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Pd-catalyzed annulation of benzene-1,2-diol and propargylic carbonates: a new example of asymmetric catalysis

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Abstract—The palladium-catalyzed cyclization of benzene-1,2-diol with various secondary propargylic carbonates in the presence of (*R*)-Binap as the chiral ligand afforded the corresponding 2,3-dihydrobenzo-1,4-dioxin derivatives in quite good yields, and also in enantioselectivities of up to 93%. The assumed enantioselective step is the protonation of a palladium–carbene intermediate.

The synthesis of compounds containing the 1,4-benzodioxin or 1,4-benzodioxan structures has been the subject of increasing interest during the last few years. One of the main reason is probably the interesting biological properties displayed by some of these compounds, especially those found in the nature.[1–5] For example, some 2-substituted 1,4-benzodioxanes exhibit antihyperglycemic properties,[6] or act as inhibitors of 5-lipoxygenase;[7] other derivatives have been used as α- or β-blocking agents or in antidepression or antihypertension therapy.[8–12] These compounds are also interesting targets for further synthetic transformations.[13–16]

The synthesis of 1,4-benzodioxin structures is now well documented in the literature.[13,17–25] Conversely the synthetic routes to 2-alkylidene-1,4-benzodioxanes are not common, and the proposed synthesis often required a tedious multistep sequence.[26–34] We reported recently a very easy and convenient access to various 2-alkylidene-2,3-dihydro-1,4-benzodioxins by a palladium-catalyzed reaction of propargylic carbonates with various substituted benzene-1,2-diols.[35,36] Moreover, we applied this methodology for the preparation of enantiomerically enriched derivatives in the presence of a chiral palladium catalyst, enantioselectivities up to 97% being obtained.[37,38]

We postulated for this cyclization process a mechanism shown in Scheme 1 and involving first the formation of a σ-allenyl complex **A** from the propargylic carbonate **1** and the Pd(0) complex via a $S_{N2'}$ mechanism. Then the carbenic complex **B** is formed by the attack of benzene-1,2-diol (**2**) on **A**; this complex **B** leads to the η^1-allylic complex **C** by protonation, that is in equilibrium with the η^3-allyl complex **D**. Attack of the nucleophile on one of the termini of this η^3-allylic complex **D** afforded the corresponding benzodioxin derivatives **3** (attack a) or **4** (attack b), respectively. In order to apply this synthetic route in an asymmetric way, we postulated that the enantioselective step was the attack of the nucleophile on the η^3-allylic intermediate **D**. So far it has been shown that in order to perform asymmetric allylic alkylation,[39,40] the η^3-allyl intermediate must have two identical substituents at one of the terminus (C-1 or C-3) of the π-allyl complex, allowing an easy racemization of this π-allyl complex, or two identical substituents at the two termini (C-1 and C-3) of the π-allyl complex ('meso' case). We have effectively shown that high enantioselectivities were obtained in our palladium-catalyzed annulation in these two cases: two identical substituents at the two termini ($R^1 = R^2$) or two identical substituents at one of the terminus ($R^1 = H$).[37,38]

In order to extend our methodology to other propargylic carbonates, we performed some experiments using racemic carbonates **1** bearing two different substituents R^1 and R^2. The palladium-catalyzed condensation of these carbonates with benzene-1,2-diol **2** was conducted under the precedent described conditions: THF was used as the solvent, $Pd_2(dba)_3$ and (*R*)-Binap as the chiral catalyst, and the reaction was performed at room

