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Palladium Catalyzed Dehydrogenative Coupling of Cyclic Enones with Thiophenes: A Rapid Access to β-Heteroarylated Cyclic Enones

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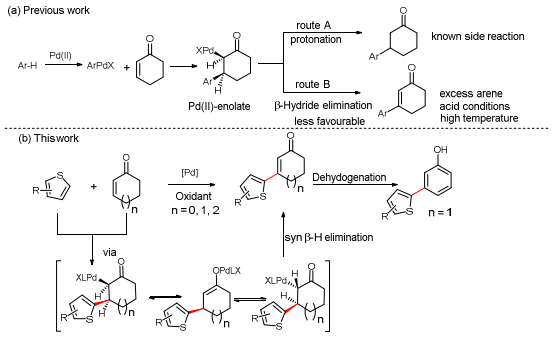
Dehydrogenative coupling of cyclic enones with heteroarenes has been a longstanding challenge because of competitive ketone dehydrogenation and conjugated addition. Reported herein is a dehydrogenative coupling reaction of different size of cyclic enones with substituted thiophenes to construct β-thienyl cyclic enone compounds through palladium catalyzed C-H functionalization under mild reaction conditions. Simple substituted thiophenes with different functional groups can be directly introduced to cyclic enones with predominant regio-selectivity at the α position of thiophene moieties and excellent functional group tolerance. Further molecular transformations of the coupling products to synthetically useful *meta*-heteroarylated phenol derivatives are also demonstrated.

The palladium catalyzed Fujiwara-Moritani-Heck[1] coupling through C-H functionalization represents an important class of powerful C-C bond forming strategy in step and atom economical manner. While significant progress has been achieved for coupling reaction between linear terminal alkenes and (hetero)arenes, [2] the direct coupling between cyclic enones and (hetero)arenes is hardly enabled to afford the desired product 3-(hetero)arylated cyclic enones, which are of great importance as structure motifs both in bioactive molecules[3] and in the synthesis of substituted phenols or anilines for drug design. [4] The reason is likely attributed to the low reactivity of simple (hetero)arenes in the absene of directing groups[1,5], side reactions of cyclic enones during the catalytic system such as ketone dehydrogenation[6] and conjugated addition[7]. In most cases the Pd(II)-enolate intermediate, which was generated by migratory insertion of aryl palladium species into conjugated enone olefin, prefers to undergo hydrolysis rather than β-hydride elimination (Scheme 1a) because of the Pd and β-hydrogen atom were in the opposite position in the Pd(II)-cyclic enolate[4c] intermediate. Thus the establishment of catalytic reactions that involve Csp^2-H activation between cyclic enones and substituted heteroarenes through Heck coupling to provide 3-(hetero)arylated cyclic enones remains great challenge. Despite the recent progress in palladium catalyzed Heck coupling of cyclic enones with arenes via arene C-H activation, a large excess of arene (neat or more than 15 equivalents) as well as an acid reaction media and high temperature (above 100°C) are typically required,[8] which limits the practicality and utility of these approaches. Herein, we report a facile method for the synthesis of β-heteroarylated cyclic enones through palladium-catalyzed cross-coupling strategy between different size of cyclic enones and readily available thiophenes under mild conditions, in which thiophene is used as a limiting reagent (Scheme 1b). To the best of our knowledge, the direct dehydrogenative cross-coupling between cyclic enones and thiophenes has not been reported to date. In addition, the derivatization of the prepared β-thienyl-substituted cyclohexenones to *meta*-substituted phenols was demonstrated, thus providing a complementary to the *meta*-phenol preparation[4c,9] which could not be accessible by typical electrophilic substitution of phenol due to its strong directing effect of hydroxyl group.

Scheme 1. Dehydrogenative coupling of cyclic enones with arenes



Our strategy focuses on developing an efficient catalytic system for facie synthesis of 3-(hetero)arylated cyclic enones

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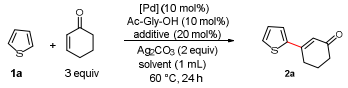
from the corresponding cyclic enones and thiophenes. This strategy avoids use of prefunctionalized aryl surrogates[10] (aryl halides, aryl boronic acids, aryl carboxylic acids) and thereby enhances synthetic efficiency. To achieve the coupling of cyclic enones and thiophenes, following challenges must be considered. First, due to the absence of directing group, the low reactivity of simple heteroarenes should be enhanced using a sufficiently reactive palludium catalyst. Secondly, side reactions such as homocoupling of thiophene[11] and overoxdiation of cyclic enones[6,12] must be inhibited. Thus, exploitation of a catalytic system via precise control over the catalytic sequence is desired.

