New chiral diamino-bis(*tert*-thiophene): an effective ligand for Pd- and Zn-catalyzed asymmetric transformations†

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Enantiomerically pure diamino-bis(*tert*-thiophene) 1b proved to be a valuable and flexible chiral ligand for Pd- and Zn-catalyzed transformations, allowing for high levels of stereocontrol in asymmetric allylic alkylation (ee up to 99%) and hydrosilylations of prochiral carbonyls (ee up to 97%).

Asymmetric organometallic catalysis is a well established route to the synthesis of stereochemically defined poly-functionalized compounds and the discovery of new sources of inspiration for the design of chiral catalysts is a long-sought goal for numerous synthetic chemists.[1,2]

In this context, we recently focused on the suitability of hybrid metallo-organic semiconductors chemistry as a valuable guideline in the development of new leads in asymmetric transformations.[3] As initial contributions, we described diamino-bithiophene **1a** (DAT2, Fig. 1) as a ligand for Pd-[4] and Cu-catalyzed[5] enantioselective reactions. The ability of oligothiophenes to shuttle charges across their skeletons enabled the modulation of the catalytic activity of Pd–**1a**-type complexes through *remote molecular* functionalization of the organic ligand.[6]

The versatility in molecular design of thiophene chemistry[7] allows for the introduction of longer oligothienyl units as sidearms, this being interesting for a variety of applications such as hybrid dyes for optoelectronics, NLO-phores and fine-tuning chiral organometallic catalysts.[8] Therefore, we decided to examine the properties of **1b** (*N,N′*-bis-[2,2′;5′,2″]*tert*-thiophen-5-ylmethyl-cyclohexane-1,2-diamine) as a chiral ligand in bench-test asymmetric organometallic transformations such as asymmetric allylic alkylation (AAA, Pd)[9] and hydrosilylations of prochiral carbonyls (Zn).[10]

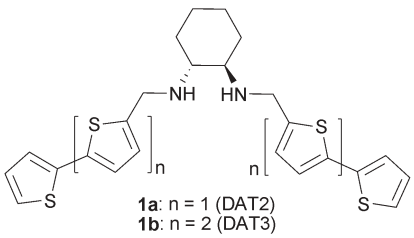

Fig. 1 Enantiomerically pure DAT ligands.

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The synthesis of T3-CHO **2**[4a] was accomplished by replacing the environmentally undesiderable Stille cross-coupling with a Suzuki reaction.[11] In particular, the direct coupling of commercially available 5-bromo-2-thiophenecarboxaldehyde and 5-(4,4,5,5-tetramethyl-1,2,3-dioxaborolan-2-yl)-2,2′-bithiophene led to T3-CHO in 55% isolated yield (Scheme 1). Ligand **1b** was finally obtained by condensing **2** with the enantiomerically pure (1*R*,2*R*)-cyclohexanediamine followed by reduction of the imine moieties with $HCl(Et_2O)$–$NaBH_3CN$ (72% overall yield).

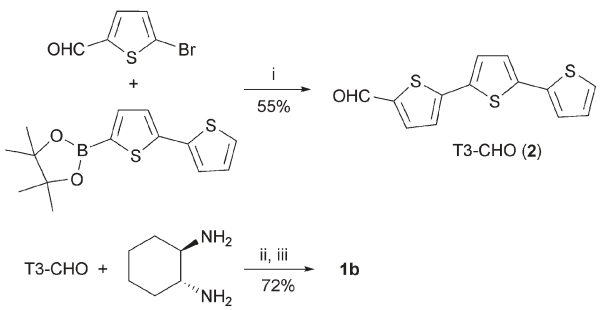
With the ligand in hand, we examined the generality in scope of the corresponding (*R,R*)-**1b**–[Pd] complex in the asymmetric Pd-catalyzed allylic alkylation.

Hindered as well as unhindered acyclic allyl carbonates (**3a–c**) were reacted with dimethyl malonates **4** as nucleophiles and the results are collected in Table 1.[12] Besides the high enantiomeric excess already recorded with sterically hindered 1,3-diphenylallyl carbonate **3a** (99% yield, 99% ee, entry 1),[4] DAT3 guaranteed good results also with the chloro-substituted carbonate **3b** (94–97% ee, entries 3–4) and a moderate drop in optical outcome was observed with dimethyl methylmalonate **4b** in combination with **3a** (85% ee, entry 2).

