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Pd-Catalyzed Sequential Reactions via Allene Intermediate for the Synthesis of Polycyclic Frameworks Containing 2,3-Dihydrofuran Units

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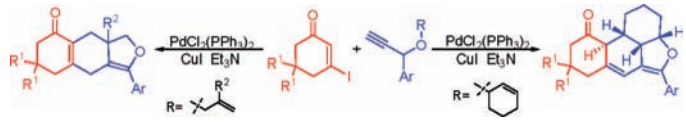
ABSTRACT



A stepwise process involving Sonogashira coupling, propargyl allenyl isomerization, and consecutive [4 + 2] cyclization has been realized, leading to an efficient synthesis of polycyclic compounds containing a 2,3-dihydrofuran unit. Most attractive for synthetic interest is the finding that up to four stereogenic centers could be generated in one step with high stereoselectivity.

Sequential reaction represents an elegant and efficient way to access novel and complex molecules from simple, readily available starting materials.[1] These reactions often involve a series of inter- or intramolecular processes wherein the product of one reaction is programmed to be the substrate for the next. Therefore, the consecutive transformations of the involved intermediates finally incorporate the powerful sequences into a designed scheme,[1,2] which are now routinely employed to construct core skeletons of many important natural products.[3]

Allenes have shown impressive synthetic potentials in organic chemistry.[4] Many novel reactions were well established in the past decades.[5,6] Intramolecular [4 + 2] cycloaddition of ene−allenes provides a convenient route for the construction of complex ring systems.[4,7,8] Compared with traditional intramolecular Diels−Alder reaction, the

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attendance of allene motif enhances the diversity of reaction possiblity. Typically, four kinds of reaction patterns can be envisioned: one C=C bond of the allene acts as dienophile to react with the intramolecular diene unit (Figure 1, types

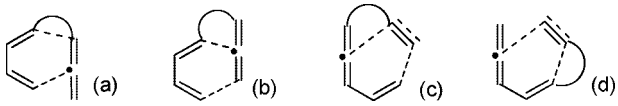


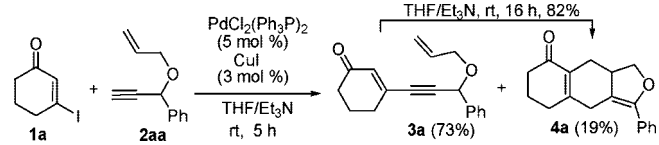
Figure 1. [4 + 2] cycloaddition models for ene−allenes.

a and b).[7] Alternatively, the vinylallene serves as diene to undergo cycloaddition with another double or triple bonds to give cyclic compounds (types c and d).[8] More importantly, due to the unusual facilitation of cycloadditon and unique geometry of allenes, these reactions often proceed efficiently in highly stereoselective control, thus providing an attractive tool for the stereoselective synthesis of polycyclic molecules including natural products such as compactin[9] and sterpurene.[10]

In this context, we consider that the development and application of sequential reactions via allene intermediate would be an attractive, useful, and in some cases advantageous way to access a variety of interesting and useful polycyclic molecules.[11] As an interest in devising novel sequential reactions,[12] herein we reported a versatile palladium-catalyzed sequential reaction, wherein the in situ-generated ene−allene would wisely undergo intramolecular [4 + 2] cyclization, leading to a facile synthesis of fused polycyclic scaffolds from 3-iodocyclohex-2-enone **1** and propargyl allyl ether **2**.

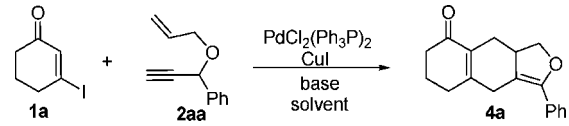
We initiated our study by attempting the reaction of **1a** and **2aa** in the presence of a catalytic amount of $PdCl_2(Ph_3P)_2$ and CuI.[13] With the assistance of suitable base, we envisioned that the formed coupling product **3a** could isomerize to produce an ene−allene intermediate in which diene and dienophile units were well installed for a subsequent intramolecular [4 + 2] cycloaddition. As expected, the reaction proceeded efficiently to give **3a** first, and gratifyingly, we observed with interest that the reaction afforded a fused tricyclic compound **4a** in 19% yield after 5 h. The following testing experiment shown that **3a** could be completely converted to **4a** with excessive Et_3N (Scheme 1).