We commenced our investigation by screening various reaction conditions for the envisioned dehydrogenative coupling of cyclohexenone with thiophene **1a** employing $Pd(OAc)_2$ as catalyst and Ag_2CO_3 as the oxidant. Given the widely applicable ligand-induced acceleration[5] in C-H activation reactions, we envisage that the judicious choice of a suitable ligand could promote direct coupling of cyclic enones with thiophene through C-H activation. Note that the combination of palladium catalyst with amino acid ligands has been well established in the C-H bond functionalization reactions.[13] Gratifyingly, preliminary attempts using Ac-Gly-OH in dioxane at 60 °C stirred for 24 h led to the coupling product **2a** in 18% yield (Table 1, entry 1). A variety of solvents screening revealed that additon of 5% mildly acidic HFIP in dioxane provided the desired coupling product in 32% yield (entries 2-9), although the role of HFIP was unclear. Other single solvents such as THF and HFIP proved less effective.

Table 1. Optimization Conditions[a]



entry[a]	catalyst	solvent	yield[b]
1	$Pd(OAc)_2$	dioxane	18%
2	$Pd(OAc)_2$	THF	8%
3	$Pd(OAc)_2$	DCE	5%
4	$Pd(OAc)_2$	DMF	trace
5	$Pd(OAc)_2$	DMSO	trace
6	$Pd(OAc)_2$	DMA	trace
7	$Pd(OAc)_2$	HFIP	8%
8	$Pd(OAc)_2$	HFIP/dioxane (1:1)	22%
9	$Pd(OAc)_2$	5% HFIP/dioxane	32%
10	$PdCl_2$	5% HFIP/dioxane	38%
11	$Pd(TFA)_2$	5% HFIP/dioxane	<10%
12[c]	$PdCl_2$	5% HFIP/dioxane	23%
13[d]	$PdCl_2$	5% HFIP/dioxane	15%
14[e]	$PdCl_2$	5% HFIP/dioxane	<10%
15	$PdCl_2$/ KPF_6	5% HFIP/dioxane	33%
16	$PdCl_2$/$AgSbF_6$	5% HFIP/dioxane	46%
17	$PdCl_2$/$(BnO)_2P(O)OH$	5% HFIP/dioxane	20%
18[f]	**$PdCl_2$/$AgSbF_6$**	**5% HFIP/dioxane**	**64%**

[a]Conditions: The reaction was conducted with thiophene (0.25 mmol, 1 equiv), cyclohexenone (0.75 mmol, 3 equiv), $Pd(OAc)_2$ (0.025 mmol, 0.1 equiv), Ac-Gly-OH (0.025 mmol, 0.1 equiv), Ag_2CO_3 (0.5 mmol, 2 equiv) in 1 mL solvent at 60 °C for 24 h. [b]Isolated yield. [c]AgOAc (4 equiv) as oxidant [d]Ag_2O (2 equiv) as oxidant, [e]$Cu(OAc)_2$ (4 equiv) as oxidant [f]DMSO (0.05 mL) was added as the minor cosolvent. HFIP = 1,1,1,3,3,3-Hexafluoro-2-propanol

Polar solvents including DMSO, DMA, DMF led to trace of product formation. Interestingly, neither thiophene dimerization nor overoxidation side product was observed. A brief examination of palladium catalysts revealed that **2a** could be isolated in 38% yield when $PdCl_2$ was used (entry 10), while use of more ionic $Pd(TFA)_2$ was found much less effective (entry 11). Oxidants survey showed that Ag_2CO_3 was suitable oxidant for this reaction (entries 12-14). In order to improve the reaction efficiency, the combination of $PdCl_2$ with additives in 1:2 ratio was examined. Pleasingly, $AgSbF_6$ as additive could afford **2a** in 46% yield, other additives such as KPF_6 or dibenzyl phosphate resulted in a decreased yield (entries 15-17). Finally, when using 0.05 mL DMSO as a minor cosolvent, the yield of **2a** increased up to 64%, which was expected to stablize Pd (0) species and inhibit undesired inert palladium black formation (entry 18). Control experiment revealed that palladium catalyst and Ac-Gly-OH were crucial for this coupling, and no reaction occurred in the absence of them (for detailed optimization, see the Supporting Information). Thus, the standard condition was established as following: the mixture of thiophene (0.25 mmol), cyclohexenone (0.75 mmol), DMSO (0.05 mL), $PdCl_2$ (0.1 equiv), Ac-Gly-OH (0.1 equiv), $AgSbF_6$ (0.2 equiv), Ag_2CO_3 (2 equiv) in 5% HFIP/dioxane (0.05 mL/1 mL) at 60 °C stirred for 24 h.

