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N-Methylanilines as Simple and Efficient Promoters for Radical-Type Cross-Coupling Reactions of Aryl Iodides

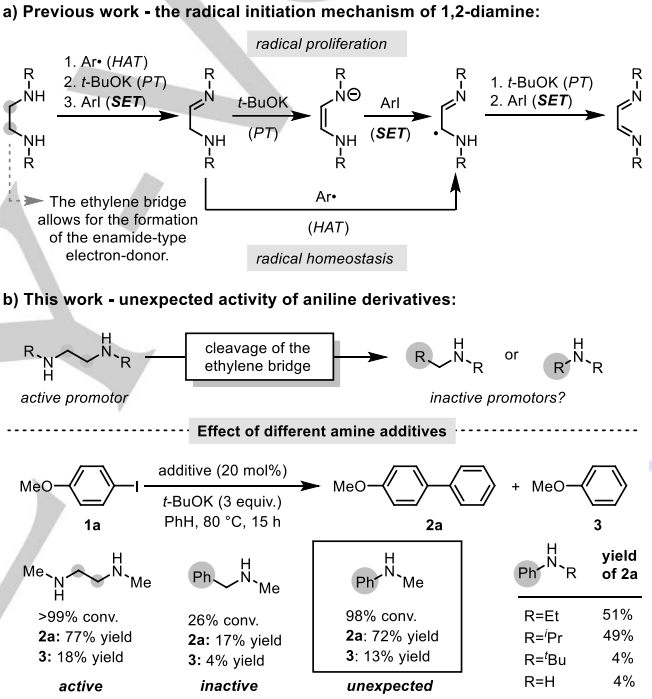
Huan Yang, Li Zhang, and Lei Jiao*

Dedication

Abstract: Activation of the carbon-halogen bonds in aryl halides is a key step in transition-metal-free cross-coupling reactions. In this paper a new and efficient radical initiation system for the activation of iodoarenes to produce aryl radicals was discovered, which employed the combination of *N*-methylanilines and *t*-BuOK. This radical initiation system is robust and versatile, enabling various types of aryl radical-related reactions.

Cross-coupling reactions catalyzed by transition metals have been studied for a long time and are widely employed in laboratory and industry.[1,2] In these reactions, aryl halides are among the most frequently used coupling components and the activation of a carbon-halogen bond by transition metals lays the foundation for the traditional cross-coupling chemistry. Very recently, a series of cross-coupling reactions involving aryl halides have been found to proceed under transition-metal-free conditions,[3] in which the combination of a small molecule organic additive and *t*-BuOK promotes the carbon-halogen bond cleavage and carbon-carbon bond formation efficiently. Typical examples include inter- and intramolecular aryl-aryl coupling,[4] aryl-olefin coupling,[5] and aryl alkoxycarbonylation reactions.[6] These reactions have attracted great interest due to their intriguing reaction mechanism and promising synthetic potential.

These transition-metal-free cross-coupling reactions are generally accepted to proceed through a radical chain mechanism and the chain propagation process is regarded as the base-promoted homolytic aromatic substitution (BHAS).[7] Compared with chain propagation, the radical initiation mechanism in these reactions is more complicated. Though challenging, it is important to identify the role of the small molecule organic additives in the activation of aryl halides,[8] not only to understand the molecular basis for the radical initiation chemistry, but also to guide the development of new and efficient promoter molecules for synthetic use.[4j,o,8f] In this context, Murphy and co-workers have systematically studied the radical initiation mechanism of these reactions.[8a,b,f] A unified conclusion was that various organic additives serve as precursors to electron donors, which then initiate the radical process by electron transfer to aryl halide. Lei and co-workers studied the 1,10-phenathroline/*t*-BuOK reaction system,[8d] and found that the complexation between 1,10-phenanthroline and *t*-BuOK was important for the electron transfer. We recently investigated the radical initiation mechanism of the 1,2-diamine/*t*-BuOK system using the model coupling reaction of iodoarene **1a**, and recognized that a mechanistic network functions to initiate the chain reaction, where the ethylene bridge in 1,2-diamine plays an important role (Scheme 1a).[9]



Scheme 1. Radical initiation mechanism of the 1,2-diamine/*t*-BuOK system and control experiments leading to an unexpected result. HAT = hydrogen atom transfer, PT = proton transfer, SET= single electron transfer.

