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Synthesis of Complex Allylic Esters via C−H Oxidation vs C−C Bond Formation

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Abstract: A highly general, predictably selective C−H oxidation method for the direct, catalytic synthesis of complex allylic esters is introduced. This Pd(II)/sulfoxide-catalyzed method allows a wide range of complex aryl and alkyl carboxylic acids to couple directly with terminal olefins to furnish (*E*)-allylic esters in synthetically useful yields and selectivities (16 examples, $E/Z \geq 10{:}1$) and without the use of stoichiometric coupling reagents or unstable intermediates. Strategic advantages of constructing allylic esters via C−H oxidation vs C−C bond-forming methods are evaluated and discussed in four "case studies".

Introduction

Well-accepted bond-forming strategies exist for the construction of heteroatom rich complex compounds through the coupling of simple preoxidized molecules. Inherently, oxygenated functional groups often require oxidation state changes and protection/deprotection sequences both to install and be compatible with further manipulations on the molecule. Selective C−H oxidation of preassembled hydrocarbon frameworks represents an alternative strategy for the rapid assembly of complex oxygen[1,2] and nitrogen[1,3] rich structures at late stages of synthesis. When these reactions are predictably selective, mild, and incorporate the desired functionality without the need for further manipulation, unnecessary functional group manipulations (FGMs) can be bypassed, reducing synthetic steps and increasing overall yield.[4]

Complex Allylic Ester Synthesis. Esterification, one of the most important reactions in organic synthesis, involves coupling preoxidized carboxylic acid and alcohol fragments.[5] Significant "synthetic overhead" is required to install these oxidized moieties in the correct oxidation state. Moreover, coupling generally involves stoichiometric amounts of a condensation reagent or the generation of an activated, and often unstable, acid derivative. Although catalytic esterification methods exist, they suffer from limited scope and often require one coupling partner to be used in large excess.[5] A catalytic, general esterification method that oxidatively couples a hydrocarbon with a carboxylic acid would be a significant advance.

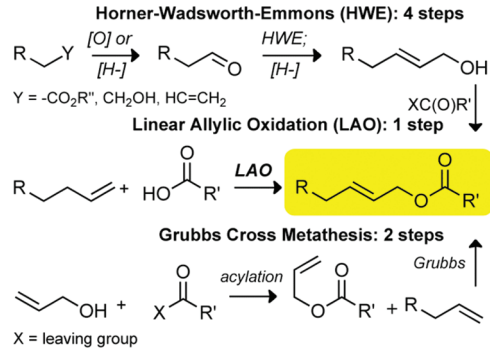

Figure 1. Common strategies for generating complex allylic esters.

Common approaches to linear (*E*)-allylic esters are shown in Figure 1. A Horner−Wadsworth−Emmons (HWE) or

(1) General C−H oxidation, aminations, alkylations: (a) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Espino, C. G.; DuBois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 379. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439, and references therein. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (f) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (g) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (h) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (i) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (k) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (l) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566. (m) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (n) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941.

(2) Pd-catalyzed allylic C−H oxidations: (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032. (d) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (e) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448. (f) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481. (g) Pilarski, L. T.; Selander, N.; Bose, D.; Szabo, K. J. *Org. Lett.* **2009**, *11*, 5518. (h) Lin, B.-L.; Labinger, J. A.; Bercaw, J. E. *Can. J. Chem.* **2009**, *87*, 264. (i) Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Le Bras, J.; Muzart, J. *J. Org. Chem.* **2010**, *75*, 1771. (j) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 824.

