JOC Article

Synthesis and Crystallographic Characterization of Chiral Bis-oxazoline-amides. Fine-Tunable Ligands for Pd-Catalyzed Asymmetric Alkylations

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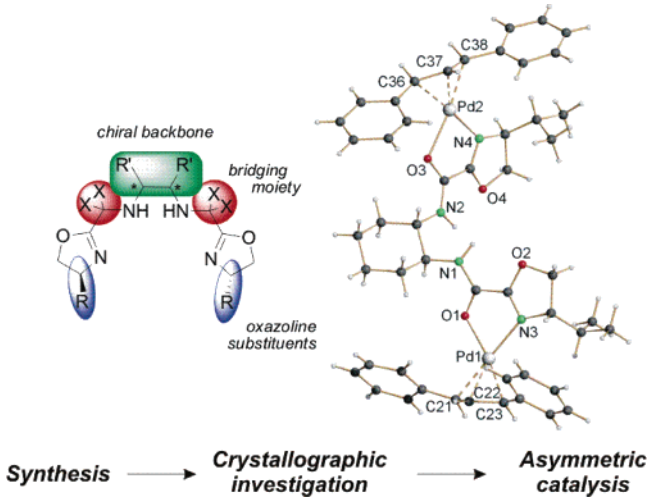

New chiral chelating C_2 bis-oxazoline-amide ligands (**1**) exhibiting a highly flexible molecular structure have been prepared in high yield through a versatile synthetic pathway. Combined crystallographic, variable temperature (VT)-NMR, IR, and ESI-MS studies have been carried out to investigate the nature of the **1**−Pd complexes that are effective tools in controlling the stereochemical outcome of Pd-catalyzed allylic alkylations (ee up to 98%).

Introduction

Design and synthesis of chiral ligands represent central issues for chemists working in a number of areas: catalysis, new materials, and medicinal chemistry.[1] In particular, the search for innovative, effective, and low cost asymmetric organometallic catalysts continues to gain interest for practical and environmental reasons.[2]

During the development of new chiral metal-based catalytic systems, the complementary organic and inorganic approaches are crucial to design chiral ligand motifs (chiraphoric units) and to properly choose the appropriate inorganic counterpart (catalaphoric unit). Fine-tuning the catalytic properties of chiral ligands, by varying their electronic and steric features, is of major interest for the development of new classes of chiral catalysts of wide interest. This target is pursued often by condensing molecular frameworks present in different "privileged ligands" to create new effective asymmetric environments.[3]

We have recently described a new class of C_2-symmetric diamino-oligothiophene ligands[4] that exhibited high effective-

† Fax: Int. Code +39(51)2099456.

(1) Elsevier, C. J.; Reedijk, J.; Walton, P. H.; Ward, M. D. *J. Chem. Soc., Dalton Trans.* **2003**, 1869−1880.

(2) (a) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: New York, 2000. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, N. E., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999.

(3) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691−1693.

(4) (a) Albano, V. G.; Bandini, M.; Melucci, M.; Monari, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2005**, *347*, 1507−1512. (b) Albano, V. G.; Bandini, M.; Barbarella, G.; Melucci, M.; Monari, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A. *Chem.− Eur. J.* **2006**, *12*, 667−675.

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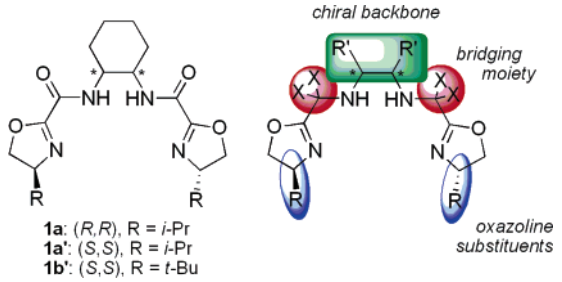


FIGURE 1. Structural flexibility of bis-oxazoline-amides.

ness in promoting Pd-catalyzed asymmetric allylic alkylation (AAA)[5] allyl carbonates. In view of their potentialities, chiral polyaza ligands have had a deep impact in the asymmetric synthesis scenario: (i) large availability in enantiomerically pure form, (ii) ready modulation of the coordinating nitrogen group, (iii) high stability under oxidative conditions (advantage over phosphines), and (iv) flexibility of the coordination chemistry (no restriction to exclusive noble metals chemistry).[6] In this context, we have been attracted by a valuable class of potentially bi-, tri-, and tetradentate C_2-tetraza ligands, namely, bis-oxazoline-amides (**1a**, **1a′**, **1b′**, Figure 1) that recently were introduced by Pfaltz and co-workers as promoters of molybdenum-catalyzed AAA.[7]

The potentialities of this family of compounds lay on their molecular skeleton, which allows large chemical diversities to be obtained by combining different chiral acyclic and cyclic backbones, bridging units, and substituents in the dihydroxazole rings.

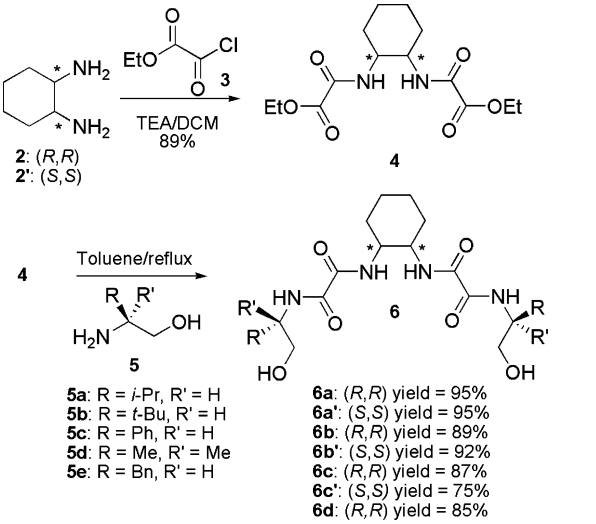
To further exploit the properties of type-**1** ligands, we first reexamined their synthesis and found a three-step synthetic route more convenient than that previously reported (yield: **5a**, 15%; **5a′**, 14%; **5b′**, 9%).[7] This strategy enabled us to obtain a wide library of structural analogues of **1** in good yields. The modular compounds then were tested in the Pd-catalyzed AAA processes in the presence of hindered and unhindered allyl carbonates with the isolation of the corresponding products in quantitative yields and ee up to 98%. Finally, we investigated the coordination chemistry of **1a′** in the Pd-allyl species through a combined crystallographic, variable temperature (VT)-NMR, IR, and ESI-MS study. Here, a C_1-symmetrical **26d**-type N,O-coordination mode is proposed to be involved as the active complex during the enantiodiscriminating step of the reaction.

