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Generation of Dithianyl and Dioxolanyl Radicals Using Photoredox Catalysis: Application in the Total Synthesis of the Danshenspiroketallactones via Radical Relay Chemistry

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Abstract

Visible-light-induced generation of dithianyl and dioxolanyl radicals via selective hydrogen atom transfer (HAT) has been achieved. This radical relay tactic enables remote $C(sp^3)$—H functionalization to permit rapid access to polyol and spiroketal segments, and in turn has been exploited as a key synthetic construct in the total synthesis of the danshenspiroketallactones. The conformational stability of the danshenspiroketallactones has also been defined via experiments and DFT calculations.

Graphical Abstract
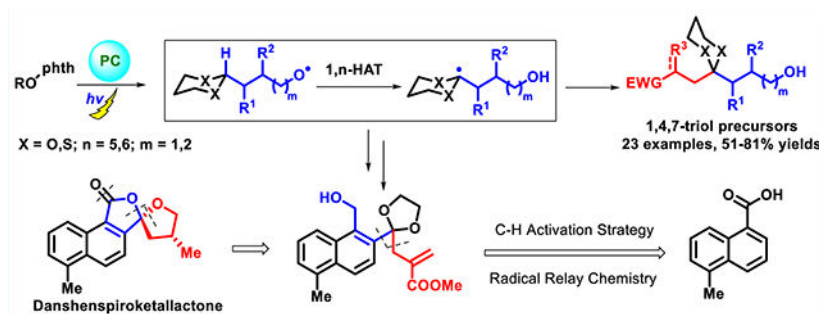
Anion Relay Chemistry (ARC) comprises a one-flask multicomponent union tactic employing solvent-controlled Brook rearrangements.[1] Central to the ARC tactic are dithiane-containing linchpins, in which the dithiane moiety serves as an acyl anion equivalent for the construction of carbon—carbon bonds.[2] The significance of this synthetic tactic comprises the efficient rapid assembly of natural products with diverse architectural

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features, ranging from polyols, spiroketals, and polyene macrolides to polypropionate scaffolds, and as such has been a recent theme in our laboratory.[3]

The multicomponent ARC union protocol relies on [1,4]-Brook rearrangements[4] wherein an initially generated alkoxy anion can be triggered to undergo *in situ* 1,4-silyl group migration to afford a new carbanion (Scheme 1a), which in turn can be readily trapped by diverse electrophiles. The resulting coupled products provide ample bandwidth for downstream functionalization to furnish various 1,3,5-polyol motifs. Brook rearrangements involving 1,5-negative charge migration, although recently studied by us and others,[5] are for the most part synthetically not viable, primarily due to the harsh conditions required to initiate the silyl group migration.

Recently, radical relay chemistry has been developed to functionalize remote $C(sp^3)$—H bonds via 1,5-hydrogen atom transfer (1,5-HAT).[6] For example, initially generated alkoxyl[6a–c] or aminyl radicals[6d–f] are known to undergo *in situ* 1,5-or 1,6-HAT to furnish carbon radicals via a photoredox catalysis cycle. As such, this reactivity migration, although a challenge via remote Brook anionic rearrangement, would comprise an important extension and complement to the ARC tactic (Scheme 1b). We therefore explored 1,5- and 1,6-HAT radical relay chemistry to access various 1,4,7-polyol or 1,4,8-polyol fragments via visible-light photoredox catalysis.

Spiroketals possessing [5.5]- or [5.6]-oxygen architectures are abundant in a wide array of natural products possessing diverse biological activities (Figure 1).[7] Examples include: cephalosporolide I (**1**),[8] isolated from a marine-derived fungus that inhibits both $3a$-hydroxysteroid dehydrogenase and xanthine-oxidase; berkelic acid (**2**),[9] a fungal metabolite that exhibits activity against ovarian cancer; aquilarinoside A (**3**),[10] the principal component of *Aquilaria sinensis,* a highly valuable agarwood; and danshenspiroketallactone (**4**)[11] and the epimer (**5**),[12] both isolated from *Salvia miltiorrhiza,* known as *Danshen,* which is employed in traditional Chinese medicine as a remedy for renal failure, stroke and heart disease. Most synthetic strategies to construct the core architecture of such [5.5]- or [5.6]-spiroketals rely on acid-catalyzed cyclization of 1,4,7- or 1,4,8-polyol precursors (or their equivalents). However, compared to 1,3,5-polyols, synthetic methods to access 1,4,7-polyol precursors remain limited, usually requiring multiple oxidation states or protecting group manipulations.[7] An effective catalytic method to rapidly access such precursors, especially via direct $C(sp^3)$-H functionalization, would thus be of considerable interest.

