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Steric hindrance versus asymmetric induction: new PN-ligands for carbon–carbon coupling reactions

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Abstract

Two new aminophosphine ligands **4** and **5** with increased steric interaction in proximity to the N-coordination site have been prepared. Their asymmetric induction in five model reactions was tested and compared to results obtained with the parent ligand **2**. This resulted in improved enantioselectivity in only one case, from 5 to 68% e.e., while in all the other cases the more crowded ligands exhibited significantly lower reactivity accompanied by decreased enantioselectivity. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

A high degree of structural complementarity of chiral auxiliary and substrate is usually assumed to be a *condicio sine qua non* for obtaining high enantiodifferentiation in asymmetric catalysis. In order to tune steric and electronic properties of the ligands with respect to a given substrate and reaction mechanism, often a stepwise — frequently empirical — modification of the ligand structure is required until an optimal fit is found.[1] The availability of groups of ligands with different steric interactions near to potential complexation sites is therefore highly desirable not only for their practical application but also for mechanistic studies.

We and others recently reported the synthesis of aminophosphine ligands like **1**–**3** containing a chiral dihydroazepine moiety (Scheme 1).[2] Although these ligands proved to be highly efficient in the Pd-catalyzed asymmetric allylic substitution of 1,3-diphenylpropenyl acetate, much poorer results were obtained with alkyl substituted substrates, for the allylation of methyl N-diphenylmethyleneglycinate and for the cross coupling of vinyl bromide and 2-phenethyl magnesium chloride.[2b,c] Since the latter ones generate the new asymmetric center in the prochiral nucleophile (with or without prior coordination at the metal center) which attacks a π-allyl or σ-vinyl complex, respectively, appropriate chiral interactions near to the nitrogen coordination site were expected to improve the enantioselectivity.[3] One possibility

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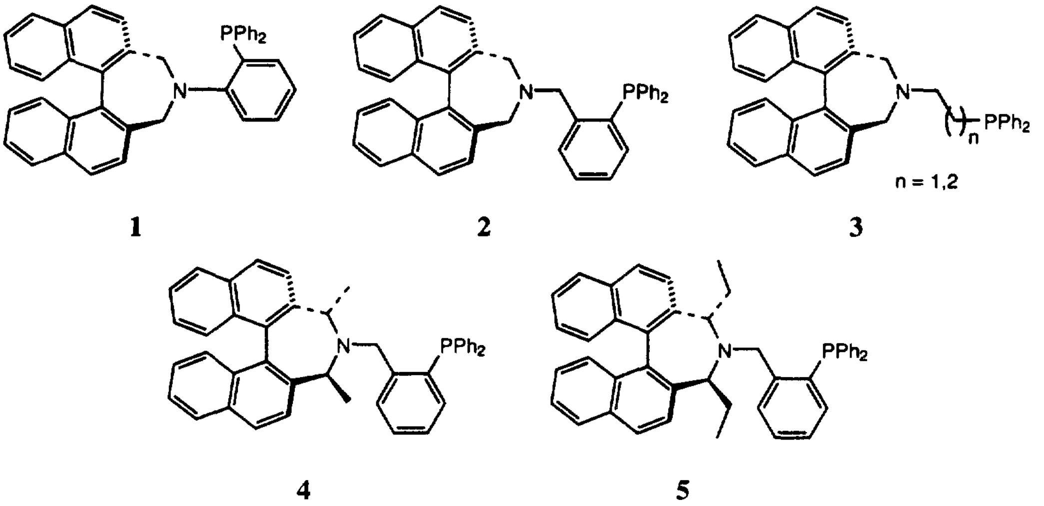
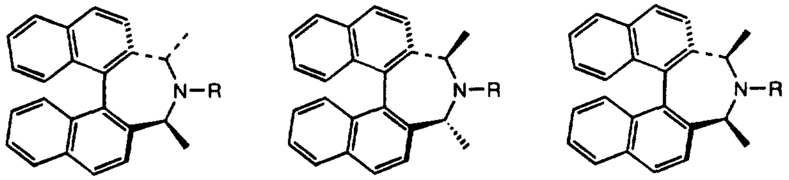
to achieve stepwise structural modification was the introduction of substituents in position 3 and 5 of the dihydroazepine fragment.



Scheme 1.

If considering ligand structures such as **4** and **5**, the introduction of two additional stereogenic centers in the course of a twofold benzylic substitution will give access to three chiral diastereomers (Scheme 2), two with C_2 symmetry and one with C_1 symmetry. Inspection of a Dreiding model revealed that only the diastereomer (a) with both substituents in a pseudo-axial position will give a pronounced steric interaction in the proximity of the nitrogen coordination. Therefore the synthesis of this stereoisomer has been exclusively attempted.



