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Novel Chiral Diamino-Oligothiophenes as Valuable Ligands in Pd-Catalyzed Allylic Alkylations. On the "Primary" Role of "Secondary" Interactions in Asymmetric Catalysis

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Abstract: A new class of chiral C_2-symmetrical diamino-oligothiophenes is described to be effective in catalyzing Pd-mediated asymmetric allylic alkylations in a highly enantioselective manner. The combination of experimental as well as crystallographic evidence revealed the key role played by sulfur-based heteroaromatic rings in the stereodiscriminating step of the procedure. In particular, unprecedented non-covalent secondary interactions between the inner thiophene and the metal center proved to be essential to create the stereochemical environment necessary in order to guarantee excellent levels of chemical and optical yields.

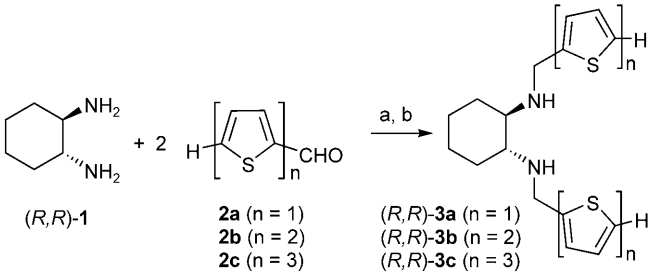
Keywords: asymmetric catalysis; crystal structure; oligothiophenes; secondary interactions; palladium complexes

Asymmetric organic as well as organometallic catalysis has blossomed into a mature field over the last decades.[1,2] Accordingly, the search for new chiral organic molecules effectively acting in the control of stereochemical outcomes of organic transformations is almost a daily task for numerous synthetic chemists.

Oligothiophene molecular motifs are pivotal candidates in the molecular material scenario due to their remarkable electrical and optical properties.[3,4] Taking advantage of the extremely flexible coordination mode of the sulfur-containing five-membered rings,[5,6] much effort has also been devoted to the preparation and characterization of several metallo-oligo- and polythiophene hybrid materials.[7] The unique coordinating features in combination with their ready synthetic accessibility render chiral thiophene derivatives potential candidates as ligands also in the field of asymmetric organometallic catalysis. However, only a few examples of their application have been reported to date.[8]

Herein, we describe our preliminary findings in the synthesis, structural characterization and application of a new class of C_2-symmetrical diamino-oligothiophenes (**3**, DATs)[9] in the highly stereoselective Pd(0)-catalyzed asymmetric allylic alkylation (AAA) of malonates with both linear hindered and unhindered substrates.[10] Moreover, the presence of an intramolecular "secondary/weak" interaction[11] in the catalytic complex between one of the thienyl rings and the palladium center is discovered to play an active role in order to guarantee chemo-enzymatic levels of chemical as well as optical yields in the final product.

A series of new chiral (*R,R*)-diamino-oligothiophenes (**3**) bearing one (T1), two (T2) or three (T3) thienyl units in each *N*-pendant, was prepared in high yields under mild conditions following the strategy depicted in Scheme 1.



Scheme 1. *Reagents and conditions:* a) $MgSO_4$, CH_2Cl_2, room temperature, 24–48 h; b) $NaBH_4$, MeOH, room temperature or $NaBH_3CN$/HCl, THF/MeOH, 0 °C to room temperature for **3c**.

In detail, the chiral C_2-symmetrical thienyldiamines **3a**–**c** were isolated by treating the commercially available enantiomerically pure (*R,R*)-1,2-cyclohexanediamine (**1**)[12] with the thienylaldehydes **2a**–**c** followed by reduction of the intermediate diimines. Best experimental conditions were found in the use of $NaBH_4$ as a reductant for **3a** and **b** (overall yield 88% and 50% respectively) and $HCl_{dry}/NaBH_3CN$[13] in the case of **3c** (yield 72%, two steps).

It is worthy to note that all these diamino ligands **3a**–**c** can be obtained in relatively large amounts without any time-consuming intermediate/final chromatographic purification.

Due to the well known affinity of functionalized thienyls and oligothienyls for Pd(II),[14] we decided to explore these compounds as chiral ligands in the Pd-catalyzed allylic substitution of carbonate **4** as the probe reaction.

