LETTER

Decarboxylative alkenylation

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Olefin chemistry, through pericyclic reactions, polymerizations, oxidations, or reductions, has an essential role in the manipulation of organic matter¹. Despite its importance, olefin synthesis still relies largely on chemistry introduced more than three decades ago, with metathesis² being the most recent addition. Here we describe a simple method of accessing olefins with any substitution pattern or geometry from one of the most ubiquitous and variegated building blocks of chemistry: alkyl carboxylic acids. The activating principles used in amide-bond synthesis can therefore be used, with nickel- or iron-based catalysis, to extract carbon dioxide from a carboxylic acid and economically replace it with an organozinc-derived olefin on a molar scale. We prepare more than 60 olefins across a range of substrate classes, and the ability to simplify retrosynthetic analysis is exemplified with the preparation of 16 different natural products across 10 different families.

An analysis of available routes to olefin-containing sterol acetate **2a** points to retrosynthetic deficiencies that still exist (Fig. 1a). Seven conventional steps are required to convert steroid derivative **1** to **2a** (ref. 3), only one of which forms a strategic C–C bond. The entire strategy is built around the Wittig transform⁴, which requires redox-adjustment of the free carboxylate to the aldehyde, necessitating protecting-group manipulations. By this route only steroid **2a** is accessible, because related methyl- and ethyl-containing sterol acetates (**2b**, **2c**) would require more complex designs. The inefficiency of this sequence is a well known problem that has yet to be solved despite the attraction of a hypothetical method that would directly convert acylated **1** to **2a**.

Although 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 used in decarboxylative cross-coupling⁵⁻¹⁰, novel synthetic pathways could be accessed. For example (Fig. 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.

Here we present the invention of a general, scalable, chemoselective method for decarboxylative alkenylation that exhibits broad scope across a range of both olefin (from mono-substituted to fully substituted) and carboxylic acid (primary, secondary and tertiary) coupling partners (>60 examples, Fig. 1c). Decarboxylative alkenylation dramatically simplifies retrosynthetic analysis¹¹. To demonstrate this, 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 syntheses (see Methods for more information).

The optimization of decarboxylative alkenylation is briefly summarized in Fig. 1d. In general, the reaction proceeded smoothly when using the tetrachloro-N-hydroxyphthalimide (TCNHPI, commercially available) esters, an inexpensive Ni(II) source, and the abundant ligand 2,2'-bipyridine (bipy, L1). Using the piperidinederived redox-active ester (RAE) 6, cyclohexenylation could be achieved at room temperature with 10 mol% of Ni(acac)₂•xH₂O, 10 mol% bipy, and 2.0 equivalents (equiv.) of alkenylzinc reagent 7 to furnish olefin 8 in 75% isolated yield. As has been demonstrated in previous work⁵⁻⁷, the RAE could also be generated in situ (entry 1 in the table of Fig. 1d) without any purification or even solvent removal. TCNHPI appears to be the optimal RAE (entries 2 and 3), and Ni(acac)₂•xH₂O proved superior to the more air- and moisturesensitive NiCl₂•glyme (entry 4). In general, most common solvents were tolerated in this reaction (see Supplementary Information for details). Alternative ligands were also screened, and L1 was chosen as it is the least expensive (entries 5 and 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 used as well (entry 7).

The scope of this new decarboxylative alkenylation reaction is striking because all possible classes of olefin coupling partners could be employed with exquisite control of olefin geometry. The scope of alkenylzinc reagents that can be used in this coupling are exemplified in Fig. 2a, b. 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 from a piperidone. The selection of which method to use when constructing an olefin (for example, 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 produce the precise *E* or *Z* geometry of an alkenyl-organometallic, which can then be used 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 carbometallation¹⁴ 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/transmetallation¹⁵ can also be used 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 laboratory has taught that cross-couplings at the D-ring of a steroid can be challenging¹⁶; therefore the formation of

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a Decarboxylative alkenylation: strategic simplification



C Decarboxylative alkenylation: invention

Figure 1 | Development of Ni- and Fe-catalysed decarboxylative alkenylation. a, Conventional route to sterol acetates (2a–2c). Red text highlights inefficiencies in the traditional approach. Green text refers to the carbon–carbon bond forming step in the synthetic sequence. b, Utilization of previously unavailable electrophiles in cross-coupling reactions. c, Decarboxylative alkenylation presents a potential solution. R¹, R² and R³ from the carboxylic acid are coloured blue, and R⁴, R⁵ and R⁶ from alkenylzinc reagent are coloured green. d, Optimization of decarboxylative alkenylation. ^bYield by ¹H nuclear magnetic resonance (NMR) analysis with CH₂Br₂ internal standard. ^c0.25 mmol scale, isolated. ^d1.1 equiv. TCNHPI, 1.1 equiv. DIC, CH₂Cl₂ (0.2 M). ^e20 mol% [Ni] and

19 from the easily obtained alkenylzinc species bodes well for future applications in such contexts.

