

Nickel Catalysis

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Nickel-Catalyzed Barton Decarboxylation and Giese Reactions: A Practical Take on Classic Transforms

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Abstract: Two named reactions of fundamental importance and paramount utility in organic synthesis have been reinvestigated, the Barton decarboxylation and Giese radical conjugate addition. *N*-hydroxyphthalimide (NHPI) based redox-active esters were found to be convenient starting materials for simple, thermal, Ni-catalyzed radical formation and subsequent trapping with either a hydrogen atom source (PhSiH_3) or an electron-deficient olefin. These reactions feature operational simplicity, inexpensive reagents, and enhanced scope as evidenced by examples in the realm of peptide chemistry.

Sir Derek Barton's interactions with Schering-Plough in the 1970s radically expanded the paradigm of organic chemistry.^[1] The acclaimed Barton–McCombie deoxygenation was born out of this experience, enlisting radical reactivity to selectively remove secondary hydroxy groups in aminoglycosides for improved antibacterial activity.^[2] Subsequent efforts to utilize carboxylate groups in similar radical reactions had an equally profound impact, culminating in the invention of Barton esters (**1**, Figure 1 A) in 1983.^[3] These thiohydroxamic anhydrides can be conveniently obtained when ubiquitous carboxylic acids are coupled with pyrrithione (readily accessible from industrial feedstock). They undergo visible light-induced fragmentation to liberate carbon dioxide while furnishing alkyl radicals that can be converted into a myriad of functional groups.^[4] Reductive decarboxylation with tin hydride or an alkyl thiol (**1** to **2**) and Giese reaction with Michael acceptors (**1** to **3**) are two notable examples. The thiocarbonyl group, in Barton's own words, acts as a “disciplinary group”, conferring the process chemoselectivity and functional group compatibility, leading to numerous applications over four decades. Although photoinduced electron transfer processes with carboxylic acid derivatives have been surveyed as an alternative to Barton esters beginning with Okada's work in 1988,^[5] these methods require specialized

equipment, expensive catalysts, and prolonged reaction times. Notwithstanding the need for a photochemical setup (for both decarboxylation and conjugate addition) and the use of toxic and odorous reductants (for decarboxylation), chemists remain beholden to the venerable Barton reaction, as evidenced by its use in many recent total syntheses.^[6,7] The low stability of Barton esters stemming from their photo- and thermal sensitivity adds another layer of difficulty. Although alternative reductants such as tris(trimethylsilyl)silane^[8] or chloroform have been introduced for the decarboxylation reaction,^[9,10] the other problems have remained largely