Toward this end, the reaction sequence based on Chen's cleavage–translocation–allylation sequence was proposed as outlined in Scheme 2. We envisioned that, under visible light, the photocatalyst *fac*-Ir(ppy)$_3$ could be excited and reduced by the Hantzsch ester, known to furnish a reduced photocatalyst, which would reduce *N*-alkoxyphthalimides (**6**) to yield alkoxyl radicals (Scheme 2) via the Hantzsch ester radical cation.[6a,13] The resulting alkoxyl radical **A** could then undergo a 1,5-HAT reaction to generate either a dithianyl or dioxolanyl radical **B**, which comprise carbonyl or methylene radical equivalents, that in turn could engage with an acceptor (**7a**) to yield coupled adducts. Although dithianes and ketals are extensively employed in various reactions, dithianyl and dioxolanyl radicals generated via photoredox catalysis are much less studied.[14]

To initiate this study, we selected 2-[3-(1,3-dioxolan-2-yl)propoxy]-isoindoline-1,3-dione **6a** (Table 1) as a model substrate and 2 equiv of methyl 2-[(phenylsulfonyl)methyl]-acrylate (**7a**) as the radical acceptor. After extensive screening, we found that employing *fac*-Ir(ppy)₃ as the photoredox catalyst in THF led to coupled product **8a** in 45% yield (entry 1), whereas other photocatalysts gave only lower yields (entries 2–3). Interestingly, the choice of solvent proved crucial to achieve efficiency for the 1,5-HAT process. Less polar ether solvents, such as 1,4-dioxane or methyl *tert*-butyl ether (MTBE), led to higher yields, along with less of the quenched byproduct **8aa′** (entries 4–5). Further investigation of the reaction solvent revealed that a combination of MTBE and dioxane (9:1) provided the best results, with an isolated yield of **8a** of 73% (entry 6), employing 2 equiv of the acceptor **7a**. Pleasingly, the loading of the acceptor (**7a**) could be decreased to 1.5 equiv and still resulted in a 68% yield (entry 7). Control experiments demonstrated the essential role of photoredox catalyst and visible light for this reaction (entries 8–9).

With these conditions established, we examined the scope of the reaction with respect to the structural diversity of the *N*-alkoxyphthalimides (Table 2). Dioxolanyl, dioxanyl, dithiolanyl, and dithianyl radicals in turn can be successfully generated under the above conditions, leading to allylated products **8a**–**8d** in moderate to good yields (61–73%). Importantly, steric hindrance at the *α*- or *β*-position did not influence the reaction. Instead, the Thorpe—Ingold effect appears to increase the efficiency of 1,5-HAT to provide higher yields of **8e** (80%) and **8f** (72%). Also noteworthy, the generated dioxolanyl radical was tolerated with a stereogenic center at the *α*-position (**6g**), without erosion of the enantiomeric excess (97% *ee*). We were also pleased to discover that with **6h** the dioxolanyl radical could be generated by exploiting 1,6-HAT, leading to the C—H allylated product **8h** in 59% yield. This result demonstrates the potential of this method for the construction of various [5.6]-spiroketal scaffolds. In addition to aliphatic substituents, aromatic substituents are also tolerated in this HAT reaction. With a phenyl group at the *α*-position (**6i**), a small decrease in the yield of **8i** was obtained. We further tested whether the radical translocation could proceed at an *ortho* benzylic carbon. However, when **6j** was treated via our standard protocol with 2 equiv of the radical acceptor, only a trace amount of desired product **8j** was observed. The major result was a pair of diastereomers **8l** in a 1:1 ratio (Table 2b). To elucidate the structure, oxidation with Dess-Martin periodinane afforded the bisalkylated ketone **8j′** in 56% overall yield, the structure of which was assigned by extensive NMR/HRMS analysis. The interesting structure of **8j′** revealed that a *tandem* 1,5-HAT/1,6-HAT sequence had occurred in the reaction (Scheme 3). This unique radical relay reaction, different from the radical process with aliphatic substrates (**6a**–**6i**), is presumably favored by both the conformational restraints of intermediate **C** (Scheme 3) and the resultant more stable benzyl radical **D**. Decreasing the acceptor loading to 1 equiv significantly increased the yield of monoallylated products, leading to benzyl C—H functionalized products (**8j**–**8k**) in 51–54% yield. This result is important because it provides a novel tactic to construct benzannulated spiroketal moieties, which will be demonstrated as the key step in the total synthesis of danshenspiroketallactone **4** and *epi*-danshenspiroketallactone **5** (*vide infra*).

