JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Direct Construction of Quaternary Carbons from Tertiary Alcohols via Photoredox-Catalyzed Fragmentation of *tert*-Alkyl *N*-Phthalimidoyl Oxalates

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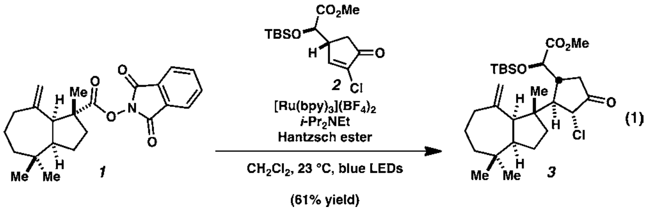
Supporting Information

ABSTRACT: A convenient method for the direct construction of quaternary carbons from tertiary alcohols by visible-light photoredox coupling of *tert*-alkyl *N*-phthalimidoyl oxalate intermediates with electron-deficient alkenes is reported.

Forming sterically demanding quaternary carbons by the reaction of nucleophilic carbon radicals with electron-deficient alkenes is attractive for several reasons: the forming bond is unusually long in calculated transition structures (2.2–2.5 Å);[1] the rates of addition of tertiary radicals to electron-deficient alkenes are faster than those of Me, primary, and secondary radicals;[2] and stereoselectivity in the addition of tertiary radicals to prochiral alkenes is typically larger than that of primary or secondary radicals.[2a,3,4] Although these appealing features have been recognized for many years,[2a,5] this method is not mentioned in a recent comprehensive survey of methods to construct quaternary carbons.[6] The considerable potential such bond constructions hold was suggested in our recent formal total synthesis of (−)-aplyviolene, wherein the stereoselective coupling of a tertiary carbon radical, generated by visible-light photoredox decarboxylative fragmentation of *N*-(acyloxy)-phthalimide **1**, to *α*-chlorocyclopentenone **2** was the central step (eq 1).[7a] This result represented the first utilization of such substrates in a C–C bond-forming reaction since their initial disclosure by Okada.[8] We surmise that the reason tertiary carbon radicals have not heretofore played a significant role in assembling quaternary carbons is the lack of convenient methods for generating these intermediates from widely available tertiary alcohols.[4] Furthermore, despite the pronounced advancement of visible-light photoredox-catalyzed transformations in recent years, methods that generate tertiary carbon radicals remain largely unexplored.[7b,9] In this Communication, we report such a method.



The method we developed was inspired by Barton's pioneering introduction of *tert*-alkyl *N*-hydroxypyridine-2-thionyl oxalates for generating carbon radicals from alcohols.[10] Although Barton oxalate intermediates can be formed from tertiary alcohols, the instability of these intermediates, which prevents their isolation, and their light sensitivity are likely responsible for their limited use in the formation of quaternary carbons.[11−15] Anticipating that related *tert*-alkyl *N*-phthalimidoyl oxalates would be more convenient precursors of tertiary carbon radicals, we initially explored conditions to access these compounds.