With the optimized reaction conditions in hand, we attempted the dehydrogenative coupling reactions of cyclic enones with various substituted thiophenes (Scheme 2). Pleasingly, all reactions proceeded smoothly to provide the coupling products in moderate to high yields at α position of thiophenes. 2-Methyl thiophene gave 68% yield of the corresponding product **2b** under the standard reaction conditions. Interestingly, 3-Methyl thiophene gave an inseparable mixture of **2ca** and **2cb** (83:17) in 70% yield through the C-H functionalization of thiophene at the 5 and 2 position, while 3-methoxylthiophene afforded a single product **2d** in 63% yield. It's noteworthy that various functional groups (**2e**-**2g**, **2i**, **2j**) such as chloro, boromo, enolizable methyl ketones and esters were all tolerated under this catalytic reaction conditions, thus offered a great potential for further transformation of these products to more complicated molecules. 2-Phenylthiophene also reacted successfully, affording the corresponding product **2h** in 75% yield. When 3,4-ethylenedioxythiophene was used to react with cyclohexenone, the desired product **2k** was obtained in 29% yield. Benzothiophene was also suitable substrate in this catalytic reaction conditions, gave the corresponding product (**2la**, **2lb**) with a mixture of α and β funtionalized isomers (67:33) in 24% yield. Other heterocyclic analogues such as furan and 2-methylfuran worked efficiently in this protocol, affording the products at α-position of furans in moderate yields (**2m**, **2n**). Furthermore, more steric hindered 2,4-disubstituted thiophenes, which are untouched substrates in previously reprorted thiophene functionalization reactions, [14]

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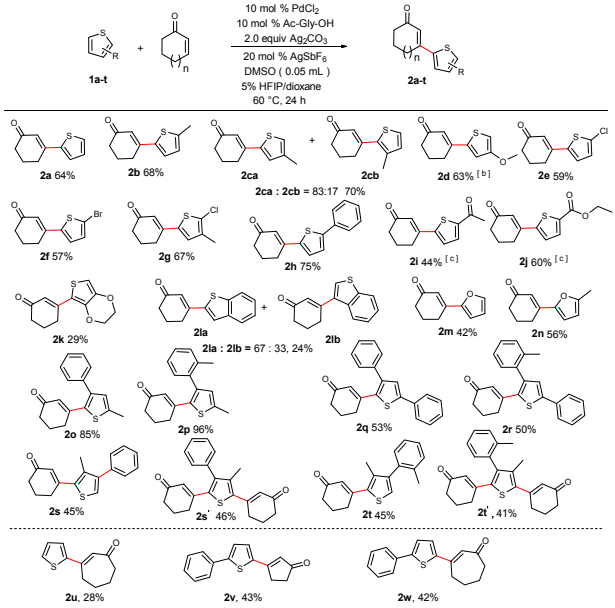
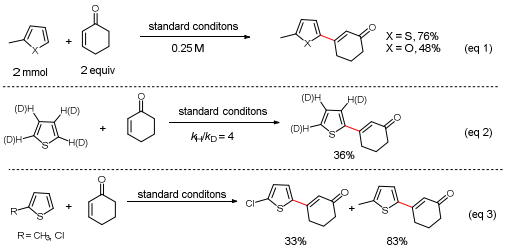
were employed in this transformation and gave the products (**2o**-**2r**) in moderate to high yield, Moreover, when 3, 4-disubstituted thiophenes were used, the mono- and di-coupling cyclohexenone products (**2s**, **2s'**, **2t**, **2t'**) were isolated in high yields. Finally, different size of cyclic enones such as cyclopentenone and cycloheptenone were suitable substrates to couple with thiophene or 2-phenylthiophene, providing the desired coupling products in moderate yields (**2u**, **2v**, **2w**).

