ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Y. Zhao, Y. Luo, Z. Wang and P. Xu, *Chem. Commun.*, 2018, DOI: 10.1039/C8CC01486H.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C8CC01486H

Journal Name

COMMUNICATION

A New Approach to Access Difluoroalkylated Diarylmethanes *via* Visible-Light Photocatalytic Cross-Coupling Reactions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Yin-Na Zhao, Yong-Chun Luo, Zhu-Yin Wang and Peng-Fei Xu*

Difluoroalkylated diarylmethanes with biological and pharmacological potentials were synthesized from *para*-quinone methides (*p*-QMs) and difluoroalkylating reagents *via* a visible light photocatalysis strategy. Mechanism studies showed that the excited photocatalyst **fac*-Ir(ppy)$_3$ was primarily quenched by *p*-QMs and the generated diarylmethane radical intermediates then underwent a radical-radical cross-coupling reaction with difluoroalkyl radicals. This reaction features mild conditions, high efficiency and wide functional group compatibility.

Diarylmethane scaffold widely exists in natural products and pharmaceuticals such as podophyllotoxin,[1c] tolterodine,[1d] latifolin,[1e] isochromans derivatives[1f] and kadangustin J,[1g] which exhibit antimicrobial, antiviral, anticancer and/or antioxidant activities (Figure 1).[1] In the past decade, the synthesis of hybrid systems with multiple biological and pharmacological properties is attracting more and more attention.[2] The incorporation of difluoromethylene group (typically catalyzed by transition-metal[3]) which can function as a bioisostere for an oxygen atom or a carbonyl group,[4a-b] can significantly affect the electronic, chemical and reaction activities of the parent molecules.[4] Considering all these, incorporation of difluoromethylene group into diarylmethane unit to construct the difluoroalkylated diarylmethane skeleton can increase the diversity of diarylmethanes with new bioactivities.

para-Quinone methides (*p*-QMs), characterized by the unique assembly of carbonyl and olefinic moieties, are chemically defined as neutral and zwitterionic resonance entities (Scheme 1a).[5] Therefore, p-QMs are usually used in 1,6-conjugate addition/aromatization reactions as Michael acceptors to access biologically active diarylmethane compounds,[6] although several other methods have been reported.[7] In 1985, Kurreck's group found that di- and triphenylmethyl radicals could be formed by treating galvinols (with structures similar to *p*-QMs) with a sodium amalgam in hydrocarbon solvents by a single electron reduction process (Scheme 1b).[8] However, no further research is reported.

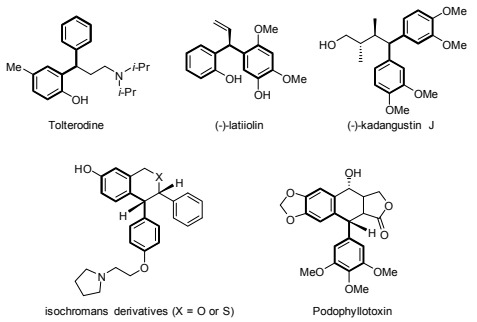
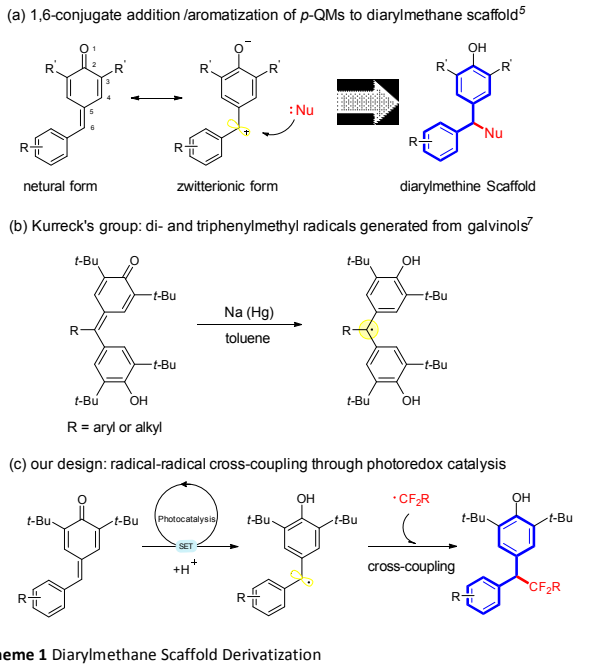


