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Synthesis of Multisubstituted Allenes, Furans, and Pyrroles via Tandem Palladium-Catalyzed Substitution and Cycloisomerization

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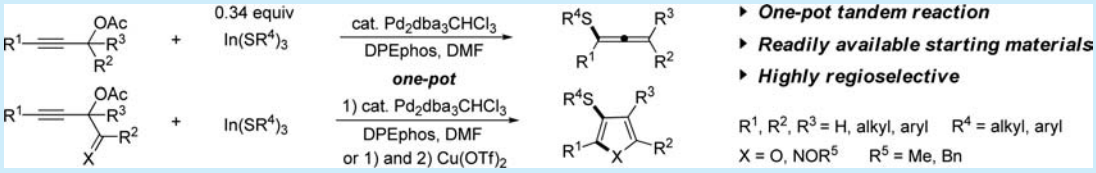
Supporting Information

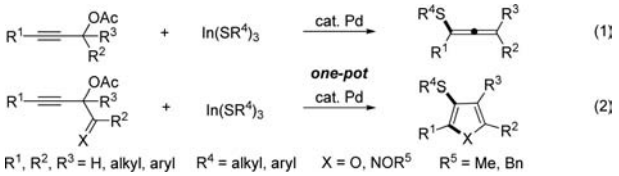


ABSTRACT: A palladium-catalyzed propargyl substitution reaction of propargyl acetates with indium organothiolates is developed for the synthesis of multisubstituted allenyl sulfides. This procedure can be applied to the synthesis of multisubstituted furans and pyrroles via tandem palladium-catalyzed propargyl substitution and cycloisomerization reaction in one pot.

Furans[1] and pyrroles[2] are ubiquitous scaffolds in a large number of natural products, pharmaceuticals, and materials science.[3] As a consequence, their synthesis has been an active area of research for over a century, and many methods for the streamlined synthesis of furans and pyrroles have been reported, including classical procedures such as the Paal−Knorr, Hantzsch, and Feist−Bénary syntheses.[4] In addition, the intramolecular cyclizations catalyzed by transition metals, including Cu, Ag, Pd, and Zn, have attracted increasing attention from the viewpoint of atom economy or environmental concern.[5] Although these reactions are advantageous, most of the methods still require investigation in terms of the substrate scope and limitations, regioselective introduction of substituents, catalyst loadings, yields, and reaction conditions.

Recently, an efficient synthetic method toward multisubstituted furans and pyrroles bearing heterosubstituents was reported through metal-catalyzed 1,2-shifts of diverse migrating groups in allenyl systems.[6] However, the introduction of a wide variety of substituents at the 4-position of furans and pyrroles is impossible due to requirement of a [1,3]-H shift in these methods. Therefore, the development of an efficient synthetic method for multisubstituted furans and pyrroles bearing 3-heteroatom substituents as well as substituents at the 4-position has been a continuing challenge. Recently, we reported that indium organothiolate is an effective nucleophilic coupling partner in Pd-catalyzed C−S cross-coupling reactions.[7] On the basis of these results, we envisioned that if Pd-catalyzed propargyl substitution reactions of propargyl acetates with indium organothiolates proceed, multisubstituted allenyl sulfides might be produced, and as a result, multisubstituted furans and pyrroles could be produced via tandem Pd-catalyzed propargyl substitution and cycloisomerization reactions.[8] Herein, we report Pd-catalyzed propargyl substitution reactions of propargyl acetates with indium organothiolates for the synthesis of multisubstituted allenyl sulfides (Scheme 1, eq 1). This procedure employed tandem Pd-catalyzed propargyl substitution and cycloisomerization reactions from indium organothiolates and propargyl acetates bearing acyl and imidoyl groups for the synthesis of multisubstituted furans and pyrroles in one pot (Scheme 1, eq 2).

