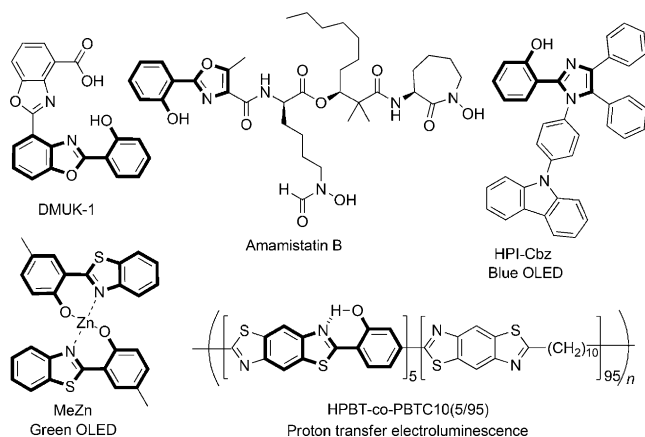


Rhodium(III)-Catalyzed *ortho*-Heteroarylation of Phenols through Internal Oxidative C–H Activation: Rapid Screening of Single-Molecular White-Light-Emitting Materials

Bijin Li, Jingbo Lan,* Di Wu, and Jingsong You*

Abstract: Reported herein is the first example of a transition-metal-catalyzed internal oxidative C–H/C–H cross-coupling between two (hetero)arenes through a traceless oxidation directing strategy. Without the requirement of an external metal oxidant, a wide range of phenols, including phenol-containing natural products, can undergo the coupling with azoles to assemble a large library of highly functionalized 2-(2-hydroxyphenyl)azoles. The route provides an opportunity to rapidly screen white-light-emitting materials. As illustrative examples, two bis(triphenylamine)-bearing 2-(2-hydroxyphenyl)oxazoles, which are difficult to access otherwise, exhibit bright white-light emission, high quantum yield, and thermal stability. Also presented is the first example of the white-light emission, in a single excited-state intramolecular proton transfer system, of 2-(2-hydroxyphenyl)azoles, thus highlighting the charm of C–H activation in the discovery of new organic optoelectronic materials.

The 2-(2-hydroxyphenyl)azoles are important scaffolds in various natural products, pharmaceuticals, and organic functional materials (Scheme 1).^[1] In principle, the highly func-

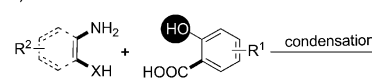


Scheme 1. Select natural products, pharmaceuticals, and organic functional material molecules containing 2-(2-hydroxyphenyl)azole.

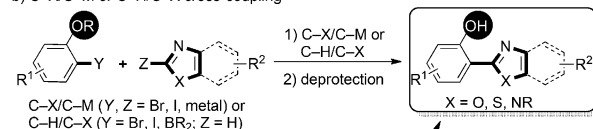
[*] B. Li, Prof. Dr. J. Lan, Prof. Dr. D. Wu, Prof. Dr. J. You
Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Medical School, Sichuan University
29 Wangjiang Road, Chengdu 610064 (PR China)
E-mail: jingbolan@scu.edu.cn
jsyou@scu.edu.cn

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201507272>.

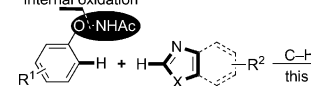
a) Condensation reaction



b) C–X/C–M or C–H/C–X cross-coupling



c) Internal oxidative C–H/C–H cross-coupling



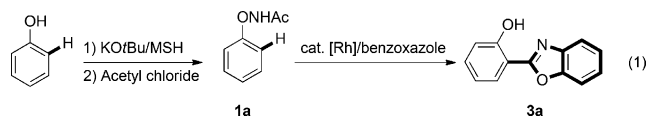
- Easily available starting materials
- Tolerance of wide functional groups
- Without extra steps for removal of undesired directing groups
- Rapid access to a structurally diverse library
- Without the stoichiometric external metal oxidant

Scheme 2. Synthetic strategy for 2-(2-hydroxyphenyl)azoles.