We next explored various radical acceptors including allyl sulfones and Michael acceptors (Scheme 4). Here we discovered that allyl sulfones with ethyl ester or cyanide as the

electron-withdrawing group react smoothly with the dioxolanyl and dithianyl radicals to furnish C(sp^3)—H allylation adducts **9a**–**9d** in good yield (70–78%). Best results were obtained when 2 equiv of the acceptors were employed. However, with phenyl as the electron-withdrawing group, the radical addition of the dioxolanyl radical to allyl sulfones was not successful (**9e**); only quenched byproduct **8aa′** (Table 1) was observed. Acceptors with remote functional groups, such as alkynes and dienes, were also tested; **9f** and **9g** were obtained in 56% and 75% yield respectively, thus providing a scaffold amenable to additional synthetic applications. Interestingly, Michael acceptors (**7g**–**7k**) readily reacted with the dioxolanyl radical to yield alkylated products (**9h**–**9l**), although a slightly more polar solvent was required (MTBE/dioxane = 1:1). In these reactions, Hantzsch ester served as the reductant to reduce the ensuing radicals. For example, aryl acrylates with different functional groups on the aromatic ring (**7g**–**7j**) were explored; all were well tolerated to deliver the desired products **9h**–**9k** in 53–63% yield. The dioxolanyl radical also underwent radical addition to 2-methylenemalonate **7k** to furnish product **9l** in 81% yield.

To demonstrate the utility of this radical relay chemistry, we devised a synthesis of the danshenspiroketallactones **4** and **5** (Scheme 5). Both danshenspiroketallactones **4** and **5** comprise monobenzannulated [5.5]-spiroketals, a rare spirocyclic unit in natural products.[15] The first total synthesis of the danshenspiroketallactones **4** and **5**, reported by Brimble and co-workers in 2012,[16a] employed directed metalation and a late-stage oxidative spiroketalization.[16b] In both the original isolation paper[12] and the Brimble synthesis, a mixture of **4** and **5** was obtained without further separation. Here, we record the total synthesis of the danshenspiroketallactones **4** and **5** utilizing [1,5]-radical relay chemistry, wherein the generation and functionalization of the dioxolanyl radical plays a key role in the construction of the 1,4,7-polyol precursor (**8k**, Scheme 5). Noteworthy here, the pure format of **4** and **5** were obtained with high performance liquid chromatography (HPLC).

Our synthesis began with commercially available 5-methyl-1-naphthoic acid **10** (Scheme 5). Palladium(II)-catalyzed *ortho* C—H activation[17] followed by a base workup furnished an ortho-hydroxymethyl-naphthoic acid, which in turn was elaborated to **11** by a two-step sequence involving oxidation and methylation. The ethylene acetal was then installed in **12**, followed by reduction and a Mitsunobu reaction with *N*-hydroxyphthalimide to yield **6k** that sets the stage for the envisaged [l,5]-radical relay reaction sequence using photoredox catalysis.