Scheme 2. Scope of the dehydrogenative coupling between substituted thiophenes with cyclic enones



[a]Reaction condition: Thiophene homologues (0.25 mmol), 2-cyclohexen-1-one (0.75 mmol, 3 equiv), $PdCl_2$ (0.025 mmol), Ac-Gly-OH (0.025 mmol), Ag_2CO_3 (0.5 mmol), $AgSbF_6$ (0.05 mmol), DMSO (0.05 mL), HFIP (0.05 mL), dioxane (1 mL), 60 °C, 24 h. [b]$AgSbF_6$ was not added. [c]0.5 equiv Ac-Gly-OH were used, HFIP (0.5 mL)/dioxane (0.5 mL) instead of HFIP (0.05 mL)/dioxane (1 mL), 110 ℃.

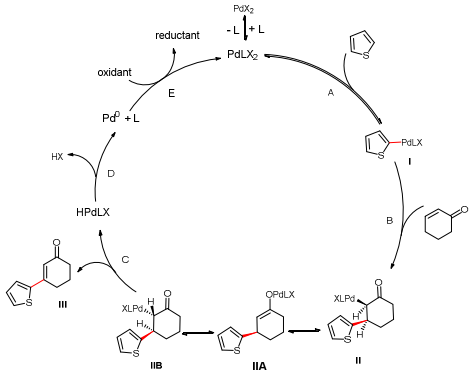
To examine the potential use of current method in organic synthesis, a 2 mmol scale-up reactions between 2-methylthiophen or 2-methylfuran and cyclohexenone were performed (eq 1), the direct cross-coupling products were isolated in 76% yield and 48% yield respectively.



To gain further insight into the mechanism of palladium catalyzed cross-coupling of cyclohexenone with thiophene, an intermolecular kinetic isotope effect (KIE) experiment was performed under the standard reaction conditions (eq 2). As a result, a significant KIE value (k_H/k_D = 4) was observed, thus suggesting the thiophene C–H bond cleavage is probably involved in the rate-determining step of this dehydrogenative cross-coupling reaction. Moreover an intermolecular competition reaction between 2-methyl thiophene and 2-chloro thiophene with cyclohexenone was also conducted under the standard reaction conditions (eq 3), the remarkable difference of coupling product yields verified the reaction efficiency was dependent on the electron properties of thiophenes, thus providing indirect support for thiophene C-H cleavage step was involved in the rate-determining step.

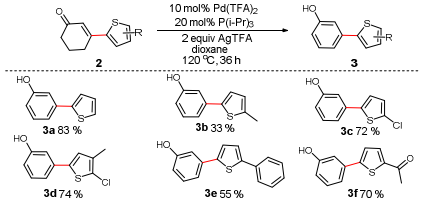
Based on these results, a plausible proposed catalytic mechanism for the dehydrogenative coupling reaction was described in Scheme 3. Starting with a thiophene and a Pd(II) catalyst, a thienyl-Pd(II) species **I** can be formed (Step A). Subsequently, migratory insertion of the produced thienyl-Pd(II) into conjugated enone olefin would afford a thiophene based Pd-enolate intermediate **II** (Step B), which should undergo a rapid isomerization (**II**, **IIA**, **IIB**) for the facile *syn* β-hydride elimination (Step C) to give the desired coupling product **III** and restore Pd(0) (Step D). Finally, with a suitable oxidant the active Pd(II) could be regenerated to complete the cytalytic cycle (Step E).

Scheme 3. Proposed Mechanism



To demonstrate the utility of this transformation, derivatization reactions of the coupling products to *meta*-phenols were consequently conducted by using a phosphine

Scheme 4. Application of palladium catatlyzed dehydrogenation reactions in the synthesis of *meta*-thiophene substituted phenols.



