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# Tandem Metal Relay Catalysis: From Cyclopropene to Polysubstituted Furan

Chuanling Song, Jianwu Wang and Zhenghu Xu\*

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Transmetalation is a key step in traditional coupling reactions. Herein we discuss the most recent progress on the metal-metal relay catalysis based on transmetallation strategy. An efficient synthetic strategy for the formation of polysubstituted furan derivatives from cyclopropenes based on the Tandem Metal Relay Catalysis (TMRC reaction) are summarized.

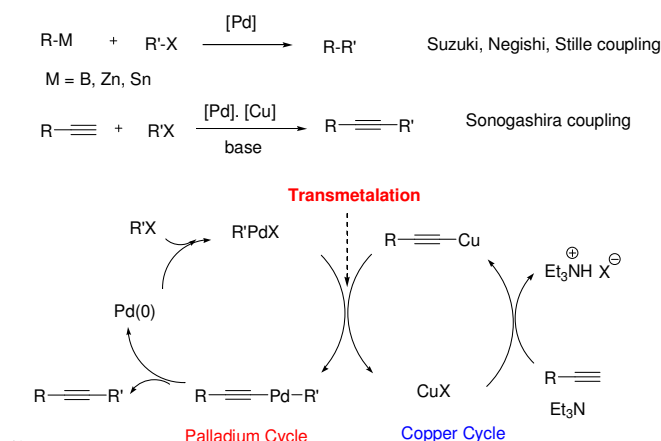
## Introduction

Transmetalation is a type of organometallic reaction that involves the transfer of ligands from one metal to another. In traditional cross-coupling reactions such as Suzuki-Miyaura coupling, Negishi coupling, and Stille coupling, a general accepted reaction pathway is a sequential three-stage process: oxidative addition, transmetalation and reductive elimination. Transmetalation is the key step that bridges the two organic moieties together, however its mechanism is not as well known as oxidative addition and reductive elimination steps. Only recently, this elementary reaction was studied by Hartwig,<sup>1</sup> Jutand,<sup>2</sup> Espinet,<sup>3</sup> and others. For example, in Suzuki-Miyaura coupling reaction, the versatility of transmetalation from organoboron reagents to palladium(II) complexes has allowed this reaction to develop into such an important coupling process widely used in academic and industrial process, so that it has been named as the “fork in the trail” to highlight its importance.<sup>4</sup> Recently Lei group studied the reaction mechanism of the Pd-catalyzed Negishi coupling of ArI and Ar'ZnX through kinetic investigation, and found out that the transmetallation was the rate-limiting step.<sup>5a</sup>

It is important to note that in most of the reactions, that involve reagents such as organoborons, organozincs, and organo stannanes need to be prepared in advance. However, in a classic Sonogashira coupling reaction, a copper acetylide complex is formed in situ from the alkyne in the presence of base and a catalytic amount of copper(I) catalyst. Both the palladium cycle and a copper cycle are involved in this reaction and the key transmetalation step from copper(I) to Pd(II) bridges the two cycles (Scheme 1). A recent study from Lei group demonstrated that the transmetallation step of the Sonogashira coupling reaction was the rate-limiting step and this cross-coupling reaction was a Pd-catalyzed and Cu-catalyzed synergistic process, which exhibits a first-order kinetic dependence on the [Pd] and [Cu] catalysts, respectively.<sup>5b</sup>

Thus transmetalation is a basic strategy to form a new M<sup>2</sup>-C bond from a known M<sup>1</sup>-C bond. Through rational design, and using transmetallation as the key step, multimetallic cooperative catalysis could be developed to achieve exquisite one-pot cascade reactions, which require multiple reaction

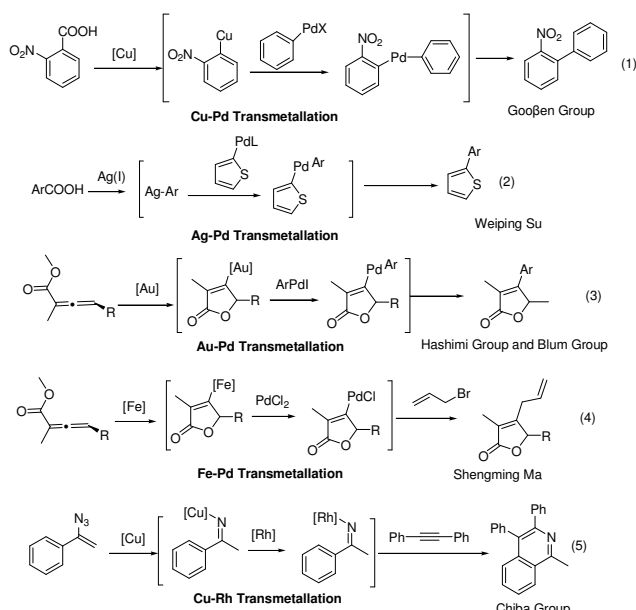
steps with the traditional one-catalyst one-reaction approach. In principle, this type of metal-metal relay catalysis through transmetalation could deliver new transformations by combining the catalytic natures of transition metals. To the best of our knowledge, except the above mentioned traditional coupling reactions, only very limited examples have been reported regarding transmetalation between different metals. The major difficulties maybe due to the slow transmetalation process which is the rate-limiting step in most cases and can not overcome the undesired side reactions in multimetallic catalysis.



