Synthesis of Thiourea−Oxazolines, a New Class of Chiral S,N-Heterobidentate Ligands: Application in Pd-Catalyzed Asymmetric Bis(methoxycarbonylation) of Terminal Olefins

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A new chiral S,N-heterobidentate thiourea−oxazoline ligand was synthesized and isolated as two atropoisomers (**4a**, **4b**). The ligands were employed in Pd-catalyzed enantioselective bis(alkoxycarbonylation)s of terminal olefins under mild conditions, giving high yields and modest ee values, demonstrating the potential of such ligands for use in Pd-catalyzed carbonylative reactions. Molecular structures of **4a** and of the $PdCl_2$ complexes of **4a** and **4b** have been determined by single-crystal X-ray diffraction. In both complexes, the ligands exhibit a bidentate S,N bonding mode.

Introduction

Optically active succinic acid derivatives are present in a variety of biologically active molecules[1] and are also useful materials for the production of macromolecules.[2]

Because of their utility as flexible synthons for the functionalization of the carbon backbone, methods for the synthesis of succinic acid or its derivatives have been actively investigated.[3] Among them, the Pd-mediated carbonylation of olefins (Figure 1), first disclosed by Heck in 1968, is particularly interesting to us.[4]

However, the asymmetric version of the reaction has been relatively undeveloped due to the ambiguity of its mechanism. The first paper in this field was published by Consiglio and co-workers[5] in 1992. In their study, several atropoisomeric diphosphines were used in the Pd-catalyzed alkoxycarbonylation of olefins, and high enantioselectivity (90% ee) was achieved when styrene was used as the substrate; however, the reactions were low yielding, and a pressurized autoclave was required to carry out the reactions.

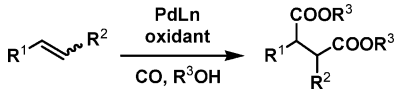

Figure 1. Pd-catalyzed biscarbonylation of olefins.

In 1996, Inomata et al. employed chiral bisoxazolines as ligands for Pd-catalyzed asymmetric biscarbonylations of structurally diverse homoallylic alcohols and terminal olefins. The product yields ranged from 35% to 74%, with moderate ee

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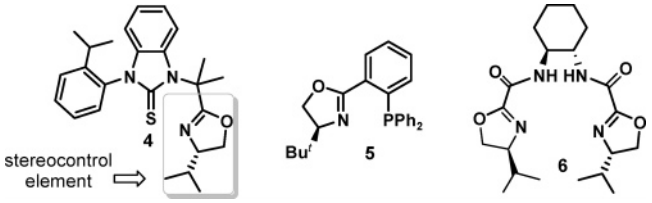
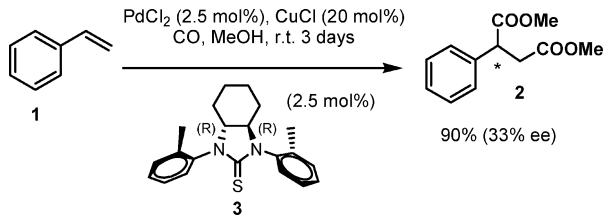


Figure 2. Heterobidentate ligands.

Scheme 1. Biscarbonylation of Styrene[8b]



(40−66%).[6] In 1998, Saigo's group reported their efforts to use chiral phosphine sulfides as ligands for Pd-catalyzed asymmetric biscarbonylations of styrene; however, the results were less satisfactory as both the yields and ee values of the products were low.[7]

More recently, Chan and co-workers reported the use of chiral dipyridylphosphines for Pd-catalyzed asymmetric bis(methoxycarbonylation) of styrene, reaching up to 84% ee and 79% chemoselectivity for dimethyl 2-phenylsuccinate (DMPS) under optimal conditions.[8]

