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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6577–6581

Pd-catalyzed asymmetric allylic alkylation with nitromethane using a chiral diaminophosphine oxide: (S,R_P)-Ph-DIAPHOX. Enantioselective synthesis of (R)-preclamol and (R)-baclofen

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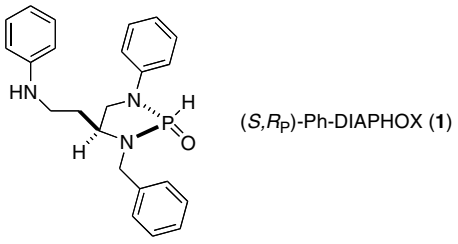
Received 15 June 2006; revised 1 July 2006; accepted 6 July 2006
Available online 1 August 2006

Abstract—A Pd-catalyzed asymmetric allylic alkylation with nitromethane using an aspartic acid-derived P-chirogenic diaminophosphine oxide [(S,R_P)-Ph-DIAPHOX] is described. This method was successfully applied to enantioselective synthesis of (R)-preclamol and (R)-baclofen.

Pd-catalyzed asymmetric allylic alkylation is one of the most useful synthetic methods for constructing an allylic asymmetric carbon center. Various stabilized carbon nucleophiles, as well as nitrogen, oxygen, and sulfur nucleophiles, are applicable to this reaction process.[1] Nitronate nucleophiles are versatile reagents in organic synthesis, because the reaction adducts can be converted into a variety of synthetically useful compounds.[2] Therefore, several catalytic asymmetric C–C bond-forming reactions using nitronate nucleophiles have been developed.[3,4] There are, however, only a few reports of Pd-catalyzed asymmetric allylic alkylation using nitronate nucleophiles, perhaps due to multiple alkylations and the formation of side products.[5] Thus, the development of an efficient catalyst system for this type of asymmetric reaction is still necessary. Herein, we report a Pd-catalyzed asymmetric allylic alkylation with nitromethane using an aspartic acid-derived P-chirogenic diaminophosphine oxide: (S,R_P)-Ph-DIAPHOX **1** (Fig. 1). Asymmetric synthesis of biologically active compounds using the developed method is also described.

We recently reported Pd-catalyzed asymmetric allylic substitution reactions using pentavalent chiral phosphorus preligands: aspartic acid-derived P-chirogenic diaminophosphine oxides (DIAPHOXs).[6,7] We first examined



(S,R_P)-Ph-DIAPHOX (**1**)

Figure 1.

catalytic asymmetric allylic alkylation of 1,3-diphenylallyl ethyl carbonate **2a** with nitromethane using similar conditions to those of asymmetric allylic alkylation with dimethyl malonate, [(η^3-$C_3H_5PdCl)_2$ (2.5 mol %), **1** (10 mol %), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (3 equiv), CH_3NO_2 (3 equiv), CH_2Cl_2, 24 h, rt].[6b] Unfortunately, the desired product **3a** was obtained in only 5% yield and 66% ee, accompanied by the formation of **4** and some other side products. Although the chemical yield was low, there was a significant improvement in the enantioselectivity when nitromethane was used as the solvent (4 h, 26% yield, 96% ee). Increasing the reaction time, however, resulted in decreased chemical yield and enantioselectivity (12 h, 12% yield, 92% ee) (Table 1, entries 1 and 2). Silyl nitronates are efficiently generated from nitroalkanes in the presence of BSA and amine.[8] Therefore, the addition of amine to the reaction was examined in detail (Table 1, entries 3–8). Catalytic amounts of amine increased the chemical yield. *N*,*N*-Diisopropylethylamine was the best amine for reaction

Keywords: Asymmetric allylic amination; Catalysis; Diaminophosphine oxide; Nitromethane; Palladium.
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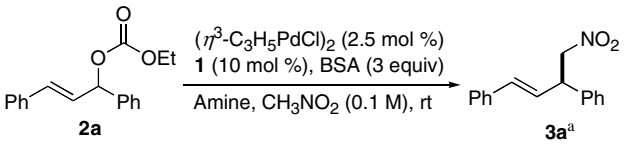
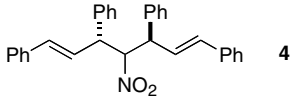
doi:10.1016/j.tetlet.2006.07.029

Table 1. Pd-catalyzed asymmetric allylic alkylation of **2a** with nitromethane



Entry	Amine (mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	—	4	26	96
2	—	12	12	92
3	*N*-Methylmorpholine (25)	8	69	97
4	DABCO[d] (25)	2	62	97
5	PMP[d] (25)	3	77	97
6	TMP[d] (25)	4	86	97
7	*i*-Pr_2NEt (25)	5	86 (6)[e]	97
8	*i*-Pr_2NEt (50)	3.5	88 (3)[e]	98



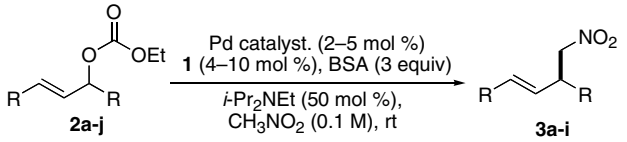
[a] The absolute configuration was determined to be *R*, by comparison with the reported optical rotation after converting into *N*-benzyl-3-phenylpiperidine. See Supplementary data for details.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] DABCO: 1,4-diazabicyclo[2,2,2]octane; PMP: 1,2,2,6,6-pentamethylpiperidine; TMP: 2,2,6,6-tetramethylpiperidine.
[e] Isolated yield of **4**.

