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UV Light-Mediated Difunctionalization of Alkenes through Aroyl Radical Addition/1,4-/1,2-Aryl Shift Cascade Reactions

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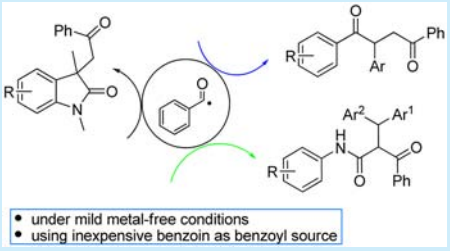
Supporting Information

ABSTRACT: UV light-mediated difunctionalization of alkenes through an aroyl radical addition/1,4-/1,2-aryl shift has been described. The resulted aroyl radical from a photocleavage reaction added to acrylamide compounds followed by cyclization led to the formation of oxindoles, whereas the addition to cinnamic amides aroused a unique 1,4-aryl shift reaction. Furthermore, the difunctionalization of alkenes of prop-2-en-1-ols was also achieved through aroyl radical addition and a sequential 1,2-aryl shift cascade reaction.



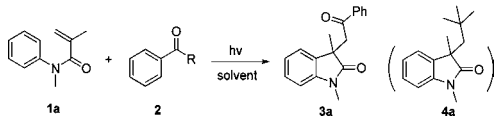
Difunctionalization of alkenes has become increasingly popular because of their high efficiency in the preparation of significant building blocks of natural products and pharmaceutical molecules.[1] Thus, considerable efforts were made for the development of novel and highly efficient methods in this field. Recent studies mainly focused on transition-metal catalyzed C−H functionalization/carbocyclization of alkenes by simultaneous formation of two C−C bonds.[2] Yet, to our knowledge, work on the carbonylarylation of alkenes is quite rare. In this context, Li et al. developed oxidative coupling of alkene with an aldehyde C(sp^2)−H bond and aryl C(sp^2)−H bond to form two C(sp^2)−C(sp^3) bonds using TBHP at 105 °C.[3] Subsequently, the Duan and Li groups respectively reported Ag and Fe catalyzed carbonylarylation of alkenes of acrylamides to synthesize oxindoles[4] under heating.[5] Despite these advances, room still exists for developing more alternative and environmentally friendly approaches associated with this field.

Recently, organic photochemical reactions have attracted considerable interest from chemists in the realm of organic synthesis, synthetic methodologies, and radical chemistry, and therefore a variety of photoreactions have been reported up to now.[6] Based upon our previous work on the chemical behavior of radicals,[7] we envisioned that a benzoyl radical selectively generated from a photochemical cleavage reaction might add to an alkene followed by C−C bond formation to realize the difunctionalization of alkenes.

Therefore, we initially chose 2,2-dimethyl-1-phenylpropan-1-one **2a** (Table 1, entry 1, R = *t*Bu) as the source of the benzoyl radical and acrylamide **1a** as the radical acceptor. Irradiation of the mixture of the above two compounds in acetonitrile with a 450 W high-pressure mercury lamp using a Pyrex filter led to the desired product **3a** in 20% yield accompanied by the alkylarylation product **4a** as well as the product of the photoreaction of **1a** itself (Table 1, entry 1).[8]

Such a result prompted us to improve the selectivity of the photoreaction by screening the wavelength to selectively excite compound **2a** over compound **1a**, and finally a 350 nm wavelength was chosen as the light source. Irradiation of the same reaction mixture with a 350 nm wavelength afforded **3a** in 51% and **4a** in 40% yield (entry 2). A solvent screening, including toluene, methanol, and benzene, led to lower yields (entries 3−

Table 1. Screening for Optimal Reaction Conditions[a]



entry	2	hv	solvent	yield **3a** (%)[b]
1	R =	high pressure mercury lamp	MeCN	20
2[c]		350 nm	MeCN	51
3		350 nm	Toluene	45
4	**2a**	350 nm	Methanol	45
5		350 nm	Benzene	43
6	R = **2b**	350 nm	MeCN	58
7[d]	R = Ph **2c**	350 nm	MeCN	63
8		350 nm	MeCN	60
9[e]	R = OH Ph **2d**	350 nm	MeCN	70
10[f]		**350 nm**	**MeCN**	**85**

[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.45 mmol), hv, solvent (anhydrous 50 mL) under N_2 for 1 h. [b]Isolated yield. [c]Product **4a** (40%). [d]5 h, 76% conversion. [e]**2d** (0.9 mmol). [f]**2d** (1.5 mmol).

