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Modular Synthesis of Multisubstituted Furans through Palladium-Catalyzed Three-Component Condensation of Alkynylbenziodoxoles, Carboxylic Acids, and Imines

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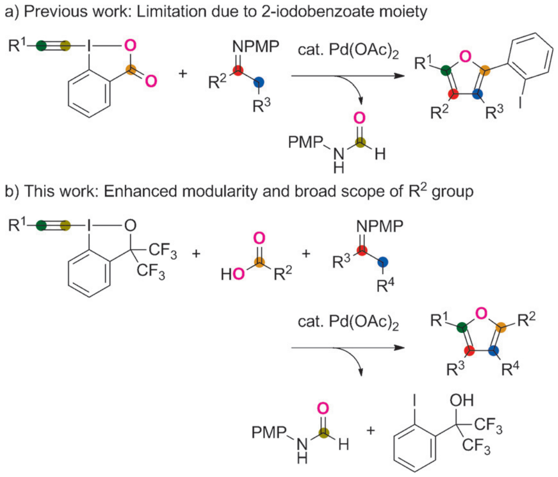
Abstract: *Mild and regiocontrolled synthesis of a multisubstituted furan is achieved through Pd(OAc)$_2$-catalyzed room-temperature condensation of an alkynylbenziodoxole, a carboxylic acid, and an enolizable ketimine, which contribute to C1, CO, and C2 fragments, respectively, to the furan skeleton. The reaction tolerates a broad range of functional groups in each of the reaction components, and enables highly modular and flexible synthesis of variously substituted furans. The reaction is particularly effective for the rapid generation of tri- and tetraarylfurans and furan-containing oligoarylenes without relying on conventional cross-coupling chemistry.*

Because of the frequent occurrence of substituted furans in natural products, pharmaceuticals, and other functional molecules[1] as well as their utility as synthetic intermediates,[2] the efficient and regioselective synthesis of furans has been among important subjects in heterocyclic chemistry.[3] Although cyclocondensation and cycloisomerization of single precursors represent established approaches to furans,[3b,c,4] they usually require multistep preparation of each precursor and hence are unsuitable for the rapid generation of a library of substituted furans. As such, modular approaches such as a [3+2]-type coupling of two simple starting materials[5] and a cycloisomerization–cross-coupling cascade[6] have recently gained a great deal of interest. Although a [2+2+1]-type coupling of three distinct reactants, in which each of the reactants contributes to the carbon skeleton of furan, potentially allows even more modular synthesis of multisubstituted furans, such reactions are rare and of limited scope.[7]

We recently discovered a Pd^{II}-catalyzed condensation reaction of an alkynylbenziodoxolone and an enolizable *N*-aryl ketimine to afford a multisubstituted furan, which involves cleavage of the C≡C bond and elimination of *N*-arylformamide as a coproduct (Scheme 1a).[8] A major limitation of this reaction is the lack of structural variation of the 2-iodobenzoate moiety, which ends up in the C5-substituent of the furan. Here we have removed this limitation by the development of a three-component condensation reaction of an alkynylbenziodoxole,[9–11] a carboxylic acid, and an *N*-aryl imine under Pd^{II} catalysis (Scheme 1b). The reaction represents a new example of [2+2+1]-type furan synthesis, enabling rapid construction of a diverse set of highly substituted furans including furan-containing oligoarylenes.[12]



Scheme 1. Pd^{II}-catalyzed furan synthesis from imines and alkynyliodine(III) reagents (PMP = *p*-MeOC$_6$H$_4$).

