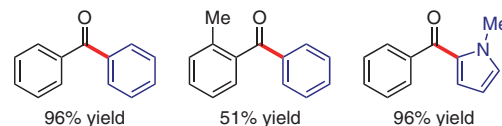
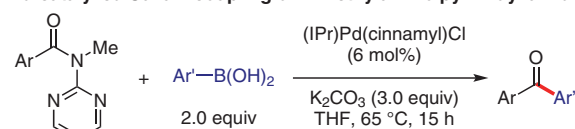


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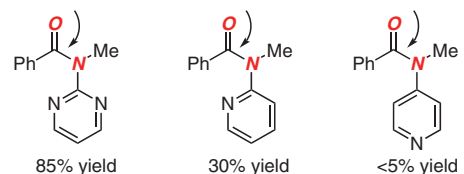
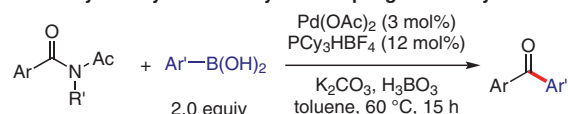
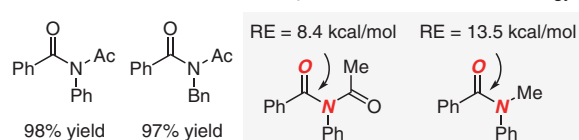
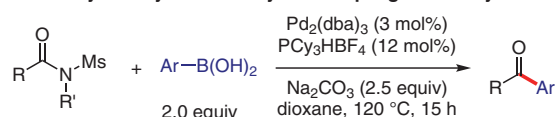
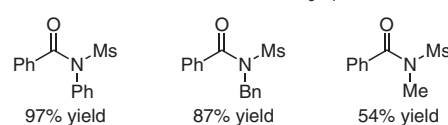
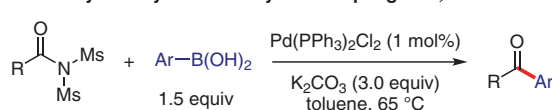
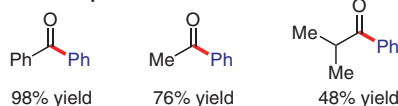
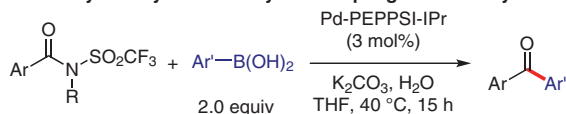
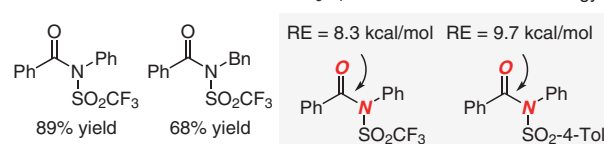
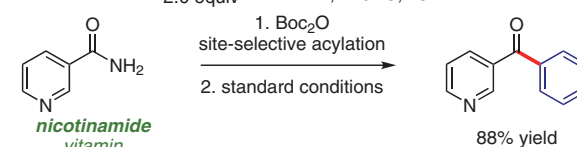
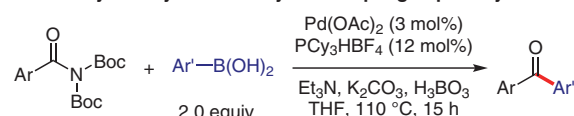
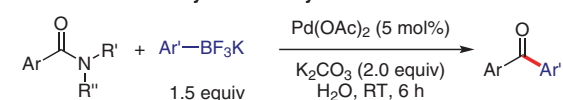
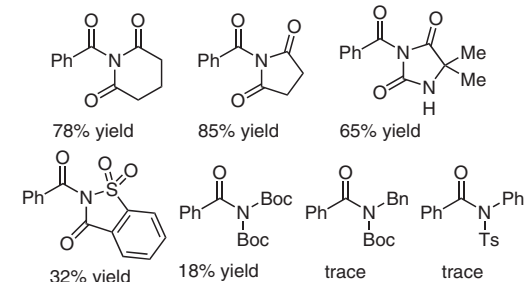
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Figure 1 Amide bond activation: concept and discoveries<sup>1</sup>

**Nickel-catalyzed acyl Suzuki–Miyaura reaction of amides**

**Selected scope**
(2a) Weires, *Nat. Chem.* **2016**, *8*, 75.
**Pd-catalyzed Suzuki coupling of *N*-methylamino pyrimidyl amides**

