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# Decarboxylative Alkenylation

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## Abstract

Olefin chemistry, through pericyclic reactions, polymerizations, oxidations, or reductions, plays an essential role in the foundation of how organic matter is manipulated.[1] Despite its importance, olefin synthesis still largely relies upon chemistry invented more than three decades ago, with metathesis[2] being the most recent addition. Here we describe a simple method to access olefins with any substitution pattern or geometry from one of the most ubiquitous and variegated building blocks of chemistry: alkyl carboxylic acids. The same activating principles used in amide-bond synthesis can thus be employed, under Ni- or Fe-based catalysis, to extract $CO_2$ from a carboxylic acid and economically replace it with an organozinc-derived olefin on mole scale. Over sixty olefins across a range of substrate classes are prepared, and the ability to simplify retrosynthetic analysis is exemplified with the preparation of sixteen different natural products across a range of ten different families.

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An analysis of available routes to olefin-containing sterol acetate **2a** points to retrosynthetic deficiencies that still exist in the modern era (Figure 1A). Seven conventional steps are required to convert steroid derivative **1** to **2a**,[3] only one of which forms a strategic C–C bond. The entire strategy is built around the Wittig transform[4] which requires redox-adjustment of the free carboxylate to the aldehyde, necessitating protecting group manipulations. By this route only steroid **2a** is accessible as related methyl and ethyl-



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**Author Contributions**

J. T. E, R. R. M. and P. S. B. conceived the work; J. T. E., R. R. M., K. S. M., K. W. K., L. R. M., T. Q., B. V., S. A. S., M. D. E., and P. S. B. designed the experiments and analyzed the data; J. T. E., R. R. M., K. S. M., K. W. K., L. R. M., T. Q., B. V. performed the experiments; D.-H. B., F.-L. W., and T. Z. performed mole scale experiments; P. S. B. wrote the manuscript; and J. T. E., R. R. M., K. W. M., K. W. K. assisted in writing and editing the manuscript.

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containing sterol acetates (**2b**, **2c**) would require more complex designs. This inefficient sequence is a well-recognized problem that has yet to be solved despite the obvious attraction of a hypothetical method that would directly convert acylated **1** to **2a**.

Whereas olefins have the most richly developed reactivity and highest abundance (via the petrochemical industry), the diversity of alkyl carboxylic acid building blocks available is unmatched. If the aforementioned versatile olefin-based cross-coupling partners could be employed in decarboxylative cross-coupling,[5–10] novel synthetic pathways could be accessed. For example (Figure 1B), one could envisage the total synthesis of diol-containing natural products such as **3** and **4** as arising from tartaric acid, perhaps the most inexpensive chiral building block available. This new disconnection could only be conceived in a decarboxylative fashion as the corresponding tartrate halides do not exist, and if they did, would most certainly not be stable.

Herein the invention of a general, scalable, chemoselective method for decarboxylative alkenylation is presented that exhibits broad scope across a range of both olefin (from mono- to fully-substituted) and carboxylic acid (1° and 2°) coupling partners (>60 examples, Figure 1C). Decarboxylative alkenylation dramatically simplifies retrosynthetic analysis.[11] To demonstrate this fact, total syntheses of sixteen natural products across ten different natural product families spanning a range of steroids, polyketides, vitamins, terpenes, fragrances, and prostaglandins are reported and directly compared to prior art (see Methods for more information).

The optimization of decarboxylative alkenylation is briefly summarized in Figure 1D. In general, the reaction proceeded smoothly when employing the tetrachloro-*N*-hydroxyphthalimide (TCNHPI, commercially available) esters, an inexpensive Ni(II) source, and the abundant ligand 2,2′-bipyridine (bipy, **L1**). Using piperidine-derived redox-active ester (RAE) **6**, cyclohexenylation could be achieved at room temperature with 10 mol% of $Ni(acac)_2{\cdot}xH_2O$, 10 mol% bipy, and 2.0 equiv. of alkenylzinc reagent **7** to furnish olefin **8** in 75% isolated yield. As has been demonstrated in prior work,[5–7] the RAE could also be generated *in situ* (entry 1) without any purification or even solvent removal. TCNHPI appears to be the optimal RAE (entries 2–3), and $Ni(acac)_2{\cdot}xH_2O$ proved superior to the more air- and moisture-sensitive $NiCl_2{\cdot}$glyme (entry 4). In general, most common solvents were tolerated in this reaction (see SI for details). Alternative ligands were also screened, and **L1** was chosen as it is the least expensive (entries 5–6). Finally, as will be shown in several cases, the Fe-based catalytic system developed previously for RAE-cross-coupling[7,12,13] could be employed as well (entry 7).

