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Highly Diastereoselective Synthesis of 2,6-Di[1-(2-alkylaziridin-1-yl)alkyl]pyridines, Useful Ligands in Palladium-Catalyzed Asymmetric Allylic Alkylation

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Dedicated to Professor Achille Umani-Ronchi on the occasion of his 70th birthday.

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Abstract: C_2-Symmetrical, enantiopure 2,6-di[1-(1-aziridinyl)alkyl]pyridines (DIAZAPs) were prepared by a high-yielding, three-step sequence starting from 2,6-pyridinedicarbaldehyde and (*S*)-valinol or (*S*)-phenylglycinol. The new compounds were tested as ligands in palladium-catalyzed allylation of carbanions in different solvents. Almost quantitative yield and up to 99% enantiomeric excess were obtained in the reactions of the enolates derived from malonate, phenyl- and benzylmalonate dimethyl esters with 1,3-diphenyl-2-propenyl ethyl carbonate.

Keywords: allylation; amines; asymmetric catalysis; palladium; substituent effects

Introduction

Nitrogen-containing ligands are being increasingly applied in asymmetric catalysis,[1] since they present several advantages with respect to the more conventional phosphorus-containing ligands, even in transition metal-catalyzed reactions. Indeed, the amine functionality can coordinate any metal species, ranging from lithium and magnesium to zinc, copper, early transition metal complexes and also precious metals. Moreover, the amine group can be converted to other nitrogen-containing functional groups with different electronic and chemical (acid, base) properties, e.g., amides and imines. The availability of optically active amines from the chiral pool, by resolution processes and in part by stereoselective syntheses makes the use of nitrogen-containing ligands convenient as bases and auxiliaries in asymmetric syntheses, or as ligands of metal species in catalytic reactions. A significant niche in the domain of nitrogen ligands is held by *N,N′,N″*-terdentate ligands, especially those having C_2-symmetry. The pyridine ring is present in most compounds of this type (Figure 1), where it has the role of a spacer between two identical N-containing moieties, e.g., the widely used, high-performing pyridine-bis(oxazolines) **1** (*Pybox*s)[2] as well as the more recently developed pyridine-bis(oxazines) (*Pyboxazine*s) ligands **2**[3] and pyridine-bis(imidazolidines) **3**.[4] Both ligands **1** and **2** are readily prepared from 2,6-pyridinedicarboxylic acids and enantiopure β- and γ-amino alcohols, respectively, without the need to construct new stereocenters.

Pyridinediimines **4**, which are similarly prepared from 2,6-pyridinedicarbaldehyde, have been also used as ligands in metal-catalyzed asymmetric reactions.[5] Moreover, *N,N′,N″*-terdentate ligands **5**[6] bearing two chiral amine functions in the lateral chains of the pyridine ring were prepared from 2,6-di(chloromethyl)-pyridine, then used in transamination reactions with moderate enantioselectivities. However, only a few compounds with stereocenters at the benzylic positions have been described. The (*R*,*R*)- and (*S*,*S*)-enantiomers of the ligands **6**[6a] and **7**[7] were obtained after separation from the *meso*-compounds and resolution of the racemic mixture or copper complex, but no application of these ligands in asymmetric syntheses has been hitherto described. Also, chiral C_2-symmetric, substituted bipyridines and terpyridines have been exploited as metal ligands for asymmetric synthesis.[1c]

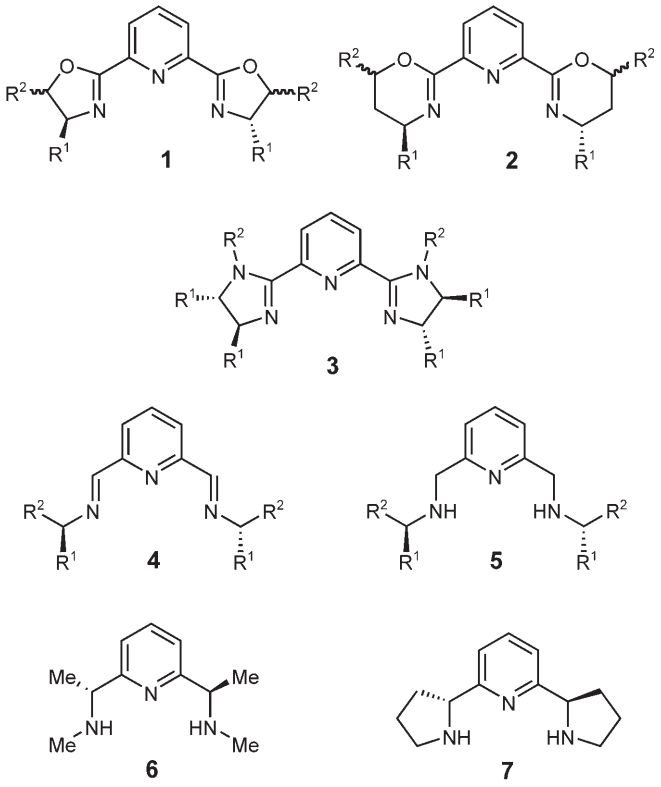


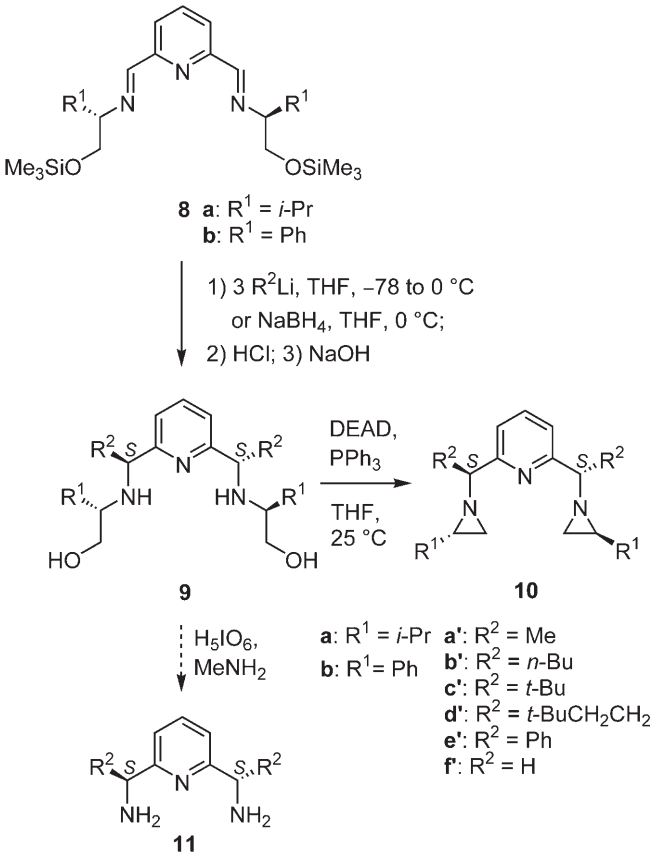
Figure 1. C_2-Symmetrical, pyridine-based *N,N,N*-terdentate ligands.