Following this mechanistic interpretation, an interesting control experiment would be to block the radical proliferation pathway by breaking the ethylene bridge of 1,2-diamine to see whether the initiation activity diminishes. Indeed, if the active promoter *N*,*N*'-dimethyl-1,2-ethylenediamine (DMEDA) was replaced by *N*-methylbenzylamine, which has only one half of the DMEDA structure and a phenyl termini, dramatic decrease in activity was observed (Scheme 1b). This indicates that the secondary amine functionality is not sufficient for efficient radical initiation, in agreement with the previous mechanism. However, rather unexpectedly, *N*-methylaniline, in which a phenyl group is directly attached to the secondary amine, exhibited comparable activity to DMEDA. Further examination showed that *N*-alkylanilines with an α-hydrogen were all efficient promoters for this transformation (Scheme 1b). This result prompted us to investigate the role of such a simple small molecule in the radical initiation process, and

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led to the discovery of *N*-methylanilines as simple yet one of the most efficient organic additives for the activation of aryl halides to promote aryl-radical-related reactions.

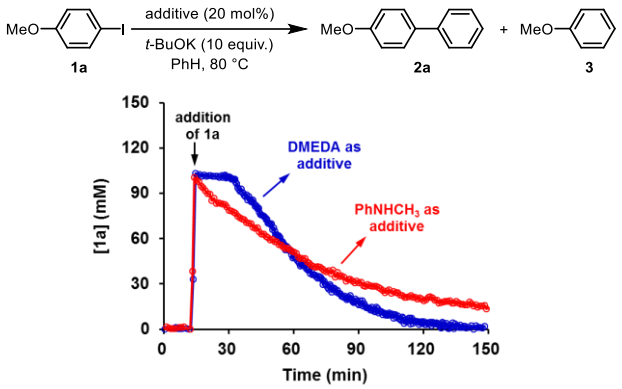

Figure 1. Kinetic profiles of aryl iodides **1a** for the coupling reaction employing DMEDA and $PhNHCH_3$ as additives.

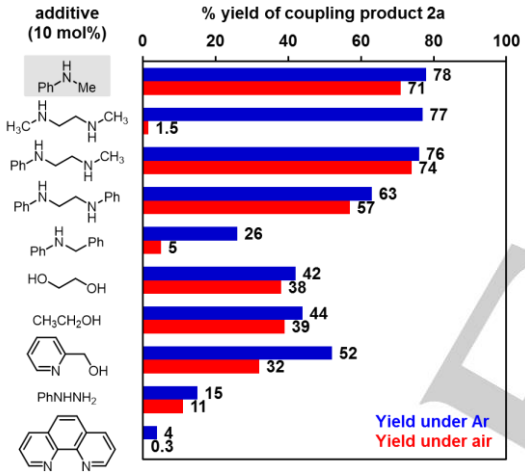

Figure 2. Yields of the cross-coupling product **2a** in the reaction between **1a** and benzene employing various additives under Ar (blue) and air (red) atmosphere. Reaction conditions: **1a** (0.5 mmol), organic additive (10 mol%), *t*-BuOK (1.5 mmol), 4 mL benzene, 80 ºC for 20 h.

We first tried to figure out the difference between *N*-methylaniline and DMEDA by reaction kinetics. The kinetic profiles revealed that, the cross-coupling reaction promoted by DMEDA exhibited a significant induction period,[9] while the reaction promoted by *N*-methylaniline did not (Figure 1). Meanwhile, an extensive survey on the activities of representative organic additives for the same model reaction disclosed the unique feature of *N*-methylaniline (Figure 2): it was superior to many previously reported promoter molecules, including 1,2-diamine[4a,h], alcohols[4e,j,5a], phenyl hydrazine[4i,j], and 1,10-phenanthroline[4b,c,f,l,5b,c], making it among the most efficient additive under 80 ºC. Remarkably, the activity of *N*-methylaniline almost remained unchanged when the reaction was conducted under air, while the DMEDA/*t*-BuOK system was completely ineffective. Interestingly, when the aniline moiety was introduced into the diamine backbone, the resulting molecules, *N*-methyl-*N*'-phenyl-1,2-ethylenediamine and *N,N*'-diphenyl-1,2-ethylenediamine, showed similar activity and air resistance to *N*-methylaniline. However, when the methyl group in *N*-methylaniline was replaced by a benzyl group, the activity decreased dramatically. The above experimental results confirmed that the *N*-methylaniline/*t*-BuOK system is highly efficient and robust for the initiation of transition-metal-free coupling reaction, and implied that this system must functions in a quite different way from the 1,2-diamine/*t*-BuOK system.