The scope of this new decarboxylative alkenylation reaction is striking as all possible classes of olefin coupling partners could be employed with exquisite control of olefin geometry. The scope of alkenylzinc reagents that can be employed in this coupling are exemplified in Panels A and B of Figure 2. Simple mono-, di-, tri-, and tetra-substituted olefins are easily accessible (**9–12, 16, 17**). From a strategic perspective, the cycloalkenyl products (**8**, **13–14**) would be challenging to make in a more direct way from either the same starting material or even a piperidone. Selecting which method to use when constructing an olefin (e.g. Wittig or metathesis) is usually linked to the underlying mechanism of the process to enable

production of the desired stereochemistry of the newly formed olefin. Decarboxylative alkenylation divorces the C–C bond forming event from such stereochemical concerns. As such, conventional techniques can be used to dial in the precise *E* or *Z* geometry of an alkenyl-organometallic which can then be employed without any isomerization. For example, olefin **12** is produced as a 1:1.5 mixture of *E/Z* isomers because the starting commercial Grignard reagent from which it was derived exists as a mixture. Similarly, styrenyl derivative **15** could be procured with high geometrical purity (>20:1 *E/Z*) as controlled by the starting alkenylzinc species (derived from lithium-halogen exchange of the corresponding styrenyl iodide). The power of stereocontrolled alkyne carbometallation[14] can be coupled with this method to produce geometrically pure alkenyl iodides. Alkenylzinc reagents derived therefrom (lithium-halogen exchange/transmetallation) afford tri-substituted olefin products such as **18** and **24** that would be otherwise challenging to make in a single step (*in situ* RAE) with complete stereopurity. One-pot alkyne hydrozirconation/transmetallation[15] can also be employed to access stereodefined *E*-olefins such as **20**, **25**, and **26**. Despite the presence of low-valent Ni-species, butadiene-containing products such as **21** do not inhibit the reaction, and the *E/Z* ratio of the starting dienyl species is maintained. Experience from this lab has taught that cross-couplings at the D-ring of a steroid can be challenging;[16] the formation of **19** from the easily obtained alkenylzinc species bodes well for future applications in such contexts.

Pioneering work from the Knochel group[17] has provided robust methods for generating vinylogous zinc reagents for use in cross-coupling chemistry. These species could also be used in the decarboxylative sense (Panel B) to furnish a range of functionalized building blocks that may be otherwise challenging to access. Both *cis* and *trans* alkenylzinc reagents can be prepared with high geometric purity, leading smoothly to **27** and **28**. This method provides a complimentary strategy to olefin cross-metathesis[18] to access such structures. It is also worth noting that the butenolide (**29**) has never been prepared before. Cross-coupling using butenolides, a motif oft found in natural products, as a nucleophile has only been accomplished through a Stille-coupling of the corresponding stannylated species.[16] The adducts with dimedone represent an orthogonal pathway to Stork-Danheiser type adducts[19] that, in some cases, would not be easily accessed (**31**, **32**, **35**). The magnesium bromide diethyl ether complex ($MgBr_2 \cdot OEt_2$) was found to be an essential additive for reactions with alkenylzinc reagents derived from alkenyl iodides via lithium-halogen exchange, direct zinc insertion of electron-withdrawn α,β-unsaturated alkenyl iodides, and hydrozirconation/transmetallation of terminal alkynes. All alkenylzinc reagents were prepared as documented in the Supporting Information.

