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Pd- and Cu-Catalyzed One-Pot Multicomponent Synthesis of Hetero α,α'-Dimers of Heterocycles

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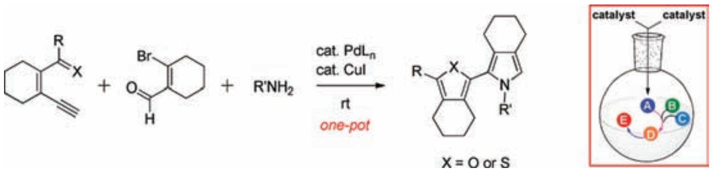
ABSTRACT



A novel palladium- and copper-catalyzed one-pot multicomponent synthesis of hetero α,α'-dimers of heterocycles via Sonogashira coupling and double cyclization cascade involving imine formation has been developed. This reaction cascade proceeded under mild conditions, providing a powerful synthetic tool for the assembly of π-conjugated systems with a combination of palladium-catalyzed post-direct C−H bond arylations.

The efficient synthesis of novel functional organic molecules has become an important challenge at the cutting edge between organic chemistry and materials sciences.[1] In particular, the design of the multicatalytic cascade processes, in which two or more distinct chemical transformations are promoted sequentially by one or more catalysts, is highly desirable because they achieve high molecular complexity, forming several bonds from readily accessible starting materials, and they make isolation of intermediates unnecessary.[2] Molecules containing conjugated heterocycles based on pyrroles, furans, and thiophenes are attractive targets for these transformations because they are promising materials for organic field-effect transistors (OFETs), organic light-emitting diodes (OLEDs), dye-sensitized organic solar cells (DSSCs), and many other potential applications.[3] While conjugated heterocycles based on α,α'-linked oligoheterocycles are promising in the area of organic electronics,[4] much attention has recently been paid to mixed-heterocyclic oligomers with pyrroles, furans, and thiophenes.[5] Precisely controlled chemical structures exhibit improved light absorption, electronic compatibility with fullerene acceptors such as PCBM, charge transport characteristics, thin-film morphology, and molecular packing.[6] In order to acquire a better understanding of the structure−property relationships that govern material performance, the development of facile and flexible access to new tailor-made functional

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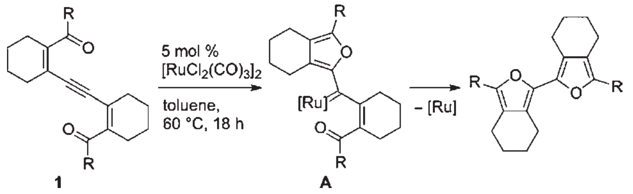
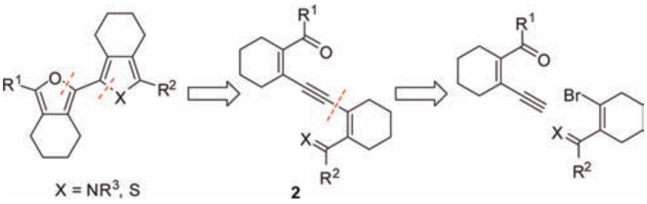
mixed-heterocyclic oligomers has the potential to give ready access to a wide variety of novel materials. Despite the significant interest, however, these approaches have been limited to stepwise cross-coupling reactions of stannyl or boryl heterocycles with heteroaryl halides or conventional Paal–Knorr-type dehydrative cyclization of the 1,4-diheteroaroylethane derivatives.[5] Although these methods are highly useful, there are some drawbacks such as low stability of some heteroaryl halides and poor tolerance of functional groups under acidic conditions. Herein we report a new approach toward hetero dimers of heterocycles through palladium- and copper-catalyzed Sonogashira coupling and double-cyclization cascade involving imine formation.[7]

Recently, we have reported a preliminary study of a ruthenium-catalyzed cycloisomerization of 1,2-di(carbonyl-ene)yne compounds **1** leading to 2,2′-bifurans (Scheme 1).[8,9] The reaction mechanism involves the generation of (2-furyl)-carbene complexes **A** via the nucleophilic attack of carbonyl oxygen atoms to alkyne moieties, in which carbene complex **A** undergoes nucleophilic attack of the neighboring carbonyl oxygen atom to furnish 2,2′-bifurans (double cyclization). These successful results prompted us to investigate the transition-metal-catalyzed cycloisomerization of nitrogen and sulfur analogues **2**, prepared by Sonogashira coupling of two coupling partners, which leads to 2-(2′-furyl)pyrrole and 2-(5′-thienyl)furan (Scheme 2).

