Palladium-Catalyzed Allylic Substitution of Allyl Vinyl Carbonate

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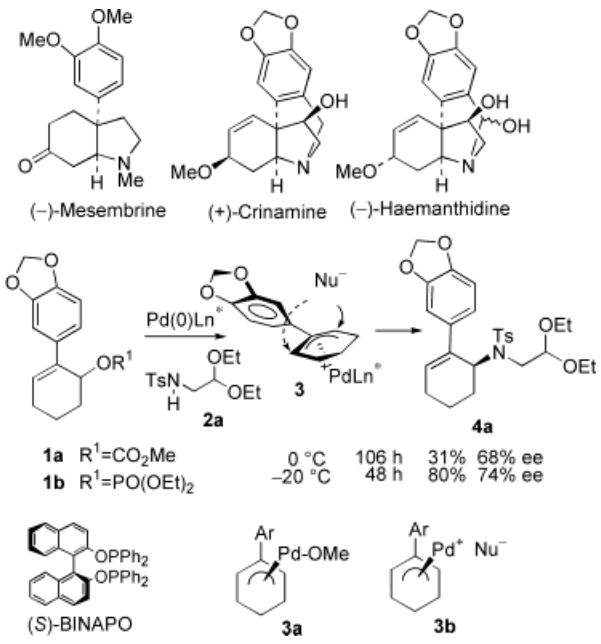
During the course of our study of the syntheses of (−)-mesembrine,[1] (+)-crinamine,[2] and (−)-haemanthidine,[2] we developed a novel method for the palladium-catalyzed asymmetric synthesis of 2-arylcyclohexenylamine.[2] The reaction rate of allyl methyl carbonate having a large group on the 2-position with a nucleophile in the presence of a palladium catalyst decreased remarkably compared with that of allyl methyl carbonate having no substituent on the 2-position. When the reaction of compound **1a** with tosyl amide **2a** in the presence of $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%) and (*S*)-BINAPO (5 mol%) in THF was carried out at 0 °C, the desired tosyl amide **4a** was obtained in 31% yield along with the starting material in 38% yield after 106 h (Scheme 1). Thus, for the asymmetric total syntheses of these alkaloids,[2] we used ethyl phosphate as the leaving group and obtained **4a** in 80% yield with 74% ee, which was recrystallized from MeOH to give **4a** with 99% ee.

Among the many leaving groups for palladium-catalyzed allylic substitutions,[3] the alkyl allyl carbonate[4] is unique in that a base is not required because methoxide anion is generated. Although phosphate is a good leaving group in palladium-catalyzed allylic substitutions, we searched for another effective leaving group. The palladium-catalyzed allylic substitution reaction proceeds via the formation of a π-allylpalladium complex. When an alkyl allyl carbonate is used for this reaction, complex **3a** is formed from **1a** and Pd(0), and then is converted to complex **3b** by abstraction of a proton from the nucleophile. Thus, the nucleophile can attack the π-allylpalladium complex even in the absence of a base.

If a vinyl carbonate **I** is used for this reaction, the oxo-π-allylpalladium complex **II c** would be formed. Complex **II c** is a strong base and would be stable.[5] It could be expected that the reaction rate might be accelerated. When a THF solution of allyl vinyl carbonate **5c** and tosyl amide **2a** was stirred in the presence of $Pd_2dba_3 \cdot CHCl_3$ and (*S*)-BINAPO at 0 °C, surprisingly, the desired product **6a** was obtained in 90% yield with 88% ee after only 2 h (Table 1, run 2). In the case of the methyl carbonate **5a**, compound **6a** was obtained in 30% yield after 330 h under the same reaction conditions, but the same enantiometric excess (ee) was observed (run 1). Even at −20 °C, the reaction took place and the desired product **6a** with 92% ee was obtained in 78% yield (run 3). The reactivity of isopropenyl carbonate **5d** was slightly lower than that of vinyl carbonate **5c** because of steric hindrance (runs 2 and 4). A similar result was also obtained when the vinyl carbonate **1c** was used for this reaction; the desired product **4a** was obtained in 69% yield after 2.5 h (run 7).