Panel C outlines decarboxylative alkenylations using eighteen different primary carboxylic acids, only six of which were not commercially available (**41**, **52**, **54**, **56**, **57, 58**) but very easily prepared. In contrast, significantly fewer of these electrophiles are available as a halide or an alcohol (from which a tosylate or halide could be made) whereas some substrates would be unstable if they were obtainable (**43–46**, **49**, **51**). This points again to the undeniable convenience of a cross-coupling that employs readily available starting materials. Amino acid-derived (**38**, **42**), α-oxy (**43–46**), benzylic (**48**, **50–51**), fusidane-based (**52–53**), and heterocycle-containing (**55**) acids could be successfully transformed into olefins of

various types. Even peptides (**58**, **59**) with unprotected residues are competent coupling partners under the reaction conditions. Efficient synthesis of naftifine (**57**), an antifungal pharmaceutical, was accomplished in high yield with excellent selectivity. Amino acid containing substrates showed no base-mediated erosion of *ee* (**38**, **42**) or epimerization (**58**, **59**), and benzylic acid **50** showed no loss of the aromatic bromide. Similarly, other known coupling partners in low-valent Ni-chemistry[20] such as aromatic C–O (**48**, **51**) and C–Cl (**45**) bonds, and hydrolytically sensitive phenol acetate esters (**54**) remained untouched. Lewis-basic heteroatoms are tolerated (**55**, **57**), and a formal synthesis of (β)-santalene could be accomplished in short order (addition of MeLi to ketone **56** and elimination leads to the natural product).[21]

Secondary (**60–69**) and tertiary bridgehead (**70**) RAEs can be easily alkenylated, as well, as shown in Panel D. Of note here is that diastereoselective alkenylations can be predictably incorporated into synthesis plans as demonstrated with substrates **64**, **65**, **68**, and **69**. Spirocyclic substrates **65** and **66** are of interest to a medicinal chemistry program (Bristol-Myers Squibb), the latter of which highlights how ethylvinyl ether (zincated) can be used in this coupling as an alternative to Grignard/organolithium addition to an ester or Weinreb amide (see SI for further details and comparison). To probe for the intermediacy of radical species in the decarboxylative alkenylation reaction, radical-ring opening experiments (Panel E) were performed with **71** and **73**, affording the corresponding ring-opened products **72** and **74**, respectively.

Of the 65 substrates depicted in Figure 2, several were also performed with an *in situ* protocol (especially in such cases where the RAE was not stable) or using an Fe-based system. The SI contains a detailed troubleshooting guide and a graphical user tutorial. The reaction has been field tested at Bristol-Myers Squibb in many different contexts, and the robustness was demonstrated by conducting the reaction of **38** on a mole scale (63% yield, >600 grams, >99% *ee*, carried out at Asymchem). As a testament to the robustness of this reaction, no significant modifications to the general procedure were necessary when scaling this reaction up from millimole to mole scale. Currently there are not many glaring limitations for this method as one can generally expect a serviceable yield across a range of substrates; there are relatively more limitations in the chemistry of preparing the alkenyl zinc species.

To demonstrate a small snapshot of the vast options that exist to apply this new transformation, Figure 3 summarizes the total synthesis of fifteen different natural products (full details of these sequences can be found in the SI). As mentioned above (Figure 1A), steroidal substrate **2a** exemplifies the inefficiency of previous approaches to olefin synthesis as a consequence of chemoselectivity issues surrounding the Wittig reaction and the incorrect oxidation state of the starting material (**1**). With decarboxylative alkenylation (Figure 3A), the same starting material can be employed and the desired product **2a** can be accessed in two steps. Of note is that the current method can be used to make not only **2a** but also related natural products that would be otherwise inaccessible (in a direct fashion) such as **2b** and **2c**.

The clerodane diterpene family consists of over 650 members that are broadly characterized as having a decalin framework appended to side chains with variegated substituents.[22] From a strategic perspective, it would be ideal if a single starting material could be used and divergently converted to multiple family members using a single reaction type. Decarboxylative alkenylation enables the synthesis of the same three natural isolates from **75**, a material that is made in 6 steps from readily available (−)-5-methyl Wieland-Miescher ketone. Thus, in only 9 steps from commercially available materials, a simple alkyne, an iodobutenolide, and a bromofuran, served as organozinc precursors that when coupled with **75**, enabled access to (−)-kolavenol (**76a**), (−)- solidagolactone (**76b**), and (−)-annonene (**76c**), respectively.

With decarboxylative alkenylation, one can access methyl trans-chrysanthemate (78, Figure 2C) from commercially-available caronic anhydride (**77**), which after one-pot methanolysis and radical cross-coupling delivers **78** in 31% yield with excellent diastereoselectivity (*>20:1*).