**Scheme 1** Transmetalation in Sonogashira coupling reaction

In 2006, Goßen group reported the first copper(I)-catalyzed decarboxylation of readily available arylcarboxylic acid and palladium(II)-catalyzed cross coupling relay sequence for the convenient synthesis of biaryls (Scheme 2, eq.1).<sup>6a, b</sup> The key step in this reaction is the transmetalation of aryl copper intermediate to the palladium catalyst. Another example was demonstrated by Su group in 2012 in which silver-palladium bimetallic catalysis was utilized for the efficient decarboxylative C-H bond arylation of thiophenes. (Scheme 2, eq.2).<sup>6c</sup> (Scheme 2, eq.2).<sup>6c</sup> Besides these decarboxylative reactions, Blum group<sup>6d</sup> and Hashimi group<sup>6e</sup> reported a very novel Au-Pd bimetallic relay catalysis almost at the same time, where a gold catalyzed cyclization of allene esters and palladium-catalyzed cross coupling sequence were bridged by Au-Pd transmetalation. (Scheme 2, eq.3). Very

recently Ma group showed another Fe-Pd bimetallic relay reaction in which the FeCl<sub>3</sub>-catalyzed cyclization and PdCl<sub>2</sub>-catalyzed allylic substitution were connected via Fe-Pd transmetalation (Scheme 2, eq.4).<sup>6f</sup> In 2011 Chiba group developed the first Cu-Rh bimetallic relay reaction for the synthesis of isoquinolines. The reaction went through copper mediated decomposition of the vinyl azide, Cu-Rh transmetalation, rhodium-catalyzed C-H activation and cycloaddition with internal alkynes to generate the product (Scheme 2, eq.5).<sup>6g,h</sup>



**Scheme 2** Representative transmetalation relay catalysis

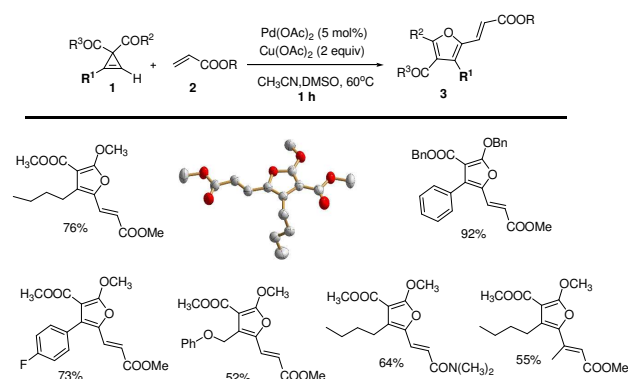
These examples demonstrated that transmetalation relay strategy has the advantage in combining the rich chemistry of totally two different transition-metals to accomplish the activation and functionalization steps in one pot. Since current research mainly focuses on the decarboxylative reaction and allene substrates, a rational design of multimetallic relay catalytic systems and an extension of this strategy to other useful organic transformations is highly desirable. Recently we developed a highly efficient one-pot copper-catalyzed activation and Pd-catalyzed functionalization relay strategy for the efficient construction of tetrasubstituted furans from cyclopropenes.