Figure 1 Typical Biologically Active Molecules with the Diarylmethane Unit



Scheme 1 Diarylmethane Scaffold Derivatization

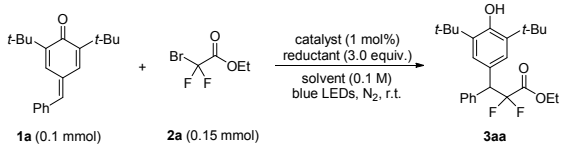
State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China
E-mail: xupf@lzu.edu.cn; Fax: +86-931-8915557; Tel: +86-931-8912281

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8CC01486H

Photoredox catalysis has become a powerful tool for organic synthesis in the past decade owing to its inherently mild, green and highly-efficient characteristics.[9] This catalysis strategy is well-known by its single electron transfer (SET) process.[4f-g,4i] Inspired by Kurreck's work, we envisioned that *p*-QMs (**1a** , $E_{1/2}$ red = - 0.20 V vs SCE, see Supporting Information Figure S1) could be radical precursors for generating diarylmethyl radical intermediates through a photocatalytic single electron reduction process. Thus, we proposed a new approach involving *p*-QMs and difluoroalkylating reagents to construct difluoroalkylated diarylmethane compounds *via* visible light photocatalytic radical-radical cross-coupling reactions (Scheme 1c).

Table 1 Optimization of the Reaction Conditions[a]



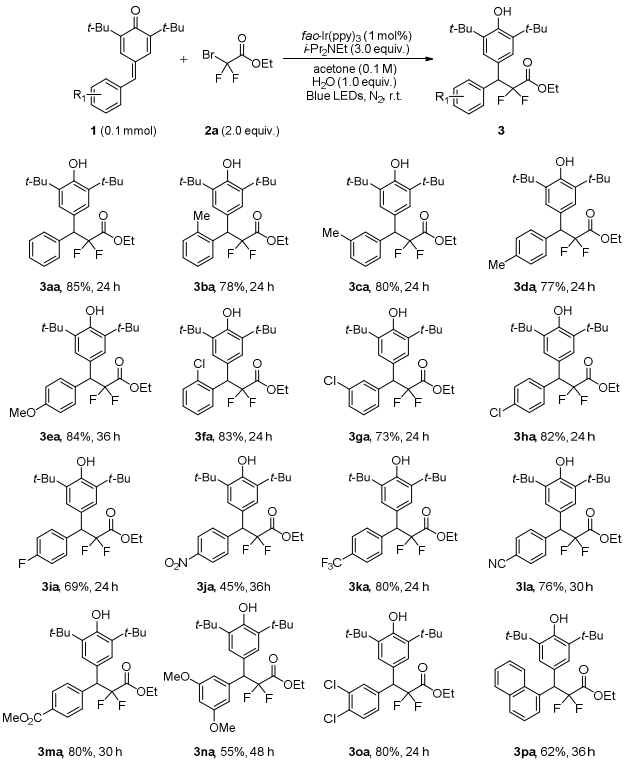
1a (0.1 mmol) **2a** (0.15 mmol) **3aa**

Entry	Catalyst	Reductant	Solvent	Yield[b]
1	*fac*-Ir(ppy)$_3$	*i*-Pr$_2$NEt	MeCN	65
2	Ru(bpy)$_3$Cl$_2$•6H$_2$O	*i*-Pr$_2$NEt	MeCN	32
3[c]	Eosin Y	*i*-Pr$_2$NEt	MeCN	38
4[d]	*fac*-Ir(ppy)$_3$	*i*-Pr$_2$NEt	MeCN	NR[e]
5	-	*i*-Pr$_2$NEt	MeCN	trace
6	*fac*-Ir(ppy)$_3$	HE[f]	MeCN	11
7	*fac*-Ir(ppy)$_3$	Et$_3$N	MeCN	32
8	*fac*-Ir(ppy)$_3$	*i*-Pr$_2$NEt	Toulene	47
9	*fac*-Ir(ppy)$_3$	*i*-Pr$_2$NEt	MeOH	14
10	*fac*-Ir(ppy)$_3$	*i*-Pr$_2$NEt	THF	40
11	*fac*-Ir(ppy)$_3$	*i*-Pr$_2$NEt	1,4-dioxane	69
12	*fac*-Ir(ppy)$_3$	*i*-Pr$_2$NEt	acetone	72
13[g]	*fac*-Ir(ppy)$_3$	*i*-Pr$_2$NEt	acetone	76
14[h]	*fac*-Ir(ppy)$_3$	*i*-Pr$_2$NEt	acetone	65
15[gij]	*fac*-Ir(ppy)$_3$	*i*-Pr$_2$NEt	acetone	85