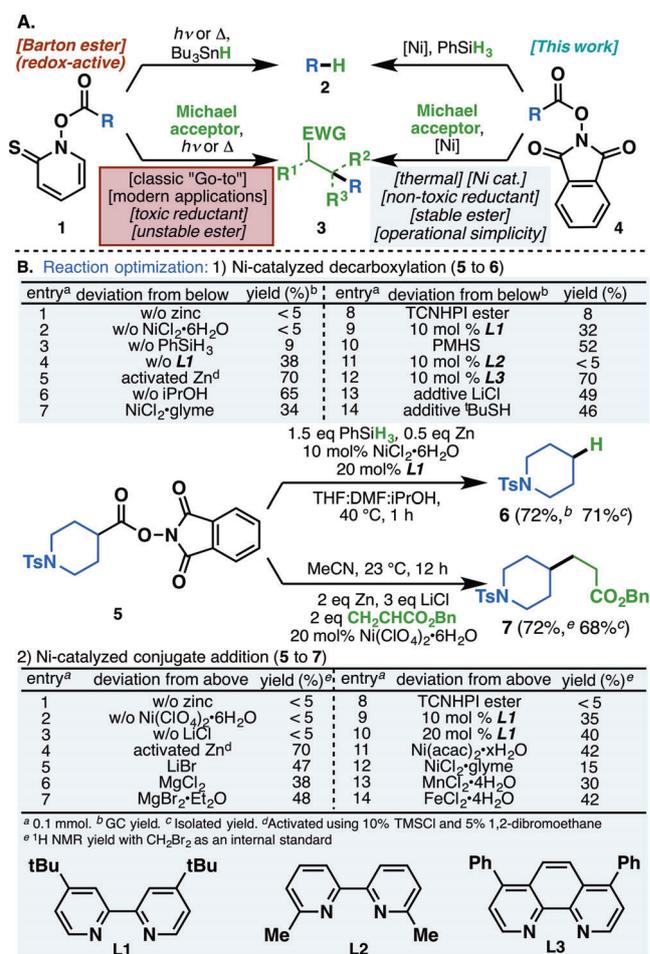


Figure 1. A) Use of redox active esters in reductive decarboxylation and Giese reactions. B) Optimization of Ni-catalyzed decarboxylation and conjugate additions. NHPI = *N*-hydroxyphthalimide, TCNHPI = tetrachloro-*N*-hydroxyphthalimide.

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unmitigated. Thus, thermally driven and operationally simple means of Barton decarboxylation and decarboxylative Giese reactions remain highly desirable.

Efforts in our laboratory beginning in 2015 led to the realization that Barton esters (**1**) are redox-active species that readily accept electrons from metal complexes through a purely thermal single electron transfer (SET) process.^[11–14] This property is shared by various activated carboxylates commonly employed in amide coupling. Collectively termed redox-active esters (RAEs), these compounds (exemplified by NHPI ester **4**) undergo facile SET reduction with inexpensive nickel^[11–13] or iron catalysts.^[14] The ensuing radical anion fragments to afford alkyl radicals under thermal conditions. Combination of the alkyl radical with a metal center by virtue of the persistent radical effect (PRE) enables cross-coupling of various modalities. Herein, reductive decarboxylation (**4** to **2**) and Giese reaction (**4** to **3**) of NHPI RAEs are disclosed, exhibiting broad substrate scope, chemoselectivity, and scalability while obviating the need for toxic reductants and photochemical irradiation. The bench stability of **4** offers another advantage although as shown below its discreet isolation is not necessary.

Though conceptually straightforward, both transformations were only realized after considerable experimentation. Figure 1B provides the optimal reaction parameters along with a simplified picture of the optimization process on piperidine derivative **5**.

Zinc (0.5 equiv) (entry 1, Figure 1B1) was necessary to reduce the Ni^{II} species in the decarboxylation reaction, while PhSiH₃ was found to be the most effective source of hydrogen (entries 3, 10, and 14). The ternary mixture comprising THF, DMF, and iPrOH delivers the highest yield whereby iPrOH is believed to provide activation of the silane.^[15] A 1:2 mixture of NiCl₂·6H₂O and **L1** provided the best catalyst system. Addition of tBuSH or LiCl as additives had deleterious effects on the yield (entries 13 and 14).

Meanwhile, LiCl was identified as an essential additive in the conjugate addition (Figure 1B2, entry 3). In the absence of a terminal silane reductant, zinc was required in stoichiometric quantities. Ni(ClO₄)₂·6H₂O (\$120 mol⁻¹) performed the best for this reaction; addition of Lewis acids, bipyridine ligands, or the use of other metal salts all led to diminished yields. In both transformations, the choice of RAE was critical; while NHPI esters reacted efficiently, use of TCNHPI esters led to lower yields. Zinc (ca. \$5 mol⁻¹) could be used straight out of the bottle, as the use of activated zinc had minimal impact in either reaction. Overall, decarboxylation was complete within 1 h at 40 °C, while the conjugate addition proceeded smoothly at ambient temperature.