Results and Discussion

Synthesis of the Ligands. After several attempts, we have found optimal reaction conditions for the synthesis of bis-oxazolines anchored to 1,2-cyclohexane diamine backbones (**1**, Schemes 1 and 2).

The three-step procedure involves the initial condensation under basic conditions (triethylamine, TEA) of the enantiomerically pure 1,2-cyclohexane diamine (**2**/**2′**) with ethyl chlorooxocetate (**3**) in DCM that provides the bis-amide **4** in 89% yield without time-consuming purification steps. The

SCHEME 1. Two-Step Sequence for the Synthesis of Tetra-amide Intermediates 6



reaction of **4** with 2 equiv of the desired β-amino alcohol **5** (toluene, reflux, 72 h) gives rise to the corresponding diols, **6,** as white solids with chemical purity >95% by HPLC/^{1}H NMR determinations (isolated yield in the range of 75−95%, Scheme 1). In the final ring-closing step, a number of conventional synthetic protocols were tested, namely, TsCl/NaOH,[8] Burgess reagent,[9] and sulfur tetrafluoride (DAST).[10] However, complex mixtures of unknown products always were obtained; this highlighted the poor chemoselectivity of the transformations. Luckily, excellent results in terms of isolated compounds were recorded using the nucleophilic fluorinating agent Deoxo-Fluor (bis-(2-methyoxyethyl)aminosulfur trifluoride) as the ring-closing promoter. This reagent, which already was successfully adopted by Wipf and co-workers to promote the direct cyclization of amino alcohols to oxazoline rings,[11] is a common fluorinating agent, which has a higher thermal stability than that of DAST. It also can be utilized at more convenient temperatures (usually 0 vs −78 °C for DAST). The accepted mechanistic pathway for the cyclization step is depicted in Scheme 2.

The O−S intermediate, which is postulated to be formed rapidly first, rearranges to give a C−F species that, by adding a base, evolves to the desired oxazoline ring. The protocol adopted offers the remarkable advantage to avoid flash chromatographic purifications of the final ligands **1** that are highly acid-sensitive.

Notably, the bis-oxazoline-amides have been isolated in high chemical purity (>95%, HPLC) by consecutive washings of the reaction crude product with appropriate solvents. Remarkably, **6a′** undergoes the double cyclization in 91% yield. Moreover, the ring-closing procedure was tolerant to steric and electronic constraints. In fact, *tert*-leucinol and phenylglycinol derivatives (**6b** and **6c′**, respectively) smoothly cyclized under optimal conditions affording the corresponding ligands in reasonable yields (65−71%). The final purification by flash chromatography was necessary only for **1c** and the isolated yield

(5) (a) Trost, B. M.; Van Vraken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1−14. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943. (d) Pfaltz, A.; Drudy, J. D., III *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5723−5726.

(6) For a recent review on chiral tetraza ligands see: Fonseca, M. H.; Konig, B. *Adv. Synth. Catal.* **2003**, *345*, 1173−1185.

(7) (a) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141−144. (b) Glorius, F.; Neuburger, M.; Pfaltz, A. *Helv. Chim. Acta* **2001**, *84*, 3178−3196.

(8) Bonini, F. S.; Giordano, M.; Fochi, M.; Comes-Franchini, M.; Bernardi, L.; Capitò, E.; Ricci, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1043−1051.

(9) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907−910.

(10) Harm, A. M.; Knight, J. G.; Stemp, G. *Synlett.* **1996**, 677−678.

(11) Philips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165−1168.

SCHEME 2. Reaction Mechanism for the Deoxo-Fluor Promoted Bis-oxazoline Ring Formation

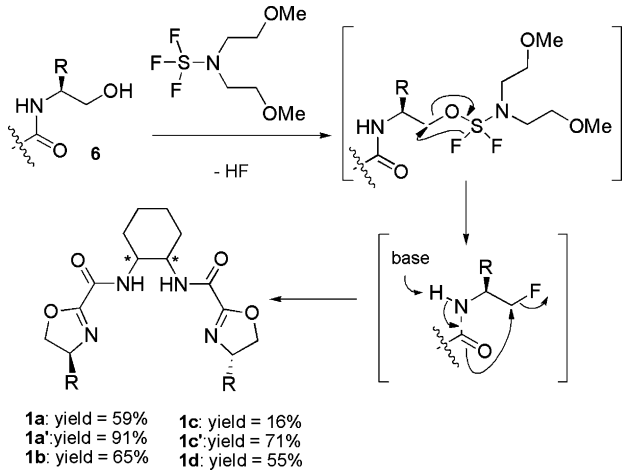
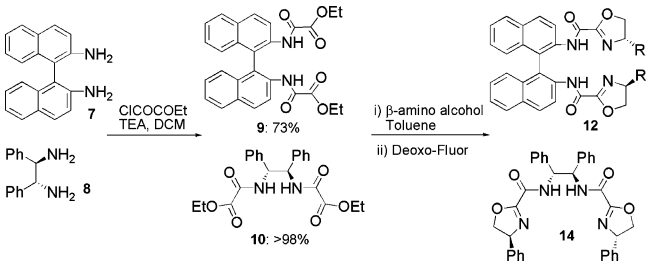


TABLE 1. Synthesis of Binaphthyl and DPEA-Based Ligands 12 and 14



entry	amine	R	yield (%)[a] diol **11**/**13**[b]	yield (%)[a] ligand[c]
1	(*R*)-**7**	*i*-Pr	87 (**11a**)	61 (**12a**)
2	(*R*)-**7**	Ph	89 (**11c**)	22 (**12c**)
3	(*R*)-**7**	Bn	95 (**11e**)	69 (**12e**)
4	(*S*)-**7**	*i*-Pr	97 (**11a′**)	66 (**12a′**)
5	(*S*)-**7**	Bn	86 (**11e′**)	17 (**12e′**)
6	(*R*,*R*)-**8**	Ph	95 (**13**)	94 (**14c**)

[a] Isolated yields (purity >95% by HPLC). [b] Toluene, reflux, 48 h. [c] Deoxo-Fluor, CH_2Cl_2, −10 °C → rt, $NaHCO_3$, 5 h.