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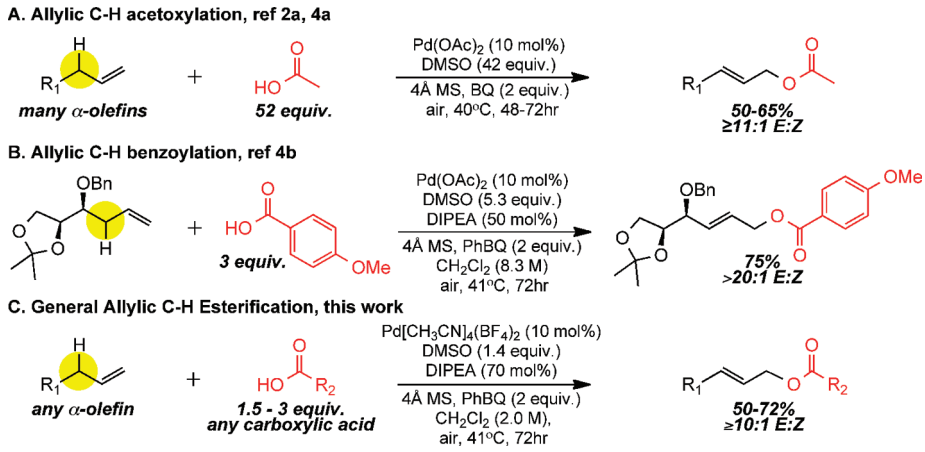


Figure 2. Progress toward a general allylic C−H esterification protocol.

stabilized Wittig olefination approach generally involves taking a preoxidized starting material through a four-step route: (1) aldehyde formation via oxidation [O] or reduction [H−], (2) olefination to form the α,β-unsaturated ester, (3) reduction to the allylic alcohol, and (4) acylation to obtain the target ester. If other functionality on the molecule is incompatible with this diverse set of conditions (i.e., oxidation, base, reduction), protecting group manipulations are also required. An alternative olefination strategy involves cross-metathesis of a terminal olefin with a preformed allylic ester.[6] Although highly efficient, challenges associated with this route are predictable control of olefin geometry and the requirement for an excess of one of the olefin coupling partners to achieve high yields. Additionally, as in the HWE route, esterification often requires extensive screening of stoichiometric reagents, many of which generate waste that is difficult to remove from the product. We anticipated that the direct, catalytic coupling of terminal olefins with carboxylic acids via a predictably selective C−H esterification reaction would streamline the synthesis of certain (*E*)-allylic esters by minimizing the need for oxygenated intermediates.

Allylic C−H Esterification. In 2004, we first described a DMSO-promoted, $Pd(OAc)_2$-catalyzed allylic C−H oxidation of α-olefins with solvent quantities of acetic acid (AcOH) to furnish linear (*E*)-allylic acetates with high regio- and stereoselectivities and outstanding functional group tolerance (Figure 2A).[2a] As synthetic intermediates acetates often serve as precursors to more complex esters via the intermediacy of alcohols. Ideally, any carboxylic acid could be directly incorporated into the hydrocarbon framework via C−H oxidation to furnish complex esters. Although this allylic C−H acetoxylation method has since been explored extensively by other researchers with respect to ligands, oxidants, and activators,[2f,h−j] no general linear allylic esterification method has emerged. In a preliminary study directed toward streamlining polyol synthesis, we developed specific conditions to couple *p*-anisic acid and a chiral homoallylic ether to directly furnish a hexose precursor (Figure 2B).[4b] Unfortunately, these conditions did not prove to be general (*vide infra*). In this article, we describe a general reaction manifold for the linear allylic C−H oxidation reaction (LAO) that enables coupling of a wide range of carboxylic acids and α-olefins to furnish complex linear (*E*)-allylic ester products (Figure 2C).