The alkynylbenziodoxolone/imine condensation (Scheme 1a) involves independent incorporation of the alkynyl and the 2-iodobenzoate moieties into the product.[8] This prompted us to explore the feasibility of a three-component furan synthesis by replacing the alkynylbenziodoxolone with a combination of a different alkynyliodine(III) compound and a carboxylic acid. A proof-of-concept result was obtained by the reaction of alkynyliodonium tosylate **1a**-OTs (0.4 mmol), benzoic acid **2a** (0.3 mmol), and 4′-methoxyacetophenone imine **3a** (0.2 mmol) in the presence of Pd(OAc)$_2$ (10 mol %), which afforded a triarylfuran **4a** in 45 % NMR yield (entry 1, Table 1). While replacement of the tosylate of **1a**-OTs with trifluoroacetate or triflate only caused adverse effects (entries 2 and 3), the use of an alkynylbenziodoxole **1a** bearing bis-trifluoromethyl groups[10,11] resulted in a significant improvement of the yield (entry 4). An analogous bridged alkynyliodine(III) reagent bearing dimethyl groups was prone to decomposition during preparation, whereas the one containing a sulfate bridge (**1a**-SO$_3$) showed poor solubility in toluene and failed to participate in the reaction (entry 5). Upon a brief survey of the reaction stoichiometry, **4a** was isolated in near quantitative yield (92 %) with a 2:2:1 ratio of the starting materials (entry 6). For this particular reaction, we confirmed the formation of the expected

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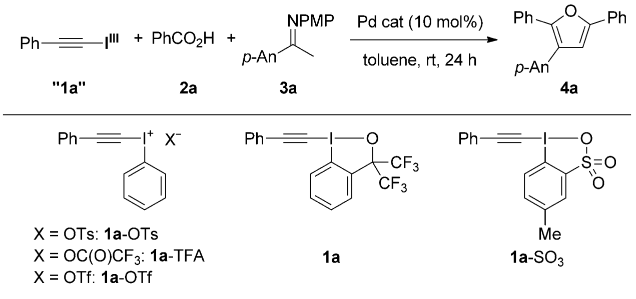
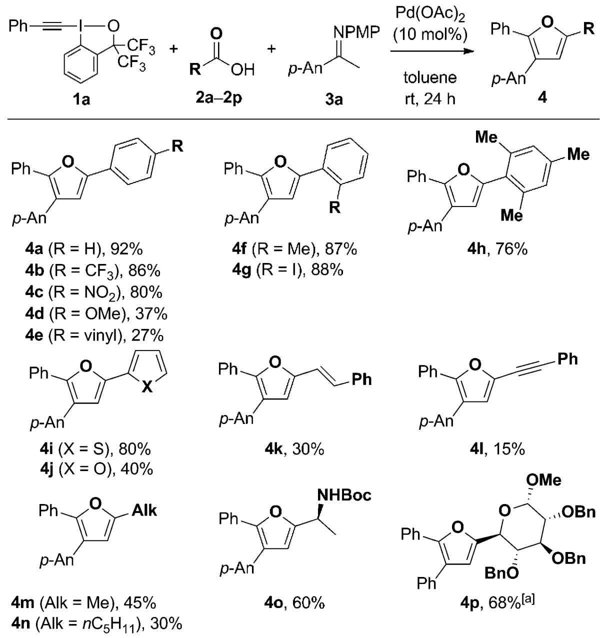
Table 1: Screening of reaction conditions.[a]



Entry	Iodine(III) reagent	Pd cat	Yield [%][b]
1	**1a**-OTs	Pd(OAc)$_2$	45
2	**1a**-TFA	Pd(OAc)$_2$	28
3	**1a**-OTf	Pd(OAc)$_2$	0
4	**1a**	Pd(OAc)$_2$	85
5	**1a**-SO$_3$	Pd(OAc)$_2$	0
6[c]	**1a**	Pd(OAc)$_2$	97 (92)
7[c,d]	**1a**	Pd(OAc)$_2$	84
8	**1a**	Pd(TFA)$_2$	85
9[c]	**1a**	PdCl$_2$	64
10[c]	**1a**	Pd$_2$(dba)$_3$	69

[a] Reaction conditions: iodine(III) reagent (0.4 mmol), **2a** (0.3 mmol), **3a** (0.2 mmol), Pd catalyst (10 mol%), toluene, rt, 24 h. [b] Determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard; yields of isolated products in parentheses. [c] 0.4 mmol of **2a** was used. [d] 5 mol% of Pd(OAc)$_2$ was used. *p*-An = 4-methoxyphenyl, dba = dibenzylideneacetone, TFA = trifluoroacetate.



Scheme 2. Scope of carboxylic acids. The reaction was performed on a 0.2 mmol scale under the conditions given in Table 1, entry 5.
[a] Acetophenone-derived imine (**1b**) was used in place of **1a**.