(16%, chemical purity >95%, ^{1}H NMR dropped as a result). Because of their intrinsic structural properties (i.e., dihedral angles), enantiopure 1,2-diamines remarkably influence the catalytic activity of many C_1 and C_2 chiral ligands.[12] We have accounted for the effect of different chiral diamino units on the coordination chemistry of type-**1** ligands by applying the previously described methodology to commercially available 1,1′-binaphthyl-2-2′-diamine (**7**, DABN) and 1,2-diphenylethylene-diamine (**8**, DPEA) in enantiomerically pure form.

Here, the coupling between the diester intermediates **9** and **10** with the corresponding *β*-amino alcohols proceeded smoothly providing the desired diols in 86−97% yield (Table 1).

Analogously, the following ring-closing procedure gave ligands **12** and **14** in appreciable to excellent yields (up to 94%, entry 6). Only in a few cases (**12c**, **12e′**), the yields dropped significantly (22% and 17%, respectively) because of the required chromatographic purification of the reaction crude product.

Among the investigated ligands, the procedure failed only with **1b′** (Scheme 3) and **18** with 1,2-phenylenediamine (**15**) as the achiral backbone (Scheme 4), which yielded 43% and 17%, respectively, through conventional (TsCl/NaOH) strategy on the corresponding bis-amide precursors **6b′** and **17**, respectively.

The influence of the intramolecular distance between amidic moieties and oxazoline rings also was evaluated. With this aim, a new class of isopropylidene-bridged ligands **22** was designed with the related synthesis involving the use of malonic derivative **19** as the starting material.[13]

Optimal conditions were obtained in the condensation of **2** and **2′** with **19** by using HBTU[14] as the coupling agent that led to **20** and **20′** in 43% yield. Then, after selective removal of the benzylic groups by Pd/C catalyzed hydrogenolysis (balloon) in methanol, the crude diacid adduct was coupled directly with (*S*)-valinol **5a** in the presence of HBTU/TEA to give **21a**/**21a′** in 62% and 81% yield (two steps) from **20** and **20′**, respectively. Finally, the Deoxo-Fluor based cyclization (DCM, 0 °C, $NaHCO_3$) proved its efficiency also with this class of compounds furnishing the desired bis-oxazoline ligands **22a** and **22a′** in 22% and 37% yield, respectively (Scheme 5).

Solid-State Structure of 1a. To gain more information about the conformational features of the ligand and make reasonable assumptions on its coordination abilities, the X-ray structure of the title molecule was determined. The molecule **1a**, which contains the (*R*,*R*)-cyclohexyl-*N*,*N*-diamide inner core, has been found in two conformations in the crystal. The molecular models (A and B) are shown in Figure 2 with the same orientation of the cyclohexyl backbone.

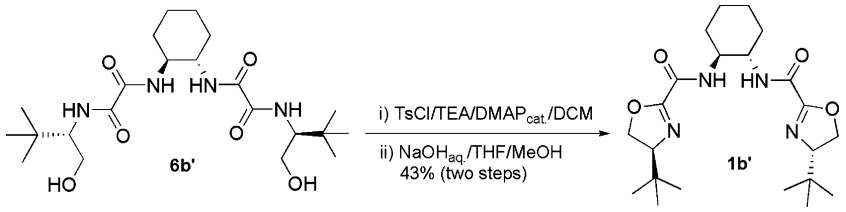
The molecules, which have potential symmetry C_2, exhibit asymmetric conformations. Significant differences because of packing effects are observed at the level of the oxazoline rings. The two conformers are almost superimposable and maintain C_2 symmetry up to the amide groups. The asymmetric conformation is stabilized in both molecules by an intramolecular hydrogen bond between the N−H group in one appendage and the carbonylic oxygen in the other (N(3)−H(41)···O(4) in A and N(7)−H(43)···O(8) in B). The bond distances indicate an interaction stronger in A (H(41)···O(4), 2.14(3) Å) than in B (H(43)···O(8), 2.42(3) Å). Also, this difference is considered a packing effect, the hydrogen bond being a soft interaction. It is worth mentioning the tendency to coplanarity between amide and pertinent oxazoline groups [dihedral angle 33.2(4)° and 6.7(6)° in A; 1.0(8)° and 5.3(6)° in B]. Interestingly, the largest deviation from coplanarity is associated to the longer C(amide)−C(oxazoline) distance (C(14)−C(15), 1.515(5) Å vs C(34)−C(35), 1.479(5) Å) and to the stronger hydrogen bond. Although the solid-state asymmetric conformation has not been detected in solution even in non-hydrogen-bonding solvents (CH_2Cl_2), it should be a preferred one among the transient conformations. When the bonding abilities of **1a** are considered, the solid-state structure suggests that the amide nitrogens are unlikely to take part in bonding to metal ions because their lone pairs are delocalized in *π* bonding. This is indicated by the short value of the N(amide)−C(amide) bonds (average value 1.32(1) Å) compared to the N(amide)−C(cyclohexyl) value (average 1.46(1) Å). The tendency to interchain hydrogen bridging and the hindered rotation around the amide−oxazoline bonds signifi-

(12) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159−2231.

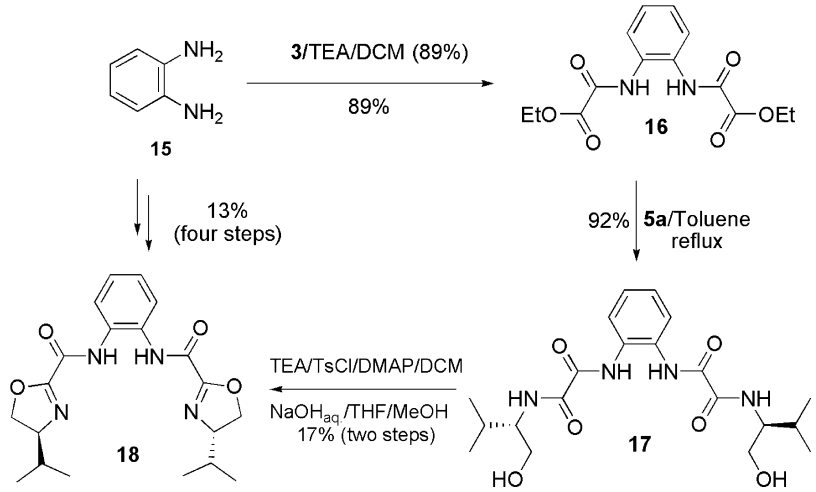
(13) Ceretti, S.; Luppi, G.; De Pol, S.; Formaggio, F.; Crisma, M.; Toniolo, C.; Tomasini, C. *Eur. J. Org. Chem.* **2004**, *20*, 4188−4196.