Scheme 1. Synthesis of Multisubstituted Allenyl Sulfides, Furans, and Pyrroles



We began our investigations by examining the reaction of 2-phenylbut-3-yn-2-yl acetate (**2a**) with indium 4-methylbenzenethiolate (**1e**) using palladium catalysts and ligands in DMF (*N*,*N*-dimethylformamide) (Table 1). $Pd(PPh_3)_4$ (4.0 mol %) is ineffective in DMF at 25 °C for 5 h (entry 1). Thus, various ligands were screened in the presence of 2.0 mol % of $Pd_2dba_3CHCl_3$ (entries 2−9). DPEphos gave the best result among the ligands (entry 9). Among the catalytic systems examined, the best results were obtained with $Pd_2dba_3CHCl_3$ (2.0 mol %) and DPEphos (8.0 mol %) in DMF at 25 °C for 5 h under a nitrogen atmosphere, leading to the formation of allenyl sulfide **3ae** in 74% isolated yield (entry 9). The fact that 0.34 equiv of **1e** gave the best results indicates that all of the 4-methlybenzenethiolate groups attached to the indium metal are efficiently transferred to **2a**. Efficient transfer of the three organic groups attached to indium to electrophiles can be explained in connection with the weak bond strength between sulfur and indium. In addition, the large differences in the heats of formation between In−S and In−O support the present results.[9]

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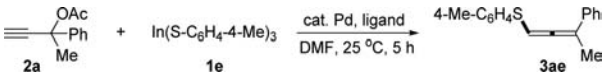
Table 1. Reaction Optimization[a]



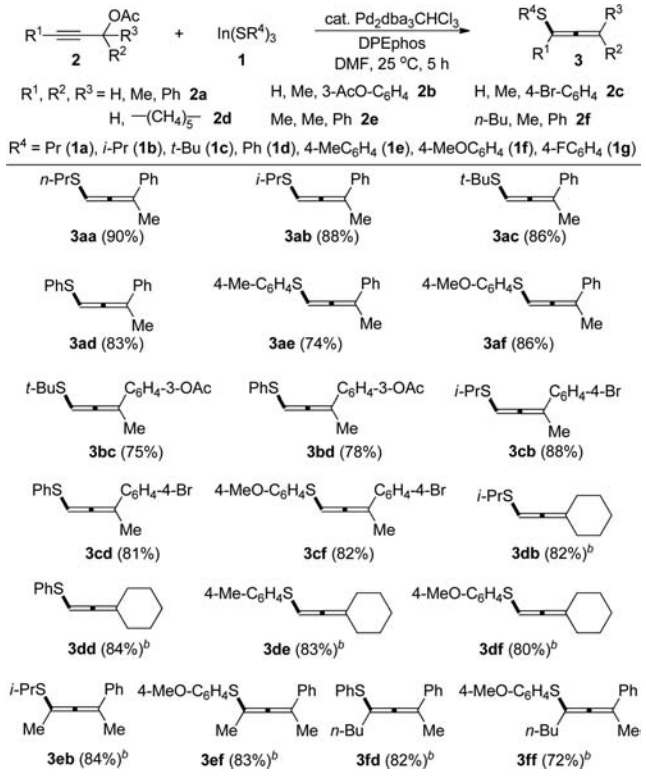
entry	cat.	ligand	yield[b] (%)
1[c]	$Pd(PPh_3)_4$		0
2	$Pd_2dba_3CHCl_3$	DPPE	0
3	$Pd_2dba_3CHCl_3$	DPPP	0
4	$Pd_2dba_3CHCl_3$	DPPF	0
5[d]	$Pd_2dba_3CHCl_3$	$P[(2,6\text{-}(MeO)_2C_6H_3]_3$	0
6[d]	$Pd_2dba_3CHCl_3$	$P(4\text{-}CF_3C_6H_4)_3$	0
7	$Pd_2dba_3CHCl_3$	Xantphos	0
8[d]	$Pd_2dba_3CHCl_3$	P(biphenyl)Cy_2	0
9	$Pd_2dba_3CHCl_3$	DPEphos	86 (74)[e]
10[f]	$Pd_2dba_3CHCl_3$	DPEphos	16 (60)[g]
11[c]	$Pd(OAc)_2$	DPEphos	24

[a]Reactions were carried out with **2a** (0.3 mmol, 1 equiv) and **1e** (0.34 equiv) in the presence of 2.0 mol % of catalyst and 8.0 mol % of ligand. [b]NMR yield using CH_2Br_2 as an internal standard. [c]4.0 mol % catalyst was used. [d]16.0 mol % ligand was used. [e]Isolated yield of **3ae**. [f]THF was used. [g]Recovered yield of **2a**.

