Title
Fragment Coupling with Tertiary Radicals Generated by Visible-Light Photocatalysis

Journal
Accounts of Chemical Research, 49(8)

ISSN
0001-4842

Authors
Jamison, Christopher R
Overman, Larry E

Publication Date
2016-08-16

DOI
10.1021/acs.accounts.6b00284

Peer reviewed

ACCOUNTS of chemical research

Article

pubs.acs.org/accounts

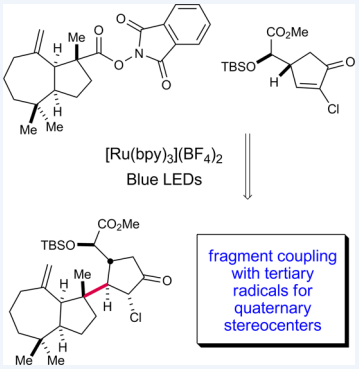
Fragment Coupling with Tertiary Radicals Generated by Visible-Light Photocatalysis

Published as part of the Accounts of Chemical Research special issue "Photoredox Catalysis in Organic Chemistry".

Christopher R. Jamison and Larry E. Overman*

Department of Chemistry, University of California, Irvine, California 92697-2025, United States

CONSPECTUS: Convergent synthesis strategies in which a target molecule is prepared by a branched approach wherein two or more complex fragments are combined at a late stage are almost always preferred over a linear approach in which the overall yield of the target molecule is eroded by the efficiency of each successive step in the sequence. As a result, bimolecular reactions that are able to combine complex fragments in good yield and, where important, with high stereocontrol are essential for implementing convergent synthetic strategies. Although intramolecular reactions of carbon radicals have long been exploited to assemble polycyclic ring systems, bimolecular coupling reactions of structurally complex carbon radicals have rarely been employed to combine elaborate fragments in the synthesis of structurally intricate molecules. We highlight in this Account recent discoveries from our laboratories that demonstrate that bimolecular reactions of structurally elaborate tertiary carbon radicals and electron-deficient alkenes can unite complex fragments in high yield using nearly equimolar amounts of the two coupling partners.



Our discussion begins by considering several aspects of the bimolecular addition of tertiary carbon radicals to electron-deficient alkenes that commend these transformations for the union of structurally complex, sterically bulky fragments. We then discuss how in the context of synthesizing rearranged spongian diterpenoids we became aware of the exceptional utility of coupling reactions of alkenes and tertiary carbon radicals to unite structurally complex synthetic intermediates. Our initial investigations exploit the early report of Okada that *N*-(acyloxy)phthalimides reductively fragment at room temperature in the presence of visible light and catalytic amounts of the photocatalyst $Ru(bpy)_3Cl_2$ to form carbon radicals that react with alkenes. We show that this reaction of a tertiary radical precursor and an enone can combine two elaborate enantioenriched fragments in good yield with the formation of new quaternary and secondary stereocenters. As a result of the ready availability of tertiary alcohols, we describe two methods that were developed, one in collaboration with the MacMillan group, to generate tertiary radicals from tertiary alcohols. In the method that will be preferred in most instances, the tertiary alcohol is esterified in high yield to give a *tert*-alkyl hemioxalate salt, which—without purification—reacts with electron-deficient alkenes in the presence of visible light and an Ir(III) photocatalyst to give coupled products having a newly formed quaternary carbon in high yield. Hemioxalate salts containing Li, Na, K, and Cs countercations can be employed in this reaction, whose only other product is CO_2. These reactions are carried out using nearly equimolar amounts of the addends, making them ideal for coupling of complex fragments at the late stage in a synthetic sequence. The attractive attributes of the fragment-coupling chemistry that we discuss in this Account are illustrated by an enantioselective total synthesis of a tricyclic *trans*-clerodane diterpenoid in eight steps and 34% overall yield from commercially available precursors. We anticipate that bimolecular reactions of carbon radicals will be increasingly used for fragment coupling in the future.

1. INTRODUCTION

Convergent synthesis strategies are fundamental to the efficient preparation of complex organic molecules. However, the challenge of uniting polyfunctionalized fragments generally limits such strategies to the use of a few privileged reactions that are robust, chemoselective, and high-yielding. The venerable Diels–Alder reaction and recently developed metal-catalyzed transformations such as transition metal (Pd, Ni, Fe, etc.)-catalyzed cross couplings, Nozaki–Hiyama–Kishi coupling, and olefin metathesis are arguably the most important of these existing methods.[1]

Especially demanding are fragment couplings that form sp^3–sp^3 σ bonds and two stereocenters, particularly when the two stereocenters reside in different rings. When at least one of these stereocenters is quaternary, the challenge is enhanced substantially.[1e] Molecules such as azadirachtin (**1**),[2] ditryptophenaline (**2**),[3] tyrinnal (**3**),[4] aplyviolene (**4**),[5] and dendrillolide A (**5**)[5] illustrate this challenge; the critical bond linking the fragments in each of these molecules is highlighted in bold red font in Figure 1. The hurdles that had to be surmounted to

Received: June 8, 2016
Published: August 4, 2016

DOI: 10.1021/acs.accounts.6b00284
Acc. Chem. Res. 2016, 49, 1578–1586

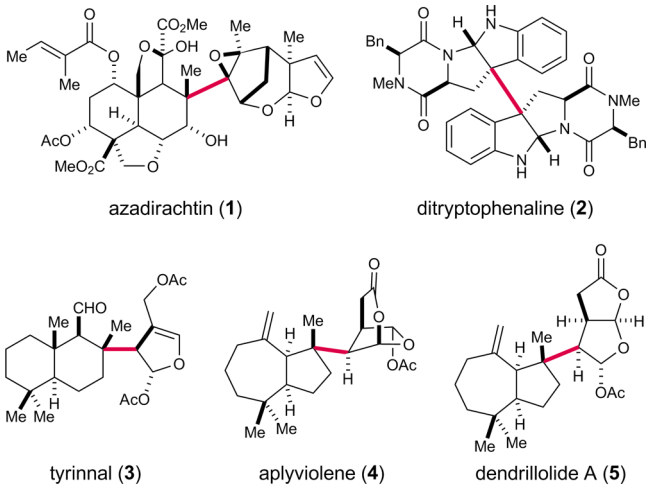


Figure 1. Natural products with ring systems joined via stereogenic carbons. The red bonds highlight ideal disconnections for convergent synthesis by intermolecular fragment coupling.

fashion this sterically hindered bond in the synthesis of azadirachtin are legendary.[2] The final solution, forming this bond by an intramolecular reaction (in this case a sigmatropic rearrangement), is the standard method to surmount this challenge.[6] Much less common is the use of a bimolecular reaction to join two complex fragments and form two new stereocenters, at least one of which is quaternary.[7,8]

Reactions between nucleophilic carbon radicals and electron-deficient alkenes have several attractive features for use in coupling of complex fragments, and in particular, tertiary carbon radicals are especially well-suited for forming quaternary stereocenters by uniting complex fragments through sp^3–sp^3 σ bonds.[9−11] Foremost, the transition state for addition of a nucleophilic carbon radical to a π bond is relatively early with an attendant long forming bond (~2.5 Å),[12] which reduces the enthalpic penalty incurred from steric interactions as bulky fragments approach one another (Figure 2).[13] Furthermore, the

