

# Ketones from Nickel-Catalyzed Decarboxylative, Non-Symmetric Cross-Electrophile Coupling of Carboxylic Acid Esters

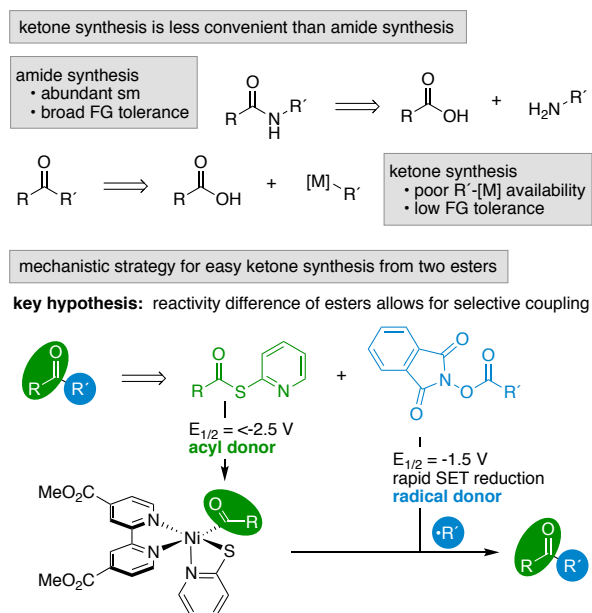
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ABSTRACT. While the coupling of carboxylic acid derivatives to form new C-N and C-O bonds is a staple of organic synthesis and has been automated, the synthesis of the C-C bonds of ketones generally requires the use of reactive organometallic reagents incompatible with many functional groups. We demonstrate here a new approach to ketone synthesis that couples two different carboxylic acid esters, *N*-hydroxyphthalimide esters (NHP esters) and *S*-2-pyridyl thioesters (SPy esters), to form aryl-alkyl and dialkyl ketones in high yields. The keys to the approach are the use of a nickel catalyst with an electron-poor bipyridine or terpyridine ligand, a THF/DMA mixed solvent system, and ZnCl<sub>2</sub> to enhance the reactivity of the NHP ester. The resulting reaction can be used to form ketones that have previously been difficult to access, such as hindered tertiary-tertiary ketones with strained rings and ketones with heterocycles. The conditions can be employed in the coupling of complex fragments, including a 20-mer peptide, an analogue of Exendin(9-39), on solid support.

While ketones are among the most versatile of functional groups in organic synthesis<sup>1</sup> and commonly found in drugs and natural products; their synthesis still requires starting materials of low abundance, such as reactive organometallic reagents or organic iodides (Scheme 1).<sup>2</sup> This is in contrast to the robust chemistry that has been developed for the formation of amides, which tolerates a wide variety of functional groups and utilizes abundant substrate pools – carboxylic acids and amines. We, and others, have developed more functional-group compatible methods for the synthesis of ketones, but these reactions still suffer from the use of substrates that are too reactive (organometallic reagents) and have low commercial availability (organic iodides).<sup>3,4</sup> A more attractive approach would be a decarboxylative coupling of two different carboxylic acids, as these are among the most abundant of alkyl substrates.<sup>5</sup>

### Scheme 1. Strategies in Ketone Synthesis.



We hypothesized that this challenge could be addressed by the union of two recent developments in cross-electrophile coupling: the finding that *N*-hydroxyphthalimide esters

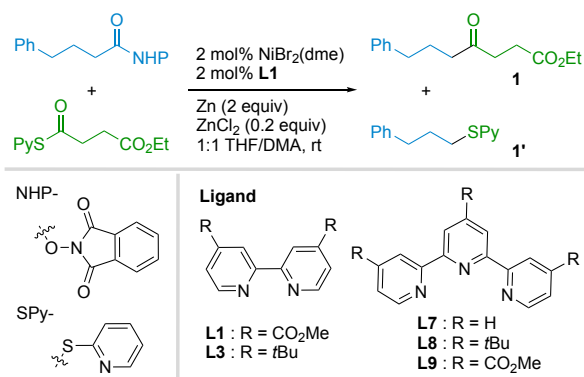
(NHP esters) react under nickel catalysis to form alkyl radicals after decarboxylation<sup>6</sup> and the finding that acylnickel(II) intermediates can capture radicals to form ketones in high yield.<sup>4e,7</sup> Ketones could then be synthesized by the union of two activated esters – one tuned to form a metal acyl and one tuned to form a radical (Scheme 1).<sup>8</sup>