Scheme 1. Ru-Catalyzed Double Cyclization of **1**

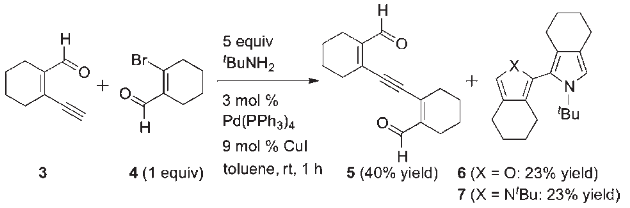


Scheme 2. Transition-Metal-Catalyzed Synthesis of Hetero Dimers of Heterocycles



To synthesize the precursor **2**, we first examined the Sonogashira coupling of formyl-ene-yne compound **3** with 2-bromocyclohexenal **4** in the presence of $Pd(PPh_3)_4$ (3 mol %), CuI (9 mol %), and various amines. When *tert*-butylamine was used as a base, we unexpectedly observed the formation of 2-(2′-furyl)pyrrole **6** and 2,2′-bipyrrole **7**, each in 23% yield, together with the expected 1,2-di-(formyl-ene)yne compound **5** in 40% yield, respectively (Scheme 3). This result indicates that the Sonogashira coupling, imine formation, and double cyclization successively took place under the present reaction conditions.

Scheme 3. Pd- and Cu-Catalyzed Reaction of **3** with **4**



To our delight, 2-(2′-furyl)pyrrole **9a** was obtained selectively in 70% yield without forming the corresponding 2,2′-bipyrrole when keto-ene-yne compound **8a** was used instead of formyl-ene-yne compound **3** (Scheme 4). Furthermore, studies revealed that the yield of **9a** increased up to 92% when the combination of $Pd_2(dba)_3$, PPh_3, and CuI was employed as catalysts.

These interesting results stimulated us to investigate the generality of the present three-component coupling reactions. The results are summarized in Table 1. Not only keto-ene-yne compounds **8b** and **8c**, which possess electron-donating substituents such as *N*,*N*-diphenylamino and methoxy groups, but also **8d** and **8e** having electron-withdrawing substituents such as trifluoromethyl and cyano groups at the *para* position of the benzene ring

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(5) For recent examples, see: (a) Fujii, M.; Nishinaga, T.; Iyoda, M. *Tetrahedron Lett.* **2009**, *50*, 555. (b) Woo, C. H.; Beaujuge, P. M.; Holcombe, T. W.; Lee, O. P.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2010**, *132*, 15547. (c) Nishinaga, T.; Tateno, M.; Fujii, M.; Fujita, W.; Takase, M.; Iyoda, M. *Org. Lett.* **2010**, *12*, 5374. (d) Oliva, M. M.; Pappenfus, T. M.; Melby, J. H.; Schwaderer, K. M.; Johnson, J. C.; McGee, K. A.; da Silva Filho, D. A.; Brédas, J.-L.; Casado, J.; Navarrete, J. T. L. *Chem.—Eur. J.* **2010**, *16*, 6866. (e) Bijleveld, J. C.; Karsten, B. P.; Simon, G. J. M.; Wienk, M. M.; de Leeuw, D. M.; Janssen, R. A. J. *J. Mater. Chem.* **2011**, *21*, 1600. (f) Li, Y.; Sonar, P.; Singh, S. P.; Zeng, W.; Soh, M. S. *J. Mater. Chem.* **2011**, *21*, 10829. (g) Nishinaga, T.; Miyata, T.; Tateno, M.; Koizumi, M.; Takase, M.; Iyoda, M.; Kobayashi, N.; Kunugi, Y. *J. Mater. Chem.* **2011**, *21*, 14959.

(6) For recent examples, see: (a) Beaujuge, P. M.; Pisula, W.; Tsao, H. N.; Ellinger, S.; Müllen, K.; Reynolds, J. R. *J. Am. Chem. Soc.* **2009**, *131*, 7514. (b) Peet, J.; Heeger, A. J.; Bazan, G. C. *Acc. Chem. Res.* **2009**, *42*, 1700. (c) Piliego, C.; Holcombe, T. W.; Douglas, J. D.; Woo, C. H.; Beaujuge, P. M.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2010**, *132*, 7595. (d) Johns, J. E.; Müller, E. A.; Fréchet, J. M. J.; Harris, C. B. *J. Am. Chem. Soc.* **2010**, *132*, 15720. (e) Zhou, H.; Yang, L.; Price, S. C.; Knight, K. J.; You, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 7992. (f) Varotto, A.; Treat, N. D.; Jo, J.; Shuttle, C. G.; Batara, N. A.; Brunetti, F. G.; Seo, J. H.; Chabinyc, M. L.; Hawker, C. J.; Heeger, A. J.; Wudl, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 5166.