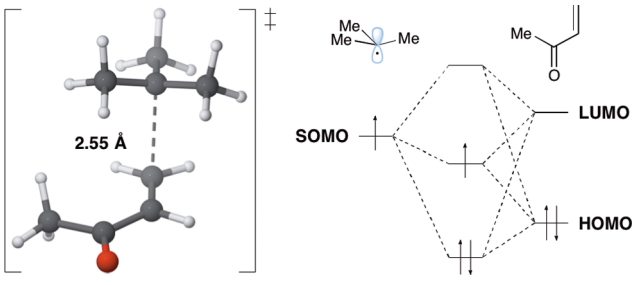


Figure 2. Depiction of the calculated long forming bond in the transition state for the addition of a nucleophilic tertiary carbon radical (*tert*-butyl radical) to the π bond of an electron-deficient alkene (methyl vinyl ketone)[13] and a frontier molecular orbital analysis of the reaction of a nucleophilic carbon radical and methyl vinyl ketone.

rates of addition of tertiary radicals to electron-deficient alkenes are higher than those of Me, primary, and secondary radicals (*t*-Bu· and $EtMe_2C$· ~10 × Me·, Ad· ~1000 × Me·; the nonplanar Ad· is not representative of typical tertiary radicals).[14−16] Moreover, stereoselection in the addition of tertiary radicals to prochiral alkenes is typically higher than that for reactions of Me, primary, or secondary radicals.[15,17] The stereoselective nature of these reactions seems somewhat paradoxical given the aforementioned long (~2.5 Å) forming bond in the transition state. Such a long bond might be expected to correlate to a "loose" transition state, wherein existing stereocenters from the substrates are too remote from one another to exert significant influence over the stereochemical course of the reaction. Nevertheless, tertiary radicals are indeed large enough to impose significantly differentiated amounts of steric strain in diastereotopic transition states, leading to reliable stereochemical outcomes.

Despite the aforementioned appealing features, which were well-appreciated by the leading researchers in the field of radical reactions in the 1980s,[15,18] bimolecular radical reactions are typically not used to unite complex fragments in the context of convergent total synthesis. In fact, no examples of the stereoselective formation of quaternary carbon stereocenters by intermolecular additions of prochiral trialkyl tertiary carbon radicals to alkenes are mentioned in a comprehensive survey published in 2005.[19] Furthermore, inspection of the literature revealed a short list of syntheses[20] in which bimolecular addition of a carbon radical to an alkene is used to unite complex fragments, and only a single, recent example from the list involved uniting fragments to generate a quaternary stereocenter.[20f] Common to almost all of the previously published total syntheses utilizing such intermolecular radical couplings was the use of one of the coupling components in large excess (commonly 3−10-fold). We surmised that this use of multiple equivalents of one coupling partner was a major impediment to the widespread adoption of convergent radical fragment coupling strategies, as it is simply unfeasible in most cases to waste an advanced intermediate by using it in excess.

The side reactions and the attendant low yields often associated with bimolecular radical reactions of delicate, highly functionalized molecules often are the result of the unattractive conditions used for radical generation (e.g., high reaction temperatures, stoichiometric tin reagent, or high-energy light). The use of visible-light photoredox catalysis as a means of generating and processing radicals under mild conditions seemed to offer a solution to this problem.[21] Furthermore, visible-light photoredox reactions are compatible with most polar functional groups that typically decorate structurally intricate molecules. These attractive features of visible-light photoredox catalysis would ultimately enable our development of new methods to stereoselectively unite complex fragments in 1:1 stoichiometry concomitantly with the formation of a new quaternary stereocenter.

2. HOW WE BECAME INVOLVED—THE SPONGIAN DITERPENOIDS MACFARLANDIN E AND APLYVIOLENE

In 2010, we and our UC Irvine cell biology collaborator, Professor Christine Sütterlin, reported that the rearranged spongian diterpenoid macfarlandin E (**6**) induced a novel morphological change in Golgi structure in which Golgi stacks were fragmented irreversibly and the resulting Golgi fragments remained localized in the pericentriolar region of the cell.[22] After identifying that the 2,7-dioxabicyclo[3.2.1]octan-3-one fragment of macfarlandin E (depicted in blue for **6** in Figure 3) was responsible for eliciting this unique phenotype,[23] we turned to pursue the total synthesis of aplyviolene (**4**), a potential progenitor of **6**.

The central challenge in a convergent synthesis of aplyviolene would be linking the two chiral bicyclic fragments. After first verifying an approach that paralleled our earlier total

DOI: 10.1021/acs.accounts.6b00284
Acc. Chem. Res. 2016, 49, 1578−1586

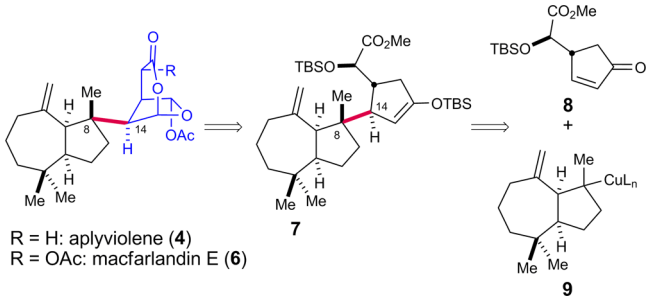
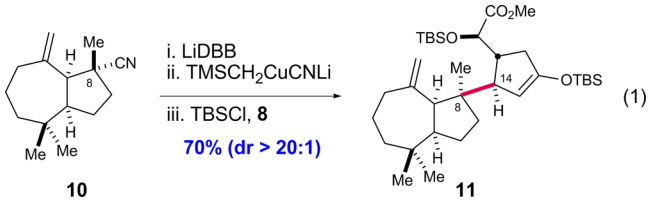


Figure 3. Plan to prepare aplyviolene by the convergent coupling of a tertiary cuprate with a cyclopentenone.

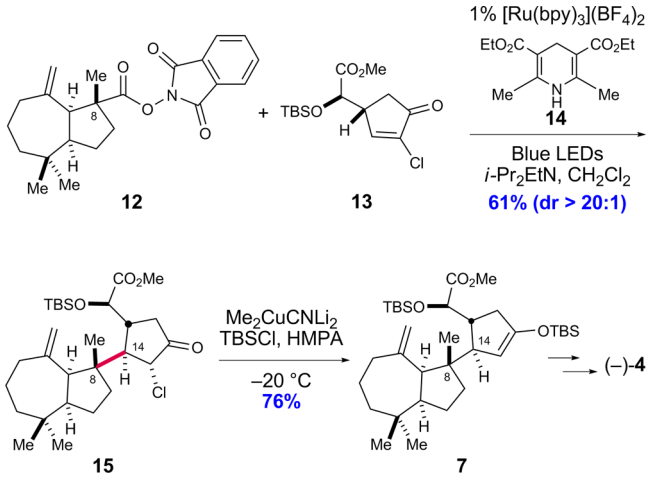
synthesis of a structurally simpler rearranged spongian diterpenoid, shahamin K,[24] we turned to the more attractive strategy depicted in Figure 3, in which the fragments would be joined and the C-8 quaternary stereocenter constructed by the reaction of tertiary organocuprate **9** and cyclopentenone **8**. We anticipated that this union would correctly set the configuration of the C-8 and C-14 stereocenters of aplyviolene, as we expected the reaction to proceed from the sterically less hindered faces of nucleophile **9** and enone **8**.[24] In the event, the coupling of a tertiary cuprate intermediate (generated by reductive lithiation and transmetalation of tertiary nitrile precursor **10**) with cyclopentenone **8** took place in good yield (eq 1). However, to our surprise, the coupling proceeded



from the sterically more hindered concave face of the cuprate intermediate to form adduct **11** having the undesired configuration of the C-8 quaternary stereocenter.[25] Upon further investigation we found that the tertiary organolithium intermediate also reacted with electrophiles preferentially from the concave face, and computational studies revealed that the epimer with lithium on the concave face is thermodynamically more stable.[25] Although full mechanistic details of the reaction depicted in eq 1 are not yet in hand, it was clear at the time that the metal must play the decisive role in orchestrating the unexpected stereochemical outcome. In retrospect, the undesired outcome of the cuprate coupling was most fortunate, as it directed us to employ a nucleophilic tertiary carbon radical in a related coupling reaction as a way to avoid the metal.