Pleasingly, alkoxyl radical generation followed by 1,5-HAT under the above conditions using photoredox catalysis converted **6k** to **8k** in a 54% yield, which in turn was subjected to hydrogenation using Wilkinson's catalyst to deliver **13**. Upon exposure to LiAlH$_4$ and acidification, the ester group in **13** was reduced and the resulting diol underwent cyclization to furnish two diastereomers, **14** and **15**, in 2:1 *d.r.* as an inseparable mixture. Formation of the minor diastereomer is presumed to result from the weak dependence of [5.5]-spiroketals on the anomeric effect.[7] Completion of the total synthesis of danshenspiroketallactones **4** and **5** was then achieved via benzylic oxidation of the mixture of **14** and **15**. Notably, by employing peroxide **16**,[18] the *α*-alkoxy benzyl carbon could be chemoselectively oxidized in 80% yield, thus providing a mixture of danshenspiroketallactones **4** and **5**. Separation of **4**

and **5** via silica gel chromatography proved not possible, because *epi*-danshenspiroketallactone **5** was found to undergo rapid isomerization to **4** on silica gel.[12] Pleasingly, employing HPLC, we were able to separate successfully the mixture and obtained pure danshenspiroketallactone **4** and the epimer **5**, with ^{1}H and ^{13}C NMR data identical in all respects with the published data.[11,12,16a] Noteworthy, this is the first time that pure synthetic danshenspiroketallactones (**4** and **5**) have been obtained. The total synthesis was achieved in 10 steps with an 11% overall yield.

Not surprisingly, treatment of the synthetic sample of either **4** or the mixture of **4** and **5** (1:1) with TFA in CH_2Cl_2 led to a mixture of **4** and **5** in a ratio of 1:0.4. To evaluate the thermodynamic stability of **4** and **5**, DFT calculations were conducted.[19] The optimized structures are shown in Figure 2. Isomer **4** is 0.8 kcal/mol more stable than **5**, in agreement with the observed experimental ratio. Analysis of the optimized structures (Figure 2; **4** and *ent*-**5**) reveals that the methyl substituent (C17) achieves an equatorial conformation in both diastereomers. In the case of **4**, this can be achieved in such a way that the conformation of the tetrahydrofuran ring has mostly staggered arrangements about the CC bonds (see Newman projection below **4**), whereas **5** has eclipsing interactions that destabilize this conformation.[20]

