Synthetic Methods

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Pd-Catalyzed C–H Olefination of (Hetero)Arenes by Using Saturated Ketones as an Olefin Source**

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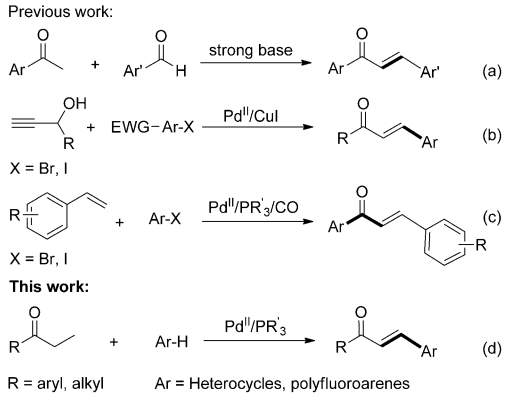
Chalcones and their heterocyclic analogues represent an important class of naturally occurring and synthetic compounds, which display a wide range of pharmacological properties,[1] including cytotoxicity towards cancer cell lines;[2a,b] antimitotic[2c] and antimutagenic[2d] activities; antibacterial,[2e] antiviral,[2f] and anti-inflammatory activity.[2g] Recently, several chalcone-based drug candidates have entered into preclinical trial stages for the development of antimalarial and antileishmanial drugs.[2h] Furthermore, these compounds are of great importance as intermediates both in the syntheses of a large number of heterocyclic systems[3] and in functional materials.[4]

Traditionally, chalcones and their heterocyclic analogues are synthesized by the aldol condensation between aromatic aldehydes and ketones (Scheme 1a).[5] Because the aldol condensation often requires strongly basic reaction conditions, the functional groups sensitive to bases cannot be tolerated in such a condensation reaction. To overcome this limitation, the research groups of Müller and Beller independently developed a Pd-catalyzed Sonogashira coupling of electron-deficient aryl halides with aryl 1-propargyl alcohols (Scheme 1b)[6] and a Pd-catalyzed carbonylative Heck coupling of aryl halides with styrenes (Scheme 1c)[7] for the syntheses of chalcones, respectively.



Scheme 1. The syntheses of chalcones. EWG = electron-withdrawing groups.

The rapid development in the metal-catalyzed C–H bond functionalization reactions have demonstrated the great potential of these chemical transformations to synthesize valuable products from simple starting materials in concise steps and therefore minimize waste formation in the synthesis process.[8] Recently, we have achieved decarboxylative vinylation of aryl carboxylic acids with nitroethane[9a] or propiophenones.[9b] These encouraging achievements led us to consider whether the dehydrogenative cross-coupling between (hetero)arenes and saturated ketones could directly afford chalcones or heterocyclic chalcone analogues. Herein, we report a versatile method for the facile syntheses of chalcone or heterocyclic chalcone analogues through Pd-catalyzed dehydrogenative cross-coupling between (hetero)arenes and (hetero)aryl ethyl ketones (Scheme 1d) and demonstrate that unsymmetrical dialkyl ketones also undergo this coupling reaction with reaction occurring exclusively on the less sterically hindered moiety. The mechanistic studies revealed that this reaction proceeds through dehydrogenation to form an olefin intermediate in situ and a subsequent C–H olefination sequence.

Although transition-metal-catalyzed Heck coupling of aryl halides or (hetero)arenes with (hetero)aryl vinyl ketones would directly generate chalcones or their heterocyclic analogues in principle, the examples of this type of reaction are scarce, presumably because (hetero)aryl vinyl ketones are not commercially available. Our protocol allows using saturated ketones as equivalents of olefins for the direct olefination of (hetero)arenes and thereby enhances transformation efficiency, which is further illustrated by the troublesome preparation of α,β-unsaturated carbonyl compounds. Typically, the preparation of α,β-unsaturated carbonyl compounds require two or more than two steps starting from the corresponding saturated carbonyl compounds;[10–13] examples of such methods are Pd-mediated dehydrosilylation of silyl enol ethers (Saegusa oxidation),[10] halogenation–dehalogenation sequence,[11] and/or use of stoichiometric reagents such as 2-iodoxybenzoic acid (IBX)[12] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[13] The Pd-catalyzed aerobic oxidative dehydrogenation of ketones represents a promising method for the facile synthesis of α,β-unsaturated ketones, but is still limited to cyclic enones or β-arylated enones.[14] Consequently, the reactions that combine in situ dehydrogenation to form reactive olefin intermediates with secondary coupling process are attracting attention from synthetic chemists.[15] In this context, pioneer-