We chose to employ a carboxylic acid derivative as the radical precursor because the carboxylic acid was available from nitrile **10**. In considering what acid derivative to use, we were attracted to Okada's 1991 report that *N*-(acyloxy)phthalimides, when exposed to visible light, a catalytic amount of $[Ru(bpy)_3]Cl_2$, and the hydrogen donor 1-benzyl-1,4-dihydronicotinamide, fragment to form carbon radicals that can be captured by α,β-unsaturated ketones to produce coupled products in good yield.[26] It was remarkable that the use of *N*-(acyloxy)-phthalimides as radical precursors in conjugate addition reactions had not been described since this initial disclosure and that this method of radical formation had rarely been employed in any context. Nonetheless, we anticipated that a particular advantage of using an oxyphthalimide ester as the radical precursor, in contrast to a Barton thiohydroxamic ester,[27] would be the stability and potential crystallinity of the *N*-(acyloxy)phthalimide precursor. To allow the coupled product to be transformed regioselectively to an enoxysilane intermediate, chlorocyclopentenone **13** was chosen as the coupling partner (Scheme 1). When crystalline ester **12** was

Scheme 1. Fragment Coupling Using a Tertiary Carbon Radical Generated by Visible-Light Photoredox Catalysis en Route to (−)-Aplyviolene



coupled with 1.5 equiv of enone **13** using the slight modification of Okada's conditions depicted in Scheme 1, adduct **15** was formed in 61% yield, with bond formation occurring exclusively [diastereomer ratio (dr) > 20:1] from the expected less hindered face of the intermediate *cis*-perhydroazulene tertiary radical.[28] As the major byproduct in this reaction was the dechloro analogue of adduct **15**, undoubtedly produced by photoredox-catalyzed reduction of **15**,[29] the yield for forging the congested σ bond linking the quaternary C-8 and tertiary C-14 stereocenters was nearly 80%. With this notable result in hand, we turned to an in-depth exploration of the utility of fragment coupling reactions of tertiary carbon radicals. In particular, we sought to ascertain whether such reactions in general could be accomplished using nearly equimolar amounts of the addends, which would be essential if structurally elaborate fragments were to be united in this way.

3. FURTHER EXPLORATIONS OF FRAGMENT COUPLING OF TRIALKYL TERTIARY RADICALS GENERATED USING VISIBLE-LIGHT PHOTOREDOX CATALYSIS

Our initial studies focused on extending this method to the synthesis of additional spongian diterpene natural products. Figure 4 shows three spongian diterpenoids wherein a *cis*-dioxabicyclo[3.3.0]octanone unit is joined by an sp^3–sp^3 σ bond to a polycyclic hydrocarbon fragment. The coupling of an enantioenriched tertiary radical and an enantioenriched 4-alkoxybutenolide could offer a concise approach to diterpenoids of this type (Figure 4). Although an *N*-(acyloxy)phthalimide ester could serve as the radical precursor, tertiary alcohols appeared to be more attractive because they are easily prepared by robust chemistry.

There are many methods for the conversion of alcohols into activated intermediates for radical generation.[30] However, radical formation from tertiary alcohols is particularly

DOI: 10.1021/acs.accounts.6b00284
Acc. Chem. Res. 2016, 49, 1578−1586

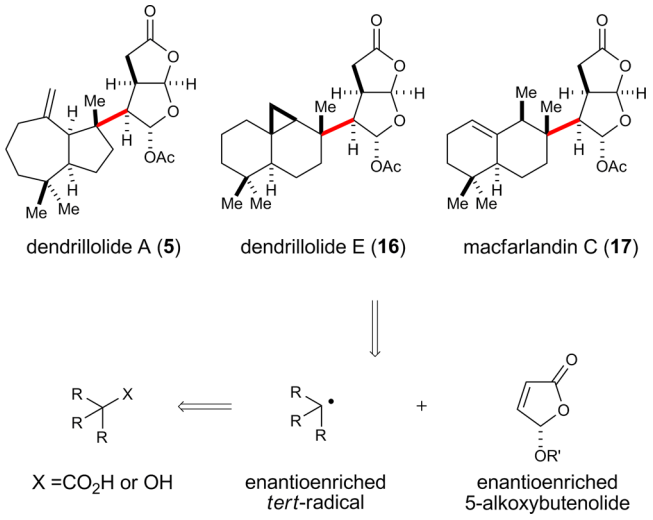


Figure 4. Spongian diterpenoid natural products with potential convergent disconnections suited for the development of visible-light photoredox radical coupling.

challenging because the activated derivatives are far less stable than those derived from primary or secondary alcohols. The previously best-known method for activating tertiary alcohols for radical generation is the use of Barton oxalates **18** (Figure 5).[31,32] However, these intermediates are highly sensitive and

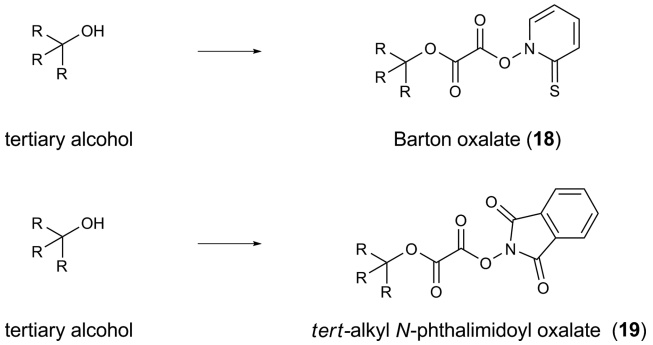
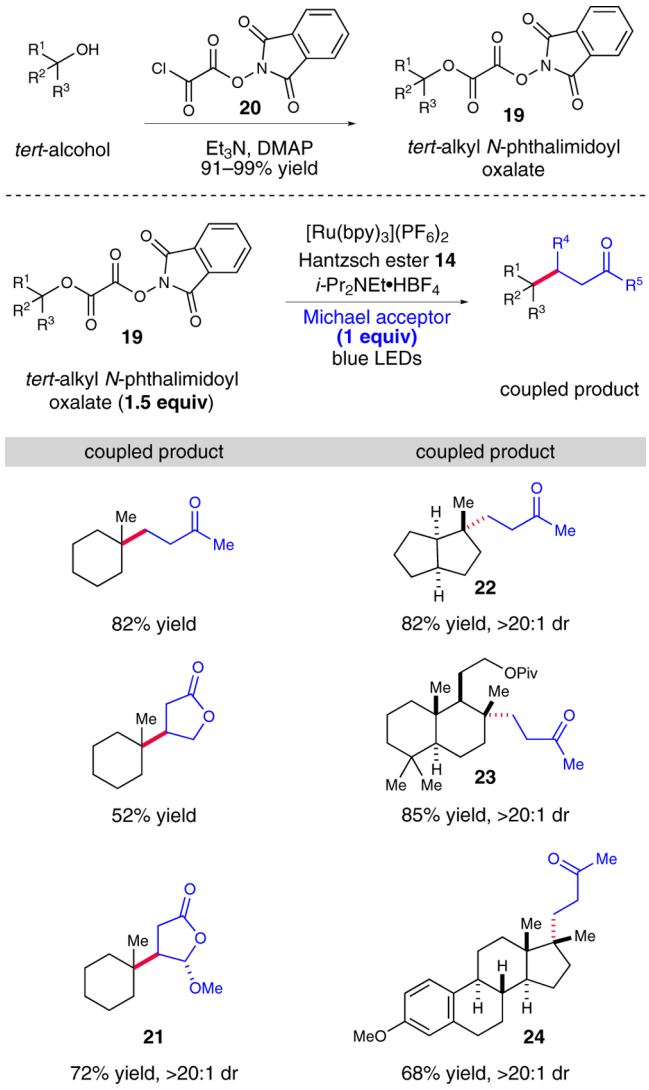