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.5 equiv.), catalyst (1 mol%), reductant (3.0 equiv.), solvent (1 mL), and blue LEDs under N_2 at room temperature for 36 h. [b]Isolated yield. [c]Green LEDs. [d]No light. [e]NR (No Reaction). [f]HE (Hantzsch Ester). [g]**2a** (2.0 equiv.). [h]**2a** (3.0 equiv.). [i]H_2O (1.0 equiv.) as additive. [j]Reacted for 24 h.

The study was initiated by using *p*-QM **1a** and ethyl bromodifluoroacetate **2a** ($E_{1/2}$ red = - 0.89 V vs SCE, see Supporting Information Figure S2) as model substrates (Table 1). Fortunately, the desired diarylmethane product **3aa** was obtained in 65% yield in the presence of *fac*-Ir(ppy)$_3$ (1 mol%) and *i*-Pr$_2$NEt (3.0 equiv.) in MeCN (entry 1). However, when the catalyst was replaced by Ru(bpy)$_3$Cl$_2$•6H$_2$O or Eosin Y, the yield of **3aa** was dramatically decreased to 32% (entry 2) and 38% (entry 3), respectively. Control experiments were then performed and the results confirmed the necessity of both light and *fac*-Ir(ppy)$_3$ (entries 4, 5). Compared with *i*-Pr$_2$NEt, neither Hantzsch ester nor Et$_3$N was a better reductant (entries 6, 7). After screening a series of solvents (entries 8-12), it was found that acetone was an ideal solvent with a yield of 72% (entry 12). With the loading of **2a** increased to 2.0 equiv., the yield of the desired product **3aa** was further increased to 76% (entry 13). However, the yield of the desired product was decreased to 65% when the loading of **2a** was increased to 3.0 equiv. (entry 14). Finally, it was found that the yield of the reaction increased to 85% when H_2O was added as an additive (entry 15). We speculated that H_2O could promote the protonation of the reaction process as discussed in the mechanism section.

With the optimal conditions established, we next evaluated the substrate scope of *p*-QMs **1** (Scheme 2). To our delight, a variety of substituented *p*-QMs could smoothly react to provide the desired diarylmethane products with moderate to excellent yields (45-85%). Both electron-donating substituents (**3ba-3ea**) and electron-withdrawing substituents (**3fa-3ma**) were compatible in the reaction system. Notably, the nitro group (**3ja**) gave a lower yield (45%), probably owing to its strong oxidizing ability. Bis-substituted *p*-QMs (**1o**, R_1 = 3,4-dichloro and **1n**, 3,5-dimethoxyl) and *p*-QM with naphthyl (**1p**) could also take part in the reaction with good yields.

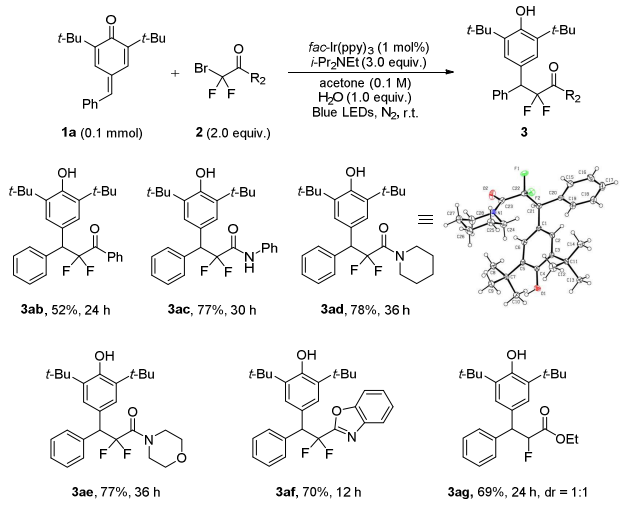


Scheme 2 The Scope of para-Quinone Methides (*p*-QMs)