(a) C_2 symmetry

(b) C_2 symmetry

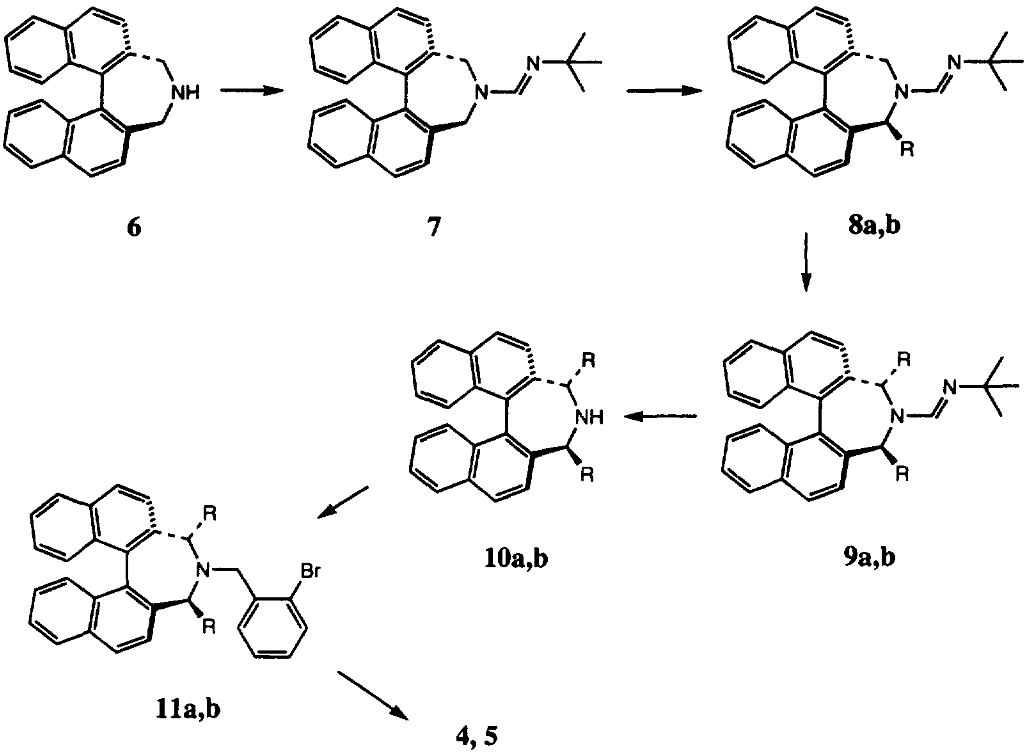
(c) C_1 symmetry

Scheme 2.

2. Results and discussion

We set out to synthesize the dimethyl and diethyl substituted analogues of **2**, **4** and **5**, respectively (Scheme 3). A highly stereoselective access to the required key intermediate **10a** *via* a stepwise deprotonation–methylation sequence of the N-t-butylformamidoyl amidine of **6** followed by hydrazinolysis was briefly reported by Meyers.[4] Aminophosphine **4** was accessible via alkylation of **10a** to give bromide **11a** which was subsequently treated with n-BuLi/ClPPh$_2$ (12% from **6**). Ligand **5** was prepared in a similar way in 11% overall yield. All ligands proved to be largely air-stable compounds and could be handled without precautions.

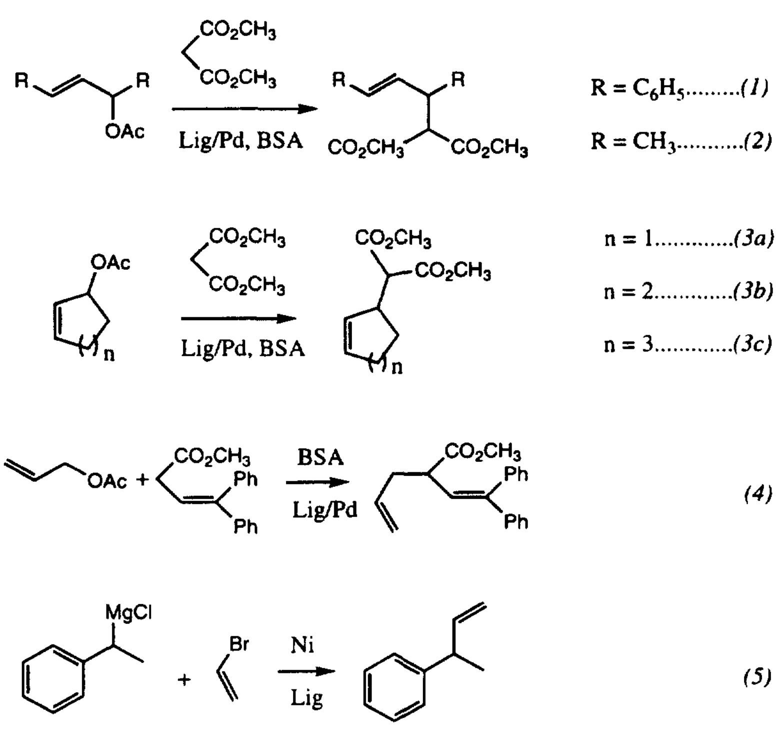
($R=CH_3$ ....**a**; $R=C_2H_5$ ....**b**)



Scheme 3.

In order to investigate the ability of new ligands to control the enantioselectivity in asymmetric C–C coupling reactions we performed allylic alkylations and a cross-coupling reaction with typical substrates to find out how increased steric congestion near to the reacting terminus of the allylic moiety would influence reactivity and enantioselectivity (Scheme 4). Results for reactions 1–5 are summarized in Table 1

We found that steric interaction in direct proximity to the coordination sites will improve the enantioselectivity of Pd-catalyzed allylic alkylations only in a limited number of cases. It was observed that low asymmetric induction is usually paralleled by markedly decreased reactivity, especially with cyclic substrate structures in combination with rigidity or with bulky substituents. Only for the substrate with high flexibility and low steric repulsion (reaction 2) was the expected improvement of enantioselectivity — up to 68% e.e. — achieved. This behavior can be rationalized on the basis of the accepted mechanism (Fig. 1); introduction of benzylic substituents in ligand **2** causes an efficient shielding of the metal center in Pd(0) complexes of **4** and **5**. As a consequence, the oxidative addition (I) or even the preceding association step will only tolerate substrates which are able to adopt the 'correct' geometry. On the other hand, ligands affecting particularly oxidative addition are expected to show pronounced kinetic resolution of racemic substrates. We further speculated that a slow step (I) and a fast step (II) should give a time-dependent enantioselectivity of the product formed, provided that the rate for equilibration



Scheme 4.