Figure 5. Barton oxalates and *tert*-alkyl *N*-phthalimidoyl oxalates as radical precursors derived from tertiary alcohols.

thus are generally prepared and coupled in situ without isolation. The instability of Barton oxalates is not problematic for simple substrates, and this method has been utilized by Barton for generation of quaternary carbons.[31] However, in the context of multistep total synthesis applications, the inability to purify and characterize structurally complex activated alcohols can be problematic. This instability is likely the reason that the Barton oxalate method has not been utilized in complex molecule synthesis. We hypothesized that the use of *tert*-alkyl *N*-phthalimidoyl oxalates **19** (Figure 5) in lieu of Barton oxalates **18** would offer a stability advantage to enable the functionalization of complex tertiary alcohols. Furthermore, incorporation of the reductively labile *N*-phthalimidoyloxy functionality would allow the visible-light photoredox reaction conditions introduced by Okada to be employed.

As shown in Table 1, *tert*-alkyl *N*-phthalimidoyl oxalates **19**, which are readily generated from the acylation of tertiary alcohols, do indeed function as effective radical precursors under visible-light photoredox conditions.[33,34] In this method, tertiary alcohols are condensed with *N*-phthalimidoyl chlorooxoacetate (**20**) at room temperature under mildly basic conditions to generate the activated intermediates **19** in excellent yield. These *tert*-alkyl *N*-phthalimidoyl oxalates are isolable by filtration, are typically solids, and are not light-sensitive; however, they are unstable toward silica gel chromatography and aqueous workup. Irradiation of a slight excess of *tert*-alkyl *N*-phthalimidoyl oxalates **19** (1.5 equiv) with visible light from a blue light-emitting diode (LED) as the light source in the presence of catalytic $[Ru(bpy)_3](PF_6)_2$, Hantzsch ester **14** (1.5 equiv), and a Michael acceptor (1 equiv) results in efficient coupling of the tertiary radical to the alkene with concomitant formation of a quaternary stereocenter. As expected, good levels of diastereocontrol were observed in the assembly of complex substrates bearing additional stereocenters (**21**–**24**) when the diastereotopic faces of the radical carbon differ substantially in steric access. The good yield in forming estrone analogue **24** in this way is particularly notable, as synthetically demanding contiguous quaternary stereocenters are produced.[35] The efficient formation of coupled product **21**, derived from the reaction with 5-methoxybutenolide as an

Table 1. Selected Examples of the Preparation of *tert*-Alkyl *N*-Phthalimidoyl Oxalates from Complex Tertiary Alcohols and Their Subsequent Reaction with Michael Acceptors under Visible-Light Photoredox Conditions



DOI: 10.1021/acs.accounts.6b00284
Acc. Chem. Res. 2016, 49, 1578−1586

acceptor, suggested that the *tert*-alkyl *N*-phthalimidoyl oxalate method could potentially be utilized to prepare spongian diterpenoids such as dendrillolide A (**5**), dendrillolide E (**16**), and macfarlandin C (**17**) (Figure 4).

Although the *tert*-alkyl *N*-phthalimidoyl oxalates proved to be useful for generating radicals from tertiary alcohols, we were interested in pursuing additional activation strategies. This aim stemmed from a desire to identify a more stable and easily handled radical precursor and avoid the formation of stoichiometric amounts of phthalimide and a pyridine (the oxidation product of Hantzsch ester **14**) as byproducts. Shortly after the disclosure of our results with *tert*-alkyl *N*-phthalimidoyl oxalates **19** (eq 2), a publication from the MacMillan lab attracted our attention (Figure 6).[36] As shown in

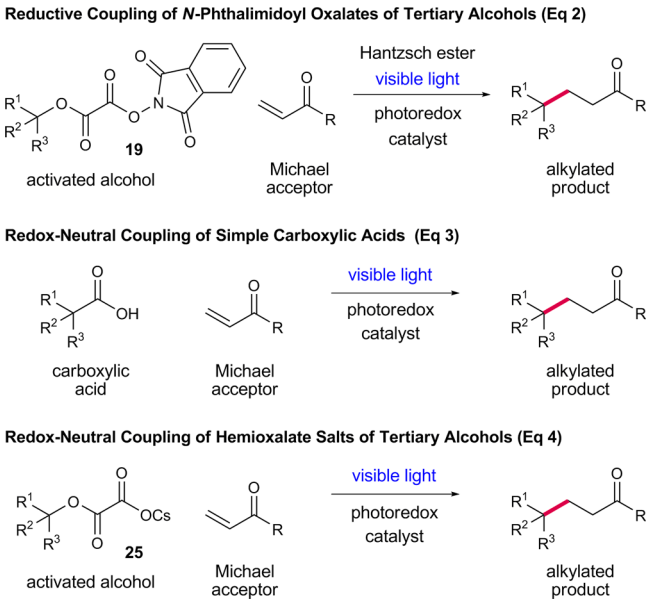
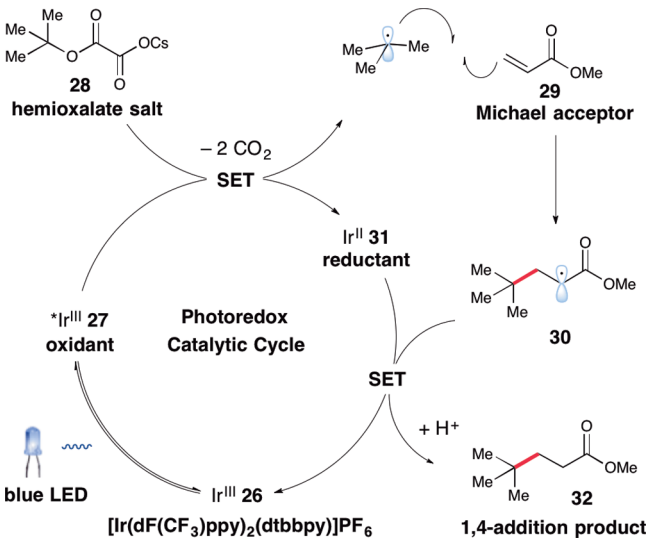


Figure 6. *tert*-Alkyl hemioxalate salts as radical precursors.

eq 3, MacMillan and co-workers reported visible-light photoredox conditions for the radical-based decarboxylative coupling of carboxylic acids and Michael acceptors. Notably, this reaction both utilized a bench-stable carboxylic acid as a radical precursor and accomplished the desired coupling without any added stoichiometric oxidants or reductants. This report led us to a collaboration with the MacMillan lab wherein we developed a hybrid method to utilize simple and stable *tert*-alkyl hemioxalate salts **25** as radical precursors in a net redox-neutral fashion (eq 4).[37]