To demonstrate the scope and limitations of the present method, we applied this catalytic system to diverse propargyl acetates **2** and indium organothiolates **1** (Scheme 2). The various indium reagents **1** bearing alkyl and aryl thiolates showed little effect on the product yield as well as the reaction rate. Under the optimized conditions, treatment of **2a** with **1d** and **1f** produced the desired allenyl sulfides **3ad** and **3af** in 83% and 86% yields, respectively. Indium alkylthiolates are applicable to the present transformation, providing the corresponding alkyl allenyl sulfides. For example, **1a** and **1b** took part in propargyl substitution reactions with **2a** to afford **3aa** (90%) and **3ab** (88%). *tert*-Butyl allenyl sulfide **3ac** was obtained in 86% yield even if the sterically hindered **1c** was used. It is noteworthy that indium alkylthiolates generated from volatile alkyl thiols operated as efficient nucleophiles, resulting in the formation of alkyl allenyl sulfides. Acetoxy groups on the aryl ring were tolerated in the propargyl substitution reaction, producing **3bc** (75%) and **3bd** (78%). Moreover, substrate (**2c**) bearing a bromide group on the aryl ring was smoothly converted to the desired allenyl sulfides (**3cb**, **3cd**, and **3cf**) in high yields. These results exhibited the preference of the propargyl substitution reaction over the cross-coupling reaction. Because sterically congested alkynes were less reactive, the propargyl substitution reactions did not proceed even at prolonged reaction time at room temperature. The propargyl substitution reactions of **2d** with **1** occurred at 100 °C for 1 h, affording the desired allenyl sulfides (**3db**, **3dd**, **3de**, and **3df**) in good yields. Internal propargyl acetates (**2e** and **2f**) were found to be compatible with the propargyl substitution reaction using **1** at 100 °C for 1 h. When **2e** was reacted with **1b** and **1f**, tetrasubstituted allenyl sulfides **3eb** and **3ef** were obtained in 84% and 83% yields, respectively. To our delight, the Pd-catalyzed propargyl substitution reactions of **2f** with **1d** and **1f** took place to give tetrasubstituted allenyl sulfides **3fd** and **3ff** in good yields.

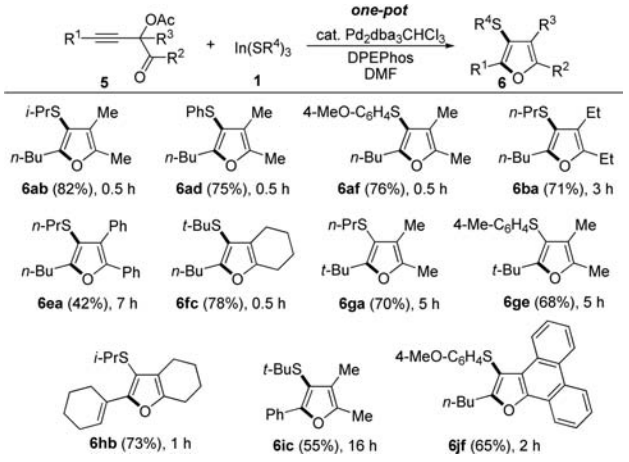
Encouraged by these results, we envisioned that if propargyl acetates bearing acyl groups underwent a propargyl substitution reaction with indium organothiolates, allenyl ketones bearing sulfenyl groups might be produced and the sequential cycloisomerization reaction might occur, leading to the formation of multisubstituted furans in one pot. To our delight, reaction of 3-methyl-2-oxonon-4-yn-3-yl acetate (**5a**) with **1d** (0.34 equiv) in the presence of $Pd_2dba_3CHCl_3$ (4.0 mol %) and DPEphos (16.0 mol %) furnished **6ad** in 75% yield in DMF at 150 °C within a short time (30 min) (see the Supporting Information). Having established the tandem Pd-catalyzed propargyl substitution and cycloisomerization reactions, we next explored the scope of both propargyl acetates **5** bearing acyl groups and indium reagents **1** (Scheme 3). Various moieties of propargyl acetates, such as methyl, ethyl, *tert*-butyl, cyclohexyl,