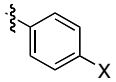
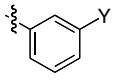
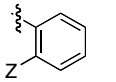
promotion, and 50 mol % of amine produced the desired product in 88% yield and in 98% ee.[9]

The scope and limitation of different substrates were further examined under optimized reaction conditions (Table 2). When 2–5 mol % of Pd catalyst and 4–10 mol % of **1** were used, asymmetric allylic alkylation of 1,3-diaryl allyl carbonates with an electron-donating substituent and an electron-withdrawing substituent on the aromatic rings, proceeded at room temperature to afford the corresponding products in good yield with excellent enantioselectivity.[10] No reaction, however, occurred when 1,3-dialkyl allyl carbonates were utilized as the substrate.

Thus, the present catalytic asymmetric reaction had broad generality for 1,3-diaryl-substituted allyl carbonates. To demonstrate the synthetic utility, we applied the developed method to the catalytic asymmetric synthesis of two biologically active compounds: (*R*)-

Table 2. Pd-catalyzed asymmetric allylic alkylation of 1,3-diaryl allyl carbonates with nitromethane



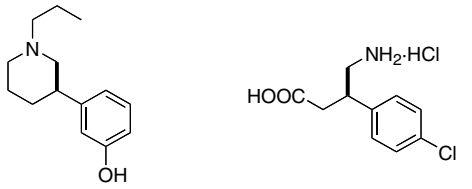
Entry	R			Time (h)	Yield[a] (%)	ee[b] (%)
1[c]		X = H	**2a**	3.5	88	98 (*R*)
2[d]		X = H	**2a**	11	78	97 (*R*)
3[c]		X = CH_3	**2b**	4	87	92
4[c]		X = Cl	**2c**	3	92	97 (*R*)
5[c]		X = F	**2d**	3	91	97
6[c]		X = OMe	**2e**	3.5	91	98 (*R*)
7[c]		Y = F	**2f**	3	87	96
8[c]		Z = CH_3	**2g**	28	78	95
9[c]		Z = F	**2h**	4	86	98
10[c]	R = 2-Naphthyl		**2i**	4	83	94
11[c]	R = CH_2CH_2Ph		**2j**	24	No reaction	

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] 5 mol % of the Pd catalyst and 10 mol % of **1** were used.
[d] 2 mol % of the Pd catalyst and 4 mol % of **1** were used.

preclamol (**5**) and (*R*)-baclofen hydrochloride (**6**) (Fig. 2).

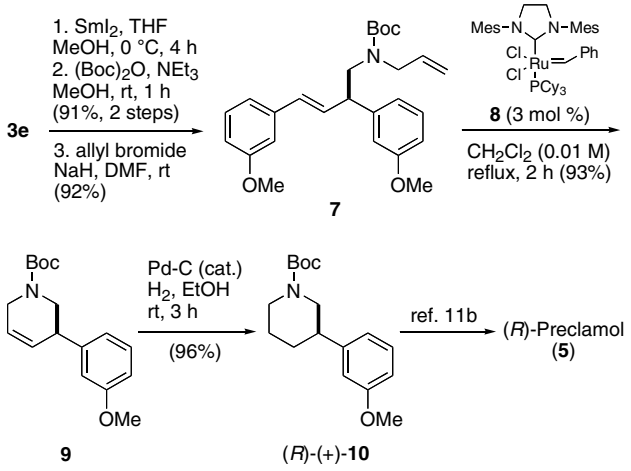
(*R*)-Preclamol [(+)-3-PPP] (**5**), a selective dopamine D_2 autoreceptor agonist, has been extensively studied both as a pharmacological tool to investigate dopaminergic mechanisms, and from a therapeutic point of view.[11,12] Despite the interesting biological activities of preclamol and structurally related 3-aryl piperidines, there are few reports of the enantioselective synthesis of **5**. This might be due to the difficulty in synthesizing 3-aryl piperidines as optically active compounds.[13,14] The synthetic route of catalytic asymmetric synthesis of (*R*)-preclamol is outlined in Scheme 1. Our synthesis started with **3e**, which was obtained in 98% ee using the Pd–(S,R_P)-Ph-DIAPHOX catalyst system (Table 2, entry 6). Reduction of the nitro group with SmI_2,[15] followed by protection of the resulting amine with a Boc group and allylation, gave **7**. The enantiomeric excess of **7** was determined by HPLC analysis[16] (98% ee), and the reduction processes did not decrease enantiomeric excess. Subsequently, **7** was treated with 3 mol % of the Grubbs catalyst (**8**)[17] to afford the corresponding cyclic product **9**, which was successfully transformed into a chiral piperidine intermediate (*R*)-(+)-**10** ($[\alpha]_D^{22}$ +49.1 (*c* 1.36, $CHCl_3$), lit.[13b] $[\alpha]_D^{22}$ −50.7 (*c* 0.8, $CHCl_3$), (*S*)-isomer). The known intermediate **10** can be converted into (*R*)-preclamol (**5**) using the reported procedure.[11b]