(III) was slow or similar to (II). In this case, not only thermodynamic reasons (equilibrium III) but also relative reaction rates of I, II and III could be responsible for the observed asymmetric induction.

With this reasoning we conducted kinetic measurements with simultaneous estimation of e.e. of educt and product. 1,3-Diphenylpropenylacetate was chosen as the substrate (reaction 1) since this permitted the estimation of conversion and e.e. of both educt and product by HPLC in a single run (see Experimental). Results are depicted in Fig. 2.

We found that the overall reaction rate is strongly affected by the bulkiness of substituents in the N-benzylic position. If applying typical conditions — 1 mol% of catalyst at RT in CH_2Cl_2 and BSA as base — the reaction with **2** was complete in approximately 15 min, corresponding to 600–700 turnovers per hour. Methyl or ethyl substitution causes a drop of reactivity to 110±10 and 60±5 turnovers per hour, respectively. This decrease in the overall reaction rate is paralleled by a significant increase of the kinetic resolution of the educt (Fig. 2b). With ligands **2**, **4** and **5**, enantiomerically enriched 1,3-diphenylpropenyl acetate was obtained with 16, 31 and 43% e.e., respectively, at 75% conversion. In contrast to this, no conversion dependence of e.e. of the product was observed; this is obviously not affected by the actual enantiomeric composition of the educt. Qualitatively the same trend was found for pentenyl acetate as the substrate (reaction 2) but the reaction turned out to be too fast for monitoring at RT with convenient methods; about 600 and 350 turnovers per hour were estimated in a preliminary experiment.

From this we conclude that the oxidative addition step (I) (Fig. 1) is most susceptible to steric hindrance and is probably rate determining. However, this does not affect the enantioselectivity of the conversion which seems to be exclusively governed by thermodynamics, i.e. the relative stabilities of intermediate palladium allyl complexes. The time-independence of the asymmetric induction of the process can be attributed to a very fast equilibration (III) preceding the (fast) nucleophilic 'outer-sphere' attack (II) of malonate. At least for the aminophosphine ligands under investigation, it turned out that changes in the

Table 1
Palladium-catalyzed asymmetric allylic alkylation reactions[a)]

entry	reaction[b)]	ligand[c)], mol%	react.time [h]	isol.yield[d)] [%]	e.e. [%][d)e)] (config.)	notes
1	1	(S)-**2**, 2	4	95	97 (S)	see[2c]
2	1	(S)-**4**, 2	4	76	55 (S)	59 (S) at -10 °C
3	1	(S)-**5**, 2	52	85	34 (S)	37 (S) in CH_3CN
4	2	(S)-**2**, 2	18	80	5 (+)	see[2c]
5	2	(S)-**4**, 2	15	79	50 (-)	68 (-) at -20 °C
6	2	(S)-**5**, 2	65	73	32 (-)	in CH_3CN 87% yield in 15 h
7	3a	(S)-**2**, 2	18	63	15 (R)	
8	3a	(S)-**4**, 2	18	12	4 (R)	
9	3a	(S)-**5**, 2	21	60	21 (R)	
10	3b	(S)-**2**, 2	18	86	28 (R)	see[2c]
11	3b	(S)-**4**, 2	18	n.r.	--	
12	3b	(S)-**5**, 2	18	n.r.	--	
13	3c	(S)-**2**, 2	18	74	63 (R)	
14	3c	(S)-**4**, 2	16	41	24 (R)	
15	3c	(S)-**5**, 2	20	31	22 (R)	
16	4	(S)-**2**, 2	20	76	41 (S)	see[2c]
17	4	(S)-**4**, 2	17	60	9 (S)	
18	4	(S)-**5**, 2	1 week	45	7 (S)	
19	5	(S)-**2**, 0.5	24	67	46 (R)	see[2c]
20	5	(S)-**4**, 0.5	24	34	5 (S)	
21	5	(S)-**5**, 0.5	24	42	4 (S)	

[a)] *Reactions 1-4*: 1 mmol scale with BSA in CH_2Cl_2 at RT; *Reaction 5*: 7.1 mmol scale in Et_2O; for experimental details see [2c,5]. [b)] see *Scheme 4*. [c)] Catalysts prepared in situ from 0.5 mol% of $[Pd(\pi\text{-allyl})Cl]_2$ or $NiCl_2$ (entry 19-21) and 0.5 or 2 mol% of ligands (S)-**2**, (S)-**4** or (S)-**5**. [d)] All entries were conducted at least in duplicate to confirm chemical yield and enantioselectivity. [e)] E.e. was estimated on the basis of specific rotation (*Reaction 1-5*), gas chromatography on modified cyclodextrine columns (*Reaction 2 and 5*) and HPLC on a chiral column (Daicel® OD-H, *Reaction 1 and 4*); for experimental details see [2c,5].

reaction rate did not alter general features of the mechanism. The sources of chiral discrimination are mainly differences in thermodynamic stabilities of allyl complexes caused by steric interactions with the ligand.

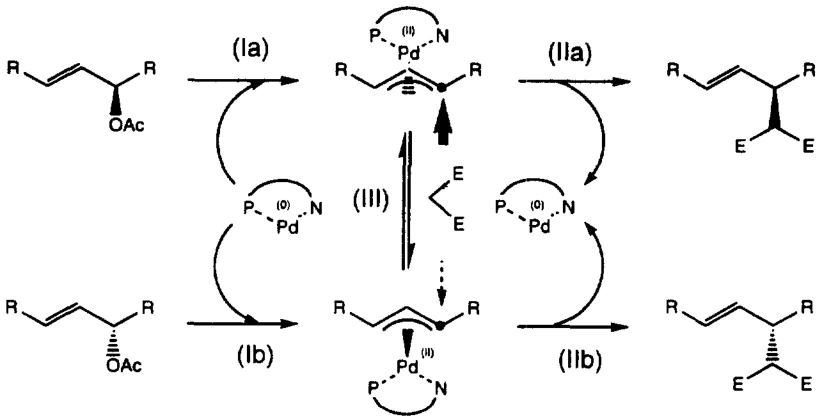


Fig. 1.

