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Letter

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Pd-Catalyzed Migratory Cycloisomerization of *N*-Allyl-*o*-allenylaniline Derivatives

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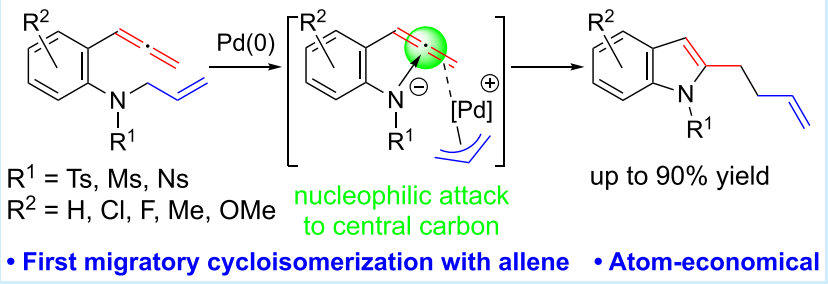
Supporting Information



ABSTRACT: The Pd-catalyzed migratory cycloisomerization of *N*-allyl-*o*-allenyl aniline derivatives is first reported to give indoles having a substituent at the 2-position.

Transition-metal-catalyzed migratory cycloisomerization provides a powerful approach in organic synthesis.[1,2] In particular, migratory cycloisomerizations of *o*-alkynylaryl ethers and amines having a migrating group on the heteroatom have been used to the synthesis of 2,3-disubstituted benzofurans and indoles (Scheme 1, eq 1). As migrating groups, α-alkoxyalkyl,[3] allyl,[3b,4] propargyl,[5] benzyl,[3b,6] acyl,[3g,7] methyl,[8] sulfonyl,[4l,9] silyl,[10] boryl[11] groups, and so on[12] have been employed.

Allenes, a class of readily accessible, air- and water-stable compounds, show interesting and varied reactivity patterns as a result of their unique chemical properties,[13] and are now becoming an integral part of modern synthetic methods in cyclization to yield complex skeletons.[14] Allenes have been found to possess unique reactivity toward a number of transition metals, such as Pd,[15] Ni,[16] Ru,[17] Rh,[18] and Au.[19] Recently, we also reported the Ru-catalyzed [2 + 2] reaction of *N*-allenyl-*o*-vinyl aniline derivatives.[17c] However, to the best of our knowledge, there have been no reports of migratory cycloisomerizations between allenes and amines having a migrating group on the heteroatom that could lead to a variety of substituted heterocycles.

In this letter, we report an unprecedented Pd-catalyzed migratory cycloisomerization of *N*-allyl-*o*-allenyl aniline derivatives **1** (Scheme 1, eq 2).

First, the reaction of *N*-allyl-*N*-toluenesulfonyl-*o*-allenyl aniline **1a** with various transition metal catalysts in toluene as solvent was investigated. When an organometallic catalyst (Ru, Au, Pt, In, Ni, Rh, and so on), which has worked well in cycloisomerization or migratory cycloisomerization, was used, no cyclization proceeded. However, when palladium acetate, $Pd(OAc)_2$ (10 mol %), and triphenylphosphine, PPh_3 (20 mol %), were used, migratory cycloisomerization proceeded to give 2-butenylindole **2a** in 42% yield (Table 1, entry 1).

In entries 1−5, 10 mol % of $Pd(OAc)_2$ was used and the catalytic amount of PPh_3 as ligand was investigated. As a result, when the amount of ligand was reduced from 20 mol %, the yield of **2a** decreased (entry 2), and **2a** was not obtained in the absence of the ligand (entry 3). When the amount of ligand was increased from 20 mol %, the yield of **2a** increased; when 45 mol % PPh_3 was used, the yield of **2a** reached 75% (entry 5). In entries 6−8, the Pd catalyst was changed. When