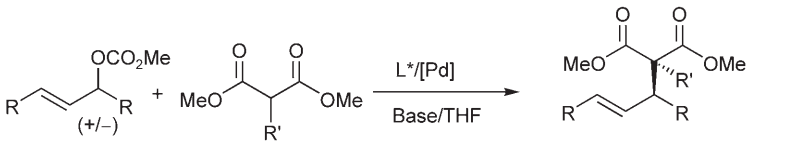
The data collected in Table 1 reveal that the diamines **3** are efficient ligands in the $[Pd_2(dba)_3]\cdot CHCl_3$-catalyzed AAA of **4a**,**b** with dimethyl malonate (**5a**). In particular, the desired (*S*)-dimethyl 1,3-diphenylallylmalonate (**6aa**) was isolated in variable yields and enantiomeric excess.

To our delight, we recorded the unique activity of A-T2 (**3b**) and A-T3 (**3c**), which afforded **6aa** and **6ba** in quantitative isolated yields and 99%, 95% ee, respectively (entries 2, 3, 5). During the preparation of the manuscript, Kim and co-workers reported on the synthesis and application of **3a** in the AAA of 1,3-diphenyl-2-propenyl acetate under different reaction conditions ($[Pd]=[Pd(\eta^3\text{-}C_3H_5)Cl]_2$), obtaining **6aa** in 50% GC conversion and 88.5% ee.[15]

It is worthy to note that this level of stereoinduction is one of the highest obtained in Pd-catalyzed AAA processes by using C_2-phosphine-free chiral ligands.[16] Remarkably high was also the enantiodiscrimination reached with **3b** in the presence of the more challenging dimethyl methylmalonate (**5b**) which afforded (*R*)-**6ab** in 80% yield as a single enantiomer (ee > 98% by chiral shift ^{1}H NMR, entry 4, Table 1).

Although many papers and ligands have been reported describing highly stereoselective AAA of malonates in the presence of hindered allylic compounds such as **4a**,**b**, only very few of them involved classes of chiral ligands that displayed poor substrates specificity.[17] In this scenario, asymmetric alkylation of the unhindered 1,3-dimethylallyl carbonate (**4c**) constitues a much more probing test in order to evaluate the catalytic activity of chiral ligands. In the light of these considerations, we tested the effectiveness of our ligand of choice (**3b**) in AAA with dimethylallyl carbonate (**4c**). After a brief survey of experimental conditions that involved palladi-

Table 1. Screening of chiral ligands in the Pd-catalyzed allylic substitution with carbonates **4**.[a]



4a: R = Ph
4b: R = *p*-ClC$_6$H$_4$
4c: R = Me

5a: R' = H
5b: R' = Me

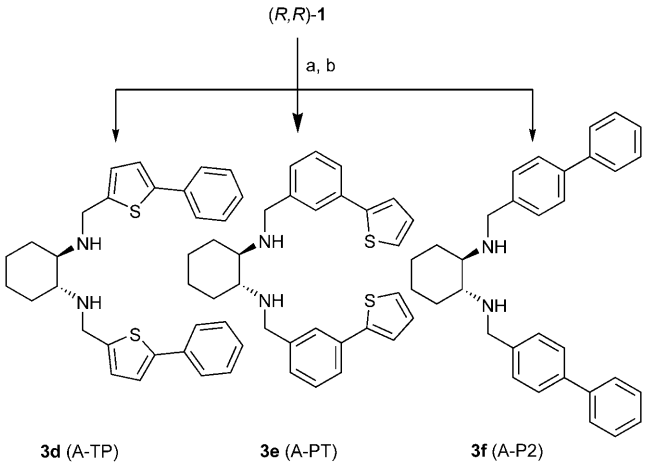
(*S*)-**6aa**: R = Ph, R' = H
(*R*)-**6ab**: R = Ph, R' = Me
6ba: R = *p*-ClC$_6$H$_4$, R' = H
(*S*)-**6ca**: R = Me, R' = H