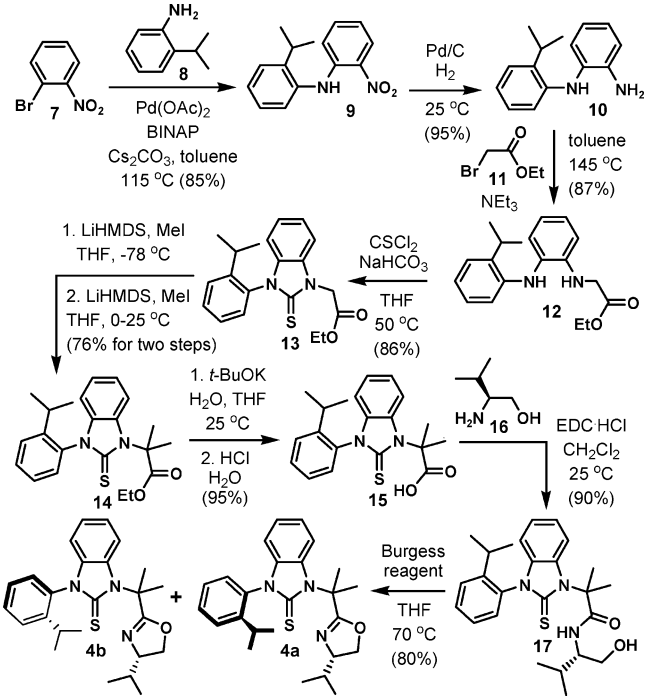
We have shown that Pd−thiourea complexes can catalyze a variety of carbonylative reactions under a balloon pressure of CO.[9] When we used chiral thiourea **3** (Scheme 1) as the ligand in the Pd-catalyzed bis(methoxycarbonylation) of styrene **1**, succinate **2** was obtained in 90% yield with 33% ee.

Therefore, we initiated a program focused on the development of chiral thiourea−oxazolines. In this paper, we describe the synthesis of the first member of this new class of ligands and its application in asymmetric catalysis, namely, the Pd-catalyzed bis(methoxycarbonylation) of terminal olefins.

Results and Discussion

The structure of thiourea **4** was designed on the basis of currently well-established heterobidentate ligands such as **5**[10] and **6**[11] (Figure 2), and its stereocontrol element is derived from oxazoline[12] chirality. As the Pd-catalyzed bis(alkoxycarbonylation) was found to correspond to a *syn*-addition to the olefin double bond,[4e,5a] we therefore envisaged that the ee values of the formed products would depend on the ability of the Pd−ligand complex to differentiate the two faces of the double bond, as well as its orientation.

Scheme 2. Synthesis of Thiourea Atropoisomers 4a and 4b



Several features of ligand **4** are attractive. First, the two incorporated binding sites on the backbone of **4** should afford a rigid metal−ligand complex with the bulky substituent on the oxazoline ring close to the metal center, which might enhance the facial differentiation ability of the complex toward its substrates and consequently lead to good ee values of the products. Second, thioureas are renowned for their great tunability;[13] thus, their steric and electronic properties can be modified by fine-tuning the nitrogen substituents. Third, ligand **4** is bidentate, which is good for preventing Pd(0) aggregation.[14] In addition, its stability to air and moisture might allow the use of O_2 as an oxidant in Pd-catalyzed carbonylative reactions. This is an important consideration with regard to oxygen's unique features in terms of resource efficiency, operational simplicity, and health and environmental safety.[15]

With the above in mind, we synthesized the heterobidentate ligand **4**, as shown in Scheme 2. Thus, 1-bromo-2-nitrobenzene

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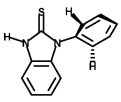
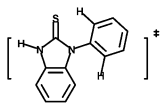
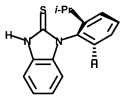
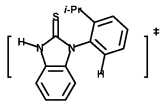
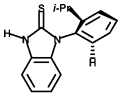
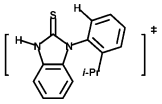
Table 1. Calculated Barriers for Rotation around the Phenyl C−N Bond in the Gas Phase (g) or in Methanol (s) Using DFT (B3LYP, 6-31G*)[a]

Ground state	Transition state	$\Delta E(s)^{\neq}$	$\Delta G(g)^{\neq}$	$\Delta G(s)^{\neq}$
		11.4	11.9	12.0
		34.5	36.9	36.8
		34.9	37.9	37.1

[a] The IEFPCM model and UAHF radii were used to model solvent (MeOH) effects.

(**7**) first underwent Pd-catalyzed coupling[16] with 2-isopropylphenylamine **9**, and the nitro group of the monoarylated amine product **9** was then reduced to the corresponding amine **10** by Pd-catalyzed hydrogenation. Alkylation of **10** with bromoacetic acid ethyl ester in the presence of Et_3N gave ester **12** in 87% yield. Thiourea **13** was obtained in 86% yield via treatment of **12** with thiophosgene[9d] in the presence of $NaHCO_3$.