The structure of this small molecule organic additive enabled us to investigate the electronic effect on its radical initiation activity. Initial rate experiments on the model reaction were conducted with a series of *N*-methylanilines baring electronic substituents at the *para*-positon. The electronic nature of *N*-methylaniline was found to have a major impact on its activity: electron-donating groups enhanced the activity, while electron-withdrawing groups diminished activity (Figure 3). *N*-methyl-4-methoxyaniline (**A2**) was figured out as the most suitable additive for synthetic purposes, due to its relatively high activity and commercial availability.

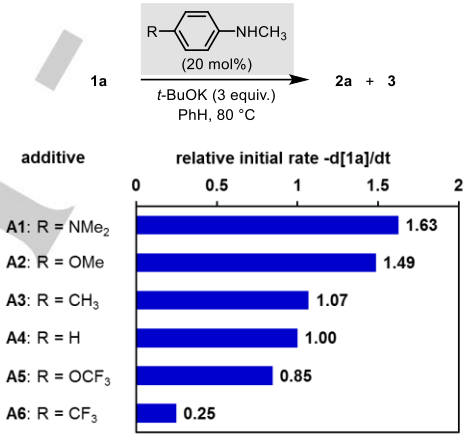

Figure 3. Comparison of the initial rates of *N*-methyl anilines with different electronic substitutions.

The synthetic utility of this new promoter was explored. It was found that, in aryl-aryl cross-coupling reactions, aniline **A2** as the additive could promote the coupling of a wide range of aryl iodides **1** and benzene (Table 1). Both electron-rich and electron-deficient aryl iodides underwent efficient couplings with benzene to give the corresponding biaryls (**2a-j**) in good yields. Naphthyl iodide **1k** and heteroaryl iodide **1l** also participated in the coupling reaction smoothly to give the desired products in good yields. These results demonstrated that the *N*-methylaniline/*t*-BuOK system is indeed a unique and highly efficient system for the activation of iodoarenes.

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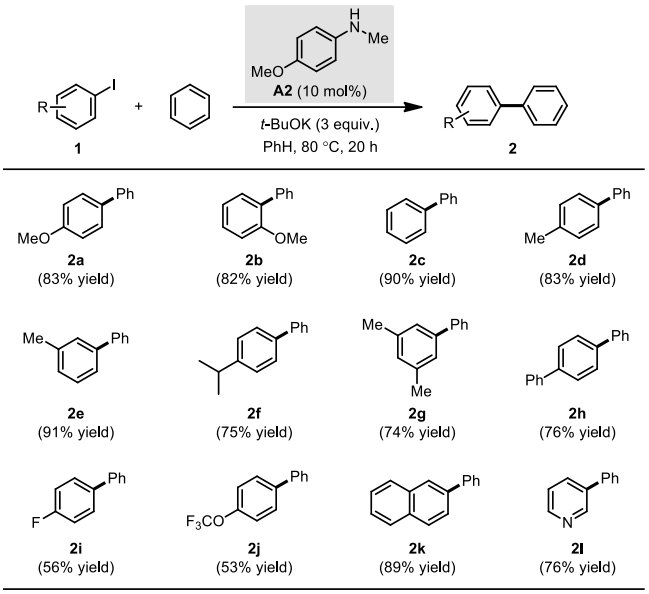
Table 1. Intermolecular aryl-aryl coupling reactions.[a]

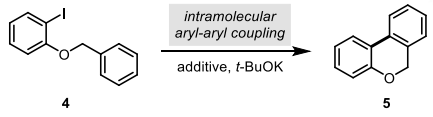
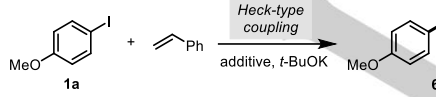
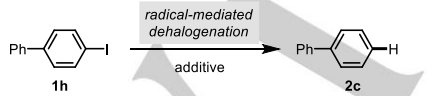
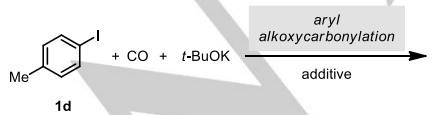


[a] Reaction conditions: **1** (1 mmol), **A2** (10 mol%), *t*-BuOK (3 equiv.), benzene (8 mL), 80 °C for 20 h. Yields after column chromatography were reported.