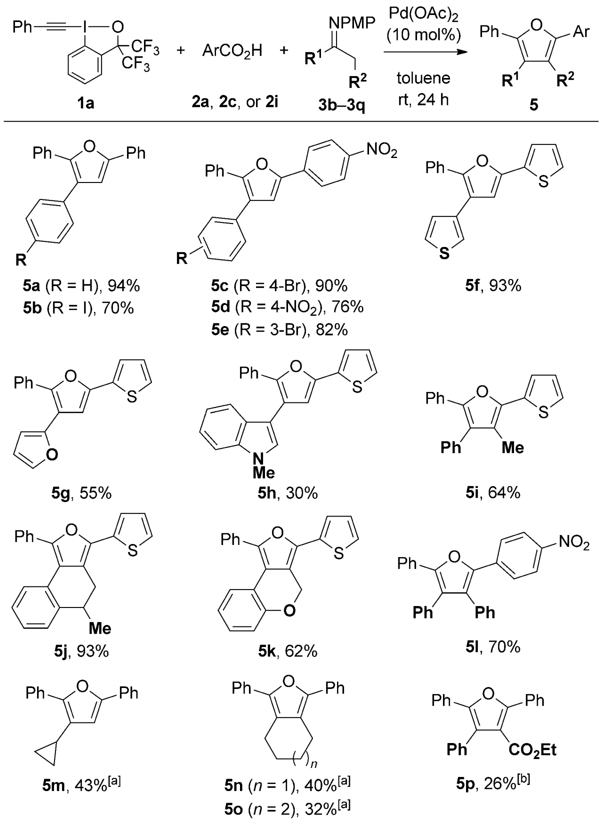
coproducts, *N*-(4-*m*ethoxyphenyl)formamide (87%) and 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (78% based on **1a**; see Scheme 1b). Note that reduction of the loading of Pd(OAc)$_2$ to 5 mol% led to a slight decrease in the yield of **4a** (entry 7). Other palladium sources such as Pd(TFA)$_2$, PdCl$_2$, and Pd$_2$(dba)$_3$ also promoted the three-component coupling albeit in lower yields (entries 8–10).

With the optimized conditions in hand, we explored the scope of the present three-component furan synthesis. First, we focused on the variation of the most readily available component, carboxylic acid (Scheme 2). Various aromatic and heteroaromatic acids participated in the reaction with **1a** and **3a** to afford the corresponding triarylfurans **4a**–**4j** in moderate to good yields. Whereas electron-poor acids afforded the desired furans (**4b** and **4c**) in high yields, electron-rich 4-methoxybenzoic acid reacted sluggishly (**4d**). The reaction of 4-vinylbenzoic acid was also sluggish (**4e**), which may be ascribed to the interference of the Pd catalyst by the coordination of the vinyl moiety. Sterically hindered mesitoic acid was well tolerated (**4h**). Cinnamic acid and phenylpropiolic acid also afforded the desired furan products albeit in low yields (**4k** and **4l**). Notably, the scope of carboxylic acids could be extended to simple aliphatic acids (**4m** and **4n**) as well as to protected amino acid and glucuronic acid (**4o** and **4p**). Note that a low-yielding reaction was typically accompanied by complete decomposition of the rest of **1a** into intractable products whereas the unreacted acid and **3a** were recovered partially and largely, respectively.

We next examined various imines using **1a** and benzoic acid (**2a**), 4-nitrobenzoic acid (**2c**), or 2-thiophenecarboxylic acid (**2i**) as the reaction partners (Scheme 3). (Hetero)aryl methyl imines smoothly participated in the three-component coupling to afford the corresponding 2,3,5-triarylfurans **5a**–**5h** in moderate to good yields with tolerance of bromo, iodo, and nitro groups. Likewise, imines derived from propiophenone, tetralone, chromanone, and 2-phenylacetophenone afforded the desired tetrasubstituted furans (**5i**–**5l**). Notably, acyclic and cyclic dialkylimines also reacted with **1a** and **2a** at an elevated temperature of 80 °C (**5m**–**5o**), despite their failure in the condensation with alkynylbenziodoxolones.[8] An enamine derived from a β-ketoester also served as a viable reactant, affording a tetrasubstituted furan **5p** in 26% yield.