RAEs derived from primary (**10**, **13**, **15**, and **17**), secondary (**6**, **12**, and **14**), and tertiary (**8**, **9**, **11**, **16**, **18**, and **19a**) carboxylic acids are all competent substrates in the decarboxylation reaction (Scheme 1). Though **10** and **12** are also accessible from the corresponding Barton esters, the classical conditions enlist stoichiometric amounts of pungent tBuSH.^[16] Conversely, **8** can be made in comparable yield using Tsanaktisidis and Williams's modified protocol with chloroform as the hydrogen donor; the need for photoirradiation, however, still presents an inconvenience (espe-

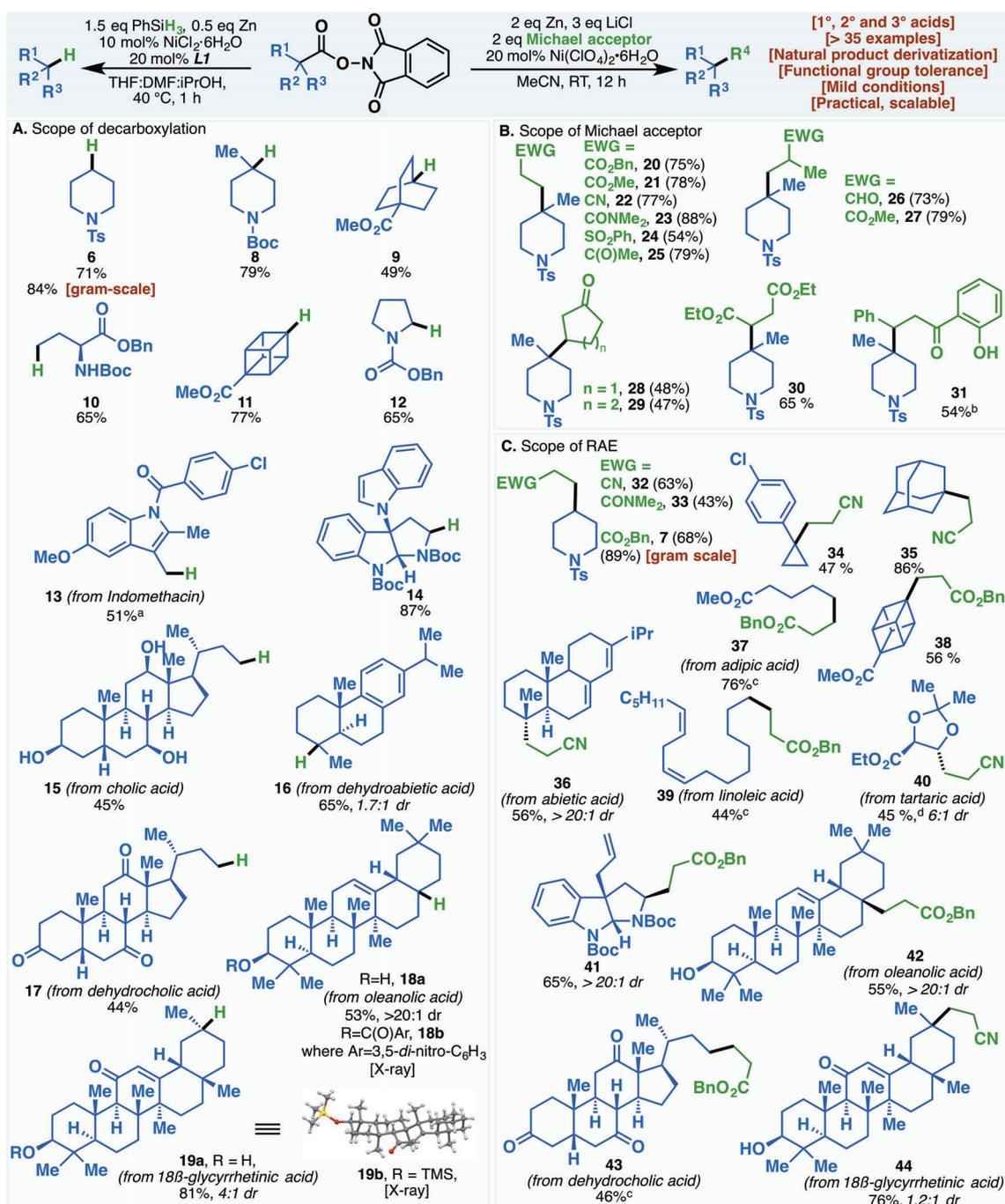
cially on large scale).^[9] Densely functionalized natural products were decarboxylated in high yields:^[17] indole (**13**), hydroxy (**15**, **18a**, and **19a**), ketones (**17** and **19a**), and olefins (**18a** and **19a**) were left unscathed. The alternative route to **15** involves dissolving metal reduction of the corresponding nitrile.^[18] Although **19a** can be furnished in good yields through PET-mediated decarboxylation, long reaction times (24 h), an expensive solvent (TFE), and Fukuzumi's photosensitizer (more expensive than the starting carboxylic acid) are required.^[5d] Barton decarboxylation has been applied numerous times to access pyrroloindoline alkaloids from tryptophan derivatives.^[19] Substrate **14**, though not natural product-derived *per se*, showcases the viability of this methodology to synthesize these alkaloids in a highly practical fashion.