The proposed mechanism of the coupling reaction is shown in Scheme 2. Irradiation of the heteroleptic photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**26**) [$dF(CF_3)ppy$ = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine] with visible light leads to the formation of a long-lived (τ = 2.3 μs) excited state, $^*Ir^{III}$ (**27**), which is a strong oxidant ($E^{red}_{1/2}[^*Ir^{III}/Ir^{II}]$ = +1.21 V vs SCE in MeCN).[38] Oxidation of *tert*-alkyl hemioxalate salt **28** ($E^{red}_{1/2}$ = +1.28 V vs SCE in MeCN for *t*-BuOCOCO$_2$Cs)[37] by $^*Ir^{III}$ via single-electron transfer (SET) is thermodynamically feasible. After oxidation, stepwise loss of two molecules of CO_2 results in the formation of a tertiary alkyl radical. This nucleophilic carbon-centered radical reacts with an electron-deficient alkene such as methyl acrylate (**29**). Finally, we expected that reduction of the resulting adduct radical **30** ($E^{red}_{1/2}$

Scheme 2. Proposed Mechanism for Radical Coupling of *tert*-Alkyl Hemioxalate Salts with Michael Acceptors



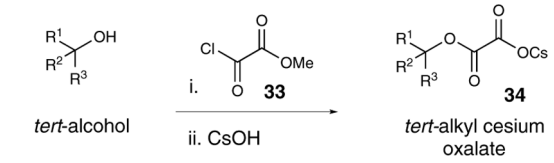
= −0.59 to −0.73 V vs SCE in MeCN)[37] by SET from the available Ir^{II} species **31** ($E^{red}_{1/2}[Ir^{III}/Ir^{II}]$ = −1.37 V vs SCE in MeCN)[38] should lead to the coupled product **32** and regenerate the ground-state photocatalyst **26**.

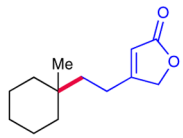
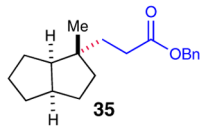
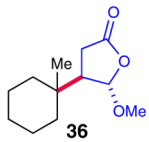
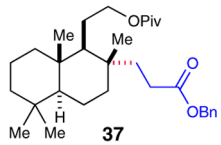
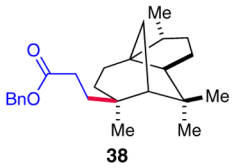
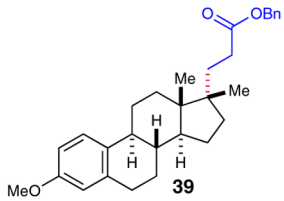
As shown in Table 2, *tert*-alkyl hemioxalate salts are effective radical precursors under visible-light photoredox conditions.[37] Tertiary alcohols react with methyl chlorooxoacetate (**33**) at room temperature under mildly basic conditions to generate the mixed methyl *tert*-alkyl oxalates, which are stable toward aqueous workup with either mild acid or mild base and are also stable toward silica gel chromatography. Typically, these intermediates were isolated and then hydrolyzed with 1 equiv of aqueous base in a subsequent step. However, acylation and hydrolysis could also be performed in a one-pot operation without diminished yield or purity to furnish the hemioxalate salt (e.g., **34**) directly from a tertiary alcohol. *tert*-Alkyl hemioxalic acids also functioned as effective radical precursors in the presence of weak inorganic bases but upon storage were prone to disproportionation into di-*tert*-alkyl oxalates and oxalic acid and thus were not ideal radical precursors. *tert*-Alkyl hemioxalate salts **34** based on lithium, sodium, potassium, and cesium all gave similar results, however, cesium oxalates were chosen for development under the assumption that they were likely to have favorable physical properties over a wide range of substrates.

Irradiation of a slight excess of *tert*-alkyl hemioxalate salts **34** (1.1 equiv) with a blue LED light source in the presence of catalytic **26** (1 mol %) and a Michael acceptor (1 equiv) results in efficient coupling of the tertiary radical to the alkene with concomitant formation of a quaternary stereocenter. As expected, good levels of diastereocontrol were observed for complex substrates bearing additional stereocenters (**35**−**39**). Coupled product **38** was prepared from the commercial tertiary alcohol cedrol via the corresponding lithium *tert*-alkyl hemioxalate, which was found to give slightly superior yields in this case. Notably, as was observed for *tert*-alkyl *N*-phthalimidoyl oxalates **19**, cesium *tert*-alkyl hemioxalates couple efficiently with 5-methoxybutenolide to generate coupled products such as **36**, which suggests potential application to the preparation of spongian diterpenoids (Figure 4). The ease of preparing and handling of *tert*-alkyl hemioxalate salts, the redox-neutral nature

DOI: 10.1021/acs.accounts.6b00284
Acc. Chem. Res. 2016, 49, 1578−1586

Table 2. Selected Examples of the Preparation of *tert*-Alkyl Hemioxalate Salts from Complex Tertiary Alcohols and Their Subsequent Reaction with Michael Acceptors under Net Redox-Neutral Visible-Light Photoredox Conditions



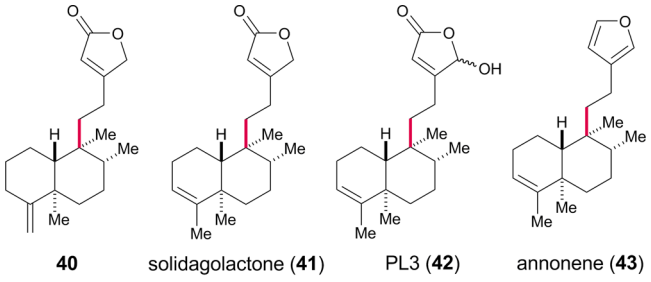
coupled product	coupled product
 89% yield	 35 85% yield, >20:1 dr
 36 73% yield, >20:1 dr	 37 96% yield, >20:1 dr
 38 79% yield, >20:1 dr	 39 85% yield, >20:1 dr

of their addition to electron-deficient alkenes, and the nearly 1:1 stoichiometry of the coupling partners make this the current state-of-the-art method for the synthesis of quaternary stereocenters from tertiary alcohols.

4. APPLICATION TO THE CONCISE ENANTIOSELECTIVE TOTAL SYNTHESIS OF *trans*-CLERODANE DITERPENOIDS

The clerodanes are a family of more than 650 diterpenoid natural products that have been isolated from various plant sources.[39] The *trans*-clerodane subset of these secondary metabolites are exemplified by the structures shown in Figure 7. As with the spongian diterpenes, this family of compounds is ideally disconnected by a fragment coupling strategy to form an sp^3-sp^3 σ bond at a quaternary stereocenter.

The visible-light photoredox-catalyzed coupling reaction of *tert*-alkyl hemioxalate salts and electron-deficient alkenes enabled an eight-step enantioselective total synthesis of *trans*-clerodane **40**, which is also a convenient precursor of diterpenoids **41**–**43** (Scheme 3).[40] Ketone **44** was available in four steps with 84% ee by a general route reported earlier by



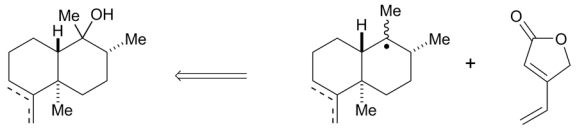
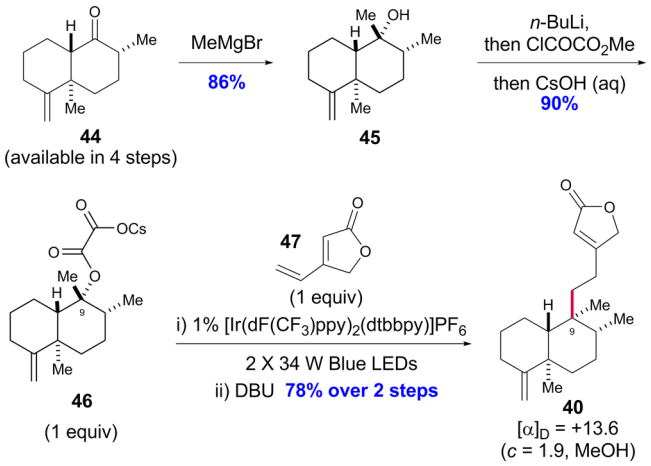


Figure 7. Representative *trans*-clerodane natural products and a convergent strategy for their synthesis. The red bonds highlight ideal disconnections for convergent synthesis.