At the outset, we foresaw several challenges related to the identity of the acyl donor. The ideal acyl donor should react to form an acylnickel(II) rapidly, but should not be so reactive as to limit functional-group compatibility, react with in-situ-generated zinc phthalimide,<sup>9</sup> be prone to scrambling with the *N*-hydroxyphthalimide, or prevent isolation and purification. For example, our previous coupling of an acid chloride with an NHP ester formed the ketone product, but the high reactivity of the acid chloride limited utility and a large excess was required for high yields.<sup>6,9</sup> Reactions that require a large excess of one component can be valuable, but limit application to complex or valuable fragments. Further, the use of unstable intermediates limits options in synthesis because no purification is possible. Ideally, a reaction would be amenable to coupling two activated esters that were isolable, even if this was not always required. We quickly found that *S*-2-pyridyl thioesters<sup>10</sup> (SPy esters) fit all of these criteria: they are easily synthesized directly from carboxylic acids and are stable to chromatography on silica gel, yet react more rapidly with nickel than even alkyl iodides, presumably due to chelation effects.<sup>3,10</sup> We show here that the resulting reaction is a new, remarkably general ketone synthesis.

Reaction optimization naturally started with the conditions we had previously reported for the coupling of activated esters with alkyl halides and NHP esters.<sup>3b,6</sup> In contrast to these earlier studies, more electron-poor bipyridine and terpyridine ligands provided better results than electron-rich ligands (Table 1, entries 1-5). Reactions conducted with electron-rich ligands resulted in incomplete conversion of NHP ester and increased amounts of thioether product **1'**

(entries 4 and 5). A mixture of THF and DMA (1:1 ratio) provided better results than either solvent alone by tuning the reactivity of the NHP ester<sup>11</sup> (Table 1, entries 6-7) and reactions that contained a catalytic amount of ZnCl<sub>2</sub> improved the rate of conversion of NHP ester (Table 1, entry 8). While nickel is required for ketone formation, the reaction with zinc in the absence of nickel (entry 9) converted the NHP ester into decarboxylated alkane. This suggests that Zn might play a role in ketone-forming reactions by assisting in alkyl radical generation (entry 9).<sup>12</sup>

**Table 1.** Optimized Reaction Conditions.



entry	change in conditions from scheme	1 (%) <sup>b</sup>	1' (%) <sup>b</sup>
1	none	78 (78)	0
2	L7 instead of L1	65	7
3	L9 instead of L1	64	0
4	L8 instead of L1	19	28
5	L3 instead of L1	38 <sup>c</sup>	1
6	THF instead of 1:1 THF/DMA	29 <sup>c</sup>	0
7	DMA instead of 1:1 THF/DMA	38	5
8	No added ZnCl <sub>2</sub>	53	0
9	No nickel	0 <sup>d</sup>	0
10	No ligand	19	3
11	No Zn reductant	0 <sup>e</sup>	0