Scheme 2. Preparation of Multisubstituted Allenyl Sulfides[a]



[a]Reactions were carried out with **2** (0.3 mmol, 1 equiv) and **1** (0.34 equiv) in the presence of 2.0 mol % of $Pd_2dba_3CHCl_3$ and 8.0 mol % of DPEphos in DMF at 25 °C. [b]For 1 h at 100 °C.

Scheme 3. Synthesis of Tetrasubstituted Furans[a]



[a]Reactions were carried out with **5** (0.3 mmol, 1 equiv) and **1** (0.34 equiv) in the presence of 4.0 mol % of $Pd_2dba_3CHCl_3$ and 16.0 mol % of DPEphos in DMF at 150 °C.

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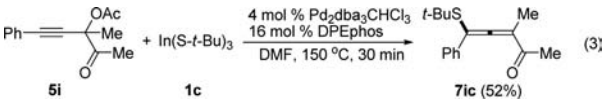
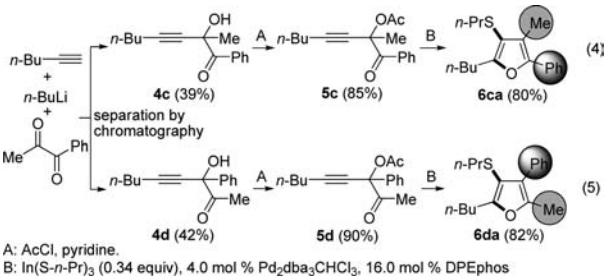
cyclohexen-1-yl, phenyl, and phenanthrenyl groups, demonstrated similar efficiencies. Substrate **5a** was found to react with **1b** and **1f** to afford the corresponding furans **6ab** and **6af** in 82% and 76% yields, respectively. Treatment of propargyl acetate (**5b**) with **1a** furnished the desired furan **6ba** in 71% yield. However, benzoyl- and phenyl-substituted propargyl acetate **5e** was less effective, resulting in the production of **6ea** in 42% yield. In addition, substrate **5f** is applicable to the present transformation with sterically hindered **1c**, affording the corresponding bicyclic furan **6fc**. Propargyl acetate (**5g**) bearing a sterically hindered *tert*-butyl group with **1a** and **1e** is compatible to the tandem reactions to provide the desired furans **6ga** and **6ge** in good yields. The present method worked equally well with cyclohexen-1-yl-substituted propargyl acetate (**5h**) and **1b** to give **6hb** in 73% yield. When **5i** was reacted with a sterically congested **1c** in the presence of palladium catalyst, allenyl ketone **7ic** bearing a *tert*-butylsulfenyl group was obtained in 52% yield in DMF at 150 °C for 30 min (eq 3).



(3)

A full conversion was observed with a prolonged reaction time (16 h), leading to furan **6ic** in 55% yield. These results indicate that tetrasubstituted furan **6ic** is produced through the formation of allenyl ketone **7ic**. Easily accessible propargyl acetate **5j** from phenanthrene-9,10-dione was found to be compatible with the reaction conditions.

In addition, propargyl acetates **5c** and **5d** bearing benzoyl and acetyl groups easily prepared from nonsymmetrical 1-phenyl-1,2-propanedione are applicable to the present transformation, providing **6ca** and **6da** in 80% and 82% yields, respectively (eqs 4 and 5). These transformations afforded an efficient strategy to synthesize selectively isomeric tetrasubstituted furans.

