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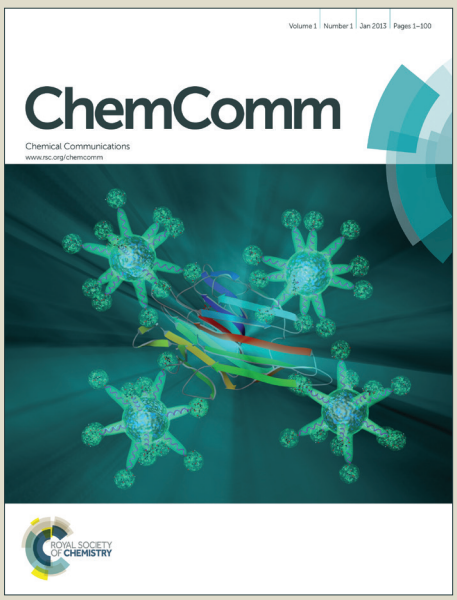

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Orthogonal Selectivity with Cinnamic Acids in 3-substituted Benzofuran Synthesis through C–H Olefination of Phenols

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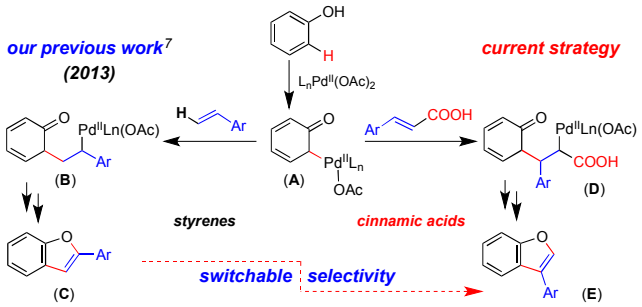
A palladium catalyzed intermolecular annulation of cinnamic acids and phenols has been achieved for the selective synthesis of 3-substituted benzofurans. Isotope labeling, competition experiments, kinetic studies, and intermediate trapping have supported a sequence of C–C bond formation, decarboxylation followed by C–O cyclization pathway.

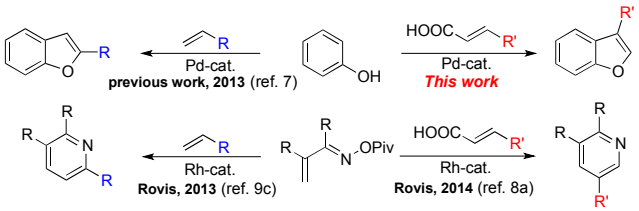
Benzofurans are one of the most prevalent structural motifs in natural products[1] and synthetic compounds, which show a variety of biological activities.[2] Tradionally transition-metal-catalyzed inter/intra molecular condensation reactions using prefunctionalized substrates (such as *ortho*-alkynyl or –halo phenol) are utilized for bezofuran synthesis.[3] Recent efforts are focused on benzofuran synthesis *via* ortho C–H activation of phenols.[4] Significant recent achievement includes iron-catalyzed oxidative Pechmann condensation reaction between phenol and *β*-keto ester for generating polybenzofuran in a single-step.[4a] Efficient synthesis of dibenzofuran through novel C–H activation/C–O cyclization from 2-hydroxy biphenyl has also been reported.[4b] An oxidative annulation of phenol and internal alkyne has been achieved for the synthesis of 2,3-disubstituted benzofuran derivatives.[4c-e] A Ru-catalyzed dehydrative C–H alkenylation/annulation reaction of phenols with 1,2-diols has also been utilized efficiently for the synthesis of benzofuran.[4f] Triflic anhydride mediated Pummer annulation reaction is another concise route to access substituted benzofurans.[4g, 4h] Despite these significant advances, selective synthesis of *3-substituted* benzofurans from readily accessible phenols remain a challenging task.[5] Notably a significant number of natural products and synthetic compounds are based on 3-substituted benzofuran motif.[1c, 6]



Scheme 1. Synthesis of benzofurans by multiple C–H bond functionalization

We have recently reported palladium-catalyzed synthesis of 2-*substituted* benzofurans by reacting phenols and olefins *via* sequential C–H functionalization (Scheme 1, left side).[7] Herein, 3-*substituted* benzofurans are synthesized from widely available phenols and cinnamic acids. Importantly, the carboxylic acid moiety acts as a traceless directing group[8] for the exclusive synthesis of benzofuran derivatives.