Scheme 1



Our further studies show that a combination of Et_3N and THF in 1:3 as solvents was appropriate; 5 mol % of $PdCl_2(Ph_3P)_2$ and 3 mol % of CuI were sufficient. A clean and complete conversion was observed in 16 h with 75% yield of **4a** isolated (Table 1, entry 1). Other triamine bases

Table 1. Amine Base Effects on the Sequential Reaction[a]



entry	solvent	base	yield[b] (%)
1	THF	Et_3N	75
2	THF	$(n\text{-}C_4H_9)_3N$	72
3	THF	Et_2NH	*c*
4	THF	pyrrolidine	*c*
5	THF	$i\text{-}Pr_2NH$	*c*
6	THF	TMEDA	68
7	Toluene	Et_3N	74
8	MeCN	Et_3N	71

[a] Reactions were carried out using **1a** (0.5 mmol), **2aa** (0.6 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), and CuI (3 mol %) in 3 mL of solvent and 1 mL of amine at rt for 16 h. [b] Isolated yields. [c] No product was obtained.

such as tributylamine (entry 2, 72% yield) and TMEDA (entry 6, 68% yield) could also be applied to the reaction, but secondary amines, e.g., diethylamine, pyrrolidine, and diisopropylamine, which were frequently employed in the Sonogashira coupling reactions, were turned out to be totally disfavored (entries 3−5), which apparently indicates that the reaction was very sensitive to the type of amine base. The reaction could also be conducted in toluene or MeCN with comparable yield observed (entries 7 and 8).

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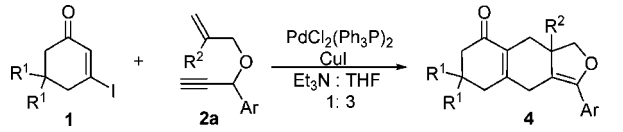
Table 2. Sequential Reaction for the Synthesis of Tricycles **4**[a]

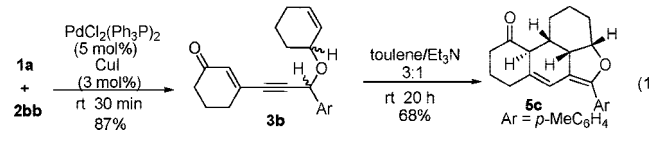


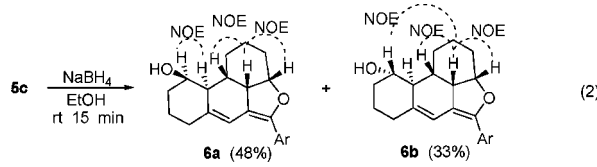
		2a			
entry	**1** (R^1)	R^2	Ar	**4**	yield[b](%)
1	**1b** (Me)	H	C_6H_5 (**2aa**)	**4b**	73
2	**1b**	H	*p*-MeC_6H_4 (**2ab**)	**4c**	80
3[c]	**1b**	H	*o*-BrC_6H_4 (**2ac**)	**4d**	68
4	**1b**	H	*p*-FC_6H_4 (**2ad**)	**4e**	79
5[6]	**1a** (H)	H	*o*-BrC_6H_4 (**2ac**)	**4f**	65
6	**1a**	H	*p*-MeC_6H_4 (**2ab**)	**4g**	76
7	**1b**	H	*m*-BrC_6H_4 (**2ae**)	**4h**	81
8[c]	**1b**	H	*o*-$MeOC_6H_4$ (**2af**)	**4i**	71
9	**1b**	Me	C_6H_5 (**2ag**)	**4j**	85
10	**1a**	Me	C_6H_5 (**2ag**)	**4k**	81
11	**1b**	Me	*p*-FC_6H_4 (**2ah**)	**4l**	85
12	**1a**	Me	*p*-MeC_6H_4 (**2ai**)	**4m**	75
13	**1a**	Me	*p*-FC_6H_4 (**2ah**)	**4n**	80

[a] Unless otherwise specified, the reaction was carried out at rt for 16−20 h. [b] Isolated yields. [c] Reactions were carried out at 70 °C.