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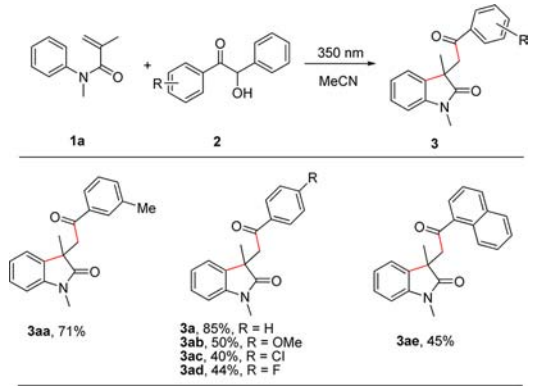
5). After examination of other benzoyl radical sources (entries 6−10), the reaction conditions were optimized to use 350 nm wavelength as the light source, 5 equiv of benzoin **2d** as the benzoyl radical source, and acetonitrile as the solvent.

With these optimized reaction conditions, we focused on the scope of substrates (Schemes 1 and 2). As shown in Scheme 1, a

Scheme 1. Scope of Substrates 2[a,b]

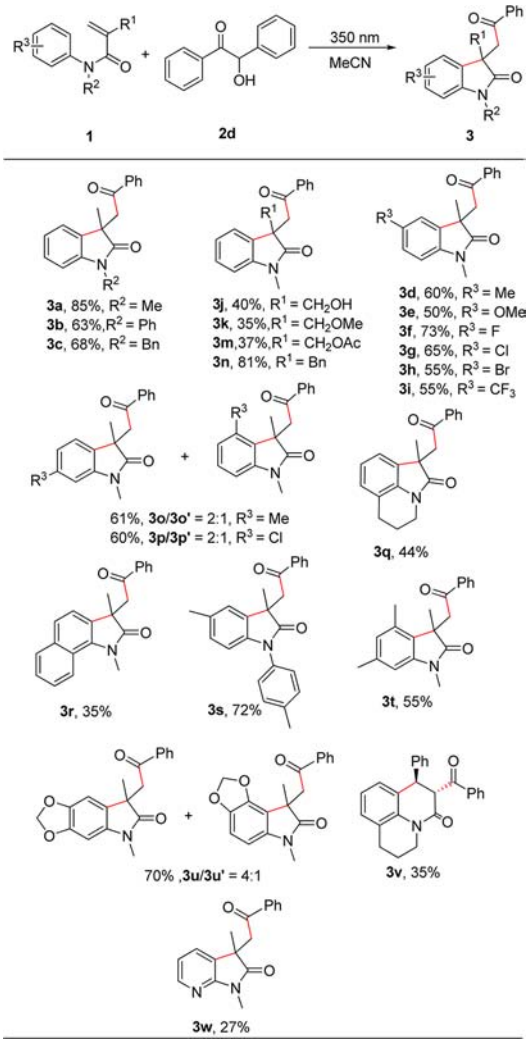


[a]Reaction conditions: **1a** (0.3 mmol), **2** (1.5 mmol), hv (350 nm), MeCN (anhydrous 50 mL) under N_2 for 1 h. [b]Isolated yield.

variety of substituted benzoins, including 2-hydroxy-2-phenyl-1-*m*-tolylethanone (**2da**), 2-hydroxy-1-(4-methoxyphenyl)-2-phenylethanone (**2 db**), 1-(4-chlorophenyl)-2-hydroxy-2-phenylethanone (**2dc**), and 1-(4-fluorophenyl)-2-hydroxy-2-phenylethanone (**2dd**), were successfully reacted with acrylamide **1a** to give the desired products in moderate to good yields. Interestingly, 2-hydroxy-1-(naphthalen-1-yl)-2-phenylethanone (**2de**) was also suitable for the reaction in moderate yield, making this method more potentially useful.