Mechanistic study of our recently reported *2-substituted* benzofuran synthesis from phenol and olefin revealed that palladium center is located at the *α*-position of the olefin substituent in the intermediate **B**. Complementary to this approach, we envisioned, *3-substituted benzofuran* (**E**) synthesis will require intermediate **D**, wherein palladium will be attached at the *β*-position. Formation of this new intermediate **D** will be possible if C–Pd bond inserts in an orthogonal fashion to that of the terminal olefin (Scheme 1, right side). Cinnamic acid in conjunction with readily available phenols will produce **D** since introduction of carboxylic acid group in olefin will reverse the electronic nature of two carbon centers as compared to simple olefin (Scheme 1).[8a, 9]



Scheme 2. Selective synthesis of benzofuran and pyridine

This work in combination with our previous report on substituted benzofuran synthesis,[7] in essence, parallel the recent studies from Rovis group for the synthesis of substituted pyridine derivatives (Scheme 2).[8a, 9c] In this regard, Miura have contributed significantly by introducing decarboxylation strategy in various synthetic transformation like regio-selective olefination, arylation and cyclization reactions.[10]

After extensive experimentations, desired 3-arylbenzofuran in dichloroethane (DCE) was obtained with substituted phenol and

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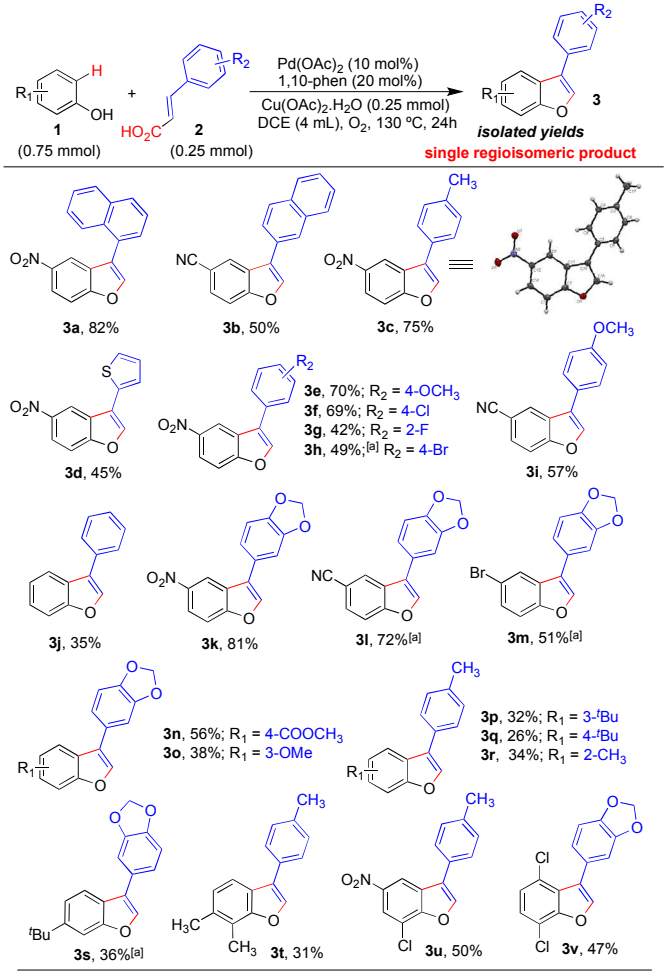
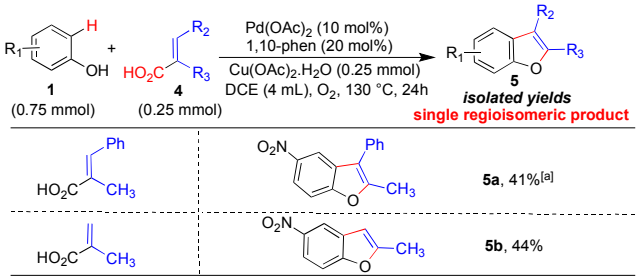
cinnamic acid under O_2 atmosphere (Table 1).[11] Notably, related 2-arylbenzofuran was not detected even in trace amount. With cinnamic acid derivatives, substituted phenols produced 3-arylated benzofuran in 26-82% isolated yield (**3a-3v**). Naphthyl- and *para*-tolyl- substituted cinnamic acids gave the 3-arylbenzofuran exclusively in 82% (**3a**) and 75% (**3c**) yields, respectively. Thiophenylacrylic acid provided the desired benzofuran product in moderate yield (**3d**, 45%). Further, nitro (**3k**), halogen (**3f-3h**), ester (**3n**), and cyano (**3l**) groups were tolerated under the standard condition. Next, we probed the scope of our method with different electron rich phenols (**3o-3t**). Notably, lower yield of the desired benzofuran products were obtained in every cases.