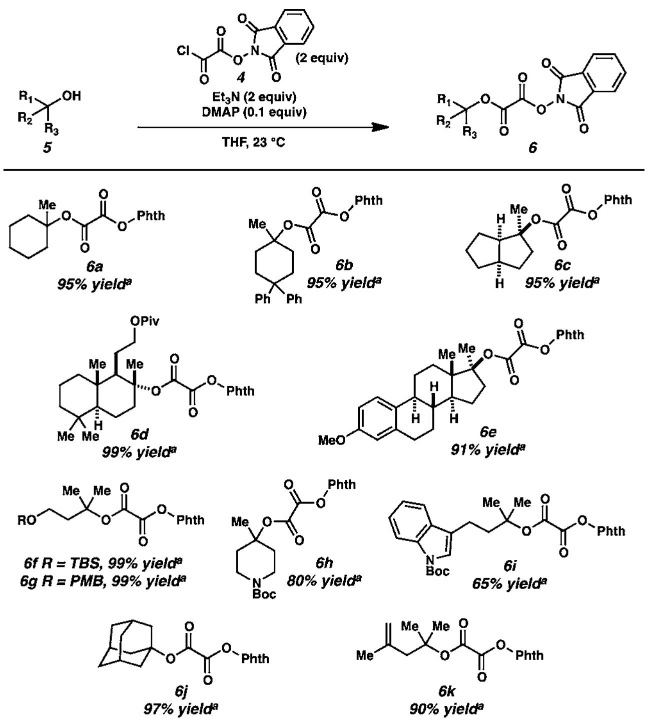


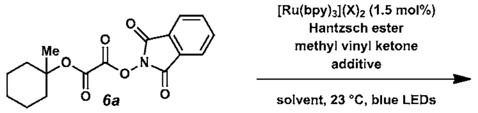
Figure 1. Synthesis of *tert*-alkyl *N*-phthalimidoyl oxalates. [a]Isolated yield. [b]Phth = *N*-phthalimido.

After examining several potential methods for preparing these mixed oxalate diesters, we found that tertiary alcohols smoothly underwent acylation with chloro *N*-phthalimidoyl oxalate (**4**, generated *in situ* from oxalyl chloride and *N*-hydroxyphthalimide) at room temperature in the presence of Et_3N and catalytic DMAP to afford *tert*-alkyl *N*-phthalimidoyl

Received: August 29, 2013
Published: September 27, 2013

dx.doi.org/10.1021/ja408971t | *J. Am. Chem. Soc.* 2013, 135, 15342−15345

Table 1. Optimization for the Coupling of 6a with Methyl Vinyl Ketone



entry	oxalate equiv	MVK equiv	Hantzsch ester equiv	additive (equiv)	solvent[a]	X	yield (%)
1	1.0	1.5	1.0	i-Pr_2NEt (2.2)	CH_2Cl_2	BF_4	16[b]
2	1.0	1.5	1.0	none	CH_2Cl_2	BF_4	36[b]
3	1.0	1.5	1.0	i-$Pr_2NEt\cdot HBF_4$ (2.2)	CH_2Cl_2	BF_4	40[b]
4	1.0	5.0	1.0	i-$Pr_2NEt\cdot HBF_4$ (2.2)	CH_2Cl_2	BF_4	22[b]
5	1.0	1.0	1.0	i-$Pr_2NEt\cdot HBF_4$ (2.2)	CH_2Cl_2	BF_4	56[b]
6	1.5	1.0	1.5	i-$Pr_2NEt\cdot HBF_4$ (2.2)	CH_2Cl_2	BF_4	77[b]
7	1.5	1.0	1.5	i-$Pr_2NEt\cdot HBF_4$ (1.0)	CH_2Cl_2	BF_4	82[b]
8	1.5	1.0	1.5	i-$Pr_2NEt\cdot HBF_4$ (1.0)	THF/CH_2Cl_2[a]	BF_4	92[b]
9	1.5	1.0	1.5	i-$Pr_2NEt\cdot HBF_4$ (1.0)	THF/CH_2Cl_2[a]	PF_6	92[b] 82[c]
10	1.5	1.0	1.5	none	THF/CH_2Cl_2[a]	PF_6	65[c]

[a]1:1 mixture of THF/CH_2Cl_2; Hantzsch ester = diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. [b]Yield determined by ^1H NMR. [c]Isolated yield after silica gel chromatography.

oxalates in high yields (**5**→**6**, Figure 1). In contrast to *N*-(acyloxy)phthalimides, which are generally quite stable to aqueous workup and silica gel chromatography, oxalates **6** proved to be much more sensitive. However, we found that the byproducts of their synthesis typically could be removed by simple filtration to furnish the desired product in acceptable purity. *tert*-Alkyl *N*-phthalimidoyl oxalates **6a**−**6k** are stable to ambient light and can be easily prepared on multigram scale. Confirmation that this sequence did provide the previously unknown alkyl *N*-phthalimidoyl oxalates was secured by single-crystal X-ray analysis of oxalate diester **6j**.