tionalized 2-(2-hydroxyphenyl)azole scaffolds can be synthesized through condensation reactions (Scheme 2a) and classical transition-metal-catalyzed C–X/C–M cross-coupling reactions as well as recently developed direct C–H bond arylation of azoles with 2-halophenols (C–H/C–X; Scheme 2b).^[2] However, these methods typically suffer from several disadvantages such as tedious multiple-step synthesis, protection and deprotection of the phenolic hydroxy group, and selective *ortho*-halogenation of phenols, which significantly restrict the rapid construction of structurally diverse 2-(2-hydroxyphenyl)azoles. In recent years, transition-metal-catalyzed oxidative C–H/C–H cross-coupling between a simple arene and a heteroarene has received much attention, and can circumvent prefucionalization of both coupling partners.^[3] Given that both phenols and azoles are widespread compounds, the oxidative C–H/C–H cross-coupling of a phenol with an azole would be the most straightforward and convenient access to a large library of 2-(2-hydroxyphenyl)azoles (Scheme 2c).

Despite great effort in C–H/C–H cross-couplings of two (hetero)arenes, the *ortho*-selective C–H/C–H couplings of phenols with azoles to access 2-(2-hydroxyphenyl)azoles still remain unsolved so far. Thus, innovative strategies to address such a challenge are needed. Recently, the use of a traceless oxidizing directing group as both the directing group and the internal oxidant has emerged as a promising strategy in the field of oxidative C–H activation, and it not only has clear advantages of high *ortho* selectivity and monocoupling, but also avoids the use of stoichiometric amounts of an external metal oxidant and extra steps for removal of undesired

directing groups from the products.^[4] Despite significant progress, most of the precedented examples are restricted to alkenylation and annulation of arenes with olefins or alkynes,^[5] and internal oxidative *ortho*-C–H (hetero)arylation of arenes with (hetero)arenes still remains unprecedented. As part of our continuing efforts to extend π -conjugated systems through C–H activation strategy, we herein report the discovery and development of an innovative catalytic system to accomplish this transformation (Scheme 2 c).



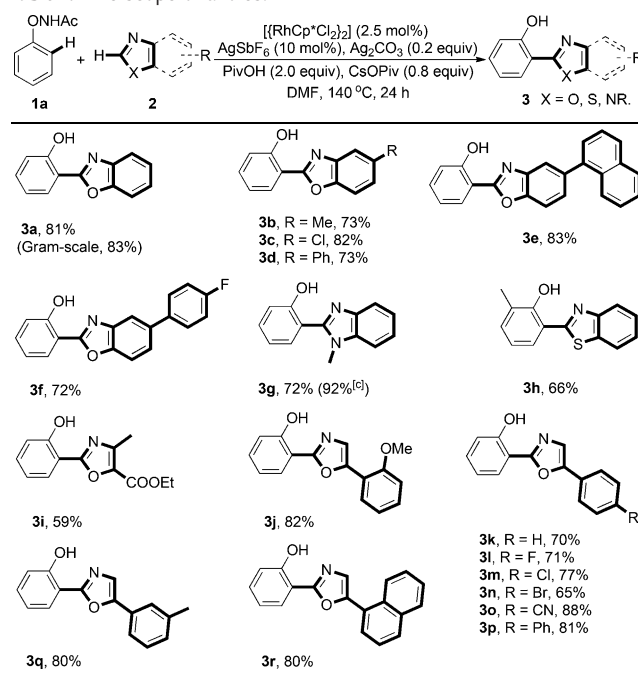
We initiated our investigation by using *N*-phenoxyacetamide (**1a**) as a model substrate to evaluate the feasibility of the traceless oxidation directing strategy [see Table S1 in the Supporting Information; Eq. (1); MSH: *O*-mesitylsulfonylhydroxylamine]. By employing the commonly used $[\{\text{RhCp}^*\text{Cl}_2\}_2]/\text{AgSbF}_6$ catalytic system, the reaction of **1a** with benzoxazole (**2a**) delivered the desired 2-(2-hydroxyphenyl)benzoxazole (**3a**) in 19% yield with the concomitant removal of the amide directing group (Table S1, entry 1). To our delight, addition of 0.2–0.4 equivalents of a silver(I) salt as the co-base greatly improved the yield of **3a** (Table S1, entries 10–13). Among the silver salts investigated (e.g., AgOAc, AgOPiv, and Ag₂CO₃), AgOPiv was the most effective. In view of commercial availability, Ag₂CO₃ was selected instead of AgOPiv, thus affording **3a** in 81% yield (Table S1, entry 13).