Results and Discussion

Design Principles. Our working mechanistic hypothesis for the $Pd(OAc)_2$/DMSO catalyzed LAO reaction suggests that a carboxylate counterion on the palladium is needed to effect C−H cleavage to form a π-allylPd intermediate and that high concentrations of DMSO and AcOH are optimal for effecting functionalization.[7] Within this original reaction manifold, challenges encountered in expanding the scope of the LAO to a general esterification method included (1) formation of allylic acetate byproduct from the $Pd(OAc)_2$ catalyst, (2) requirement for high equivalents of carboxylic acid, and (3) poor solubilities of many carboxylic acids in DMSO. Switching to a $Pd(CH_3CN)_4(BF_4)_2$ catalyst that can undergo counterion exchange with the carboxylic acids eliminated acetate byproduct. The introduction of *N*,*N*-diisopropylethylamine (DIPEA), believed to promote functionalization through deprotonation of the acid, enabled lowering the amount of carboxylic acid from solvent quantities to 1.5−3 equiv.[3,4b] Increasing the amount of DIPEA from 50 to 70 mol % and lowering the amount of DMSO to 1.4 equiv made possible using more CH_2Cl_2 as a solvent to improve the solubility of both the α-olefin and the carboxylic acid. Collectively, these changes significantly widened the range of complex allylic esters that could be generated via C−H oxidation.

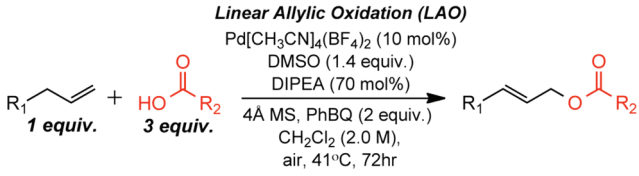
Reaction Scope. The expansive scope and streamlining potential of this methodology is represented in the construction of known allylic ester intermediates (Table 1). Oxidative coupling of unsaturated aryl acids and α-bromo-carboxylic acids with allyl arenes provides a direct and modular route to compounds **1**[8] and **2**[9] (entries 1−5), some of which have been shown to exhibit antibacterial and antifungal activities[8] (entry 1). It is notable that 1.5 equiv of acid can be used with only a moderate reduction in isolated yield (entry 2). This feature of the reaction is particularly significant when using complex carboxylic acids that require lengthy synthetic sequences to

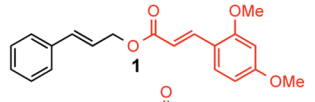
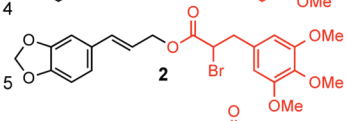
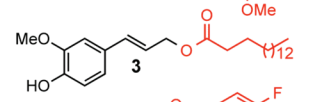
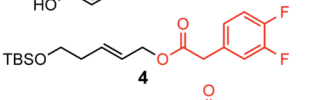
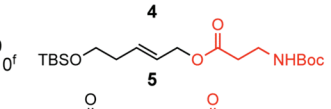
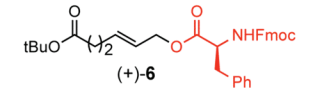
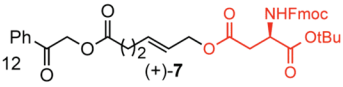
(4) Streamlining synthesis via late-stage C−H oxidation: (a) For first explicit demonstration of this concept, see: Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223. (b) Covell, D. J.; Vermeulen, N. A.; White, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 8217. (c) Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547. For excellent reviews, see: (d) Hoffman, R. W. *Synthesis* **2006**, *21*, 3531. (e) Hoffman, R. W. In *Elements of Synthesis Planning*; Springer: Heidelberg, 2009. For some elegant examples of late stage C−H hydroxylation and amination, see: (f) Wender, P. A.; Hilinski, M. K.; Mayweg, A. V. W. *Org. Lett.* **2005**, *7*, 79. (g) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (h) Reference 1e,1l.

(5) (a) Otera, J. *Esterification*; Wiley-VCH: Weinheim, 2003 and references therein. (b) Ishihara, K. *Tetrahedron* **2009**, *65*, 1085.