Similarly, the conjugate addition exhibited broad scope with respect to both reaction partners. Michael acceptors bearing assorted electron-withdrawing groups (EWGs) such as esters, ketones, sulfones, and nitriles were all shown to react in good yields. These functional groups open up many opportunities for product diversification. It is also of note that the addition is unencumbered by α or β substitutions on the Michael acceptor (**26–27**, **28–29**). Whereas similar conjugate additions with Barton esters oftentimes require large excesses of Michael acceptors, two equivalents of these activated olefins was deemed sufficient in the nickel catalyzed reaction.^[20]

As with the decarboxylation, RAEs of primary, secondary and tertiary acids, bearing multiple functional groups, can be used in this Giese-type reaction (**32–44**).^[21] Good levels of stereocontrol were observed on several substrates (**36**, **40–42**). Many substrates represent derivatives of natural products which are difficult to access through alternative routes. For example, a previous synthesis of the acid corresponding to **42** requires a laborious six-step sequence from the same starting material.^[22] Moreover, attempts to make **35** and structural analogs of **40** through the decarboxylative conjugate addition of Barton esters were reportedly complicated by the competing coupling of the 2-thiopyridone byproduct with the intermediate β radical, requiring a separate step of thiopyridyl removal.^[20] To this end, the use of an NHPI redox-active ester circumvents this lingering problem in classical Barton chemistry.

Across the many substrates examined, both reactions were found to be impervious to moisture and required minimal precautions. This robustness, in combination with the inexpensive reagents employed bode well for large-scale reactions. Indeed, gram-scale decarboxylation and Giese addition using **5** delivered **6** and **7** in high yields.

While RAEs employed in these transformations are readily diversifiable building blocks which can be conveniently purified and stored without special precautions, further experimentations revealed that isolation of the RAEs was not necessary: decarboxylation and conjugate addition can be performed on RAEs generated in situ. For example, a simple activation of acid **45**, followed by the decarboxylation or conjugate addition protocols, furnished **6** and **7** in comparable yields (Scheme 2A). Owing to the ubiquity and availability of carboxylic acids, such one-pot procedures may have a tangible