Scheme 3. Eight-Step Enantioselective Total Synthesis of *trans*-Clerodane 40

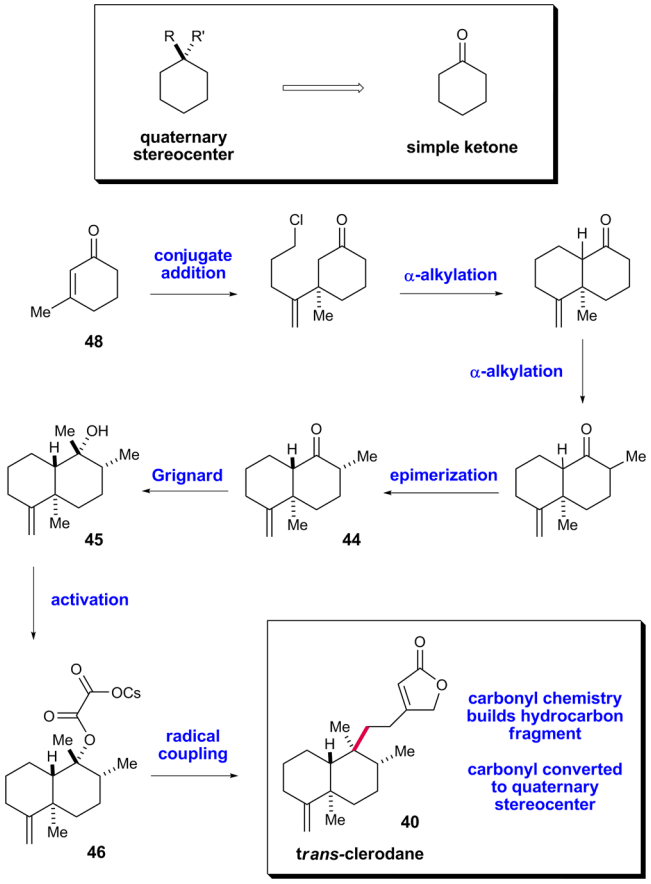


Piers for preparing the racemate,[41] using a catalytic enantioselective copper-catalyzed conjugate addition to construct its quaternary carbon stereocenter.[42] Methylation of **44** provided alcohol **45** in 86% yield as a single epimer. Earlier attempts to activate tertiary alcohol **45** as a *tert*-alkyl *N*-phthalimidoyl oxalate (e.g., **19**) were thwarted by the highly hindered nature of this axial alcohol and the instability of the derived activated ester. In marked contrast, activation of tertiary alcohol **45** by a one-pot acylation/saponification sequence readily furnished *tert*-alkyl hemioxalate salt **46** in 90% yield. The visible-light photoredox-catalyzed coupling of *trans*-decalin cesium hemioxalate **46** and vinylbutenolide **47** was carried out using equimolar amounts of the two coupling partners and yielded adduct **40** as a mixture of α,β- and β,γ-unsaturated isomers. Both double-bond regioisomers of the product had the desired configuration at the newly formed C-9 quaternary carbon stereocenter, and no trace of possible epimeric minor diastereomers was observed by NMR analysis of the crude material. Exposure of this crude product mixture to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature furnished *trans*-clerodane **40** {$[\alpha]_D$ +12.9 (c = 0.43, $CHCl_3$) and +13.6 (c = 1.9, MeOH)} in 78% yield.

DOI: 10.1021/acs.accounts.6b00284
Acc. Chem. Res. 2016, 49, 1578−1586

It is interesting to note that chemistry of the carbonyl group harbored in the original starting material, 3-methyl-2-cyclohexenone (**48**), is utilized in essentially every step of the *trans*-clerodane synthesis. As shown in Scheme 4, the carbonyl group

Scheme 4. Utility of Disconnecting Quaternary Stereocenters to Carbonyls via the Intermediacy of Activated Tertiary Alcohols



is utilized to form carbon−carbon bonds in an initial conjugate addition step and then two sequential α-alkylation reactions. Epimerization under thermodynamic control then sets two stereocenters before yet another carbon−carbon bond is formed by a Grignard reaction. The resultant tertiary alcohol **45** derived from the carbonyl is then activated and coupled with the vinylbutenolide to forge the final carbon−carbon bond and set a quaternary stereocenter. This sequence underscores the usefulness of disconnecting quaternary stereocenters to ketones through the intermediacy of tertiary alcohols. In this example, such a synthetic maneuver allowed us to efficiently build a stereochemically complex hydrocarbon fragment that bears no useful or obvious native functional handles for its synthesis simply by using robust and reliable carbonyl-based transformations before finally converting the carbonyl group to a quaternary stereocenter in a streamlined fashion. This strategy is potentially generalizable to a wide number of quaternary-stereocenter-containing natural products and druglike molecules, and we therefore believe that this method will find broader application within the synthetic community.

5. CONCLUSION AND OUTLOOK

Reactions that allow complex molecular fragments to be combined in high yield occupy an exalted position in organic synthesis because they are fundamental to convergent synthesis strategies. Highlighted in this Account are recent discoveries from our laboratories showing that bimolecular reactions of structurally elaborate tertiary carbon radicals and electron-deficient alkenes can unite complex fragments by forming a new sp^3-sp^3 σ bond in good yield using nearly equimolar amounts of the two coupling partners. Reflecting the large steric bulk of tertiary carbon radicals, these reactions can take place with high stereoselectivity to form new quaternary and secondary carbon stereocenters. The tertiary radical is generated using visible-light photocatalysis, which offers distinct advantages over older, less-green methods for forming carbon radicals. The results summarized here and recent developments from other laboratories[43] in using carbon radicals in sp^3-sp^3 coupling reactions ensure that bimolecular reactions of carbon radicals will play an increasing role in the convergent construction of complex molecules.

AUTHOR INFORMATION

Corresponding Author

*E-mail: leoverma@uci.edu.

Notes

The authors declare no competing financial interest.

Biographies

Christopher R. Jamison earned his Ph.D. degree in Organic Chemistry at Princeton University in 2014 under the supervision of Professor David MacMillan and has since been involved with postdoctoral training at the University of California, Irvine under the supervision of Professor Larry Overman.

Larry E. Overman was born in Chicago, Illinois, in 1943 and raised in Hammond, Indiana. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral dissertation in 1969 with Professor Howard W. Whitlock, Jr., at the University of Wisconsin. After an NIH Postdoctoral Fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine in 1971, where he is now Distinguished Professor of Chemistry. Professor Overman was Chair of the UC Irvine Department of Chemistry from 1990 to 1993.

ACKNOWLEDGMENTS

Our research in this area has been supported by the National Science Foundation (CHE1265964) and the National Institute of General Medical Sciences (R01-GM098601). We thank Dr. Mikko Muuronen for computational assistance in preparing this Account.