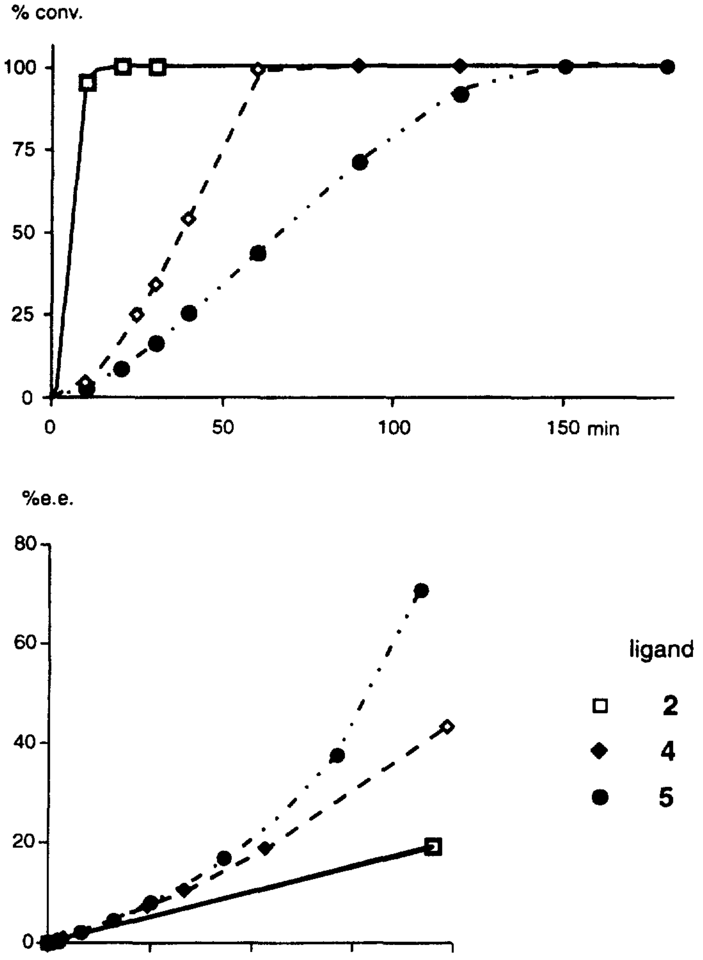


Fig. 2. Pd-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate with dimethylmalonate. (a) Kinetics at 22°C in CH_2Cl_2; 1 mol% of catalyst; for details see Experimental. (b) Kinetic resolution of the educt

3. Experimental

3.1. General

Melting points: Kofler melting point apparatus, uncorrected. NMR: Bruker AM 400 spectrometer at 400.13 MHz (^{1}H) and 100.61 MHz (^{13}C) in $CDCl_3$; chemical shifts are reported in ppm rel. to TMS (0.00 ppm) or $CHCl_3$ (7.24 or 77.00 ppm, respectively) if not otherwise noted. Coupling patterns are designated as s(inglet), d(oublet), t(riplet), p(seudo), and b(road). ^{13}C NMR spectra are recorded in a J-modulated mode, undesignated signals refer to CH resonances. MS: MAT 900, EI (70 eV) or FD. Optical rotation: Perkin–Elmer 241, thermostatted.

Petroleum ether (PE), CH_2Cl_2, $CHCl_3$ and ethyl acetate (EtOAc) were distilled, N,N,N′,N′-tetramethylethylenediamine (TMEDA) was distilled from CaH_2, THF from potassium benzophenone ketyl, diethylether from $LiAlH_4$. Triethylamine was filtered over alumina (activity I), n-BuLi was used as a 1.6 molar solution in hexane (Aldrich), s-BuLi as a 1.3 molar solution in cyclohexane (Fluka). Chlorodiphenylphosphine was distilled and stored under argon. Column chromatography was performed on silica gel Si 60, 40–63 μm (Merck). All the other chemicals were analytical grade and used without further purification.

3.2. *N-(N′-tert-Butylformamidoyl)-3,5-dihydro-4H-dinaphth[2,1-c:1′,2′-e]azepine* 7

N,N-Dimethyl-N′-tert-butylformamidine[6] (15.80 g, 123.2 mmol, 5.64 equiv.) and a catalytic amount of ammonium sulfate (660 mg) were added to a degassed solution of **6** (6.45 g; 21.8 mmol) in 35 ml of xylene under argon. The reaction was heated to reflux for 48 h and after removing the solvent in vacuo the residue was purified by column chromatography on silica gel (60×5 cm; PE:CH_2Cl_2:Et_3N=75:20:5; 310 nm) to give 6.21 g (75%) of **7** as an off-white powder; mp: 150–153°C. ^{1}H-NMR δ: 1.18 (9H, s); 3.73 (2H, d, J=12.9 Hz); 4.54 (2H, d, J=12.9 Hz); 7.25 (2H, ddd, J=8.5, 6.6, 1.1 Hz); 7.43 (2H, bd, J=8.0 Hz); 7.45 (2H, ddd, J=8.0, 6.6, 1.1 Hz); 7.56 (1H, s); 7.57 (2H, d, J=8.2 Hz); 7.93 (2H, bd, J=8.0 Hz); 7.95 (2H, d, J=8.5 Hz). ^{13}C-NMR δ: 31.26 (CH_3); 50.40 (CH_2); 53.33 (C); 125.59; 125.89; 127.22; 127.47; 128.25; 129.02; 131.56 (C); 133.18 (C); 133.48 (C); 134.93 (C); 149.37. MS (FD, 70°C) m/z: 378.4 (100%, M^+). The same reaction conditions applied to (S)-**6** (6.67 g, 22.5 mmol) afforded 77% of (S)-**7** as a glassy product. $[\alpha]^{20}_{589}=-57.9$ (c=1.00, $CHCl_3$).