With compounds **13** in hand, we then started to make the key intermediate **17** for the formation of the chiral oxazoline ring of the target ligand. To this end, **13** underwent sequential methylations (LiHMDS/MeI) to install the *gem*-dimethyl groups, and the desired product **14** was obtained in 76% yield. The installation of the two methyl groups should increase both the rigidity and the stability of ligand **4** on the basis of previous experimental results which showed that the presence of two hydrogens α to the enamine led to decomposition of the ligands under the catalytic reaction conditions.

To prepare the final target, compound **14** was first hydrolyzed under basic conditions, and the acid formed was coupled with amino alcohol **16** to afford **17** in 90% yield. Oxazoline ring formation was achieved using the Burgess reagent[17] to give equal amounts of targets **4a** and **4b** in 80% yield. It is important to note that **4a** and **4b** are atropoisomers, differing in the orientation of the 2-^{i}Pr substituent on the phenyl ring attached to one of the two thiourea nitrogen atoms. These isomers were separated by chromatography on silica (see the Experimental Section) and are configurationally stable in solution, as evidenced by NMR spectroscopy of the free ligands and their $PdCl_2$ complexes, vide infra. In fact, via DFT calculations (Table 1), we have evaluated the barriers to interconversion of the two atropoisomers via rotation around the C_{phenyl}−N bonds in either direction. For an unsubstituted phenyl ring, both directions of ring rotation are equivalent, and the computed barriers in MeOH solution or in the gas phase are both ca. 12 kcal mol^{-1}. For the 2-isopropylphenyl analogue (akin to **4a,b**), the barriers are also similar in solution and in the gas phase, as well as for rotation in either direction, with computed free energies of activation of ca. 37 kcal mol^{-1}. This high barrier is consistent with our experimental observations that even in the melt, at a temperature of 125 °C, the two atropoisomers do not interconvert.

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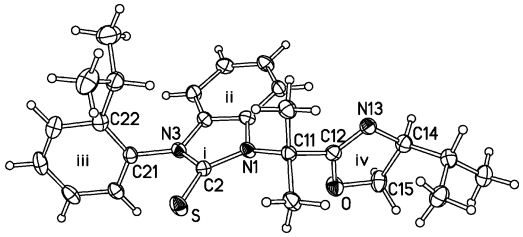


Figure 3. Molecular structure of ligand **4a**.

Table 2. Selected Bond Distances (Å) and Angles (deg) in 4a, $PdCl_2$/4a, and $PdCl_2$/4b

	4a		$PdCl_2$/**4a**	$PdCl_2$/**4b**
Pd−Cl(1)			2.312(2)	2.318(1)
Pd−Cl(2)			2.299(2)	2.275(1)
Pd−S			2.271(3)	2.268(1)
Pd−N(13)			2.021(7)	2.001(3)
S═C(2)	1.663(2)	1.656(2)	1.678(10)	1.708(4)
N(1)−C(2)	1.384(3)	1.387(3)	1.398(11)	1.364(4)
N(3)−C(2)	1.378(3)	1.384(3)	1.374(10)	1.357(4)
S−C(2)−N(1)	131.4(2)	131.2(2)	137.0(7)	135.2(3)
S−C(2)−N(3)	122.4(2)	123.2(2)	117.4(7)	116.3(3)
S−Pd−N(13)			93.2(2)	94.18(8)
S−C(2)−N(3)−C(21)	−171.1(2)	−9.0(3)	−8(1)	5.8(5)
C(2)−N(3)−C(21)−C(22)	90.6(3)	90.4(3)	100(1)	−91.8(4)
C(2)−N(1)−C(11)−C(12)	149.7(2)	144.9(2)	60.4(9)	60.6(4)
N(1)−C(11)−C(12)−N(13)	129.3(2)	129.9(2)	−85(1)	−88.2(4)
dihedral angle[a] i/ii	8.2	5.0	4.1	9.2
i/iii	86.4	79.2	86.8	86.9
i/iv	83.9	76.2	77.1	73.1
i/v			37.7	34.8
iv/v			53.6	53.6

[a] For a definition of the planes, see the text and Figure 3.

The molecular structure of ligand **4a**, determined by single-crystal X-ray diffraction, is illustrated in Figure 3.

The asymmetric unit of **4a** comprises two molecules of similar conformation (Figure 3, Table 2). The central N_2CS moiety (i) is slightly inclined to the fused benzene ring (ii) and almost normal to the isopropylated phenyl ring (iii) and the mean plane of the oxazoline ring (iv).

