ChemComm

Enantioselective synthesis of tetrahydroisoquinolines and benzazepines by silane terminated Heck reactions with the chiral ligands (+)-TMBTP and (*R*)-BITIANP

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Received (in Cambridge, UK) 9th December 1999, Accepted 10th February 2000

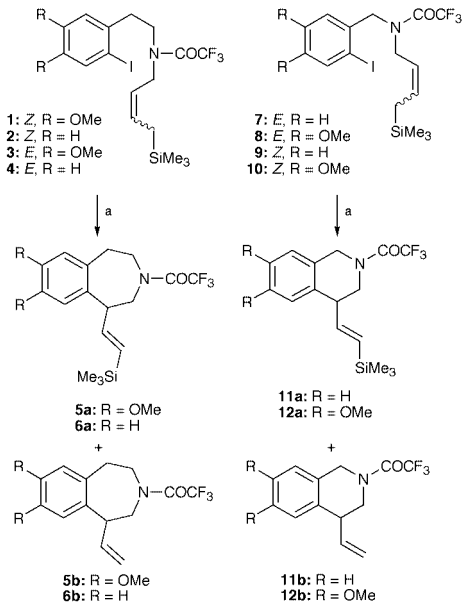
The intramolecular Heck reaction of the iodoaryl compound 1 with a (*Z*)-allyl silane moiety in the presence of the chiral ligand (+)-TMBTP 13 leads to the benzazepine 5b with 92% ee, whereas 3 with an (*E*)-allyl silane moiety in the presence of the chiral ligand (*R*)-BITIANP 14 gives 5a with 91% ee; in a similar way, 9 and 10 were transformed in the presence of 13 into the tetrahydroisoquinolines 11b and 12b with 86 and 84% ee, respectively.

The Heck reaction,[1] the Pd(0) catalyzed coupling of an aryl or alkenyl halide or triflate with an alkene, is nowadays one of the most important C–C bond forming transformations and has been used in numerous syntheses of natural products;[2] extensive work has also been done in the enantioselective series.[3] Here, we describe the enantioselective intramolecular silane terminated Heck reaction[3g–i] of the substrates **1**–**4** and **7**–**10** with the novel chiral ligands (+)-4,4′-bis(diphenylphosphino)-2,2′,5,5′-tetramethyl-3,3′-bithiophene [(+)-TMBTP] **13**[4a] and (*R*)-(+)-2,2′-bis(diphenylphosphino)-3,3′-bibenzo[*b*]thiophene [(*R*)-BITIANP] **14**[4b] as well as, for comparison, also with the well known and widely used ligands (*R*)-MeO-BIPHEP **15**[5] and (*R*)-BINAP **16**,[6] to give the substituted benzazepines **5a**/**b** and **6a**/**b** and the tetrahydroisoquinolines **11a**/**b** and **12a**/**b** (Scheme 1). In addition, we have used phosphinooxazolines[3c,e] as chiral ligands, however, in our systems these ligands show low reactivity.

We have recently shown that one of the main disadvantages of the Heck reaction, namely the low selectivity in the elimination of the L_nPd–H species to form the double bond as the last step in the catalytic cycle, can be overcome by using allyl silanes as terminating alkenes.[3g–i] This allowed the selective formation of tertiary stereogenic centers starting from acyclic alkenes for the first time. However, the use of this procedure for the synthesis of chiral heterocyclic compounds such as benzazepines and tetrahydroisoquinolines with **16** as ligand was rather disappointing owing to its low enantioselectivity.[3i] By contrast, employing the novel chiral ligands **13** and **14** (Scheme 2) we are now able to synthesize these heterocycles with up to 92% ee.

13 had not been used successfully previously for enantioselective transformations, whereas **14** was employed with great success in the hydrogenation of C–C and C–O double bonds[4b] and in intermolecular Heck reactions.[3a] In our investigations we used (*E*)- and (*Z*)-allyl silanes as substrates, which not only gave different enantioselectivities using the various ligands, but also allowed us to control the formation of the different side chains in the products, namely a vinyl or a trimethylsilylvinyl group.

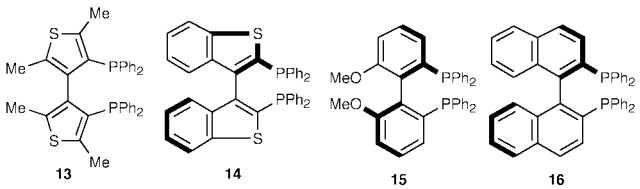
The selective formation of the (*Z*)-allyl silanes **1**, **2** and **9**, **10**, respectively, was performed by a Ni catalyzed hydrogenation of the corresponding propargyl silanes **17**–**20**. For the synthesis of the (*E*)-compounds **3**, **4** and **7**, **8**, respectively, the propargyl amine **21** was reduced with $LiAlH_4$, the obtained allyl amine **22** alkylated with **23**, **24**, **25** or **26** and finally treated with trifluoroacetyl anhydride (Scheme 3).