As illustrated in Scheme 4a, alkynylbenziodoxoles derived from a series of arylacetylenes participated in the condensation with **2a** and **3a**, affording the triarylfurans **6a**–**6g** in moderate to good yields. Although both electron-donating (OMe) and electron-withdrawing (CF$_3$, CN) groups on the aryl ring could be tolerated, the reaction became sluggish with an *o*-tolyl group (**6g**). 2-Ethynylthiophene- and enyne-derived benziodoxoles were also amenable to the three-component coupling (**6h** and **6i**). As an additional demonstration, hitherto unknown tetrathienylfuran **7** could be prepared from appropriate thiophene-containing starting materials (Scheme 5b). Note that alkynylbenziodoxoles derived from alkyl- and silylacetylenes failed to afford the desired products.

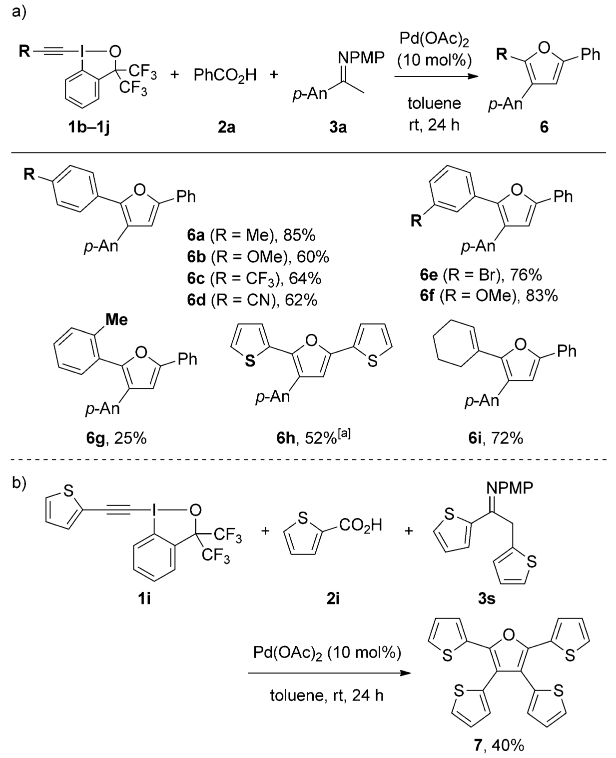
The present reaction further enables the construction of oligoarylenes containing 2,3,5-triarylfuran units.[12] Twofold condensation reactions of bis-imines **3t** and **3u** using **1a** and **2a** as the reaction partners afforded 1,4-di(3-furyl)- and 1,3-di(3-furyl)benzene derivatives **8** and **9**, respectively, in modest yields (Scheme 5a). Bis-alkynylbenziodoxole **1k** also under-



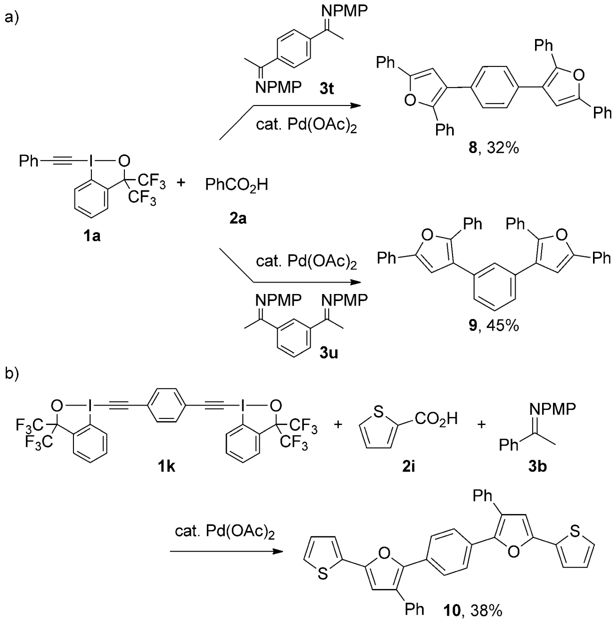
Scheme 3. Scope of imines. The reaction was performed on a 0.2 mmol scale under the conditions given in Table 1, entry 5. [a] The reaction was performed at 80 °C for 12 h. [b] The starting material was in the enamine form.

went twofold furan formation with 2-thiophenecarboxylic acid **2i** and acetophenone imine **3b** to furnish a heptaaryl **10** (Scheme 5 b), which exhibited absorption and emission maxima at 392 nm ($\varepsilon = 6.25 \times 10^4\ \mathrm{cm^{-1}M^{-1}}$) and 451 nm ($\Phi = 0.31$ determined using quinine as a standard), respectively. Note, however, that dicarboxylic acids such as terephthalic acid and 2,5-thiophenedicarboxylic acid failed to undergo twofold condensation.