REFERENCES

(1) For reviews, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. The Diels−Alder Reaction in Total Synthesis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489. (c) Fürstner, A. Carbon−Carbon Bond Formations Involving Organochromium(III) Reagents. *Chem. Rev.* **1999**, *99*, 991−1046. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Metathesis Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527. (e) Quasdorf, K. W.; Overman, L. E. Catalytic Enantioselective

DOI: 10.1021/acs.accounts.6b00284
Acc. Chem. Res. 2016, 49, 1578−1586

Synthesis of Quaternary Carbon Stereocentres. *Nature* **2014**, *516*, 181−191.
(2) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. Synthesis of Azadirachtin: A Long but Successful Journey. *Angew. Chem., Int. Ed.* **2007**, *46*, 7629−7632.
(3) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. Concise Total Synthesis of (+)-WIN 64821 and (−)-Ditryptophenaline. *Angew. Chem., Int. Ed.* **2008**, *47*, 1485−1487.
(4) Fontana, A.; Muniain, C.; Cimino, G. First Chemical Study of Patagonian Nudibranchs: A New Seco-11, 12-Spongiane, Tyrinnal, from the Defensive Organs of *Tyrinna nobilis*. *J. Nat. Prod.* **1998**, *61*, 1027−1029.
(5) Gonzalez, M. Spongiane Diterpenoids. *Curr. Bioact. Compd.* **2007**, *3*, 1−36.
(6) Also see: Faber, J. M.; Williams, C. M. A Concise Total Synthesis of (±)-Cipadonoid B from Synthetic Azedaralide. *Chem. Commun.* **2011**, *47*, 2258−2260.
(7) For example, see: Wang, W.; Kishi, Y. Synthesis and Structure of Tolyporphin A *O*,*O*-Diacetate. *Org. Lett.* **1999**, *1*, 1129−1132.
(8) For example, see: Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. Enantioselective Total Synthesis of Shahamin K. *J. Am. Chem. Soc.* **2001**, *123*, 4851−4852.
(9) Rowlands, G. J. Radicals in Organic Synthesis. *Tetrahedron* **2009**, *65*, 8603−8655 and refs 34 and 35 therein.
(10) Srikanth, G. S. C.; Castle, S. L. Advances in Radical Conjugate Additions. *Tetrahedron* **2005**, *61*, 10377−10441.
(11) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2.
(12) (a) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. Diastereofacial Selectivity in Reactions of Substituted Cyclohexyl Radicals. An Experimental and Theoretical Study. *J. Am. Chem. Soc.* **1992**, *114*, 4067−4079. (b) Arnaud, R.; Postlethwaite, H.; Barone, V. Theoretical Study of the Addition of *tert*-Butyl and Benzyl Radical to Ethene. *J. Phys. Chem.* **1994**, *98*, 5913−5919.
(13) The transition state calculation for Figure 2 was performed by Dr. Mikko Muuronen. The transition state was optimized at the RPA/def2-TZVP//TPSS-D3/def2-TZVP/COSMO level according to the procedure published in the following reference (and references therein): Tao, D. J.; Muuronen, M.; Slutskyy, Y.; Le, A.; Furche, F.; Overman, L. E. Diastereoselective Coupling of Chiral Acetonide Trisubstituted Radicals with Alkenes. *Chem. Eur. J.* **2016**, *22*, 8786−8790.
(14) Beckwith, A. L.; Poole, J. S. Factors Affecting the Rates of Addition of Free Radicals to Alkenes - Determination of Absolute Rate Coefficients Using the Persistent Aminoxyl Method. *J. Am. Chem. Soc.* **2002**, *124*, 9489−9497.
(15) Giese, B. Formation of CC Bonds by Addition of Free Radicals to Alkenes. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753−764.
(16) Fischer, H.; Radom, L. Factors Controlling the Addition of Carbon-Centered Radicals to Alkenes−An Experimental and Theoretical Perspective. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340−1371.
(17) Hayen, A.; Koch, R.; Saak, W.; Haase, D.; Metzger, J. O. 1,3-Stereoinduction in Radical Reactions: Radical Additions to Dialkyl 2-Alkyl-4-Methyleneglutarates. *J. Am. Chem. Soc.* **2000**, *122*, 12458−12468.
(18) (a) See: Barton, D. H. R.; Sas, W. The Invention of Radical Reactions. Part XIX. The Synthesis of Very Hindered Quinones. *Tetrahedron* **1990**, *46*, 3419−3430. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. Radical Reactions in Natural Product Synthesis. *Chem. Rev.* **1991**, *91*, 1237−1286.
(19) *Quaternary Stereocenters—Challenges and Solutions for Organic Synthesis*; Christoffers, J.; Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 287−314.
(20) (a) Stork, G.; Sher, P.; Chen, H. Radical Cyclization-Trapping in the Synthesis of Natural Products. A Simple, Stereocontrolled Route to Prostaglandin F2.alpha. *J. Am. Chem. Soc.* **1986**, *108*, 6384−6385. (b) Keck, G. E.; Burnett, D. A. beta.-Stannyl Enones as Radical Traps: A Very Direct Route to PGF2.alpha. *J. Org. Chem.* **1987**, *52*, 2958−2960. (c) Keck, G. E.; Tafesh, A. M. Free-Radical Addition-Fragmentation Reactions in Synthesis: A "Second Generation" Synthesis of (+)-Pseudomonic Acid C. *J. Org. Chem.* **1989**, *54*, 5845−5846. (d) Bacque, E.; Pautrat, F.; Zard, S. A Flexible Strategy for the Divergent Modification of Pleuromutilin. *Chem. Commun.* **2002**, 2312−2313. (e) Ling, T.; Poupon, E.; Rueden, E. J.; Kim, S. H.; Theodorakis, E. A. Unified Synthesis of Quinone Sesquiterpenes Based on a Radical Decarboxylation and Quinone Addition Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 12261−12267. (f) Sun, Y.; Li, R.; Zhang, W.; Li, A. Total Synthesis of Indotertine A and Drimentines A, F, and G. *Angew. Chem., Int. Ed.* **2013**, *52*, 9201−9204. (g) Murai, K.; Katoh, S.-I.; Urabe, D.; Inoue, M. A Radical-Based Approach for the Construction of the Tetracyclic Structure of Resiniferatoxin. *Chem. Sci.* **2013**, *4*, 2364−2368. (h) Wang, L.; Wang, H.; Li, Y.; Tang, P. Total Synthesis of Schilancitrilactones B and C. *Angew. Chem., Int. Ed.* **2015**, *54*, 5732−5735.
(21) For recent reviews of photoredox catalysis, see: (a) Tucker, J. W.; Stephenson, C. R. J. Shining Light on Photoredox Catalysis: Theory and Synthetic Applications. *J. Org. Chem.* **2012**, *77*, 1617−1622. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322−5363. (c) Schultz, D. M.; Yoon, T. P. Solar Synthesis: Prospects in Visible Light Photocatalysis. *Science* **2014**, *343*, 1239176.
(22) Schnermann, M. J.; Beaudry, C. M.; Egorova, A. V.; Polishchuk, R. S.; Sütterlin, C.; Overman, L. E. Golgi Modifying Properties of Macfarlandin E and the Synthesis and Evaluation of Its 2,7-Dioxabicyclo[3.2.1]octan-3-one Core. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 6158−6163.
(23) Schnermann, M. J.; Beaudry, C. M.; Genung, S. N.; Canham, E. M.; Untiedt, N. L.; Karanikolas, B. D. W.; Sütterlin, C.; Overman, L. E. Divergent Synthesis and Chemical Reactivity of Bicyclic Lactone Fragments of Complex Rearranged Spongian Diterpenes. *J. Am. Chem. Soc.* **2011**, *133*, 17494−17503.
(24) Schnermann, M. J.; Overman, L. E. Enantioselective Total Synthesis of Aplyviolene. *J. Am. Chem. Soc.* **2011**, *133*, 16425−16427.
(25) Schnermann, M. J.; Untiedt, N. L.; Jiménez-Osés, G.; Houk, K. N.; Overman, L. E. Forming Tertiary Organolithium and Organocuprates from Nitrile Precursors and their Bimolecular Reactions with Carbon Electrophiles to Form Quaternary Carbon Stereocenters. *Angew. Chem., Int. Ed.* **2012**, *51*, 9581−9586.
(26) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. Photosensitized Decarboxylative Michael Addition through *N*-(Acyloxy)phthalimides via an Electron-Transfer Mechanism. *J. Am. Chem. Soc.* **1991**, *113*, 9401−9402.
(27) For a review, see: Saraiva, M. F.; Couri, M. R. C.; Le Hyaric, M.; de Almeida, M. V. The Barton ester free-radical reaction: a brief review of applications. *Tetrahedron* **2009**, *65*, 3563−3572.
(28) Schnermann, M. J.; Overman, L. E. A Concise Synthesis of (−)-Aplyviolene Facilitated by a Strategic Tertiary Radical Conjugate Addition. *Angew. Chem., Int. Ed.* **2012**, *51*, 9576−9580.
(29) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. Electron-Transfer Photoredox Catalysis: Development of a Tin-Free Reductive Dehalogenation Reaction. *J. Am. Chem. Soc.* **2009**, *131*, 8756−8757.
(30) Crich, D.; Quintero, L. Radical Chemistry Associated with the Thiocarbonyl Group. *Chem. Rev.* **1989**, *89*, 1413−1432.
(31) Barton, D. H. R.; Crich, D. Formation of Quaternary Carbon Centres from Tertiary Alcohols by Free Radical Methods. *Tetrahedron Lett.* **1985**, *26*, 757−760.
(32) Barton, D. H. R.; Crich, D.; Kretzschmar, G. The Invention of New Radical Chain Reactions. Part 9. Further Radical Chemistry of Thiohydroxamic Esters; Formation of Carbon-Carbon Bonds. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39−53.
(33) Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. Direct Construction of Quaternary Carbons from Tertiary Alcohols via Photoredox-Catalyzed Fragmentation of *tert*-Alkyl *N*-Phthalimidoyl Oxalates. *J. Am. Chem. Soc.* **2013**, *135*, 15342−15345.