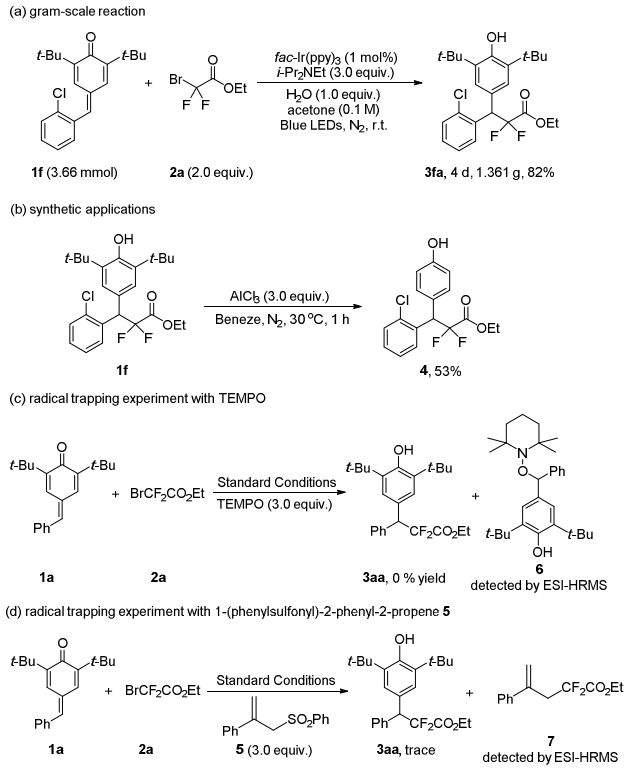
Next, we explored the scope of difluoroalkylating reagents **2** to examine their applicability in our system (Scheme 3). Difluoroalkylating reagents with different functional groups including carbonyl, esteryl, acylamino and heteroaryl groups, proceeded well with **1a** to achieve the expected products in 52% to 77% yields (**3ab-3ag**). Moreover, ethyl

View Article Online
DOI: 10.1039/C8CC01486H

bromofluoroacetate **2g** could also be applied to this reaction system and afforded the product **3ag** (69% yield) albeit with a low diastereoselectivity (dr = 1:1). Additionally, the structure of **3ad** was confirmed by X-ray analysis (see Supporting Information).



Scheme 3 The Scope of Bromodifluoroacetates



Scheme 4 Applications of Difluoroalkylation of *p*-QMs and Radical Trapping Experiments

To demonstrate the synthetic value of this work, the gram-scale reaction was conducted with **1f** (1.205 g) and **2a** (Scheme 4a) to give the corresponding diarylmethane product **3fa** (1.361 g) in the yield of 82%. *p*-QMs bearing 2,6-di-*tert*-butyl groups are useful synthons because of their facile synthesis and inherent stability.[10] $AlCl_3$ mediated de-*tert*-butylation reaction produced the diphenolmethane derivative **4** with a moderate yield (Scheme 4b).[5b,10]

To gain insight into the mechanism of this reaction, several control experiments were performed. Stern-Volmer fluorescence quenching experiments revealed that *fac*-Ir(ppy)$_3$ was primarily quenched by *p*-QM **1a** while ethyl bromodifluoroacetate **2a** and *i*-Pr_2NEt showed a much less effect (Figure 2**)**. The radical trapping experiments were conducted with different scavengers to capture the radical intermediates in the system, and the products were detected by ESI-HRMS techniques (see Supporting Information). Under the standard conditions, TEMPO-trapped product **6** was observed when TEMPO was used as the scavenger with no product **3aa** detected (Scheme 4c). Moreover, both product **3aa** and **7** were observed when 1-(phenylsulfonyl)-2-phenyl-2-propene **5** was added to the reaction (Scheme 4d). These observations indicated the existence of diarylmethyl radical and difluoroacetate radical intermediates.