### Development of Cu-Pd relay catalysis with cyclopropenes

Furans represent an important class of five-membered heterocycles which are prevalent in a number of biologically active natural products as well as pharmaceuticals. Therefore, significant efforts have been made to synthesize this heterocyclic ring.<sup>7</sup> Furans which possess four substituents are even more difficult to access synthetically. Thus, a modular synthesis of tetrasubstituted furan from simple and readily available starting material and the possibility to install the four substituents very freely is still a great challenge. Cyclopropene as the smallest unsaturated ring, shows unique and interesting reactivities in the presence of transition metal

because of the tremendous ring strain. In recent years, abundant types of reactions and novel transformations have been developed based on the rich transition metal chemistry of cyclopropenes.<sup>8</sup> Very recently we presented an efficient synthetic methodology of tetrasubstituted furans from cyclopropenes with Cu-Pd relay catalysis.<sup>9</sup>

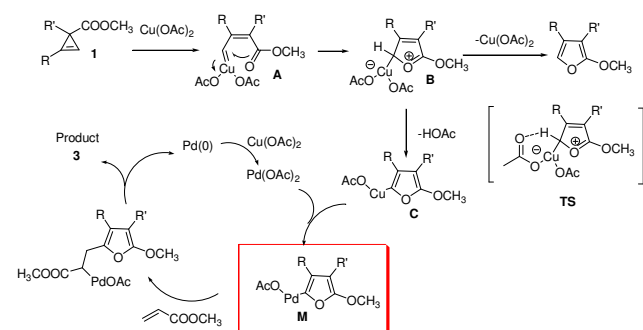
The original proposal was to realize the palladium-catalyzed cyclopropene sp<sup>2</sup> C-H bond functionalization through oxidative Heck reaction using Cu(OAc)<sub>2</sub> as the oxidant. To our surprise, the tetrasubstituted furan **3a** was achieved instead of the target cyclopropene (Scheme 3). A series of alkene functionalized tetrasubstituted furans with wide substrate scope were prepared in good yields.<sup>9a</sup> The most amazing part of this methodology is the reaction efficiency. This intermolecular dehydrogenative Heck reaction (DHR) was completed in 1 hour at 60 °C with only 5 mol% Pd(OAc)<sub>2</sub> leading to 92% yield, a sharp contrast to the known DHRs which usually need quite harsh conditions (high temperature over 100 °C and acid additive) with prolonged reaction time.<sup>10</sup>



**Scheme 3** The intermolecular dehydrogenative Heck reaction of cyclopropenes

After some detailed experiments and analysis, we proposed the copper-palladium relay mechanism to explain this unusual high efficiency (Scheme 4). It is generally accepted that copper acetate could react with cyclopropene generating the unsaturated copper carbene **A**,<sup>11</sup> followed by intramolecular cyclization leading to the carbonyl ylide species **B**. This intermediate went through a six-membered ring transition state **TS** to eliminate a HOAc to form the furan copper intermediate **C**. Subsequent transmetalation would generate the key furan palladium intermediate **M**, then the regular insertion into alkene, β-H elimination afforded the products. Finally the Pd(0) was reoxidized by Cu(OAc)<sub>2</sub> to regenerate the catalyst. Cu(OAc)<sub>2</sub> not only acts as the oxidant, but also promotes the first isomerization. Since two equivalents of Cu(OAc)<sub>2</sub> are used, the isomerization step into furan copper will be very fast and thus leading to the very high reaction efficiency. This sequence avoided the direct C-H metallation step, which normally requires high energy input to overcome the high activation energy of C-H bond, so very mild conditions were enough for this transformation.

The most important feature of this methodology is the transmetalation relay strategy to form the key C-Pd bond which is greatly different from the general C-H activation mode. To further prove the formation of this furan palladium



**Scheme 4** Proposed copper-palladium relay catalysis mechanism

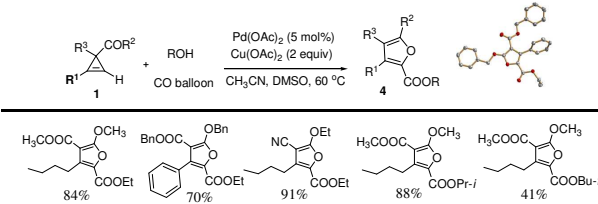
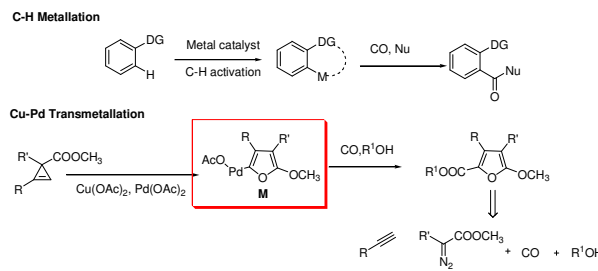
intermediate **M**, we carried out the carbonylation reaction to trap this Pd intermediate. To our delight, the expected tetrasubstituted furan carboxylate **4** could be isolated in very good yield (Scheme 5). Since cyclopropene can easily be prepared from different terminal alkynes and different diazo compounds, a very general synthetic protocol of tetrasubstituted furan carboxylates has been successfully developed from alkynes, diazo compounds, CO and alcohols. This methodology makes it possible to introduce four substituents very easily under mild conditions.