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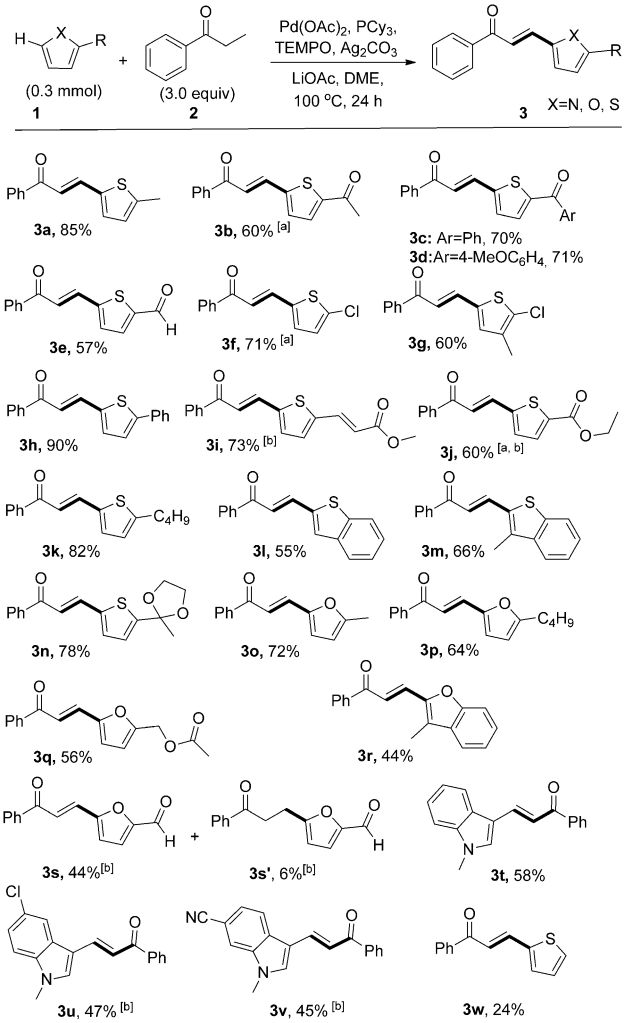
ing studies have emerged, including the Pd-catalyzed dehydrogenative β-arylation of alkyl aryl ketones with aryl bromides,[15a] Ni-catalyzed dehydrogenative amination of propiophenones,[15b] the Pd-catalyzed dehydrogenative Diels–Alder reaction of terminal olefins with dienes,[15c] the Pd-catalyzed dehydrogenative β′-functionalization of β-keto esters with indoles,[15d] and the dehydrogenative cross-coupling of cyclic β-heteroatom-substituted ketones with benzenes.[15e] Despite these advances, the dehydrogenative cross-coupling between (hetero)arenes and saturated ketones through in situ dehydrogenation to generate olefin intermediates is an almost untouched area.

The challenge posed by our targeted reaction is the identification of suitable reaction conditions that are compatible with both the oxidative dehydrogenation of saturated ketones to olefin intermediates and C–H olefination of (hetero)arenes, and also allow these two processes to operate in a tandem manner. Elegant studies on C–H bond functionalization of (hetero)arenes[16–18] provided useful starting points for our investigation of dehydrogenative cross-coupling of this type. The reaction of 2-methylthiophene (**1a**) with propiophenone (**2a**; 3.0 equiv) in 1,2-dimethoxyethane (DME; 2.0 mL) at 100 °C was chosen as a model system for the optimization studies using $Pd(OAc)_2$ (10 mol %) as a catalyst, and Ag_2CO_3 (2.5 equiv) as an oxidant (see the Supporting Information for details).[19] The initial reaction conditions did not give the desired cross-coupling product in any detectable amount; instead a large amount of homocoupling product from thiophene was formed.[17a] Three critical parameters were identified, the modification of which led to a high-yielding reaction. First, the use of PCy_3 as a ligand efficiently suppressed the homocoupling of thiophene and dramatically improved the efficiency of this reaction, probably because the strongly electron-donating PCy_3 may reduce the electrophilicity of palladium and thus inhibit further electrophilic attack of palladium to the second thiophene molecule after the palladation of thiophene. The second critical parameter proved to be the additional base. Of the examined bases, LiOAc provided the best result. The use of TEMPO (0.4 equiv; TEMPO = 2,2,6,6-tetramethyl piperidine-*N*-oxyl) as a cooxidant led to an increase in yield presumably owing to its ability to accelerate reoxidation of Pd^0 to Pd^{II}.[20]

