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Palladium-catalyzed tandem allylation of 1,2-phenylenediamines with *cis*-1,4-diacetoxy-2-butene

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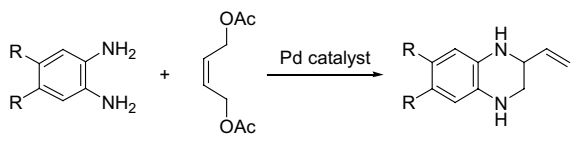
Abstract—The activation of C–O bonds in *cis*-1,4-diacetoxy-2-butene has been accelerated by carrying out the reactions in the presence of palladium complexes associated with ligands. Palladium-catalyzed tandem allylation of 1,2-phenylenediamines with *cis*-1,4-diacetoxy-2-butene leads to 1,2,3,4-tetrahydro-2-vinylquinoxalines in good yields.

Piperazine derivatives have aroused increasing interest due to their presence in a large number of therapeutically and biologically active compounds.[1] Numerous quinoxaline derivatives have been prepared to get biologically active compounds, and the research continues to synthesize new compounds having unusual skeletons.[2] Transition metal η^3-allyl complexes, as well as transition metal σ-alkyl complexes, play important roles as active species and key intermediates in many reactions catalyzed by transition metal complexes.[3] The palladium-catalyzed allylation of nucleophiles is an established, efficient, and highly stereo- and chemoselective method, which has been widely applied to organic chemistry.[4] The catalytic cycle requires the formation of the cationic η^3-allylpalladium(II) complex, an intermediate that is generated by oxidative addition of allylic compounds including allylic halides,[5] acetates,[6] and carbonates[7] to a Pd(0) complex and which can be attacked by nucleophiles at both termini of the allylic system. We have used palladium catalyzed for the N-allylation of aminonaphthalenes[8a] and for regiospecific tandem allylation of 2-aminophenols into 3,4-dihydro-2-vinyl-2*H*-1,4-benzoxazines.[8b] The reactions should be promoted in the presence of titanium reagent. However, there are few reports on palladium(0)-catalyzed reaction of bifunctional allylic diacetates and dicarbonates with nucleophiles featuring their bifunctionality.[9] It was reported by Massacret that (*Z*)-1,4-bis(methoxycarbonyloxy)but-2-ene reacted with unprotected 1,2-phenylenediamine in the presence of a palladium catalyst could not give 1,2,3,4-tetrahydro-2-vinylquinoxaline directly.[10] We now study the tandem allylation of 1,2-phenylenediamines with *cis*-1,4-diacetoxy-2-butene for the construction of 1,2,3,4-tetrahydro-2-vinylquinoxalines. This is, to our knowledge, the first example of palladium-catalyzed tandem allylation of 1,2-phenylenediamines by the use of *cis*-1,4-diacetoxy-2-butene.

The palladium-catalyzed cyclization of 1,2-phenylenediamines with *cis*-1,4-diacetoxy-2-butene was investigated under various conditions (Scheme 1). When a mixture of 1,2-phenylenediamine (**1a**, 2 mmol) and *cis*-1,4-diacetoxy-2-butene (**2**, 1.6 mmol) was heated in the presence of catalytic amounts of $PdCl_2(MeCN)_2$ (0.1 mmol), and PPh_3 (0.4 mmol) in benzene (5 mL) under nitrogen at 50 °C for 3 h, 1,2,3,4-tetrahydro-2-vinylquinoxaline (**3a**) was formed in 69% yield (entry 1 in Table 1). The ^1H and ^{13}C NMR of NCH appear at δ 3.85 and 53.0 ppm for **3a**. In the reaction under reflux for 3 h, the yield of product **3a** was increased to 99% (entry 2).[11] The reaction did not occur in the absence of



1a, R=H **b**, R=Me **c**, R=Cl — **2** — **3a**, R=H **b**, R=Me **c**, R=Cl

Scheme 1.

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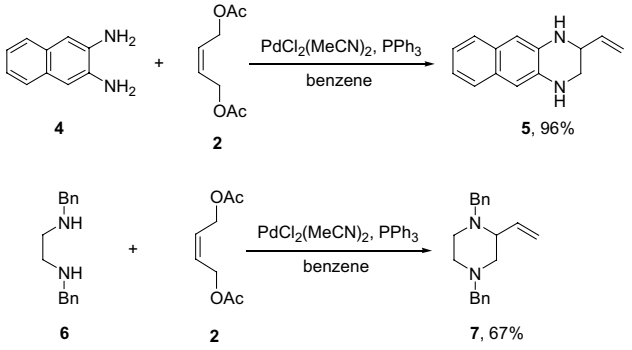
Table 1. Reaction of 1,2-phenylenediamines (**1**) with *cis*-1,4-diacetoxy-2-butene (**2**)[a]