Entry	L*	[Pd]	Base	4	5	6	Yield [%][b]	ee [%][c]
1	**3a**	$[Pd_2dba_3]\cdot CHCl_3$	BSA/KOAc	**4a**	**5a**	**6aa**	65	45 (*S*)
2	**3b**	$[Pd_2dba_3]\cdot CHCl_3$	”	**4a**	**5a**	**6aa**	96	99 (*S*)
3	**3c**	$[Pd_2dba_3]\cdot CHCl_3$	”	**4a**	**5a**	**6aa**	99	99 (*S*)
4	**3b**	$[Pd_2dba_3]\cdot CHCl_3$	”	**4a**	**5b**	**6ab**	80	>98[d] (*R*)
5	**3b**	$[Pd_2dba_3]\cdot CHCl_3$	”	**4b**	**5a**	**6ba**	99	95
6	**3b**	$[Pd_2dba_3]\cdot CHCl_3$	”	**4c**	**5a**	**6ca**	71	10 (*S*)
7	**3b**	$[Pd_2dba_3]\cdot CHCl_3$	NaH	”	”	**6ca**	20	36 (*S*)
8	**3b**	$[Pd(\pi\text{-}C_3H_5)Cl]_2$	NaH	”	”	**6ca**	83[e]	77 (*S*)
9	**3b**	$[Pd(\pi\text{-}C_3H_5)Cl]_2$	Cs_2CO_3	”	”	**6ca**	98[f]	80 (*S*)
10	**3b**	$[Pd(\pi\text{-}C_3H_5)Cl]_2$	Cs_2CO_3	”	”	**6ca**	45[g]	90 (*S*)

[a] All the reactions were carried out in anhydrous THF at room temperature, by using a 1:1 L:Pd ratio (16 h).
[b] Isolated yields after flash chromatography.
[c] Determined by chiral HPLC (**6aa**, **6ab**) and by chiral GC for **6ca**. The absolute configuration was assigned by comparison with the known optical rotation value.
[d] Determined by ^{1}H NMR with Eu(hfc)$_3$.
[e] Reaction time 36 h.
[f] Reaction time 36 h in the presence of $AgSbF_6$ (10 mol %).
[g] Reaction carried out at 0 °C, with $AgSbF_6$ (10 mol %), 72 h.

um salts, bases, solvents and additives (a collection of results is reported in Table 1, entries 6–10), we were delighed to find out that, by using $[Pd(\pi\text{-}C_3H_5)Cl]_2$ as the palladium source, Cs_2CO_3 (2 equivs.) as the base and 10 mol % of $AgSbF_6$,[17a] **3b** furnished (*S*)-**6ca** in almost quantitative yield and with high ee (80%, entry 9). Again, to further improve the enantioselectivity in **6ca**, the influence of the temperature was envisaged by running the model reaction at 0 °C. Herein, beside the observed drop in reaction rate (yield 45%), the enantiomeric excess reached 90%, that represents one of the highest levels of stereoinduction obtained to date for **4c** in the presence of phosphorus-free ligands (entry 10).

To gain some insights into the factors governing the activity of these oligothienyl ligands in Pd species we synthesized and tested, in the aforementioned model allylic substitution, a series of properly designed chiral C_2-diamine ligands (**3d**–**3f**, Scheme 2) in which one or both the thienyl rings were alternatively replaced by benzene rings.



Scheme 2. *Reagents and conditions:* a) aldehyde, $MgSO_4$, CH_2Cl_2, room temperature, 24–48 h; b) $NaBH_4$, MeOH, 0 °C to room temperature. Overall yield: **3d**: 40%; **3e**: 39%; **3f**: 60%.

From the data collected in Table 2 some conclusions can be drawn. i) The crucial participatory role of the thienyl rings in the enantiodiscriminating step of the process was unambiguously proved by employing A-P2 as the chiral promoter. In this case in fact, **6aa** was isolated in poor yield (30%) and low enantioselectivity (33%, entry 2). ii) The pivotal role of the closest thienyl units (inner thiophenes) to the stereogenic centers of the ligand was demonstrated by comparative stereoselective allylic substitutions of **5** in the presence of A-TP (yield: 99%, ee: 97%) and A-PT (yield: 60%, ee: 50%). iii) The second (outer) rings (thienyl, **3b** or phenyl, **3d**) exerted a positive influence on the stereochemical outcome of the process [A-T1, (**3a**) ee: 45%; A-T2, (**3b**) ee: 99%; A-TP (**3d**) ee: 97%].

Table 2. Proving the role of thienyl rings in the Pd-catalyzed allylic substitution with carbonate **4a**.[a]

Entry	L*	Time [h]	**6**	Yield [%][b]	ee [%][c]
1	**3d**, (A-TP)	48	**6aa**	99	97 (*S*)
2	**3e**, (A-PT)	24	**6aa**	60	50 (*S*)
3	**3f**, (A-P2)	48	**6aa**	30	33 (*S*)

[a] All the reactions were carried out in anhydrous THF at room temperature, by using 5 mol % of $[Pd_2(dba)_3]\cdot CHCl_3$ as the Pd source and 1:1 L:Pd ratio.
[b] Isolated yields after flash chromatography.
[c] Determined by HPLC analysis with chiral column (Chiralcel AD). The absolute configuration was assigned by comparison with the known optical rotation value.