With the optimized reaction conditions in hand ($Pd(OAc)_2$ (10 mol %), PCy_3 (20 mol %), TEMPO (0.4 equiv), LiOAc (1.5 equiv), Ag_2CO_3 (3.0 equiv), DME (2.0 mL), and 100 °C), we first examined the substrate scope of this reaction with respect to heterocycles. As shown in Scheme 2, this reaction was applicable to a variety of substituted thiophenes, furans, and indoles, and gave the corresponding products in synthetically useful yields with excellent selectivity (the reaction occurred exclusively at the 5-position of monosubstituted thiophene or furan rings, and at the 3-position of indoles, $E/Z > 99{:}1$). In contrast, unsubstituted heteroarenes such as thiophene afforded the product in poor yields (**3w**). A broad range of functional groups were tolerable, including base-sensitive formyl and acetyl groups, an acid-sensitive ketal group, and easily leaving acetate groups, which provided useful handles for further transformations. Note that furans and *N*-methylindoles underwent this reaction at elevated temperature (120 °C) to afford the corresponding products in synthetically useful yields. Interestingly, the reaction of 2-formylfuran produced the desired product along with a saturated by-product (**3s′**) with an 8:1 selectivity.



Scheme 2. The scope of heterocycles. Conditions: $Pd(OAc)_2$ (10 mol %), PCy_3 (20 mol %), TEMPO (0.4 equiv), LiOAc (1.5 equiv), Ag_2CO_3 (3.0 equiv), DME (2.0 mL). Yields of isolated products are reported. [a] NaOAc (0.45 mmol) was used instead of LiOAc. [b] Carried out at 120 °C.

Next, we evaluated the scope of (hetero)aryl ethyl ketones by using 2-methyl thiophene as a coupling partner (Scheme 3). Both electron-withdrawing and electron-donating substituents on the benzene ring of (hetero)aryl ethyl ketones furnished good to excellent yields with the exception of the dimethylamino substitutent. Variations of substitution positions did not much influence the product yields, as illustrated by the reactions of three fluoro-substituted propiophenone isomers. 1-(2-Naphthyl)-1-propanone also exhibited excellent reactivity towards this reaction. For most of the propiophenones bearing electron-withdrawing substituents, reducing the amount of PCy_3 to 10 mol % was required to achieve satisfying yields. Notably, as exemplified by 1-(3-

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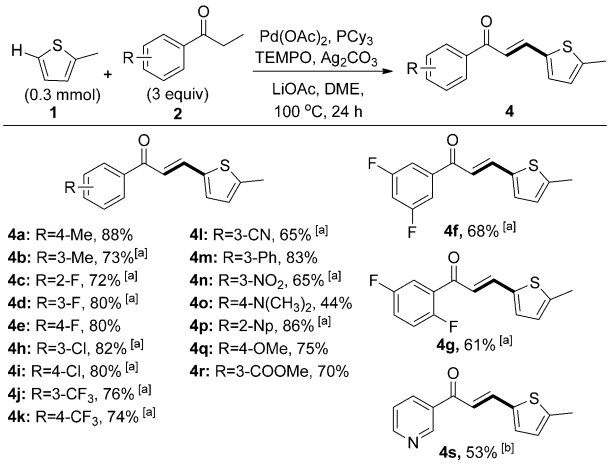
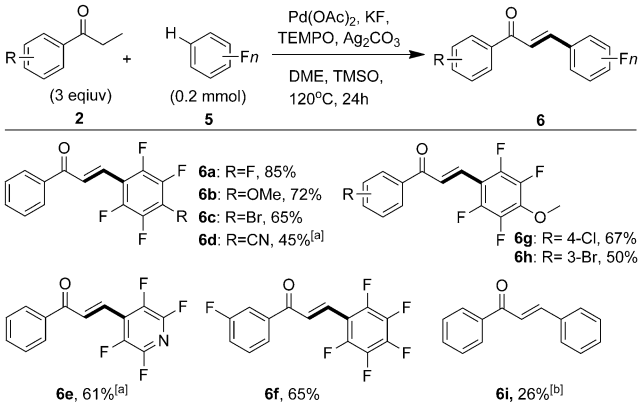
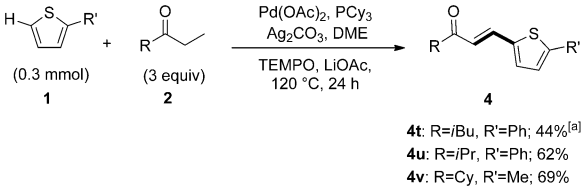