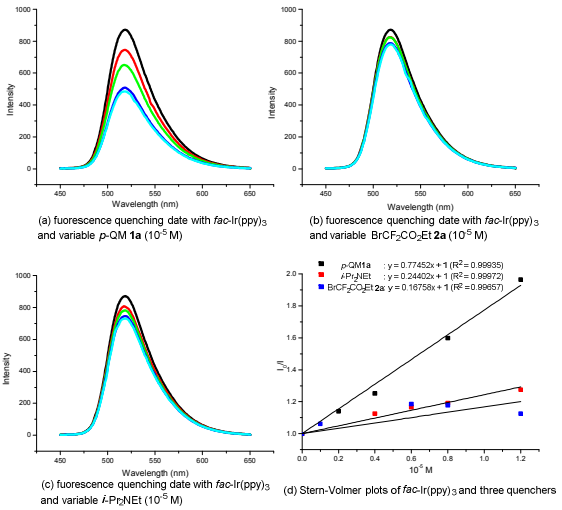


Figure 2 Stern-Volmer Fluorescence Quenching Experiments

On the basis of our findings and previous studies, a possible mechanism is illustrated in Figure 3**.** Upon visible light irradiation, the excited **fac*-Ir(ppy)$_3$ engages in single electron transfer (SET) with *p*-QM **1a** followed by a protonation process to give the radical intermediate **I** as well as the oxidized *fac*-^{IV}Ir(ppy)$_3$. Then the photocatalytic cycle is closed by a SET process between *i*-Pr_2NEt and *fac*-^{IV}Ir(ppy)$_3$, delivering the radical intermediate **II**. The resultant α-amino alkyl radical **III** from sequential deprotonation of intermediate **II**, known as a strong reducing agent,[11-14] can easily reduce ethyl bromodifluoroacetate **2a** to generate radical intermediate **IV** and bromide-iminium ion pair **V**. Finally, a radical–radical cross-coupling of intermediates **I** and **IV** leads to the target diarylmethane product (**3aa**).

View Article Online
DOI: 10.1039/C8CC01486H

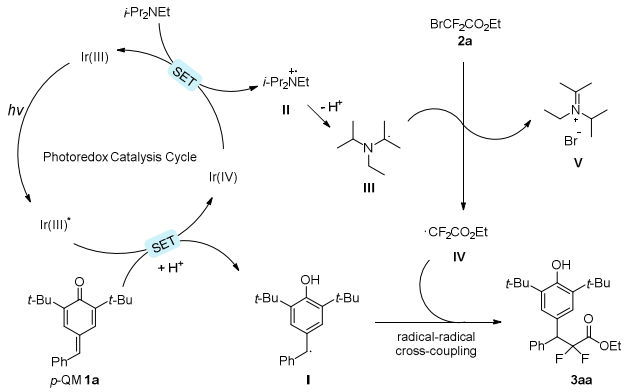


Figure 3 Proposed Mechanism

In summary, we have developed a novel photocatalytic radical-radical cross-coupling reaction under mild conditions to access difluoroalkylated diarylmethane compounds with pharmaceutical potentials, the reaction features high efficiency and wide functional group compatibility. It is noteworthy that the reaction was mediated by a diarylmethyl radical intermediate generated from the single electron reduction and protonation processes of *p*-QMs.

We are grateful to the NSFC (21632003 and 21572087), the key program of Gansu province (17ZD2GC011) and the "111" program from the MOE of P. R. China for financial support.

Notes and references

1 (a) M. Recanatini, A. Cavalli and P. Valenti, *Med. Res. Rev.*, 2002, **22**, 282; (b) H. A. I. Yoshihara, J. W. Apriletti, J. D. Baxterb and T. S. Scanlan, *Bioor. Med. Chem. Lett.*, 2001, **11**, 2821; (c) C. Canela, R. M. Moraesb, F. E. Dayana and D. Ferreira, *Phytochemistry*, 2000, **54**, 115; (d) P. Abrams, R. Freeman, C. Anderström and A. Mattiasson, *British J. Urol.*, 1998, **81**, 801; (e) R.-B. An, G.-S. Jeong and Y.-C. Kim, *Chem. Pharm. Bull.*, 2008**, 56***,* 1722; (f) J. Liu, E. T. Birzin, W. Chan, Y. T. Yang, L.-Y. Pai, C. DaSilva, E. C. Hayes, R. T. Mosley, F. DiNinno, S. P. Rohrer, J. M. Schaeffer and M. L. Hammond, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 715; (g) S. J. Davidson and D. Barker, *Tetrahedron Lett.*, 2015, **56**, 4549.