(7) The present method is defined as a time- and space-integrated process, because it can construct molecular diversity and structural complexity by successive reactions in a one-shot reaction without separation and purification of intermediates. *The time and space integration* in synthetic organic reactions refers to (a) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404. (b) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011**, *9*, 1189.

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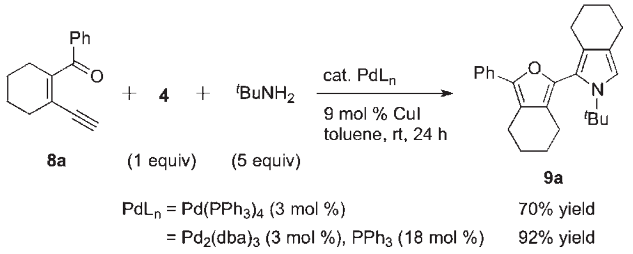
(9) The similar double cyclization of 1,2-di(carbonyl-ene)ynes leading to bifurans proceeded under the photoirradiated conditions. See: (a) Nakatani, K.; Adachi, K.; Tanabe, K.; Saito, I. *J. Am. Chem. Soc.* **1999**, *121*, 8221. (b) Zhang, H.; Wakamiya, A.; Yamaguchi, S. *Org. Lett.* **2008**, *10*, 3591. In the present study, all Sonogashira coupling reactions were carried out in the dark.

Scheme 4. One-Pot Three-Component Synthesis of **9a**

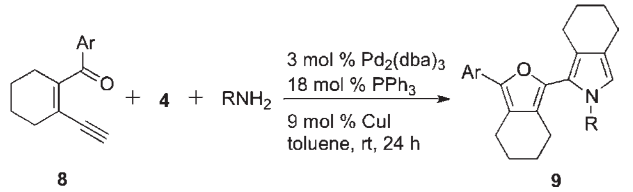


produced the corresponding 2-(2′-furyl)pyrroles **9b**–**e** in good to high yields, respectively (entries 1–4). It is worth mentioning that the reaction of **8f** afforded pyrrole-, furan-, and thiophene-conjugated heterocycle **9f** in 68% yield (entry 5). Furthermore, benzylamine and allylamine instead of *tert*-butylamine were applicable to the present three-component coupling reaction to afford 1-benzyl-2-(2′-furyl)pyrrole **9g** and 1-allyl-2-(2′-furyl)pyrrole **9h**[10] in 71% and 54% yields, respectively (entries 6 and 7).

To shed light on the reaction mechanism, the reaction of **8a** with imine **10** as a coupling partner was carried out under identical reaction conditions. However, neither 2-(2′-furyl)pyrrole **9a** nor 1-(imino-ene)-2-(keto-ene)yne compound **11** was observed, 2-bromocyclohexenal **4** that was formed via the hydration of **10** being obtained in 95% yield (Scheme 5). This result clearly indicates that Sonogashira coupling of **8** with **4** proceeds faster than the condensation with amines, and resulting **11** undergoes double cyclization to afford the 2-(2′-furyl)pyrrole **9**.

We next examined the reaction of 1-formyl-6-benzoyl-1,5-dien-3-yne **12**, which was prepared by Sonogashira coupling of **8a** and **4**, with *tert*-butylamine at room temperature in C_6D_6, and the time course of the reaction was monitored by ^{1}H NMR spectroscopy. The reaction without palladium and copper catalysts reached equilibrium between **9a** and **12**, and 53% of **12** was still observed even after 24 h (Figure S1a in Supporting Information). In contrast, with 9 mol % of CuI was added, the reaction proceeded rapidly, and **9a** was obtained in 96% yield in 24 h (Figure S1b). These observation indicate that CuI, which is known to possess both oxophilic and carbophilic characters,[11] seems to effectively activate both the carbonyl group and the C–C triple bond to promote the condensation between *tert*-butylamine and the formyl group of **12** to form imine **11** and the following double cyclization leading to **9a** (Figure 1).[12]