(14) Carpino, L. A.; Imazumi, H.; El-Faham, A.; Ferrer, F. J.; Zhang, C.; Lee, Y.; Foxman, B. M.; Henklein, P.; Hanay, C.; Mügge, C.; Wenschuh, H.; Klose, J.; Beyermann, M.; Bienert, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 441−445.

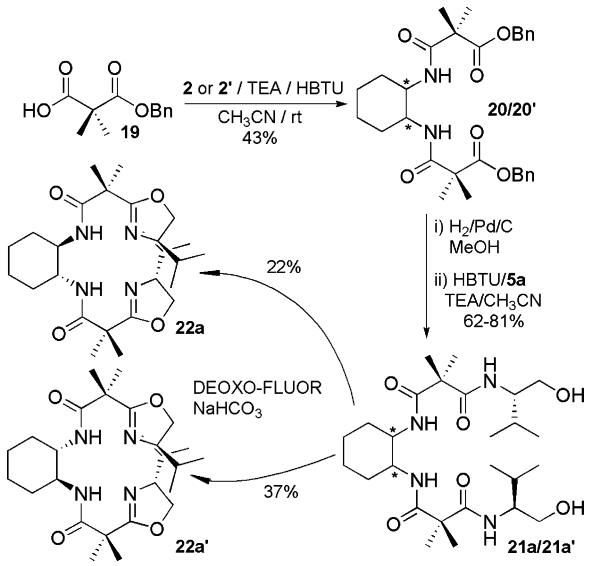
SCHEME 3. Alternative Ring-Forming Method for the Synthesis of 1b′



SCHEME 4. Preparation of 1,2-Phenylendiamine Based Ligand 18

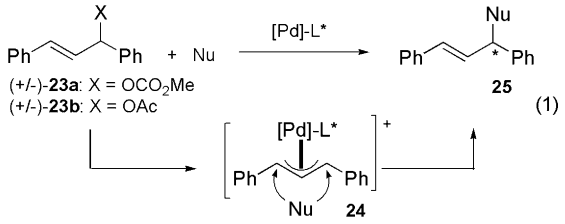


SCHEME 5. Multistep Synthesis of Malonyl Derivative Ligands 22



cantly reduces the conformational liberties of the molecule and makes more probable interchain chelation to metal centers (O(carboxamide)···N(oxazoline) or N(oxazoline)···N(oxazoline)). The following contacts present in the conformation frozen in the crystal are worth attention: O(4)···N(2), 3.522(4) Å and O(8)···N(5), 3.700(4) Å. These values easily can adjust to the ideal one in the case of coordination to a metal ion (ca. 3.06 Å) (see further on). Although these considerations are given for **1a**, they also are valid for the diastereoisomeric **1a′**, which exhibits the same trans-stereochemistry between the two appendages.

Pd-Catalyzed AAA. The AAA of 1,3-diphenyl-2-propenyl carbonate (**23a**) is employed largely as a bench test reaction for novel Pd-mediated stereoselective transformations.[5,15] The protocol allows polyfuctionalized compounds (**25**) to be synthesized in a stereocontrolled manner through the addition of both soft and hard nucleophiles to chiral π-allylpalladium intermediates (**24**) (eq 1).



The AAA of **23a** was chosen as the model reaction, and an initial survey of reaction media was carried out in the presence of the diastereoisomeric ligands **1a** and **1a′**. The reactions were conducted with 8 mol % of chiral Pd complex, which was synthesized in situ by stirring the ligand and [Pd(η^3-C_3H_5)Cl]$_2$ in 2:1 ratio in the presence of BSA/KOAc as the base system. The results obtained in several solvents are summarized in Scheme 6.

From an analysis of the data, several conclusions can be drawn. First, analogously to the findings described by Pfaltz and co-workers in the Mo-mediated AAA,[7] ligand **1a′** proved to be the matched system among the possible stereochemical combinations because it constantly delivered **25a** (Nu = DMM) with both yield and ee higher than **1a**. As expected, the stereochemistry of the process was strongly affected by the reaction medium,[16] which was the choice solvent THF. Under these conditions, product **25** was isolated in quantitative yield and with ee up to 91% in the case of **1a′**. The overall efficiency of this catalytic system also relies on the reaction temperature.

(15) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339−345.

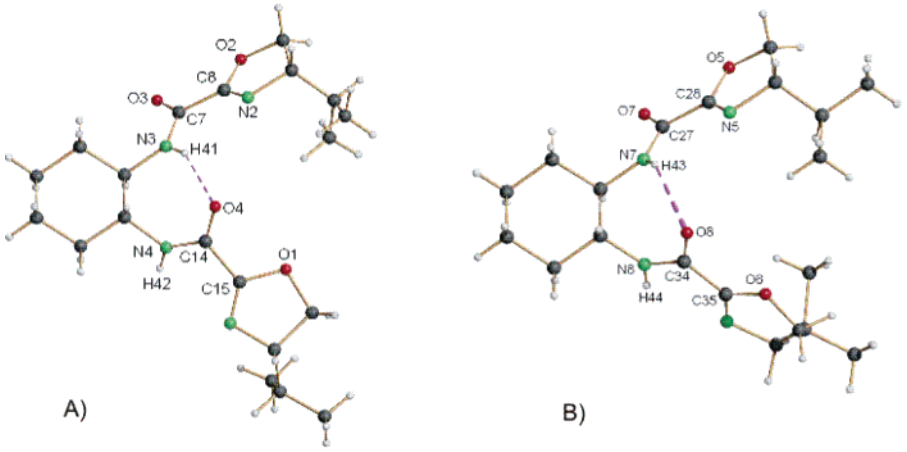
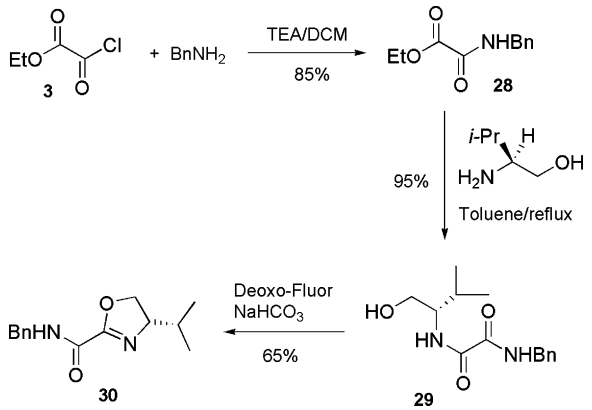


FIGURE 2. Molecular structure for the A and B conformers of **1a** determined by X-ray diffraction.