Scheme 1 Syntheses of benzazepines **5** and **6** and tetrahydroisoquinolines **11** and **12** by silane terminated enantioselective Heck reaction. *Reagents* a, $Pd_2dba_3{\cdot}CHCl_3$, ligand, Ag_3PO_4 (1.1 eq.), DMF.

The Heck reaction of the (*Z*)-allyl silane **1** in the presence of triphenylphosphane gave nearly exclusively the benzazepine **5b** with a vinyl side chain (Table 1, entry 1); using the chiral ligands **15** (entry 2) and **14** (entry 3), **5b** again was the main product, however, the enantioselectivity was < 50% ee; with (*S*)-BINAP *ent*-**16** (entry 4), **5b** was formed with 64% ee. In contrast, using **13**, the product **5b** could be obtained in good yield, with complete regioselectivity and 92% ee (entry 5). Similar results were found with the (*Z*)-allyl silane **2**, but here the highest ee value using **13** as chiral ligand was only 70% ee (entry 9). This could probably be ascribed to the lower ligand Pd ratio, which was necessary owing to the low reactivity using higher ratios. This, however, is a general problem in enantioselective Heck reactions.

Employing the (*E*)-allyl silane **3** again an excellent enantioselectivity of 91% ee was obtained (entry 10). For the first time in the enantioselective silane terminated Heck reation, **5a** with a



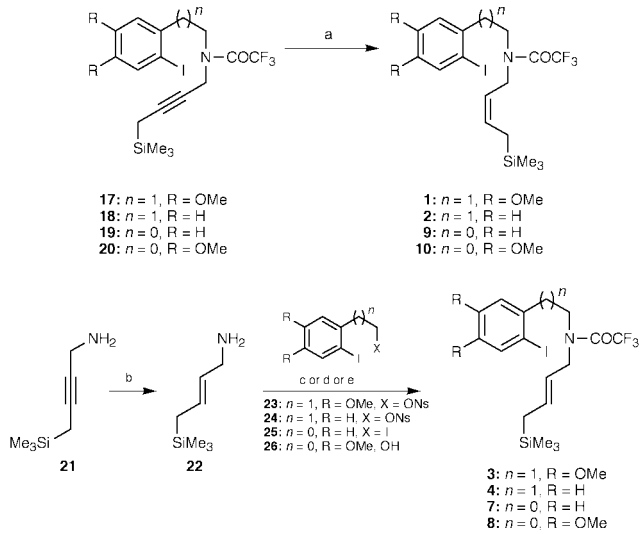
Scheme 2 Ligands for the enantioselective Heck reaction: (+)-TMBTP **13**, (*R*)-BITIANP **14**, (*R*)-MeO–BIPHEP **15** and (*R*)-BINAP **16**.

DOI: 10.1039/a909689b

Table 1 Enantioselective silane terminated Heck reactions of the allyl silanes **1**–**4** and **7**–**10** to give the benzazepines **5** and **6** and the tetrahydroisoquinolines **11** and **12**