With a general route to *tert*-alkyl *N*-phthalimidoyl oxalates in hand, we examined the coupling of oxalate **6a** with methyl vinyl ketone (MVK). Employing conditions similar to those used in our earlier studies with *N*-(acyloxy)phthalimides[7] resulted largely in decomposition of the oxalate, furnishing coupled product **7a** in only small amounts (Table 1, entry 1). Omission of i-Pr_2NEt provided an improvement in yield (entry 2), reflecting the instability of **6a** to the presence of this amine. The use of i-$Pr_2NEt\cdot HBF_4$ resulted in improved yields of **7a** (entries 3−9). Whereas using an excess or equal amount of MVK relative to **6a** proved detrimental (entries 1−5),[16] optimal yields were obtained when oxalate **6a** was present in slight excess (entries 6−10). It was also found that a 1:1 THF/CH_2Cl_2 solvent mixture was superior to either CH_2Cl_2 or THF alone (entries 8 and 9). The i-$Pr_2NEt\cdot HBF_4$ additive was found to be beneficial even under optimized conditions, as its omission led to lower product yields (entry 10). Finally, $[Ru(bpy)_3](BF_4)_2$ or the commercially available $[Ru(bpy)_3](PF_6)_2$ performed comparably in the reaction (entries 8 and 9). Under the optimized reaction conditions, the coupling of oxalate **6a** with MVK gave ketone product **7a** in 82% yield.

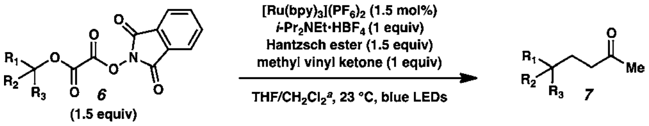
The results of our initial survey of the scope of the coupling of *tert*-alkyl *N*-phthalimidoyl oxalates with MVK are summarized in Table 2. In most cases, yields of the coupled products were excellent, 68−85% (entries 1−7). Chiral oxalates **6c**, **6d**, and **6e** coupled with high diastereoselectivity (>20:1) from the sterically most accessible face (entries 3−5). The coupling of the estrone-derived precursor **6e** is significant as it demonstrates the construction of vicinal-quaternary carbon centers (entry 5). Two nitrogen-containing heterocyclic substrates were also investigated (entries 7 and 8). Piperidinone-derived **6h** furnished coupled product **7h** in 82% yield, whereas the coupling of indole-containing oxalate **6i** proceeded in diminished yield. As expected from our exploratory studies, carrying out the coupling of **6d** and **6e** with equal equivalents of the oxalate precursor and MVK gave the coupled products in somewhat diminished yields (entries 4 and 5). The reaction of adamantyl oxalate **6j** led to the expected product **7j** in low yield, with the major product deriving from coupling of the intermediate alkoxycarbonyl radical with MVK (entry 9). To no surprise, homoallylic oxalate **6k** coupled with MVK to give butyrolactone **7k** (entry 7).[15a,17]