As reported previously, the reaction of alkynylbenziodoxolone **1a′** and 4-pyridyl imine **3r** failed to give the desired furan but afforded 2-oxo-2-phenylethyl 2-iodobenzoate **11** (Scheme 6).[8] An attempted three-component coupling of **1a**, 2-iodobenzoic acid **2g**, and **3r** also afforded **11** without formation of the desired furan. Interestingly, ^{18}O-labeling experiments on these reactions suggested that not only the ester oxygens but also the keto oxygen of **11** are derived from the 2-iodobenzoate oxygens (Scheme S1).

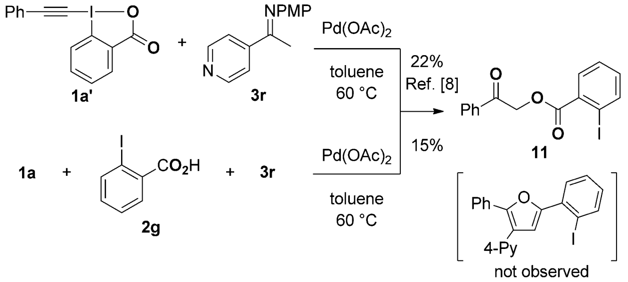


Scheme 4. Scope of alkynylbenziodoxoles. The reaction was performed on a 0.2 mmol scale under the conditions in Table 1, entry 5. [a] 2-Thiophenecarboxylic acid was used in place of **3a**.

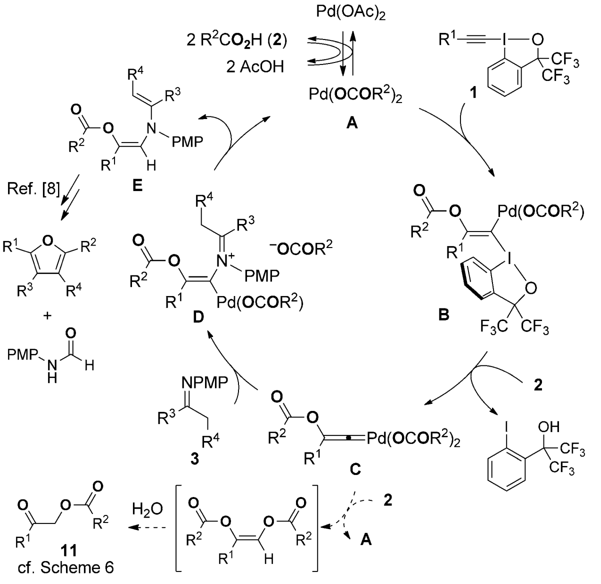


Scheme 5. Synthesis of oligoarylene derivatives containing furan moieties through twofold condensation. See the Supporting Information for detailed reaction conditions.

We speculate that the present three-component condensation shares the same mechanistic features as the alkynylbenziodoxolone/imine condensation (Scheme 1 a),[8] and involves 1) Michael addition of a palladium carboxylate **A** (formed from $Pd(OAc)_2$ and carboxylic acid **2**) to the alkynylbenziodoxole **1**, 2) conversion of the adduct **B** into a Pd-vinylidene species **C** with concomitant elimination of the iodoarene coproduct,[9] 3) addition of the imine nitrogen to **C**, and 4) protodepalladation of the intermediate **D** to afford an enamine derivative **E** and regenerate **A** (Scheme 7). The enamine **E** would further collapses into the furan and *N*-(4-methoxyphenyl)formamide through multiple steps.[8]



Scheme 6. Reaction using **1a**, 2-iodobenzoic acid **2g**, and 4-pyridylimine **3r**.



Scheme 7. Proposed catalytic cycle.