Scheme 3. The scope of (hetero)aryl ethyl ketones. Conditions: $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), TEMPO (0.4 equiv), LiOAc (1.5 equiv), Ag_2CO_3 (3.0 equiv), DME (2.0 mL). Yields of isolated products are reported. Np = naphthyl. [a] PCy_3 (10 mol%) was used. [b] Carried out at 120 °C.



Scheme 5. The dehydrogenative cross-coupling between fluorobenzenes with propiophenones. Conditions: $Pd(OAc)_2$ (10 mol%), KF (3 equiv), TEMPO (0.2 equiv), Ag_2CO_3 (2.5 equiv), DME (2.0 mL), TMSO (2 equiv). Yields of isolated products are reported. In all cases the E/Z ratios were > 99:1. [a] Without TMSO. [b] For the detailed experimental process see the Supporting Information.

pyridinyl)-1-propanone, replacing the phenyl moiety of propiophenone with a heterocyclic group has only a slight effect on the reactivity of substrates.

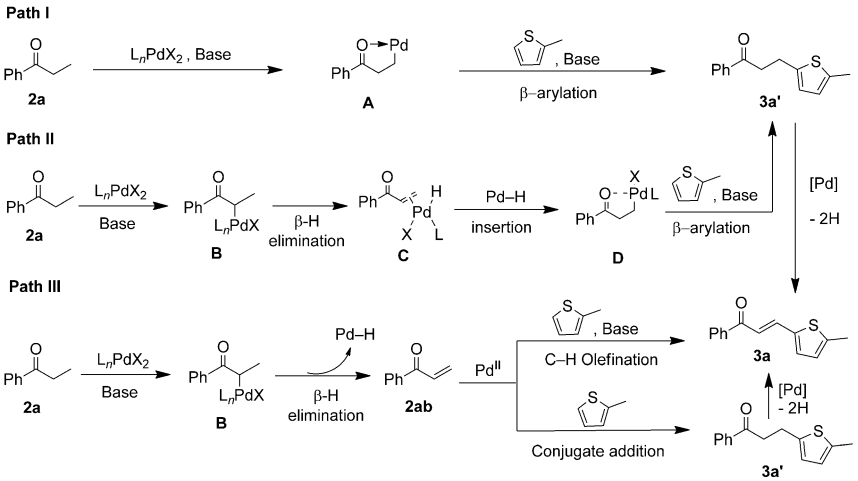


Scheme 4. Dehydrogenative cross-coupling of dialkyl ketones with thiophenes. Conditions: Conditions: $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), TEMPO (0.4 equiv), LiOAc (1.5 equiv), Ag_2CO_3 (3.0 equiv), DME (2.0 mL). Yields of isolated products are reported. [a] PCy_3 (10 mol%) was used.

Gratifyingly, dialkyl ketones can participate in this dehydrogenative cross-coupling (Scheme 4). Although unsymmetrical dialkyl ketones have two accessible reaction sites, reactions occurred exclusively on the less sterically hindered ethyl group.

To show the generality of this reaction, we further expanded the substrate scope to electron-deficient benzenes (Scheme 5). An array of polyfluorobenzenes exhibited good reactivity towards this reaction, and afforded the desired products in reasonable yields. Benzene also participated in this reaction, albeit in diminished yield. In this case, TMSO (2.0 equiv; TMSO = tetramethylene sulfoxide) was used as ligand rather than PCy_3, and KF was the base of choice.