We envisioned a three-step route to enantiopure C_2-symmetrical *N,N′,N″*-terdentate ligands mimicking our previously described synthesis of pyridine-aziridine ligands[8] and involving the addition of organometallic reagents to a chiral diimine derived from 2,6-pyridinedicarbaldehyde. Taking advantage from our experience in the asymmetric synthesis of amines from imines,[9] particularly concerning the addition of organometallic reagents to chiral pyridineimines,[10] we have investigated the addition of allylic zinc reagents and organolithium compounds to the diimines **8a** and **8b** derived from (*S*)-valinol and (*S*)-phenylglycinol, respectively. As a matter of fact, preliminary experiments showed that Grignard reagents were less effective. While the reactions with allylic zinc reagents will be described elsewhere, we report here the reactions of these imines with organolithium compounds and the subsequent conversion of the β-amino alcohol products **9** to 2,6-***di***[1-(1-***az***iridinyl)***a***lkyl]***p***yridines (DIAZAPs) **10** following Mitsunobu cyclization. By this strategy, the carbon skeleton of the starting chiral amino alcohol and the absolute configuration of the inherent stereocenters are retained in the final molecule. The new ligands are then used in the palladium-catalyzed asymmetric allylic alkylation (AAA) of stabilized carbanions, providing higher enantioselectivity with respect to the analogous, previously described, bidentate pyridine-aziridine ligands.[8] The intermediates **9** can also be used for the preparation of 2,6-***di***(1-***am***ino***a***lkyl)***p***yridines (DIAMAPs) **11**, by oxidative cleavage of the chiral auxiliaries, and their *N*-substituted derivatives, of potential interest as ligands or auxiliaries in asymmetric reactions. The results of ongoing studies on this theme will be reported in due course.

Results and Discussion

Preparation of the Ligands

The sequence of steps described in Scheme 1 was followed to prepare the DIAZAP ligands **10a** and **b**. The starting *O*-silylated diimines **8a** and **b** were prepared in almost quantitative yields from the corresponding diimines bearing unprotected OH groups by the protocol previously described for the analogous monoimines,[8,9] and then used directly in the following step without purification. Organolithium compounds were found to be the reagents of choice to achieve a highly efficient, regio- and diastereoselective double addition to the azomethine groups in anhydrous tetrahydrofuran (THF) at −78 °C under an inert atmosphere. The outcomes of such reactions



Scheme 1.

using methyl-, *n*-butyl-, *tert*-butyl- (in Et_2O), 3,3-dimethylbutyl-, and phenyllithium together with the subsequent transformations of the products **9a** and **b** to the DIAZAPs **10**, are reported in Table 1. Of particular note, 3,3-dimethylbutyllithium was easily and effectively prepared by the reaction of *tert*-butyllithium (2 equivalents) with THF (solvent) at room temperature, involving the addition of *tert*-butyllithium to ethylene, which is formed together with the lithium enolate of acetaldehyde, following the initial cleavage of THF by *tert*-butyllithium.[10] It is noteworthy that almost all the reactions gave the expected products **9a** and **b** in high yields and with very high diastereoselectivities. As a matter of fact, apart from the addition of *tert*-butyllithium to both imines (entries 3 and 8), which provided the corresponding amino alcohols with low diastereomeric ratios (*dr*), the reactions of organolithium reagents with the valinol-derived imine **8a** occurred in most cases with higher diastereoselectivities (*dr* of **9a** 94:6) with respect to the phenylglycinol-derived imine **8b** (*dr* of **9b** 91:9). For the imine **8a**, the best result was obtained with phenyllithium, which afforded the amino alcohol **9ae′** in 95% yield and *dr* 98:2. However, the addition of methyllithium to **8b** (entry 6) was even more diastereoselective, as the pure diastereomer (*S*,*S*)-**9ba′** was obtained in 94% yield after column chromatography of the crude reaction product, where no other diastereomer was detected by ^{1}H NMR spectroscopy.

It should be observed that all the organometallic additions produced only two of three possible diastereomers of the compounds **9**: the prevalent one had C_2 symmetry, as observed by ^{1}H NMR spectroscopy. The *S*,*S* configuration of the two newly formed stereocenters at the benzylic positions was at first assumed considering the sense of asymmetric induction previously observed in the addition of organolithium reagents to the analogous 2-pyridine monoimine,[8] and then was confirmed by the X-ray structure obtained for one palladium complex derived from one of these ligands (see below). Column chromatography of the crude reaction products often allowed isolation of the main diastereomer only, however, enriched chromatographic fractions of the minor diastereomer were obtained, allowing its C_1 symmetry to be determined. In particular, the separation of the diastereomers was difficult for **9aa′** and **9ac′**, and low yields of the pure main (*S*,*S*)-diastereomer were obtained. In these cases, it was preferable to merely filter the crude reaction mixtures through a small pad of silica and use the diastereomeric mixtures in the subsequent step, that is the cyclization to DIAZAPs **10aa′** and **10ac′**, since the diastereomers of the latter compounds were more readily separated by chromatography. The aziridine ring was built from the intermediate compounds **9a** and **b** by applying the Mitsunobu methodology, i.e., by reaction with diethyl azadicarboxylate (DEAD) and triphenylphosphine in THF at room temperature. In fact, the DIAZAPs **10a** and **b** were obtained with high yields, as the coproducts could often be separated by column chromatography. In the case of phenylglycinol derivatives, the diastereomers of both the amino alcohols **9bb′**, **9bc′** and **9be′** and the corresponding aziridines **10bb′**, **10bc′**and **10be′** could not be separated. Other methods to achieve the cyclization of the β-amino alcohol moieties to aziridines

Table 1. Addition of organolithium reagents (3 equivalents) to the imines **8a** and **8b** dissolved in THF at −78 °C.