3.3. *N-(N′-t-Butylformamidoyl)-5-methyl-3,5-dihydro-4H-dinaphth[2,1-c:1′,2′-e]azepine* 8a

A solution of s-BuLi (10.2 ml, 13.2 mmol, 5 equiv.) was added to a degassed solution of **7** (1.00 g, 2.65 mmol) in 100 ml of THF at −78°C under argon. The dark red mixture was stirred for 0.5 h before adding MeI (1.88 g, 13.2 mmol, 5 equiv.) at the same temperature. After 1 h the reaction was quenched with 50 ml of MeOH. The solvent was evaporated in vacuo and the residue was partitioned between 100 ml of CH_2Cl_2 and 100 ml of water. The aqueous phase was extracted with 3×50 ml of CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and concentrated. Column chromatography of the residue on silica gel (30×4.5 cm; PE:CH_2Cl_2:Et_3N=75:20:5; 310 nm) afforded 918 mg (89%) of **8a** as a crystalline powder; mp: 170–172°C. ^{1}H-NMR δ: 0.70 (3H, d, J=6.9 Hz); 1.20 (9H, s), 3.96 (1H, d, J=13.2 Hz); 4.56 (1H, d, J=13.2 Hz); 5.21 (1H, q, J=7.2 Hz); 7.23 (2H, m); 7.35–7.48 (4H, m); 7.49 (1H, s); 7.55 (1H, d, J=8.5 Hz); 7.60 (1H, d, J=8.5 Hz); 7.94 (4H, m). ^{13}C-NMR δ: 19.88 (CH_3); 31.27 (3×CH_3); 50.60 (CH_2); 53.23 (C); 58.33; 125.55; 125.58; 125.72; 126.00; 127.02; 127.33; 127.42; 128.03; 128.25; 128.51; 128.95; 129.10; 132.09 (C); 132.16 (C); 132.95 (C); 133.08 (C); 133.71 (C); 134.32 (C); 135.22

(C); 138.12 (C); 148.20. MS (40°C) m/z: 392 (29%, M^+). The same reaction conditions applied to (S)-**7** (2.20 g, 5.81 mmol) gave 1.90 g (84%) of (S)-**8a** as a glassy product. $[\alpha]^{20}_{589}=-140$ (c=1.02, $CHCl_3$).

3.4. N-(N′-t-Butylformamidoyl)-3,5-dimethyl-3,5-dihydro-4H-dinaphth[2,1-c:1′,2′-e]azepine ***9a***

A solution of s-BuLi (17.8 ml, 23.16 mmol, 10 equiv.) was added to a degassed solution of **8a** (909 mg, 2.30 mmol) in 110 ml of THF at −20°C under argon. The dark red mixture was stirred for 0.5 h before adding MeI (3.28 g, 23.16 mmol, 10 equiv.) at the same temperature. After 0.5 h the reaction was quenched with 20 ml of MeOH. The solvent was evaporated in vacuo, the residue was partitioned between 100 ml of CH_2Cl_2 and 100 ml of water. The aqueous phase was extracted with 3×40 ml of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. Chromatographic purification of the residue on silica gel (column: 25×5 cm; PE:CH_2Cl_2:Et_3N=90:5:5; 310 nm) afforded 751 mg (80%) of **9a**; mp: 201–203°C. ^{1}H-NMR δ: 0.73 (6H, d, J=7.2 Hz); 1.18 (9H, s); 7.20 (2H, ddd, J=8.3, 6.6, 1.4 Hz); 7.32 (2H, bd, J=8.3 Hz); 7.43 (2H, ddd, J=8.0, 6.6, 1.1 Hz); 7.42 (1H, s); 7.54 (2H, bd, J=8.3 Hz); 7.89 (2H, bd, J=8.3 Hz); 7.91 (2H, bd, J=8.3 Hz). ^{13}C-NMR[8] δ: 31.30 (3×CH_3); 53.27 (C); 125.59; 125.83; 127.26; 128.03; 128.40 (b); 128.92; 132.61 (C); 132.90 (C); 134.24 (C); 138.24 (b, C); 148.11 (CH). MS (60°C) m/z: 406 (38%, M^+). Similar reaction conditions applied to (S)-**8a** (1.87 g, 4.76 mmol) gave 1.44 g (74%) of (S)-**9a**; $[\alpha]^{20}_{589}=-161$ (c=1.03, $CHCl_3$).