Pioneering work from the Knochel group¹⁷ has provided robust methods for generating vinylogous zinc reagents for use in crosscoupling chemistry. These species could also be used in the decarboxylative sense (Fig. 2b) 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 complementary strategy to olefin cross-metathesis¹⁸ to access such structures. It is also worth noting that the alkenylzinc reagent for butenolide (29) has never been prepared before. Cross-coupling using butenolides, a motif often found in natural products, as a nucleophile has only been accomplished through a Stille-coupling of the corresponding stannylated species¹⁶. The adducts with dimedone (30-37) represent an orthogonal pathway to Stork-Danheiser type adducts¹⁹ that, in some cases, would not easily be accessed (31, 32, 35). The magnesium bromide diethyl ether complex (MgBr₂•OEt₂) was found to be an essential additive for reactions with alkenylzinc reagents derived from alkenyl iodides via lithiumhalogen 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 Supplementary Information.

Figure 2c outlines decarboxylative alkenylations using eighteen different primary carboxylic acids, only six of which were not

L (L1, L2, or L3), 3.0 equiv. alkenylzinc. ^f10 mol% [Fe], 12 mol% dppBz, 1.5 equiv. dialkenylzinc. See Supplementary Information for additional details. PG, protecting group; [Fe], [Ni], general nickel or iron precatalyst; CO₂Et, ethyl ester; Ts, tosyl; X, halide; DIC, *N*,*N*'-diisopropylcarbodiimide; acac, acetylacetonate; L, ligand; dppBz, 1,2-bis(diphenylphosphino) benzene; THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide; RT, room temperature; 'Bu, *tert*-butyl; A*, activating group; NHPI, *N*-hydroxyphthalimide; TCNHPI, *N*-hydroxytetrachlorophthalimide; HATU, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b] pyridinium 3-oxide hexafluorophosphate; glyme, 1,2-dimethoxyethane.

commercially available (41, 52/53, 54, 56, 57 and 58/59) but very easily prepared. In contrast, substantially 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 and 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 enantiomeric excess (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-chemistry²⁰, 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 Fig. 2d. Of note here is that diastereoselective alkenylations can be predictably incorporated into synthesis plans, as demonstrated with substrates **64**, **65**, **68** and **69**.

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MgBr₂•OEt₂. ¹20 mol% Ni/L, 5 equiv. alkenylzinc, 5 equiv. MgBr₂•OEt₂. ¹Alkenylzinc derived from OBO-ester; see Supplementary Information for the work-up details. ^k3 equiv. alkenylzinc, 3 equiv. MgBr₂•OEt₂. ^lSee Supplementary Information for details regarding mole-scale reaction. ^m4 equiv. alkenylzinc, 4 equiv. MgBr₂•OEt₂. ^o10 mol% NiCl₂•glyme/4,4'-di-tBuBipy. ^pSee Supplementary Information for details regarding peptide substrates. ^q20 mol% Ni/L, 5 equiv. alkenylzinc, NMP. DCM, dichloromethane; OBO, 4-methyl-2,6,7-trioxa-bicyclo[2.2.2] octan-1-yl; TBS, *tert*-butyldimethylsilyl; CEHC, carboxyethyl-hydroxychroman; d.r.; diastereomeric ratio; 4,4'-di-tBuBipy, 4,4'-di-*tert*-butyl-2,2'-dipyridyl; NMP, 1-methylpyrrolidin-2-one.

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Spirocyclic substrates **66** and **67** are of interest to a medicinal chemistry programme (Bristol-Myers Squibb); **67** 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 Supplementary Information for further details and comparison). To probe for the intermediacy of radical species in the decarboxylative

full synthetic details and schemes. LLS, longest linear sequence. HWE, Horner–Wadsworth–Emmons; THP, tetrahydropyran; LAH, lithium aluminium hydride; MOM, methoxymethyl; [H], reduction.

alkenylation reaction, radical ring-opening experiments (Fig. 2e) were performed with **71** and **73**, affording the corresponding ring-opened products **72** and **74**, respectively.