Unfortunately, attempts to identify any of the proposed intermediates leading to the furan product have not been successful. Nevertheless, we have accumulated pieces of experimental information that are consistent with the early part of the proposed mechanism (see the Supporting Information for detail). The ^{18}O-labeling experiments on the reactions in Scheme 6 (Scheme S1) were consistent with the Michael addition of the carboxylate to **1** and the formation of the putative vinylidene species **C**. Thus, the formation of the ketoester **11** may be explained by addition of the acid **2g** to **C** and subsequent hydrolysis of the resulting 1,2-diacyloxyalkene. The intermediacy of the palladium carboxylate **A** was supported by control experiments using a stoichiometric amount of Pd(OBz)$_2$ or Pd(OAc)$_2$ (Scheme S2). A competition reaction using benzoic acid and 4-methoxybenzoic acid resulted in the predominant participation of the former (Scheme S3), which may be ascribed to more facile carboxylate exchange of Pd(OAc)$_2$ with benzoic acid than with less acidic 4-methoxybenzoic acid.

In summary, we have developed a palladium-catalyzed three-component condensation reaction of alkynylbenziodoxoles, carboxylic acids, and imines that allows for the synthesis of highly substituted furans in a regiocontrolled manner. The reaction is notable for the high level of modularity and the broad scope of each reaction component, and is particularly useful for the rapid generation of a library of oligoaryls featuring 2,3,5-triarylfuran motifs.[12] Further synthetic and mechanistic studies on this reaction and palladium catalysis of imines[13] and hypervalent iodine reagents are underway.

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Keywords: furans · hypervalent iodine compounds · imines · multicomponent reactions · palladium

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[1] a) B. A. Keay, J. M. Hopkins, P. W. Dibble in *Comprehensive Heterocyclic Chemistry III*, *Vol. 3* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, **2008**, pp. 571–623; b) U. H. F. Bunz, *Angew. Chem. Int. Ed.* **2010**, *49*, 5037–5040; *Angew. Chem.* **2010**, *122*, 5159–5162; c) J. B. Sperry, D. L. Wright, *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723–740; d) A. Boto, L. Alvarez in *Heterocycles in Natural Product Synthesis* (Eds.: K. C. Majumdar, S. K. Chattopadhyay), Wiley-VCH, Weinheim, **2011**, pp. 99–152.

[2] a) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795–819; b) T. Montagnon, M. Tofi, G. Vassilikogiannakis, *Acc. Chem. Res.* **2008**, *41*, 1001–1011; c) H. N. C. Wong, K.-S. Yeung, Z. Yang in *Comprehensive Heterocyclic Chemistry III*, *Vol. 3* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, **2008**, pp. 407–496.

[3] a) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084–3213; b) S. F. Kirsch, *Org. Biomol. Chem.* **2006**, *4*, 2076–2080; c) R. C. D. Brown, *Angew. Chem. Int. Ed.* **2005**, *44*, 850–852; *Angew. Chem.* **2005**, *117*, 872–874; d) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong, H. N. C. Wong, *Tetrahedron* **1998**, *54*, 1955–2020; e) K.-S. Yeung, Z. Yang, X.-S. Peng, X.-L. Hou, *Prog. Heterocycl. Chem.* **2011**, *23*, 181–216; f) T. Graening, F. Thrun in *Comprehensive Heterocyclic Chemistry III*, *Vol. 3* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, **2008**, pp. 497–569.

[4] a) P. A. Allegretti, E. M. Ferreira, *Org. Lett.* **2011**, *13*, 5924–5927; b) R. K. Shiroodi, O. Koleda, V. Gevorgyan, *J. Am. Chem. Soc.* **2014**, *136*, 13146–13149; c) T. Schwier, A. W. Sromek, D. M. L. Yap, D. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 9868–9878.