3.5. 3,5-Dimethyl-3,5-dihydro-4H-dinaphth[2,1-c:1′,2′-e]azepine ***10a***

Acetic acid (7.56 g, 126 mmol) and hydrazine hydrate (14.83 g, 463 mmol) were added to a solution of **9a** (720 mg, 1.73 mmol) in 30 ml of ethanol at 0°C. The reaction was stirred overnight at RT. After evaporation of the solvent under vacuum, the residue was partitioned between 100 ml of EtOAc and 100 ml of sat. $NaHCO_3$ solution. The aqueous phase was extracted with 3×20 ml of EtOAc and the combined organic layers were concentrated. Chromatographic purification on silica gel (30×5 cm; $CHCl_3$:MeOH=90:10; 335 nm) left 534 mg (93%) of **10a** as a glassy product. An analytical sample was crystallized from CH_2Cl_2/Et_2O; mp: 231–235°C. ^{1}H-NMR δ: 0.78 (6H, d, J=7.2 Hz); 4.34 (2H, q, J=7.2 Hz); 7.20 (2H, ddd, J=8.8, 6.6, 1.4 Hz); 7.31 (2H, bd, J=8 Hz); 7.42 (2H, ddd, J=8.3, 6.6, 1.4 Hz); 7.47 (2H, d, J=8.3 Hz); 7.90 (2H, bd, J=8 Hz); 7.91 (2H, d, J=8.0 Hz). ^{13}C-NMR δ: 22.30 (CH_3); 56.92; 125.45; 125.75; 127.07; 128.07; 128.15; 128.87; 132.82 (C); 132.96 (C); 134.09 (C); 140.30 (C). MS m/z (230°C): 295 (20%, M^+). Similar treatment of (S)-**9a** (1.42 g, 3.50 mmol) yielded 1.03 g (92%) of (S)-**10a**; mp: 191–192°C (CH_2Cl_2/Et_2O); $[\alpha]^{20}_{589}=+400.9$ (c=0.985, $CHCl_3$) ($[\alpha]^{23}_{589}=365$ (c=1.0, CH_2Cl_2) see Meyers and Nguyen[4]).

3.6. N-(2-Bromo)benzyl-3,5-dimethyl-3,5-dihydro-4H-dinaphth[2,1-c:1′,2′-e]azepine ***11a***

Solid 2-bromobenzylbromide (336 mg, 1.20 mmol, 1.06 equiv.) and Et_3N (343 mg, 3.39 mmol, 3 equiv.) were added to a degassed suspension of **10a** (366 mg, 1.13 mmol) in 75 ml of toluene at RT under argon. The reaction was refluxed and monitored by TLC. After 4.5 h the reaction was complete and the solvent evaporated in vacuo. The residue was partitioned between 30 ml of CH_2Cl_2 and 30 ml of water. The aqueous phase was extracted with 3×10 ml of CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and concentrated. Column chromatography on silica gel (70×2 cm; PE:CH_2Cl_2=50:50; 335 nm) yielded 375 mg (67%) of **11a** as a foam. ^{1}H-NMR δ: 0.60 (6H, d, J=7.2 Hz); 4.02 (1H, d, J=14.6 Hz); 4.10 (1H, d, 14.6 Hz); 4.14 (2H, q, J=7.0 Hz); 7.11 (1H, ptd, J=7.6, 1.9 Hz); 7.21 (2H, ddd, J=8.3, 6.6, 1.4 Hz); 7.30 (1H, ptd, J=7.4, 1.1 Hz); 7.39 (2H, bd, J=8.5 Hz); 7.42 (2H, ddd, J=8.0, 6.6, 1.1 Hz); 7.50

(2H, d, J=8.3 Hz); 7.55 (1H, dd, J=8.0, 1.4 Hz); 7.62 (1H, dd, J=7.7, 1.7 Hz); 7.91 (2H, d, J=8.2 Hz); 7.93 (2H, d, J=8.2 Hz). ^{13}C-NMR δ: 18.77 (CH_3); 58.49 (CH_2); 62.19; 124.49 (b, C); 125.28; 125.67; 127.16; 127.23; 128.04; 128.31; 128.64; 128.67; 129.79 (b, C); 130.90; 132.75 (C); 132.77; 134.00 (C); 139.16 (C); 140.67 (C). MS (FD) m/z: 493 (100%, M^+). The same conditions applied to (S)-**10a** (525 mg, 1.62 mmol) gave 538 mg (67%) of (S)-**11a**; $[\alpha]^{20}_{589}$=+67 (c=0.994, $CHCl_3$). Analysis calc. for $C_{31}H_{26}BrN$: C 75.61, H 5.32, Br 16.23, N 2.84%; found: C 75.44, H 5.22, N 2.79%.

3.7. *N-(2-Diphenylphosphino)benzyl-3,5-dimethyl-3,5-dihydro-4H-dinaphth[2,1-c:1′,2′-e]azepine* **4**

To a degassed solution of **11a** (438 mg, 0.887 mmol) in 20 ml of THF was added n-BuLi solution (1.00 ml, 1.60 mmol, 1.8 equiv.) at −40°C under argon. The resulting clear brown solution was stirred for 2.5 h before addition of PPh_2Cl (0.59 ml, 2.66 mmol, 3 equiv.) at −78°C. After 1 hour the reaction was warmed to RT and stirred overnight. The solvent was removed under vacuum and the residue was partitioned between 30 ml of CH_2Cl_2 and 20 ml of water. The aqueous phase was extracted with 3×20 ml of CH_2Cl_2 and the combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography on silica gel deactivated with 13% of water (70×2 cm; PE:CH_2Cl_2=60:40; 330 nm)[7] afforded 305 mg (58%) of **4** as a white foam. ^{1}H-NMR δ: 0.43 (6H, d, J=7.2 Hz); 4.08 (2H, q, J=7.2 Hz); 4.09 (1H, dd, J=14.3, 2–3 Hz[9]); 4.20 (1H, dd, J=14.3, 2–8 Hz[9]); 6.93 (1H, m); 7.10–7.43 (20H, m); 7.72 (1H, m); 7.84 (2H, d, J=8.5 Hz); 7.88 (2H, d, J=9.4 Hz). ^{13}C-NMR δ: 18.59 (CH_3); 56.72 (CH_2, d, J_{PC}=22.9 Hz); 61.64; 125.16; 125.52; 126.97; 127.19; 127.97; 128.36 (d, J_{PC}=8.4 Hz); 128.40; 128.52 (2×CH); 128.54 (d, J_{PC}=6.9 Hz); 128.66; 128.74; 129.30 (d, J_{PC}=5.3 Hz); 132.67 (C); 132.69 (C); 133.87; 133.90 (d, J_{PC}=18.3 Hz); 133.92 (d, J_{PC}=19.8 Hz); 134.03 (C); 136.21 (C, d, J_{PC}=13.7 Hz); 137.01 (C, d, J_{PC}=10.7 Hz); 137.59 (C, d, J_{PC}=11.4 Hz); 140.84 (C); 145.25 (C, d, J_{PC}=22.9 Hz). ^{31}P-NMR δ: −15.71. MS (150°C) m/z 597 (10%, M^+). The same conditions applied to (S)-**11a** (267 mg, 0.544 mmol) gave 200 mg (62%) of (S)-**4**; $[\alpha]^{20}_{589}$=−14 (c=1.00, $CHCl_3$). Analysis calc. for $C_{43}H_{36}NP$: C 86.40, H 6.07, N 2.34, P 5.18%; found: C 85.92, H 6.37, N 2.26, P 5.34%.