The results summarized in Table 2 prove that this sequential reaction indeed provides a straightforward entry to a variety of fused tricyclic compounds with a 2,3-dihydrofuran unit in moderate to good yields (65%−85%). The reaction proceeded well at room temperature when Ar was a meta- or para-substituted phenyl group, but a higher temperature was required when an ortho-substituted phenyl group was employed (Table 2, entries 3, 5, and 8).

Further expanding the reaction scope to include propargyl cyclohexenyl ether such as **2ba** led us a tetracyclic compound **5a** in 46% yield wherein the double bonds did not migrate to conjugate with the carbonyl group. A better yield was obtained using toluene as solvent (Table 3, entry 1). Our preliminary results on these transformations show that Ar can be a para-substituted phenyl group either with an electron-donating or electron-withdrawing group (entries 2−6). When Ar = *p*-FC_6H_4, the reactions seem to proceed more efficiently and give higher yields probably because of electronic reasons (entries 5 and 6). In contrast, the presence of a substituent on the ortho position of the benzene ring of propargyl cyclohexenyl ether negatively affected the reaction. For example, when Ar = *o*-BrC_6H_4, it failed to afford the expected product (entry 7). The stereochemistry of these compounds was unambiguously established by the NOESY study of **5f** (Supporting Information). Significantly, although there were four stereocenters formed in the reaction, only one pair of enantiomorphs was produced. A controlled experiment also revealed the reaction steps and its highly stereoselective fashion. The reaction of **1a** and **2bb**, which was quenched by diluted HCl within 30 min, afforded the coupling product **3b** as a mixture of four stereoisomers in 87% yield. Then treatment of **3b** in toluene and Et_3N over 20 h ultimately gave **5c** in 68% yield as a single diasteromer (eq 1).



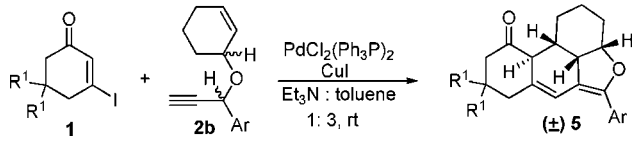


Interestingly, tetracyclic compounds **6a** and **6b** with five stereocenters were readily obtained by direct reduction of the carbonyl group of **5c** upon treatment with $NaBH_4$ (eq 2). Compounds **6a** and **6b** were easily separated by classical chromatography, and their structures were determined by spectroscopic analysis (^1H, ^{13}C, DEPT, COSY, NOESY and HMQC NMR experiments, IR, EIMS, HRMS, see the Supporting Information).

A possible mechanism is proposed as depicted in Scheme 2. Oxidative addition of **1** to the Pd(0) species, followed by transmetalation of the copper acetylide and reductive elimination, affords the coupling product **3**. The excessive Et_3N may promote a propargyl allenyl isomerization[14] to generate the ene−allene intermediate **10**. When R is an allyl group or 2-substituted allyl group, **10** may undergo an intramolecular [4 + 2] cycloaddition and subsequent C=C migration to give tricycle **4** (path a); when R is cyclohexenyl group, a highly diastereoselective [4 + 2] reaction is ready to conclude the reaction to furnish the tetracycle **5** (path b).

Based on the experiment results, it is worthy to note the following. (1) Et_3N facilitates both the coupling reaction and

Table 3. Sequential Reaction for the Synthesis of Tetracycles **5**



entry	**1**	**2b** (Ar)	time (h)	**5**	yield[a] (%)
1	**1a**	**2ba** (C_6H_5)	18	**5a**	55 (46[b])
2	**1b**	**2bb** (*p*-MeC_6H_4)	24	**5b**	63
3	**1a**	**2bb**	20	**5c**	58
4	**1a**	**2bc** (*p*-ClC_6H_4)	16	**5d**	63
5	**1a**	**2bd** (*p*-FC_6H_4)	10	**5e**	71
6	**1b**	**2bd**	10	**5f**, **NOESY**	76
7	**1b**	**2be** (*o*-BrC_6H_4)		*c*	

[a] Isolated yields. [b] Reactions were run in THF. [c] No product was obtained either at room temperature for 24 h or under reflux for 18 h.