(6) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

Table 1. Linear Allylic Oxidation (LAO) for the Construction of Known Allylic Ester Intermediates



Entry		Isolated Yield[a]	*E:Z*[b]	L:B[b] (crude)	steps C-H	steps C-C
1	 **1**	70%	>20:1	>20:1	1	3
2		61%[c]	>20:1	>20:1		ref. 8
3		53%[d]	>20:1	>20:1		
4		65%[e]	>20:1	>20:1		
5	 **2**	68%	16:1	>20:1	2	5 ref. 9
6	 **3**	64%	>20:1	>20:1	1	3 ref. 10
7	 **4**	60%	11:1	6:1	2	4
8[f]		31%	10:1	9:1		ref. 11
9	 **5**	50%	11:1	9:1	2	4
10[f]		23%	7:1	11:1		ref. 12
11	 (+)-**6**	54%[c]	17:1[h]	>20:1[i]	2	2 ref. 14
12	 (+)-**7**	72%	18:1[h]	>20:1	2	4 ref. 15

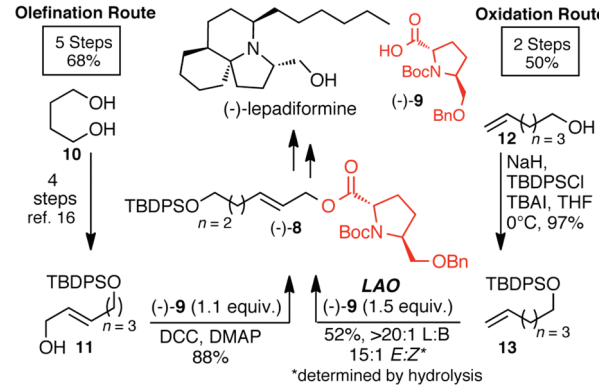
[a] Isolated yields of >20:1 L:B. Unless otherwise noted, *E*:Z does not change after purification. [b] Crude values of ^{1}H NMR. [c] 1.5 equiv of acid. [d] 24 h reaction time. [e] 5 mol % $Pd[CH_3CN]_4[BF_4]_2$. [f] Using previously published conditions, ref 4b. [g] THP protected version of this compound was made. [h] Determined after methanolysis and acetylation by ^{1}H NMR. [i] Determined by ^{1}H NMR of purified material.

prepare (*vide infra*). A decrease in the reaction time (72 h→24 h) and catalyst loadings (10 mol % →5 mol %) is possible while maintaining synthetically useful yields (entries 3 and 4, respectively). It is interesting to note that under these modified conditions even fatty acids, insoluble at high concentrations of DMSO, are useful functionalization reagents (entry 6).[10]

Bifunctional allylic esters **4**[11] and **5**[12] have been synthesized via *N*,*N*-dicyclohexyl carbodiimide/4-dimethylaminopyridine (DCC/DMAP) coupling of the respective carboxylic acids and monoprotected (*E*)-pent-2-en-1,5-diol (synthesized via a HWE route, Table 1, entries 7 and 9). Although DCC is one of the most widely used coupling reagents to form esters in organic synthesis, it is a potent skin irritant and generates byproducts (dicyclohexylurea) that are relatively insoluble and difficult to remove.[13] In contrast, direct, oxidative coupling of the same carboxylic acids with silyl-protected pentenol afforded **4** and **5** in good yields, half the number of steps, and without the use of any stoichiometric condensing reagents (entries 7 and 9). We have found that the reduced form of the quinone oxidant is easily removed via aqueous, basic extraction during the workup procedure (see Experimental Section). Significantly, reactions run under the previously reported conditions for benzoylation (Figure 2B) resulted in significantly lower yields (Table 1, entries 8 and 10).

Both α- and *β*-amino acids can be used as coupling partners in the oxidative esterification reaction without any epimerization. It is significant to note that *tert*-butyl ester (+)-**6** can be synthesized via a C−C bond-forming route with equal efficiency to the C−H oxidation route by alkylating symmetric dibromo-2-butene with the enolate of acetic acid *tert*-butyl ester (Table 1, entry 11).[14] However, when a more complex ester is required, for example, to afford orthogonally protected aspartate (+)-**7**,[15] the C−H esterification reaction enables a significant streamlining of the route (entry 12). It is notable that, in all cases examined, the *E:Z* selectivity of this C−H esterification reaction does not drop below 10:1.