**Selected amides when Ar' = 4-Me-C<sub>6</sub>H<sub>4</sub>**

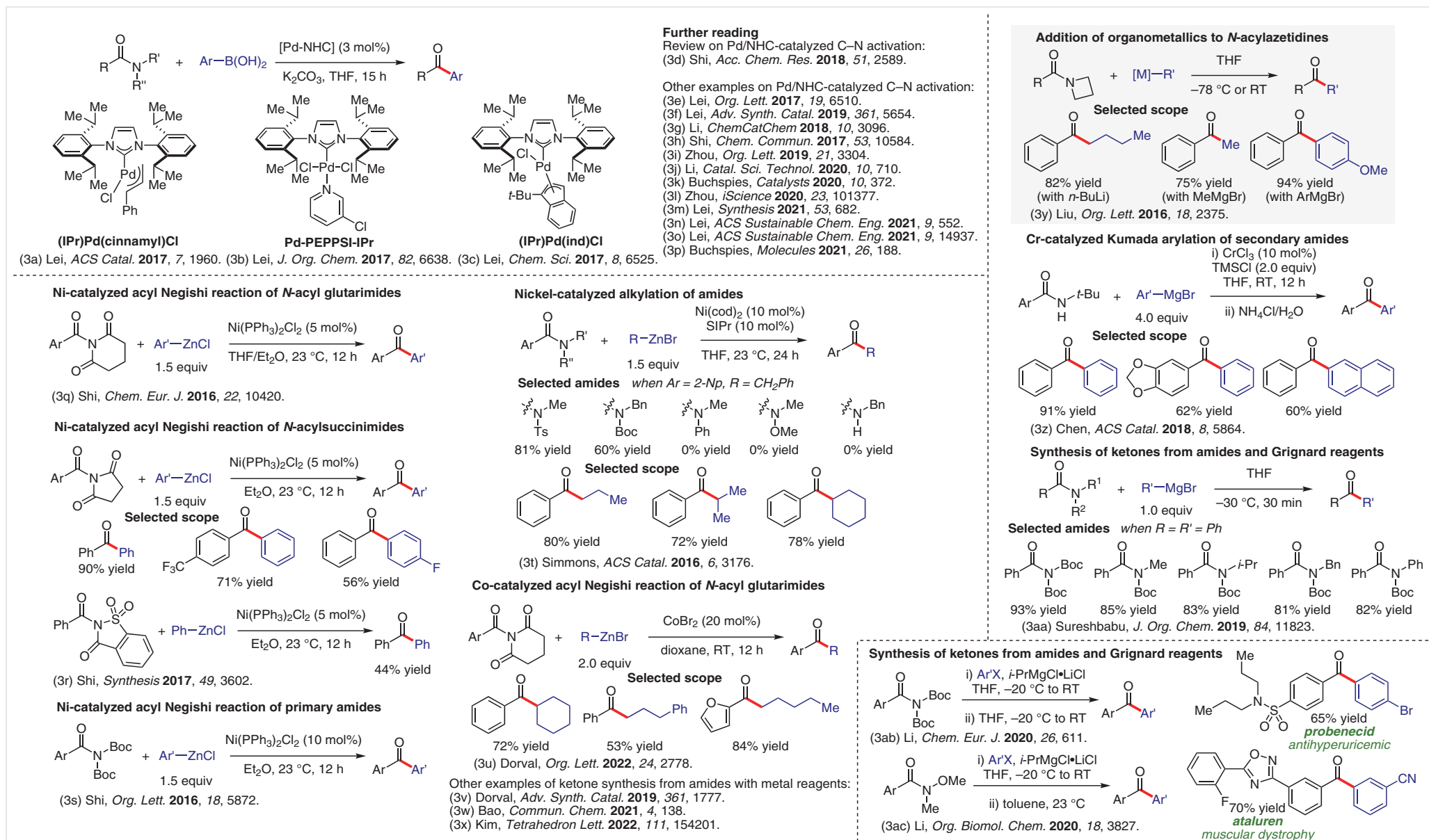
RE = 6.7 kcal/mol    RE = 8.8 kcal/mol    RE = 10.7 kcal/mol

(2b) Meng, *Org. Lett.* **2017**, *19*, 4656. RE = resonance energy
**Pd-catalyzed acyl Suzuki–Miyaura coupling of *N*-acetyl amides**

**Selected amides when Ar' = 4-Me-C<sub>6</sub>H<sub>4</sub>** RE = resonance energy
(2c) Liu, *ACS Catal.* **2018**, *8*, 9131.
**Pd-catalyzed acyl Suzuki–Miyaura coupling of *N*-mesyl amides**

**Selected amides when Ar = 4-Me-C<sub>6</sub>H<sub>4</sub>**
(2d) Liu, *Org. Lett.* **2017**, *19*, 1434.
**Pd-catalyzed acyl Suzuki–Miyaura coupling of *N,N*-di-Ms amides**

**Selected scope**
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**Pd-catalyzed acyl Suzuki–Miyaura coupling of *N*-sulfonyl amides**

**Selected amides when Ar' = 4-Me-C<sub>6</sub>H<sub>4</sub>** RE = resonance energy
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**Green method for acyl Suzuki–Miyaura reactions of amides**

**Selected amides when Ar' = Ph**
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 (2p) Szostak, *J. Org. Chem.* **2018**, *83*, 14676.  
 (2q) Ielo, *Chem. Eur. J.* **2020**, *26*, 16246.  
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 (2t) Mai, *Eur. J. Org. Chem.* **2019**, 7814.  
 (2u) Mehta, *Org. Lett.* **2020**, *22*, 1.  
 (2v) Shi, *Tetrahedron Lett.* **2020**, *61*, 152140.  
 (2w) Wang, *ACS Catal.* **2022**, *12*, 2426.  
 (2x) Zhang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202114146.  
 (2y) Li, *Chem. Eur. J.* **2021**, *27*, 2699.