SCHEME 6. Synthesis of the Ligand 30



When the asymmetric alkylation in THF was run at rt, **25a** was isolated only in traces together with decomposition products.

Products with opposite absolute configurations were systematically isolated by using **1a** and **1a′**, respectively, indicating the relevant role of the backbone stereocenters on the final stereochemical outcome. Careful anhydrous conditions were required for the best results. In fact, when we performed the AAA of the more stable **23b** in aqueous medium (THF/H_2O 9:1), only 10% of (*S*)-**25a** was obtained (stoichiometric reaction) but with high enantiomeric excess (92% ee). These findings suggest a persistence of stereoinduction in the active Pd complex even in water and degradation of the active species during the catalytic cycle. Finally, the concentration of the catalyst was a factor influencing the final outcome in **25**. High catalyst concentrations caused rapid formation of black, insoluble Pd species, which are in equilibrium with soluble catalytically active but poor stereoselective Pd(0) clusters.[17] The optimal reaction conditions (**1a′**/THF/reflux, 13 mM catalyst concentration) finally were employed in the presence of allyl acetate (±)-**23b**. In these conditions, chemical as well as optical yields comparable to (±)-**23a** were obtained (94% yield, 92% ee).

TABLE 2. Results of AAA of 23a with Dimethyl Malonate (DMM) Catalyzed by [PdCl(C_3H_5)]$_2$/12, 14c, 18a, 22

entry[a]	L	yield (%)[b]	ee (%)[c]	config.[d]
1	**12a**	86	9	*S*
2	**12a′**	80	25	*S*
3	**12c**	85	24	*R*
4	**12e**	40	8	*S*
5	**12e′**	86	28	*S*
6	**14**	71	42	*R*
7	**18**	75	42	*S*
8	**22a**	81	0	
9	**22a′**	81	10	*S*

[a] All the reactions were carried out in THF under reflux. Reaction time 16 h. [b] Isolated yields after flash chromatography. [c] Determined by chiral HPLC (Chiralcel AD). [d] The absolute configuration was assigned by comparing the optical rotation value with literature.

The effects of the type of chiral diamine in the ligand and the distance between oxazoline ring and amide function on the overall stereoefficiency of the process were systematically assessed by testing ligands **12**, **14**, **18,** and **22** under optimal conditions (Table 2).

With regard to stereoselectivity, binaphthyl- (**12**), DPEA (**14**), and 1,2-phenylendiamine-(**18**) based ligands delivered poor enantiocontrol (8−42%, entries 1−7) with the highest ee obtained when (*R*)-DPEA was used as the chiral scaffold. In the cases of ligands **22a** and **22a′**, an unsatisfactory enantiocontrol also was obtained (0% and 10% ee, respectively, Table 2).

To properly estimate the role of the oxazoline substitution on the enantiocontrol of the reaction, the entire library of cyclohexyl-based ligands **1** was tested under optimal reaction conditions (Table 3).

From an analysis of the listed results, several conclusions can be drawn. First, the relevant role of the chiral diamine backbone in controlling the stereochemistry of the reaction outcome appears evident. By use of the ligand **1d** without stereocenters in the oxazoline ring, **25** was isolated in comparable ee (82%, entry 3 in Table 3).

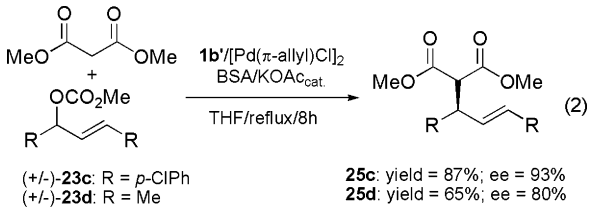
The substituents in the oxazoline units were also found to play an important role. In particular, while phenyl groups took part in the enantiocontrol only marginally (i.e., ee = 80% with **1c**, ee = 82% with **1d**, entries 2 and 3 in Table 3), hindered

(16) Interestingly, the ESI-MS performed at low potentials (10 eV) by dissolving each complex [(**1a′**)−Pd(η^3-C_3H_5)][BF_4] and [(**1a′**)−Pd(η^3-1,3-$Ph_2C_3H_3$)][BF_4] in CH_3CN showed the presence of [$(CH_3CN)_2$−Pd(η^3-C_3H_5)]$^+$ (*m*/*z* 229) and [$(CH_3CN)_2$−Pd(η^3-1,3-$Ph_2C_3H_3$)]$^+$ (*m*/*z* 381), respectively. Such evidence indicates that CH_3CN can be considered a competitive ligand for the palladium center in respect to **1a′** justifying the significant drop in catalytic activity recorded in acetonitrile under reflux (yield, 59%; ee, 47%).

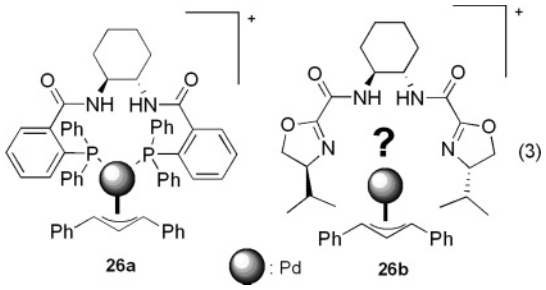
(17) For representative examples of the role of ligand-free Pd nanoparticles in catalyzing C−C bond forming reactions, see: (a) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559−1563. (b) Cassol, C. C.; Umpierre, A. P.; Machado, G.; Wolke, S. I.; Dupont, J. *J. Am. Chem. Soc.* **2005**, *127*, 3298−3299.

aliphatic groups (i.e., *i*-Pr and *t*-Bu) contributed to the enantiocontrol of the reaction as well as the stereocenters on the cyclohexyl ring (entries 1 and 4 in Table 3). Finally, among the ligands with matched configurations (*S*,*S*-diamine and *S*-amino alcohol), the one derived by **1b′** provided the highest enantiocontrol (yield = 83%, ee = 98%).

The best results were finally achieved by applying the ligand of choice (**1b′**) to the AAA with 1,3-di(4′-chlorophenyl)allyl carbonate (**23c**) and the aliphatic unhindered 1,3-dimethylallyl carbonate (**23d**). In both cases, the corresponding alkylated compounds (**25c**,**d**) were isolated in good yields and remarkable ee's (93% and 80%, respectively, eq 2).