Scheme 1. C−H Oxidation vs C−C Bond Forming Strategies for the Synthesis of Key Linear Allylic Ester Intermediate (−)-**8** in the Synthesis of (−)-Lepadiformine



Streamlining Synthesis. A series of case studies were undertaken to evaluate the strategic advantages of constructing complex allylic esters via C−H oxidation routes versus C−C bond-forming routes. A total synthesis of (−)-lepadiformine features an (*E*)-allylic ester intermediate (−)-**8** that undergoes diastereoselective amino acid enolate Claisen rearrangement followed by a ring closing metathesis to forge the complex

(7) Under a C−H cleavage reaction manifold, high linear regioselectivity may be rationalized by outer sphere functionalization at the least sterically hindered position of a cationic π-allylPd(DMSO)$_2$ intermediate. However, we cannot exclude the possibility of an alternative, albeit unprecedented, mechanism involving anti-Markovnikov oxy-palladation followed by regioselective *β*-hydride elimination.[2a] Significantly, when using catalytic amounts of a bidentate bis-sulfoxide ligand, high branched regioselectivity for ester formation is observed.[2a,b] Mechanistic studies suggest this regio-outcome arises from inner sphere functionalization from an electronically dissymmetric π-allylPd(BQ)-carboxylate species.[2b,c,4c]

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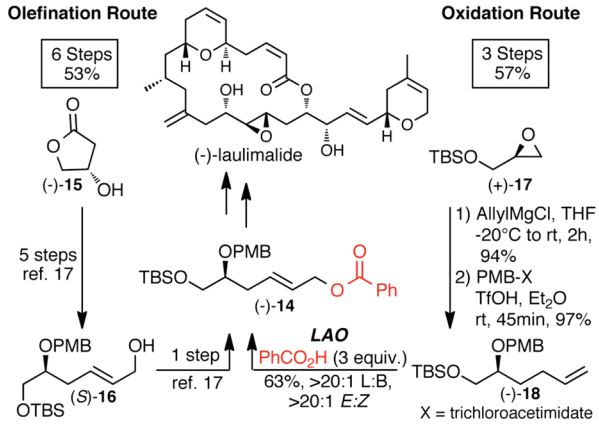
tricyclic backbone (Scheme 1).[16] Starting from a fully oxidized starting material **10** (1,4-butane-diol), allylic ester (−)-**8** was generated through a classic series of reactions: monoprotection, oxidation, HWE olefination, reduction, and DCC-mediated esterification with cyclic amino acid (−)-**9**. This route is reliable and generally high-yielding; however, it requires five steps, two of which are oxidation state manipulations. Direct installation of the (*E*)-allylic ester from the catalytic coupling of a terminal olefin and carboxylic acid affords a dramatic streamlining effect on this route. Using 1.5 equiv of the same cyclic amino acid (−)-**9**, oxidative C−H esterification of TBDPS-protected 5-hexen-1-ol **13** provided (−)-**8** in only two steps and 50% overall yield. The importance of using fragment coupling quantities of reagents is underscored here, as an eight-step sequence is required to synthesize carboxylic acid (−)-**9**.

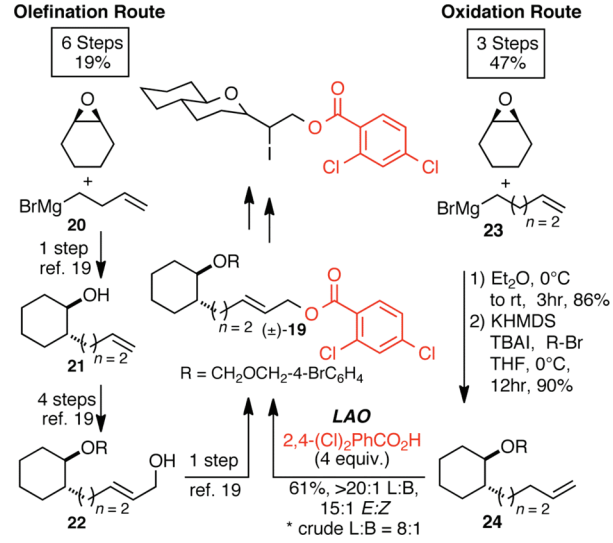
Scheme 2. C−H Oxidation vs C−C Bond Formation Routes in the Synthesis of Linear *E*-Allylic Ester Intermediate (−)-**14** en Route to (−)-Laulimalide