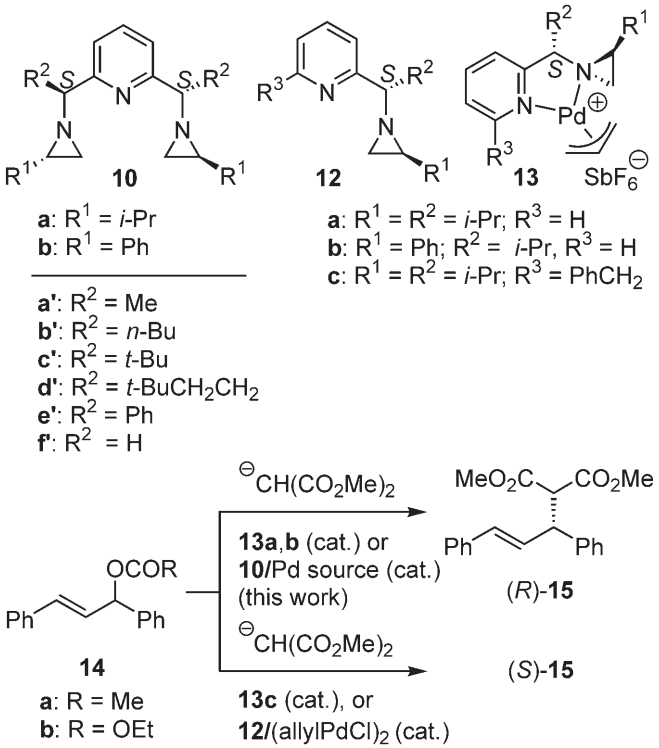
Entry	Imine (R^1)	R^2Li	Product	*dr*[a]	Yield [%] **9**[b]	**10**[c]
1	**8a** (*i*-Pr)	MeLi	**9aa′**	95:5	95	**10aa′** (85)
2	"	*n*-BuLi	**9ab′**	95:5	95 (79)[c]	**10ab′** (87)
3	"	*t*-BuLi[d]	**9ac′**	84:16	95 (54)[c]	**10ac′** (84)[e]
4	"	*t*-$BuCH_2CH_2Li$[f]	**9ad′**	94:6	84 (70)[c]	**10ad′** (86)
5	"	PhLi	**9ae′**	98:2	95	**10ae′** (90)
6	**8b** (Ph)	MeLi	**9ba′**	>99:1	94[g]	**10ba′** (85)
7	"	*n*-BuLi	**9bb′**	91:9	93 (76)	**10bb′** (90)[h]
8	"	*t*-Bu[d]	**9bc′**	86:14	94(59)	**10bc′** (86)[i]
9	"	PhLi	**9be′**	92:8	98 (84)	**10be′** (89)[j]

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction products.
[b] Yield of the crude reaction product. Unless otherwise indicated, the diastereomers were not separated.
[c] Yield of pure (*S*,*S*)-**9** isolated after column chromatography.
[d] The reaction was performed in diethyl ether.
[e] The product was obtained after column chromatography as a 89:11 mixture of diastereomers.
[f] The reagent was prepared *in situ* by adding *t*-BuLi to THF (solvent) at 0 °C.
[g] The crude product was apparently pure by ^{1}H NMR spectroscopy.
[h] The product was obtained after column chromatography as a 91:9 mixture of diastereomers.
[i] The product was obtained after column chromatography as an 86:14 mixture of diastereomers.
[j] The product was obtained after column chromatography as a 92:8 mixture of diastereomers.

were less satisfactory in our hands, affording lower yields and causing a more difficult purification of the products.

Palladium-Catalyzed AAA Reactions in the Presence of DIAZAP Ligands

We have previously described the synthesis of enantiopure (*N,N′*)-bidentate ligands, i.e., 2-[1-(1-aziridinyl)alkyl]pyridines, **12a–c**,[8] which have only one arm attached to the pyridine ring, as compared to the (*N,N′,N″*)*-terdentate DIAZAP ligands **10** described in this work. The crystalline complexes [(*N,N′*)(η^3-allyl)Pd][SbF_6] **13** prepared from those ligands were used as catalysts in the AAA of sodium dimethylmalonate with 1,3-diphenyl-2-propenyl acetate **14a** and 1,3-diphenyl-2-propenyl ethyl carbonate **14b** to give the substitution product **15** (Scheme 2).



Scheme 2.

By comparing the performances of two homochiral *N,N′*-bidentate complexes bearing the same skeleton but a different C2-aziridine substituent (Ph *vs.* *i*-Pr), a better enantioselectivity was obtained with the Ph-substituted ligand (*ee* 90% *vs.* 41%), in both cases favouring the formation of the product (*S*)-**15**. On the other hand, the complex **13c** with the C6-pyridine benzyl substituent gave the opposite enantioselectivity, as (*R*)-**15** was obtained with moderate *ee* (47%). Major drawbacks of said bisdentate ligands were their low reaction rates, even with the more reactive carbonate **14b**, and their incapability to adequately stabilize zerovalent palladium emanating from nucleophilic attack on the intermediate η^3-allylic complexes, leading to precipitation of Pd black and consequently a low to moderate yield of product **15**.

In fact, we have designed the structure of the *N,N′,N″*-terdentate DIAZAP ligands to overcome those problems. Our idea was also based on the report that a higher reaction rate was obtained using a *P,N,N*-terdentate ligand instead of a bidentate *P,N*-ligand in Pd-catalyzed AAA reactions;[11] a result that may have been the consequence of the capability of the terdentate ligand to effectively stabilize either Pd(0) or (allylic)Pd(II)$^+$ complexes involved in the catalytic cycle. However, in the case of our terdentate ligands, taking into account the effects of substituents in the bidentate ligands on enantioselectivity, it was difficult to foresee the importance of the C6 pyridine substituent (aziridine-alkyl group) in **10**, which could potentially oppose the asymmetric induction of the aziridine substituent.

A number of reactions were carried out on the allylic carbonate **14b** with the anion of dimethyl malonate, generated by treatment of dimethyl malonate with either sodium hydride or bis(trimethylsilyl)amide (BSA) and a catalytic amount of potassium acetate in different solvents (Table 2). Allylpalladium chloride dimer and the terdentate ligands **10a** and **b** were used as precursors of the effective enantioselective catalyst. The ligands derived from (*S*)-valinol were examined first. The carbonate **14b** was treated with the preformed sodium salt of dimethyl malonate (1.5 molar equivalents) and catalytic amounts of allylpalladium chloride dimer (5 mol%) and ligand **10aa′** (10 mol%) in tetrahydrofuran at room temperature. The course of the reaction was monitored by GC and TLC analysis and an almost complete conversion of the starting compounds was observed after 24 h. The product **15** was isolated in high yield and 76% *ee* in favour of the *R* enantiomer (Table 2, entry 1). It should be observed that the prior preparation of the palladium salt [(η^3-allyl)(**10aa′**)Pd][SbF_6] was unnecessary, as a smooth reaction occurred and the formation of black palladium was observed only when the reaction was almost complete. In a second run (entry 2) at −20 °C, with all the other experimental conditions being unchanged, we observed that the same *ee* was obtained, but a longer reaction time was required to obtain a satisfactory yield of product. Hence, all the successive reactions were carried out at 25 °C.