Palladium Allylic Complexes. Although no crystallographic evidence has been reported so far, Trost modular ligands are believed to coordinate the [Pd(η^3-allyl)] fragments through a P,P-coordinating mode (**26a**) forming a 13-membered metallacycle (eq 3).[5]

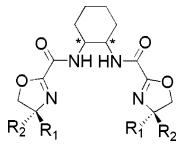


To gain information regarding the bonding modes of our class of multidentate chiral ligands (**26b**), spectroscopic as well as X-ray crystallographic analyses were performed on several [(**1a′**)−Pd(η^3-allyl)] complexes.

Here, **1a′** and [Pd(η^3-C_3H_5)Cl]$_2$ (2:1 molar ratio) were stirred at rt in the appropriate solvent for 3 h followed by exchange reaction with $AgBF_4$. The final cationic allyl complex was recovered after elimination of the insoluble materials and solvent evaporation (73% yield). The ^{1}H NMR data of a 13 mM solution of [(**1a′**)−Pd(η^3-C_3H_5)]·[BF_4] (optimal concentration for the catalytic AAA) at rt in CD_2Cl_2 and [d_8]THF appeared difficult to rationalize because of the multitude of signals. However, eight signals in the amidic proton region (7.2−8.8 ppm) were present in CD_2Cl_2 and only six in [d_8]THF. In both cases, by changing the temperature (from 30° to −90° in CD_2Cl_2 and from 50° to −90° in [d_8]THF) as well as concentrating the solution of the complex (30 mM), no coalescence was observed, but we detected a change in the relative intensities of these amidic signals. We assumed, in agreement with the recent findings by Lloyd-Jones and co-workers on Pd−allyl complexes with Trost's ligands,[18] the presence in solution of monomer−oligomer equilibria, which are affected by both temperature and concentration. Proof of oligomeric species derived from the ESI-MS:

(18) (a) Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem Commun.* **2000**, 2447−2448.

TABLE 3. Cyclohexyl-Based Ligands 1 as Chiral Promoters in the AAA of 23a[a]



			(*R*,*R*)[b]		(*S*,*S*)[b]	
entry	R_1	R_2	yield (%)[c]	ee (%)[d]	yield (%)[c]	ee (%)[d]
1	*i*-Pr	H	58	30 (*R*)	99	91 (*S*)
2	Ph	H	99	80 (*R*)	98	75 (*S*)
3	Me	Me	81	82 (*R*)		
4	*t*-Bu	H	62	44 (*S*)	83	98 (*S*)

[a] All the reactions were carried out in THF under nitrogen atmosphere by employing 8 mol % of catalyst (ratio Pd/L = 1:1) under reflux. Reaction time 16 h. [b] Configuration of the DACH-based chiral backbone. [c] Isolated yields after flash chromatography. [d] Determined by chiral HPLC (Chiralcel AD). The absolute configuration was assigned by comparing the optical rotation value with literature.

[(**1a′**)$_2$−Pd(η_3-C_3H_5)]$^+$ (50 eV, 931 *m*/*z*) and [(**1a′**)$_2$−Pd$_2$(η^3-C_3H_5)$_2$(−H)]$^+$ (50 eV, 1096 *m*/*z*).

The corresponding [(**1a′**)−Pd(η^3-1,3-$Ph_2C_3H_3$)]·[BF_4] was synthesized and isolated following the aforementioned protocol by employing [Pd(η^3-1,3-$Ph_2C_3H_3$)(μ-Cl)]$_2$[19] as the palladium source (THF−CH_2Cl_2 6:1, rt, 87% yield). The ESI-MS analysis revealed the presence of [(**1a′**)−Pd(η^3-1,3-$Ph_2C_3H_3$)] cation (*m*/*z* 691) as the major compound. The ^{1}H NMR spectra of the complex in CD_2Cl_2 and [d_8]THF (rt, 13 mM) showed only one well-defined set of signals corresponding to a C_1-symmetrical organometallic complex in 1:1 ratio between [Pd(η^3-1,3-$Ph_2C_3H_3$)] unit and **1a′** (see Experimental Section for NMR data). VT-NMR experiments in CD_2Cl_2 were conducted and a coalescence of the signals attributable to the allyl protons (H central and H anti) was observed when the temperature was lowered to −70 °C. At −90 °C, two distinct sets of signals for these protons were detected and assigned (allyl coupling constant, J = 11.0 Hz),[20] to the 1,3-disubstituted-*syn*-*syn*-allyl systems (1:1 ratio). By increase of both the temperature (50 °C, [d_8]THF, 13 mM) and the concentration (23 °C, [d_8]-THF, 64 mM) of the complex, no significant change in the spectra was observed indicating the absence of oligomeric species in solution. This fact was ascribed to the higher sterical hindrance of the diphenylallyl unit with respect to [η^3-C_3H_5], which prevents the formation of oligomeric species in solution. Interestingly, by carrying out the synthesis of [(**1a′**)−Pd(η^3-1,3-$Ph_2C_3H_3$)]·[BF_4] under catalytic conditions (THF, reflux, 13 mM, 7h), we obtained the same species synthesized at rt. NMR and IR experiments also were conducted to detect intramolecular H-bonds, which could be responsible for the C_1-symmetry in the [(**1a′**)−Pd(η^3-1,3-$Ph_2C_3H_3$)]·[BF_4] complex in solution. Both chemical shift and temperature coefficients ($\Delta\delta/\Delta T$) of the N−H amidic protons usually are employed to detect the presence of intramolecular H-bonds.[21] In the C_1-symmetrical conformation observed by NMR spectroscopy, the chemical shift

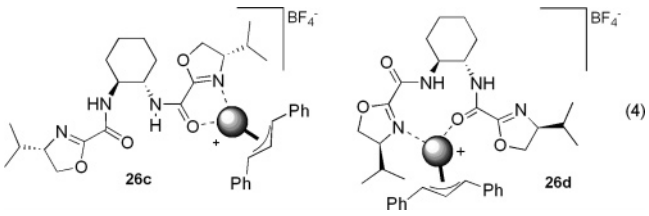
(19) Von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Rüegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265−284.

(20) Canal, J. M.; Gomez, M.; Jimenez, F.; Rocamora, M.; Muller, G.; Dunach, E.; Franco, D.; Jimenez, A.; Cano, F. H. *Organometallics* **2000**, *19*, 966−978.