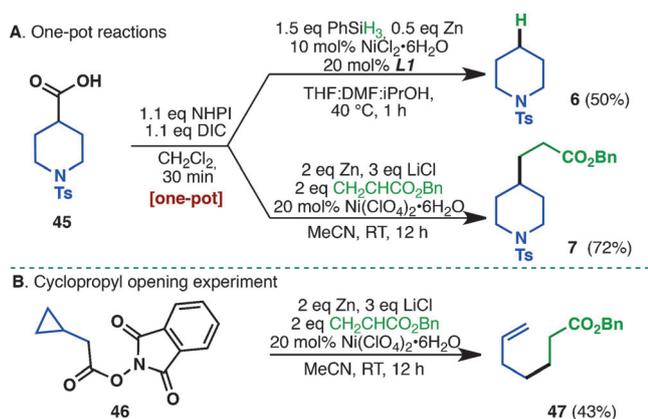


Scheme 1. Scope of the Ni-catalyzed decarboxylation and conjugate additions of NHPI redox-active esters.^[27] Reaction conditions for decarboxylation: RAE (1.0 equiv), NiCl₂·6H₂O (10 mol%), L1 (20 mol%), PhSiH₃ (1.5 equiv), Zn (0.5 equiv), THF/DMF/iPrOH (10:2:1), 0.15 M, 40 °C, 1 h. Reaction conditions for Giese conjugate addition: RAE (1.0 equiv), Ni(ClO₄)₂·6H₂O (20 mol%), Michael acceptor (2.0 equiv), LiCl (3.0 equiv), Zn (2.0 equiv), MeCN, 12 h, RT. (a) using 3.0 equiv PhSiH₃, 60 °C. (b) using 4.0 equiv Michael acceptor. (c) reaction run at 50 °C. (d) one-pot procedure from tartaric acid.

impact on medicinal chemistry to expedite the radical diversification of acids. The presence of radical intermediates was confirmed via rupture of the cyclopropyl ring in **46** to afford cyclopropane-opened product **47** as the exclusive conjugate addition product of the reaction (Scheme 2B).

Much fame has been accorded to the Barton decarboxylative and deoxygenative functionalizations because of their

unparalleled chemoselectivity. Over the years, these reactions have been shown to tolerate a host of Lewis basic functionalities.^[6] The operationally simple variants disclosed herein have the potential to enable chemoselective modifications on substrates of even greater complexity. Application of the decarboxylative conjugate addition to complex peptide modification, both on solid phase and in solution, epitomizes



Scheme 2. A) One-pot decarboxylation and conjugate addition from carboxylic acids. B) Radical ring-opening of a cyclopropyl methylene redox active ester.

this notion. Accordingly, the coupling of resin-bound acids and Michael acceptors was demonstrated (**48** to **49** and **50**, Figure 2A); such processes facilitate the late-stage introduction of designer amino acids^[23] while the sulfone and nitrile groups thus appended can serve as convenient handles for further functionalizations. Alternatively, alkyl groups can be introduced onto resin-bound peptides containing a Michael acceptor (**51** to **52**). It is noteworthy that products are isolated in synthetically useful yields after as many as 8–14 steps from the resin loading, further testifying to the robustness of the reaction. Moreover, an intramolecular variant of the Giese addition could also be performed on an unprotected peptide substrate,^[24] affording the coveted macrocycle (**53** to **54**). Macrocyclic peptides have demonstrated tremendous therapeutic potential owing to their resistance towards both exo- and endoproteases and their potential for exquisite target

selectivity.^[25] However, such macrocycles remain challenging synthetic targets for which there are limited available disconnection strategies. This radical conjugate addition approach opens new opportunities to explore the biological activities of cyclic peptides and may serve as a gateway for peptide stapling.^[26]

Nickel-catalyzed decarboxylative fragmentation of redox-active NHPI esters has enabled thermal reductive decarboxylation and Giese reactions. These operationally simple protocols circumvent several lingering shortcomings of classic Barton chemistry, avoiding the use of toxic reductants, photochemical irradiation, unstable starting materials, and in the case of conjugate addition, the formation of thiopyridyl side products. It is worth emphasizing that the total reaction cost, including solvent, for a typical 1 mmol-scale decarboxylation runs about \$1.4 without any further optimization or reduction in catalyst loading. The simple reagents and broad spectrum of substrates demonstrated should make these methods amenable to both medicinal chemistry and process development. Finally, applications to peptide syntheses illustrate their potential to effect chemoselective late-stage modifications in a particularly challenging context.