To confirm the bidentate nature of ligands **4a** and **4b**, and to observe their conformation upon binding to Pd(II), we prepared their $PdCl_2$ complexes and examined their structures by single-crystal X-ray diffraction studies (Figure 4).

The two chiral palladium complexes, which are conformational isomers, crystallize in the tetragonal space group $P4_1$ for $PdCl_2$/**4a** and orthorhombic space group $P2_12_12_1$ for $PdCl_2$/**4b**. In $PdCl_2$/**4a**, the isopropylphenyl group adopts roughly the same orientation as in free ligand **4a**, from which it was synthesized, whereas, in $PdCl_2$/**4b**, it is rotated by ca. 180° around the N(3)−C(21) bond (Figure 4) as expected. Thus, the two isopropyl groups have an *anti* disposition in $PdCl_2$/**4a** and are *syn*-related in $PdCl_2$/**4b**. The former conformation is obviously less compact, resulting in a lower (by ca. 2.5%) packing density and a wider leeway for thermal vibrations. Indeed, in $PdCl_2$/**4a**, the atomic displacement parameters are on average 1.7 times higher than in $PdCl_2$/**4b** and in some cases are large enough to suspect static disorder. In both structures, the Pd atom has a distorted square-planar coordination with the chelating ligand bound through both the thiourea S and oxazoline N atoms. In $PdCl_2$/**4a** the Pd, S, N(13), and Cl(1) atoms are coplanar within experimental error and Cl(2) deviates by 0.19 Å from their plane, whereas in $PdCl_2$/**4b** the Pd, S, N(13), and Cl(2) atoms are coplanar and Cl(1) deviates by 0.22 Å. The planar PdSNCl moiety (v) forms similar acute angles with the chelating groups (i and iv).

It is noteworthy that the sulfur atom is always tilted toward the isopropylphenyl substituent, so that the S−C(2)−N angles

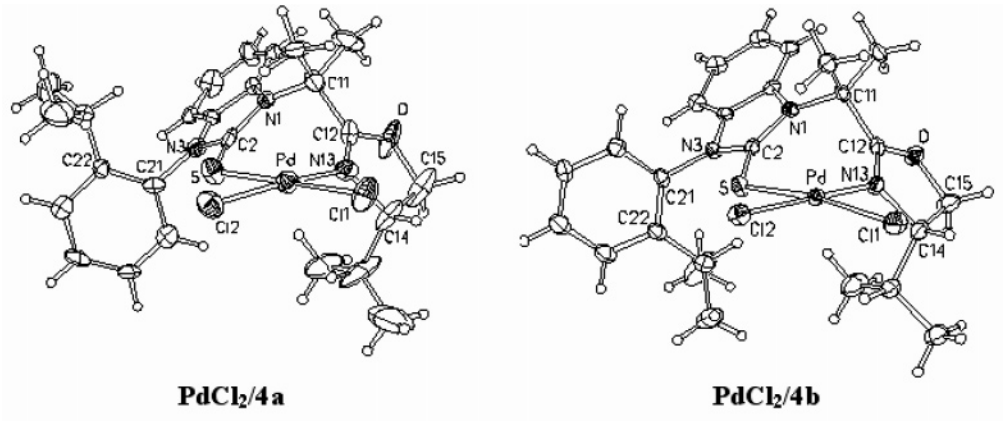
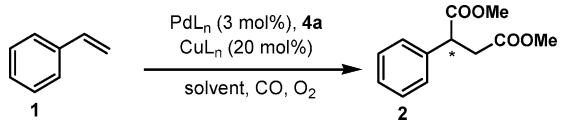


Figure 4. Molecular structure of the complexes $PdCl_2$/**4a** (left) and $PdCl_2$/**4b** (right), showing 50% thermal ellipsoids.

Table 3. Pd-Catalyzed Carbonylation Using Thiourea 4a as a Ligand[a]



entry	PdL_n	Pd:**4a**	CuL_n	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	$PdCl_2$	1:1	CuCl	MeOH	50	24	22	56
2	$Pd(OAc)_2$	1:1	CuCl	MeOH	50	24	77	60
3	$Pd(OAc)_2$	1:1	CuBr	MeOH	50	24	60	52
4	$Pd(OAc)_2$	1:1	$(CuOTf)_2C_6H_6$	MeOH	50	24	−	−
5	$[PdCl(C_3H_5)]_2$	1:1	CuCl	MeOH	50	24	41	61
6	$[PdCl(C_3H_5)]_2$	1:1	CuCl	MeOH	20	52	84	67
7	$[PdCl(C_3H_5)]_2$	1:2	CuCl	MeOH	20	52	95	75
8	$[PdCl(C_3H_5)]_2$	1:2	$(CuOTf)_2C_6H_6$	MeOH	20	52	90	58
9	$PdCl_2$	1:2	$(CuOTf)_2C_6H_6$	MeOH	20	52	90	61
10	$Pd(OAc)_2$	1:2	$(CuOTf)_2C_6H_6$	MeOH	20	52	−	−
11	$[PdCl(C_3H_5)]_2$	1:2	CuCl	MeOH/THF	20	52	94	66