Next we set out to investigate the scope of acrylamides. As shown in Scheme 2, compounds bearing different N-protecting groups including alkyl, aryl, and benzyl are viable substrates for the reaction to lead to the corresponding products (**3a**, **3b**, **3c**, and **3s**) in good yields. The substrates bearing electron-withdrawing and/or -donating groups at the *para* position of the nitrogen atom were also tolerant of the reaction conditions to provide the desired products (**3d**−**3i**) in moderate to good yields. When the *meta*-position was substituted with methyl or Cl groups, the reaction went smoothly to afford the regioisomers with a ratio of 2:1 (**3o** and **3p**). However, no reaction was observed for the *ortho*-substituted substrates owing to the effect of the steric bulk. When the benzene ring of the substrate was replaced by a naphthalene, the substrate was also suitable for the reaction (**3r**). In addition, a tetrahydroquinoline derivative furnished the tricyclic oxindole in moderate yield (**3q**). Substrates with two groups on the aryl ring (**1t** and **1u**) are still good for the transformation to form the desired products; however, the reaction of **1u** afforded the mixture of **3u** and **3u′** with a ratio of 4:1. Importantly, a pyridine group was also tolerated under the optimal conditions (**3w**). Furthermore, a series of α-substituted olefins bearing different functional groups, such as benzyl, ester, alcohol, and ether, were still tolerant with the reaction conditions to yield the corresponding products (**3j**−**3n**). Interestingly, cinnmic amide compound **1v** was also reactive with the benzoyl radical to form a six-membered ring compound **3v**. Such a unique and interesting result intrigues us to explore the chemical behavior of cinnamic amides further.

Scheme 2. Scope of *N*-Arylacrylamides 1[a,b]



[a]Reaction conditions: **1** (0.3 mmol), **2d** (1.5 mmol), hv (350 nm), MeCN (anhydrous 50 mL) under N_2 for 1 h. [b]Isolated yield.

Sequentially, a cinnamic amide **5a** (Scheme 3, R^1 = H, R^2, R^3 = phenyl) was prepared and submitted to the optimal reaction conditions. To our surprise, the reaction led to the amide compound **6a** in 53% yield through a benzoyl radical addition/1,4-aryl shift cascade reaction over the formation of a six-membered ring. Such a serendipitous and new result, to our knowledge, has not been reported up to now. Inspired by this, we therefore explored this new protocol in detail by preparation of a variety of cinnamic amides **5** and reaction with benzoin **2d**, and the results are listed in Scheme 3. As shown in Scheme 3, the aryl group at the β-position of acrylamide substituted with electron-withdrawing or -donating groups, including methyl, F, Cl, Br, methoxy, were smoothly converted to the corresponding products in moderate to good yields (**6a**−**6h**), which also indicated that the position of the substituents on the aryl group has no significant influence on the reaction. The structure of one of the products **6a** was further confirmed by X-ray single crystal analysis (see the Supporting Information (SI)).[9] However, when the aryl group was replaced by a methyl or carbonyl group, no desired product was formed. The substrates with the nitrogen atom substituted with different aryl groups are also tolerant of the optimized conditions (**6i**−**6k**), among which, for the unsym-