Many applications of this methodology to polyketide synthesis can be envisaged where the decarboxylative approach allows for innovative uses of classic chiral building blocks in highly convergent ways. For example, tartaric acid is perhaps the cheapest enantiopure chemical that can be purchased (*ca* $1/mole) and represents an ideal source of the 1,2-diol motif. The total syntheses of (−)-cladospolide B (**3**), (−)-*iso*-cladospolide B (**83**), and (+)-cladospolide C (**4**) illustrate how both enantiomers of tartaric acid can be used like simple “cassettes” and modularly incorporated to complete syntheses that are not only dramatically shorter than prior approaches but also more selective (Figure 3D). A design based on radical cross-coupling of tartrate derived acids **79** and **84** sets the stage for a triply convergent approach wherein alkyl-alkyl cross-coupling (with alkylzinc reagent **80**) precedes decarboxylative alkenylation (with either **81** or **85**) to furnish **82** and **86** in only 5 steps with excellent control of olefin geometry. If the steps are counted from alkylzinc reagent **80**, the sequence is 6 steps long indicating that the 1,2-diol motif is no longer the bottleneck of the synthesis. This approach is the most direct and inexpensive known. Similarly, monomethyl succinate (**87**), a commodity chemical, can be coupled to a stereodefined alkenylzinc reagent to furnish **88** directly, which after deprotection and known macrolactonization, delivers (−)-phoracantholide J (**89**) in only 3 steps (8 steps including the synthesis of the alkenylzinc reagent).

Prostaglandins are classic targets for total synthesis not only due to their intriguing structures and exciting medicinal uses but also because they serve as a veritable proving ground for the development of new methodologies (Figure 3E).[23] The commercially-available Corey lactone (**90**) could be employed in a four step sequence wherein two steps are non-strategic (oxidation and one-pot hydrolysis/protection) and two install the key C–C bonds with the proper olefin geometry. Thus, sequential decarboxylative cross-coupling of *E*-(**91**) and *Z*-(**92**) alkenylzinc species to the requisite carboxylic acids provides a simple route not only to **93** but is also sufficiently flexible to conceivably access a plethora of new prostaglandin analogs in a combinatorial fashion.

Aureonitol (**95**) is a tetrahydrofuran-containing natural product discovered in 1979 from *Helichrysum aureonitens* (Figure 3F).[24] A strategic decarboxylative dienylation of **94** delivers **95** in 32% yield with complete selectivity (>20:1 *E/Z*) as controlled by the chemistry used to fashion the diene nucleophile. Application of this transformation simplifies the synthesis as **94** can be made in 7 simple steps from inexpensive (+)-xylose.[25,26]

Tocotrienols, members of the vitamin E family, are dietary supplements and have been reported to have an array of beneficial health effects (Figure 3G).[27] Current extraction methods from plant materials provide these compounds as a mixture, which is both difficult and costly to separate. Synthesis offers direct access to specific members of the tocotrienol family but contemporary efforts lack selectivity in olefin formation or require concessionary redox manipulations. Trimethylhydroquinone (**96**) can be employed to furnish **99** with high selectivity (>20:1 *E/Z*) and in only four steps overall since the farnesyl group can be directly coupled as a single fragment.

Lyngbic acid (**102**), an inhibitor of quorum sensing in cyanobacteria, was prepared by Noyori asymmetric transfer hydrogenation[28] of the commercial β-keto ester **100** followed by decarboxylative cross-coupling delivers **102** with complete selectivity (>20:1 *E/Z*) in 51% isolated yield (*ca.* 98% *ee*).

## Methods

### Background: Alternative/classical routes to olefins

The vast majority of olefin syntheses commence from other unsaturated systems (e.g. olefin metathesis, Heck coupling, alkyne hydrogenation, etc.), rely on various condensations of carbonyl compounds (Wittig, Peterson, Tebbe, Nysted, Aldol, McMurry, etc), or involve the elimination of an alcohol, amine, or halide.[29] Although Negishi, Kumada-Corriu-Tamao, and Suzuki-Miyaura type reactions enable the cross-coupling of olefin-containing organometallic species with alkyl halides with precise control of olefin geometry,[30] the limited availability of the latter species diminishes the utility of such a disconnection.[31–38]

### Prior approaches to the total synthesis of natural products

Collectively, Figure 3 represents a selection of great opportunities for organic synthesis as many previously unimaginable pathways open up through the strategic application of this disconnection.

Prior approaches[39,40] to the clerodane diterpene natural products target each through a different strategy with, for example, the syntheses of **76a–c** ranging from 8–21 steps (Figure 3B).