2 (a) J. A. M. Christiaans and H. Timmerman, *Eur. J. Pharm. Sci.*, 1996, **4**, 1; (b) G. Mehta and V. Singh, *Chem. Soc. Rev.*, 2002, **31**, 324; (c) L. F. Tietze, H. P. Bell and S. Chandrasekhar, *Angew. Chem. Int. Ed.*, 2003, **42**, 3996; (d) M. Decker, *Curr. Med. Chem.*, 2011, **18**, 1464.

3 Transition-metal catalysis has been one of the attractive strategies to access difluoroalkylated compounds: (a) Z. Feng, F. Chen and X. Zhang, *Org. Lett.*, 2012, **14**, 1938; (b) Y.-L. Xiao, W.-H. Guo, G.-Z. He, Q. Pan and X. Zhang, *Angew. Chem. Int. Ed.*, 2014, **53**, 9909; (c) Z. Feng, Q.-Q. Min, X.-P. Fu, L. An and X. Zhang, *Nat. Chem.*, 2017, **9**, 918.

4 (a) C. M. Blackburn, D. A. England and F. Kolkmann, *J. Chem. Soc. Chem. Commun.*, 1981, 930; (b) A. K. Yudin, G. K. S. Prakash, D. Deffieux, M. Bradley, R. Bau and G. A. Olah, *J. Am. Chem. Soc.*, 1997, **119**, 1572; (c) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.*, 2012, **134**, 1494; (d) Z. Feng, Q. Q. Min, Y.-L. Xiao, B. Zhang and X. Zhang, *Angew. Chem. Int. Ed.*, 2014, **53**, 1669; (e) S.-L. Shi and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2015, **54**, 1646; (f) C. Yu, N. Iqbal, S. Park and E. J. Cho, *Chem. Commun.*, 2014, **50**, 12884; (g) J. Xie, T. Zhang, F. Chen, N. Mehrkens, F. Rominger, M. Rudolph and A. S. K. Hashmi, *Angew. Chem. Int. Ed.*, 2016, **55**, 2934; (h) M. Ke and Q. Song, *Adv. Synth. Catal.*, 2017, **359**, 384; (i) T. Chatterjee, N. Iqbal, Y. You and E. J. Cho, *Acc. Chem. Res.*, 2016, **49**, 2284; (j) D. E. Yerien, S. Barata-Vallejo and A. Postigo, *Chem. Eur. J.*, 2017, **23**, 14676.

5 (a) M. G. Peter, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 555; (b) T. Itoh, *Prog. Polym. Sci.*, 2001, **26**, 1019; (c) M. M. Toteva and J. P. Richard, *Adv. Phys. Org. Chem.*, 2011, **45**, 39; (d) A. Parra and M. Tortosa, *ChemCatChem*, 2015, **7**, 1524.

6 (a) W.-D. Chu, L.-F. Zhang, X. Bao, X.-H. Zhao, C. Zeng, J.-Y. Du, G.-B. Zhang, F.-X. Wang, X.-Y. Ma and C.-A. Fan, *Angew. Chem. Int. Ed.*, 2013, **52**, 9229; (b) L. Caruana, F. Kniep, T. K. Johansen, P. H. Poulsen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2014, **136**, 15929; (c) B. T. Ramanjaneyulu, S. Mahesh and R. V. Anand, *Org. Lett.*, 2015, **17**, 3952; (d) S. Mahesh, G. Kant and R. V. Anand, *RSC Adv.*, 2016, **6**, 80718; (e) Z. Wang, Y. F. Wong and J. Sun, *Angew. Chem. Int. Ed.*, 2015, **54**, 13711; (f) N. Dong, Z.-P. Zhang, X.-S. Xue, X. Li and J.-P. Cheng, *Angew. Chem. Int. Ed.*, 2016, **55**, 1460; (g) Y. Shen, J. Qi, Z. Mao and S. Cui, *Org. Lett.*, 2016, **18**, 2722; (h) C. Jarava-Barrera, A. Parra, A. López, F. Cruz-Acosta, D. Collado-Sanz, D. J. Cárdenas and M. Tortosa, *ACS Catal.*, 2016, **6,** 442; (i) K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen and D. Enders, *Angew. Chem. Int. Ed.*, 2016, **55**, 12104; (j) S. Li, Y. Liu, B. Huang, T. Zhou, H. Tao, Y. Xiao, L. Liu and J. Zhang, *ACS Catal.*, 2017, **7**, 2805; (k) R. Zhuge, L. Wu, M. Quan, N. Butt, G. Yang and W. Zhang, *Adv. Synth. Catal.*, 2017, **359**, 1028; (l) T.-C. Kang, L.-P. Wu, Q.-W. Yu and X.-Y. Wu, *Chem. Eur. J.*, 2017, **23**, 6509.