**Figure 2** Transition-metal-catalyzed acyl Suzuki–Miyaura coupling of amides<sup>2</sup>



**Figure 3** Synthesis of ketones via transition-metal catalysis and metal-free conditions<sup>3</sup>



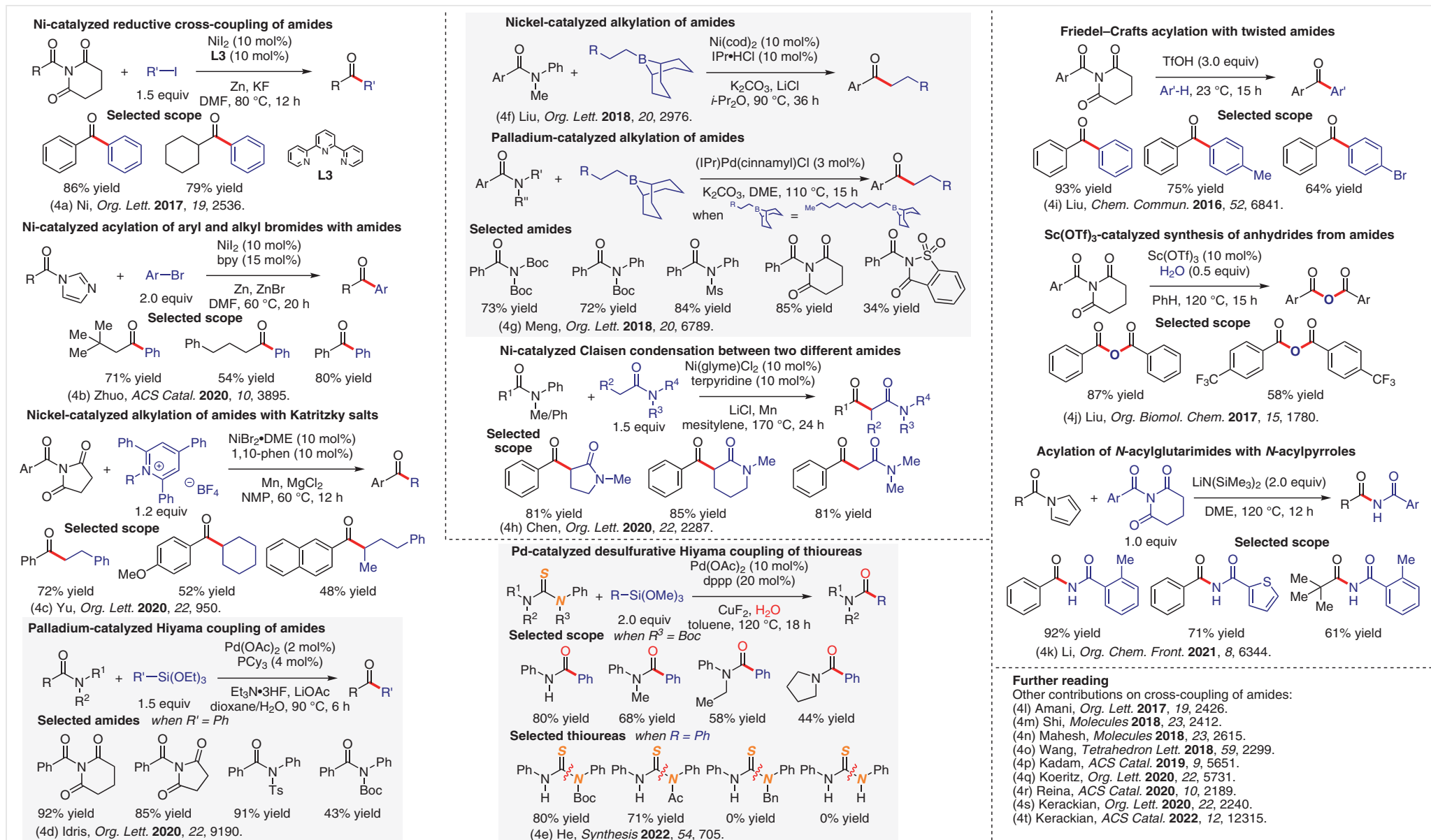
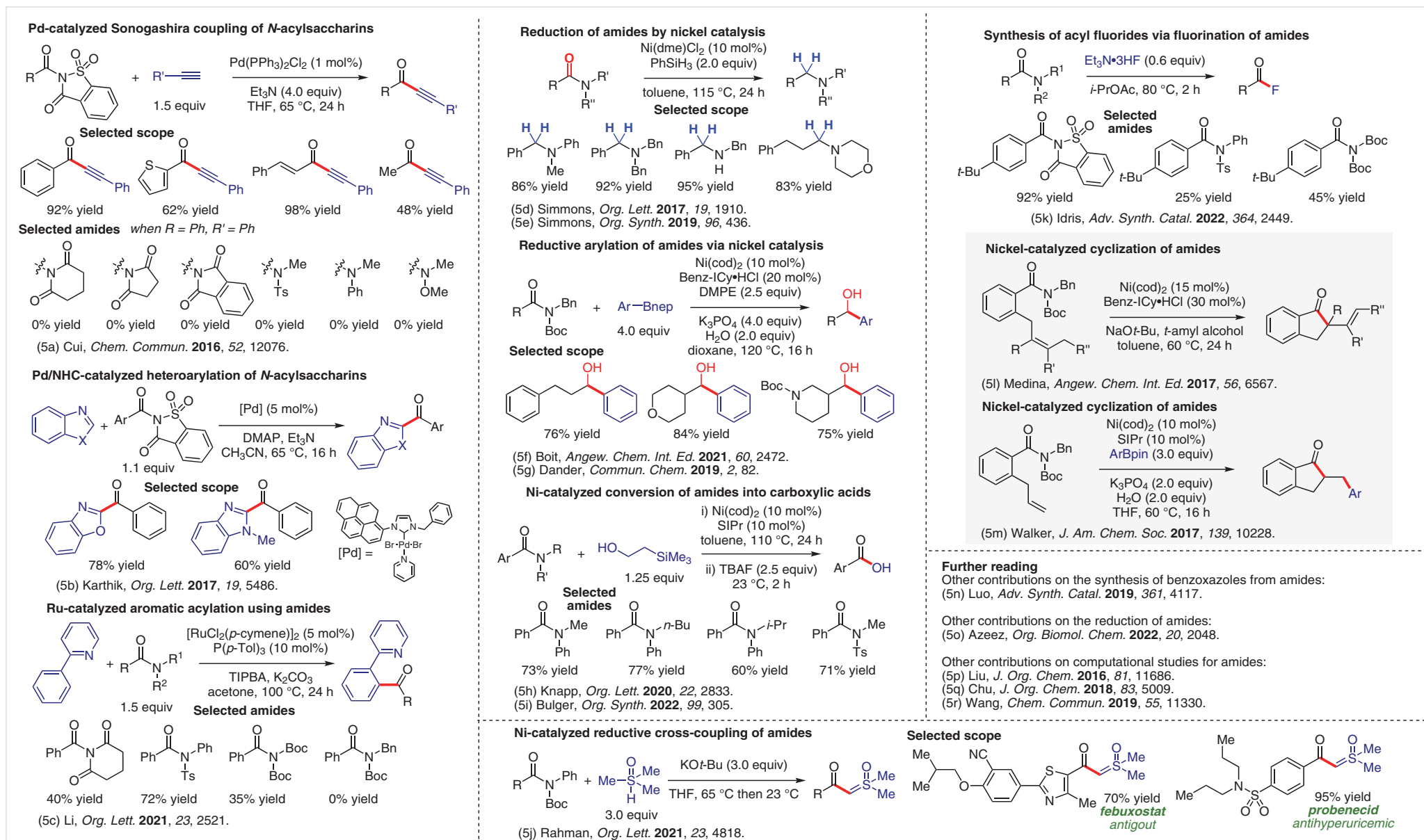
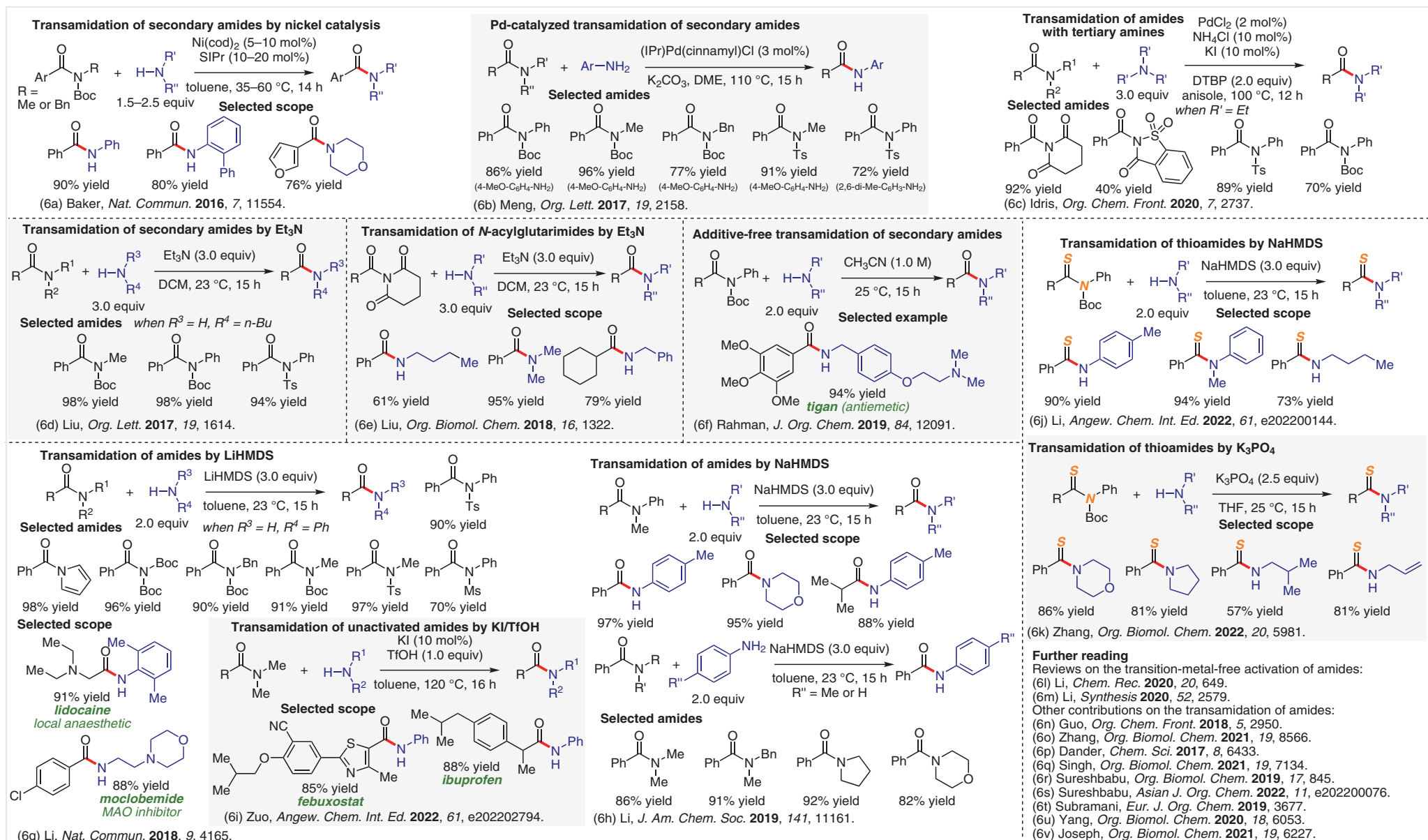