Table 1. Scope with substituted phenols and cinnamic acids[12]



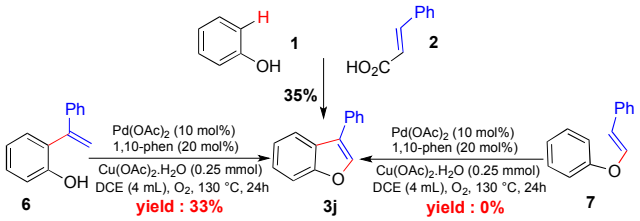
[a]bathophenanthroline as the ligand

Table 2. Reaction with internal alkenyl carboxylic acids



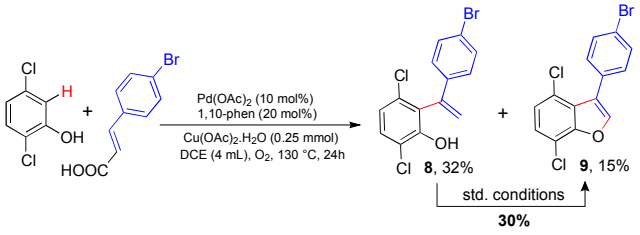
[a]bathophenanthroline as the ligand

Internal alkenyl carboxylic acids were explored subsequently under the optimal condition. Substituted benzofurans were synthesized exclusively by reacting α,β-unsaturated carboxylic acid with phenol (Table 2, **5a** and **5b**).



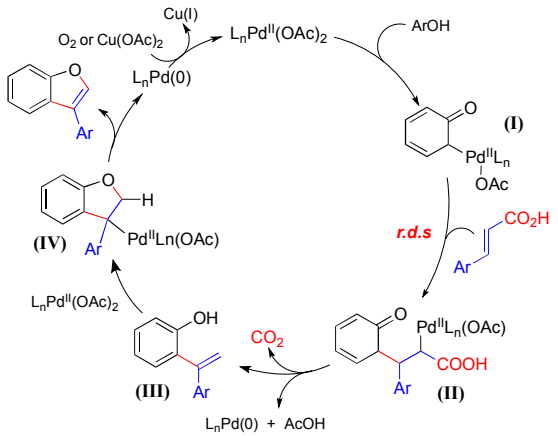
Scheme 3. Formation of 3-phenylbenzofuran from **6**

Although a C–Pd intermediate was presumed (Scheme 1), formation of O–Pd intermediate might be suggested as an alternative for the observed product formation. In order to gain insights into this C-olefination *vs.* O-olefination pathway, two probable intermediates 2-(1-phenylvinyl)phenol (**6**) and (2-phenoxyvinyl)benzene (**7**) were independently synthesized (Scheme 3). Under the reaction condition, **6** produced the expected 3-phenyl benzofuran (**3j**).[5b] In contrary, **7** failed completely to generate this product.



Scheme 4. Isolation of intermediate

Further, we succeeded in isolating the putative intermediate α,α-disubstituted olefin **8** along with the desired 3-arylated benzofuran **9** (Scheme 4). As anticipated, isolated intermediate **8** can be converted to **9** under the standard condition.



Scheme 5. Suggested mechanism of 3-arylated benzofuran synthesis

A plausible mechanism of 3-arylated benzofuran synthesis is provided in Scheme 5 based on the experimental observations. Intermediate **I** can be generated upon coordination of palladium center to the *ortho*-position of phenol.[7, 13] This step is irreversible

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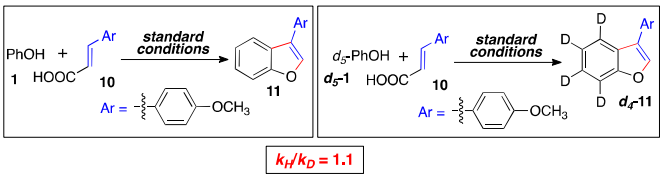
since in the absence of α,β-unsaturated carboxylic acid, no D/H exchange was observed with d_5-PhOH.[11] Electron withdrawing substituents on the phenol coupling partners stabilize the phenoxide ions. Consequently formation of intermediate **I** is more feasible for electron deficient phenols. Insertion of cinnamic acids into the C–Pd bond of **I** can lead to the C-olefinated intermediate **II**, wherein –Ar group will be at the β-position with respect to palladium center. Removal of CO_2 from intermediate **II** will result in α,α-disubstituted olefin **III**. This intermediate has been isolated and characterized from reaction mixture (Scheme 4). In presence of Pd, intermediate **III** will form **IV**, which can then undergo β-hydride elimination to provide 3-substituted benzofuran.[5b, 14]

Further, the kinetic investigation suggested a first (1.12) order rate dependency on the cinnamic acid.[11] A first order rate dependency (1.07) was also found for phenol.[11] Order with respect to phenol and cinnamic acid indicate the probable involvement of both the species in the rate determining step. Therefore, the insertion of α,β-unsaturated carboxylic acid into the C–Pd bond is likely to be occuring in the rate determining step (**I→II**).