The naturally occurring insecticide methyl-*trans*-chrysanthemate (**78**) has previously been prepared in six steps using a cyclopropanation/Wittig olefination strategy.[41,42]

Advanced intermediates **82** and **86** have been previously prepared *en route* to **3–4** and **83** using a Wittig strategy from tartrates that proceeded in 14 steps with 1:5 *Z/E* olefin

selectivity.[43] It is worth noting that other approaches to this class of natural products have used olefin-metathesis,[44] Evans aldol reaction,[45] and Os-catalyzed dihydroxylation[46] transforms. (−)-Phoracantholide J (**89**) was previously constructed through either ring-closing metathesis or Ru-catalyzed hydroalkynylation.[47,48]

Corey's 1969 synthesis of (+)-$PGF_2\alpha$ (**93**) and related family members required eight steps from the now commercially available lactone **90** (Corey lactone), with the strategy largely based on the use of two separate olefination steps (Wittg and Horner-Wadsworth-Emmons) to install the requisite side chains (colored in green).[49] A recent route to (+)-$PGF_2\alpha$ was developed by Aggarwal.[50]

Aureonitol (**95**, Figure 2F) was previously procured in 14 steps from (*S*)-serine featuring a non-selective Julia-Kocienski olefination to forge the C8–C9 linkage.[51]

One reported approach[52] to **99** commences with trimethylhydroquinone (**96**) and employs a Wittig homologation of aldehyde **97** (10:1 *E/Z*) to install a small fragment of the farnesyl side chain. The remaining C–C bond is fashioned using an $S_N2$ displacement of an alkyl iodide by an alkyl sulfone, thus requiring extra redox and functional group manipulations to afford **99** in nine steps overall.

The simple lipid lyngbic acid (**102**, Figure 2H), an inhibitor of quorum sensing in cyanobacteria, has previously been made in 3 steps using an olefin cross-metathesis approach (9:1 *E/Z*) following the enantioselective allylation of an aldehyde using an allyltin reagent (Figure 3H).[53]

Olefins are ever-present functional groups that are found throughout Nature and every sector of chemical science. Their rich and robust chemistry make them integral to the planning, logic, and reliable execution of multistep synthesis. This operationally simple method harnesses the reliable and programmable synthesis of olefin-containing zinc species and the unparalleled commercial availability and stability of alkyl carboxylic acids to access olefins in a powerful new way. Numerous applications can be anticipated of both this method and the strategy it enables in the contexts of chemoselective fragment coupling (convergent synthesis), homologation (as an alternative to Wittig olefination and related transforms), and stereospecific olefin installation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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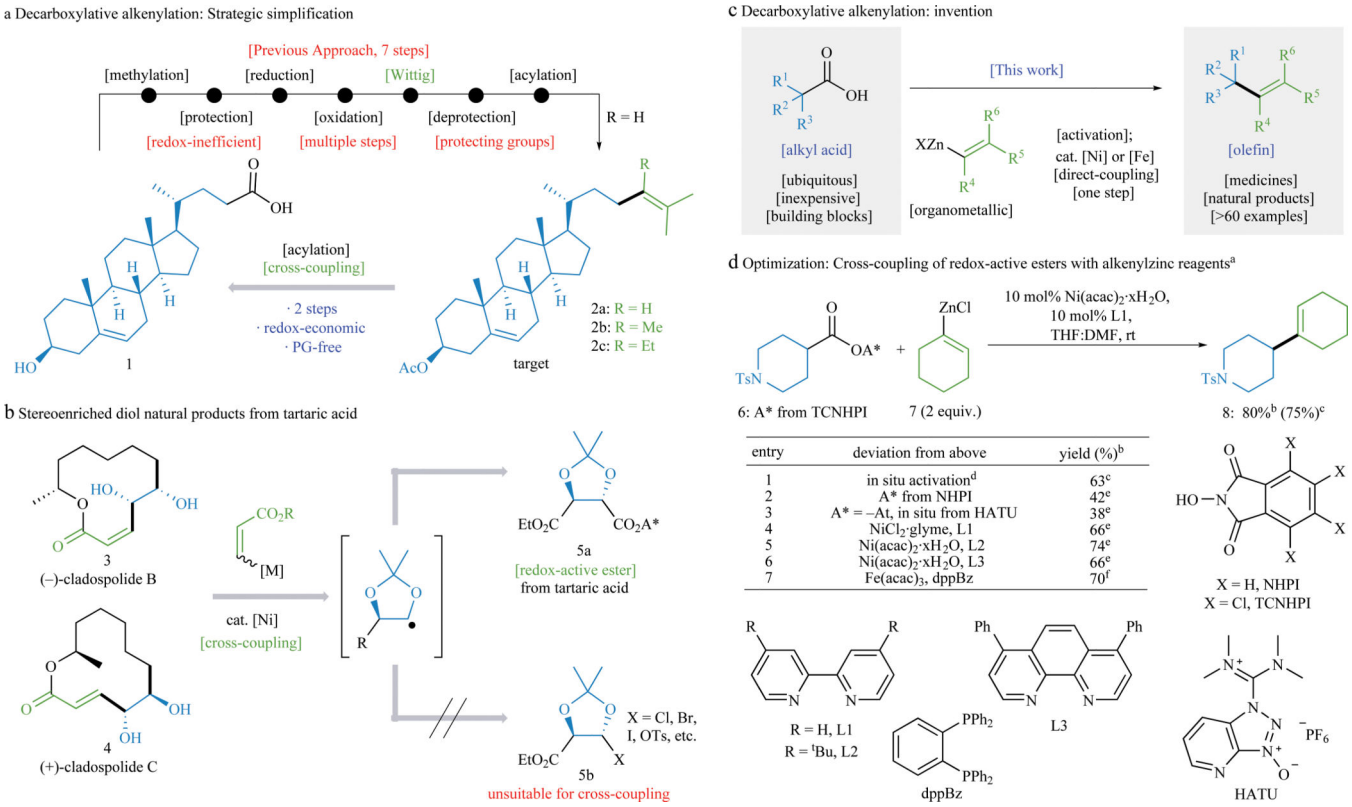