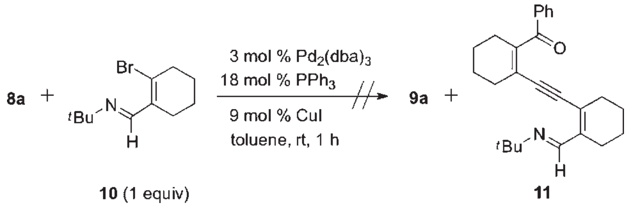
Table 1. Synthesis of 2-(2′-Furyl)pyrroles via Three-Component Coupling Reactions[a]



entry	Ar		R	product	yield of **9** (%)[b]
1	4-MeOC$_6$H$_4$	**8b**	^{t}Bu	**9b**	53
2	4-Ph$_2$NC$_6$H$_4$	**8c**	^{t}Bu	**9c**	87
3	4-CF$_3$C$_6$H$_4$	**8d**	^{t}Bu	**9d**	71
4	4-CNC$_6$H$_5$	**8e**	^{t}Bu	**9e**	86
5	2-thienyl	**8f**	^{t}Bu	**9f**	68
6	Ph	**8a**	Bn	**9g**	71
7	Ph	**8a**	allyl	**9h**	54

[a] Reaction conditions: **8** (0.30 mmol), **4** (0.30 mmol), amine (1.5 mmol), Pd$_2$(dba)$_3$ (0.0090 mmol), PPh$_3$ (0.054 mmol), and CuI (0.027 mmol) in toluene (1 mL). [b] Isolated yields based on **4**.

Scheme 5. Pd- and Cu-Catalyzed Reaction of **8a** with **10**



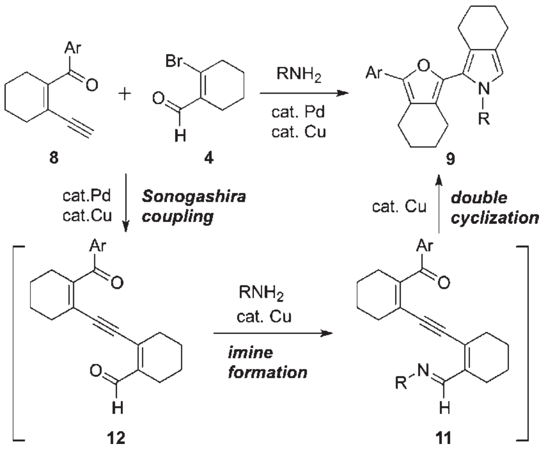


Figure 1. Plausible reaction mechanism leading to **9**.

When thiocarbamoyl-ene-yne compound **13**[13] was used instead of **8** in the presence of Pd$_2$(dba)$_3$, PPh$_3$, and CuI as catalysts and triethylamine as a base, 2-(5′-thienyl)furan **15** was obtained in 90% yield (Scheme 6, X = O). The reaction may proceed via the formation of 1-formyl-6-thiocarbamoyldienyne **14** (X = O) followed by double cyclization.

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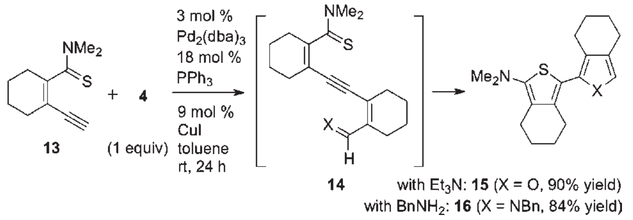
[10] An allyl group of pyrrole **9h** could be deprotected by the treatment with DIBAL in the presence of NiCl$_2$(dppp).

[11] Shirtcliff, L. D.; McClintock, S. P.; Haley, M. M. *Chem. Soc. Rev.* **2008**, *37*, 343.

[12] For the reaction of **12** with *tert*-butylamine in the presence of CuI, see Supporting Information. We suppose that double cyclization might proceed via copper-carbenoide, as depicted in Scheme 1, although the alternate pathway via direct Michael addition of an amine to a C–C triple bond cannot be ruled out.

[13] For rhodium-catalyzed carbene transfer reaction using **13** via a (2-thienyl)carbene complex, see: Tsuneishi, A.; Okamoto, K.; Ikeda, Y.; Murai, M.; Miki, K.; Ohe, K. *Synlett* **2011**, *9*, 455.