There are three possible reaction pathways for the dehydrogenative cross-coupling of aromatic heterocycles with saturated ketones (Scheme 6). Path I involves the carbonyl directed β-C–H palladation[21] followed by β-arylation with thiophene and dehydrogenation to form the target product. However, path I cannot be supported by the observation that ketones lacking an α-H atom, such as *tert*-butyl phenyl ketone, did not participate in this dehydrogenative cross-coupling. Path II comprises the initial β-C–H palladation that occurs through the process proposed by Baudoin and co-workers[22] (β-H elimination of Pd-enolate, 180° rotation of the olefin coordinating to Pd, double bond reinsertion into the Pd–H bond), the subsequent β-arylation with thiophene, and dehydrogenation to form the product. If path II operates, the hydrogen atom on the β-position of the ketone would migrate from the β-position to the α-position. Thus, β-deuterated ethyl phenyl ketone was prepared and used for a deuterium-labeling experiment. The reaction of β-deuterated ethyl phenyl ketone with 2-methylthiophene did



Scheme 6. Three possible reaction pathways.

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not generate any α-deuterated product,[19] thus eliminating the possibility of path II. Path III involves in situ dehydrogenation of a ketone to a reactive olefin, followed by C–H olefination of a heterocycle or by the 1,4-conjugate addition of a heterocycle to an α,β-unsaturated ketone and subsequent oxidative dehydrogenation. The dehydrogenation to in situ generate an olefin intermediate has independently been proposed by Pihko,[15d] Kuwano,[15b] and White[15c] to rationalize the dehydrogenative cross-coupling reactions. To explore the possibility of path III, we checked the behavior of propiophenone under our standard conditions in the absence of thiophenes, and observed that propiophenone indeed underwent dehydrogenation to generate phenyl vinyl ketone in 26% yield after 24 h.[19] Because three equivalents of propiophenone were used in the reaction, the phenyl vinyl ketone generated from dehydrogenation would be almost equimolar to 2-methylthiophene. Furthermore, the standard conditions allowed the direct olefination of thiophene with phenyl vinyl ketone in 68% yield[19].

Path III is also consistent with the results of kinetic experiments. The initial rate of dehydrogenative cross-coupling between 2-methyl thiophene (**1a**) and propiophenone (**2a**) was dependent on the concentration of **2a**. The initial rate increased with the concentration of **2a**, reached maximum at six equivalents of **2a**, and then decreased upon increasing the concentration of **2a** from six to eight equivalents (Figure S2 in the Supporting Information).[19] When excess **2a** (3 equiv or more than 3 equiv) was used, the rate of cross-coupling between **1a** and **2a** was almost constant during the whole reaction course. These data obtained from kinetic experiments could be rationalized if the dehydrogenation of **2a** to the olefin is slower than the cross-coupling of the olefin intermediate with **1a**. Although the dehydrogenation of **2a** to the olefin intermediate is a kinetically significant event, the kinetic isotope effect (KIE) values for α- and β-positions of **2a** (1.69 and 1.16, respectively) indicated that the rate-determining step does not involve the C–H cleavage of the ketone.

To distinguish between the C–H olefination and the conjugate addition of **1a** to vinyl ketone followed by dehydrogenation in the late stage of path III, we investigated the reaction of 2-methyl-5-deuterated thiophene with propiophenone.[19] This reaction did not generate the deuterated product, thereby allowing us to eliminate the possibility of the conjugate addition.

In summary, a Pd-catalyzed dehydrogenative cross-coupling reaction of (hetero)arenes with (hetero)aryl ethyl ketones has been developed. This protocol offers good yields and tolerates a broad range of functional groups, thus presenting a versatile method for the facile syntheses of chalcones or heterocyclic chalcone analogues. In addition, dialkyl ketones can also participate in this transformation with the reaction occurring exclusively on the less sterically hindered moiety and subsequent coupling between (hetero)-arenes and olefin intemediates. Since olefins are versatile intermediates, diverse types of the dehydrogenative cross-couplings via olefin intermediates can be designed and developed.

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[1] For a review on the bioactivity of chalcones, see: J. R. Dimmock, D. W. Elias, M. A. Beazely, N. M. Kandepu, *Curr. Med. Chem.* **1999**, *6*, 1125 – 1149.