3.8. *N-(N′-tert-Butylformamidoyl)-5-ethyl-3,5-dihydro-4H-dinaphth[2,1-c:1′,2′-e]azepine* **8b**

A procedure similar as in the preparation of **8a** was applied with the following variation: lithiation and subsequent addition of EtI were performed at −20°C; the reaction was quenched after 0.5 h. In a typical run, 1.00 g (2.64 mmol) of **7** afforded 902 mg (84%) of **8b** as a white foam. ^{1}H-NMR δ: 0.45 (3H, t, J=7.2 Hz); 0.57 (1H, m); 0.92 (1H, m); 1.16 (9H, s); 3.80 (1H, d, J=12.4 Hz); 4.75 (1H, d, J=12.4 Hz); 4.90 (1H, m); 7.21 (2H, ddd, J=8.3, 6.6, 1.4 Hz); 7.33 (1H, bd, J=7.7 Hz); 7.39 (1H, bd, J=7.2 Hz); 7.43 (2H, m); 7.47 (1H, s); 7.47 (1H, d, J=8.3 Hz); 7.59 (1H, d, J=8.3 Hz); 7.91 (4H, m). ^{13}C-NMR δ: 11.41 (CH_3); 27.07 (CH_2); 31.28 (3×CH_3); 49.31 (CH_2); 53.13 (C); 66.23; 125.51; 125.61; 125.73; 125.90; 127.20; 127.39; 127.45; 127.99; 128.27; 128.69; 128.95; 129.44; 131.96 (C); 132.08 (C); 132.96 (C); 133.05 (C); 133.54 (C); 134.34 (C); 135.43 (C); 136.37 (C); 149.32. MS (90°C) m/z: 406 (86%, M^+). (S)-**7** (500 mg, 1.32 mmol) gave 478 mg (89%) of (S)-**8b**; $[\alpha]^{20}_{589}$=−121 (c=1.04, $CHCl_3$).

3.9. *N-(N′-tert-Butylformamidoyl)-3,5-diethyl-3,5-dihydro-4H-dinaphth[2,1-c:1′,2′-e]azepine* **9b**

A procedure analogous to that used in the preparation of **9a** was applied. In a typical run, 873 mg (2.15 mmol) of **8b** afforded 751 mg (81%) of **9b** as a white foam. ^{1}H-NMR δ: 0.46 (6H, t, J=7.2 Hz); 0.70 (2H, m); 0.85 (2H, m); 1.15 (9H, s), 7.19 (2H, m); 7.29 (2H, bd, J=8.5 Hz); 7.41 (1H, s); 7.42 (2H, m); 7.50 (2H, bd, J=8.3 Hz); 7.89 (4H, d, J=8.3 Hz). ^{13}C-NMR[10] δ: 11.64 (CH_3); 31.30 (CH_3); 46.30 (C);

52.99 (CH_2); 125.53; 125.76; 127.19; 128.04; 128.55; 129.55 (b); 132.50 (C); 132.90 (C); 134.22 (b, C); 136.87 (b, C); 148.92. MS (80°C) m/z: 434 (10%, M^+). In a similar way, (S)-**8b** (419 mg, 1.03 mmol) gave 338 mg (76%) of (S)-**9b**; $[\alpha]^{20}_{589}=-154$ (c=0.994, $CHCl_3$).

*3.10. 3,5-Diethyl-3,5-dihydro-4H-dinaphth[2,1-c:1′,2′-e]azepine **10b***

The reaction was performed in essentially the same way as described for the dimethyl analogue **10a**. In a typical experiment, we obtained from **9b** (639 mg, 1.47 mmol) 476 mg (92%) of **10b** as a glassy product. ^{1}H-NMR δ: 0.49 (6H, t, J=7.4 Hz); 0.90 (2H, m); 1.23 (2H, m); 4.17 (2H, dd, J=9.6, 6.3 Hz); 7.20 (2H, ddd, J=8.5, 6.6, 1.4 Hz); 7.28 (2H, bd, J=7.1 Hz); 7.43 (2H, ddd, J=8.0, 6.6, 1.7 Hz); 7.48 (2H, d, J=8.2 Hz); 7.91 (2H, bd, J=8.0 Hz); 7.92 (2H, bd, J=8.2 Hz). ^{13}C-NMR δ: 11.83 (CH_3); 26.94 (CH_2); 63.48; 126.02; 126.07; 126.88; 128.22; 129.07; 129.40; 132.45 (C); 133.39 (C); 134.14 (C); 135.37 (b, C). MS (FD) m/z: 322 (100%, M^+). (S)-**9b** (1.03 g, 2.37 mmol) gave 776 mg (93%) of (S)-**10b**; $[\alpha]^{20}_{589}=+355$ (c=0.99, $CHCl_3$).

