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Enantioselective Domino Heck-Allylic Amination Reactions

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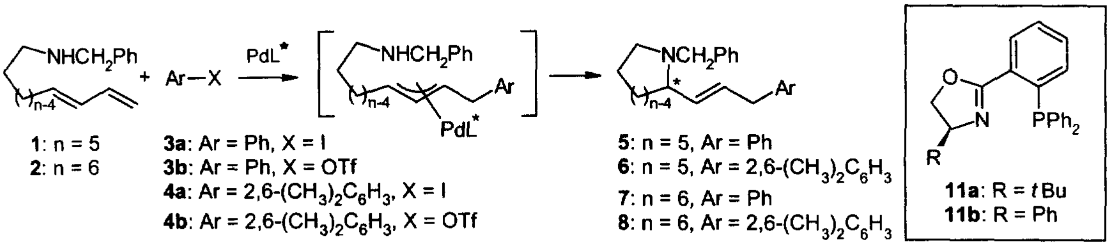
***Abstract*:** Heck induced two-component domino reactions of α,ω-amino-1,3-dienes are described. In enantioselective variants of these reactions enantiomeric excess of up to 80 % was achieved using Pd complexes of enantiomerically pure chiral phosphino-oxazolines as catalysts. © 1999 Elsevier Science Ltd. All rights reserved.

The Heck reaction[1] is a highly valuable reaction in organic synthesis. It was early recognized[1] that Heck reactions of mixtures of 1,2- or 1,3-dienes with nucleophiles allow several bonds to be constructed in a domino reaction mode. More recently interesting intramolecular variants were developed by the Larock[2] and the Shibasaki[3] groups, including enantioselective reactions and applications in natural products synthesis[4]. In the course of our work on enantioselective allylic substitutions we became interested in the Heck reaction with 1,3-dienes, as a π-allyl complex is formed as an intermediate which can react with a nucleophile (Scheme 1). We here report studies of a two-component domino reaction with α,ω-amino-1,3-dienes. Phosphino-oxazolines, which have given excellent results in allylic substitution[5] as well as in Heck reactions[6], were used as chiral ligands.



Scheme 1

The reactions corresponding to Scheme 1 were initially carried out with achiral ligands in order to establish optimal reaction conditions. In a typical run, a suspension of $Pd(OAc)_2$, ligand, base, additive, aminodiene and iodoarene in DMF was heated under an inert atmosphere at 100 °C for 36 h. Typically an orange solution was formed. When the reaction was run with Ag_3PO_4 as additive a metal mirror was deposited on the wall of the flask. The results are given in Table 1. Amine **1** could be reacted with iodobenzene (**3a**) only in the absence of a phosphine; as additive $n\mathrm{Bu_4NCl}$ ("neutral" pathway) was superior to Ag_3PO_4 ("cationic" pathway) (entries 1, 2). The reaction was also possible with the bulky iodide **4a**, but with a slightly lower yield (entry 3). In contrast, amine **2** gave excellent yields with or without a ligand (entries 4-9). As ligand, PPh_3 was superior to $AsPh_3$. The reaction with the bulky iodide **4a** gave a yield of 66 % (entry 10).

The enantioselective reactions with amine **2** were carried out with phosphino-oxazolines[7] (PHOX) and (*R*)-BINAP as ligands. In contrast to reports by Overman[8] and by Shibasaki[4], no enantioselection was obtained when $n\mathrm{Bu_4NCl}$ was used as additive (entry 11). With silver phosphate as additive the ratio of ligand:Pd was of crucial importance; with a ratio of 1.1:1 the enantiomeric excess was only 24 %, with a ratio of 2:1 a considerable improvement to 64 % ee was found for the reaction of iodide **3a** (entries 12-14). Similar results were obtained with iodide **4a** and ligands **11a** and *ent*-**11b** (entries 15, 16). Triflates often give good results in enantioselective Heck reactions[4,6,8]. Compared to the iodides, the triflates **3b** and **4b** indeed gave higher enantioselectivities; however, a reaction time of 10 d was required (entries 19-22) and yields were slightly lower than in the reactions with the iodoarenes. The use of (*R*)-BINAP as ligand generally gave low levels of enantioselectivity ($\leq$ 12 % ee, entries 17, 18).