Interestingly, in addition to intermolecular aryl-aryl coupling, *N*-methylaniline is able to promote a series of radical-based reactions requiring aryl radical formation from iodoarenes, though previously there was no unified small molecule promoter for all these reactions (Table 2). Intramolecular aryl-aryl coupling of substrate **4** to afford cyclization product **5** was achieved by employing *N*-methyl 4-methoxyaniline as the additive under milder conditions compared with those reported previously.[4c,g] The Heck-type reaction between aryl iodide **1a** and styrene was also successfully carried out to produce product **6a**.[5a,d] Radical dehalogenation of iodoarene **1h**, a recently developed procedure promoted by small organic molecules,[10] could also be achieved by employing the *N*-methylaniline/*t*-BuOK system. Finally, radical alkoxycarbonylation reaction of **1a** could also be promoted by the same additive to produce benzoate **7**,[6] albeit in a lower yield. The success of this additive in the above reactions rendered *N*-methylaniline a versatile small molecule for promoting aryl-radical-mediated reactions.

Preliminary mechanistic studies were performed to identify the role of this simple molecule in the activation of aryl halides. First, deprotonation of *N*-methylaniline by *t*-BuOK under the reaction conditions was verified by ^{1}H NMR and 1D-TOCSY spectroscopy (see the Supporting Information), indicating that *N*-methylanilide anion is the major species of the aniline in the reaction system. Second, cyclic voltammetry (CV) experiments confirmed that the *N*-methylanilide anions formed by treatment of anilines **A4** and **A2** with *t*-BuOK could act as an electron donor: *N*-methylanilide anion and *N*-methyl 4-methoxyanilide anion exhibited oxidation waves at -0.66 V and -0.93 V vs $Fc^{+/0}$, respectively. Third, the model reaction employing deuterated *N*-methylanilines showed no significant kinetic isotope effect (KIE) and a minimum extent of deuterium incorporation in product **3**, implying that the C-H or N-H bond cleavage by radical abstraction is not a significant pathway in the initiation process, and the deprotonation steps are not rate-limiting (Table 3).

Table 2. Various types of coupling reactions promoted by *N*-methylaniline additive

Entry	Reaction	Applied conditions: Literature	Applied conditions: This work[a]
1		1,10-phenathroline (50 mol%), 100 °C, 24 h, 62% yield;[4c] *or* 2,6-bis(imino)pyridine (20 mol%) 160 °C, 12 h, 75% yield.[4g]	**A2** (50 mol%), 80 °C, 20 h, 58 % yield.
2		EtOH (20 mol%), 80 °C, 2 h, 65% yield;[5a] *or* *N*,*N*'-dialkyldiketopiperazine (30 mol%), 130 °C, 3 h, 36% yield.[5d]	**A2** (20 mol%), 80 °C, 2 h, 68 % yield
3		$MeOCH_2CH_2OCH_2CH_2OH$ (7 equiv.), NaH (7 equiv.), O_2, 1,4-dioxane, rt, 24 h, >99% yield.[10]	**A2** (50 mol%), *t*-BuOK (3 equiv.), 1,4-dioxane, 80 °C, 24 h, 85% yield.
4		1,10-phenathroline (40 mol%) 90 °C, 24 h, 72% yield.[6]	**A2** (40 mol%), 90 °C, 20 h, 44 % yield.

[a] The yields of product **5**, **6a**, **2c** was 54%, 43% and 52% under air atmosphere, respectively.

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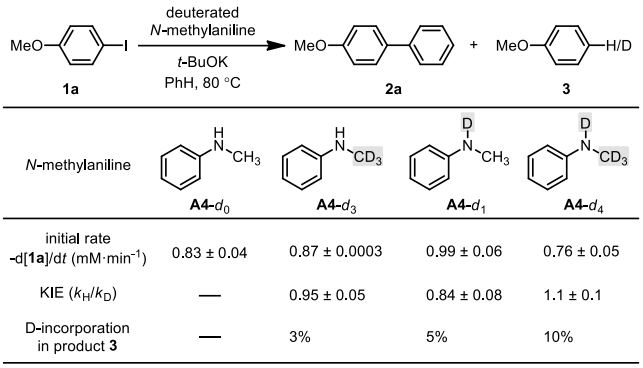
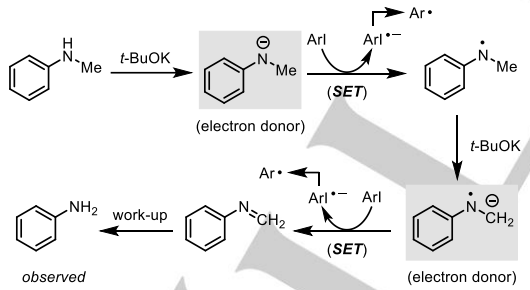
Table 3. Kinetic isotope study