In summary, we have designed and validated a new visible-light-induced protocol to generate dithianyl and dioxolanyl radicals via 1,5- or 1,6-HAT. The resulting radicals engage in conjugate additions to achieve formal allylation and alkylation. This radical relay reaction provides an efficient method to construct various 1,4,7-polyols or spiroketals and, in turn, was utilized as the key synthetic tactic in the total synthesis of danshenspiroketallactones **4** and **5**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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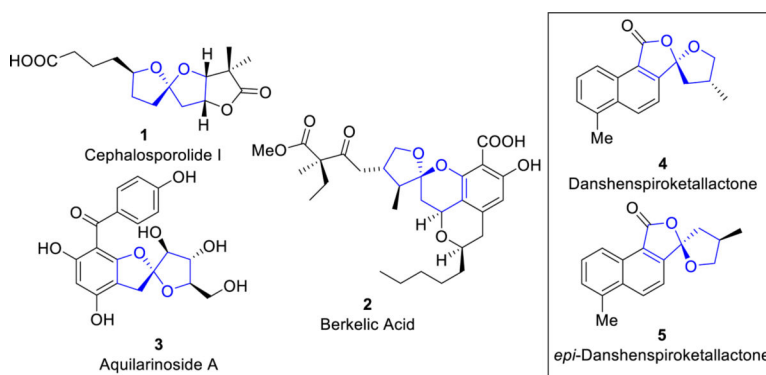