Entry	1	Palladium catalyst	Solvent	Yield (%)[b] of 3
1	**1a**	$PdCl_2(MeCN)_2$–PPh_3	Benzene[c]	69
2	**1a**	$PdCl_2(MeCN)_2$–PPh_3	Benzene	99
3	**1a**	$PdCl_2(MeCN)_2$	Benzene	0
4	**1a**	PPh_3	Benzene	0
5	**1a**	$PdCl_2(MeCN)_2$–PPh_3	Dioxane	86
6	**1a**	$PdCl_2(MeCN)_2$–PPh_3	Toluene	83
7	**1a**	$PdCl_2(MeCN)_2$–PPh_3	CH_2Cl_2	81
8	**1a**	$PdCl_2(MeCN)_2$–PPh_3	THF	79
9	**1a**	$PdCl_2(MeCN)_2$–PPh_3	MeCN	68
10	**1a**	$PdCl_2(MeCN)_2$–PPh_3	DMF	40
11	**1a**	$PdCl_2(MeCN)_2$–PPh_3	HMPA	26
12	**1a**	$Pd(OAc)_2$–PPh_3	Benzene	88
13	**1a**	$Pd(OCOCF_3)_2$–PPh_3	Benzene	76
14	**1a**	$Pd(acac)_2$–PPh_3	Benzene	79
15	**1a**	$Pd_2(dba)_3$–PPh_3	Benzene	78
16	**1a**	$PdCl_2$–PPh_3	Benzene	97
17	**1a**	$PdF_6(acac)_2$–PPh_3	Benzene	85
18	**1a**	$PdCl_2(PhCN)_2$–PPh_3	Benzene	95
19	**1a**	$Pd(propionate)_2$–PPh_3	Benzene	72
20	**1a**	$Pd(PPh_3)_4$	Benzene	62
21	**1a**	$Pd(PPh_3)_4$–PPh_3	Benzene	87
22	**1a**	$PdCl_2(MeCN)_2$–Bu_3P	Benzene	23
23	**1a**	$PdCl_2(MeCN)_2$–$(2\text{-}MePh)_3P$	Benzene	20
24	**1a**	$PdCl_2(MeCN)_2$–$(2\text{-furyl})_3P$	Benzene	98
25	**1a**	$PdCl_2(MeCN)_2$–$(2\text{-pyridyl})Ph_2P$	Benzene	92
26	**1a**	$PdCl_2(MeCN)_2$–$(3\text{-}MePh)_3P$	Benzene	82
27	**1a**	$PdCl_2(MeCN)_2$–$(4\text{-}MePh)_3P$	Benzene	88
28	**1a**	$PdCl_2(MeCN)_2$–$(4\text{-}MeOPh)_3P$	Benzene	65
29	**1a**	$PdCl_2(MeCN)_2$–$(4\text{-}FPh)_3P$	Benzene	99
30	**1a**	$PdCl_2(MeCN)_2$–$(4\text{-}ClPh)_3P$	Benzene	67
31	**1a**	$PdCl_2(MeCN)_2$–dppm[d]	Benzene	9
32	**1a**	$PdCl_2(MeCN)_2$–dppe[e]	Benzene	18
33	**1a**	$PdCl_2(MeCN)_2$–dppp[f]	Benzene	61
34	**1a**	$PdCl_2(MeCN)_2$–dppb[g]	Benzene	88
35	**1a**	$PdCl_2(MeCN)_2$–dpph[h]	Benzene	90
36	**1b**	$PdCl_2(MeCN)_2$–PPh_3	Benzene	97
37	**1c**	$PdCl_2(MeCN)_2$–PPh_3	Benzene	73

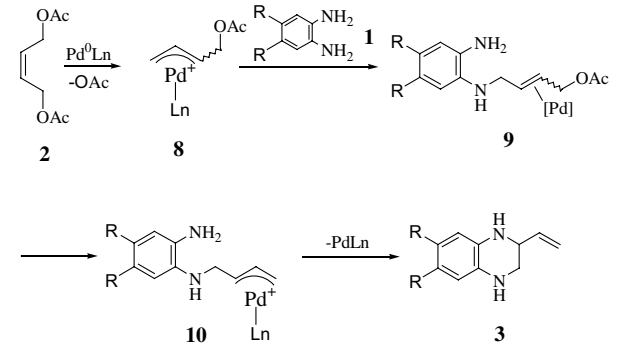
[a] Reaction conditions: **1** (2 mmol), **2** (1.6 mmol), Pd catalyst (0.1 mmol), and ligand (0.4 mmol) in a solvent (5 mL) were refluxed for 3 h.
[b] Isolated yield was based on **2**.
[c] Stirred at 50 °C.
[d] Bis(diphenylphosphino)methane.
[e] 1,2-Bis(diphenylphosphino)ethane.
[f] 1,3-Bis(diphenylphosphino)propane.
[g] 1,4-Bis(diphenylphosphino)butane.
[h] 1,6-Bis(diphenylphosphino)hexane.