In light of the above experimental results, a plausible mechanism for the activation of aryl halide by *N*-methylaniline was proposed (Scheme 2). *N*-methyl aniline is first deprotonated by *t*-BuOK to form *N*-methylanilide anion, which then acts as an electron donor to transfer an electron to aryl iodide, facilitating the formation of the aryl radical. The generated N-centered radical is then deprotonated by *t*-BuOK to form a radical anion, which is also an electron donor to initiate the radical process. *N*-methylideneaniline is produced as the end-product of *N*-methylanilene, which after work-up was converted to aniline and could be detected by GC-MS. The observed electronic effect on the activity of substituted *N*-methylanilines (Figure 3) supported this radical initiation mechanism, as the substituents on the phenyl ring influence the activity of the involved electron donors. It is worth noting that the $PhNHNH_2$/*t*-BuOK promoted cross-coupling reactions were proposed to have a similar radical initiation process.[4i] The present study demonstrates that the key structural feature for a successful promoter molecule might be the ArNH moiety but not the N-N bond.



Scheme 2. Proposed radical initiation mechanism.

In conclusion, we have disclosed that *N*-methylanilines, which are simple and easily available, could efficiently activate iodoarenes in the presence of *t*-BuOK. This new and robust radical initiation system could be employed in a series of aryl radical related reactions, including inter-/intramolecular aryl-aryl coupling, the Heck-type coupling, dehalogenation of iodoarenes, and aryl alkoxycarbonylation reactions. Preliminary mechanistic studies showed that single electron transfer from *N*-methylanilide anion to the iodoarene was the key step in radical initiation. We expect this study to provide further understanding for the initiation process in the cross-coupling reaction promoted by small organic molecules, as well as to present a general and efficient radical initiation system for this type of reactions.

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Keywords: cross-coupling • *N*-methyl aniline • radical initiation • electron donor • homolytic aromatic substitution

[1] For books, see: a) F. Diederich, P. J. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **1998**; b) S. Brase, A. de. Meijere in *Metal-Catalyzed Cross-Coupling Reactions* (Eds: A. de. Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; c) L. Ackermann, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**.

[2] For selected reviews, see: a) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev*. **2002**, *102*, 1359-1470; b) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal*. **2003**, *345*, 1077-1101; c) L. C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc*. **2006**, *128*, 581-590; d) S. E. Denmark, C. S. Regens, *Acc. Chem. Res*. **2008**, *41*, 1486-1499; e) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949-957; f) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem*. **2009**, *121*, 3698-3701; *Angew. Chem. Int. Ed*. **2009**, *48*, 9792-9826; g) G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev*. **2009**, *38*, 2447-246.

[3] For reviews, see: a) S. Yanagisawa, K. Itami, *ChemCatChem* **2011**, *3*, 827-829; b) S. C. Pan, *Beilstein. J. Org. Chem*. **2012**, *8*, 1374-1384; c) L. Wang, G. Yan, X. Zhang, *Chin. J. Org. Chem.* **2012**, *32*, 1864-1871; d) T. L. Chan, Y. Wu, P. Y. Choy, F. Y. Kwong, *Chem. Eur. J*. **2013**, *19*, 15802-15814; e) V. P. Mehta, B. Punji, *RSC Adv*. **2013**, *3*, 11957-11986; f) C.-L. Sun, Z.-J. Shi, *Chem. Rev*. **2014**, *114*, 9219-9280.