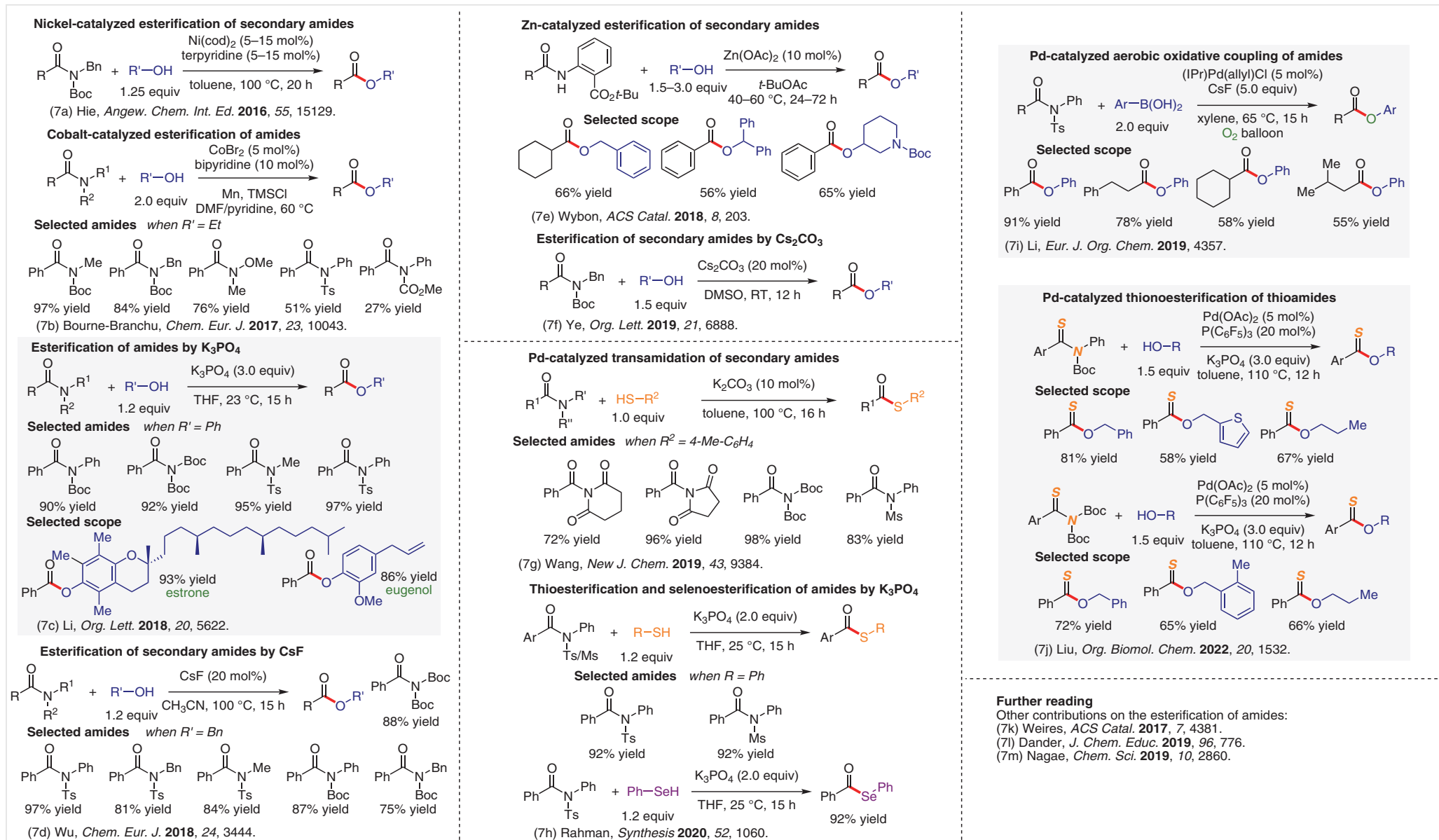
Figure 4 Amides as acylating reagents in various synthetic methodologies<sup>4</sup>