(21) Belvisi, L.; Bernardi, A.; Manzoni, L.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **2000**, 2563−2569.

of one amidic proton was non-concentration-dependent (δ(N−H) = 8.32 ppm at 13, 5, and 1 mM, CD_2Cl_2), while the chemical shift of the second one was markedly affected by the concentration (δ(N−H) = 7.35 ppm at 13 mM and 6.95 ppm at 4 and 1 mM, CD_2Cl_2). This suggests that at least one amidic proton in the Pd complex was engaged in an intermolecular hydrogen bond interaction, which breaks up at high dilution. Moreover, the non-interacting nature of this proton at low concentrations (i.e., 1 mM) was confirmed by a low coefficient temperature (−1.0 ppb/K). The non-concentration-dependent amidic proton was not engaged in any hydrogen bond interaction, as demonstrated by the low coefficient temperature (−2.0 ppb/K) and high $\Delta\delta$(N−H) (>0.2 ppm in absolute value) upon addition of a competitive solvent ([*d*6]DMSO, 25 equiv). In comparison to free **1a′**, the characteristic downfield chemical shift (1.08 ppm) of the N−H amide proton in the [(**1a′**)−Pd(η^3-allyl)] complex may be explained by assuming the coordination of the carboxamide oxygen to the Pd atom.[22] Solution IR spectroscopy confirmed these conclusions with the complex showing two distinct N−H stretching at 3372 and 3290 cm^{-1} (26 mM, CH_2Cl_2). By dilution of the solution (1 mM), the N−H stretching at 3372 cm^{-1} did not change, whereas the signal at 3290 cm^{-1} disappeared. At the same time, a sharp peak (3557 cm^{-1}) appeared in the non-hydrogen-bonded N−H stretch region. Moreover, significant changes (lower frequencies) in both C═N and C═O stretchings were observed in comparison to the new ligand, supporting a N,O-coordination mode ($\Delta\nu_{C=O}$ = 20 cm^{-1}; $\Delta\nu_{C=N}$ = 16 cm^{-1}). The close resemblance between the ^{1}H NMR/IR spectra in CD_2Cl_2 and [d_8]THF allowed us to conclude that the same organometallic species is present in both solvents.[23]

In light of this evidence, some tentative molecular structures for the precatalytic species present in solution can be drawn (eq 4).



(4)

In these structures, **26c** describes a C_1-symmetrical thermodynamically stable five-membered palladacycle with N,O complexation mode, while **26d** represents an alternative tentative coordination mode with the two binding heteroatoms belonging to different pendants.[22,24,25]

To gain some insight into the structure of the species present in solution, we studied one of the crystals precipitated from a THF solution after 30 d at 4 °C by X-ray diffraction. The molecular formula was found to be [(**1a′**)−Pd_2(η^3-1,3-$Ph_2C_3H_3$)$_2$]·$[BF_4]_2$ (**29**) (Figure 4).

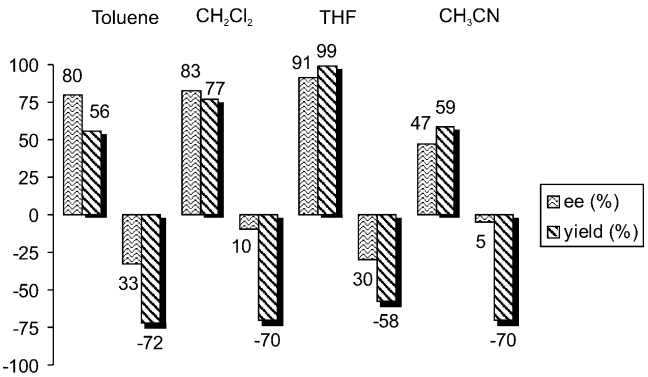


FIGURE 3. Testing the effect of the solvent in the AAA of **23a** under reflux conditions.

In complex **29,** the bis-(N,O)-complexation mode is present. In fact, each of the two [Pd(η^3-1,3-$Ph_2C_3H_3$)] units is bonded to the ligand through the oxazoline nitrogen and the amidic oxygen in each pendant forming two planar five-membered palladacycles with opposite stereochemistry of the allyl ligands (*endo*-Pd(1)(η^3-1,3-$Ph_2C_3H_3$), *exo*-Pd(2)(η^3-1,3-$Ph_2C_3H_3$)). No significant differences in the allyl−metal interactions of each diphenylallyl unit was observed as shown by the Pd−C bond lengths [C(21)−Pd(1) 2.171(8); C(22)−Pd(1) 2.110(9); C(23)−Pd(1) 2.12(1); C(36)−Pd(2) 2.14(1); C(37)−Pd(2) 2.08(1); C(38)−Pd(2) 2.18(1)]. Unfortunately, this species never has been detected in the ^{1}H NMR spectra of the allylic complex synthesized and probably derives from the initially formed complex after long standing in solution. Although **29** was not the expected species, its formation demonstrates that the N,O-bonding mode of type-**1** ligands should be taken into account.

To verify the role of the N,O-bonding mode on the active enantiodiscriminating complex in solution, we synthesized the model mono-oxazoline ligand **30**. This ligand allows only **26c**-type coordination geometry. The synthesis of C_1-amido-oxazoline **30** was conducted by initial condensation of chlorooxocetate **3** with $BnNH_2$ to give the corresponding amido-ester **28** (85% yield). After the synthesis of the (*S*)-valinol amide **29** (95% yield), the final ring-closing reaction was effectively carried out through the Deoxo-Fluor method (yield 65%, Scheme 6).

Interestingly, when **30** was used as a chiral ligand in the model reaction (THF, reflux), (*S*)-**25a** was isolated with only 19% yield and in nearly racemic form (10% ee). The poor optical and chemical yields recorded tend to exclude **26c** as a catalytically active coordination mode. Therefore, it is evident that both sidearms of the ligand are involved during either the assembling of the Pd-catalyst or the enantiodiscriminating step of the process. Further indications came also from the use in catalysis of the Boc-mono-oxazoline **34** that was readily synthesized in three steps starting from desymmetrized C_1 symmetrical **31**[25] in 38% overall yield (Scheme 7).

By use of **34** as a chiral ligand in the model reaction, (*S*)-**25a** was isolated in 85% yield and 70% ee. This result supports the Pd complexation by the carbamate carbonyl oxygen in the catalytic species and suggests an operative type-**26d** coordination mode of **1a′** justified also by the observed solid-state conformation of **1a** discussed above. The slight difference in ee between **1a′** and **34** could be attributed to steric differences between substituted oxazoline rings and the BOC protecting group.

Finally, although the data collected call for a type-**26d** coordination mode with the Pd atom in the catalytic species,

(22) Butts, C. P.; Crosby, J.; Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Commun.* **1999**, 1707−1708.