[2] a) M. T. Konieczny, W. Konieczny, M. Sabisz, A. Skladanowski, R, Wakiec, *J. Med. Chem.* **2007**, *42*, 729 – 733; b) D. Kumar, N. M. Kumar, K. Akamatsu, E. Kusaka, H. Harada, T. Ito, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3916 – 3919; c) S. Ducki, R. Forrest, J. A. Hadfield, A. Kendall, N. J. Lawrence, A. T. McGown, D. Rennison, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1051 – 1056; d) R. Edenharder, I. V. Petersdorff, R. Rauscher, *Mutat. Res.* **1993**, *287*, 261 – 274; e) S. N. Pandeya, D. Sriram, G. Nath, E. DeClercq, *Eur. J. Med. Chem.* **1999**, *9*, 25 – 31; f) J. K. Buolamwini, H. Assefa, *J. Med. Chem.* **2002**, *45*, 841 – 852; g) Z. Nowakowska, *Eur. J. Med. Chem.* **2007**, *42*, 125 – 137; h) V. J. Ram, A. S. Saxena, S. Srivastava, S. Chandra, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2159 – 2161.

[3] For selected reviews on the syntheses of heterocyclic compounds from chalcones, see: a) L. Raimondi, M. Benaglia, *Eur. J. Org. Chem.* **2001**, 1033 – 1043; b) R. Carrié, *Heterocycles* **1980**, *14*, 1529 – 1545; c) B. Stanovnik, *Tetrahedron* **1991**, *47*, 2925 – 2945; d) H. M. I. Osborn, N. Gemmell, L. M. Harwood, *J. Chem. Soc. Faraday Trans. 1* **2002**, 2419 – 2438.

[4] For selected examples of the syntheses of organic functional materials from chalcones, see: a) J.-C. Ribierre, G. Cheval, F. Huber, L. Mager, A. Fort, R. Muller, S. Mery, J. F. Nicoud, *J. Appl. Phys.* **2002**, *91*, 1710 – 1712; b) C. Melzer, M. Barzoukas, A. Fort, S. Mery, J.-C. Nicoud, *Appl. Phys. Lett.* **1997**, *71*, 2248 – 2250.

[5] C. Thebtaranonth, Y. Thebtaranonth in *The Chemistry of Enones*, *Vol. 29* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1989**, pp. 199 – 280.

[6] a) T. J. J. Müller, M. Ansorge, D. Aktah, *Angew. Chem.* **2000**, *112*, 1323 – 1326; *Angew. Chem. Int. Ed.* **2000**, *39*, 1253 – 1256; b) R. U. Braun, M. Ansorge, T. J. J. Müller, *Chem. Eur. J.* **2006**, *12*, 9081 – 9094.

[7] a) X.-F. Wu, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 5412 – 5416; *Angew. Chem. Int. Ed.* **2010**, *49*, 5284 – 5288; b) X.-F. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 14596 – 14602.

[8] For selected books and reviews, see: a) "C-H Activation": *Topics in Current Chemistry*, *Vol. 292* (Eds.: J.-Q. Yu, Z.-J. Shi), Springer, Berlin, **2010**; b) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077 – 1101; c) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200 – 205; d) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196 – 5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094 – 5115; e) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335 – 344; f) O. Daugulis, H.-D. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074 – 1086; g) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976 – 10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792 – 9826; h) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147 – 1169; i) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215 – 1292; j) X. Bugaut, F. Glorius, *Angew. Chem.* **2011**, *123*, 7618 – 7620; *Angew. Chem. Int. Ed.* **2011**, *50*, 7479 – 7481; k) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780 – 1824; l) J. Wencel-Delord, T. Drőge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740 – 4761.

[9] a) M. Zhang, J. Zhou, J. Kan, M. Wang, W. Su, M. Hong, *Chem. Commun.* **2010**, *46*, 5455 – 5457; b) J. Zhou, G. Wu, M. Zhang, X. Jie, W. Su, *Chem. Eur. J.* **2012**, *18*, 8032 – 8036.

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[10] For Pd-catalyzed dehydrosilylation of silyl enol ethers(Saegusa oxidation), see: a) Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011 – 1013; b) R. C. Larock, T. R. Hightower, G. A. Kraus, P. Hahn, D. Zheng, *Tetrahedron Lett.* **1995**, *36*, 2423 – 2426; c) J.-Q. Yu, H. C. Wu, E. J. Corey, *Org. Lett.* **2005**, *7*, 1415 – 1417.