Bifuran structure was recently recognized as a key structure unit in the optoelectronic materials.<sup>12</sup> When the cyclopropenes were subject to the similar Cu-Pd catalytic system at 80 °C, a series of multifunctionalized bifuran structures were obtained in good yields in less than 3 h (Scheme 6). For aryl substituted cyclopropenes, this formal C-H/C-H coupling reaction could even proceed at room temperature, which is much more superior than the general C-H activation method. The mechanism of this reaction is similar to that of Cu-Pd relay sequence already discussed where the key furan-palladium **M** is generated, followed by disproportionation to afford Pd(OAc)<sub>2</sub> and bifuran palladium **M1**. This undergoes reductive elimination to generate bifuran.

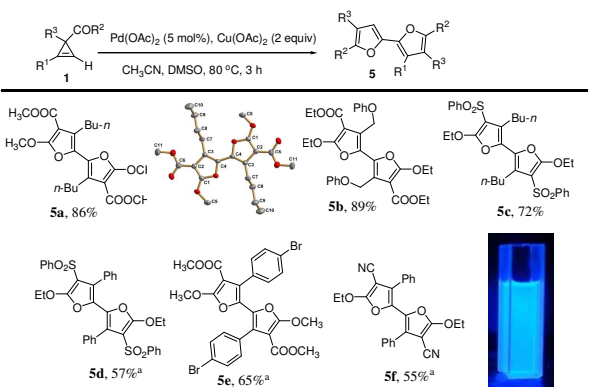
More importantly, the bifuran compounds show very promising optoelectronic properties as blue emissive materials used as OLEDs. The aryl substituted products exhibited blue emission around 445 nm. The fluorescence efficiency of the cyano-substituted compound **5f** is 97% in DCM solution comparable to the long oligofurans. More useful and interesting bifuran-based Pi-conjugated molecules can be expected following this methodology development.

## Conclusions and outlook

Based on the discussed reactions, Cu-Pd catalyzed oxidative Heck reaction, oxidative carbonylation, and dimerization reactions, it could be concluded that this methodology is a Tandem Metal Relay Catalysis (TMRC reaction). This strategy is not only complementary to the current transition-metal catalyzed C-H activation, but also a novel fundamentally different strategy. In these systems, copper acts as the perfect activator of cyclopropenes and palladium takes charge of further functionalization role. Based on the key furan palladium intermediate, other functionalization reactions



**Scheme 5** Modular synthesis of tetrasubstituted furan carboxylates with Cu-Pd relay catalysis



**Scheme 6** Dimerization of cyclopropenes to bifurans with Cu-Pd relay catalysis

such as arylation, borylation, trifluoromethylation, cyanation, and also other cross coupling reactions could be realized paving the way for more and more tetrasubstituted furans. Other functionalized bifuran structures bearing interesting optoelectronic properties could also be expected.

Even though Tandem Metal Relay Catalysis strategy has been proved to be a very powerful methodology, current research is limited to cyclopropene substrates, allene and carboxylic acids. Expanding this useful method to other important substrates is very urgent but a challenging task. Further detailed mechanism investigations such as kinetic study of these transmetalation reactions may help us to understand this process better and thereby extending the understanding to other systems.

Another important issue is that once ligands are introduced into the bimetallic system,<sup>13</sup> undesired coordination between ligand and metals usually happens. Avoiding this undesirable coordination is vital and must be considered when developing more complex system or trying to render the bimetallic



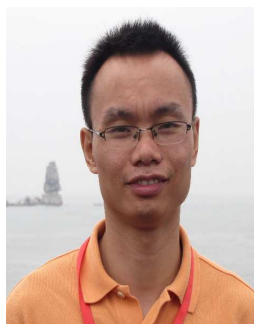
catalysis asymmetric. Hence, asymmetric tandem metal relay catalysis is another promising direction but challenging.