Interestingly, the longer thienyl sidearms of **1b**, with respect to **1a**, engendered higher stereoinduction and activity with challenging 1,3-dimethylallyl carbonate **3c** (yield 55%, ee 91%, entry 5).[4a]

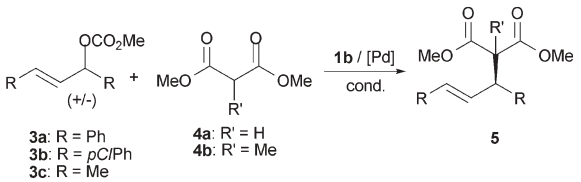
In this case, a brief survey of reaction conditions indicated the use of $[PdCl(\pi\text{-allyl})]_2$, in combination with $AgSbF_6$ as optimal reaction parameters. It is known that the use of scavengers for halide counterions speeds up the reaction rates of Pd-catalyzed AAA[13] and cross-couplings.[14]

Interestingly, the recently described X-ray structure for C_1-symmetry *R,S*-(1*R*,2*R*)-**1b**–$[Pd(\eta^3\text{-}C_3H_5)][PF_6]$[15] provides insight into the effect of the *tert*-thienyl ancillary pendants on



Scheme 1 Synthesis of **1b**. *Reagents and conditions*: i. $PdCl_2(PPh_3)_2$, Na_2CO_3, EtOH, DME, 24 h, reflux; ii. $MgSO_4$, DCM, rt; iii. HCl, $NaBH_3CN$, THF, 0 °C → rt.

Table 1 Use of **1b** as the ligand in Pd-catalyzed asymmetric allylic alkylation[a]



Entry	Cond.	3/4	5	Yield [%][b]	Ee [%][c]
1	A	**3a/4a**	**5aa**	99	99 (*S*)
2	A	**3a/4b**	**5ab**	95	85 (*S*)
3	A	**3b/4a**	**5ba**	82	94 (–)
4	A	**3b/4b**	**5bb**	85	97 (–)
5	B	**3c/4a**	**5ca**	55	91 (*S*)[d]

[a] A: $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol%), BSA, AcOK, THF, rt. B: $[PdCl(\pi\text{-allyl})]_2$ (5 mol%), $AgSbF_6$, NaH, THF, 0 °C. [b] Isolated yields after flash chromatography. [c] Determined by HPLC with chiral column (OD, AD). [d] Determined by GC (crosslinked 5% PH ME Siloxane, Megadex 5).

the stereochemical outcome of the reactions (Fig. 2). In particular, **1b**–$[Pd(\eta^3\text{-}C_3H_5)][PF_6]$ displayed a similar conformation to the corresponding **1a**–$[Pd(\eta^3\text{-}C_3H_5)][BF_4]$,[4a] in which the *tert*-thienyl substituents at the nitrogen atoms showed both pseudo equatorial and pseudo axial configuration.[16]

It is noteworthy that the long and electron-rich oligoaryl sidearms of **1b** concur in tightening the intramolecular sulfur–palladium contact (S(4)…Pd(1): 3.306(2) Å), with a consequent enhancement in enantiodifferentiation during the nucleophilic attack.[6]

Moreover, the known tendency of electron-rich ancillary ligands to accelerate oxidative additions of Pd(0) species could account for the observed improvement in overall reaction rate with ligand **1b**.[17]

The precatalytic **1b**–$[Pd(\eta^3\text{-}Ph_2C_3H_3)][PF_6]$ complex was synthesized in 87% yield through a variation of a known procedure (see ESI for details).[4a]

Although all attempts to obtain crystallographic information on **1b**–$[Pd(\eta^3\text{-}Ph_2C_3H_3)][PF_6]$ were unfruitful, a ^{1}H-NMR investigation (CD_2Cl_2, VT) revealed the presence of two *C*-1 symmetrical species (65 : 35 ratio at rt)[18] carrying *syn–syn* allyl units exclusively (J = 11–13 Hz).[19] The similarity of this spectrum with that of **1a**–$[Pd(\eta^3\text{-}Ph_2C_3H_3)]$ [4.64 (d, J = 9.2 Hz, $1H_{anti}$), 5.46 (d, J = 9.2 Hz, $1H_{syn}$), 6.64–6.71 (m, $1H_{central}$)][6] calls for an analogous five-membered *N*,*N*-palladacycle motif to be present in solution for **1b**, as well.

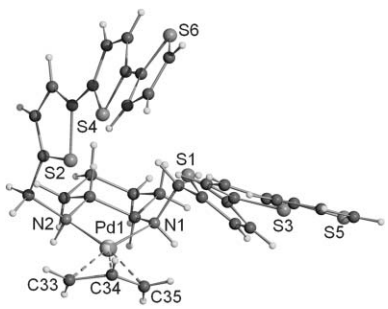


Fig. 2 X-ray molecular structure of **1b**–$[Pd(\eta^3\text{-}C_3H_5)]^+$ as a $[PF_6]^-$ salt.