[11] For the syntheses of α,β-unsaturated carbonyls through a halogenation–dehalogenation sequence, see: a) B. Miller, H.-S. Wong, *Tetrahedron* **1972**, *28*, 2369 – 2376; b) A. E. Greene, J.-C. Muller, G. Ourisson, *Tetrahedron Lett.* **1972**, *13*, 3375 – 3378; c) P. L. Stotter, K. A. Hill, *J. Org. Chem.* **1973**, *38*, 2576 – 2578.

[12] For the methods using IBX, see the following leading references: a) K. C. Nicolaou, Y. L. Zhong, P. S. Baran, *J. Am. Chem. Soc.* **2000**, *122*, 7596 – 7597; b) K. C. Nicolaou, T. Montagnon, P. S. Baran, *Angew. Chem.* **2002**, *114*, 1035 – 1038; *Angew. Chem. Int. Ed.* **2002**, *41*, 993 – 996; c) M. Uyanik, M. Akakura, K. Ishihara, *J. Am. Chem. Soc.* **2009**, *131*, 251 – 262.

[13] For the review on the method using DDQ, see: D. Walker, J. D. Hiebert, *Chem. Rev.* **1967**, *67*, 153 – 195.

[14] a) J. Muzart, *Eur. J. Org. Chem.* **2010**, 3779 – 3790; b) T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566 – 14569; c) W. Gao, Z. He, Y. Qian, J. Zhao, Y. Huang, *Chem. Sci.* **2012**, *3*, 883 – 886; d) T. Diao, T. J. Wadzinski, S. S. Stahl, *Chem. Sci.* **2012**, *3*, 887 – 891.

[15] For the reactions that involve dehydrogenation to olefins followed by a coupling process, see: a) Y. Terao, Y. Kametani, H. Wakui, T. Satoh, M. Miura, M. Nomura, *Tetrahedron* **2001**, *57*, 5967 – 5974; b) S. Ueno, R. Shimizu, R. Kuwano, *Angew. Chem.* **2009**, *121*, 4613 – 4615; *Angew. Chem. Int. Ed.* **2009**, *48*, 4543 – 4545; c) E. M. Stang, M. C. White, *J. Am. Chem. Soc.* **2011**, *133*, 14892 – 14895; d) M. V. Leskinen, K.-T. Yip, A. Valkonen, P. M. Pihko, *J. Am. Chem. Soc.* **2012**, *134*, 5750 – 5753; e) Y. Moon, D. Kwon, S. Hong, *Angew. Chem.* **2012**, *124*, 11495 – 11498; *Angew. Chem. Int. Ed.* **2012**, *51*, 11333 – 11336.

[16] a) K. Ueda, S. Yanagisawa, J. Yamaguchi, K. Itami, *Angew. Chem.* **2010**, *122*, 9130 – 9133; *Angew. Chem. Int. Ed.* **2010**, *49*, 8946 – 8949; b) M. Steinmetz, K. Ueda, S. Grimme, J. Yamaguchi, S. Kirchberg, K. Itami, A. Studer, *Chem. Asian J.* **2012**, *7*, 1256 – 1260; c) Y. Huang, F. Song, Z. Wang, P. Xi, N. Wu, Z. Wang, J. Lan, J. You, *Chem. Commun.* **2012**, *48*, 2864 – 2866.

[17] a) K. Masui, H. Ikegami, A. Mori, *J. Am. Chem. Soc.* **2004**, *126*, 5074 – 5075; b) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu, J. You, *J. Am. Chem. Soc.* **2010**, *132*, 1822 – 1824; c) C.-Y. He, S. Fan, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 12850 – 12852; d) S. Pivsa-Art, T. Satph, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467 – 473; e) J. Fournier Dit Chabert, L. Joucla, E. David, M. Lemaire, *Tetrahedron* **2004**, *60*, 3221 – 3230; f) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc.* **2009**, *131*, 14622 – 14623; g) B. Join, T. Yamamoto, K. Itami, *Angew. Chem.* **2009**, *121*, 3698 – 3701; *Angew. Chem. Int. Ed.* **2009**, *48*, 3644 – 3647; h) S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748 – 11749; i) H.-Q. Do, R. M. Kashif Khan, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 15185 – 15192; j) S. Kirchberg, S. Tani, K. Ueda, J. Yamaguchi, A. Studer, K. Itami, *Angew. Chem.* **2011**, *123*, 2435 – 2439; *Angew. Chem. Int. Ed.* **2011**, *50*, 2387 – 2391; k) P. Hu, M. Zhang, X. Jie, W. Su, *Angew. Chem.* **2012**, *124*, 231 – 235; *Angew. Chem. Int. Ed.* **2012**, *51*, 227 – 231; l) O. René, D. Lapointe, K. Fagnou, *Org. Lett.* **2009**, *11*, 4560 – 4563; m) N. Kuhl, M. N. Hopkinson, F. Glorius, *Angew. Chem.* **2012**, *124*, 8354 – 8358; *Angew. Chem. Int. Ed.* **2012**, *51*, 8230 – 8234.