The role of the solvent was then examined and it was found that the reaction takes place also in dichloromethane, despite the poor solubility of sodium dimethyl malonate and the consequent lower reaction rate, but a slightly lower *ee* was obtained (entry 3).

Table 2. Enantioselective alkylation of dimethyl malonate with 1,3-diphenyl-2-propen-1-yl acetate **14a** and ethyl carbonate **14b**.[a]

Entry	Ligand (mol%)	Base	Solvent	Time [h]	Yield [%]	*ee* [%]
1	**10aa′** (10)	NaH	THF	24	79	76
2	**10aa′** (10)[b]	"	THF	96	69	76
3	**10aa′** (10)	"	CH_2Cl_2	48	85	73
4	**10ab′** (10)	"	THF	24	81	63
5	**10ab′** (10)	"	CH_2Cl_2	48	86	60
6	**10ac′** (10, *dr* 89:11)	BSA/AcOK	CH_2Cl_2	48	84	69
7	**10ad′** (10)	NaH	THF	48	86	70
8	**10ad′** (10)	BSA/AcOK	CH_2Cl_2	16	90	62
9	**10ae′** (10)	NaH	THF	24	85	76
10	**10ae′** (10)	NaH	CH_2Cl_2	18	89	86
11	**10ae′** (10)	BSA/AcOK	CH_2Cl_2	15	90	82
12	**10ae′** (10)	BSA/AcOLi	CH_2Cl_2	24	89	88
13	**10af′** (10)	BSA/AcOK	CH_2Cl_2	24	87	13
14	**10ba′** (10)	NaH	THF	72	82	82
15	**10ba′** (10)	NaH	CH_2Cl_2	3	90	98
16	**10ba′** (10)	BSA/AcOK	CH_2Cl_2	2	92	98
17	**10ba′** (3)	BSA/AcOK	CH_2Cl_2	8	87	98
18	**10ba′** (3)	BSA/AcOLi	CH_2Cl_2	5	90	98
19	**10bb′** (10, *dr* 91:9)	NaH	THF	48	77	80
20	**10bb′** (10, *dr* 91:9)	BSA/AcOK	CH_2Cl_2	16	89	81
21	**10bc′** (10, *dr* 86:14)	BSA/AcOK	CH_2Cl_2	48	64	70
22	**10be′** (10, *dr* 92:8)	BSA/AcOK	CH_2Cl_2	16	88	83
23	**10bf′** (10)	BSA/AcOK	CH_2Cl_2	24	92	76

[a] The reactions were performed on the carbonate **14b** at 25 °C generating the nucleophile by two protocols: A) dimethyl malonate (1.5 equivs.) and NaH (1.5 equivs.), or B) dimethyl malonate (2.5 equivs.), bis(trimethylsilyl)acetamide (BSA, 3 equivs.) and KOAc or LiOAc (0.1 equiv).

[b] The reaction was carried out at −20 °C.

The same trend was observed when the *n*-butyl substituted ligand **10ab′** was used in both solvents, but the *ee*s (60–63%) were lower (entries 4, 5). Similar results were obtained with the *tert*-butyl substituted ligand **10ac′** (used as a 84:16 mixture of inseparable diastereomers) and the ligand **10ad′** ($R^2 = t\text{-}BuCH_2CH_2$) in different experimental conditions. Finally, the phenyl substituted ligand **10ae′** provided high levels of enantioselectivity (*ee* up to 88% in entry 12).

At this point, we wanted to demonstrate the need or usefulness of a substituent, and hence a stereocenter, at the benzylic positions. In our opinion, this would induce the stereoselective formation of the N-aziridine stereocenter in the cationic palladium complex. It should be observed that *N*-alkylaziridines are not pyramidally stable at room temperature, and the bulkiness of the substituent decreases the barrier of inversion.[12] As a matter of fact, all the previously prepared η^3-allylic palladium complexes carrying bidentate (*N,N*)*-ligands displayed a unique configuration of the aziridine nitrogen atoms, that is dictated by the configuration of the benzylic carbon stereocenters and minimizes the steric interactions between the benzylic (R^2) and aziridine (R^1) substituents. To that purpose, we synthesized the ligand **10af′** by reduction of the diimine **8a** to give the intermediate diaminediol **9a,f′**, followed by the usual cyclization step (Scheme 1). The correctness of our hypothesis was demonstrated by the observation that the typical allylic alkylation of sodium dimethyl malonate with the allylic carbonate **14a** in THF at 25 °C in the presence of 10 mol% of ligand **10af′** occurred with very low enantioselectivity (13% *ee*, entry 13).

The terdentate ligands **10b**, derived from (*S*)-phenylglycinol and hence carrying phenyl substituents on the aziridine rings, were then examined in the same typical AAA reaction. (*R*)-**15** was formed in all cases with *ee*s definitely superior to those obtained with the corresponding (*S*)-valinol-derived ligands **10a**. For example, using sodium hydride as the base in THF in the presence of allylpalladium chloride dimer (5 mol%) and the ligand **10ba′** (10 mol%) the product (*R*)-**15** was obtained with 82% yield and 82% *ee* after 72 h (entry 14). Then, we observed that in dichloromethane, despite the very low solubility of sodium dimethyl malonate, the reaction with the ligand **10ba′** was almost complete after only 3 h and the product was obtained with excellent yield and 98% *ee* (entry 15). The same level of enantioselectivity was obtained by performing the reaction with the same ligand and generating the nucleophile by the alternative protocol (BSA-AcOK in CH_2Cl_2, entry 16),

even with reduced amounts of ligand (3 mol%, entries 17 and 18).

It was apparent that an increase in the bulkiness of the R^2 substituents in the ligands **10b** caused a decrease of the reaction rate. The *n*-butyl- and phenyl-substituted ligands **10bb′**, **10bc′** and **10be′** were used as an inseparable mixture of diastereomers, with the (*S*,*S*) and (*S*,*R*) configurations of the two benzylic stereocenters (*dr* 91:9, 86:14 and 92:8, respectively); nevertheless high *ee*s were obtained (*ee*s 80, 81, 70 and 83% in entries 19 to 22). Finally, we were surprised to find that the ligand **10bf′** (R^2 = H, Scheme 1), in contrast to the analogous (*S*)-valinol-derived **10af′** (13% *ee*, entry 13), provided a moderate enantioselectivity (76% *ee*, entry 23).