Synthetic routes for chiral molecules are often driven by practical considerations of availability of chiral starting material. In addition to providing more expedient routes to (*E*)-allylic esters, a C−H oxidation approach expands the options for using simpler chiral starting materials by minimizing total oxygenation. Chiral (*E*)-allylic ester (−)-**14**, an intermediate en route to (−)-laulimalide, was previously obtained from a highly oxygenated chiral pool material (*S*)-β-hydroxy-γ-butyrolactone (−)-**15**.[17] Manipulation of the preinstalled oxygen functionality to arrive at the desired structure required a six-step HWE route comprised of two protections, serial reductions, and esterification (Scheme 2). In contrast, C−H esterification is a simplifying transform that enables targeting less oxygenated intermediates. For example, precursors for LAO, optically enriched bis-homoallylic alcohols, can be directly accessed via allylation of chiral terminal epoxides that are now readily available via hydrolytic kinetic resolution (HKR) methodology.[18] Thus, an alternative approach to (−)-**14** starts with allylation and protection of commercially available *tert*-butyldimethylsilyl (*S*)-(+)-glycidyl ether to afford enantiomerically enriched bis-homoallylic ether (−)-**18** in just two steps. Benzoic acid was used as the coupling partner to afford the desired (*E*)-allylic ester (−)-**14** in half the number of steps (three steps) and comparable overall yield to the olefination route (Scheme 2).

While terminal olefins may also be used as intermediates in olefination sequences, FGMs are generally required. To illustrate this point, we compare a C−H oxidation strategy to an olefination strategy to allylic ester (±)-**19**, which serves as a precursor to trans-fused polycyclic ethers in brevetoxins (Scheme 3).[19] Both routes start with alkylation and protection of cyclohexene oxide to rapidly afford homologous terminal olefin intermediates **21** and **24**. The established HWE sequence to allylic alcohol **22** requires that the terminal olefin be oxidatively cleaved to afford the aldehyde precursor for olefination followed by reduction of the allylic ester to the desired oxidation state. The resulting (*E*)-allylic alcohol **22** was subsequently coupled to an acylchloride to form the desired (*E*)-allylic ester (±)-**19** in a total of six steps and 19% overall yield (Scheme 3). In the C−H esterification route, olefin **24** can be coupled directly to 2,4-dichlorobenzoic acid to furnish desired product (±)-**19** in a total of only three steps and 47% overall yield (Scheme 3).

Scheme 3. C−H Oxidation vs C−C Bond Forming Routes Proceeding via Analogous Terminal Olefin Intermediates



An olefination strategy that is analogous to a C−H oxidation strategy for the construction of (*E*)-allylic esters is cross metathesis. These C−C bond-forming routes are expedient because they also utilize terminal olefins and install the desired oxygen moiety directly without further manipulation (Figure 1). Challenges associated with this method center around the ability to control and predict the *E:Z* selectivity of the newly formed internal olefin. In contrast, linear C−H oxidation methodology under these mild conditions generates *E*-allylic oxygenates with selectivities that are 10:1 or higher. Both the olefination and C−H oxidation routes to macrocyclic lactam (+)-**25**, a peptidomimetic, began with alkylation of macrocyclic amide **26** to furnish homologous compounds **27** and **30** (Scheme 4).[20] Allylation of the amino acid Boc-L-phenylalanine via DIC-mediated esterification was required to furnish metathesis coupling partner (−)-**29**. Cross-metathesis coupling of allylated compounds **27** and (−)-**29** (2 equiv) provided phenylalanine derived macrocycle (+)-**25** in 28% overall yield with an *E:Z* selectivity of 1.2:1. Using a linear C−H esterification strategy, direct C−H esterification of **30** with 1.5 equiv of commercial Boc-L-phenylalanine (+)-**28** furnished (+)-**25** in 40% overall yield with an *E:Z* selectivity of 17:1 (Scheme 4).