Scheme 1.

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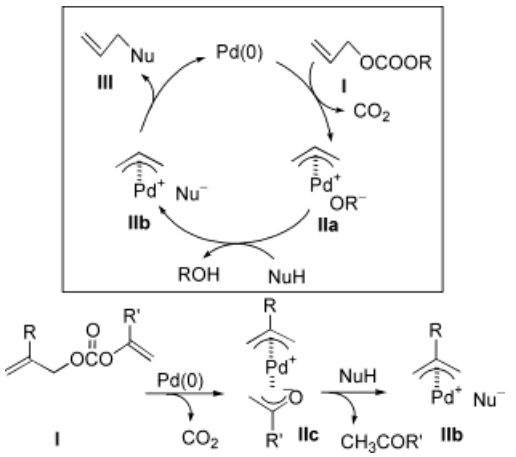
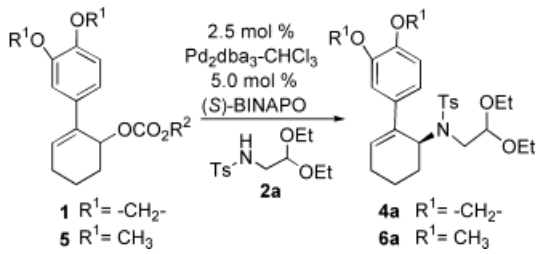


Scheme 2.

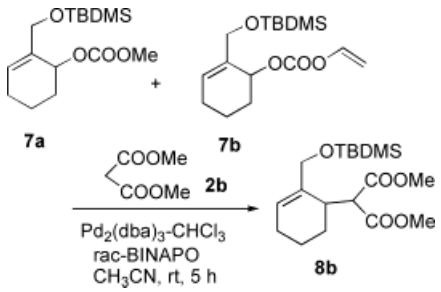


Scheme 3.

The reactivity of isopropenyl carbonate **1d** was lower than that of vinyl carbonate **1 c** (runs 8 and 9). In each case, the leaving group did not affect the ee of **4 a** or **6 a** while the reaction temperature did affect their ees.

Next, competitive reactions of allyl methyl carbonate **7 a** and allyl vinyl carbonate **7 b** were carried out. The reaction of 1.5 equiv. each of **7 a** and **7 b** with methyl malonate **2 b** in the presence of Pd_2dba_3-$CHCl_3$ (2.5 mol%) and *rac*-BINAPO (10 mol%) in CH_3CN at room temperature was monitored by gas chromatography (Scheme 4). The results are shown in Figure 1.

Apparently, vinyl carbonate **7 b** was consumed each time, but most of the methyl carbonate **7 a** remained unchanged. After 5 h, the desired **8 b** was obtained in 75% yield and methyl carbonate **7 a** was recovered in 86% yield based on the initial amount of **7 a** (Table 2, run 1).



Scheme 4.

Similarly, various nucleophiles **2** were used for this reaction. In each case, methyl carbonate **6 a** was recovered unchanged (Table 2, see experimental section).

Subsequently, the differences in reactivity between the methyl carbonate and the vinyl carbonate in the same molecule were examined. When a THF solution of compound **9**, **2 d**, a catalytic amount of Pd_2dba_3-$CHCl_3$ (2.5 mol%), and *rac*-BINAPO (10 mol%) was stirred at room temperature for 2 h, the amide **10** was obtained in 68% yield. In this reaction, methyl carbonate did not react with the nucleophile **2 d**. Treatment of **10** with $Pd(PPh_3)_4$ in AcOH[6] at 90 °C for 19 h gave the quinoline derivative **11** in 56% yield. Further studies are in progress.