In an effort to learn more about the nature of these unprecedented chiral Pd catalysts, we synthesized and characterized the $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3b})][BF_4]$ and $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3f})][BF_4]$ that were isolated as air/moisture stable yellow solids (64%, 80% yields, respectively) by reacting **3b**/**3f** with $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ (2:1 ratio) followed by an exchange reaction with $AgBF_4$. The structure of the cation $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3b})]^+$ was established by X-ray diffraction and its stereogeometry is illustrated in Fig. 1A.

Interestingly, the potentially multidentate ligand **3b** coordinates to Pd(II) through the nitrogen atoms forming a five-membered palladacycle in an envelope conformation, with the nitrogen donors exhibiting opposite configurations.[18] The bithiophene pendants are packed in an orderly way and S(2) exhibits a significant van der Waals interaction with palladium [3.34(1)Å].[19] It is reasonable to attribute attractive character to this contact as the estimated sum of the van der Waals radii is 3.4 Å.[20] The allyl unit is coordinated almost symmetrically but some 20% of the molecules show the alternative orientation with the central carbon pointing downwards. As usual with the allyl ligand the asymmetric environment is not fully successful in influencing its way of coordination.

The determining role of the intramolecular S(2)...Pd interaction in the enantiodiscriminating step of the reaction can be appreciated by inspection of the molecular structure of the poorly effective $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3f})][BF_4]$ complex (Fig. 1B). Here, although a similar overall coordination geometry is found, the phenyl-Pd interaction is not of special significance [Pd···C(13) 3.55(1)Å and Pd···H(13) 3.20(2)Å].[21] Even more telling is the superimposition diagram of these structures containing **3b** and **3f** (Fig. 2). It is evident that the 1,4-diphenyl unit is less effective in producing beneficial steric hindrance than the bent bithienyl counterpart when properly oriented by the sulfur-palladium interaction. Therefore, the weak Pd···S interaction is crucial in generating a more stringent chiral environment around the metal center.[22] Moreover, since the catalytic efficiency of li-