7 (a) T. P. Pathak and M. S. Sigman, *Org. Lett.*, 2011, **13**, 2774; (b) S. M. Podhajsky, Y. Iwai, A. Cook-Sneathen and M. S. Sigman, *Tetrahedron*, 2011, **67**, 4435; (c) K. M. Gligorich, Y. Iwai, S. A. Cummings and M. S. Sigman, *Tetrahedron*, 2009, **65**, 5074; (d) Y. Iwai, K. M. Gligorich and M. S. Sigman, *Angew. Chem. Int. Ed.*, 2008, **47**, 3219; (e) K. M. Gligorich, S. A. Cummings and M. S. Sigman, *J. Am. Chem. Soc.*, 2007, **129**, 14193; (f) F. Jin, Y. Zhong, X. Zhang, H. Zhang, Q. Zhao and W. Han, *Green Chem.*, 2016, **18**, 2598; (g) E. N. Bess and M. S. Sigman, *Org. Lett.*, 2013, **15**, 646; (h) J. Ghorai and P. Anbarasan, *J. Org. Chem.*, 2015, **80**, 3455; (i) S. Y. Lee, A. Villani-Gale and C. C. Eichman, *Org. Lett.*, 2016, **18**, 5034.

8 B. Kirste, W. Harrer and H. Kurreck, *J. Am. Chem. Soc.*, 1985, **107**, 20.

9 (a) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (b) R. Brimioulle, D. Lenhart, M. M. Maturi and T. Bach, *Angew. Chem. Int. Ed.*, 2015, **54**, 3872; (c) K. L. Skubi, T. R. Blum and T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035; (d) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075; (e) M. H. Shaw, J. Twilton and D. W. C. MacMillan, *J. Org. Chem.*, 2016, **81**, 6898.

10 S. A. Saleh and H. I. Tashtoush, *Tetrahedron,* 1998, **54**, 14157.

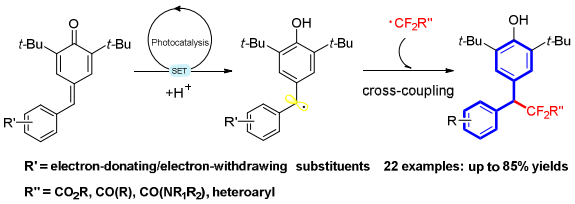
11 (a) K. Bhattacharyya and P. K. Das, *J. Phys. Chem.*, 1986, **90**, 3987; (b) D. D. M. Wayner, D. J. McPhee and D. Griller, *J. Am. Chem. Soc.*, 1988, **110**, 132; (c) M. Jonsson, D. D. M. Wayner and J. Lusztyk, *J. Phys. Chem.*, 1996, **100**, 17539.

12 A. Bahamonde and P. Melchiorre, *J. Am. Chem. Soc.*, 2016, **138**, 8019.

13 H. Ismaili, S. P. Pitre and J. C. Scaiano, *Catal. Sci. Technol.*, 2013, **3**, 935.

14 D. B. Freeman, L. Furst, A. G. Condie and C. R. J. Stephenson, *Org. Lett.*, 2012, **14**, 94.

View Article Online
DOI: 10.1039/C8CC01486H



A *para*-quinone methides and difluoroalkylating reagents involved radicals cross-coupling reaction was described, through the photocatalytic generated diarylmethane radical intermediates.