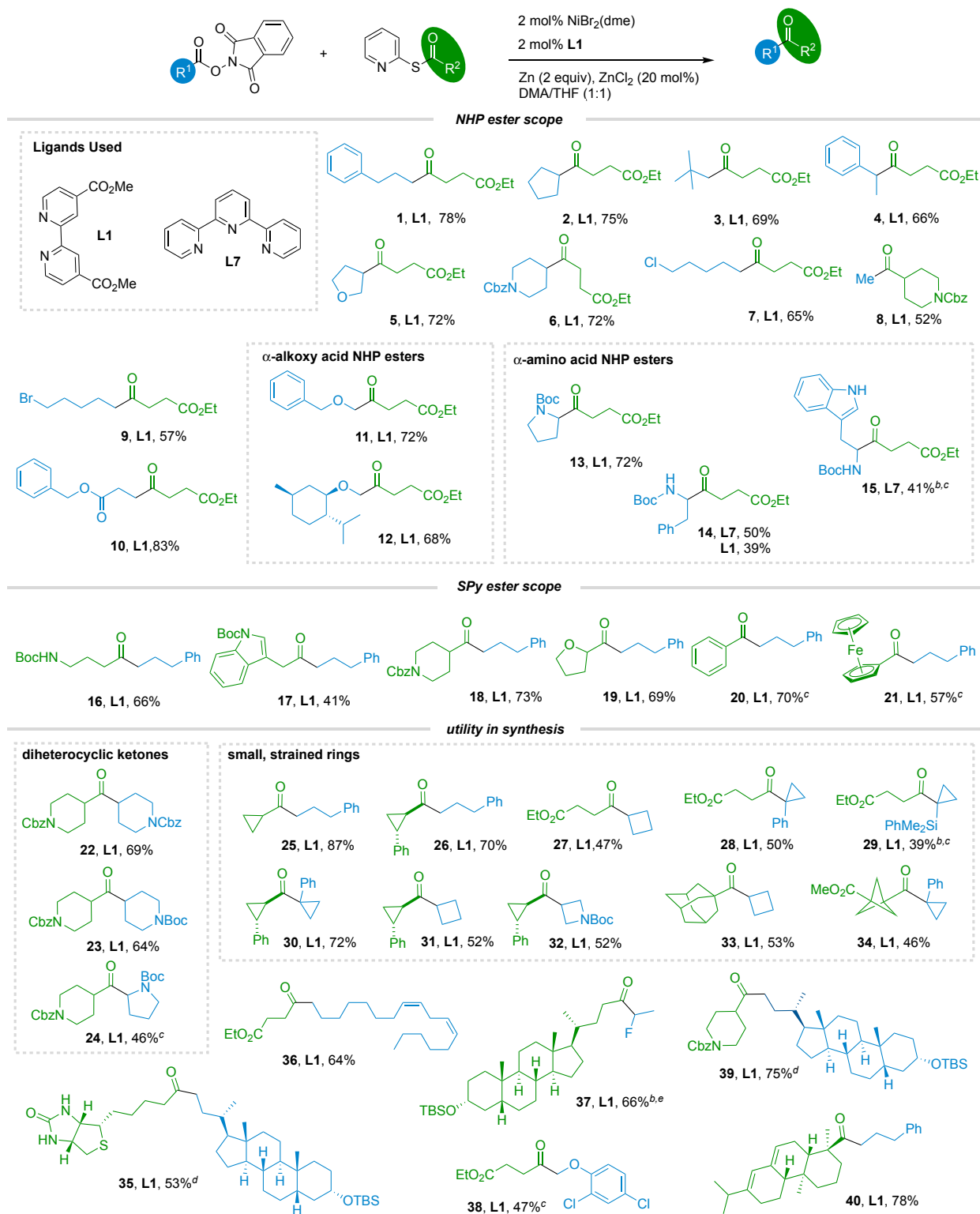
<sup>a</sup> A mixture of NHP ester (0.25 mmol), thioester (0.25 mmol), NiBr<sub>2</sub>(dme) (2 mol%), ligand (2 mol%), Zn (0.5 mmol) and ZnCl<sub>2</sub> (0.05 mmol) was stirred in THF/DMA (1:1, 0.5 mL) at rt for 24 h. For additional data on reactions with **L2** and **L4-L6**, see the Supporting Information. <sup>b</sup> corrected GC yield using *n*-dodecane as internal standard. Isolated yield after chromatography in parentheses. <sup>c</sup> Significant NHP ester remained. <sup>d</sup> NHP ester consumed to *n*-propylbenzene quantitatively. <sup>e</sup> Both starting materials recovered.