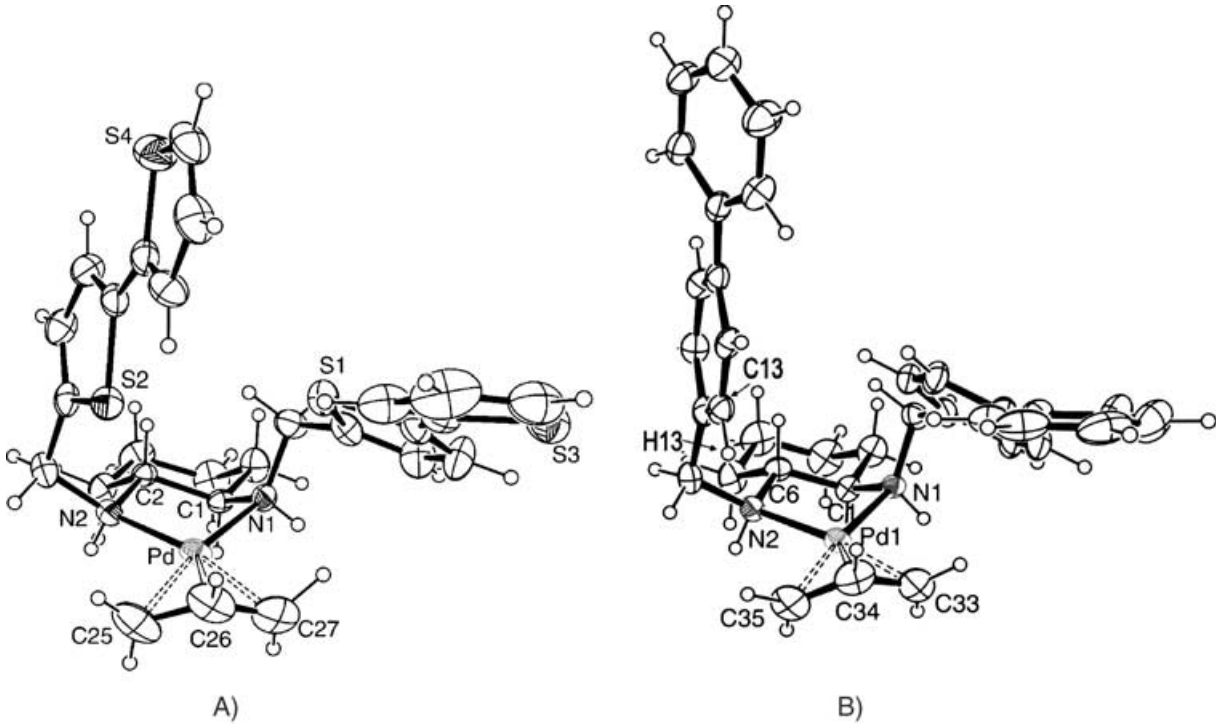


Figure 1. A) X-ray molecular structure of $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3b})]^+$ as $[BF_4]^-$ salt. The dominant orientation (80%) of the allyl ligand is shown. Selected bond lengths (Å): Pd–C(25) 2.103(6), Pd–C(26) 2.126(7), Pd–C(27) 2.112(6), Pd–N(1) 2.111(4), Pd–N(2) 2.143(3), C(25)–C(26) 1.402(12), C(26)–C(27) 1.323(14). Configurations of the stereogenic centers: N(1)(*R*), N(2)(*S*), C(1)(*R*), C(2)(*R*), conformation of the chelate ring λ. **B)** X-ray molecular structure of $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3f})]^+$ as $[BF_4]^-$ salt. The dominant orientation (60%) of the allyl ligand is shown. Selected bond lengths (Å): Pd(1)–C(33) 2.066(6), Pd(1)–C(34) 1.999(9), Pd(1)–C(35) 2.066(5), Pd(1)–N(1) 2.086(4), Pd(1)–N(2) 2.081(4), C(33)–C(34) 1.283(19), C(34)–C(35) 1.306(16). Configurations of the stereogenic centers: N(1)(*R*), N(2)(*S*), C(1)(*R*), C(2)(*R*), conformation of the chelate ring λ.

gands **3b** and **3c** on aromatic carbonates are almost equal, we can conclude that the third thienyl ring in **3c**, bonded with 2,2′ connectivity, has no significant role in the enantioselectivity of the reaction.

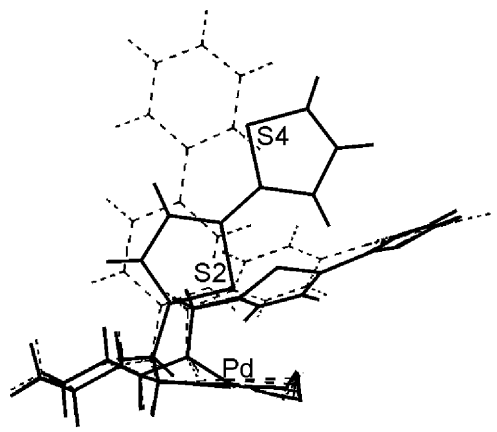


Figure 2. Superimposition of the $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3b})]^+$ (solid lines) and $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3f})]^+$ (dashed lines) complexes.

Finally, to prove that the crystallographic information was consistent with the species present in solution, we synthesized the $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(\mathbf{3b})][BF_4]$ and the isolated complex was tested in the model reaction. In particular, the air-stable orange solid (95% yield) showed a less fluxional ^1H NMR spectrum (room temperature, CD_3CN) with respect to $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3b})][BF_4]$, in which the presence of a single conformer, probably controlled by the phenyl/thienyl sterical constrains, was observed. Attempts to prepare crystals of the $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(\mathbf{3b})][BF_4]$ have not been successful so far, however, the isolated cationic tetrafluoroborate 1,3-diphenylallyl-Pd species confirmed its authenticity as the catalyst in the AAA of **4** with **5a**, giving rise to (*S*)-**6aa** in 75% yield and 99% ee.

In conclusion, in this communication we have presented our preliminary findings in the synthesis, crystallographic characterization and application in asymmetric catalysis of a new series of chiral thiophene-based oligomers. The unprecedented coordination features revealed by DATs candidate such a type of chiral motif as easily tunable ligands for asymmetric metallo-catalyzed transformations. Moreover, studies addressed towards the investigation of chirooptical/electrochemical prop-

erties of these systems both in liquid and solid phases are currently under way and will be published in due course.