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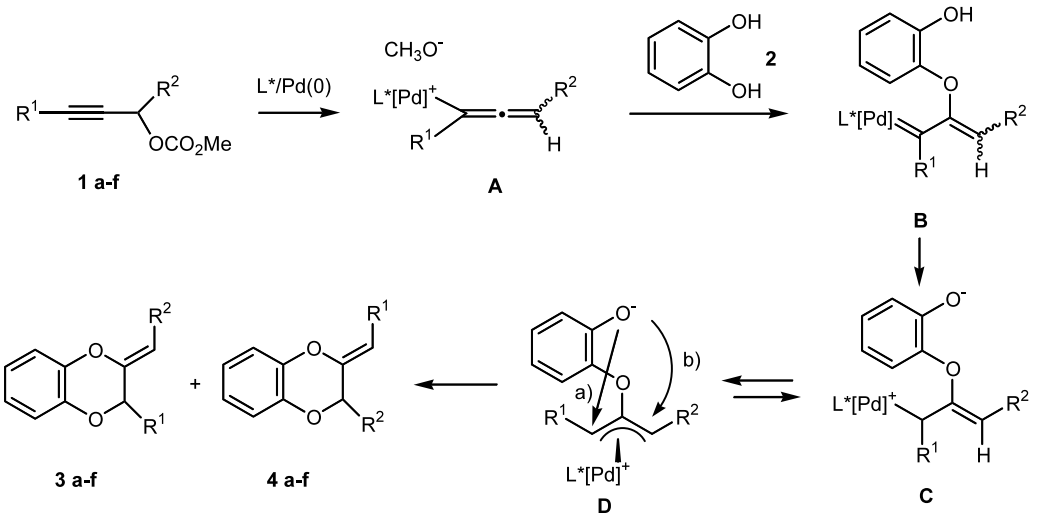


a: $R^1 = C_6H_5$, $R^2 = CH_3$; **b**: $R^1 = C_6H_5$, $R^2 = C_2H_5$; **c**: $R^1 = C_6H_5$, $R^2 = CH(CH_3)_2$; **d**: $R^1 = C_5H_{11}$, $R^2 = C_6H_4$-*p*-CH_3 ;
e: $R^1 = C_5H_{11}$, $R^2 = C_6H_4$-*p*-OCH_3 ; **d**: $R^1 = C_5H_{11}$, $R^2 = C_6H_4$-*p*-CN

Scheme 1.

temperature. The cyclization products were carefully purified and the enantiomeric excess of each regioisomer was determined by HPLC, when possible. The results are summarized in Table 1.

The cyclized products are generally obtained in quite good yields. It is to be noticed that the lowest yields, although not optimized, were obtained when propargylic acetates **1e** and **1f** were used instead of the carbonates; the corresponding carbonates cannot be used in these two examples, since they are unstable.

The obtained regioselectivities are in quite good agreement with the preceding published results.[36] In the case of propargylic carbonates **1a**–**b**, the attack on the π-allyl intermediate occurred on the terminus of the π-allyl bearing the alkyl substituent, leading predominantly to the regioisomer **4a**–**b** (Table 1, entries 1 and 2). The stereochemistry at the double bond for the two regioisomers was *Z* as shown using NOE NMR experiments. The enantioselectivities of the cyclized products **4a** and **4b** were 70 and 85% ee, respectively. The enantioselectivities of the minor regioisomers **3a** and **3b** could not be determined, whatever the conditions used.

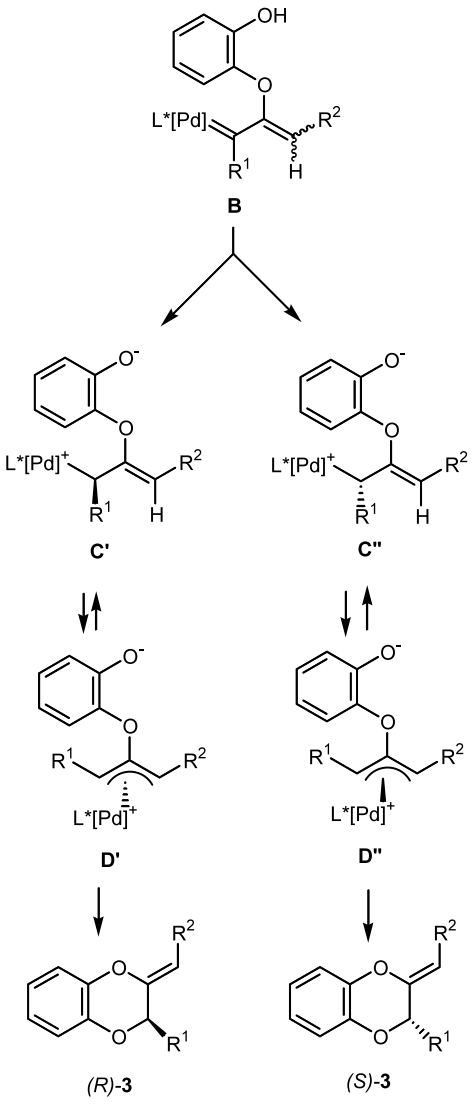
Increasing the steric bulk of the substituent R^2 and going from -CH_3 or -C_2H_5 to -$CH(CH_3)_2$ as in **1c** reversed the regioselectivity of the attack, leading predominantly to the regioisomer **3c** (Table 1, entry 3). The enantiomeric excesses of **3c** and **3d** were 93 and 83% ee, respectively. In the case of **1c**, modification of the ratio carbonate/benzene-1,2-diol from 1 to 4 gave exactly the same results (Table 1, entries 4 and 5).