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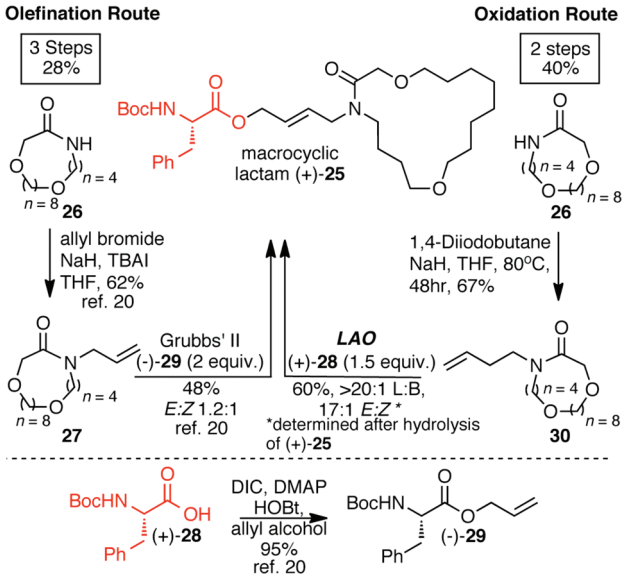
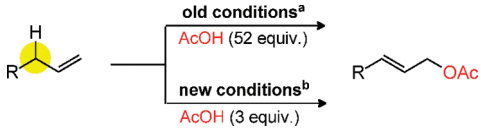
Scheme 4. C−H Oxidation vs Cross-Metathesis Route for the Formation of Complex Allylic Esters



Allylic C−H Acetoxylation Revisited. Although our previously reported allylic C−H acetoxylation reaction showed broad functional group tolerance, acid-sensitive substrates were not well tolerated under those conditions which employed solvent quantities of AcOH. We hypothesized that these new conditions employing only 1.5−3.0 equiv of carboxylic acid and 70 mol % base may further expand the scope of this powerful transformation (Table 2).

Table 2. Linear Allylic C−H Acetoxylation (LAO) with Acid Sensitive Substrates



Entry	Product	Conditions	Isolated Yield[c]	*E*:*Z*[d]	L:B (crude)[d]
1	BocTsN, 31, OAc	old	51%	8:1	12:1
2		new	75%	9:1	>20:1
3	32, OAc	old	50%[e]	>20:1	>20:1
4		new	64%	>20:1	>20:1
5	33, OAc, PMP	old	<5%	---	---
6		new	53%	12:1	12:1
7	TBSO, 34, OAc	old	17%	8:1	4:1
8		new	58%	12:1	8:1
9		old[f, g]	7%	5:1	3:1
10	TrO, 35, OAc	old	34%	8:1	4:1
11		new	68%	11:1	10:1

[a] $Pd(OAc)_2$ (10 mol %), DMSO/AcOH (1:1; 0.17 M), 4 Å MS, BQ (2 equiv), air, 41 °C, 72 h. [b] $Pd[CH_3CN]_4(BF_4)_2$ (10 mol %), DMSO/CH_2Cl_2 (1:5; 2.0 M), AcOH (3 equiv), 4 Å MS, PhBQ (2 equiv), air, 41 °C, 72 h. [c] Isolated yields of >20:1 L:B. Unless otherwise noted, *E*:Z does not change after purification. [d] Crude values by ^1H NMR. [e] Previously reported; see ref 4. [f] $Pd(OAc)_2$(10 mol %), DMSO (0.17 M), AcOH (3 equiv), 4 Å MS, BQ (2 equiv), air, 41 °C, 72 h. [g] When the reaction was run under the "old" conditions at 0.33 M DMSO, 3 equiv of AcOH, only trace reactivity was observed: 10% yield.