| entry | deviation from above | yield (%)[b] |
|---|---|---|
| 1 | in situ activation[d] | 63[c] |
| 2 | A* from NHPI | 42[e] |
| 3 | A* = –At, in situ from HATU | 38[e] |
| 4 | $NiCl_2$·glyme, L1 | 66[e] |
| 5 | $Ni(acac)_2·xH_2O$, L2 | 74[e] |
| 6 | $Ni(acac)_2·xH_2O$, L3 | 66[e] |
| 7 | $Fe(acac)_3$, dppBz | 70[f] |

**Figure 1. Development of Ni– and Fe–catalyzed decarboxylative alkenylation**

**a**, Conventional route to sterol acetates (**2a**–**c**). **b**, Utilization of previously unavailable electrophiles in cross-coupling reactions. **c**, Decarboxylative alkenylation presents a potential solution. **d**, Optimization of decarboxylative alkenylation. [a]0.1 mmol. [b]Yield by $^1H$ NMR with $CH_2Br_2$ internal standard. [c]0.25 mmol scale, isolated. [d]1.1 equiv. TCNHPI, 1.1 equiv. DIC, $CH_2Cl_2$ (0.2 M). [e]20 mol% [Ni] and L, 3.0 equiv. alkenylzinc. [f]10 mol% [Fe], 12 mol% dppbz, 1.5 equiv. dialkenylzinc. See Supporting Information for additional details.