The versatility of **1b** in asymmetric synthesis was also highlighted in zinc-catalyzed stereoselective hydrosilylations of prochiral arylketones by using PMHS as an environmentally benign reducing agent (Table 2).‡ This ligand accelerated protocol, introduced earlier by Mimoun,[20] is of great interest also for large scale production and involves chiral diamine–zinc complexes as active catalytic species.[21] Gratifyingly, the *in situ* formed (*R*,*R*)-**1b**–$ZnEt_2$ complex (5 mol%) proved to be better performing with respect to the analogous (*R*,*R*)-**1b**–$ZnMe_2$ in the reduction of **6a** (entries 1 and 2).

To determine functional group compatibility, a series of aryl alkyl ketones **6** were subjected to reduction. Substituents on the aryl ring as well as in the aliphatic chain were tolerated with ee up to 83%. Remarkably, the present level of stereoinduction is among the highest recorded to date in zinc-catalyzed PMHS-based reductions.[22]

Prompted by these promising results, **1b** was efficiently employed also in the hydrosilylation of the challenging phosphoimine **8** (model substrate) in the presence of a catalytic amount of $ZnEt_2$ (5 mol%). Here, (*S*)-(−)-**9** was isolated in 70% yield and ee = 97% after 3 h reaction time (0 °C, THF, MeOH, Scheme 2).

Worthy of note is the short reaction time required for completion at 0 °C (3 h) which markedly distinguishes our catalyst from previously described bis-amino Zn-based chiral catalysts.[23]

In conclusion, we have reported on the versatility of readily accessible chiral diamino-bis(*tert*-thiophene) **1b** which has found successful applications as a chiral ligand in Pd- and Zn-catalyzed stereoselective processes. Good yields and high levels of enantioselectivity were obtained in asymmetric allylic alkylation and hydrosilylation of prochiral ketones and phosphinyl imines. Studies addressing functional chiral diamino compounds bearing longer and variously functionalized oligothiophene pendants are under way.

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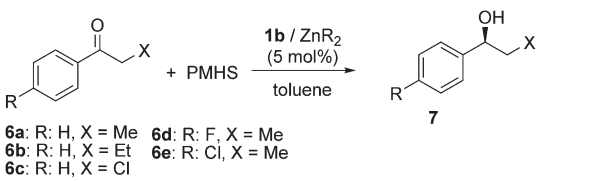
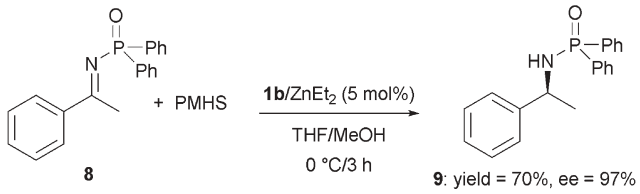
Table 2 Enantioselective reduction of arylketones with PMHS catalyzed by **1b**–Zn complex[a]



Entry	ZnR_2	6	7	Yield [%][b]	Ee [%][c]
1	$ZnMe_2$	**6a**	**7a**	70	80 (*S*)
2	$ZnEt_2$	**6a**	**7a**	73	83 (*S*)
3	”	**6b**	**7b**	75	82 (*S*)
4	”	**6c**	**7c**	55	72 (*R*)
5	”	**6d**	**7d**	60	80 (*S*)[d]
6	”	**6e**	**7e**	52	80 (*S*)[d]

[a] All reactions were carried out at rt for 16 h. [b] Isolated yields. [c] Determined by chiral HPLC (OD). Absolute configurations were assigned by comparison with known products. [d] Determined by chiral GC (crosslinked 5% PH ME Siloxane, Megadex 5).



Scheme 2 Enantioselective hydrosilylation of diphenylphosphinyl ketoimine **8**.

of Bologna. Prof. G. Gigli and Dr M. Mazzeo are kindly acknowledged for the spectroscopic characterization of **1b**.

Notes and references

‡ *Typical procedure for stereoselective hydrosilylation of ketones*: a flamed 25 mL two-necked flask was charged with diamine **1b** (6.2 mg, 0.01 mmol), 1 mL of anhydrous toluene and 9.1 μL of Et_2Zn (1.1 M, toluene). The mixture was stirred at rt for 30 min, then **6a** (0.2 mmol) and PMHS (65 μL, 1 mmol) were sequentially added. The reaction was stirred at rt and after 16 h judged complete by GC-MS. After quenching (3 ml of KOH, 45%, wt., 1 h), the two phases were separated and the aqueous layer extracted with Et_2O (3 × 5 mL). Finally, the collected organic phases were dried over Na_2SO_4 and concentrated under vacuum. The desired product **7a** was purified by flash chromatography (yield = 73%, ee = 83%).

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