With the optimal system in hand, a range of azoles was investigated. As shown in Table 1, a variety of azoles including benzoxazoles, benzoimidazoles, benzothiazoles, and oxazoles smoothly reacted with **1a**, thus affording the coupled products **3a–r** in good to excellent yields. The coupling reaction could also be performed to produce **3a** on a gram scale without problems, and thus reveals a bench-scale preparation.

Next, we turned our attention to phenol substrates. To our delight, a broad range of phenols with either *ortho*-, *meta*-, or *para*-substituents could couple with **2a** in good yields (Table 2, **4a–l**). Notably, this coupling reaction could tolerate reactive functional groups such as ester, amino, keto, chloride, and the even more challenging bromide and iodide, which are useful for further synthetic transformations. Phenol-containing natural products such as L-tyrosine and estrone underwent the coupling with **2a** at the position *ortho* to the phenolic hydroxy group to afford 2-(2-hydroxyphenyl)azole scaffolds, which are hard to access by traditional synthetic disconnections without C–H activation. Such reactions demonstrate the potential of C–H activation in a late-stage functionalization of natural products (**4m** and **4n**).^[6]

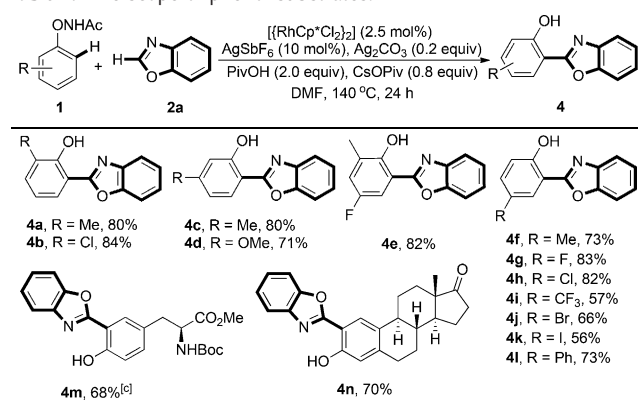
To gain mechanistic insight into the oxidative cross-coupling, deuterium-labeling experiments of **1a** and **2a** were performed. When **1a** was treated with D₂O under the standard reaction conditions for 0.5 hours it led to significant deuterium incorporation at the *ortho*-position (95% D),

Table 1: The scope of azoles.^[a,b]



[a] Reaction conditions: **1a** (0.2 mmol) and **2** (0.3 mmol) in DMF (1.0 mL) under N₂ atmosphere. [b] Yield of isolated product. [c] $[\{\text{RhCp}^*\text{Cl}_2\}_2]$ (5.0 mol%), AgSbF₆ (20 mol%), and Ag₂CO₃ (0.4 equiv). Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl, DMF = *N,N*-dimethylformamide, Piv = pivaloyl.

Table 2: The scope of phenol substrates.^[a,b]



[a] Reaction conditions: **1** (0.2 mmol) and **2a** (0.3 mmol) in DMF (1.0 mL) under N₂ atmosphere. [b] Yield of isolated product. [c] $[\{\text{RhCp}^*\text{Cl}_2\}_2]$ (5.0 mol%), AgSbF₆ (20 mol%), and Ag₂CO₃ (0.4 equiv). Boc = *tert*-butoxycarbonyl.