the phosphine ligand (entry 3) or palladium catalyst (entry 4). Eight solvents were investigated, HMPA, DMF, and MeCN gave worst results while benzene gave the best results (entries 2 and 5–11). The yield of **3a** decreased as the polarity of the solvent increased. Ten palladium catalysts were investigated, $PdCl_2(MeCN)_2$ (entry 2), $Pd(OAc)_2$ (entry 12), $Pd(OCOCF_3)_2$ (entry 13), $Pd(acac)_2$ (entry 14), $Pd_2(dba)_3$ (entry 15), $PdCl_2$ (entry 16), $PdF_6(acac)_2$ (entry 17), $PdCl_2(PhCN)_2$ (entry 18), $Pd(propionate)_2$ (entry 19), and $Pd(PPh_3)_4$ (entry 20), with $PdCl_2(MeCN)_2$, $PdCl_2$, and $PdCl_2(PhCN)_2$ showed the best catalytic activity. Using $Pd(PPh_3)_4$ with extra PPh_3 as catalyst increased the yield of products (entry 21). In the presence of various monodentate ligands including PPh_3 (entry 2), Bu_3P (entry 22), $(2\text{-}MePh)_3P$ (entry 23), $(2\text{-furyl})_3P$ (entry 24), $(2\text{-pyridyl})Ph_2P$ (entry 25), $(3\text{-}MePh)_3P$ (entry 26), $(4\text{-}MePh)_3P$ (entry 27), $(4\text{-}MeOPh)_3P$ (entry 28), $(4\text{-}FPh)_3P$ (entry 29), and $(4\text{-}ClPh)_3P$ (entry 30) showed that PPh_3, $(2\text{-furyl})_3P$, $(2\text{-pyridyl})Ph_2P$, and $(4\text{-}FPh)_3P$ were the most effective ligands. The bidentate ligand including dppm (entry 31), dppe (entry 32), and dppp (entry 33) decreased the yield of products. Dppb (entry 34), and dpph (entry 35) gave high yields of **3a**. Compound **1b** was treated with $PdCl_2(MeCN)_2$–PPh_3 to give the cyclized product **3b** in 97% yield (entry 36). Similarly, compound **1c** gave **3c** in a yield of 73% (entry 37).

We studied the extension of this reaction for the construction of benzo[*g*]quinoxaline. When a mixture of 2,3-diaminonaphthalene (**4**, 2 mmol) and *cis*-1,4-diacetoxy-2-butene (**2**, 1.6 mmol) was refluxed in the presence of catalytic amounts of $PdCl_2(MeCN)_2$ (0.1 mmol) and PPh_3 (0.4 mmol) in benzene (5 mL) under nitrogen for 3 h, 1,2,3,4-tetrahydro-2-vinylbenzo[*g*]quinoxaline **5** was formed in 96% yield (Scheme 2). The ^1H and ^{13}C NMR



Scheme 2.



Scheme 3.

of NCH appear at δ 3.97 and 53.0 ppm for **5**. This cyclization proceeds through tandem allylic substitution reactions between 2,3-diaminonaphthalene and *cis*-1,4-diacetoxy-2-butene via π-allylpalladium intermediates. Similarly, *N*,*N*′-dibenzylethylenediamine (**6**) gave **7**[9f] in a yield of 67%.

A plausible reaction pathway for this tandem allylation is shown in Scheme 3. The first nucleophilic allylic substitution on π-allylpalladium intermediate **8**, which is generated by the reaction of *cis*-1,4-diacetoxy-2-butene with a palladium(0) species. Intermolecular nucleophilic substitution of the amino group of **1** takes place at the less hindered terminus of the π-allyl system to give the allylic amine **9**. Intramolecular nucleophilic attack on the second π-allylpalladium intermediate **10** at the more substituted internal allylic carbon atom produces **3**.

In summary, we have prepared 1,2,3,4-tetrahydro-2-vinylquinoxalines in high yields in the presence of a palladium catalyst. This cyclization proceeds through tandem allylic substitution reaction between 1,2-phenylenediamines and *cis*-1,4-diacetoxy-2-butene via π-allylpalladium intermediates. The reaction did not occur in the absence of the phosphine ligand or palladium catalyst. The yield of products decreased as the polarity of the solvent increased.

Acknowledgements

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11. A typical example for the palladium-catalyzed tandem allylation of 1,2-phenylenediamines with *cis*-1,4-diacetoxy-2-butene: A mixture of **1a** (162 mg, 2 mmol), **2a** (206 mg, 1.6 mmol), $PdCl_2(MeCN)_2$ (19 mg, 0.1 mmol), and PPh_3 (79 mg, 0.4 mmol) in refluxing benzene (5 mL) under nitrogen for 3 h. After cooling, the reaction mixture was filtered through Celite and the solvent was distilled under reduced pressure. The residue was purified by chromatography on silica gel (*n*-hexane/EtOAc, 3:1) to give the cyclized product **3a**.