Of the 65 substrates depicted in Fig. 2, several were also performed with an *in situ* protocol (especially in cases where the RAE was not stable) or using an Fe-based system. Supplementary Information

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 the mole scale (63% yield, >600 g, >99% enantiomeric excess, carried out at Asymchem). As a testament to the robustness of this reaction, no substantial modifications to the general procedure were necessary when scaling this reaction up from the millimole to the mole scale. At present, there are not many obvious limitations for this method given that one can generally expect a serviceable yield across a range of substrates; there are relatively more limitations in the chemistry of preparing the alkenylzinc species.

To illustrate a few of the vast number of ways to apply this new transformation, Fig. 3 summarizes the total synthesis of fifteen different natural products (full details of these sequences can be found in Supplementary Information). As mentioned above (Fig. 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 (Fig. 3a), the same starting material can be used 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 sterol acetates 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 substituents²². 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 six steps from readily available (–)-5-methyl Wieland–Miescher ketone. Thus, in only nine 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 transchrysanthemate (**78**, Fig. 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 (about US\$1 per 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', modularly incorporated to complete syntheses that are not only dramatically shorter than prior approaches but also more selective (Fig. 3d).

A design based on radical cross-coupling of tartrate derived acids **79** and **84** sets the stage for a triply convergent approach wherein alkylalkyl cross-coupling (with alkylzinc reagent **80**) precedes decarboxylative alkenylation (with either **81** or **85**) to furnish **82** and **86** in only five steps with excellent control of olefin geometry. If the steps are counted from alkylzinc reagent **80**, the sequence is six 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 three steps (eight steps including the synthesis of the alkenylzinc reagent).

Prostaglandins are classic targets for total synthesis not only owing to their intriguing structures and exciting medicinal uses but also because they serve as a proving ground for the development of new methodologies (Fig. 3e)²³. The commercially available Corey lactone (**90**) could be used 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 conceivably sufficiently flexible to access many new prostaglandin analogues in a combinatorial fashion.

Aureonitol (95) is a tetrahydrofuran-containing natural product discovered in 1979 from Helichrysum aureonitens (Fig. 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 because 94 can be made in seven 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 (Fig. 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 hydrogenation²⁸ 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 (about 98% enantiomeric excess).

Olefins are ever-present functional groups that are found naturally and in 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.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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Supplementary Information is available in the online version of the paper.

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METHODS

Alternative or classical routes to olefins. The vast majority of olefin syntheses commence from other unsaturated systems (such as olefin metathesis, Heck coupling and alkyne hydrogenation), rely on various condensations of carbonyl compounds (Wittig, Peterson, Tebbe, Nysted, Aldol, McMurry, and so on), or involve the elimination of an alcohol, amine or halide²⁹. 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 geometry³⁰, the limited availability of alkyl halides diminishes the utility of such a disconnection^{31–38}.

Previous approaches to the total synthesis of natural products. Collectively, Fig. 3 represents a selection of excellent opportunities for organic synthesis as many previously unimagined pathways open up through the strategic application of this disconnection. Previous approaches^{39,40} to the clerodane diterpene natural products target each through a different strategy with, for example, the syntheses of **76a**–**76c** ranging from 8 to 21 steps (Fig. 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 selectivity⁴³. It is worth noting that other approaches to this class of natural products have used olefin-metathesis⁴⁴, Evans aldol reaction⁴⁵, and Os-catalysed dihydroxylation⁴⁶ transforms. (–)-Phoracantholide J (**89**) was previously constructed through either ring-closing metathesis or Ru-catalysed hydroalkynylation^{47,48}.

Corey's 1969 synthesis of (+)-PGF_{2α} (**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 (Wittig and Horner–Wadsworth–Emmons) to install the requisite side chains of **93** (coloured in green)⁴⁹. A recent route to (+)-PGF_{2α} has been developed⁵⁰. Aureonitol (**95**, Fig. 2f) was previously procured in 14 steps from (*S*)-serine featuring a non-selective Julia–Kocienski olefination to forge the C8–C9 linkage⁵¹.

One reported approach⁵² 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**, Fig. 2h), an inhibitor of quorum sensing in cyanobacteria, has previously been made in three steps using an olefin cross-metathesis approach (9:1 E/Z) following the enantioselective allylation of an aldehyde using an allyltin reagent (Fig. 3h)⁵³.

Data availability. Data generated in this study is available in Supplementary Information or on request from the authors.

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