Figure 5 Cross-coupling of amides with versatile partners<sup>5</sup>



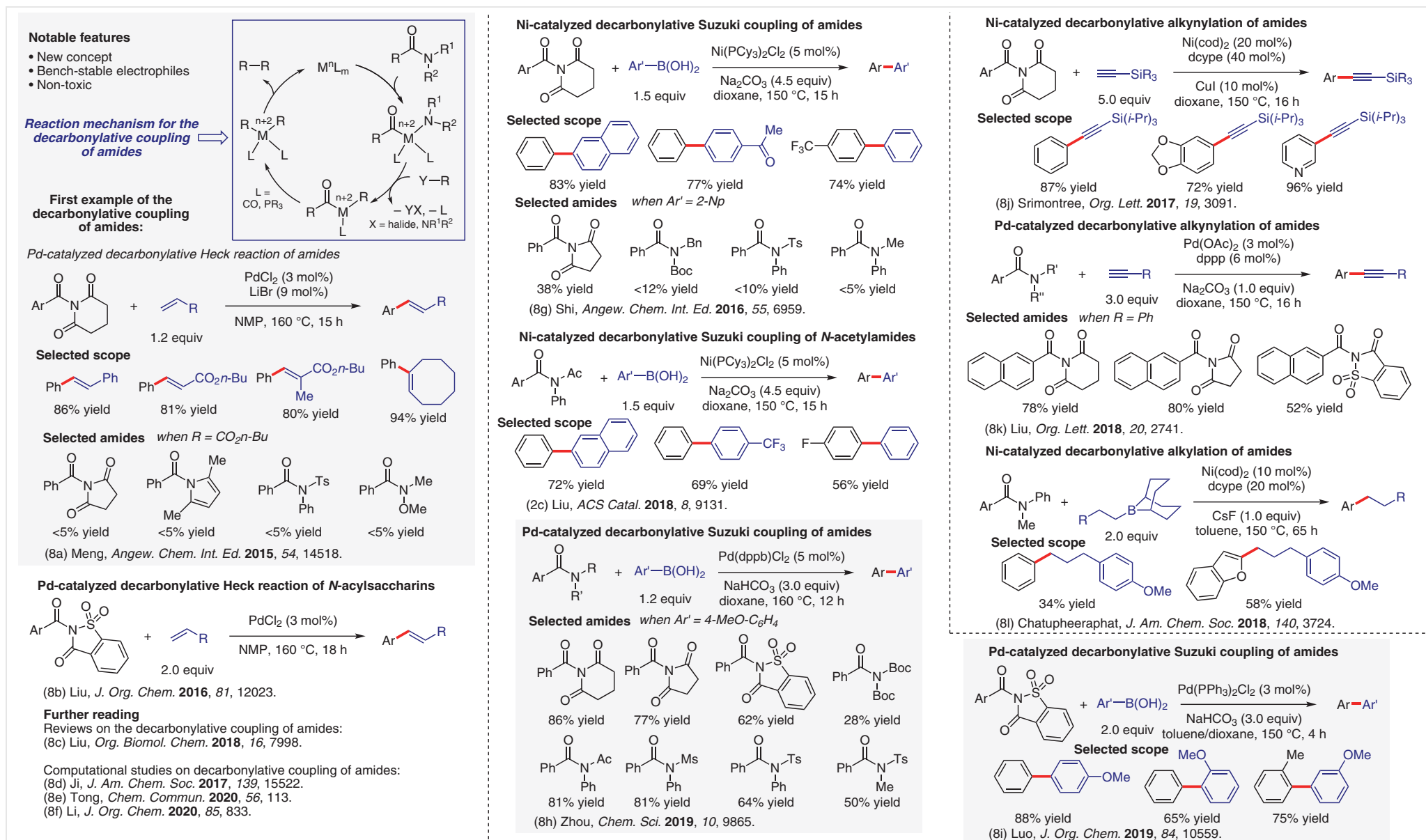
**Figure 6** Transamidation of amides under metal catalysis and metal-free conditions<sup>6</sup>