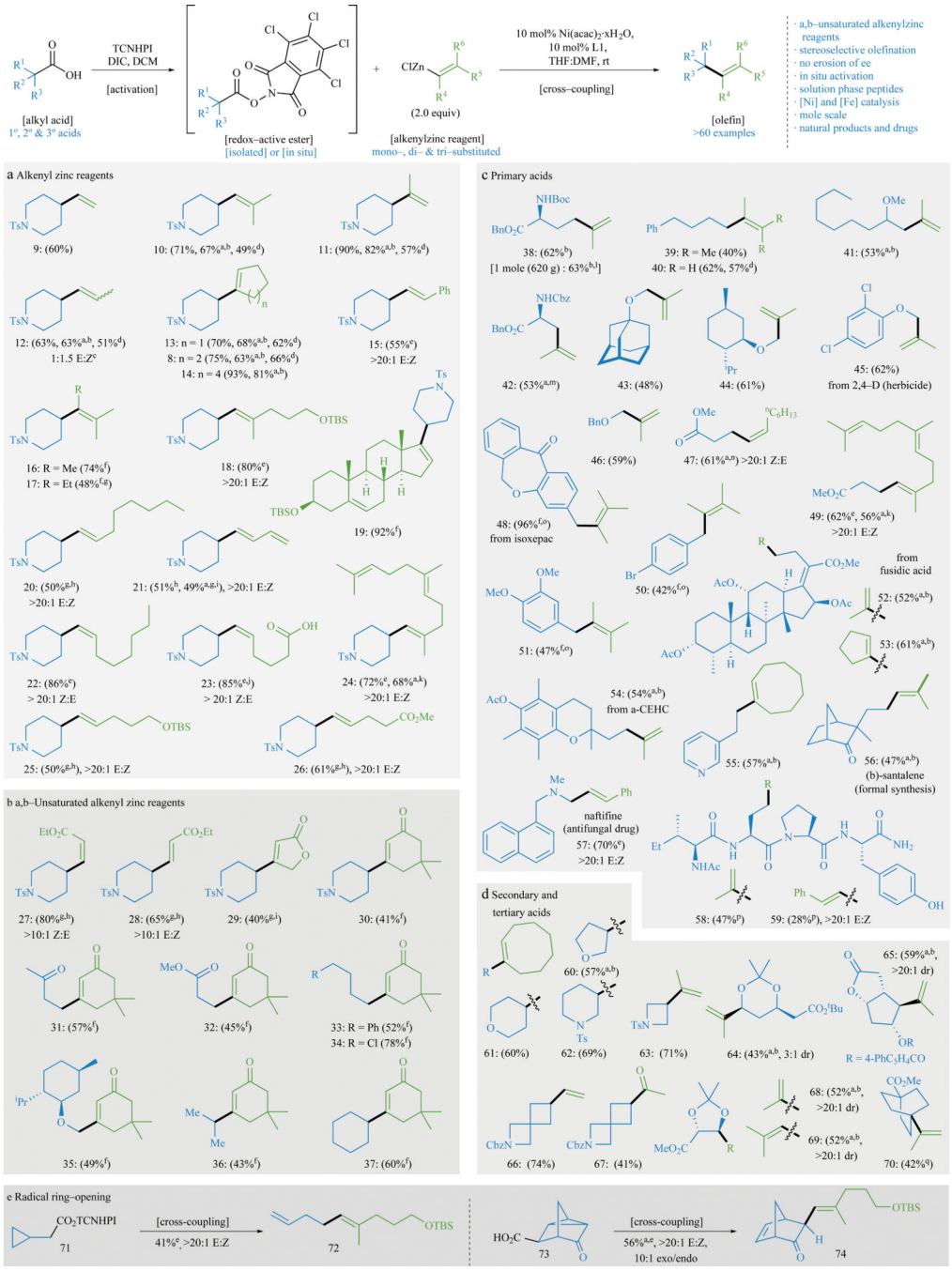


**Figure 2. Substrate scope of decarboxylative alkenylation**

The carboxylic acid component is shown in blue and the alkenyl zinc reagent is shown in green. Cross-coupling using various alkenyl zinc reagents (**a**, **b**) and different primary (**c**), secondary and tertiary (**d**) acids evaluated. Yields refer to isolated yields of products after chromatography on $SiO_2$. [a] *in situ* activation. [b] 3 equiv. alkenylzinc. [c] alkenylzinc derived from commercial Grignard that exists as a mixture of olefin isomers. [d] 10 mol% $Fe(acac)_3$, 12 mol% dppbz, 1.5 equiv. dialkenylzinc. [e] 2 equiv. alkenylzinc, 2 equiv. $MgBr_2 \cdot OEt_2$. [f] MeCN as solvent. [g] 60 °C. [h] 20 mol% Ni/L, 3 equiv. alkenylzinc, 3 equiv. $MgBr_2 \cdot OEt_2$. [i] 20

mol% Ni/L, 5 equiv. alkenylzinc, 5 equiv. $MgBr_2 \cdot OEt_2$. [j] alkenylzinc derived from OBO-ester; see SI for work up details. [k] 3 equiv. alkenylzinc, 3 equiv. $MgBr_2 \cdot OEt_2$. [l] See SI for details regarding mol-scale reaction. [m] 4 equiv. alkenylzinc. [n] 4 equiv. alkenylzinc, 4 equiv. $MgBr_2 \cdot OEt_2$. [o] 10 mol% $NiCl_2$·glyme/4,4′-di-*t*BuBipy. [p] See SI for details regarding peptide substrates. [q] 20 mol% Ni/L, 5 equiv. alkenylzinc, NMP.