To get further insights, isotope labeling experiment was also conducted.[11] Palladium-catalyzed benzofuran synthesis with PhOH and isotopically labeled phenol, d_5-PhOH, revealed an intermolecular kinetic isotope effect (KIE) of k_H/k_D = 1.1 (Scheme 6). Such a low kinetic isotope effect implies that C–H metalation step (step **I**) is not the rate determining step.[15]



Scheme 6. Studies of the kinetic isotope effect

A number of competition experiments revealed that electron-deficient phenols were preferred over neutral and electron rich phenols.[11] In addition, electron-rich cinnamic acids were favored compared to neutral- and electron-poor cinnamic acids. Competition experiments between styrene and cinnamic acid showed a preference for the 2-arylated benzofuran over 3-arylated benzofuran (Scheme 1).[7,11]

In conclusion, we have developed a straightforward synthesis of 3-substituted benzofurans from readily available phenols and cinnamic acid. With respect to simple olefin, cinnamic acid offers an orthogonal selectivity. An inverse insertion, compared to alkene, has been proposed upon *ortho*-palladation (C–Pd) of phenol. The equilibrium concentration of the key C–Pd intermediate is depended on C–H bond breaking and the insertion of cinnamic acid into this C–Pd bond is likely to be the rate determining step. Complete regioselectivity and avoidance of expensive additive make this method synthetically useful. Further mechanistic investigations and expansion of such strategies are currently underway in our laboratory.

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Notes and references

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Electronic Supplementary Information (ESI) available: [NMR studies, optimization table, general procedure, detailed control experiments and the physical data for the compounds.] See DOI: 10.1039/c000000x/

1. (a) J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, Modern Heterocyclic Chemistry; Wiley-VCH: Weinheim, 2011, Vol. 1; (b) J. J. La Clair, A. L. Rheingold and M. D. Burkart, *J. Nat. Prod.*, 2011, **74**, 2045-2051; (c) S. O. Simonetti, E. L. Larghi, A. B. J. Bracca and T. S. Kaufman, *Nat. Prod. Rep.*, 2013, **30**, 941-969.
2. (a) B. Carlsson, B. N. Singh, M. Temciuc, S. Nilsson, Y.-L. Li, C. Mellin and J. Malm, *J. Med. Chem.*, 2002, **45**, 623-630; (c) B. L. Flynn, E. Hamel and M. K. Jung, *J. Med. Chem.*, 2002, **45**, 2670-2673; (c) Y. Okamoto, M. Ojika and Y. Sakagami, *Tetrahedron Lett*, 1999, **40**, 507-510.
3. For selected examples of benzofuran synthesis via prefunctionalized substrate, see : (a) K. W. Anderson, T. Ikawa, R. E. Tundel and S. L. Buchwald, *J. Am. Chem. Soc.*, 2006, **128**, 10694-10695; (b) K. C. Nicolaou, S. A. Snyder, A. Bigot and J. A. Pfefferkorn, *Angew. Chem. Int. Ed.*, 2000, **39**, 1093-1096; (c) M. Carril, R. SanMartin, E. Dominguez and I. Tellitu, *Green Chem.*, 2007, **9**, 219-220; (d) M. C. Willis, D. Taylor and A. T. Gillmore, *Org. Lett.*, 2004, **6**, 4755-4757; (e) N. A. Markina, Y. Chen and R. C. Larock, *Tetrahedron*, 2013, **69**, 2701-2713.
4. For selected examples of benzofuran synthesis *via* ortho C–H activation of phenol, see : (a) X. Guo, R. Yu, H. Li and Z. Li, *J. Am. Chem. Soc.*, 2009, **131**, 17387-17393; (b) B. Xiao, T.-J. Gong, Z.-J. Liu, J.-H. Liu, D.-F. Luo, J. Xu and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 9250-9253; (c) M. R. Kuram, M. Bhanuchandra and A. K. Sahoo, *Angew. Chem. Int. Ed.*, 2013, **52**, 4607-4612; (d) R. Zhu, J. Wei and Z. Shi, *Chem. Sci.*, 2013, **4**, 3706-3711 (e) W. Zeng, W. Wu, H. Jiang, L. Huang, Y. Sun, Z. Chen and X. Li, *Chem. Commun.*, 2013, **49**, 6611-6613; (f) D.-H. Lee, K.-H. Kwon and C. S. Yi, *J. Am. Chem. Soc.*, 2012, **134**, 7325-7328; (g) T. Kobatake, D. Fujino, S. Yoshida, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2010, **132**, 11838-11840; (h) Y. Ookubo, A. Wakamiya, H. Yorimitsu and A. Osuka, *Chem. Eur. J.*, 2012, **18**, 12690-12697.
5. For selected examples of 3-substituted benzofuran synthesis, see: (a) T. Pei, C.-y. Chen, L. DiMichele and I. W. Davies, *Org. Lett.*, 2010, **12**, 4972-4975; (b) M. J. Moure, R. SanMartin and E. Dominguez, *Angew. Chem. Int. Ed.*, 2012, **51**, 3220-3224. (c) D. Kundu, M. Samim, A. Majee and A. Hajra, *Chem. Asian J.*, 2011, **6**, 406-409.
6. (a) H. Dehmlow, J. D. Aebi, S. s. Jolidon, Y.-H. Ji, E. M. von der Mark, J. Himber and O. H. Morand, *J. Med. Chem.*, 2003, **46**, 3354-