(*R*)-Baclofen hydrochloride (**6**) is a $GABA_B$ receptor agonist, that is widely utilized as an antispastic agent. Although baclofen is used therapeutically in a racemic

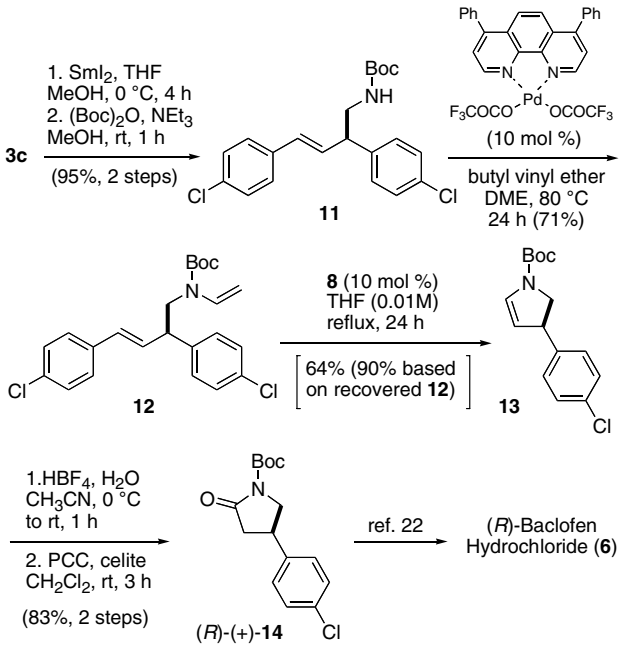


(*R*)-Preclamol [(+)-3-PPP] (**5**) (*R*)-Baclofen hydrochloride (**6**)

Figure 2.



Scheme 1. Enantioselective synthesis of (*R*)-preclamol.



Scheme 2. Enantioselective synthesis of (*R*)-baclofen·HCl.

form, the biological activity resides exclusively in its (*R*)-enantiomer.[18] Therefore, there have been several studies on the catalytic asymmetric synthesis of (*R*)-baclofen.[19] Enantioselective synthesis of (*R*)-baclofen using Pd-catalyzed asymmetric allylic alkylation with nitromethane is outlined in Scheme 2. First, **3c** (Table 2, entry 4) was transformed into **11** using the same method as in the case of **3e**. After formation of enamide **12** using Pd-catalyzed vinyl transfer reaction,[20] ring-closing metathesis was performed in the presence of **8**, affording cyclic compound **13**.[21] Introduction of a hydroxyl group, followed by oxidation of the resulting crude lactamol with PCC gave the known lactam (*R*)-(+)-**14** ($[\alpha]_D^{23}$ +3.4 (*c* 0.83, $CHCl_3$), lit.[22a] $[\alpha]_D^{20}$ +4.5 (*c* 0.2, $CHCl_3$), (*R*)-isomer). The obtained lactam could be transformed into (*R*)-baclofen hydrochloride (**6**) ($[\alpha]_D^{23}$ −1.5 (*c* 0.2, H_2O), lit.[19a] $[\alpha]_D^{23}$ −1.5 (*c* 1.0, H_2O)) using the reported procedure.[22]

In conclusion, we achieved a Pd-catalyzed asymmetric allylic alkylation of 1,3-diaryl-substituted allyl carbonates with nitromethane using a Pd–DIAPHOX catalyst system, which afforded the corresponding products in good yield and in up to 98% ee. In addition, the developed method was successfully applied to catalytic asymmetric synthesis of two biologically active compounds: (*R*)-preclamol and (*R*)-baclofen. Further investigations to develop a more atom economic C–C bond-forming reaction using catalytic asymmetric allylic alkylation with nitroalkanes are in progress.

Acknowledgments

This work was supported in part by a Grant-in Aid for Encouragement of Young Scientists (A) from the Ministry of Education, Culture, Sports, Science, and

Technology, Japan, and the Banyu Award in Synthetic Organic Chemistry, Japan.

Supplementary data

General procedure of Pd-catalyzed asymmetric allylic alkylation, other experimental procedures, and compound characterization of all new compounds, can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.029.

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21. In the ring-closing metathesis, olefin isomerization of **13** occurred using other solvents such as dichloroethane and toluene, affording a 3-pyrroline derivative as a byproduct.

(Representative data: Dichloromethane, reflux, 24 h: trace yield of **13**. Dichloroethane, reflux, 24 h: 21% of **13**, 29% of **12**, and 48% of the byproduct. Toluene, reflux, 24 h: 52% of **13**, 12% of **12**, and 35% of the byproduct.) This side reaction was relatively depressed using THF as the solvent (64% of **13**, 29% of **12**, and trace yield of the byproduct).

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