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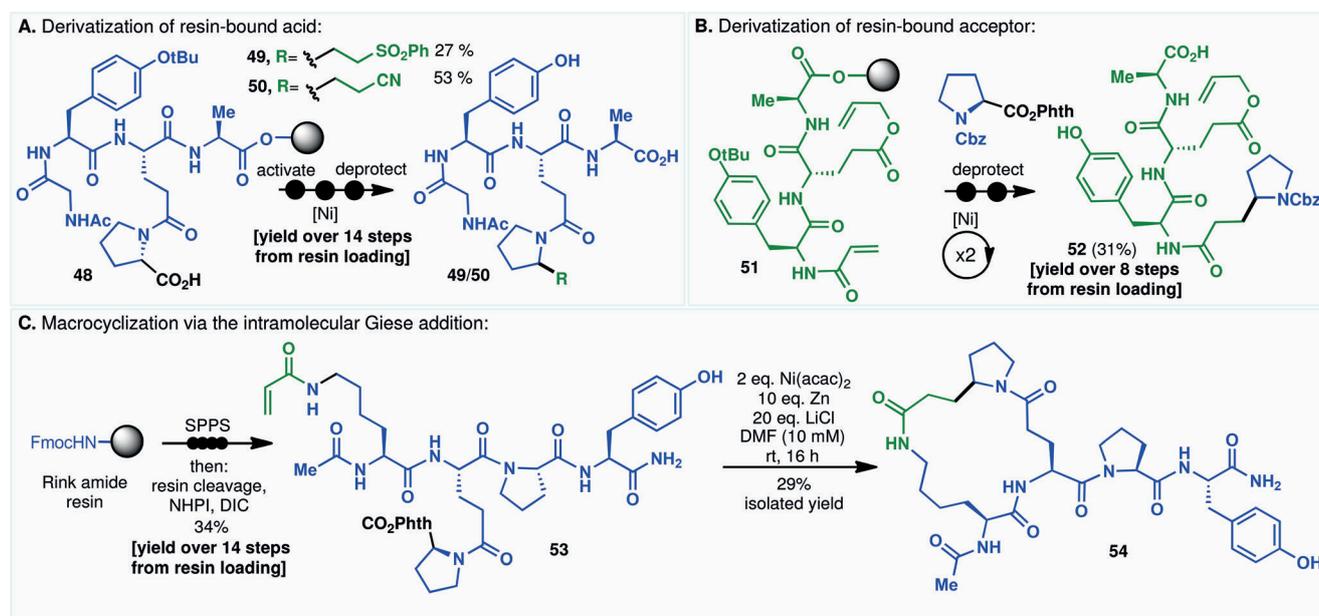


Figure 2. Use of Ni-catalyzed decarboxylative conjugate addition in complex peptide modification (see the Supporting Information for experimental details).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: conjugate addition · decarboxylation · esters · nickel catalysis · redox-active

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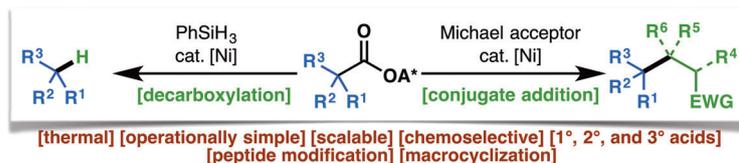
Communications



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Simple, thermal, and practical Barton-type decarboxylation and decarboxylative Giese addition have been developed based on nickel-catalyzed fragmentation of *N*-hydroxyphthalimide redox active

esters. The operational simplicity and chemoselectivity of these reactions allow for expedient preparations of various building blocks and late stage modifications of complex molecules.