In the case of the carbonates **1d**–**f**, the attack occurred also predominantly on the terminus of the π-allyl bearing the alkyl substituent, the regioisomer **3d**–**f** being the

Table 1. Enantioselective palladium-catalyzed condensation of benzene-1,2-diol (**2**) with propargylic carbonates **1**[a]

Entry	Compound **1**	Yield (%) of (**3**+**4**)[b]	% **3**/% **4**[c]	ee (%) of **3** [d]	ee (%) of **4**[d]
1	**1a**	70	20:80	nd	70
2	**1b**	95	32:68	nd	85
3	**1c**	70	68:32	93	83
4	**1c**[e]	61	68:32	89	82
5	**1c**[f]	61	66:34	89	80
6	**1d**	84	76:24	86	nd
7	**1e**[g]	35	61:39	80	78
8	**1f**[g]	49	90:10	85	52

[a] Conditions: [**1**]/[**2**]/[$Pd_2(dba)_3$]/[(*R*)-Binap]=48:40:1:4; 25°C; THF as the solvent.
[b] After column chromatography.
[c] Determined by GC.
[d] Determined by HPLC using a chiral column Chiralpak AD (25 cm×4.6 mm) using hexane/*i*-propanol as the eluent, nd means that no separation could be observed whatever the conditions used.
[e] [**1**]/[**2**]=40:40.
[f] [**1**]/[**2**]=80:40.
[g] The propargylic acetate was used instead of the carbonate, in the presence of NEt_3 ([**1**]/[NEt_3]=1:2).



Scheme 2.

predominant one; the ratio of the two regioisomers depends strongly on the nature of the substituent of the phenyl ring, the presence of an electron-withdrawing group increasing the attack on the terminus of the π-allyl bearing the alkyl substituent (Table 1, entries 6–8). The enantiomeric excesses of the major regioisomers **3d–f** were 86, 80, and 85%, respectively. For the minor isomers **4d–f**, the enantiomeric excesses could be determined only for **4e** and **4f**: values of up to 78 and 52% were obtained, respectively.

These results (one major regioisomer, high enantioselectivities for the two regioisomers) could not be explained using the model shown in Scheme 1. Effectively, since now the π-allyl intermediate **D** bears different substituents at C-1 and C-3, the enantioselective step could not be the attack of the nucleophile on this π-allyl intermediate. A possible mechanism that could be invoked is the racemization of the intermediate π-allyl complex **D** via a nucleophilic substitution of PdL_n by another PdL_n molecule with inversion of configuration. Such a mechanism has been postulated by different groups.[40–44] Another mechanism is proposed in Scheme 2. We expect that the enantioselective step in this annulation is now the protonation of the carbene species **B**. Effectively protonation of this intermediate bearing a chiral ligand gives two diastereomeric σ-alkyl complexes **C′** and **C″**, in equilibrium with the corresponding diastereomeric π-allyl complexes **D′** and **D″**, respectively. As noticed previously, the π-σ-π sequence does not lead to epimerization at the allylic C-atoms. Attack of the nucleophile on one of the terminus of the π-allyl intermediate **D′** or **D″** gives (*R*)-3 or (*S*)-3, respectively. Attack on the other terminus will give the two enantiomers of compound **4**. It should be noted that this scheme is further complicated by *syn-anti* isomerization of these intermediates, which is not shown.

In conclusion, we have extended the asymmetric palladium-catalyzed annulation of benzene-1,2-diol with racemic secondary propargylic carbonates bearing two different substituents (≠H), both on the *sp* carbon and the carbon bearing the carbonate (or acetate) function. The high enantioselectivities observed could be explained by a highly stereospecific protonation of the intermediate palladium–carbene complex. Work is in progress in order to prove this hypothesis and to extend this asymmetric palladium-catalyzed cyclization reaction to other bis-nucleophiles as well as other propargylic carbonates.

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