*3.11. N-(2-Bromo)benzyl-3,5-diethyl-3,5-dihydro-4H-dinaphth[2,1-c:1′,2′-e]azepine **11b***

The reaction was performed in essentially the same way as given for **11a** except that the reaction time was increased to 24 h. In a typical experiment, secondary amine **10b** (304 mg, 0.866 mmol) was converted to 332 mg (74%) of **11b** (foam). ^{1}H-NMR δ: 0.25 (6H, t, J=7.4 Hz); 0.53 (2H, m); 1.08 (2H, m); 3.83 (2H, dd, J=10.5, 5.8 Hz); 4.01 (1H, d, J=14.7 Hz); 4.18 (1H, d, J=14.7 Hz); 7.10 (1H, ptd, J=7.7, 1.7 Hz); 7.19 (2H, ddd, J=8.0, 6.6, 1.4 Hz); 7.29 (1H, ptd, J=7.4, 1.4 Hz); 7.34 (2H, bd, J=7.4 Hz); 7.41 (2H, ddd, J=8.0, 6.6, 1.1 Hz); 7.46 (2H, d, J=8.3 Hz); 7.53 (1H, dd, J=8.0, 1.4 Hz); 7.57 (1H, dd, J=7.7, 1.7 Hz); 7.90 (4H, bd, J=8.2 Hz). ^{13}C-NMR δ: 11.93 (CH_3); 25.00 (CH_2); 58.95 (CH_2); 69.50; 124.63 (C); 125.24; 125.59; 127.06; 127.13; 128.00; 128.29; 128.33; 129.83; 130.91; 132.48 (C); 132.72 (C); 132.75; 133.80 (C); 138.91 (C); 139.93 (C). MS (FD) m/z: 519/521 (80/100%, M^+). (S)-**10b** (756 mg, 2.15 mmol) gave 941 mg (84%) of (S)-**11b**; $[\alpha]^{20}_{589}=+54$ (c=0.99, $CHCl_3$). Analysis calc. for $C_{33}H_{30}BrN$: C 76.15, H 5.81, Br 15.35, N 2.69%; found: C 75.93, H 5.54, N 2.63%.

*3.12. N-(2-Diphenylphosphino)benzyl-3,5-dihydro-3,5-diethyl-4H-dinaphth[2,1-c:1′,2′-e]azepine **5***

The reaction was performed in essentially the same way as given for **4**. In a typical experiment **11b** (291 mg, 0.559 mmol) was converted to 214 mg (61%) of **5** (foam). ^{1}H-NMR δ: 0.21 (6H, t, J=7.4 Hz); 0.45 (2H, m); 1.07 (2H, m); 3.80 (2H, dd, J=10.3, 4.9 Hz); 4.18 (1H, dd, J=14.8, 2.5 Hz); 4.37 (1H, dd, J=14.8, 3.0 Hz); 6.93 (1H, m); 7.18 (3H, m); 7.25–7.43 (17H, m); 7.76 (1H, m); 7.86 (2H, d, J=8.4 Hz); 7.90 (2H, d, J=8.4 Hz). ^{13}C-NMR δ: 12.03 (CH_3); 24.85 (CH_2); 56.94 (CH_2, d, J_{PC}=23.7 Hz); 69.18; 125.14; 125.45; 126.93; 127.11; 127.97; 128.11; 128.38 (d, J_{PC}=6.9 Hz); 128.52; 128.56; 128.57 (d, J_{PC}=5.3 Hz); 128.67; 129.21 (d, J_{PC}=5.3 Hz); 129.98; 132.40 (C); 132.66 (C); 133.67; 133.78 (C); 133.87 (d, J_{PC}=13.7 Hz); 133.87 (d, J_{PC}=13.7 Hz); 133.88 (d, J_{PC}=25.2 Hz); 139.03 (C); 135.79 (C, d, J_{PC}=13.7 Hz); 136.97 (C, d, J_{PC}=11.4 Hz); 137.43 (C, d, J_{PC}=10.7 Hz); 145.45 (C, d, J_{PC}=22.9 Hz). ^{31}P-NMR δ: −15.70. MS (FD) m/z: 625.3 (100%, M^+). (S)-**11b** (917 mg, 1.76 mmol) gave 608 mg (55%) of (S)-**5**; $[\alpha]^{20}_{589}=-9.6$ (c=0.97, $CHCl_3$). Analysis calc. for $C_{45}H_{40}NP$: C 86.37, H 6.44, N 2.24, P 4.95%; found: C 86.36, H 6.71, N 2.17, P 5.10%.

3.13. Kinetic experiments

All reactions were conducted on a 1 mmol scale in CH_2Cl_2 (1 ml) at 22±1°C in 10 ml Schlenk tubes in essentially the same way as given for batch experiments by Widhalm et al.[5] Samples of 80 μl were taken after 10, 20, 30, 40, 60, 90, 120 and 180 min using a microliter syringe and immediately mixed with sat. NH_4Cl solution (2 ml) and ether (2 ml). The ether phase was separated, dried (Na_2SO_4), concentrated and finally filtered over a short bed of silica gel (2 cm height in a Pasteur pipette), eluting with 5 ml of CH_2Cl_2. The sample was then carefully dried and dissolved in 5 ml of 2-PrOH:n-hexane (5:95). Samples (5 μl) were injected onto a Daicel-ODH column and eluted with 2-PrOH:n-hexane (2:98). The following retention times (T=21±1°C) were found: educt 13.9±0.1/15.6±0.1 min; product 18.1±0.1/19.6±0.1 min. The UV response for educt and product at 254 nm was found to be the same within 1% as checked by NMR integration.

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