Applying these optimized conditions to a variety of different carboxylic acid pairs demonstrated that the chemistry was robust for the synthesis of dialkyl ketones and aryl-alkyl ketones (Scheme 2). Functional group compatibility included acidic N-H bonds (**14**, **15**, **16**, **35**) protected nitrogens (**6**, **13**, **23**, **32**) and protected alcohols (**37**, **39**). Notably, an alkyl bromide (**9**) was tolerated, even though similar conditions are commonly employed in nickel-catalyzed couplings of alkyl bromides. Generally, primary and secondary carboxylic acids could be coupled as either the acyl donor (thioester) or the radical donor (NHP ester), allowing for the easy synthesis of otherwise rare ketones, such as diheterocyclic ketones (**22-24**) and ketones with two strained rings (**30-34**).<sup>13</sup> The coupling could be used to join two larger fragments, such as biotin or isonipecotic acid with a steroid core (**35**, **39**). Because carboxylic acids are often found in natural products and in intermediates towards medicinal compounds, complex ketones can be made in a single step starting from these unusual starting materials, such as broadleaf herbicide 2,4-D (**38**) or the natural product abietic acid (**40**, a component of rosin). While not a focus of this report, this method could also be used to make an  $\alpha$ -fluoroketone (**37**, from 2-fluoropropanoic acid) and aryl-alkyl ketones from aryl thioesters (**20**, **21**).<sup>14</sup>

In some cases, the use of a different ligand on nickel could improve low-yielding reactions. For example, an L-proline derived NHP ester coupled well with ligand **L1** (**13**), but this ligand was ineffective for reaction with Boc-L-phenylalanine (39% yield) due to significant  $\beta$ -hydride elimination. Improved results (**14**, 50 %) could be obtained by switching from ligand **L1** to tridentate ligand **L7**.

While these conditions are general, two notable limitations should be noted. First, while most thioester substrates tested coupled in reasonable yield, reactions with thioesters derived from  $\alpha$ -amino acids and 2-picolinic acid were low yielding. Second, most *N*-hydroxyphthalimide esters coupled in high yield, but reactions with esters derived from secondary cyclopropyl carboxylic acids, difluoroacetic acid, and unstrained tertiary carboxylic acids (such as pivalic acid) were low yielding. The secondary cyclopropane limitation could be worked around by using an  $\alpha$ -silyl group (**29**), which is easily introduced and removed.<sup>15</sup>

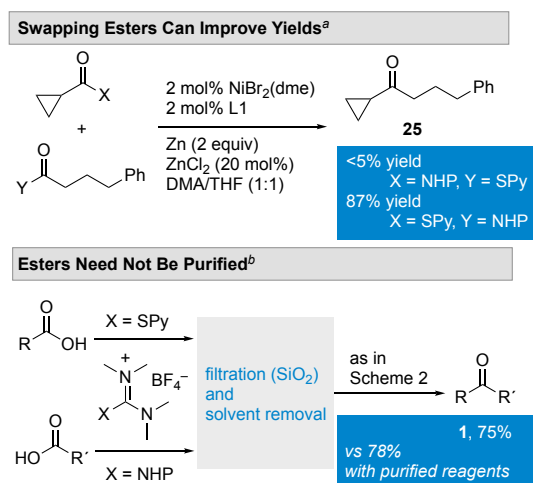
**Scheme 2.** Substrate Scope for the Decarboxylative Coupling of NHP Esters with Thioesters.