Entry	Substrate (Config.)	R	Product	Pd Catalyst (mol%)	Ligand (mol%)	*t*/h	*T*/°C	Yield (%)		Ee[a] (%)	
								a	**b**	**a**	**b**
1	**1** (*Z*)	OMe	**5**	5[b]	PPh_3 (10)[c]	6	80	4	70	—	—
2	**1** (*Z*)	OMe	**5**	3	**15** (7)	65	80	15	42	< 5 (*S*)	< 25 (*R*)
3	**1** (*Z*)	OMe	**5**	3	**14** (7)	19	80	2	42	—[d]	< 20 (*R*)
4	**1** (*Z*)	OMe	**5**	3	*ent*-**16** (7)	40	80	7	72	< 18 (*R*)	64 (*S*)
5	**1** (*Z*)	OMe	**5**	1.5	**13** (15)	68	80	—	71	—	92 (*S*)
6	**2** (*Z*)	H	**6**	3	**16** (15)	27	90	4	73	—[d]	48 (*R*)
7	**2** (*Z*)	H	**6**	3	**15** (15)	168	90	6	49	—[d]	28 (*R*)
8	**2** (*Z*)	H	**6**	3	**14** (15)	24	90	—	72	—	42 (*R*)
9	**2** (*Z*)	H	**6**	3	**13** (15)	27	90	6	71	—[d]	70 (*S*)
10	**3** (*E*)	OMe	**5**	1.5	**14** (10)	24	80	66	21	91 (*S*)	≈ 60 (*S*)
11	**3** (*E*)	OMe	**5**	3	**13** (7)	45	80	57	33	8 (*R*)	≈ 45 (*S*)
12	**4** (*E*)	H	**6**	1.5	**14** (15)	26	80	42	41	86 (*S*)	22 (*S*)
13	**4** (*E*)	H	**6**	1.5	**13** (15)	16	80	25	43	12 (*R*)	64 (*R*)
14	**7** (*E*)	H	**11**	3	**16** (7)	20	80	40	32	2 (*R*)	67 (*R*)
15	**7** (*E*)	H	**11**	3	**14** (7)	14	70	14	51	0	50 (*R*)
16	**7** (*E*)	H	**11**	3	**13** (7)	46	80	38	35	< 5 (*R*)	< 5 (*S*)
17	**8** (*E*)	OMe	**12**	3	**14** (7)	48	80	42	24	30 (*R*)	34 (*R*)
18	**8** (*E*)	OMe	**12**	3	**13** (10)	48	80	9	56	76 (*R*)	56 (*R*)
19	**9** (*Z*)	H	**11**	1.5	**13** (10)	65	80	—	80	—	84 (*S*)
20	**9** (*Z*)	H	**11**	1.5	**13** (15)	63	90	—	61	—	86 (*S*)
21	**10** (*Z*)	OMe	**12**	3	**14** (7)	20	80	6	80	< 10 (*R*)	16 (*S*)
22	**10** (*Z*)	OMe	**12**	1	**13** (20)	64	80	—	73	—	84 (*S*)

[a] Determined by chiral HPLC (Baker CHIRALCEL OD-R). [b] $Pd(OAc)_2$ was used instead of $Pd_2dba_3{\cdot}CHCl_3$. [c] KOAc (4 eq.) and NPr_4Br (1 eq.) were used instead of Ag_3PO_4. [d] Not determined.



Scheme 3 Syntheses of the (*E*)- and (*Z*)-allyl silane precursors. *Reagents and conditions*: a, H_2, $Ni(OAc)_2$, $NaBH_4$, ethylenediamine, EtOH; **1**: 65%, **2**: 90%, **9**: 88%, **10**: 60%; b, $LiAlH_4$, THF, heat; 50%; c, 1. Pr^i_2NEt, MeCN–MeOH, 50 °C; 2. $(CF_3CO)_2O$, NEt_3, THF, 0 °C → r.t.; **3**: 42%, **4**: 40%; d, 1. $(CF_3CO)_2O$, NEt_3, THF, 0 °C → r.t.; 2. NaH, DMF, 0 °C → r.t.; **7**: 75%; e, 1. $(CF_3CO)_2O$, NEt_3, THF, 0 °C → r.t.; 2. MsCl, NEt_3, CH_2Cl_2, 0 °C → r.t.; NaH, DMF, 0 °C → r.t.; **8**: 39%.

trimethylsilylvinyl side chain is the main product, with **14** as the best ligand; thus, **13** gave **5a** with only 8% ee (entry 11). Interestingly, in the Heck reaction of the (*Z*)- and the (*E*)-allyl silanes with **14** and **13** the opposite enantiomers of **6b** were formed, whereas in the presence of **16** the double bond configuration had virtually no influence on the facial selectivity.

Astoundingly, the Heck reactions of the (*E*)-allyl silanes **7** and **8** were only marginally successful. Here the regio- and enantio-selectivity were rather low. However, the (*Z*)-compounds **9** and **10** gave much better results. Using **13** as chiral ligand, the vinyl substituted tetrahydroisoquinolines **11b** and **12b** were obtained with high enantioselectivities of 86 and 84% ee, and complete regioselectivity (entries 20 and 22).

These results together with the investigations of intermolecular Heck reactions[3a] clearly show that the novel ligands **13** and **14** are superior to known ligands, at least in the investigated transformations.

This work has been supported by the Fonds der Chemischen Industrie. We thank the Degussa AG for a generous gift of precious metals and the Hoffmann-La Roche AG for ligand **15**. We are also greatly indebted to Dr S. Console (Chemi SpA) for providing the new ligands.

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Communication a909689b