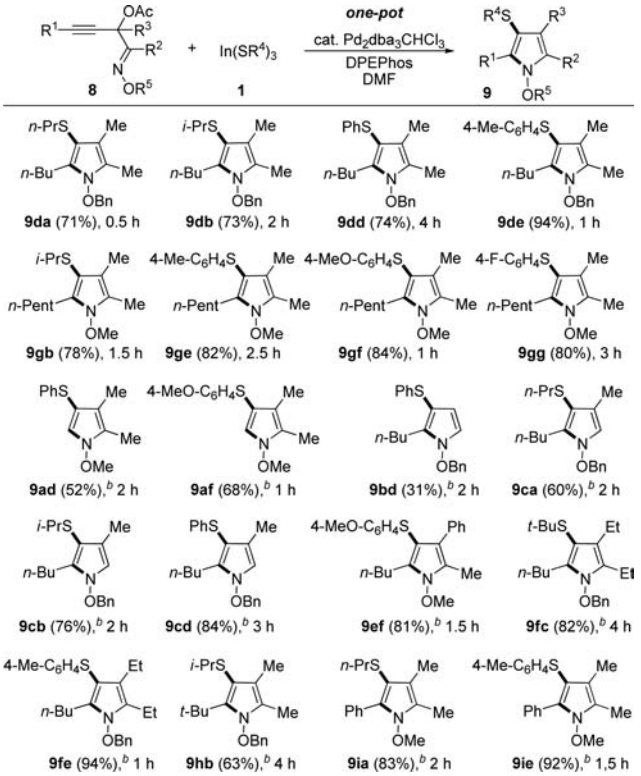


(4)

(5)

We applied the optimized conditions for the synthesis of multisubstituted furans in tandem Pd-catalyzed propargyl substitution and cycloisomerization reactions using imidoyl propargyl acetates **8** for the synthesis of multisubstituted pyrroles (Scheme 4). Propargyl acetates **8** bearing a wide range of substituents such as methyl, ethyl, *tert*-butyl, and phenyl were investigated under the optimized conditions, producing multisubstituted pyrroles in good yields. For example, when R^1, R^2, and R^3 are *n*-Bu, Me, and Me, respectively, tandem reactions using **1a** and **1b** smoothly proceeded in the presence of $Pd_2dba_3CHCl_3$ (4.0 mol %) and DPEphos (16.0 mol %), providing pyrroles **9da** (71%) and **9db** (73%). The present method worked equally well with **1d** and **1e**, producing **9dd** (74%) and **9de** (94%) in one pot. In addition, *n*-pentyl- and methyl-substituted propargyl acetates **8g** were found to react

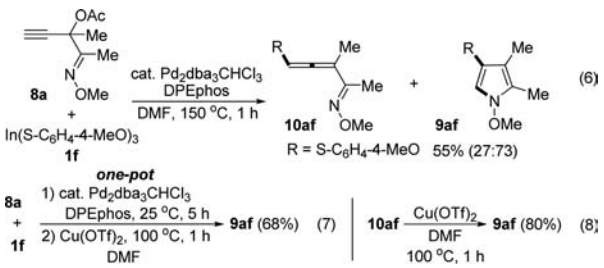
Scheme 4. Synthesis of Multisubtituted Pyrroles[a]



[a]Reactions were carried out with **8** (0.3 mmol, 1 equiv) and **1** (0.34 equiv) in the presence of 4.0 mol % of $Pd_2dba_3CHCl_3$ and 16.0 mol % of DPEphos in DMF at 150 °C (step 1). [b]After step 1, reaction mixture was cooled to 100 °C and then, $Cu(OTf)_2$ (0.5 equiv) was added and reactions performed at 100 °C.

with **1b**, **1e**, **1f**, and **1g** to provide the corresponding pyrroles in high yields.