The role of different palladium sources was briefly investigated carrying out the allylation of the malonate anion (BSA, AcOK) with the carbonate **14b** in the presence of the ligand **10ba′** in dichloromethane at 25°C (Table 3). In comparison with the reaction

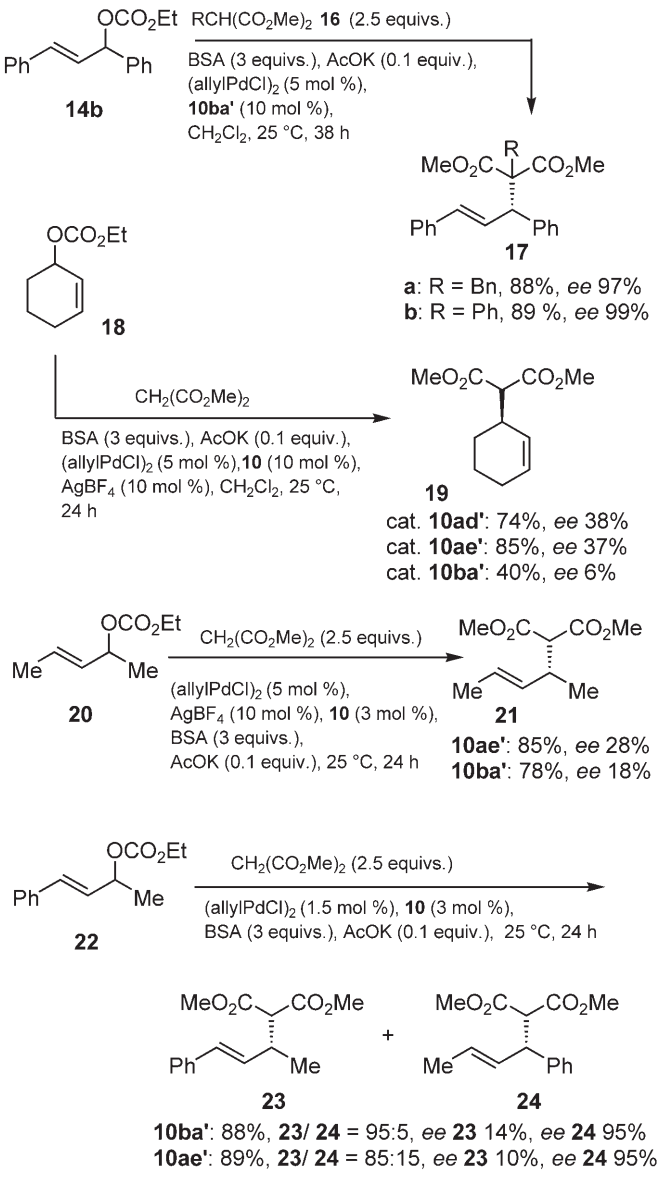
Table 3. Different palladium sources for the enantioselective alkylation of dimethyl malonate with 1,3-diphenyl-2-propen-1-yl ethyl carbonate **14b** in the presence of ligand **10ba′**.[a]

Entry	Pd catalyst (3 mol%)	Time [h]	Yield [%] of (*S*)-**15**	*ee* [%]
1	$(allylPdCl)_2$	3	87[b]	98
2	$Pd(OAc)_2$	24	76	87
3	$PdCl_2$	24	81	94
4	$Pd(dba)_2CHCl_3$	24	85	96

[a] The reactions were performed on the carbonate **14b** in dichloromethane at 25°C using dimethyl malonate (2.5 equivs.), bis(trimethylsilyl)acetamide (BSA, 3 equivs.), KOAc (0.1 equiv.) and ligand **10ba′** (3 mol%).

catalyzed by allylpalladium chloride dimer (entry 1), which was almost complete after only 3 h, the reactions catalyzed by palladium acetate, palladium chloride and the dibenzylideneacetonate complex required 24 h to give comparable yields and slightly lower *ee*s; up to 85% yield and 96% *ee* were obtained with the latter catalyst (entry 4).

Then, to extend the scope of our catalytic system, we investigated the AAA reactions of other stabilized enolates as well as diversely substituted allylic carbonates (Scheme 3). The enolates derived from substituted malonates have been relatively less employed as nucleophiles, and chiral P,P, P,N and N,P,N ligands have been used.[13] We were pleased to find that the alkylations of the benzyl- and phenyl-substituted malonate esters **16a** and **b**, respectively, proceeded smoothly in the presence of the ligand **10ba′** to give the products **17a** and **b** in high yields and with 97–99% *ee*s. The *S* configuration of the stereocenter in



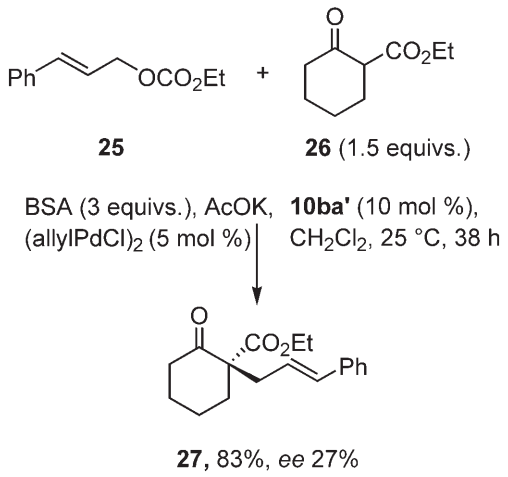
Scheme 3.

17a was assigned on the basis of the optical rotation (−).[13e] Since the previously unknown compound **17b** has the same sense of optical rotation of **17a**, the same configuration is assumed.

The cyclohexenyl carbonate **18** was poorly reactive in the usual experimental conditions and the *ee* of the derived product **19**[14] was low. For example, using ligand **10ba′**, a 40% yield and 6% *ee* were achieved, whereas a 68% yield and 37% *ee* were obtained with the ligand **10ae′**, in both cases after 3 days. The reaction rate could be slightly increased in the presence of silver tetrafluoroborate, and good yields of the cyclohexenyl-substituted malonate **19** were obtained after 2 days using either ligand **10ad′** or **10ae′**, but the *ee* did not exceed 38%. Surprisingly, the use of ligand **10ba′** resulted in a low yield of **19** (40%) and very

low *ee* (6%). Similarly, the reaction of dimethyl malonate anion with ethyl 3-penten-2-yl carbonate **20** in the presence of the ligands **10ae′** and **10ba′** afforded the substitution product **21** in good yields in the presence of $AgBF_4$ but with low *ee*s (up to 28%). Utilizing the unsymmetrically disubstituted allylic carbonate **22**, a mixture of products (ratio 95:5) was obtained, as usually found with other ligands:[15] the prevalent product **23** was formed by reaction at the methyl-substituted allylic terminus with low enantioselectivity (*ee* 14%), whereas the minor regioisomer **24** was obtained with 95% *ee* (Scheme 3).