Figure 1.
Natural products containing [5.5]- or [5.6]-spiroketal skeleton.
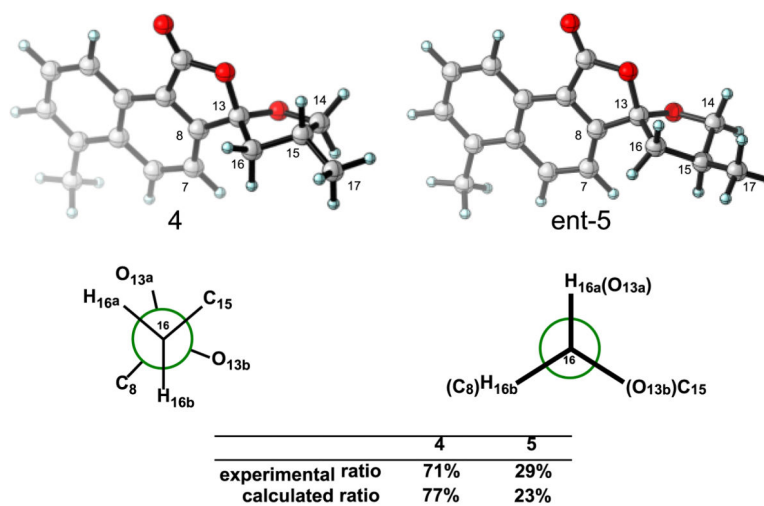
Figure 2.
Conformational structures of 4 and 5 (ent-5 is Shown). Newman projections along the C13–C16 bond are shown.
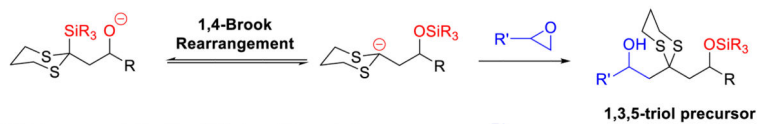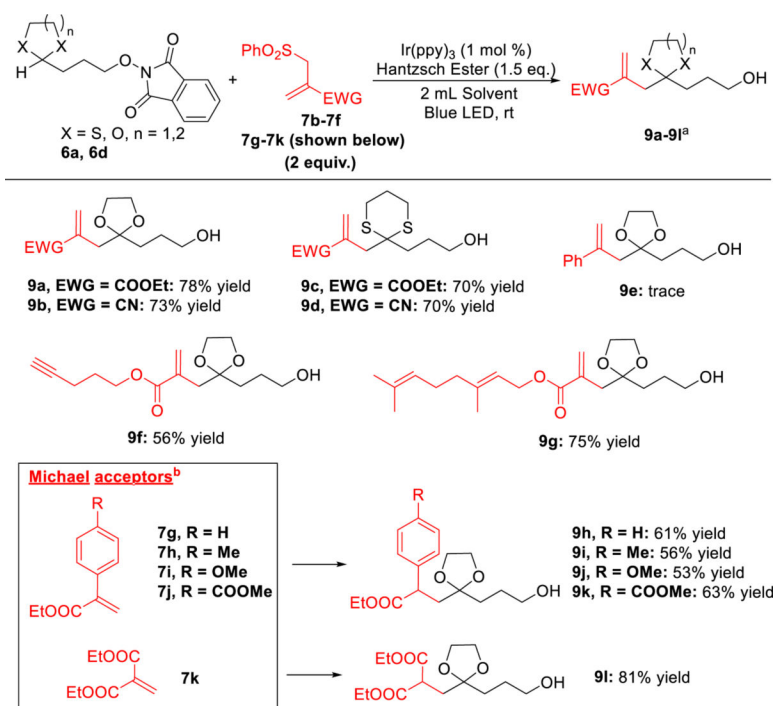
Scheme 1.
Anion Relay Chemistry and Proposed Radical Relay Chemistry
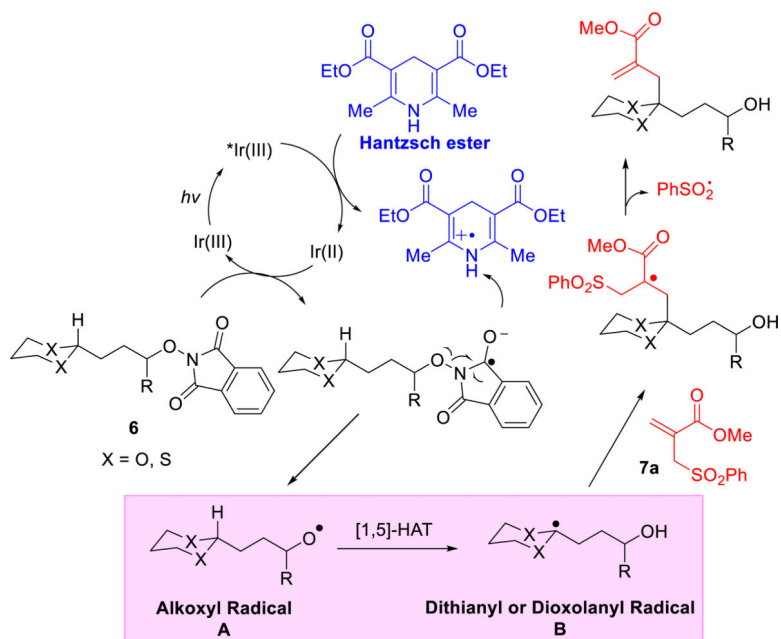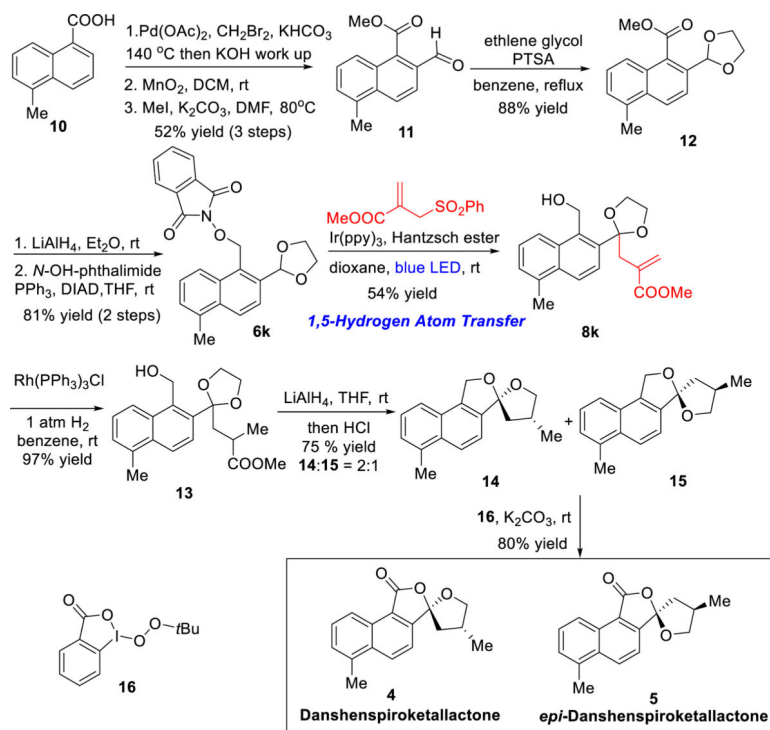
Scheme 2.
Proposed Reaction Sequence
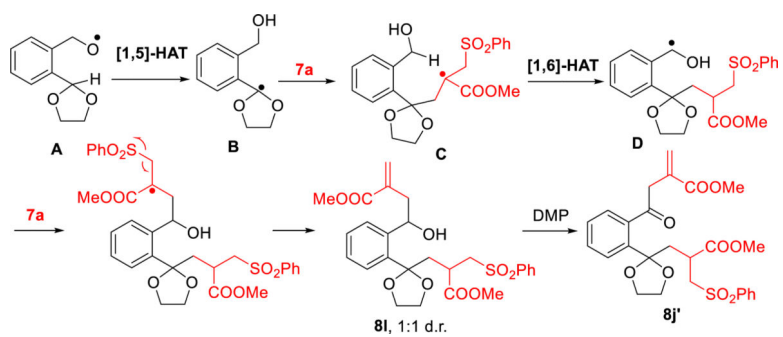
Scheme 3.
Possible Mechanism for the Generation of 8j′