<sup>a</sup> Reactions were conducted on 0.5 mmol scale in 1 mL of solvent for 24 h. Yields are isolated yields after purification unless otherwise noted. <sup>b</sup> 1.5 equiv of NHP ester used. <sup>c</sup> 10 mol% NiBr<sub>2</sub>(dme) and ligand were used. <sup>d</sup> Lower concentration (0.5 mmol in 2 mL). <sup>e</sup> Reaction run on 0.2 mmol scale at standard concentration. Boc = *tert*-butoxycarbonyl, Cbz = carboxybenzyl, TBS = *tert*-butyldimethylsilyl

In cases where a coupling provided a low yield, it was usually possible to obtain a higher yield by swapping the identity of the NHP ester and the thioester (Scheme 3). For example, simple cyclopropane and adamantane carboxylic acids did not couple well as an NHP ester, but this could be worked around by coupling them as the corresponding thioesters (**25**, **33**). Similarly, thioesters of  $\alpha$ -amino acids did not couple well, but NHP esters of these  $\alpha$ -amino acids were effective (**13** – **15**).

**Scheme 3.** Flexibility in substrate activation has strategic advantages.



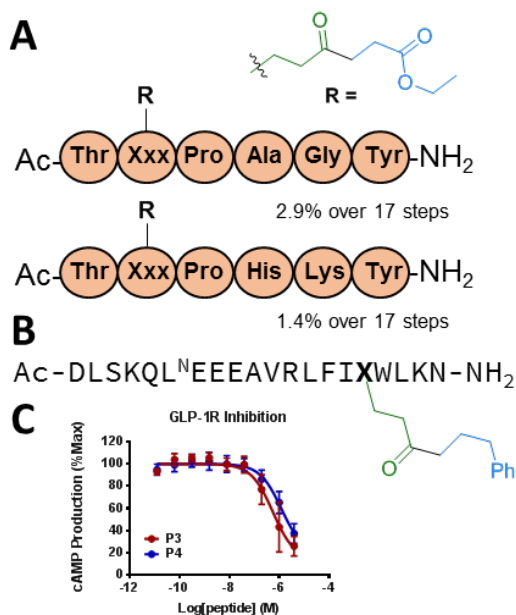
<sup>a</sup> As in Scheme 2. <sup>b</sup> R' = 4-phenylbutyric acid (0.5 mmol, 1 equiv) and R = ethyl succinate (0.75 mmol, 1.5 equiv). Yield is corrected GC yield. See Supporting Information for full details.

While this work was being completed, Baran reported a different approach to the coupling of two different carboxylic acids that utilized in-situ generated mixed anhydrides as the acyl donor.<sup>8</sup> The methods are complementary in many ways: while the Baran method avoids pre-formation of one of the activated esters, our approach allows for greater selectivity (1:1 substrate ratio instead of 2:1 ratio); our electron-poor ligands appear to allow for lower catalyst loading (2



mol% instead of 20 mol%); and, the use of thioesters appears to provide better scope with hindered carboxylic acids (**34**, **40**). In addition, the Baran work contains valuable mechanistic experiments that are consistent with previous studies on related systems.<sup>7</sup>

The simplicity of both sets of conditions and the broad functional-group tolerance suggested to us that this chemistry could be applied to a more challenging class of substrates – peptides on solid support.<sup>16</sup> Ketones in polypeptides are useful in peptidomimetic backbones as ketomethylene isosteres,<sup>17</sup> and ketones in side chains can undergo chemoselective functionalization via reductive amination or oxime/hydrazone ligation.<sup>1,18</sup> While the solid support and the solid reductant might be expected to cause a problem, the soluble nickel catalyst<sup>7</sup> can shuttle between the two solid phases, avoiding the “three-phase problem.”<sup>19</sup> We are not aware of a prior example of any cross-electrophile coupling on a solid supported substrate, but we found that the chemistry worked as expected (Figure 1). Informed by previous reports on the coupling of NHP esters with radical acceptors (eg acrylates) or organozinc reagents,<sup>20</sup> we explored this cross-electrophile ketone synthesis using a similar approach to site-selective coupling: an L-glutamic acid ( $\gamma$ -allyl ester) residue was incorporated, orthogonally deprotected,<sup>21</sup> and converted to the SPy ester with an “all-in-one” *S*-2-pyridyl thiol uronium reagent.<sup>10</sup> In contrast to previous reports focused on small, non-polar peptides, this chemistry could be applied to larger peptides with various polar residues: a 20-mer that contains several Glu residues. Our target sequence, **P3**, is a fragment analogue of well-studied peptide Exendin(9-39), which is an antagonist of the glucagon-like peptide-1 receptor (GLP-1R).<sup>22</sup> Exendin(9-39) itself is currently in clinical trials to treat postbariatric hypoglycemia. Tandem mass-spectrometry established ketone incorporation at the desired site in **P4**. Both **P3** and **P4** displayed dose-dependent inhibition of GLP-1 activity at GLP-1R.