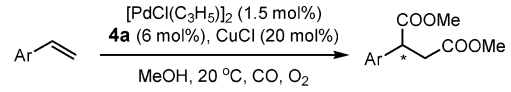
[a] Reaction conditions: styrene (1.0 mmol), PdL_n (0.03 mmol), ligand **4a** (0.03 or 0.06 mmol), CuL_n (0.2 mmol), and solvent (4.0 mL) under a balloon pressure of CO and O_2 (ca. 4:1). Dashes in the table refer to reactions in which the starting materials decomposed after 52 h. [b] Isolated yield after silica gel chromatography. [c] The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OJ-H).

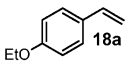
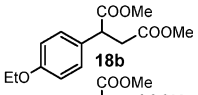
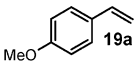
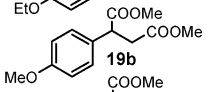
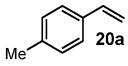
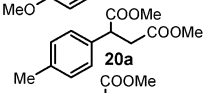
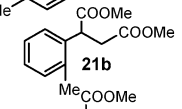
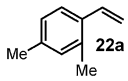
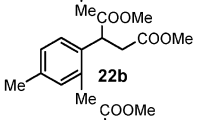
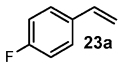
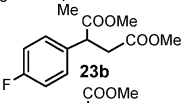
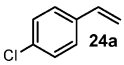
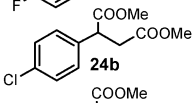
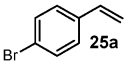
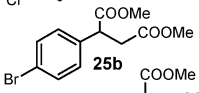
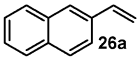
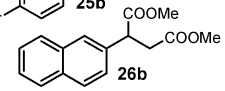
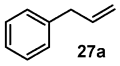
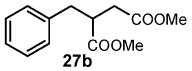
differ by 8−9° in uncoordinated **4a** and slightly more so in the complexed ligand. The oxazoline ring in **4a** shows a slight envelope-like distortion; in one molecule, C(14) deviates from the plane of the other four atoms by 0.10 Å, whereas in the other molecule C(15′) deviates by 0.13 Å. The latter conformation also occurs in $PdCl_2$/**4b**, C(15) deviating by 0.16 Å, whereas in $PdCl_2$/**4a**, C(14) and C(15) deviate from the OC(12)N(13) plane in opposite directions by 0.08 and 0.10 Å. Upon coordination to Pd, the C═S bond lengthens noticeably with concomitant shortening of the two adjacent N−C bonds, reflecting a redistribution of electrons in the N_2CS unit of the thiourea ligand. This is more evident in the more accurate structure of $PdCl_2$/**4b**. In addition, it is clear that the thiourea exerts a stronger *trans* influence than the oxazoline, as judged by the lengthening of the Pd−Cl distances *trans* to S compared with those *trans* to N in both Pd complexes.

With thioureas **4a** and **4b**, as well as the structures of their complexes with $PdCl_2$ in hand, we turned our attention to investigating their potential in the Pd-catalyzed enantioselective carbonylation of styrene.[9b] For the catalytic studies, we first selected **4a** as the ligand for the carbonylations using in situ generated Pd catalysts. $PdCl_2$ (3.0 mol %) and **4a** (3.0 mol %) were premixed in the presence of CuCl (20.0 mol %) at room temperature in methanol under N_2 to allow formation of the Pd complex, then styrene **1** was injected, and a balloon attached to the flask was charged with a mixture of CO and O_2 (ca. 4:1). The enantiomeric excess (ee) of product **2** was determined by chiral HPLC after workup. Details are listed in Table 3.