whereas the H–D exchange ratio of **2a** was only 38% [see Eqs. (S1) and (S2)]. Moreover, the exposure of **1a** and **2a** to D₂O in one pot gave rise to a similar deuterated ratio [see Eq. (S3)]. These observations suggest that the reaction might start from the cyclometalation of **1a**.^[7] Subsequently, kinetic isotope effects (KIE) were investigated with regard to the C–H/D bonds for both the coupling partners [see Eqs. (S4) and (S5)]. No significant KIE value ($k_{\text{H}}/k_{\text{D}} = 1.04$) was observed in two parallel competition reactions between **1a** and the deuterated derivative [D₅]-**1a** with **2a**, whereas

a significant KIE of 2.89 was obtained between **2a** and [D₁]-**2a** with **1a**. These observations revealed that the C–H bond breaking of benzoxazole might be involved in the rate-limiting step.^[8] Furthermore, addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a radical scavenger had a negligible effect on the reaction between **1a** and **2a**, and thus ruled out a radical pathway (Table S1, entry 18). Thus, a tentative mechanism is proposed (see Figure S11). First, the coordination of the amide nitrogen atom to Rh^{III} and subsequent carboxylate-assisted *ortho*-C–H bond activation of phenol produce a cyclorhodium intermediate,^[5a,9] which then reacts with benzoxazole to give the key benzoxazoly–Rh^{III}–phenyl intermediate. This intermediate then undergoes reductive elimination to a form Rh^I intermediate. Subsequently, intramolecular oxidative addition of the N–O bond to Rh^I generates a Rh^{III} intermediate, which upon protonation by PivOH, forms **3a** along with the regeneration of the Rh^{III} catalyst.

White organic light-emitting diodes (WOLEDs) have attracted much interest because of their great potential in flat panel displays and illuminations.^[10] Single-molecular white-light-emitting materials have many advantages such as long-term color balance, stability, and simple device fabrication process. However, it remains a challenge to discover a single chromophore that exhibits a broad emission covering the whole visible range ($\lambda = 400\text{--}700\text{ nm}$). Up to now, the examples describing single-molecular white-light-emitting materials are very rare.^[11,12] In principle, 2-(2-hydroxyphenyl)azoles enable a dual-emission behavior involving an enol-form emission with a relatively short wavelength and a keto-form emission with a relatively long wavelength owing to the excited-state intramolecular proton transfer (ESIPT),^[13] and thus are regarded as ideal candidates to design single-molecular white-light-emitting materials. Unfortunately, the typical 2-(2-hydroxyphenyl)azoles, including the coupled products **3a–r** and **4a–n** described herein, exhibit solely the keto-form emission and lack the enol-form emission in both the solid state and in nonpolar solvents, and therefore hardly generates a broadband emission covering the whole visible range. The protocol to attain white light is not yet established in a single ESIPT system.^[12] Given that triphenylamine (TPA) possesses good electron-donating properties, hole-transporting capability, and propeller-like nonplanar geometry,^[13] we envisioned that the incorporation of TPA into 2-(2-hydroxyphenyl)azole skeletons could prevent the molecular aggregation, and may thus lead to a strong emission. More importantly, the excellent electron-donating ability of TPA is capable of lowering the acidity of the phenolic hydroxy group, and may be beneficial to the enol-form species in the excited state, and thus lead to a dual emission covering the entire visible range.

Given that the competition from the highly electron-rich TPA makes the selective halogenation of both the TPA-bearing phenols and the TPA-bearing azoles more difficult, common synthetic disconnections for the rapid construction of TPA-bearing 2-(2-hydroxyphenyl)azoles are difficult. The internal oxidative coupling strategy developed herein could greatly streamline access to such scaffolds. No matter whether TPA is located on the phenol or azole moiety, both substrates

Table 3: Synthesis of TPA-bearing 2-(2-hydroxyphenyl)oxazoles.^[a,b]