[5] a) X. Cui, X. Xu, L. Wojtas, M. M. Kim, X. P. Zhang, *J. Am. Chem. Soc.* **2012**, *134*, 19981–19984; b) C. He, S. Guo, J. Ke, J. Hao, H. Xu, H. Chen, A. Lei, *J. Am. Chem. Soc.* **2012**, *134*, 5766–5769; c) S. Kramer, T. Skrydstrup, *Angew. Chem. Int. Ed.* **2012**, *51*, 4681–4684; *Angew. Chem.* **2012**, *124*, 4759–4762; d) X. L. Huang, B. Peng, M. Luparia, L. F. R. Gomes, L. F. Veiros, N. Maulide, *Angew. Chem. Int. Ed.* **2012**, *51*, 8886–8890; *Angew. Chem.* **2012**, *124*, 9016–9020; e) Y. Lian, T. Huber, K. D. Hesp, R. G. Bergman, J. A. Ellman, *Angew. Chem. Int. Ed.* **2013**, *52*, 629–633; *Angew. Chem.* **2013**, *125*, 657–661; f) Y. Yang, J. Yao, Y. Zhang, *Org. Lett.* **2013**, *15*, 3206–3209; g) M. Zheng, L. Huang, W. Wu, H. Jiang, *Org. Lett.* **2013**, *15*, 1838–1841; h) Y. Ma, S. Zhang, S. Yang, F. Song, J. You, *Angew. Chem. Int. Ed.* **2014**, *53*, 7870–7874; *Angew. Chem.* **2014**, *126*, 8004–8008.

[6] a) R. Vicente, J. González, L. Riesgo, J. González, L. A. López, *Angew. Chem. Int. Ed.* **2012**, *51*, 8063 – 8067; *Angew. Chem.* **2012**, *124*, 8187 – 8191; b) J. González, J. González, C. Pérez-Calleja, L. A. López, R. Vicente, *Angew. Chem. Int. Ed.* **2013**, *52*, 5853 – 5857; *Angew. Chem.* **2013**, *125*, 5965 – 5969; c) Y. Xia, S. Qu, Q. Xiao, Z.-X. Wang, P. Qu, L. Chen, Z. Liu, L. M. Tian, Z. Huang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 13502 – 13511; d) Y. Xia, Y. Xia, R. Ge, Z. Liu, Q. Xiao, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 3917 – 3921; *Angew. Chem.* **2014**, *126*, 3998 – 4002.

[7] a) D. Suzuki, Y. Nobe, Y. Watai, R. Tanaka, Y. Takayama, F. Sato, H. Urabe, *J. Am. Chem. Soc.* **2005**, *127*, 7474 – 7479; b) N. Iwasawa, K. Maeyama, M. Saitou, *J. Am. Chem. Soc.* **1997**, *119*, 1486 – 1487; c) K. Takai, M. Tezuka, Y. Kataoka, K. Utimoto, *J. Org. Chem.* **1990**, *55*, 5310 – 5312.

[8] B. Lu, J. Wu, N. Yoshikai, *J. Am. Chem. Soc.* **2014**, *136*, 11598 – 11601.

[9] a) V. V. Zhdankin, P. J. Stang, *Tetrahedron* **1998**, *54*, 10927 – 10966; b) J. P. Brand, J. Waser, *Chem. Soc. Rev.* **2012**, *41*, 4165 – 4179; c) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299 – 5358.

[10] V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547 – 6551.

[11] a) Y. Li, J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 6743 – 6747; *Angew. Chem.* **2013**, *125*, 6875 – 6879; b) Y. Li, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 5438 – 5442; *Angew. Chem.* **2015**, *127*, 5528 – 5532; c) X. Wu, S. Shirakawa, K. Maruoka, *Org. Biomol. Chem.* **2014**, *12*, 5388 – 5392.

[12] a) C.-F. Lee, L.-M. Yang, T.-Y. Hwu, A.-S. Feng, J.-C. Tseng, T.-Y. Luh, *J. Am. Chem. Soc.* **2000**, *122*, 4992 – 4993; b) C.-C. Wu, W.-Y. Hung, T.-L. Liu, L.-Z. Zhang, T.-Y. Luh, *J. Appl. Phys.* **2003**, *93*, 5465 – 5471.

[13] a) Y. Wei, I. Deb, N. Yoshikai, *J. Am. Chem. Soc.* **2012**, *134*, 9098 – 9101; b) A. Hajra, Y. Wei, N. Yoshikai, *Org. Lett.* **2012**, *14*, 5488 – 5491; c) Z. Chen, B. Lu, Z. Ding, K. Gao, N. Yoshikai, *Org. Lett.* **2013**, *15*, 1966 – 1969.

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