Scheme 1. Migratory Cycloisomerizations

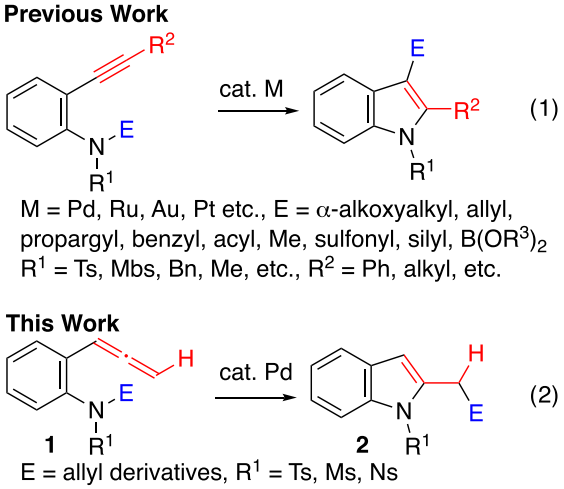


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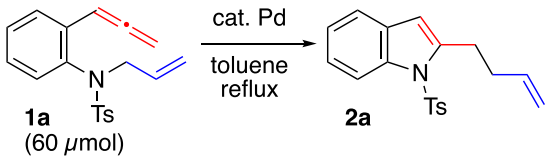
Table 1. Reaction Conditions Optimization; Migratory Cycloisomerization of 1a



entry	cat. Pd (mol %)[a]	ligand (mol %)	time (h)	yield of **2a** (%)
1	$Pd(OAc)_2$ (10)	PPh_3 (20)	3	42
2	$Pd(OAc)_2$ (10)	PPh_3 (15)	3	28
3	$Pd(OAc)_2$ (10)	–	3	0
4	$Pd(OAc)_2$ (10)	PPh_3 (30)	3	58
5	$Pd(OAc)_2$ (10)	PPh_3 (45)	3	75
6	$Pd_2(dba)_3$ (10)	PPh_3 (45)	3	83
7	$Pd_2(dba)_3$ (10)	–	3	0
8	$Pd(PPh_3)_4$ (10)	–	3	83
9	$Pd_2(dba)_3$ (10)	P(*o*-tol)$_3$ (45)	3	0
10	$Pd_2(dba)_3$ (10)	P(*t*-Bu)$_3$ (45)	3	0
11	$Pd_2(dba)_3$ (10)	PCy_3 (45)	3	0
12	$Pd_2(dba)_3$ (10)	$P(OPh)_3$ (45)	3	82
13	$Pd_2(dba)_3$ (10)	$P(OMe)_3$ (45)	3	83
14	$Pd_2(dba)_3$ (2)	PPh_3 (9)	3	77
15	$Pd_2(dba)_3$ (1)	PPh_3 (4.5)	5	49
16[b]	$Pd_2(dba)_3$ (10)	PPh_3 (45)	3	77

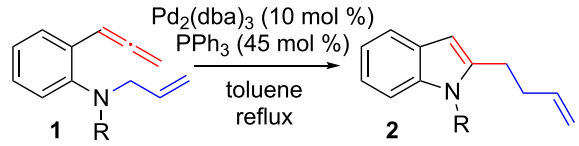
[a]Based on the catalyst complex. [b]1 mmol-scale reaction.

$Pd_2(dba)_3$ and 45 mol % PPh_3 were used, **2a** was obtained in 83% yield (entry 6). When $Pd(PPh_3)_4$ was used, **2a** was obtained in the same yield even in the absence of a ligand (entry 8). These results proved that zerovalent Pd is a reactive species.[20] Subsequently, we decided to study the reaction solvent and temperature using the conditions of entry 6.

Next, we decided to investigate the effect of the ligand on this reaction (entries 9–13). In investigations using ligands bulkier than triphenylphosphine (cone angle θ = 145°) (entries 9–11),[21] the reaction did not proceed. Then we examined ligands less bulky than triphenylphosphine (entries 12–13). As a result, product **2a** was obtained in the same yield as when triphenylphosphine was used. The bidentate ligands (±)-BINAP and 2,2′-bipyridyl were used, but this reaction did not proceed. From the above results, it was found that the reaction did not proceed when the bulkiness of the ligand was increased above a certain extent, so triphenylphosphine was selected as the optimum ligand in consideration of its stability. From entries 6, 14, and 15, we knew that we could reduce the amount of catalyst to 2 mol % palladium. Also, even in a 1-mmol-scale reaction, we could obtain the product **2a** in almost the same yield (entry 16).