DOI: 10.1021/acs.accounts.6b00284
Acc. Chem. Res. 2016, 49, 1578−1586

(34) Lackner, G. L.; Quasdorf, K. W.; Pratsch, G.; Overman, L. E. Fragment Coupling and the Construction of Quaternary Carbons Using Tertiary Radicals Generated From *tert*-Alkyl *N*-Phthalimidoyl Oxalates By Visible-Light Photocatalysis. *J. Org. Chem.* **2015**, *80*, 6012−6024.
(35) For a review, see: Büschleb, M.; Dorich, S.; Hanessian, S.; Tao, D.; Schenthal, K. B.; Overman, L. E. Synthetic Strategies Toward Natural Products Containing Contiguous Stereogenic Quaternary Carbons. *Angew. Chem., Int. Ed.* **2016**, *55*, 4156−4186.
(36) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. Carboxylic Acids as A Traceless Activation Group for Conjugate Additions: A Three-Step Synthesis of (±)-Pregabalin. *J. Am. Chem. Soc.* **2014**, *136*, 10886−10889.
(37) Nawrat, C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. Oxalates as Activating Groups for Alcohols in Visible Light Photoredox Catalysis: Formation of Quaternary Centers by Redox-Neutral Fragment Coupling. *J. Am. Chem. Soc.* **2015**, *137*, 11270−11273.
(38) Lowry, M. S.; Goldsmith, J. L.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium(III) Complex. *Chem. Mater.* **2005**, *17*, 5712−5719.
(39) For general information on the clerodane diterpenoids, see: (a) Merritt, A. T.; Ley, S. V. Clerodane Diterpenoids. *Nat. Prod. Rep.* **1992**, *9*, 243−287. (b) Tokoroyama, T. Synthesis of Clerodane Diterpenoids and Related Compounds-Stereoselective Construction of the Decalin Skeleton with Multiple Contiguous Stereogenic Centers. *Synthesis* **2000**, *2000*, 611−633.
(40) (a) Slutskyy, Y.; Jamison, C. R.; Lackner, G. L.; Müller, D. S.; Dieskau, A. P.; Untiedt, N. L.; Overman, L. E. Short Enantioselective Total Syntheses of trans-Clerodane Diterpenoids: Convergent Fragment Coupling Using a *trans*-Decalin Tertiary Radical Generated from a Tertiary Alcohol Precursor. *J. Org. Chem.* **2016**, DOI: 10.1021/acs.joc.6b00697. (b) Müller, D. S.; Untiedt, N. L.; Dieskau, A. P.; Lackner, G. L.; Overman, L. E. Constructing Quaternary Stereogenic Centers Using Tertiary Organocuprates and Tertiary Radicals. Total Synthesis of *trans*-Clerodane Natural Products. *J. Am. Chem. Soc.* **2015**, *137*, 660−663.
(41) Piers, E.; Wai, J. S. M. Stereoselective Total Synthesis of the Marine Sesterterpenoid (±)-Palauolide. *Can. J. Chem.* **1994**, *72*, 146−157.
(42) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. Formation of Vinyl-, Vinylhalide- or Acyl-Substituted Quaternary Carbon Stereogenic Centers through NHC−Cu-Catalyzed Enantioselective Conjugate Additions of Si-Containing Vinylaluminums to β-Substituted Cyclic Enones. *J. Am. Chem. Soc.* **2011**, *133*, 736−739.
(43) For representative examples, see: (a) Movassaghi, M.; Ahmad, O. K.; Lathrop, S. P. Directed Heterodimerization: Stereocontrolled Assembly via Solvent-Caged Unsymmetrical Diazene Fragmentation. *J. Am. Chem. Soc.* **2011**, *133*, 13002−13005. (b) Grandjean, J.; Nicewicz, D. A. Synthesis of Highly Substituted Tetrahydrofurans via Catalytic Polar-Radical Crossover Cycloadditions of Alkenes and Alkenols. *Angew. Chem., Int. Ed.* **2013**, *52*, 3967−3971. (c) Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C. Direct β-Alkylation of Aldehydes via Photoredox Organocatalysis. *J. Am. Chem. Soc.* **2014**, *136*, 6858−6861. (d) Lo, J. C.; Yabe, Y.; Baran, P. S. A Practical Catalytic Reductive Olefin Coupling. *J. Am. Chem. Soc.* **2014**, *136*, 1304−1307. (e) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. O-H Hydrogen Bonding Promotes H-Atom Transfer from α C-H Bonds for C-Alkylation of Alcohols. *Science* **2015**, *349*, 1532−1536. (f) Espelt, L. R.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. Enantioselective Conjugate Addition of α-Amino Radicals via Cooperative Photoredox and Lewis Acid Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 2452−2455. (g) Chinzei, T.; Miyazawa, K.; Yasu, Y.; Koike, T.; Akita, M. Redox-Economical Radical Generation from Organoborates and Carboxylic Acids by Organic Photoredox Catalysis. *RSC Adv.* **2015**, *5*, 21297−21300. (h) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. Asymmetric Catalytic Formation of Quaternary Carbons by Iminium Ion Trapping of Radicals. *Nature* **2016**, *532*, 218−222. (i) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. Metallaphotoredox-Catalyzed sp^3−sp^3 Cross-Coupling of Carboxylic Acids with Alkyl Halides. *Nature* **2016**, in press.

DOI: 10.1021/acs.accounts.6b00284
Acc. Chem. Res. 2016, 49, 1578−1586