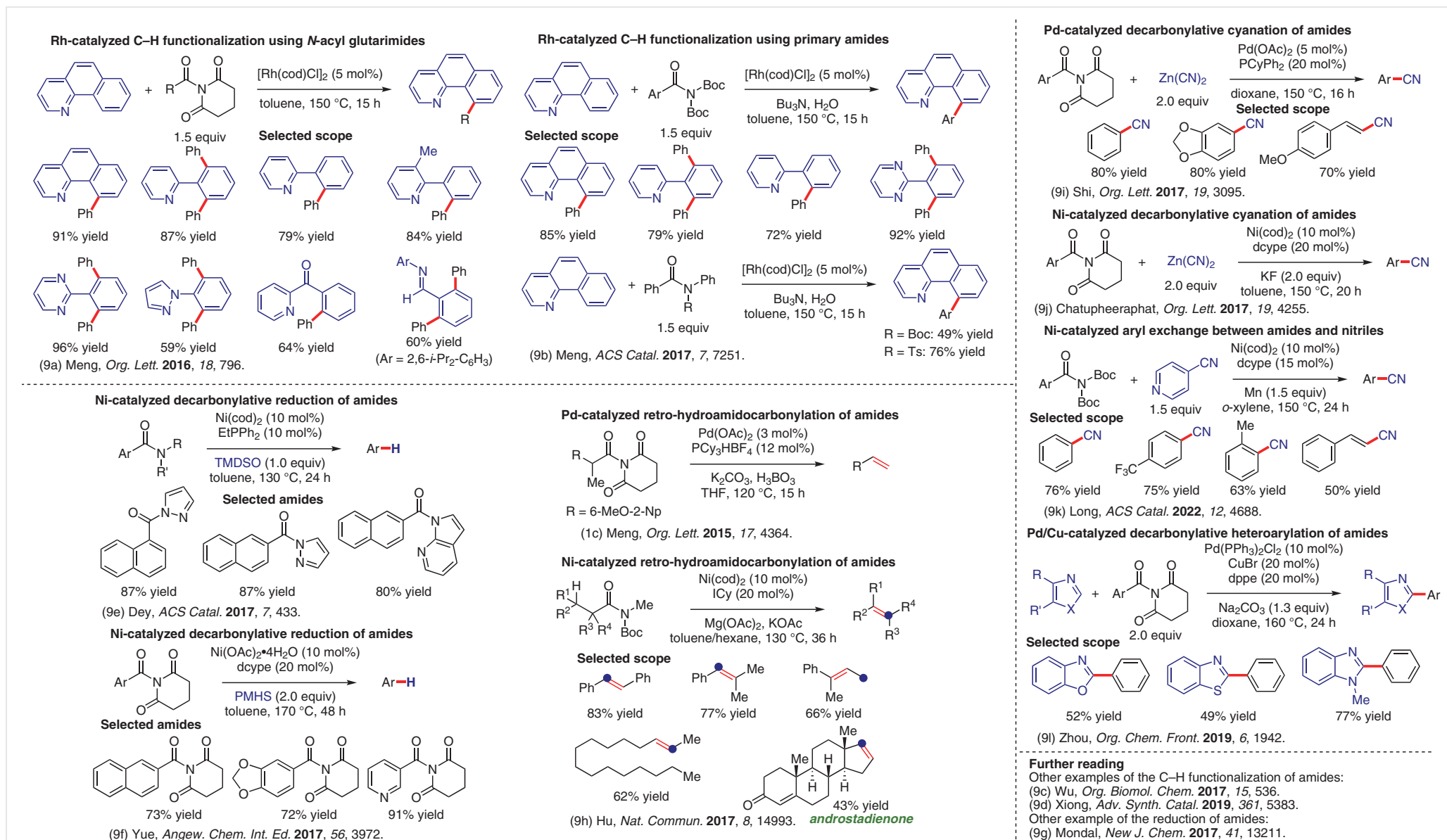


**Further reading**

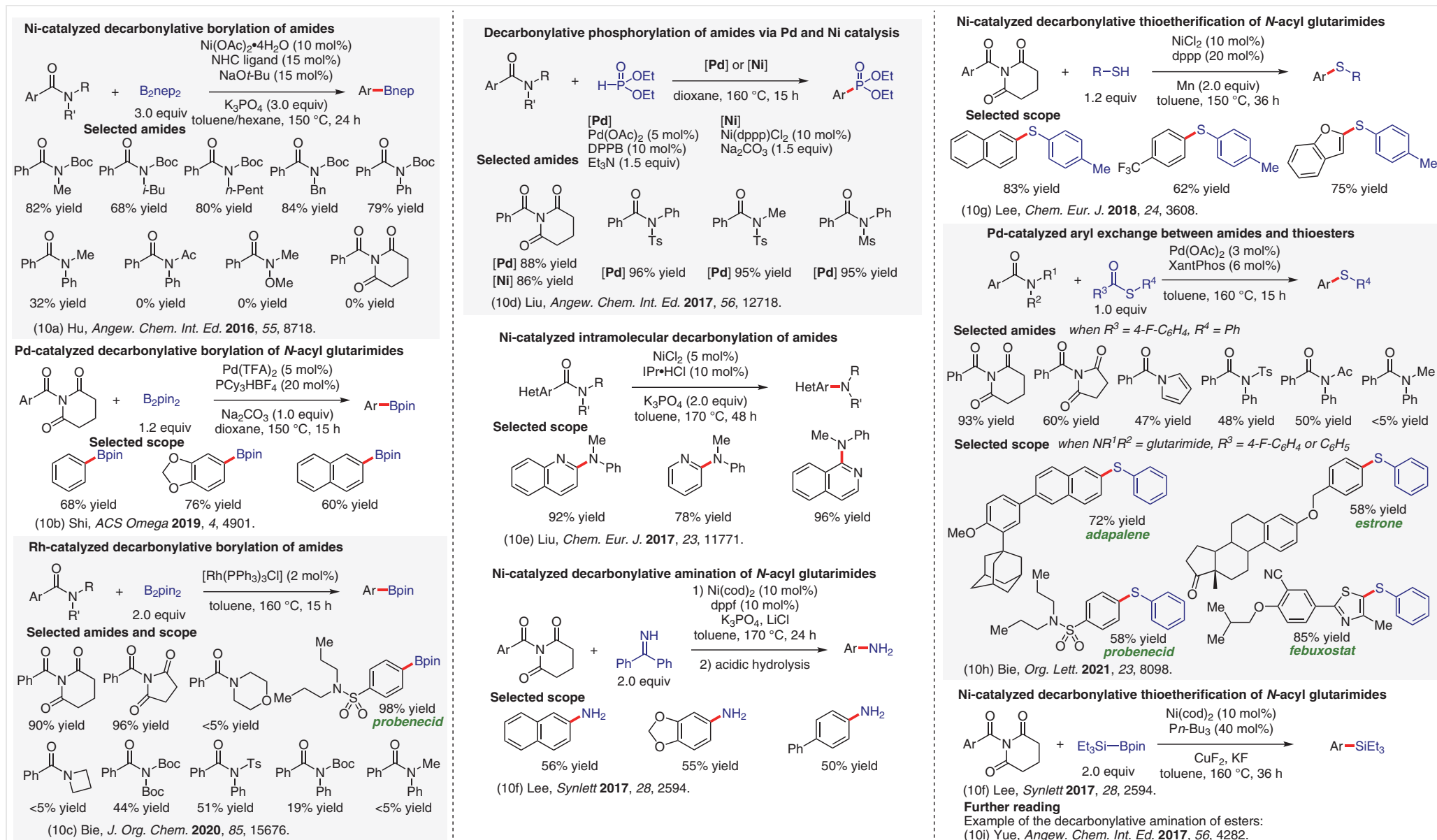
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**Figure 7** Esterification of amides via metal catalysis and metal-free conditions<sup>7</sup>

Figure 8 Decarbonylative cross-coupling of amides: discoveries and mechanism<sup>8</sup>



**Figure 9** Decarbonylative cross-coupling of amides: construction of carbon–carbon and carbon–hydrogen bonds<sup>9</sup>



**Figure 10** Decarbonylative cross-coupling of amides: construction of carbon–heteroatom bonds<sup>10,11</sup>



## Conflict of Interest

The authors declare no conflict of interest.

## Funding Information

We thank the National Science Foundation (NSF) (CAREER CHE-1650766), the National Institutes of Health (NIH) (R35GM133326), Rutgers University, the Overseas High-Level Talents Fund of Shanghai, and Shanghai University for generous support.

## Acknowledgment

We thank the current and former members of the Szostak group who have contributed to establishing the concept of amide bond activation.

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