[a]Reaction condition: $Pd(TFA)_2$ (10 mol%), silver trifluoroacetate (2.0 equiv), triisopropylphosphane (20 mol%) and substrate 2 (0.15 mmol) were stirred in 1,4-dioxane (0.75 mL) at 120 °C for 36 h.

based electron rich palladium catalyst, and the representative results are shown in Scheme 4. We are pleased to observe that β-heteroarylated cylcohexenones with different electron properties worked well and gave the desired *meta*-phenol derivatives in moderate to high yields. It's noteworthy that when the reaction is performed under Stahl's conditions

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where an electrophilic palladium catalyst was employed, [4c] no phenol products were observed. Interestingly, the chloro and enolizable methyl ketone substituted thiophene moieties were also tolerated in this transformation, which provides a straightforward route for further elaboration of complicated phenol molecules.

In conclusion, we have developed palladium catalyzed dehydrogenative cross-coupling of cyclic enones with thiophenes to prepare β-thienyl cyclic enone molecules. Remarkable regioselectivity and high functional group compatability were achieved. The resulting β-thienyl cyclohexenone compounds could be derivatized to useful *meta*-heteroarylated phenol derivatives. We expect that these dehydrogenative cross-coupling processes will provide new routes to construct *meta*-heteroarylated phenol scaffolds with omnipotent uses in synthetic and medicinal applications.

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Notes and references

1 a) C. G. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res*. **2001**, *34*, 633; b) C. G. Jia, D. P. Piao, J. Oyamada, W. J. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992; c) C. G. Jia, W. J. Lu, T Kitamura, Y. Fujiwara, *Org. Lett*. **1999**, *1*, 2097; d) Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc*. **1969**, *91*, 7166; e) I. Moritani, Y. Fujiwara, *Tetrahedron Lett*. **1967**, *8*, 1119.

2 For selected reviews and examples, see: a) L. H. Zhou, W. J. Lu, *Chem. Eur. J*. **2014**, *20*, 634; b) S. I. Kozhushkov, L. Ackermann, *Chem. Sci*. **2013**, *4*, 886; c) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev*. **2012**, *112*, 5879; d) J. Le Bras, J. Muzart, *Chem. Rev*. **2011**, *111*, 1170; e) T. Satoh, M. Miura, *Chem. Eur. J*. **2010**, *16*, 11212; f) M. Dams, D. E. De Vos, S. Celen, P. A. Jacobs, *Angew. Chem. Int. Ed.* **2003**, *42*, 3512; g) T. Yokota, M. Tani, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc*. **2003**, *125*, 1476.

3 a) S. Radomkit, A. H. Hoveyda, *Angew. Chem. Int. Ed*. **2014**, *53*, 3387; b) P. Kwiatkowski, K. Dudziński, D. Łyżwa, *Org. Lett*. **2011**, *13*, 3624; c) S. Kehrli, D. Martin, D. Rix, M. Mauduit, A. Alexakis, *Chem. Eur. J*. **2010**, *16*, 9890; d) I. H. Chen, L. Yin, W. Itano, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc*. **2009**, *131*, 11664; e) M. E. Jimenez, K. Bush, J. Pawlik, L. Sower, J. W. Peterson, S. R. Gilbertson, *Bioorg. Med. Chem. Lett*. **2008**, *18*, 4215; f) F. J. Moreno-Dorado, F. M. Guerra, F. J. Aladro, J. M. Bustamante, Z. D. Jorge, G. M. Massanet, *Tetrahedron* **1999**, *55*, 6997.

4 For recent examples, see: a) T. Boibessot, C. P. Zschiedrich, A. Lebeau, D. Bénimèlis, C. Dunyach-Rémy, J. P. Lavigne, H. Szurmant, Z. Benfodda, P. Meffre, *J. Med. Chem*. **2016**, *59*, 8830; b) T. Diao, D. Pun, S. S. Stahl, *J. Am. Chem. Soc*. **2013**, *135*, 8205; c) Y. Izawa, C. Zheng, S. S. Stahl, *Angew. Chem. Int. Ed*. **2013**, *52*, 3672; d) M. O. Simon, S. A. Girard, C. J. Li, *Angew. Chem. Int. Ed*. **2012**, *51*, 7537; e) S. Quideau, D. Deffieux, C. Douat-Casassus, L. Pouységu, *Angew. Chem. Int. Ed*. **2011**, *50*, 586.