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Table 1. Heck reactions with amino-1,3-dienes **1** and **2** according to Scheme 1.[a]

Entry	Amine	Ar-X	Ligand	Additive[b]	Base[c]	t [d]	*E* : *Z*[d]	Yield [%][e]	Ee [%] (Conf.)[f]
1	**1**	**3a**	-	$n\mathrm{Bu_4NCl}$	Na_2CO_3	1.5	n. d.	66	
2	**1**	**3a**	-	Ag_3PO_4	-	1.5	n. d.	34	
3	**1**	**4a**	-	$n\mathrm{Bu_4NCl}$	Na_2CO_3	1.5	n. d.	59	
4	**2**	**3a**	-	$n\mathrm{Bu_4NCl}$	Na_2CO_3	1.5	99 : 1	81	
5	**2**	**3a**	-	Ag_3PO_4	-	1.5	97 : 3	67	
6	**2**	**3a**	PPh_3	$n\mathrm{Bu_4NCl}$	Na_2CO_3	1.5	98 : 2	95	
7	**2**	**3a**	PPh_3	Ag_3PO_4	-	1.5	97 : 3	73	
8	**2**	**3a**	$AsPh_3$	$n\mathrm{Bu_4NCl}$	Na_2CO_3	1.5	98 : 2	86	
9	**2**	**3a**	$AsPh_3$	Ag_3PO_4	-	1.5	97 : 3	59	
10	**2**	**4a**	PPh_3	$n\mathrm{Bu_4NCl}$	Na_2CO_3	1.5	98 : 2	66	
11	**2**	**3a**	**11a**[g]	$n\mathrm{Bu_4NCl}$	Na_2CO_3	2	n. d.	77	1 (*S*)
12	**2**	**3a**	**11a**[g]	Ag_3PO_4	-	2	n. d.	55	24 (*S*)
13	**2**	**3a**	**11a**	Ag_3PO_4	-	2	n. d.	54	64 (*S*)
14	**2**	**3a**	*ent*-**11b**	Ag_3PO_4	-	2	n. d.	49	65 (*R*)
15	**2**	**4a**	**11a**	Ag_3PO_4	-	2	n. d.	65	62 (*S*)
16	**2**	**4a**	*ent*-**11b**	Ag_3PO_4	-	2	n. d.	61	67 (*R*)
17	**2**	**3a**	(*R*)-BINAP	Ag_3PO_4	-	2	n. d.	88	12 (*S*)
18	**2**	**4a**	(*R*)-BINAP	Ag_3PO_4	-	2	n. d.	66	12 (*S*)
19	**2**	**3b**	**11a**	-	-	10	n. d.	61	70 (*S*)
20	**2**	**3b**	*ent*-**11b**	-	-	10	n. d.	43	59 (*R*)
21	**2**	**4b**	**11a**	-	-	10	n. d.	54	77 (*S*)
22	**2**	**4b**	*ent*-**11b**	-	-	10	n. d.	47	80 (*R*)

a) General procedure: under an inert atmosphere, a mixture of 1 mmol of diene, 1 mmol of iodoarene, 0.05 mmol of $Pd(OAc)_2$, 0.1 mmol of ligand and 5 ml of DMF was heated at 100 °C ; with the triflates 0.03 mmol of $Pd(OAc)_2$ and 0.06 mmol of ligand were used. Aqueous Na_2CO_3 was then added and the mixture was extracted with diethyl ether. The ether layer was dried and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation (180 °C/0.01 mbar). b) 1 mmol of $n\mathrm{Bu_4NCl}$ or 0.34 mmol of Ag_3PO_4 were used. c) 3.5 mmol of Na_2CO_3 were present in the reaction mixture. d) *E/Z* ratios and purities were determined by GC/MS on a HP 5970/590a instrument with a HP 1 column (crosslinked methyl silicon, 25 m x 0.2 mm, helium). e) Yield of isolated product. f) Enantiomeric purities were determined by HPLC on a DAICEL OJ column (length 25 cm and 5 cm precolumn), eluent *n*-hexane/EtOH 200:1, in combination with a UV detector (210 nm); **7**: flow 0.5 ml/min, $t_R[(R)\text{-}\mathbf{7}] = 22.3$ min, $t_R[(S)\text{-}\mathbf{7}] = 36.6$ min. **8**: flow 0.4 ml/min, $t_R[(R)\text{-}\mathbf{8}] = 18.4$ min, $t_R[(S)\text{-}\mathbf{8}] = 22.3$ min. The absolute configuration of **7** was determined by preparation from nonracemic pipecolic acid and comparison by HPLC on the Daicel OJ column. The absolute configuration of **8** is assumed by analogy. g) Ratio of Pd:ligand = 1:1.1.

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