When terminal propargyl acetate (**8a**) bearing a methoxy imidoyl group was treated with **1f**, a mixture of imidoyl allenyl sulfide **10af** and pyrrole **9af** was produced in 55% yield (27:73) (eq 6, see the SI). Thus, a variety of additives for the



(6)

(7)

(8)

cycloisomerization from **8a** were screened (see the SI). The modified optimized conditions were obtained from the propargyl substitution reaction of **8a** with **1f** in the presence of $Pd_2dba_3CHCl_3$ (4.0 mol %) and DPEphos (16.0 mol %), producing allenyl sulfides **10af** in DMF at 25 °C for 5 h, and then the addition of $Cu(OTf)_2$ (0.5 equiv) to the reaction mixture provided **9af** in 68% yield in one pot (eq 7). Moreover, treatment of **10af** with $Cu(OTf)_2$ in DMF at 100 °C for 1 h produced the desired pyrrole **9af** in 80% yield (eq 8, see the SI). These results indicate that $Cu(OTf)_2$ was involved in the cycloisomerization reactions of allenyl sulfides.

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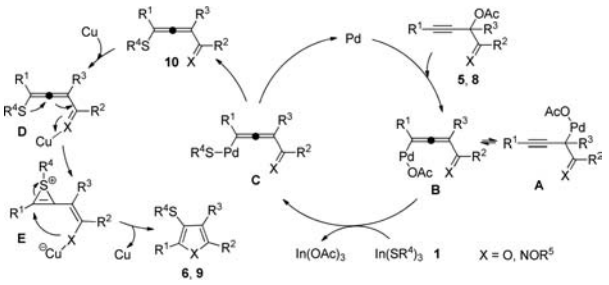
Iminopropargyl acetate (**8a**) was treated with **1d** to produce the desired pyrrole **9ad** (52%). When R^1, R^2, and R^3 were *n*-Bu, H, and Me, respectively, the tandem reactions proceeded smoothly, affording pyrroles **9ca**, **9cb**, and **9cd** in good yields. In the case of propargyl acetate **8b** derived from glyoxal, pyrrole **9bd** was produced in 31% yield due to the instability of the substrate. In the reaction with **1f**, propargyl acetate **8e** having *n*-butyl, methyl, and phenyl groups was smoothly converted to the desired pyrrole **9ef** in 81% yield. Exposure of propargyl acetates **8f** to **1c** and **1e** led to the formation of **9fc** (82%) and **9fe** (94%). Sterically hindered *tert*-butyl-substituted propargyl acetate **8h** was reacted with **1b**, producing **9hb** in 63% yield. Imino propargyl acetate (**8i**) was smoothly engaged in a tandem reaction with **1a** and **1e** to give the corresponding pyrroles **9ia** (83%) and **9ie** (92%).

A plausible mechanism for the tandem Pd-catalyzed propargyl substitution and cycloisomerization reactions of propargyl acetates (**5** and **8**) bearing acyl and imidoyl groups is described in Scheme 5. First, the *σ*-propargyl palladium(II) complex **A** is

Scheme 5. Plausible Mechanism



initially generated from propargyl acetate in the presence of Pd catalyst. Then an equilibrium occurs between **A** and *σ*-allenyl palladium complex **B**. The equilibrium lies favorably toward the *σ*-allenyl palladium(II) complex **B** due to steric congestion. Transmetalation followed by reductive elimination delivers allenyl sulfide **10**. Complexation of **10** with copper activates the allene bond via coordination between the imine or carbonyl group and copper. Afterward, we assumed that the subsequent attack of a sulfur atom at the electrophilic center carbon of allene would give thiirenium intermediate **E**.[10] Finally, intramolecular ring-opening reaction followed by decomplexation of copper produces the furans and pyrroles **6** and **9**.

In summary, a Pd-catalyzed propargyl substitution reaction of propargyl acetates with indium organothiolates is developed for the synthesis of multisubstituted allenyl sulfides. This procedure can be successfully applied to tandem Pd-catalyzed propargyl substitution and cycloisomerization reactions from indium organothiolates and propargyl acetates bearing acyl and imidoyl groups for the synthesis of multisubstituted furans and pyrroles in one pot.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03561.

Experimental procedures, characterization data, and NMR spectra for all of the products (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor Jaiwook Park (POSTECH) on the occasion of his 60th birthday.

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