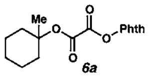
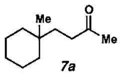
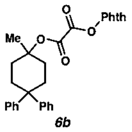
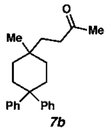
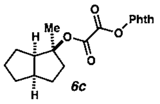
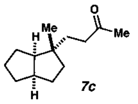
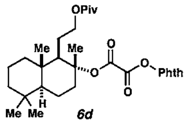
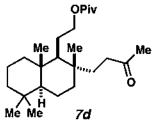
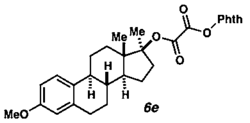
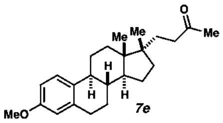
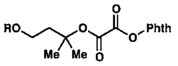
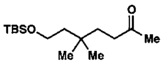
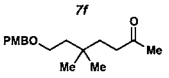
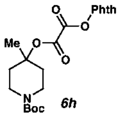
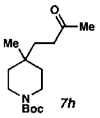
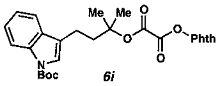
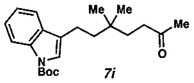
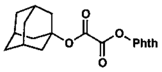
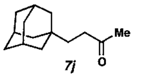
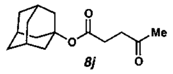
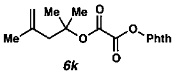
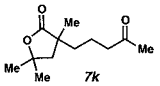
The scope of this new coupling reaction with respect to the conjugate acceptor is summarized in Table 3. Acceptors possessing a terminal double bond generally performed best in the reaction, with acrylonitrile, phenyl vinyl sulfone, and methyl acrylate providing the coupled products in excellent yield (entries 1−3); the yields were somewhat lower with dimethyl acrylamide (entry 4). Dimethyl fumarate also served as an excellent coupling partner, producing **9e** in 85% yield (entry 5).

Cyclic acceptors could be utilized also, although the yields of coupled products were slightly lower (entries 6−9). Use of a butenolide acceptor (entry 8) furnished the desired product in 72% yield, with addition occurring exclusively from the face opposite the methoxy substiuent.[18] Finally, the activated trisubstituted acceptor 2-carbomethoxycyclopent-2-en-1-one coupled with *tert*-alkyl *N*-phthalimidoyl oxalate **6a** to afford trans product **9i** in 62% yield (entry 9).

A plausible mechanism for the visible-light photoredox coupling reported herein is outlined in Scheme 1. As proposed by Okada[8] for the fragmentation of *N*-(acyloxy)phthalimides, single-electron transfer from $Ru(bpy)_3^+$ to the *tert*-alkyl *N*-phthalimidoyl oxalate, followed by homolytic cleavage of the N−O bond and subsequent decarboxylation, generates alkoxycarbonyl radical **12**. A second, slower decarboxylation leads to the formation of tertiary radical **13**,[10,19] which after addition to an electron-deficient alkene provides α-acyl radical **14**. Hydrogen atom abstraction from Hantzsch ester radical cation **10b** would furnish the final product (**14**→**7**). An alternative pathway (not shown), involving reduction of α-acyl radical **14** to the corresponding enolate and subsequent protonation, could also lead to the formation of **7**. While the presence of Hantzsch ester **10a** is necessary to realize catalytic turnover, the role of the ammonium additive is not fully

Table 2. Coupling of *tert*-Alkyl *N*-Phthalimidoyl Oxalates with Methyl Vinyl Ketone

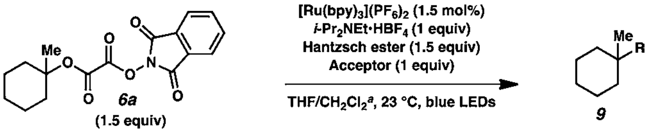


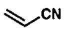
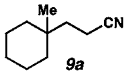
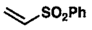
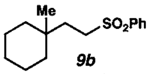
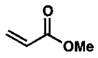
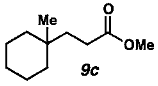
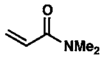
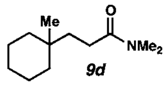
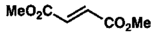
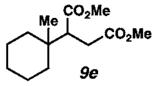
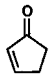
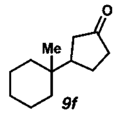
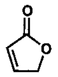
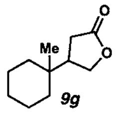
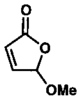
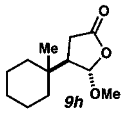
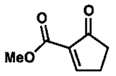
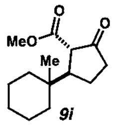
Entry	Oxalate	Product	Yield (%)[b,c]
1	 6a	 7a	82[b]
2	 6b	 7b	85[b]
3	 6c	 7c	82[b]
4	 6d	 7d	85[b] 63[c]
5	 6e	 7e	68[b] 43[c]
6	 6f R = TBS 6g R = PMB	 7f  7g	81[b] 78[b]
7	 6h	 7h	82[b]
8	 6i	 7i	36[b]
9	 6j	 7j  8j	22[b] 65[b]
10	 6k	 7k	43[b]