Terminal olefin substrates containing moderately acid-sensitive moieties such as primary *tert*-butyl *N*-tosyl carbamates and ketals showed improvements in yield (51% → 75%; 50% → 64%, respectively) with no erosion of selectivities under the new conditions (Table 2, entries 1 and 2). However, substrates containing highly acid-sensitive functionality, i.e. *p*-methoxybenzyl (PMB)-acetals, primary TBS ethers, and triphenylmethyl (Tr) ethers, all showed significant improvements in isolated yields (Table 2, entries 5−8, 10−11). Significantly, when AcOH loadings were reduced to 3 equiv under the original reaction conditions, only trace reactivity was observed (Table 2, entry 9).

Conclusion

In summary, this study introduces the first general, predictably selective C−H oxidation method for the direct synthesis of complex allylic esters. The ability to forge esters using a catalytic method that couples two highly stable compounds, carboxylic acids and terminal olefins, provides an attractive alternative to methods that use stoichiometric amounts of coupling reagents or require reactive, unstable intermediates. The milder conditions that employ low loadings of carboxylic acid and catalytic base also enable broadening the substrate scope of the allylic C−H acetoxylation reaction to include acid-sensitive moieties. Strategic as well as practical advantages emerge when comparing C−H oxidation versus C−C bond-forming routes for the synthesis of complex allylic esters. Introduction of oxygen functionality late in a sequence, without the need for further manipulation, provides a significant streamlining of the route by eliminating FGMs such as oxidation state changes, protection/deprotection sequences, and functional group transformations. Moreover, the ability to utilize simpler, less oxygenated intermediates expands the options with respect to chiral starting materials, often leading to more efficient routes. Based on the generality and predictable selectivity of this C−H oxidation method along with the strategic advantages it enables, we anticipate that it will find widespread use in complex molecule syntheses.

Experimental Procedures

A typical procedure for the Pd mediated oxidation of terminal olefins to linear *E*-allylic esters is described. To a 4 mL borosilicate vial was first added $Pd(CH_3CN)_4(BF_4)_2$ (44.4 mg, 0.1 mmol, 10 mol %) under an argon atmosphere. The following reagents were then added in one portion under an ambient atmosphere: phenyl benzoquinone (368 mg, 2.0 mmol, 2 equiv), carboxylic acid (3.0 mmol, 3.0 equiv), two 4 Å molecular beads (50 mg). Finally, DMSO (100 μL, 1.4 mmol, 1.4 equiv), CH_2Cl_2 (500 μL), and DIPEA (121.0 μL, 0.7 mmol, 0.7 equiv) were added sequentially via glass syringe followed by a Teflon stir bar. This solution was stirred at 41 °C for 5 min before starting material (1.0 mmol, 1.0 equiv) was added neat. The vial was then capped and stirred at 41 °C for 72 h. Upon completion as determined by NMR, the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL) [Note 1]. The solution was diluted with diethyl ether (50 mL) and washed with 5% K_2CO_3 (aq.) solution twice [Note 2]. The organic layer was dried with $MgSO_4$, filtered, and reduced *in vacuo*. Purification was achieved via flash silica gel chromatography. Notes: (1) The excess quinone may be reduced by addition of solid Na_2SO_3 (2 g) to a reaction mixture diluted with 50 mL of EtOAc and 50 mL of a 5% K_2CO_3 (aq.) solution. The resulting biphasic mixture is then stirred rapidly for 30 min before continuing with the extraction. (2) If an inseparable emulsion

forms, filter the solution through a pressed pad of Celite with 20−30 mL of diethyl ether.

Full experimental details and characterization data are given in the Supporting Information.

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Supporting Information Available: Experimental procedures, full characterization, and additional experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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