5 a) P. Wang, P. Verma, G. Q. Xia, J. Shi, J. X. Qiao, S. W. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K. S. Yeung, J. Q. Yu, *Nature* **2017**, *551*, 489; b) J. F. Hartwig, M. A. Larsen, *ACS Cent. Sci.* **2016**, *2*, 281; c) C.-H. Ying, S. B. Yan, W. L. Duan, *Org. Lett.* **2014**, *16*, 500; d) A. Kubota, M. H. Emmert, M. S. Sanford, *Org. Lett.* **2012**, 14, 1760; e) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; e) Y. H. Zhang, B. F. Shi, J. Q. Yu, *J. Am. Chem. Soc.* **2009**, 131, 5072.

6 For reviews and selected examples of Pd-catalyzed direct dehydrogenation of ketone, see: a) J. Muzart, *Eur. J. Org. Chem*. **2010**, 3779; b) W. Gao, Z. He, Y. Qian, J. Zhao, Y. Huang, *Chem. Sci*. **2012**, *3*, 883; c) T. Diao, T. J. Wadzinski, S. S. Stahl, *Chem. Sci*. **2012**, *3*, 887; d) T. Diao, S. S. Stahl, *J. Am. Chem. Soc*. **2011**, *133*, 14566; e) Y. Shvo, A. H. I. Arisha, *J. Org. Chem*. **1998**, *63*, 5640.

7 a) A. B. Weinstein, J. A. Ellman, *Org. Lett*. **2016**, *18*, 3294; b) X. Y. Shi, C. J. Li, *Org. lett*. **2013**, *15*, 1476; c) J. A. Jordan-Hore, J. N. Sanderson, A. L. Lee, *Org. Lett*. **2012**, *14*, 2508; d) A. L. Gottumukkala, K. Matcha, M. Lutz, J. G. de Vries, A. J. Minnaard, *Chem. Eur. J*. **2012**, *18*, 6907; e) K. Kikushima, J. C. Holder, M. Gatti, B. M. Stoltz, *J. Am. Chem. Soc*. **2011**, *133*, 6902; f) S. H. Lin, X. Y. Lu, *Org. Lett*. **2010**, *12*, 2536; g) T. Nishitaka, Y. Yamamoto, N. Miyaura, *Chem. Lett*. **2007**, *36*, 1442; h) F. Gini, B. Hessen, A. J. Minnaard, *Org. Lett*. **2005**, *7*, 5309; i) T. Nishikata, Y. Yamamoto, N. Miyaura, *Angew. Chem., Int. Ed*. **2003**, *42*, 2768.

8 a) L. G. Y. Chung, N. A. B. Juwaini, J. Seayad, *ChemCatChem* **2015**, *7*, 1270; b) N. Gigant, J.-E. Bäckvall, *Chem. Eur. J*. **2014**, *20*, 5890; c) Y. Moon, D. Kwon, S. Hong, *Angew. Chem. Int. Ed*. **2012**, *51*, 11333.

9 a) Y. F. Liang, S. Song, L. S. Ai, X. W. Li, N. Jiao, *Green Chem*., **2016**, *18*, 6462; b) J. W. Zhang, Q. Q. Jiang, D. J. Yang, X. M. Zhao, Y. L. Dong, R. H. Liu, *Chem. Sci*., **2015**, *6*, 4674.

10 For selected examples by using prefunctionalized aryl surrogates, see: a) S. E. Walker, J. Boehnke, P. E. Glen, S. Levey, L. Patrick, J. A. Jordan- Hore, A. L. Lee, *Org. Lett*. **2013**, *15*, 1886; b) A. L. Gottumukkala, J. F. Teichert, D. Heijnen, N. Eisink, S. van Dijk, C. Ferrer, A. van den Hoogenband, A. J. Minnaardb, *J. Org. Chem*. **2011**, *76*, 3498; c) Y. Fall, H. Doucet, M. Santelli, *Tetrahedron* **2009**, *65*, 489; d) K. S. Yoo, C. H. Yoon, K. W. Jung, *J. Am. Chem. Soc*. **2006**, *128*, 16384; e) X. Lu, S. Lin, *J. Org. Chem*. **2005**, *70*, 9651; f) D. Tanaka, A. G. Myers, *Org. Lett*. **2004**, *6*, 433; g) T. R. Krishna, N. Jayaraman, *Tetrahedron* **2004**, *60*, 10325; h) T. Nishikata, Y. Yamamoto, N. Miyaura, *Angew. Chem. Int. Ed*. **2003**, *42*, 2768.