[18] a) F. Zhang, M. F. Greaney, *Angew. Chem.* **2010**, *122*, 2828 – 2831; *Angew. Chem. Int. Ed.* **2010**, *49*, 2768 – 2771; b) E. M. Beck, R. Hatley, M. J. Gaunt, *Angew. Chem.* **2008**, *120*, 3046 – 3049; *Angew. Chem. Int. Ed.* **2008**, *47*, 3004 – 3007; c) E. M. Beck, N. P. Grimster, R. Hatley, M. J. Gaunt, *J. Am. Chem. Soc.* **2006**, *128*, 2528 – 2529; d) A. García-Rubia, R. G. Arrayás, J. C. Carretero, *Angew. Chem.* **2009**, *121*, 6633 – 6637; *Angew. Chem. Int. Ed.* **2009**, *48*, 6511 – 6515; e) Z. Wang, K. Li, D. Zhao, J. Lan, J. You, *Angew. Chem.* **2011**, *123*, 5477 – 5481; *Angew. Chem. Int. Ed.* **2011**, *50*, 5365 – 5369; f) J. Ryu, S. H. Cho, S. Chang, *Angew. Chem.* **2012**, *124*, 3737 – 3741; *Angew. Chem. Int. Ed.* **2012**, *51*, 3677 – 3681; g) S. H. Kim, J. H. Yoon, S. Chang, *Org. Lett.* **2011**, *13*, 1474 – 1477; h) S. J. Hwang, H. J. Kim, S. Chang, *Org. Lett.* **2009**, *11*, 4588 – 4591; i) S. J. Hwang, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 16158 – 16159; j) P. Gandeepan, C. H. Cheng, *J. Am. Chem. Soc.* **2012**, *134*, 5738 – 5741; k) S. Yang, C. Sun, B. Li, Y. Li, Z. Shi, *Angew. Chem.* **2008**, *120*, 1495 – 1498; *Angew. Chem. Int. Ed.* **2008**, *47*, 1473 – 1476; l) T.-J. Gong, B. Xiao, Z.-J. Liu, J. Wan, J. Xu, D.-F. Luo, Y. Fu, L. Liu, *Org. Lett.* **2011**, *13*, 3235 – 3237; m) S. Ding, N. Jiao, *J. Am. Chem. Soc.* **2011**, *133*, 12374 – 12377.

[19] See the Supporting Information for details.

[20] a) S. Kirchberg, T. Vogler, A. Studer, *Synlett* **2008**, 2841 – 2845; b) S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem.* **2009**, *121*, 4299 – 4302; *Angew. Chem. Int. Ed.* **2009**, *48*, 4235 – 4238; c) E. J. Yoo, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 17378 – 17380.

[21] For the first example of a palladium(0)-catalyzed directed β-arylation, see: M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886 – 9887. For a recent review, see: R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654 – 2672.

[22] a) A. Renaudat, L. Jean-Gérard, R. Jazzar, C. E. Kefalidis, E. Clot, O. Baudoin, *Angew. Chem.* **2010**, *122*, 7419 – 7423; *Angew. Chem. Int. Ed.* **2010**, *49*, 7261 – 7265; b) P. Larini, C. E. Kefalidis, R. Jazzar, A. Renaudat, E. Clot, O. Baudoin, *Chem. Eur. J.* **2012**, *18*, 1932 – 1944; c) S. Aspin, A.-S. Goutierre, P. Larini, P. Jazzar, O. Baudoin, *Angew. Chem.* **2012**, *124*, 10966 – 10969; *Angew. Chem. Int. Ed.* **2012**, *51*, 10808 – 10811.

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