Finally, we turned our attention to the capability of our catalytic system to induce enantioselectivity in the formation of a quaternary stereogenic center at the nucleophilic carbon. This goal should be achieved by the discrimination of the two diastereotopic faces of a fully substituted planar enolate attacking the η^3-allylic ligand. This is difficult to realize because the chiral N,*N*,*N*-ligand does not interfere in any way with the incoming nucleophile, and the newly formed stereocenter is more remote from the inducing stereocenter(s) than in previous experiments. Hence, we investigated the reaction of (*E*)-cinnamyl ethyl carbonate **25** with the anion derived from 2-ethoxycarbonylcyclohexanone **26** under the usual reaction conditions (BSA, AcOK, CH_2Cl_2) (Scheme 4). The reaction proceeded smoothly to give the linear alkylation product **27** with high yield but only 27% *ee*. This result can be compared with the reported Pd-catalyzed enantioselective synthesis of **27** using a P-chirogenic diaminophosphine oxide as the ligand, where 92% *ee* was obtained.[16b] We assigned the *S* configuration to the major enantiomer of **27** by comparison with the authentic enantiomer.[16b]



Scheme 4.

Tentative Explanation of Mechanism and Enantioselectivity

Different (allyl)- and (1,3-diphenylallyl)Pd^+ salts bearing the (*S*)-valinol- and (*S*)-phenylglycinol-derived ligands, **10ae′** and **10ba′**, with PF_6, SbF_6 or BF_4 counterions, were prepared by standard methodology. These salts were generally obtained as white or yellowish powders, and some of them appeared impure by ^1H NMR analysis. Up till now, we have been able to obtain crystals suitable for X-ray crystallographic structure determinations only in the case of the salt [(**10ae′**)(allyl)Pd][PF_6]. The crystal structure (Figure 2) is quite similar to those of the previously reported allylic palladium salts with pyridine-aziridine ligands,[8] featuring the bidentate coordination of the ligand to palladium cation and the η^3 hapticity of the *endo*/*exo* allyl ligand. The palladium-aziridine bond is shorter than the palladium-pyridine bond [2.109(3) *vs.* 2.158(3) Å], and the terminal allylic carbon *anti* to the aziridine forms a bond with palladium [2.178(4) Å] longer than the allylic terminus *anti* to the pyridine ring [2.126(4) Å]. This observation supports the hypothesis that the allylic terminus *anti* to the aziridine has a more electrophilic character. The ^1H NMR spectra of the CD_2Cl_2 solutions of this salt and all the other [(allyl)- or (1,3-diphenylallyl)(**10a** or **b**)]Pd^+ salts with PF_6^-, SbF_6^- and BF_4^- counterions were complex with broad absorptions, indicating the presence of several species, although the *endo*- and

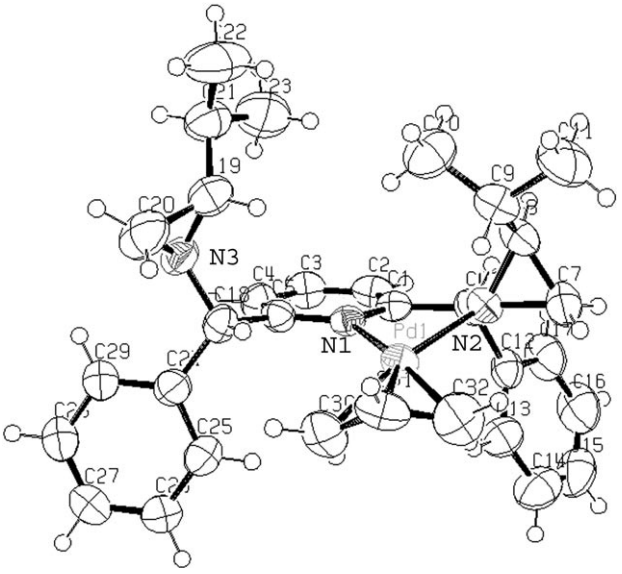


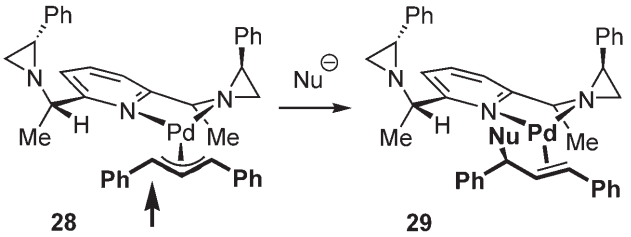
Figure 2. X-ray structure of the [(**10ae′**)(allyl)Pd]$^+$ cation. Only the dominant orientation (84%) of the allyl ligand is shown. Selected bond lengths (Å): N(1)–Pd(1) 2.158(3), N(2)–Pd(1) 2.109(3), C(30)–Pd(1) 2.178(4), C(31)–Pd(1) 2.138(4), C(32)–Pd(1) 2.126(4). Bite angle N(2)–Pd(1)–N(1): 78.06(11)°.

exo-(η^3-allyl) (N,N)Pd^+ species were predominant. Most importantly, in the case of the 1,3-diphenylallyl complexes, a higher ratio of rotamers (>3:1) was observed for the complex derived from the ligand **10ba′**, which afforded the highest enantioselectivity. Moreover, the spectra were complicated by the lack of C_2-symmetry of the ligand complex, demonstrating that only one aziridine nitrogen was involved in Pd coordination. For example, for each rotamer, distinct absorptions were observed for the two benzylic protons.