**Figure 1.** (A) Hexapeptide substrates with ketones synthesized on solid support from SPy esters using 20 equiv NHP-ester, 50 equiv Zn, 20 equiv ZnCl<sub>2</sub>, 2 equiv NiBr<sub>2</sub>dme, 2 equiv **L1**, in DMA at 20 °C for 16-24 h. Xxx indicates the L- $\alpha$ -Glutamic acid residue that has been subjected to cross-coupling following SPy ester formation. (B) Cross-electrophile coupling on an Exendin (9-39) analog. L<sup>N</sup> indicates L-norleucine. X indicates an L- $\alpha$ -Glutamic acid residue that has been subjected to cross-coupling. (C) **P3** (peptide shown in **B** except where X is glutamic acid) and **P4** (peptide shown in **B**) show dose-dependent antagonism of GLP-1 (4.5 nM, EC<sub>50</sub> ~ 0.05 nM) mediated 3',5'-cyclic adenosine monophosphate (cAMP) production in HEK293 cells expressing GLP-1R with IC<sub>50</sub> values of 560 nM and 1300 nM, respectively. N = 4, mean  $\pm$  standard deviation.

The new approach presented here and in Baran's recent work<sup>8</sup> shows that the goal of ketone synthesis with the ease of amide-bond synthesis is now within reach. The ability of a single nickel catalyst to differentiate between the two activated esters – thioester by oxidative addition,

NHP ester by single electron transfer – is crucial to this unusual, non-symmetric coupling of two carboxylic acid esters. These first-generation conditions are already competitive with the best available methods and are particularly well-suited to challenging ketones, such as those with severe steric hinderance and those that incorporate heterocycles. The versatility of the method could even be extended to the coupling of larger, functionalized fragments, including peptides on solid support. Further improvements are underway, including one-pot methods, alternative substrate pairs, and expanding the types of ketones that can be synthesized.

## ASSOCIATED CONTENT

**Supporting Information.** Detailed experimental procedures, supplementary optimization data, characterization data for all isolated products, and copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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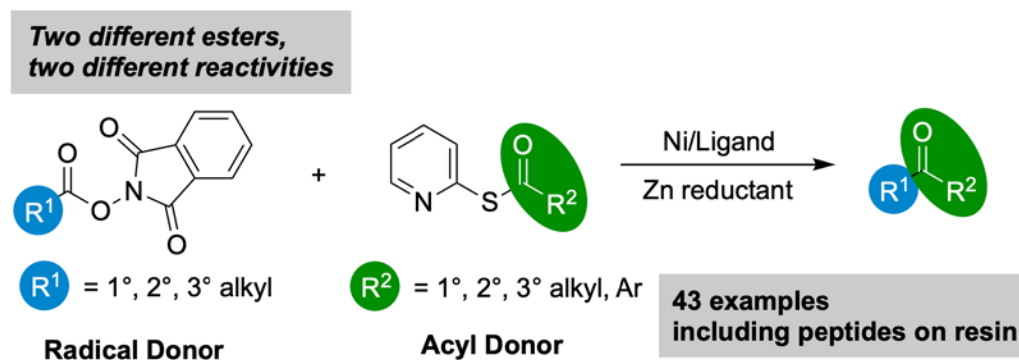
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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### TOC Graphic



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