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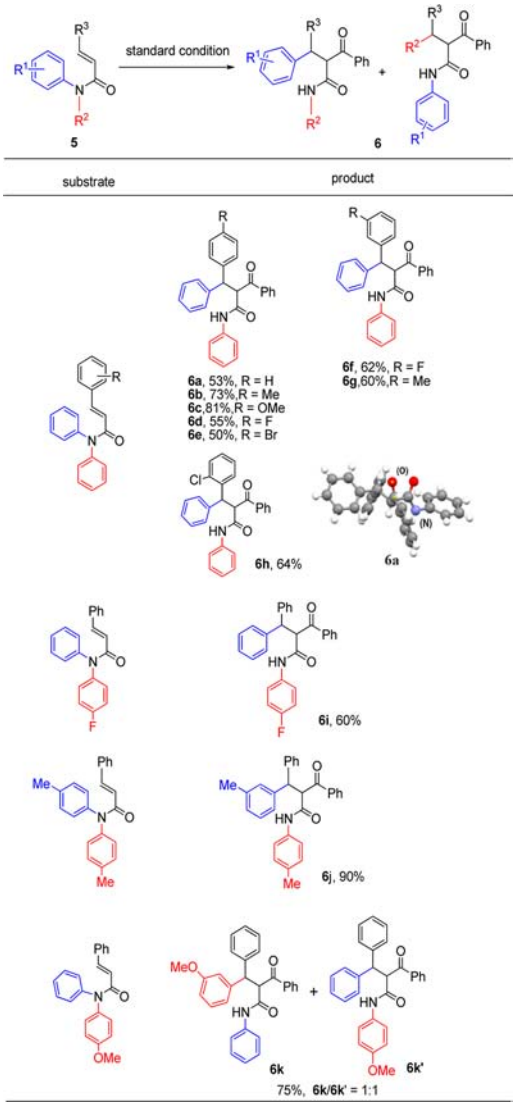
Scheme 3. Scope of UV Light-Mediated 1,4-Aryl Shift Reaction[a,b]

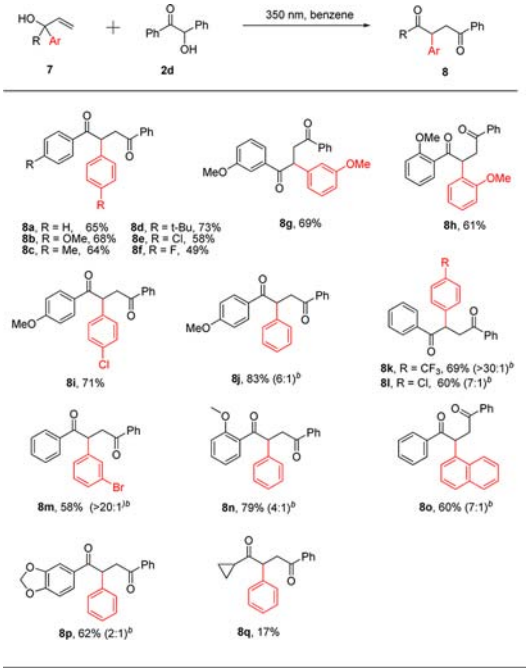


[a]Reaction conditions: **5** (0.3 mmol), **2d** (1.5 mmol), hv (350 nm), MeCN (anhydrous 50 mL), N_2, irradiation for 1 h. [b]Isolated yield.

metric amides, the compound containing an electron-withdrawing group, e.g. F, exhibited excellent regioselectivity and afforded the single product with a phenyl group shift (**6i**); in contrast, the compound containing an electron-donating group, e.g. OMe, yielded a mixture with a ratio of 1:1 (**6k**, **6k**′). Such a result suggested the stability of the nitrogen atom radical involved in the reaction procedure might play an important role in the regioselectivity.

To further investigate the applicability of this protocol, 1,1-diphenylprop-2-enol **7a** was therefore prepared and subjected to the reaction conditions. We envision that, with the generated benzoyl radical addition to the double bond of **7a**, a subsequent 1,2-phenyl shift might occur. To our delight, the desired product **8a** was obtained in 54% yield after reaction for 34 h. When the solvent CH_3CN was replaced by benzene, the yield was improved to 65%. Then a variety of symmetrically and unsymmetrically substituted prop-2-enols were prepared and submitted to the standard reaction conditions using benzene as the solvent, and the reaction results were summarized in Scheme 4.

Scheme 4. Scope of the Reaction of Symmetric and Unsymmetric Prop-2-enols[a]



[a]Reaction conditions: 7 (0.3 mmol), **2d** (1.5 mmol), hv (350 nm), benzene (anhydrous 15 mL) under N_2. [b]Ratio of isomers.