11 a) Y. D. Yang, J. B. Lan, J. S. You, *Chem. Rev.*, **2017**, *117*, 8787; b) N. N. Li, Y. L. Zhang, S. Mao, Y. R. Gao, D. D. Guo, Y. Q. Wang, *Org. Lett*., **2014**, *16*, 2732; c) K. Masui, H. Ikegami, A. Mori, *J. Am. Chem. Soc.*, **2004**, *126*, 5074.

12 a) D. Pun, T. Diao, S. S. Stahl, *J. Am. Chem. Soc*. **2013**, *135*, 8213; b) Z. X. Huang, G. B. Dong, *J. Am. Chem. Soc*. **2013**, *135*, 17747; c) Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209.

13 a) K. M. Engle, D. H. Wang, J. Q. Yu, *J. Am. Chem. Soc*. **2010**, *132*, 14137; b) Y. Lu, D. H. Wang, K. M. Engle, J. Q. Yu, *J. Am. Chem. Soc*. **2010**, *132*, 5916; c) D. H. Wang, K. M. Engle, B. F. Shi, J. Q. Yu, *Science* **2010**, *327*, 315; d) X. Wang, Y. Lu, H. X. Dai, J. Q. Yu, *J. Am. Chem. Soc*. **2010**, *132*, 12203; e) Z. K. Wen, Y. H. Xu, T. P. Loh, *Chem. Sci*., **2013**, *4*, 4520; f) Q. J. Liang, C. Yang, F. F. Meng, B. Jiang, Y. H. Xu, T. P. Loh, *Angew. Chem. Int. Ed*. **2017**, *56*, 5091.

14 For selected examples, see: a) B. J. Gorsline, L. Wang, P. Ren, B. P. Carrow, J. *Am. Chem. Soc*. **2017**, *139*, 9605; b) T. Morita, T. Satoh, M. Miura, *Org. Lett*. **2015**, *17*, 4384; c) A. Vasseur, C. Laugel, D. Harakat, J. Muzart, J. Le. Bras, *Eur. J. Org. Chem.* **2015**, 944; d) C. Y. He, C. Z. Wu, Y. L. Zhu, X. G. Zhang, *Chem. Sci*., **2014**, *5*, 1317; e) Y. P. Shang, X. M. Jie, J. Zhou, P. Hu, S. J. Huang, W. P. Su, *Angew. Chem. Int. Ed*. **2013**, *52*, 1299; f) C.Y. He, Z. Wang, C. Z. Wu, F. L. Qing, X. G. Zhang, *Chem. Sci*., **2013**, *4*, 3508; g) Y. X. Zhang, Z. J. Li, Z. Q. Liu, *Org. Lett.*, **2012**, *14*, 226; h) A. Vasseur, J. Muzart, J. Le. Bras, *Chem. Eur. J*. **2011**, *17*, 12556; i) C. Y. He, S. L. Fan, X. G. Zhang, J. *Am. Chem. Soc*. **2010**, *132*, 12850; j) P. H. Xi, F. Yang, S. Qin, D. B. Zhao, J. B. Lan, G. Gao, C. W. Hu, J. S. You, J. *Am. Chem. Soc*. **2010**, *132*, *132*, 1822; k) A. Maehara, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett*. **2008**, *10*, 1159.

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Palladium Catalyzed Dehydrogenative Coupling of Cyclic Enones with Thiophenes: A Rapid Access to β-Heteroarylated Cyclic Enones

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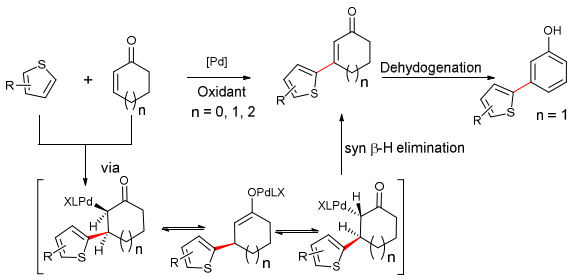
A dehydrogenative coupling reaction of cyclic enones with thiophenes to construct β-thienyl cyclic enone compounds through palladium catalyzed C-H functionalization is reported herein. Further molecular transformations of the coupling products to synthetically useful *meta*-heteroarylated phenol derivatives are also demonstrated.



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