We continued our experiments to study the scope and generality of this reaction using the conditions of Table 1, entry 6. First, the protecting group on nitrogen was studied (Table 2). The expected product was obtained from a substrate containing a *p*-toluenesulfonyl, a methanesulfonyl, or an *o*-nitrobenzenesulfonyl group (entries 1–3). But a substrate containing a less electron-withdrawing group, such as an acetyl or a *tert*-butoxycarbonyl group, was recovered unchanged (entries 4 and 5). From substrates containing a *p*-toluenesulfonyl or a methanesulfonyl group, the corresponding products were obtained in high yields of 83% and 79%, respectively, whereas, for an *o*-nitrobenzenesulfonyl-containing substrate, the yield of the corresponding product was reduced

Table 2. Effect of Substituent on Nitrogen(I)

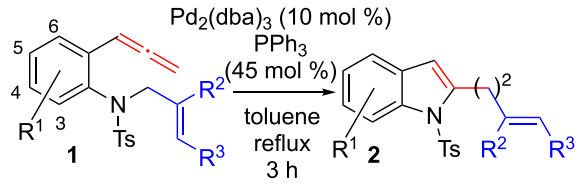


entry	substrate	R =	time (h)	product	yield (%)
1	**1a**	Ts	3	**2a**	83
2	**1b**	Ms	5	**2b**	79
3	**1c**	Ns	3	**2c**	44
4	**1d**	Ac	2.5	**2d**	0
5	**1e**	Boc	2.5	**2e**	0

to 44%. From these results, it might be considered necessary to use a substrate having electron-withdrawing groups at least to some extent on nitrogen for this reaction to proceed.

Subsequently, the effect of substituents on the aromatic ring was studied (Table 3). Substrates **1f**, **1g**, **1h**, and **1i** had chloro

Table 3. Effect of Substituent on Aromatic Ring



entry	substrate	R^1 =	R^2 =	R^3 =	product	yield (%)
1	**1a**	H	H	H	**2a**	83
2	**1f**	3-Cl	H	H	**2f**	0
3	**1g**	4-Cl	H	H	**2g**	90
4	**1h**	5-Cl	H	H	**2h**	82
5	**1i**	6-Cl	H	H	**2i**	82
6	**1j**	5-Me	H	H	**2j**	79
7	**1k**	5-OMe	H	H	**2k**	30
8	**1l**	5-F	H	H	**2l**	62
9	**1m**	H	Me	H	**2m**	56
10	**1n**	H	H	Me	**2n**	66

groups at the 3-, 4-, 5-, and 6-positions on the aromatic ring, respectively. It was confirmed that **1g**, **1h**, and **1i** were converted to the corresponding products in 90%, 82%, and 82% yield, respectively (entries 3–5). In stark contrast, **1f**, with a chloro group at the 3-position, was recovered unchanged (entry 2). In view of the fact that the present cyclization reaction was carried out in the presence of Pd, when the substituent is located at the 6-position but not when the substituent is at the 3-position, although both are 1,2,3-trisubstituted benzene, it is suggested that the catalyst reacts initially with the allyl group rather than the allene, and cyclization proceeds. In other words, when a substituent is present at the 3-position, the distance between the nitrogen and the central allene carbon becomes greater, which is considered to be difficult to cyclize. Substrates **1j**, **1k**, and **1l** having a methyl, methoxy, or fluoride group at the 5-position, as an electron-donating or much more electron-withdrawing group, respectively, reacted in 79%, 30%, and 62% yields (entries 6–8). Also, **1m** and **1n**, having a substituent at the allyl moiety, were converted to **2m** and **2n** in 56% and 66% yield, respectively (entries 9 and 10).

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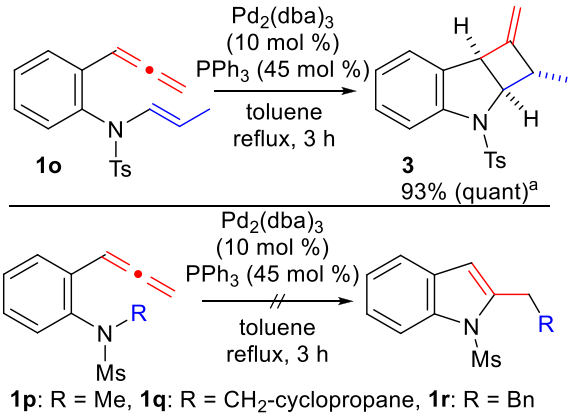
Subsequently, the effect of the allyl group on nitrogen was examined by using substrates substituted with other alkyl groups (Scheme 2). First, when the allyl group was changed to

Scheme 2. Effect of Substituent on Nitrogen(II)



[a]No catalysts were added.

a vinyl group, a product obtained by migratory cycloisomerization could not be confirmed, and compound **3**, considered to be formed by the [2 + 2] cyclization addition reaction, was obtained in 93% yield. Compound **3** was determined by X-ray crystal structure analysis (CCDC 1898621; Figure 1). As a result of various investigations, it