As shown in Scheme 4, for the symmetric substituents, the corresponding products were obtained in good isolated yields (**8a**−**h**). For the unsymmetric substituents, the electronic effect plays an important role in the aryl migration. For example, the electron-deficient aryl group was preferentially shifted over the phenyl and/or the aryl ring substituted with an electron-donating group (**8i**, **8k**−**m**, **8o**), and the phenyl group was prior to the electron-enriched aryl ring (**8j**, **8n**, **8p**). Notably, when the substituent contained a cyclopropanyl group, the corresponding product was formed in low yield with the ring unopened (**8q**). Such a result suggested the phenyl shift and formation of ketone might happen synchronously.

Before the mechanism was proposed, the kinetic isotope effect experiments were conducted using the deuterated derivatives of **1a** as shown in Scheme 1 (see the SI). Both the intermolecular ($k_{H/D}$ = 1.2) and intramolecular ($k_{H/D}$ = 1.3) isotopic effect indicated that the C−C bond formation occurs before C−H cleavage. The intramolecular KIE experiment result also suggested that the rate of the reaction was determined by the elimination of the hydrogen after C−C bond formation. The intramolecular KIE experiment result also suggested that the rate of the reaction was determined by the elimination of the hydrogen after C−C bond formation.

According to the above results, the possible mechanism is proposed as shown in Scheme 5. At first, benzoyl radical was generated through the photochemical cleavage reaction upon irradiation, which was then added to β-position of acrylamide **1** providing the intermediate **A** (blue). The addition of a radical to the aromatic ring produced the intermediate **B**, which lost a hydrogen radical rapidly to afford the oxindole **3**. In contrast, for cinnamic amide **5**, the benzoyl radical was added to the α-

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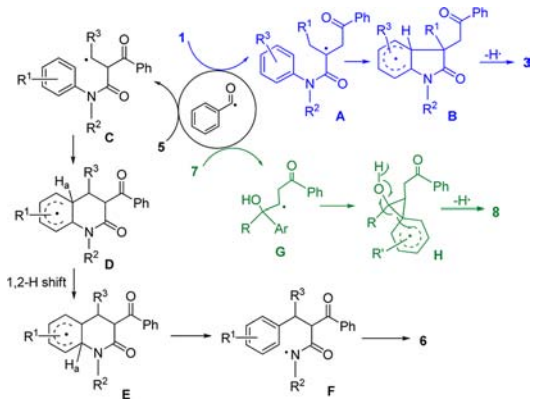
Scheme 5. Proposed Mechanism



position to form the intermediate **C** (black), and sequential cyclization led to intermediate **D**. Then a 1,2-H shift happened instead of loss of the hydrogen radical to afford the intermediate **E**. The final product **6** was formed by C−N bond cleavage followed by hydrogen radical abstraction. For prop-2-enol substrates **7**, the benzoyl radical was added to the C−C double bond to lead to the intermediate **G** (green); subsequently, the radical cyclization to the aryl ring occurred to form the intermediate **H** containing a cyclopropanyl ring. Synchronous formation of a carbonyl group through the cleavage of the O−H bond and ring opening of cyclopropane led to the final product **8**.

In summary, we have developed a novel protocol for the difunctionalization of alkenes through an aroyl radical addition/1,4-/1,2-aryl shift cascade. The method is highlighted by the use of the milder reaction conditions and is environmentally benign by using economic available benzoin as the benzoyl precursor. In addition the unique 1,2-/1,4-aryl shift reactions have been discovered through a radical pathway. Further studies on the use of these reactions are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

General procedures, materials, instrumentation, synthesis, ^{1}H, ^{13}C NMR and 2D spectra. 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.