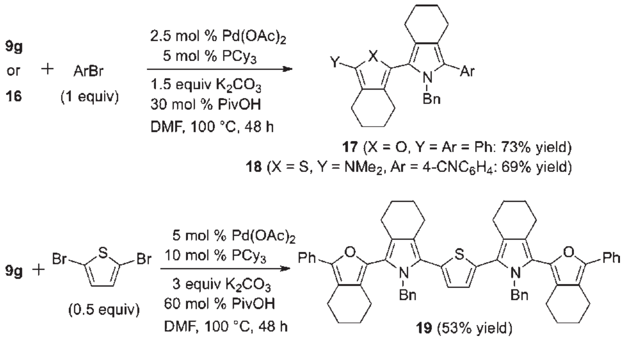
Scheme 6. Synthesis of 2-(5′-Thienyl)furan and 2-(5′-Thienyl)pyrrole via Tandem Coupling Reactions



Interestingly, when benzylamine was used in place of triethylamine under the same reaction conditions, 2-(5′-thienyl)pyrrole **16** was obtained selectively in 84% yield without forming **15** (Scheme 6, X = NBn). These results prove that the present one-pot Sonogashira coupling, imine formation, and double cyclization cascades are suitable for flexible access to tailor-made functional hetero dimers of heterocycles.

Combined further with the cross-coupling reaction, the present one-pot multicomponent synthesis for hetero dimers of heterocycles would allow rapid access to various π-conjugated heterocyclic oligomers. Over the past decades, extensive efforts have been directed toward the transition-metal-catalyzed direct C−H bond arylations of aromatics.[14] In comparison to furans and thiophenes, however, intermolecular direct C−H bond arylations of pyrroles have been limited.[15] The reported examples need to employ aryl iodides[15g] and electronically activated pyrroles[15b,d] or commercially unavailable hypervalent-iodine reagents[15a] as coupling partners. Taking these facts into consideration, first we examined palladium-catalyzed direct C−H bond arylations of 1-benzyl-2-(2′-furyl)pyrrole **9g** with bromobenzene. To our delight, the expected coupling product **17** was obtained in 73% yield, using the catalyst composed of Pd(OAc)$_2$, PCy$_3$, K$_2$CO$_3$, and pivalic acid in DMF[15c] (Scheme 7). Under the identical conditions, 2-(5′-thienyl)pyrrole **16** reacted with 4-bromobenzonitrile to give the corresponding donor−acceptor conjugate **18** in 69% yield. It is noteworthy that the coupling reaction with 2,5-dibromothiophene also took place to afford the pyrrole-, furan-, and thiophene-conjugated oligomer **19** in 53% yield.

Scheme 7. Pd-Catalyzed Direct C−H Bond Arylations of Hetero Dimers of Heterocycles



In conclusion, we have developed a one-pot synthesis of hetero dimers of heterocycles via Sonogashira coupling and double cyclization cascade involving imination. The reaction proceeds under mild conditions forming several C−C and C−N bonds to afford a variety of 2-(2′-furyl)pyrroles, 2-(5′-thienyl)furans, and 2-(5′-thienyl)pyrroles in good to excellent yields by simple alternation of the combination of reagents employed. Moreover, combined with a palladium-catalyzed post-direct C−H bond arylation, the present method provides a simple and powerful synthetic tool that permits the assembly of a π-conjugated system in a programmed and diversity-oriented format. The present strategy should find many uses for combinatorial lead structure identification and optimization in the development of functional organic materials where the structure−property relationships are often not predictable. Further investigations of the reaction scope as well as measurement of optical properties of the obtained mixed-heterocyclic oligomers are currently in progress in our laboratory.

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Supporting Information Available. General procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For recent reviews, see: (a) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (b) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(15) For palladium- or rhodium-catalyzed intermolecular direct C−H bond arylations of *N*-alkylpyrroles, see: (a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (b) Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979. (c) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (d) Gracia, S.; Cazorla, C.; Métay, E.; Pellet-Rostaing, S.; Lemaire, M. *J. Org. Chem.* **2009**, *74*, 3160. (e) Gryko, D. T.; Vakuliuk, O.; Gryko, D.; Koszarna, B. *J. Org. Chem.* **2009**, *74*, 9517. (f) Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977. (g) Jafarpour, F.; Rahiminejadan, S.; Hazrati, H. *J. Org. Chem.* **2010**, *75*, 3109.

The authors declare no competing financial interest.