[4] For selected examples, see: a) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong, A. Lei, *J. Am. Chem. Soc*. **2010**, *132*, 16737-16740; b) E. Shirakawa, K.-I. Itoh, T. Higashino, T. Hayashi, *J. Am. Chem. Soc*. **2010**, *132*, 15537-15539; c) C.-L. Sun, Y.-F. Gu, W.-P. Huang, Z.-J. Shi, *Chem. Commun*. **2011**, *47*, 9813-9815; d) Y. Wu, S. M. Wong, F. Mao, T. L. Chan, F. Y. Kwong, *Org. Lett*. **2012**, *14*, 5306-5309; e) S. Sharma, M. Kumar, V. Kumar, N. Kumar, *Tetrahedron Lett*. **2013**, *54*, 4868-4871; f) K.-S. Masters, S. Brase, *Angew. Chem.* **2013**, *125*, 899-903; *Angew. Chem. Int. Ed*. **2013**, *52*, 866-869; g) S. A, X. Liu, H. Li, C. He, Y. Mu, *Asian. J. Org. Chem*. **2013**, *2*, 857-861; h) S. De, S. Mishra, B. N. Kakde, D. Dey, A. Bisai, *J. Org. Chem*. **2013**, *78*, 7823-7844; i) A. Dewanji, S. Murarka, D. P. Curran, A. Studer, *Org. Lett*, **2013**, *15*, 6102-6105; j) Y. Wu, P. Y. Choy, F. Y. Kwong, *Org. Biomol. Chem*. **2014**, *12*, 6820-6823; k) Q. Song, D. Zhang, Q. Zhu, Y. Xu, *Org. Lett*. **2014**, *16*, 5272-5274; l) W. Liu, R. Liu, Y. Bi, *Tetrahedron* **2015**, *71*, 2622-2628;m) Z. Xu, L. Gao, L. Wang, M. Gong, W. Wang, R. Yuan, *ACS Catal* **2015**, *5*, 45-50; n) M. P. Drapeau, I. Fabre, L. Grimaud, I. Ciofini, T. Ollevier, M. Taillefer. *Angew. Chem.* **2015**, *127*, 10733-10737*; Angew. Chem. Int. Ed*. **2015**, *54*, 10587-10591; o) Y. Gao, P. Tang, H. Zhou, W. Zhang, H. Yang. N. Yan, G. Hu, D. Mei, J. Wang, D. Ma, *Angew. Chem.* **2016**, *128*, 3290-3294; *Angew. Chem. Int. Ed*. **2016**, *55*, 3124-3128; p) R. Paira, B. Singh, P. K. Hota, J. Ahmed. S. C. San, J. P. Johnpeter, S. K. Mandal, *J. Org. Chem*. **2016**, *81*, 2432-2441.

[5] For examples, see: a) E. Shirakawa, X. Zhang, T. Hayashi, *Angew. Chem.* **2011**, 123, 4767-4770; *Angew. Chem. Int. Ed*. **2011**, *50*, 4671-4674; b) C.-L. Sun, Y.-F. Gu, B. Wang, Z.-J. Shi, *Chem. Eur. J.* **2011**, *17*,

10.1002/chem.201604602

10844-10847; c) M. Rueping, M. Leiendecker, A. Das, T. Poisson, L. Bui, *Chem. Commun*. **2011**, *47*, 10627-10631; d) E. Doni, S. Zhou, J. A. Murphy, *Molecules* **2015**, *20*, 1755-1774.

[6] H. Zhang, R. Shi, A. Ding, L. Lu, B. Chen, A. Lei, *Angew. Chem.* **2012**, *124*, 12710-12713*; Angew. Chem. Int. Ed*. **2012**, *51*, 12542-12545.

[7] a) A. Studer, D. P. Curran*, Angew. Chem.* **2011***, 123*, 5122-5127; *Angew. Chem. Int. Ed.* **2011**, *50*, 5018-5022; b) A. Studer, D. P. Curran, *Nat. Chem*. **2014**, *6*, 765-773.

[8] a) S. Zhou, G. M. Anderson, B. Mondal, E. Doni, V. Ironmonger, M. Kranz, T. Tuttle, J. A. Murphy, *Chem. Sci*. **2014**, *5*, 476-482; b) J. A. Murphy, *J. Org. Chem*. **2014**, *79*, 3731-3746; c) S. Zhou, E. Doni, G. M. Anderson, R. G. Kane, S. W. MacDougall, V. M. Ironmonger, T. Tuttle, J. A. Murphyl, *J. Am. Chem. Soc*. **2014**, *136*, 17818-17826; d) H. Yi, A. Jutand, A. Lei, *Chem. Commun*. **2015**, 51, 545-548; e) M. Patil, *J. Org. Chem*. **2016**, *81*, 632-639; f) J. P. Barham, G. Coulthard, R. G. Kane, N. Delgado, M. P. John, J. A. Murphy, *Angew. Chem*. **2016**, *128*, 4568-4572; *Angew. Chem. Int. Ed*. **2016**, *55*, 4492-4496; (g) J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc*. **2016**, *138*, 7402-7410.

[9] L. Zhang, H. Yang, L. Jiao, *J. Am. Chem. Soc*. **2016**, *138*, 7151-7160.

[10] A. Dewanji, C. Muck-Lichtenfeld, A. Studer, *Angew. Chem*. **2016**, *128*, 6861-6864; *Angew. Chem. Int. Ed*, **2016**, *55*, 6749-6752.