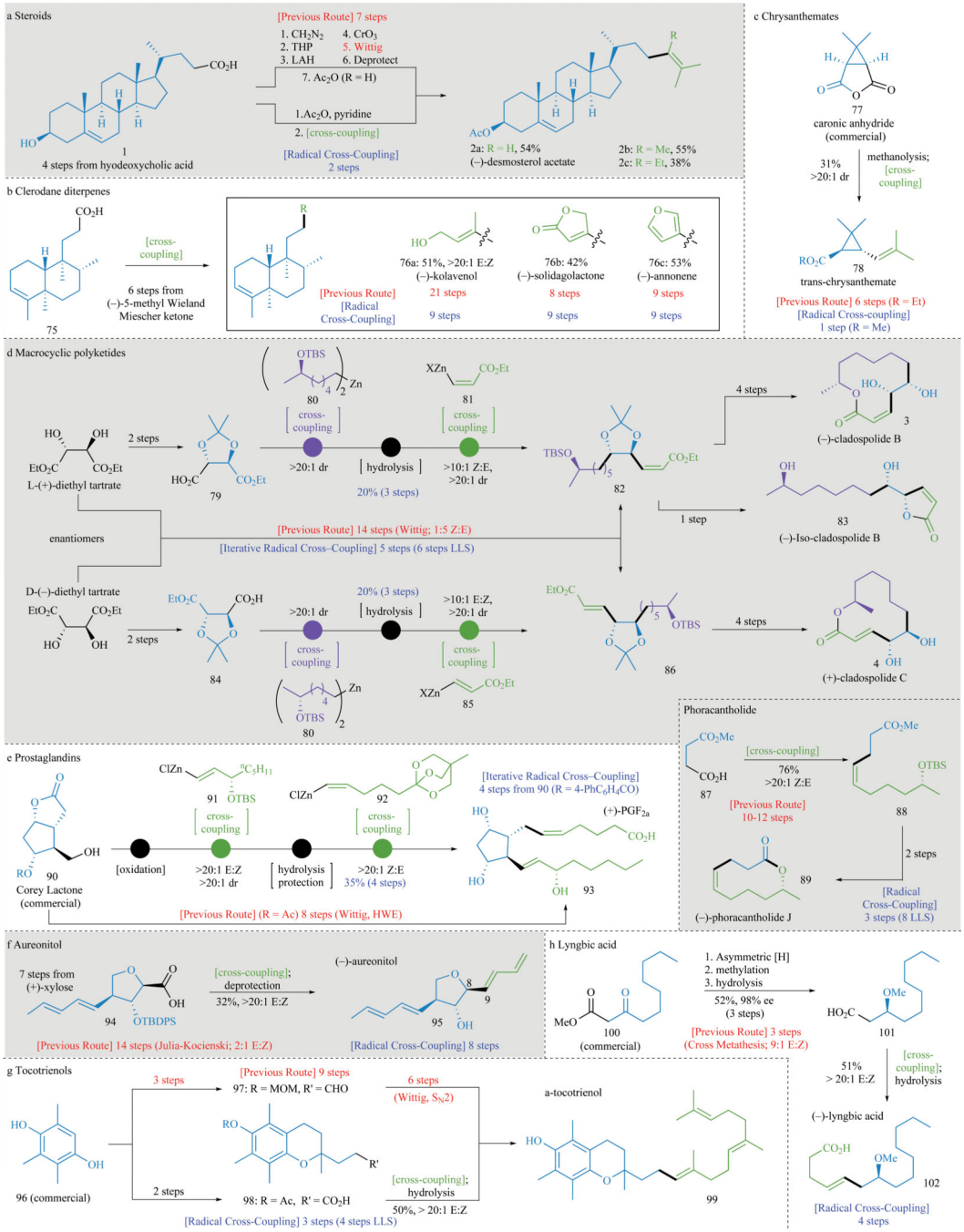


**Figure 3. Total synthesis enabled by decarboxylative alkenylation**

All decarboxylative alkenylations were performed with *in situ* activation of the carboxylic acid. See SI for full synthetic details and schemes (**a**–**h**). LLS = longest linear sequence. [H] = reduction.