(23) Both chemical shift and N−H stretching values of the amidic proton were non-concentration-dependent (δ(N−H) = 8.08 ppm and ν(N−H) = 3269 cm^{-1} at 13 and 1 mM, respectively, in [d_8]THF).

(24) For examples of chelation modes for Trost and analogous hybrid ligands to Pd see: (a) Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817−5820.

(25) Kim, Y. K.; Lee, S. J.; Ahn, K. H. *J. Org. Chem.* **2000**, *65*, 7807−7813.

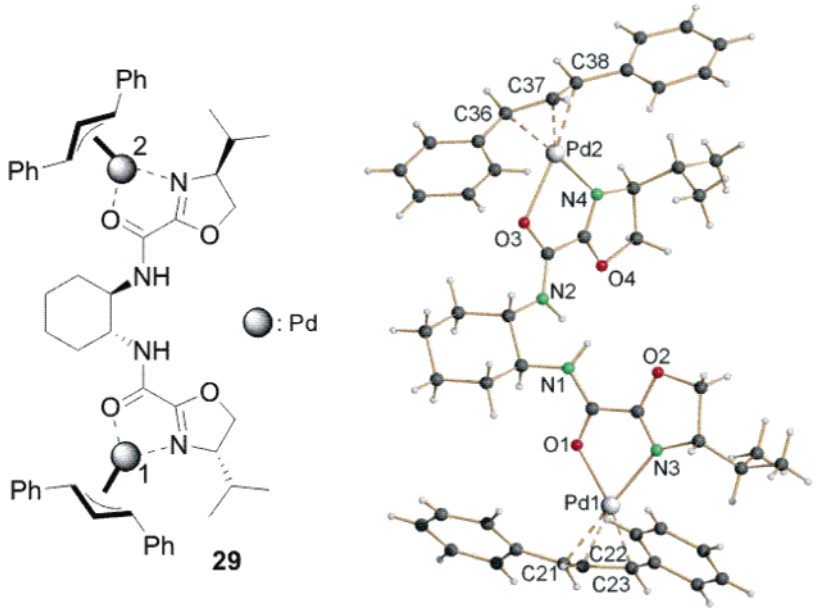
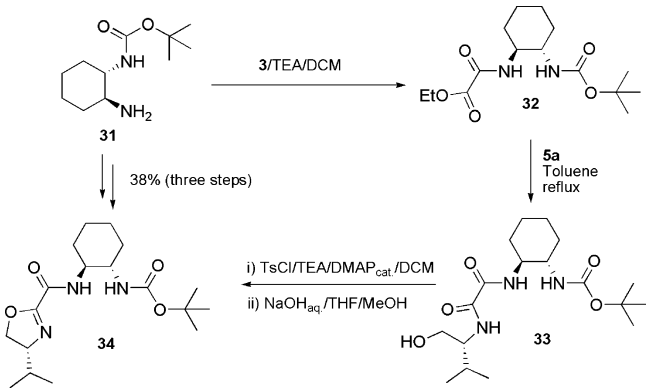


FIGURE 4. Molecular structure for the [(**1a′**)−$Pd_2(\eta^3$-1,3-$Ph_2C_3H_3)_2]^{2+}$ cation **29**, determined by X-ray diffraction. Selected bond lengths (Å) and angles (deg): O(1)−Pd(1) 2.175(6), N(3)−Pd(1) 2.146(7), O(3)−Pd(2) 2.187(6), N(4)−Pd(2) 2.104(8), O(1)−Pd(1)−N(3) and O(3)−Pd(2)−N(4) 77.5(3).

SCHEME 7. Synthesis of the C_1-Symmetrical Ligand 34



we cannot rule out that the C_2-symmetrical N,N-Pd motif might play an active role during the enantiodiscriminating step of the catalytic cycle being in rapid equilibrium with **26d**.

Conclusions

In conclusion, a new flexible three-step procedure for the synthesis of C_2-bis-oxazoline−amide ligands is described. The library of compounds was tested in Pd-catalyzed AAA isolating the desired products with high enantiomeric excess (ee up to 98%). Combined crystallographic and spectroscopic investigations call for a C_1-symmetrical N,O-chelating mode to be operating during the enantiodiscriminating step of the reaction. By virtue of the flexibility of the chiral ligands **1**, their employment in different asymmetric catalytic transformations is under way.

Experimental Section

Representative Procedure for Pd-catalyzed AAA (in situ procedure). A 25 mL two-necked flask was charged under nitrogen atmosphere with [Pd(η^3-C_3H_5)Cl]$_2$ (2.3 mg, 6.4 × 10^{-3} mmol), **1b′** (5.5 mg, 13 × 10^{-3} mmol), and 1.0 mL of anhydrous THF. The mixture was stirred at room temperature for 30 min and then allyl carbonate (0.16 mmol), dimethyl malonate (92 μL, 0.81 mmol), BSA (118 μL, 0.48 mmol), and a catalytic amount of anhydrous KOAc were added sequentially. The reaction was stirred overnight under reflux and after 16 h was judged complete by TLC analysis. Then, the reaction was quenched with a saturated solution of $NaHCO_3$ (3 mL), the two phases were separated, and the aqueous phase was extracted with AcOEt (3 × 5 mL). Finally, the organic layers were collected, dried with Na_2SO_4, and then concentrated under reduced pressure. The desired product (*S*)-**25a** was isolated as a yellow oil in 83% yield (43 mg) after flash chromatography (*c*Hex/Et_2O 90:10). The ee of the product (98%) was determined by chiral HPLC (Chiralcel AD: IPA/*n*-Hex 10:90, 1.0 mL/min flow, 214 nm, Rt_R: 9.3 min; Rt_S: 12.6 min); $[\alpha]^{25}_D = -8.8$ ($c = 0.6$ in $CHCl_3$), lit (*R*)-**25a** $[\alpha]^{25}_D = +19.2$ ($c = 1.3$ in $CHCl_3$).[26]

Acknowledgment. This work was supported by M.I.U.R. (Rome), PRIN project "Sintesi e stereocontrollo di molecole organiche per lo sviluppo di metodologie innovative di interesse applicativo" and "Nuove strategie per il controllo delle reazioni: interazione di frammenti molecolari con siti metallici in specie non convenzionali", FIRB Project (Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci innovativi), and the University of Bologna.

Supporting Information Available: Experimental procedures and analytical and spectral characterization data for all the compounds, and CIF data for **1a** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060767V

(26) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.