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## Notes and references

- 1 (a) J. Louie and J. F. Hartwig, *J. Am Chem. Soc.* 1995, **117**, 11598. (b) B.P Carrow and J. F. Hartwig, *J. Am Chem. Soc.* 2011, **133**, 2116.
- 2 (a) C. Amatore, A. Jutand and G. Le Duc, *Chem. Eur. J.* 2012, **18**, 6616. (b) C. Amatore, A. Jutand and G. Le Duc, *Angew. Chem. Int. Ed.* 2012, **51**, 1379. (c) C. Amatore, A. A. Bahoun, A. Jutand, G. Meyer, A. N. Ntepe and L. Ricard, *J. Am Chem. Soc.* 2003, **125**, 4212.
- 3 A. L. Casado, P. Espinet and A. M. Gallego, *J. Am Chem. Soc.* 2000, **122**, 11771
- 4 A. J. J. Lennox and G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.* 2013, **52**, 7362.
- 5 (a) J. Lin, L. Jin, C. Liu, A. Lei, *Org. Chem. Fron.* 2014, **1**, 50. (b) C. He, J. Ke, H. Xu, A. Lei, *Angew. Chem. Int. Ed.* 2012, **52**, 1527.
- 6 (a) L. J. Gooßen, G. Deng and L. M. Levy, *Science*, 2006, **313**, 662. (b) L. J. Gooßen, F. Rudolphi, C. Opiel, and N. Rodríguez, *Angew. Chem. Int. Ed.* 2008, **47**, 3043 (c) P. Hu, M. Zhang, X. Jie and W. Su, *Angew. Chem. Int. Ed.* 2012, **51**, 227. (d) Y. Shi, K. E. Roth, S. D. Ramgren, S. A. Blum, *J. Am Chem. Soc.* 2009, **131**, 18022. (e) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T. D. R. Ramamurthi and F. Rominger, *Angew. Chem. Int. Ed.* 2009, **48**, 8243. (f) B. Chen and S. Ma, *Chem. Eur. J.* 2011, **17**, 754. (g) Y.-F. Wang, K. K. Toh, J.-Y. Lee and S. Chiba, *Angew. Chem. Int. Ed.* 2011, **50**, 5927. (h) P. C. Too, S. H. Chua, S. H. Wong and S. Chiba, *J. Org. Chem.* 2011, **76**, 6159. (i) S. Ko, B. Kang and S. Chang, *Angew. Chem. Int. Ed.* 2005, **44**, 455.
- 7 (a) S. F. Kirsch, *Org. Biomol. Chem.* 2006, **4**, 2076. (b) A. V. Gulevich, A. S. Dudnik, N. Chernyak, and V. Gevorgyan, *Chem. Rev.* 2013, **113**, 3084.
- 8 (a) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.* 2007, **107**, 3117. (b) Z.-B. Zhu, Y. Wei and M. Shi, *Chem. Soc. Rev.* 2011, **40**, 5534.
- 9 (a) C. Song, L. Ju, M. Wang, P. Liu, Y. Zhang, J. Wang and Z. Xu, *Chem. Eur. J.* 2013, **19**, 3584. (b) C. Song, S. Dong, L. Feng, X. Peng, M. Wang, J. Wang and Z. Xu, *Org. Biomol. Chem.* 2013, **11**, 6258. (c) C. Song, D. Sun, X. Peng, J. Bai, R. Zhang, S. Hou, J. Wang, and Z. Xu, *Chem. Commun.* 2013, **49**, 9167.
- 10 J. Le Bras and J. Muzart, *Chem. Rev.* 2011, **111**, 1170.
- 11 S. Ma and J. Zhang, *J. Am. Chem. Soc.* 2003, **125**, 12386.
- 12 O. Gidron, N. Varsano, L. J. W. Shimon, G. Leitun and M. Bendikov, *Chem. Commun.*, 2013, **49**, 6256.
- 13 J. Panteleev, L. Zhang and M. Lautens, *Angew. Chem. Int. Ed.* 2011, **50**, 9089.



55 Zhenghu Xu was born in Hubei Province, China, in 1978. He received his Bachelor degree from Nanjing University in China in 2001 and his PhD from Shanghai Institute of Organic Chemistry under the supervision of professor Lixin Dai and Professor Yong Tang in 2007. Between 2007-2010, he was 60 working in Prof. Hong Wang's group at Miami University Ohio in USA as a postdoctoral fellow. Currently, he is an associate professor at Shandong University in China. His research focuses on the transition metal directed organic synthesis and cooperative catalysis.



65 Chuanling Song was born in Shandong Province of China in 1989. She received her Bachelor degree from Linyi University in 2011, and is now 70 carrying out Ph.D. research under the supervision of Prof. Jianwu Wang and Zhenghu Xu at Shandong University. Her current research interest 75 focuses on developing tandem metal relay catalysis with

cyclopropenes



80 Jianwu Wang received his Bachelor degree from Fudan University in 1982, and his Ph.D from Nankai University in 1990. He continued his research as a 85 postdoctoral fellow in New York University and Peptosyn Inc. Then he started his academic career at Shandong University in China in 1997. where he was promoted to a 90 full Professor. His research interests focus on organic synthesis and medicinal chemistry.