In the absence of information on the reactive intermediate involved in the enantioselective step, we can only speculate on the origin of the enantioselectivity. We take into account the available structural information of the bidentate complex **13** and the mechanistic hypothesis that has been suggested to explain the sense of asymmetric induction provided by such ligands.[8] Moreover, several studies on the binding properties of potentially terdentate ligands towards (allyl)Pd(II) cations have been reported.[17–19] For example, the X-ray crystal structure of a (terpyridine)-(allyl)palladium complex has been determined and its dynamic behaviour in solution has been studied by ^1H and ^{13}C NMR spectroscopy.[17] It was therein shown that terpyridine binds the (η^1-allyl)Pd^+ fragment in the terdentate fashion and (η^3-allyl)Pd^+ as a bidentate ligand. In fact, the two species are present both in the crystal and in a CD_2Cl_2 solution in a dynamic equilibrium, which is strongly displaced towards the η^3-allyl form at low temperature. On the other hand, the 2,6-bis(diphenylphosphanylmethyl)pyridine (PNP) ligand in the complex [(PNP)(allyl)Pd][BF_4] adopts the terdentate coordination mode both in the crystal and in solution, where the complex is fluxional through η^1–η^3 equilibrium processes.[18,19] This is in contrast to the behaviour of (N,P,N) ligands which act as (P,N)-bidentate ligands in (η^3-dimethylallyl)Pd^+ complexes.[20] Similarly, the presence of the pyridine ring in a chiral (P,N,N) ligand was unnecessary for high selectivity in the AAA reaction, suggesting that the ligand acts in a (P,N)-bidentate fashion.[21]

On the basis of the precedent studies, we believe that the prevalent rotamer of the reactive (η^3-1,3-diphenylallyl)(N,N,N)Pd^+ complex is **28**, featuring the *syn*,*syn*-configuration of the allylic ligand and reduced interactions of the allylic phenyl groups and the aziridine substituent. Moreover, in solution the chiral aziridinylalkyl substituent not involved in palladium chelation should take the same spatial arrangement as observed in the crystal structure, with the methine hydrogen oriented towards the allylic ligand in order to reduce the steric interactions. Obviously, owing to the C_2 symmetry of the nitrogen ligand, identical η^3-(N,N) complexes are formed when one or the other aziridine nitrogen is involved in Pd coordination.

If this assumption is correct, the sense of enantioselectivity is easily explained by the attack of the nucleophile on the more electrophilic allylic terminus *anti* to the aziridine nitrogen of the intermediate **28** to give the (η^2-alkene)Pd(^{0}) complex η^2-(N,N)-**29** (Scheme 5). The regioselectivity of the nucleophilic



Scheme 5.

attack is also favoured by the preferential clock-wise rotation of the hydrocarbon ligand occurring during the formation of the most stable (η^2-alkene)Pd complex **29**, as the steric interactions between the alkene and the nitrogen ligand are reduced concurrently.

Conclusions

C_2-Symmetrical *N,N′,N″*-terdentate ligands featuring two aziridine rings in the lateral arms of a pyridine ring are constructed by a short and efficient route starting from commercially available building blocks: 2,6-pyridinedicarbaldehyde, optically pure β-amino alcohols and organolithium reagents. These ligands (DIAZAPs) induce high levels of enantioselectivity (*ee* up to 99%) in the allylic alkylation of dimethyl malonate anion and analogous C2-substituted anions. Contrary to the corresponding bidentate ligands derived from 2-pyridinecarbaldehyde, the DIAZAP ligands are capable of stabilizing both cationic and zerovalent palladium, thus avoiding the ready interruption of the catalytic cycle by deposition of Pd black. Unfortunately, application of these ligands in the allylic alkylation of different nucleophiles has met with low enantioselectivity or no success. However, it is expected that they can be used in other transition metal catalyzed reactions.

Experimental Section

General Protocol for the Preparation of Imines

To a solution of (*S*)-valinol (6 mmol, 0.618 g) or (*S*)-phenylglycinol (6 mmol, 0.823 g) in THF (50 mL) was added anhydrous $MgS0_4$ (5 g), the aldehyde (3 mmol, 0.405 g) and the mixture was stirred overnight. The solid phase was filtered off on a pad of Celite and the organic solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and triethylamine (7 mmol, 0.708 g) and chlorotrimethylsilane (7 mmol, 0.97 mL. 0.760 g) were added

at 0 °C. After 3 h the solvent was removed under vacuum. A solution of cyclohexane/diethyl ether (1:1) was added and the solid phase was filtered off on a pad of Celite. The organic solvent was evaporated under reduced pressure to leave the imine in almost quantitative yield; this was used in the following step without further purification.

Preparation of β-Amino Alcohols 9 by Addition of Organolithium Reagents to Imines 8

The organolithium reagent (9 mmol) was added to a magnetically stirred solution of the imine **8** (3 mmol) in THF (10 mL) cooled to −78 °C. After 30 min, the reaction mixture was slowly warmed at 0 °C, and quenched after 3 h by adding 1 N HCl (10 mL). After 2 h NaOH pellets were added until the solution reached pH 11, and the organic phase was extracted with diethyl ether (3 × 10 mL). The collected ether phases were dried over Na_2SO_4 and concentrated to leave the crude products. The diastereomeric ratio was determined by ^{1}H NMR analysis. Flash column chromatography (SiO_2), eluting with cyclohexane/ethyl acetate mixtures, gave the product which was directly used in the subsequent step. In order to obtain a satisfactory elemental analysis, further purification by chromatography or crystallization was carried out.

Preparation of β-Amino Alcohols 9af′ and 9bf′ by Reduction of Imines 8a and 8b

To a solution of imine **8a** or **b** (1 mmol) in methanol (5 mL), $NaBH_4$ (2 mmol, 0.076 g) was added in one portion. After 1 h the reaction was quenched with 1 N HCl (5 mL) and further stirred for 2 h. Then NaOH pellets were added until the solution reached pH 11, and the organic phase was extracted with diethyl ether (3 × 10 mL). The collected ether phases were dried over Na_2SO_4 and concentrated to leave the crude product in quantitative yield. Pure compounds were obtained by column chromatography (SiO_2) eluting with cyclohexane/ethyl acetate mixtures.

Preparation of Aziridines 10

To a solution of β-amino alcohol **9** (2.8 mmol) in THF (20 mL) was added PPh_3 (6.2 mmol, 1.6 g). To this solution DEAD (6.2 mmol, 1.082 g) was added dropwise. After 4 h, a solution of 2 N KOH (10 mL) was added to the mixture, which was stirred for 3 h. Diethyl ether was added (30 mL) and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 × 20 mL), and the collected organic phase was washed with 2 N KOH (3 × 10 mL), then with brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was flash-chromatographed on a SiO_2 column eluting with cyclohexane/ethyl acetate mixtures. In order to obtain analytically pure samples, further purification by chromatography or crystallization was carried out.

Preparation of Allylic Palladium Complexes; Typical Procedure: [10ae′(η^3-allyl)Pd][PF_6]

Allylpalladium chloride dimer (73 mg, 0.1 mmol) was added to a solution of ligand **10ae′** (80 mg, 0.2 mmol) in CH_2Cl_2 (4 mL) in one portion. After one hour a solution of NH_4PF_6 (39 mg, 0.24 mmol) in THF (1 mL) was added. The solution was stirred overnight, then filtered through an HPLC filter (0.45 μm) and the solvent was removed under reduced pressure to give a white solid: yield: 0.130 g (91 %).