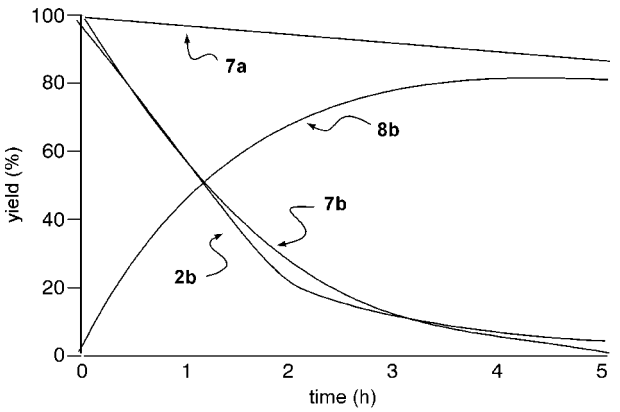


Fig. 1 Time-course of the allylic substitution of dimethyl malonate.

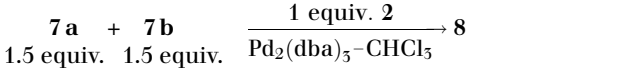
Table 1 Reaction of vinyl carbonates **1** or **5** with **2 a** in the presence of Pd(0)

Run	R^1	R^2	Substrate	Temp (°C)	Time (h)	Yield (%)	ee (%)	**1** or **5** recovered
1	Me	Me	**5 a**	0	330	30	88	31
2	Me	$CH=CH_2$	**5 c**	0	2	90	88	–
3	Me	$CH=CH_2$	**5 c**	–20	116	78	92	–
4	Me	$C(Me)=CH_2$	**5 d**	0	5	67	88	–
5	Me	$C(Me)=CH_2$	**5 d**	–20	145	50	91	19
6	$-CH_2-$	Me	**1 a**	0	106	31	68	38
7	$-CH_2-$	$CH=CH_2$	**1 c**	0	2.5	69	68	–
8	$-CH_2-$	$CH=CH_2$	**1 c**	–20	53	82	74	–
9	$-CH_2-$	$C(Me)=CH_2$	**1 d**	–20	245	39	74	30

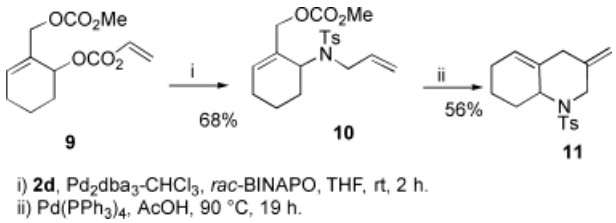
Table 2 Competitive reaction of **7a** and **7b**

Nucleophile[a]		Time (h)	Product (%)	Recovered[b] **7a** (%)	**7b** (%)
$CH_2(COOMe)_2$	**2b**	5	75	86	0
Bn–NH–CH_2–CH=CH_2	**2c**	9	81	94	39
Ts–NH–CH_2–CH=CH_2	**2d**[c]	6	85	95	35

[a] All reactions were carried out using 1.5 equiv. each of **7a** and **7b** and 1 equiv. of nucleophile **2** in the presence of Pd_2dba_3-$CHCl_3$ (2.5 mol%) and *rac*-BINAPO (10 mol%) in CH_3CN at room temperature.
[b] The recovered yield of **7a** or **7b** was calculated based on the initial amount of **7a** or **7b**.
[c] THF was used as solvent.



Scheme 5.



Scheme 6.

Experimental Section

Typical Procedure (Compound 8d)

To a solution of **2d** (63.4 mg, 0.3 mmol), $Pd_2(dba)_3$-$CHCl_3$ (7.8 mg, 7.5 μmol), and *rac*-BINAPO (19.6 mg, 0.03 mmol) in THF (0.5 mL) was added a solution of **7a** (135.3 mg, 0.45 mmol) and **7b** (140.7 mg, 0.45 mmol) in THF (4.0 mL) at room temperature. The solution was stirred at room temperature for 6 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 29/1 to 19/1 and then ethyl acetate), to give **8d** (111.3 mg, 85%), along with recovered **7a** (134 mg, 95%) and **7b** (47.2 mg, 35%).

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