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■ REFERENCES

(1) For recent reviews: (a) Jacques, B.; Muiňz, K. In *Catalyzed Carbon-Heteroatom Bond Formation*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2010; pp 119−135. (b) Sibbald, P. A. *Palladium-catalyzed oxidative difunctionalization of alkenes: New reactivity and new mechanisms*; ProQuest, UMI Dissertation Publishing: 2011. (c) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561. (d) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (e) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (f) Li, G.; Kotti, S. R. S. S.; Timmons, C. *Eur. J. Org. Chem.* **2007**, *72*, 2745. (g) Muňiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412. (h) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009. (i) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. (j) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (k) Zhang, C.; Tang, C.; Jia, N. *Chem. Soc. Rev.* **2012**, *41*, 3464.

(2) (a) Wu, T.; Mu, X.; Liu, G.-S. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578. (b) Mu, X.; Wu, T.; Wang, H.-Y.; Guo, Y.-L.; Liu, G.-S. *J. Am. Chem. Soc.* **2012**, *134*, 878. (c) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Hu, M.; Xie, P.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638. (d) Li, Y.-M.; Sun, M.; Wang, H.-L.; Tian, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972. (e) Li, X.; Xu, X.; Hu, P.; Xiao, X.; Zhou, C. *J. Org. Chem.* **2013**, *78*, 7343. (f) Matcha, K.; Narayan, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7985. (g) Meng, Y.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem. Commun.* **2013**, *49*, 7540.

(3) Zhou, M.-B.; Song, R.-J.; Ouyang, X. H.; Liu, Y.; Wei, W.-T.; Deng, G.-B.; Li, J.-H. *Chem. Sci.* **2013**, *4*, 2690.

(4) Wu, T.; Zhang, H.; Liu, G. *Tetrahedron* **2012**, *68*, 5229.

(5) (a) Jia, F.; Liu, K.; Xi, H.; Lu, S.; Li, Z. *Tetrahedron. Lett.* **2013**, *54*, 6337. (b) Wang, H.; Guo, L.-N.; Duan, X.-H. *Adv. Synth. Catal.* **2013**, *355*, 2222.

(6) (a) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052. (b) Fleck, M.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6189. (c) Selig, P.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5082. (d) Veerman, M.; Resendiz, M. J.; Garcia-Garibay, M. A. *Org. Lett.* **2006**, *8*, 2615. (e) Mortko, C. J.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2005**, *12*, 7994. (f) Fagnoni, M.; Albini, A. *Acc. Chem. Res.* **2005**, *38*, 713. (g) Roth, H. D. *Angew. Chem., Int. Ed.* **1989**, *28*, 1193. (h) Yang, C.; Xia, W.-J. *Chem.—Asian J.* **2009**, *4*, 1774. (i) Horspool, W. M. *Synthetic Organic Photochemistry*; Plenum Press: New York, 1984.

(7) (a) Xia, W.-J.; Shao, Y.-T.; Gui, W.-J.; Yang, C. *Chem. Commun.* **2011**, *47*, 11098. (b) Liu, Q.; Meng, J.; Liu, Y.; Yang, C.; Xia, W.-J. *J. Org. Chem.* **2014**, *79*, 8143. (c) Zhao, G.-L.; Yang, C.; Sun, H.-N.; Lin, R.; Xia, W.-J. *Org. Lett.* **2012**, *14*, 776. (d) Shao, Y.-T.; Yang, C.; Gui, W.-J.; Liu, Y.; Xia, W.-J. *Chem. Commun.* **2012**, *48*, 3560. (e) Gou, B.-Q.; Li, D.-Z.; Yang, C.; Xia, W.-J.; Li, Y.-L.; Chen, X.-M. *J. Photochem. Photobiol. A: Chem.* **2012**, *233*, 46. (f) Yang, C.; Xia, W.-J.; Scheffer, J. R. *Tetrahedron* **2007**, *63*, 6791. (g) Zhao, G.-L.; Yang, C.; Chen, Q.; Jin, J.; Zhang, X.; Zhao, L.-Y.; Xia, W.-J. *Tetrahedron* **2009**, *65*, 9952.

(8) Ayitou, A. J. L.; Sivaguru, J. *J. Am. Chem. Soc.* **2009**, *131*, 5036.

(9) CCDC 1026351 (**6a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (see the SI).

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