White crystals, suitable for X-ray diffraction analysis were obtained from a double-layer of CH_2Cl_2 and pentane: white crystals; mp 124–126 °C (dec); $[\alpha]_D^{20}$: +21.1 (*c* 1.2, $CHCl_3$); IR (KBr): ν = 3052, 3030, 2882, 1605, 1567, 1496, 1452, 1265, 1014, 840, 732, 701, 553 cm^{-1}.

The ^{1}H NMR spectra of all the allyl and 1,3-diphenylallyl cationic Pd complexes synthesized showed the presence of different species, but the *exo* and *endo* rotamers were prevalent with variable ratios. Specifically, the spectrum of the complex **10ae′**(1,3-diphenylallyl)PdPF_6 (600 MHz, $CDCl_3$) showed a 55:45 ratio of two rotamers, with the following absorptions of the allylic protons: major rotamer, δ = 5.98 (t, J = 11.4 Hz, 1H), 4.75 (d, J = 11.4 Hz, 1H), 4.67 (d, J = 11.4 Hz, 1H) ppm; minor rotamer, δ = 6.13 (t, J = 11.4 Hz, 1H), 5.0 (d, J = 11.4 Hz, 1H), 4.40 (d, J = 11.4 Hz, 1H) ppm. On the other hand, the ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **10ba′**(1,3-diphenylallyl)PdPF_6 showed the presence of a prevalent species (*ca.* 75 %) with the *syn*,*syn* geometry of the allylic ligand, whose protons gave absorptions at δ = 6.16 (t, J = 11.4 Hz, 1H), 4.43 (d, J = 11.4 Hz, 1H) and 3.80 (d, J = 11.4 Hz, 1H).

[(10ae′)(allyl)Pd][PF_6]

X-Ray details: Bruker APEX II CCD diffractometer (Mo-Kα radiation λ = 0.71073 Å). Results: $C_{32}H_{40}F_6N_3PPd$, M_r = 718.04, monoclinic $P2_1$, a = 11.0990(13), b = 13.3802(16), c = 11.9282(14) Å, β = 112.045(2), V = 1641.9(3) Å^3, Z = 2, ρ_x = 1.452 Mg m^{-3}, μ 0.674 mm^{-1}, $F(000)$ = 736, T = 296(2) K, θ_{max} = 28.51, 13905 reflections collected, 6099 $I > 2\sigma(I)$. Final $R1$ = 0.0347, $wR2$ = 0.0860, GOF = 0.997, absolute structure parameter = −0.04(2). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 297723. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

Palladium-Catalyzed Allylic Alkylation

To a solution of DIAZAP **10ba′** (0.03 mmol, 10 mg) in CH_2Cl_2 (2 mL) was added (allylPdCl)$_2$ (0.014 mmol, 5 mg) and the solution was degassed and stirred for 1 h. 1,3-Diphenyl-2-propenyl ethyl carbonate (**14b**) (0.27 mmol, 76 mg) was then added followed by dimethyl malonate (0.67 mmol, 90 mg), BSA (0.81 mmol, 0.165 g) and KOAc (0.02 mmol, 2 mg) after 10 min. The reaction was monitored by TLC analysis and, when complete, quenched with 1 N HCl solution (1 mL) and the organic phase was extracted with diethyl ether (3 × 10 mL). The organic layer was dried over Na_2SO_4 and the solvents were evaporated to dryness. The crude product was purified by chromatography on a silica gel column (hexane/AcOEt, 75:5) affording methyl (*R*)-(*E*)-3,5-diphenyl-2-methoxycarbonyl-4-pentenoate (**15**); yield: 73 mg (84 %). An *ee* of 99 % was determined by chiral HPLC (Chiralpak AD; 2-propanol/hexane1:9, 1.0 mL min^{-1};

250 nm); retention times: 10.7 min (major enantiomer), 14.9 min (minor enantiomer).

17a: yield: 88%, *ee*: 97%; $[\alpha]_D^{20}$: −38.7 (*c* 2.0, $CHCl_3$). The *ee* was determined by chiral HPLC (Chiralpak AD; 2-propanol/hexane 3:97; 1.0 mL min^{-1}, 250 nm); retention times: 16.6 min (major enantiomer), 17.1 min (minor enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[13e]

17b: yield: 89%, *ee*: 99%; $[\alpha]_D^{20}$: −48.4 (*c* 1.5, $CHCl_3$). The *ee* was determined by chiral HPLC (Chiralpak AD; 2-propanol/hexane 1:99, 0.8 mL min^{-1}, 250 nm); retention times: 8.3 min (minor enantiomer), 10.9 min (major enantiomer). The absolute configuration was assumed by analogy with compound **17a**.

19: yield: 40%, *ee*: 6%; $[\alpha]_D^{20}$: +5.0 (*c* 1.1, $CHCl_3$). The *ee* was determined by chiral GC: Megadex Chiral column (25 m, flow rate: 15 mL min^{-1}, 50 °C (2 min), then 3 °C min^{-1} up to 190 °C, FID detection): retention times: 27.2 min (minor enantiomer), 27.3 min (major enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[14]

21: yield: 85%, *ee*: 28%; $[\alpha]_D^{20}$: +6.5 (*c* 1.2, $CHCl_3$). The *ee* was determined by chiral GC (Megadex Chiral column (25 m, flow rate: 15 mL min^{-1}, isotherm 65 °C, FID detection); retention times: 49.5 min (minor enantiomer), 51.6 min (major enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[15]

23 and **24:** The ratio was determined by GC-MS analysis. The *ee*s of **23** and **24** were determined by chiral HPLC (Chiralpak OD, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, 250 nm); retention times of **24**: 14.2 min (major enantiomer), 15.1 min (minor enantiomer); retention times of **23**: 17.9 (minor enantiomer), 18.8 (major enantiomer).

27: yield: 83%, *ee* 27%; $[\alpha]_D^{20}$: −23.5 (*c* 1.6, $CHCl_3$). The *ee* was determined by chiral HPLC (Chiralpak OD, 2-propanol/hexane 5:95, 0.4 mL min^{-1}, 250 nm); retention times: 13.7 min (minor enantiomer), 15.6 min (major enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[16b]

Supporting Information

Characterization data for compounds **8**, **9** and **10**. Table with bond lengths and angles for the cation (**10ae′**)(allyl)Pd$^+$. ^{1}H NMR of the salt [(**10ae′**)(allyl)Pd][PF_6], ^{1}H NMR and ^{1}H COSY of the salts [(**10ae′**)(1,3-diphenylallyl)Pd][PF_6] and [(**10ba′**)(1,3-diphenylallyl)Pd][PF_6].

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