[a] 1:1 mixture of THF/CH$_2$Cl$_2$. [b] Isolated yield after silica gel chromatography (average of two experiments). [c] Isolated yield after silica gel chromatography with 1:1 ratio of oxalate precursor to acceptor. [d] Phth = *N*-phthalimido.

understood at this time. However, it could potentially serve to protonate intermediate radical anion **11** and also act as a source of BF$_4^-$ to undergo anion exchange with [Ru(bpy)$_3$](PF$_6$)$_2$, leading to the formation of the more soluble [Ru(bpy)$_3$](BF$_4$)$_2$ complex.

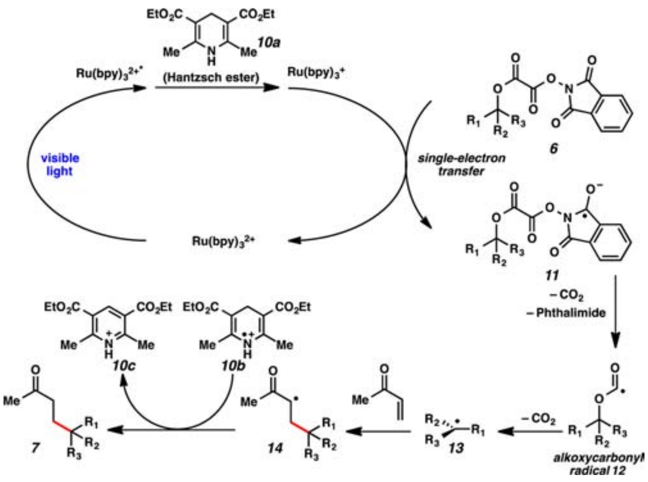
Table 3. Coupling of 6a with Various Acceptors



Entry	Acceptor	Product	Yield (%)[b]
1		 9a	92[b]
2		 9b	89[b]
3		 9c	84[b]
4		 9d	64[b]
5		 9e	85[b]
6		 9f	54[b]
7		 9g	52[b]
8		 9h	72[b]
9		 9i	62[b]

[a] 1:1 mixture of THF/CH$_2$Cl$_2$. [b] Isolated yield after silica gel chromatography (average of two experiments).

Scheme 1



In conclusion, we have developed a convenient method for the direct construction of quaternary carbons from tertiary alcohols by visible-light photoredox coupling of *tert*-alkyl *N*-phthalimidoyl oxalate intermediates with electron-deficient alkenes. In three examples, in which the intermediate tertiary carbon radical is chiral and sterically biased, diastereoselection in forming the new quaternary carbon stereocenter was excellent. Additional synthetic applications of *tert*-alkyl *N*-phthalimidoyl oxalates, as well as mechanistic studies of their reactivity in photoredox-mediated processes, are currently under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data, and CIF files for **6j** and **7d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support was provided by the National Science Foundation (CHE1265964) and the National Institute of General Medical Sciences (R01GM098601). NMR and mass spectra were determined at UC Irvine using instruments purchased with the assistance of NSF and NIH shared instrumentation grants. We thank Dr. Joseph Ziller and Dr. John Greaves, Department of Chemistry, UC Irvine, for their assistance with X-ray and mass spectrometric analyses.

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