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DOI: 10.1039/C4CC07026G
Journal Name

3370; (b) Y. Okamoto, M. Ojika, S. Suzuki, M. Murakami and Y. Sakagami, *Bioorg. Med. Chem.*, 2001, **9**, 179-183; (c) H. Greve, S. Meis, M. U. Kassack, S. Kehraus, A. Krick, A. D. Wright and G. M. Konig, *J. Med. Chem.*, 2007, **50**, 5600-5607; (d) R. Ribeiro-Rodrigues, W. G. dos Santos, A. B. Oliveira, V. Snieckus, C. L. Zani and A. J. Romanha, *Bioorg. Med. Chem. Lett*, 1995, **5**, 1509-1512.

7. U. Sharma, T. Naveen, A. Maji, S. Manna and D. Maiti, *Angew. Chem. Int. Ed.*, 2013, **52**, 12669-12673.
8. (a) J. M. Neely and T. Rovis, *J. Am. Chem. Soc.*, 2014, **136**, 2735-2738; (b) J. Cornella, M. Righi and I. Larrosa, *Angew. Chem. Int. Ed.*, 2011, **50**, 9429-9432; (c) J. Luo, S. Preciado and I. Larrosa, *J. Am. Chem. Soc.*, 2014, **136**, 4109-4112.
9. (a) A. F. Littke and G. C. Fu, *J. Org. Chem.*, 1999, **64**, 10-11; (b) A. F. Littke and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 6989-7000; (c) J. M. Neely and T. Rovis, *J. Am. Chem. Soc.*, 2013, **135**, 66-69; (d) I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009-3066; (e) R. F. Heck in *Comp. Org. Syn*; Vol. 4, Ch. 4.3, p. 833; (f) C. Gurtler and S. L. Buchwald, *Chem. Eur. J.*, 1999, **5**, 3107-3112.
10. (a) M. Yamashita, H. Horiguchi, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 7481-7488; (b) S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **76**, 3024-3033; (c) Y. Unoh, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2013, **78**, 5096-5102; (d) S. Mochida, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 5776-5779.
11. See Supporting Information for detailed description.
12. CCDC 1005517 (**3c**) can be obtained from http://www.ccdc.cam.ac.uk/data_request/cif. ed.
13. G. M. Kapteijn, D. M. Grove, H. Kooijman, W. J. J. Smeets, A. L. Spek and G. van Koten, *Inorg. Chem.*, 1996, **35**, 526-533.
14. (a) M. S. C. Pedras and M. Hossain, *Bioorg. Med. Chem.*, 2007, **15**, 5981-5996; (b) G. Casiraghi, G. Casnati, G. Puglia, G. Sartori and G. Terenghi, *Synthesis*, 1977, **1977**, 122-123.
15. (a) M. Gomez-Gallego and M. A. Sierra, *Chem. Rev.*, 2011, **111**, 4857-4963; (b) K. B. Wiberg, *Chem. Rev.*, 1955, **55**, 713-743; (c) E. M. Simmons and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2012, **51**, 3066-3072.

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