Experimental Section

Representative Procedure for Pd-Catalyzed AAA (*in situ* Procedure)

A 25-mL two-necked flask was charged, under a nitrogen atmosphere, with $[Pd_2(dba)_3]\cdot CHCl_3$ (2.6 mg, 2.5×10^{-3} mmol), diamine **3b** (2.4 mg, 5.0×10^{-3} mmol) and 1.5 mL of anhydrous THF. The mixture was stirred at room temperature for 5 min (the colour of the solution gradually turned from purple to brown) then **4a** (14 mg, 0.05 mmol), dimethyl malonate (29 μL, 0.25 mmol), BSA (12 μL, 0.05 mmol) and a catalytic amount of KOAc were added sequentially. The reaction mixture was stirred overnight at room temperature and, after 24 h, was judged complete by TLC. The reaction was then quenched with a saturated solution of $NaHCO_3$ (3 mL), the two phases 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*)-**6aa** was isolated as a yellow oil after flash chromatography (*c*-hex/Et_2O, 9/1); yield: 16 mg (96%). The ee of the product (99%) 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.). $[\alpha]_D$: −9.0 (*c* 0.7, $CHCl_3$), lit. (*R*)-**6aa** $[\alpha]_D$: +19.2 (*c* 1.3, $CHCl_3$).[23]

(*R*)-**6ab** was obtained by an analogous procedure starting from 0.05 mmol of **4a** and with use of **5b** as the malonate. Through purification (flash chromatography, *c*-hex/Et_2O, 8/2) of the reaction crude, **6ab** was isolated as a yellow oil in 99% yield (18 mg) and ee > 98%. The enantiomeric excess of the product was determined by ^1H NMR chiral shift with $Eu(hfc)_3$ (MeO groups). $[\alpha]_D$: +44.0 (*c* 0.4, $CHCl_3$), lit. (*R*)-**6ab** $[\alpha]_D$: +60.1 (*c* 1.2, CH_2Cl_2).[24]

In the case of 1,3-di(4′-chlorophenyl)allyl methyl carbonate (**4b**), the reaction was carried out with the above described conditions for 24 h. After work-up, **6ba** was isolated by flash chromatography (*c*-hex/Et_2O, 9/1) as a pale yellow oil in 99% yield and 95% ee. $[\alpha]_D$: −2.5 (*c* 1.02, $CHCl_3$), lit. (−)-**6ba** $[\alpha]_D$: −2.8 (*c* 1.12, $CHCl_3$), 93% ee.[25]

(*S*)-**6ca** was obtained by an analogous procedure starting from 0.15 mmol of **4c** and with use of **5a** as the malonate. The reaction was carried out at 0 °C for 72 h. $AgSbF_6$ (10 mol %) was added during the catalyst preparation and Cs_2CO_3 (98 mg, 0.30 mmol) proved to be the base of choice. Through purification (flash chromatography, *c*-hex/AcOEt, 95/5) of the reaction crude **6ca** was isolated as a yellow oil in 45% yield and 90% ee. The enantiomeric excess of the product was determined by chiral GC analysis (method: 50 °C for 6 min, ramp of 1 °C/min to 180 °C for 15 min, Rt_S: 43.8 min.; Rt_R: 44.0 min.). $[\alpha]_D$: −12.0 (*c* 0.7, $CHCl_3$), lit. (*S*)-**6cb** $[\alpha]_D$: −28.0 (*c* 1.4, $CHCl_3$).[26]

X-Ray Crystallographic Study

Crystal data of [Pd(η³-C₃H₅)(3b)][BF₄]: $C_{27}H_{31}BF_4N_2PdS_4$; $M=704.99$, monoclinic, $a=19.760(2)$, $b=9.7360(9)$, $c=16.183(2)$ Å, $\beta=97.694(3)^\circ$, $V=3085.2(5)$ Å^3, $T=293(2)$ K, space group *C*2, $Z=4$, $\mu=0.917$ mm^{-1}, 18613 reflections collected 7035 reflections $I>2\sigma$ (I) ($R_1=0.0531$ and $wR_2=0.1207$), CCDC 258610.

Crystal data of [Pd(η³-C₃H₅)(3f)][BF₄]: $C_{35}H_{39}BF_4N_2Pd$; $M=680.89$, monoclinic, $a=8.278(3)$, $b=17.853(6)$, $c=10.509(3)$ Å, $\beta=111.635(7)^\circ$, $V=1443.7(8)$Å^3, $T=293(2)$ K, space group $P2_1$, $Z=2$, $\mu=0.698$ mm^{-1}, 15548 reflections collected 5891 reflections $I>2\sigma$ (I) ($R_1=0.0514$ and $wR_2=0.1297$), CCDC 258611.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 258610 for $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3b})][BF_4]$ and no. CCDC 258611 for $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{3f})][BF_4]$. 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].

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