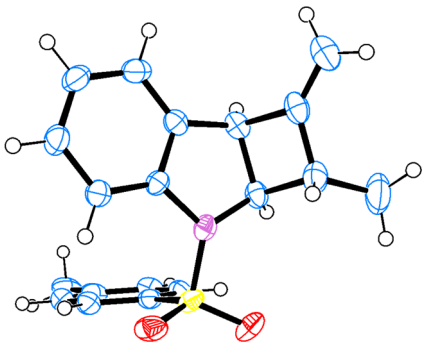


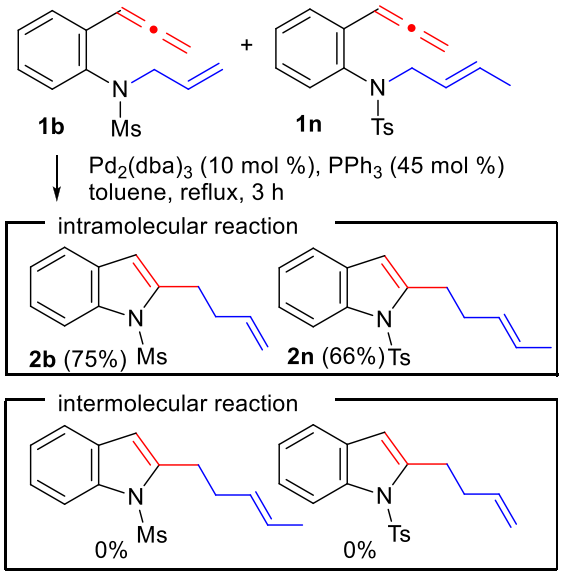
Figure 1. X-ray structure of **3**.

was found that this reaction did not require a transition metal catalyst and proceeded quantitatively by heating. In addition, when substrates **1p**, **1q**, and **1r** in which the allyl group was changed to a methyl, a cyclopropylmethyl group, or a benzyl group, respectively, were subjected to the same reaction conditions, migratory cycloisomerization did not proceed and the raw materials were recovered unchanged.

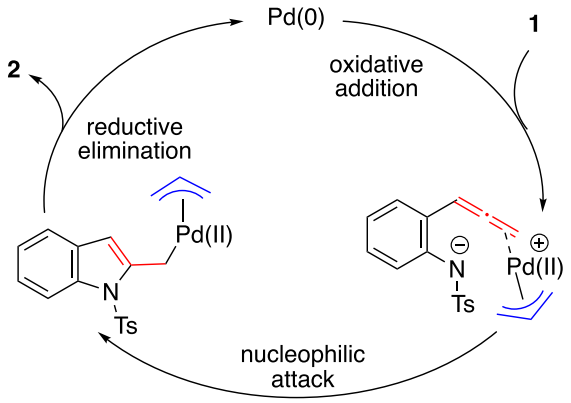
Finally, in order to ascertain whether this reaction is an intramolecular rearrangement or an intermolecular rearrangement reaction, we decided to carry out a crossover experiment. Substrate **1b**, having a mesyl group and an allyl group on the aromatic amino group, and substrate **1n**, having a *p*-toluenesulfonyl group and a 2-butenyl group, were subjected to reflux heating in toluene in the presence of a Pd catalyst. We obtained compounds **2b** and **2n** only, which result from reaction in the molecule (Scheme 3). This revealed that this reaction is an intramolecular rearrangement reaction.

Based on the experimental results, the mechanism of this reaction is proposed to be as shown in Scheme 4, which

Scheme 3. Crossover Experiments



Scheme 4. Plausible Reaction Mechanism



explains the following results: (1) The reaction is an intramolecular cyclization and does not proceed unless the ligand is sufficiently small. (2) It is necessary to stabilize the negative charge on the nitrogen of the π-allyl intermediate with a group of some electron-withdrawing character; conversely if the electron-withdrawing property is too high, the yield decreases. (3) With the substrate having a substituent at the 3-position on the aromatic ring, the reaction did not proceed due to steric hindrance.

In conclusion, we have developed, for the first time to our knowledge, a Pd-catalyzed migratory cycloisomerization of **1**, containing allene and allylic amine moieties, to give 2-substituted indoles **2**. We also found that the thermal [2 + 2] cyclization addition reaction of compound **1k**, containing allene and vinyl amine moieties, proceeded preferentially over the migratory cycloisomerization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00676.

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for compounds (PDF)

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Accession Codes

CCDC 1898621 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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