<p>5a, 63%</p> <p>$\lambda_{\text{abs}} = 315\text{ nm}$; $\lambda_{\text{em}} = 426$ (minor), 525 nm $\phi_f = 40\%$ (in solution)^[c]</p>	<p>5b, 58%</p> <p>$\lambda_{\text{abs}} = 320\text{ nm}$; $\lambda_{\text{em}} = 397$ (minor), 533 nm $\phi_f = 19\%$ (in solution)^[c]</p>
<p>5c, 89%</p> <p>$\lambda_{\text{abs}} = 366\text{ nm}$; $\lambda_{\text{em}} = 419\text{ nm}$ $\phi_f = 83\%$ (in solution)^[c]</p>	<p>5d, 81%</p> <p>$\lambda_{\text{abs}} = 368\text{ nm}$; $\lambda_{\text{em}} = 421\text{ nm}$ $\phi_f = 82\%$ (in solution)^[c]</p>
<p>5e, 44%</p> <p>$\lambda_{\text{abs}} = 310, 378\text{ nm}$; $\lambda_{\text{em}} = 423, 546\text{ nm}$ $\phi_f = 57\%$ (in solution)^[d]</p> <p>$\lambda_{\text{abs}} = 259, 310, 373\text{ nm}$; $\lambda_{\text{em}} = 445, 542\text{ nm}$ $\phi_f = 62\%$ (in PS)^[e]</p>	<p>5f, 51%</p> <p>$\lambda_{\text{abs}} = 309, 370\text{ nm}$; $\lambda_{\text{em}} = 449, 564\text{ nm}$ $\phi_f = 77\%$ (in solution)^[d]</p> <p>$\lambda_{\text{abs}} = 259, 306, 369\text{ nm}$; $\lambda_{\text{em}} = 444, 540\text{ nm}$ $\phi_f = 56\%$ (in PS)^[e]</p>

[a] Reaction conditions: **1** (0.2 mmol) and **2** (0.3 mmol) in DMF (1.0 mL) under N₂ atmosphere. [b] Yield of isolated product. [c–e] Absolute quantum yields, absorption and emission maxima were measured in toluene ($5.0 \times 10^{-5}\text{ M}$), in toluene ($1.0 \times 10^{-6}\text{ M}$) and in PS films (0.2 wt %), respectively.

afforded the desired products in satisfactory yields (Table 3). As expected, the dual emission is observed when TPA is introduced to the phenol moiety of 2-(2-hydroxyphenyl)azoles (**5a** and **5b**; Table 3 and Figure 1a). However, the enol-form emissions are not strong enough to achieve white-light generation. Surprisingly, when TPA is connected to the azole moiety, the resulting molecules exhibit only the enol-form emission (**5c** and **5d**; Table 3 and Figure 1a). To our delight, the ESIPT equilibrium between the enol-form and the keto-form could be established through introducing TPA to both the phenol and azole moieties (**5e** and **5f**; Table 3 and Figures 1b and 2a). More importantly, the ESIPT equilibrium is observed not only in solution but also in the solid state. As shown in Figure 1b, the films of **5e** and **5f** (0.2 wt %) dispersed in polystyrene (PS) clearly display both the enol- and keto-form emissions, which cover the whole visible range extending from $\lambda = 400$ to 700 nm. Both compounds exhibit bright white-light emissions with CIE coordinates of **5e** (0.32, 0.38) and **5f** (0.34, 0.39) in toluene, and **5e** (0.30, 0.33) and **5f** (0.29, 0.34) in PS films, respectively (Figure 2b,c). Notably, **5e** and **5f** exhibit high quantum yields in films (Table 3), and predicts potential high-efficiency OLEDs.

Further investigation demonstrates that **5e** and **5f** exhibit large HOMO–LUMO energy gaps and low-lying HOMO levels. The HOMO–LUMO optical energy gaps estimated from the absorption edges are 2.95 eV for **5e** and 2.92 eV for **5f**, and the HOMO levels defined by cyclic voltammetry are -5.22 eV for **5e** and -5.23 eV for **5f** (see Table S2 and