Scheme 4.
Substrate Scope for the Radical Acceptors

[a]Reaction conditions: **6a** or **6d** (0.2 mmol), 7 (0.4 mmol), Ir(ppy)$_3$ (1 mol %), Hantzsch ester (0.3 mmol), MTBE/dioxane = 9:1, rt, blue LED, 5 h. Yields of isolated products are given.
[b]MTBE/dioxane = 1:1.

Scheme 5.
Total Synthesis of the Danshenspiroketallactones

Table 1.

Optimization of Reaction Conditions

entry	photocatalyst	solvent	yield^a (%) of 8a
1	*fac*-Ir(ppy)$_3$	THF	45
2	Ru(bpy)$_3$(PF$_6$)$_2$	THF	38
3	Ir(ppy)$_2$(dtbbpy)PF$_6$	THF	34
4	*fac*-Ir(ppy)$_3$	dioxane	61
5	*fac*-Ir(ppy)$_3$	MTBE	65
6	***fac*-Ir(ppy)$_3$**	**MTBE/dioxane = 9:1**	**76 (73)**
7^b	*fac*-Ir(ppy)$_3$	MTBE/dioxane = 9:1	68
8	–	MTBE/dioxane = 9:1	trace
9^c	*fac*-Ir(ppy)$_3$	MTBE/dioxane = 9:1	trace

^{a}Reaction conditions: **6a** (0.1 mmol), **7a** (0.2 mmol), photocatalyst (1 mol %), Hantzsch ester (0.15 mmol), 1 mL solvent, rt, blue LED, 5 h. The yield of **8a** was determined by ^{1}H NMR analysis. Isolated products are obtained by flash chromatography with yields given in parentheses.
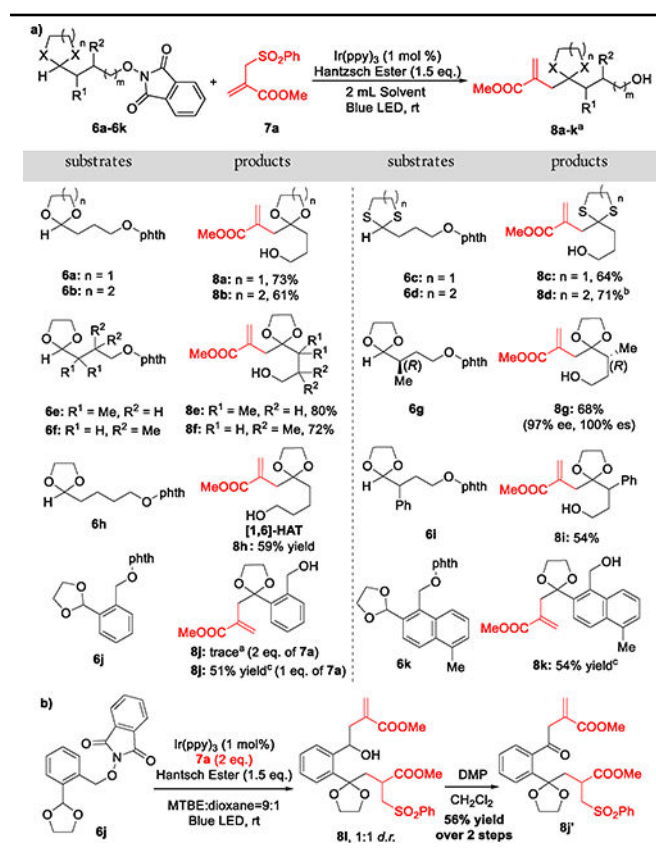
^{b}**7a** (0.15 mmol).

^{c}No light.

Table 2.

Substrates Scope for the N-Alkoxyphthalimides

[a]Reaction conditions: **6** (0.2 mmol), **7a** (0.4 mmol), Ir(ppy)**3** (1 mol %), Hantzsch ester (0.3 mmol), 2 mL of MTBE/dioxane = 9:1, rt, blue LED, 5 h. Yields of isolated products are given. [b]2 mL of THF. [c]**6j** or **6k** (0.2 mmol), **7a** (0.2 mmol), Hantzsch ester (0.24 mmol), 2 mL of dioxane.