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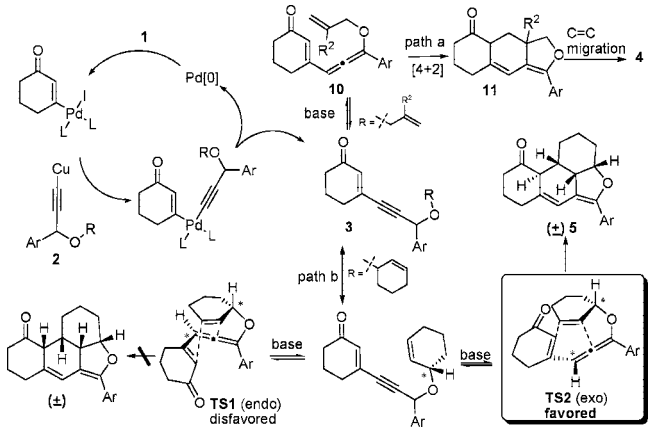
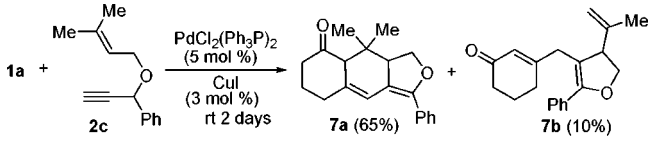
Scheme 2. Proposed Mechanism for the Pd-Catalyzed Sequential Reaction



the propargyl allenyl isomerization, and the observations that the reactions became reluctant when Ar was ortho-substituted may indicate that the steric effects play a negative role in the later process. (2) An attempt to shorten the reaction time to identify intermediate **10** was made but failed, which may suggest that it is highly reactive. However, the reaction of **1a** and **2c** led to a mixture of **7a** in 65% yield together with **7b** in 10% yield (Scheme 3). The formation of **7b** might be

Scheme 3

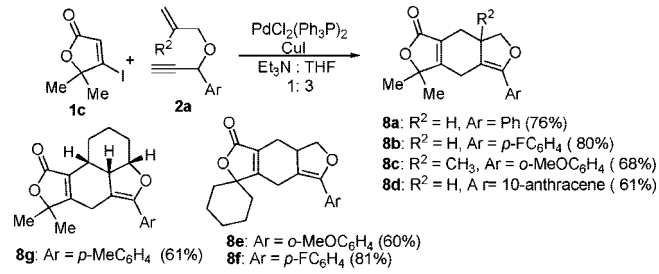


from a competitive ene pathway of a similar intermediate as **10**. Thus, the interesting discovery of this reaction should be an evidence for the existence of the allene intermediate in the reaction sequence. (3) The stereoselective formation of compounds **5** may be attributed to the fact that an exo transition state **TS2** is more favored in the Diels−Alder step than an endo-type **TS1** (Scheme 2). This transition-state selection indicates that the steric interactions rather than electronic factors play a crucial role in this case.

Moreover, it should be mentioned that the general structure of these obtained tri- and tetracyclic compounds exists frequently in many pharmacologically interesting molecules[15] as well as in a large number of biologically important natural products.[16] For example, Panepophenanthrin,[16d] which was found to be a potential inhibitor of the ubiquitin-activating enzyme in the ubiquitin−proteasome pathway (UPP) to regulate important cellular functions, possesses a skeleton very similar to those of tetracycles **5**. Considering the mild reaction conditions, easily available starting materials and highly stereoselective fashion, our protocol for the synthesis of these analogues should be potentially useful.

Finally, the reactions were also successfully applied to 3-iodobutenolides such as **1c** and **1d**, providing an efficient method to construct a class of novel framworks both with dihydrofuran and butenolide units. Several examples are presented in Scheme 4.

Scheme 4



In conclusion, we have realized a series of reactions including Sonogashira coupling, propargyl−allenyl isomerization, and [4 + 2] cycloaddition combined via an allene intermediate, affording an efficient and stereoselective synthesis of polycyclic skeletons. Most promising for potential synthetic application was the finding that up to four adjacent stereocenters could be produced with high selectivity in one step. Experiments designed to further explore the reaction scope as well as mechanism study concerning the stereoselectivity are currently underway.

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Supporting Information Available: Spectroscopic data for **4a**−**n**, **5a**−**e**, **6a**,**b**, **7a**,**b**, and **8a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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