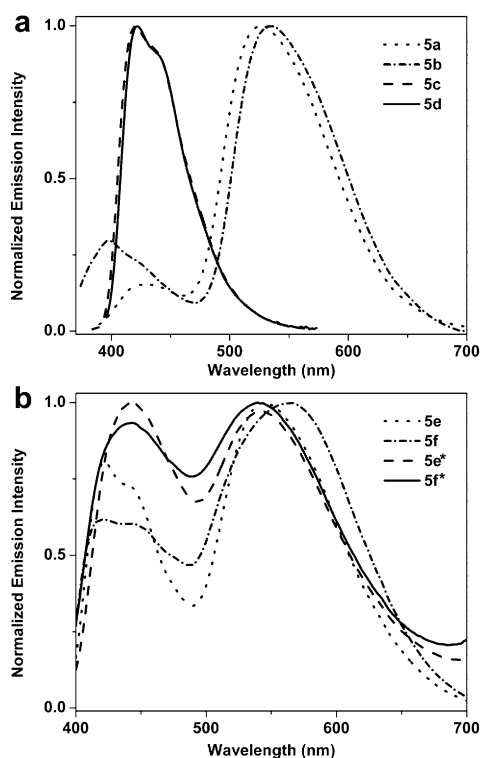


Figure 1. Emission spectra of a) **5a–d** in toluene (5.0×10^{-5} M) and b) **5e** and **5f** in toluene (1.0×10^{-6} M); **5e*** and **5f*** in PS films (0.2 wt %).

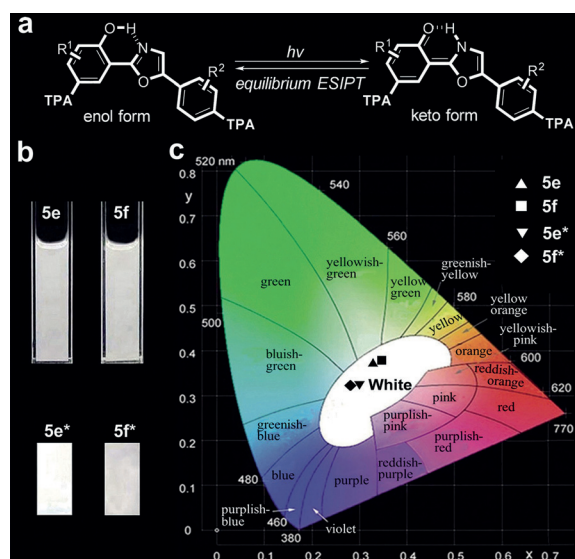


Figure 2. a) ESIPT mechanism of **5e** and **5f**. b) Fluorescence images of **5e** and **5f** in toluene (1.0×10^{-6} M), and in PS films (0.2 wt %) under UV light (365 nm). c) Emission color coordinates of **5e** and **5f** in the CIE 1931 chromaticity diagram: **5e** (0.32, 0.38) and **5f** (0.34, 0.39) in toluene (1.0×10^{-6} M); **5e*** (0.30, 0.33) and **5f*** (0.29, 0.34) in PS films (0.2 wt %).

Figure S13). The thermal decomposition temperatures (T_d) are 430 °C for **5e** and 436 °C for **5f** (see Table S2 and Figure S14), and indicate that they are thermally stable and

suitable for vacuum thermal sublimation for device fabrication.

In conclusion, a rhodium(III)-catalyzed regioselective oxidative C–H/C–H *ortho*-heteroarylation of phenols with various azoles has been developed to construct a large library of highly functionalized 2-(2-hydroxyphenyl)azoles through a traceless oxidation directing strategy, which unlocks an opportunity to rapidly screen single-molecular white-light-emitting materials. Two bis(TPA)-bearing 2-(2-hydroxyphenyl)oxazoles, which are difficult to access by common synthetic disconnections, have turned out to be a promising type of white-light-emitting single organic molecule with excellent luminescent properties, high quantum yields, and thermal stabilities. The internal oxidative protocol developed herein demonstrates the potential of C–H activation in the late-stage functionalization of natural products and in streamlining the lead-optimization phase in the discovery of organic photoelectronic materials.

Acknowledgements

This work was financially supported by grants from the National NSF of China (21432005, 21372164, 21172155, 21272160, and 21321061).

Keywords: cross-coupling · heterocycles · organic materials · oxidation · rhodium

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 14008–14012
Angew. Chem. **2015**, *127*, 14214–14218

- a) R. M. Tarkka, X. Zhang, S. A. Jenekhe, *J. Am. Chem. Soc.* **1996**, *118*, 9438; b) S.-T. Huang, I.-J. Hsei, C. Chen, *Bioorg. Med. Chem.* **2006**, *14*, 6106; c) K. A. Fennell, M. J. Miller, *Org. Lett.* **2007**, *9*, 1683; d) S. Park, J. Seo, S. H. Kim, S. Y. Park, *Adv. Funct. Mater.* **2008**, *18*, 726; e) S.-G. Roh, Y.-H. Kim, K. D. Seo, D. H. Lee, H. K. Kim, Y.-I. Park, J.-W. Park, J.-H. Lee, *Adv. Funct. Mater.* **2009**, *19*, 1663; f) J. E. Kwon, S. Y. Park, *Adv. Mater.* **2011**, *23*, 3615; g) A. P. Demchenko, K.-C. Tang, P.-T. Chou, *Chem. Soc. Rev.* **2013**, *42*, 1379.
- a) I. Bhatnagar, M. V. George, *Tetrahedron* **1968**, *24*, 1293; b) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150; c) J. Canivet, J. Yamaguchi, I. Ban, K. Itami, *Org. Lett.* **2009**, *11*, 1733.
- a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; c) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; d) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780; e) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; f) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; *Angew. Chem.* **2012**, *124*, 10382; g) K. Hirano, M. Miura, *Chem. Commun.* **2012**, *48*, 10704; h) Y. Wu, J. Wang, F. Mao, F. Y. Kwong, *Chem. Asian J.* **2014**, *9*, 26.
- F. W. Patureau, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 1977; *Angew. Chem.* **2011**, *123*, 2021.
- a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; b) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676; c) Y.-F. Wang, K. K. Toh, J.-Y. Lee, S. Chiba, *Angew. Chem. Int. Ed.* **2011**, *50*, 5927; *Angew. Chem.* **2011**, *123*, 6049; d) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350; e) L. Ackermann, S. Fenner, *Org. Lett.*

- 2011**, 13, 6548; f) B.-J. Li, H.-Y. Wang, Q.-L. Zhu, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2012**, 51, 3948; *Angew. Chem.* **2012**, 124, 4014; g) G. Liu, Y. Shen, Z. hou, X. Lu, *Angew. Chem. Int. Ed.* **2013**, 52, 6033; *Angew. Chem.* **2013**, 125, 6149.
- [6] a) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, 5, 369; b) Y. Segawa, T. Maekawa, K. Itami, *Angew. Chem. Int. Ed.* **2015**, 54, 66; *Angew. Chem.* **2015**, 127, 68.
- [7] J. Dong, Z. Long, F. Song, N. Wu, Q. Guo, J. Lan, J. You, *Angew. Chem. Int. Ed.* **2013**, 52, 580; *Angew. Chem.* **2013**, 125, 608.
- [8] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, 51, 3066; *Angew. Chem.* **2012**, 124, 3120.
- [9] J. Jayakumar, K. Parthasarathy, Y.-H. Chen, T.-H. Lee, S.-C. Chuang, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2014**, 53, 9889; *Angew. Chem.* **2014**, 126, 10047.
- [10] S. Reineke, F. Lindner, G. Schwartz, N. Seidler, K. Walzer, B. Lüssem, K. Leo, *Nature* **2009**, 459, 234.
- [11] a) K.-C. Tang, M.-J. Chang, T.-Y. Lin, H.-A. Pan, T.-C. Fang, K.-Y. Chen, W.-Y. Hung, Y.-H. Hsu, P.-T. Chou, *J. Am. Chem. Soc.* **2011**, 133, 17738; b) Q.-Y. Yang, J.-M. Lehn, *Angew. Chem. Int. Ed.* **2014**, 53, 4572; *Angew. Chem.* **2014**, 126, 4660; c) Z. Xie, C. Chen, S. Xu, J. Li, Y. Zhang, S. Liu, J. Xu, Z. Chi, *Angew. Chem. Int. Ed.* **2015**, 54, 7181; *Angew. Chem.* **2015**, 127, 7287.
- [12] White-light generation could be achieved on the basis of a compound comprising two ESIPT chromophores. See: S. Park, J. E. Kwon, S. H. Kim, J. Seo, K. Chung, S.-Y. Park, D.-J. Jang, B. M. Medina, J. Gierschner, S. Y. Park, *J. Am. Chem. Soc.* **2009**, 131, 14043.
- [13] M. Zhu, C. Yang, *Chem. Soc. Rev.* **2013**, 42, 4963.

Received: August 11, 2015

Published online: September 25, 2015