Accordingly, we evaluated the effect of various reaction parameters (Pd and Cu salts, ratio of Pd to **4a**, solvent, and temperature, etc.) on the outcome of the reaction. It was found that among the Pd and Cu salts tested ($PdCl_2$, $Pd(OAc)_2$, $[PdCl(\eta^3\text{-}C_3H_5)]_2$, CuCl, CuBr, $(CuOTf)_2C_6H_6$), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and CuCl proved to be the most efficient. Among the solvents used (MeOH, EtOH, ^{i}PrOH, THF/MeOH), MeOH was the best choice. A 1:2 Pd:**4a** ratio gave the best overall result, showing ca. 10% improvements in both yield and ee compared with the 1:1 ratio. Thus, a 95% yield of compound **2** with moderate ee was eventually obtained when a catalytic system composed of $[PdCl(\eta^3\text{-}C_3H_5)]_2$/**4a**/CuCl (Table 2, entry 7) was utilized at 25 °C for ca. 2 days under a balloon pressure of CO and O_2 (ratio ca. 4:1).[9b] It is worth noting that, in contrast to our previous observation with ligand **3**, the color of the reaction mixture was still yellow after completion of the carbonylative reactions, indicating that, as we expected, the Pd−thiourea complex, once formed, is stable under the reaction conditions. Preliminary studies suggest that the catalyst precursor is a 1:1 Pd/L species, probably analogous to the above structurally characterized complex $PdCl_2$/**4a**. Thus, using the pure, isolated complex gave a high yield in a test catalytic reaction, and the solution remained yellow throughout. The advantage of employing a 2:1 ratio of ligand to Pd in the in situ generated catalyst

Table 4. Ligand 4a Based Pd-Catalyzed Bis(methoxycarbonylation) of Terminal Alkenes[a]



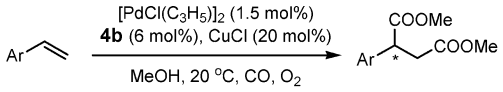
entry	starting material	product	time	yield[b]	ee [c]
1	 **18a**	 **18b**	52h	96%	65%
2	 **19a**	 **19b**	52h	93%	65%
3	 **20a**	 **20a**	52h	95%	65%
4	 **21a**	 **21b**	52h	76%	60%
5	 **22a**	 **22b**	52h	94%	60%
6	 **23a**	 **23b**	52h	92%	55%
7	 **24a**	 **24b**	80h	95%	46%
8	 **25a**	 **25b**	80h	92%	44%
9	 **26a**	 **26b**	52h	90%	56%
10	 **27a**	 **27b**	52h	91%	32%

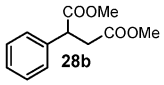
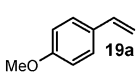
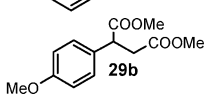
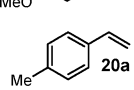
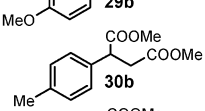
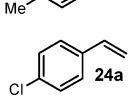
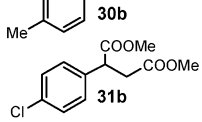
[a] Reaction conditions: styrene (1.0 mmol), $[PdCl(C_3H_5)]_2$ (0.015 mmol), ligand **4a** (0.06 mmol), and CuCl (0.2 mmol) in MeOH (4.0 mL) at 20 °C under a balloon pressure of CO and O_2 (ca. 4:1). [b] Isolated yield after silica gel chromatography. [c] The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OJ-H).

systems is therefore likely to be enhanced formation of the active complex, as $PdCl_2$ itself is a poor catalyst which, due to the lack of chiral ligands, will generate racemic product, lowering the observed ee values, and which rapidly deposits inactive Pd black.

To assess the generality of the optimized carbonylation conditions using in situ generated catalysts, other terminal olefins were selected for the biscarbonylation reaction (Table 4). From the results in Table 4, we can make the following observations: (1) The selected substrates gave high yields of carbonylation products (range from 90% to 96%), with the exception of the *o*-methylstyrene **21a** (entry 4). (2) The lower ee values for the products derived from substituted styrenes (entries 1−10), relative to styrene (see Table 2, entry 7), indicate that the catalyst is sensitive to the substitution pattern of the substrates. (3) Substituted styrenes with methyl, alkoxy, and halide moieties at the *para* position afforded high yields of their corresponding succinic acid derivatives, but only moderate ee values (44−65%) were obtained. (4) The more hindered *ortho*-substituted styrene (entry 4) gave a low yield of product; however, the ee value was within the same range as that obtained with the *para*-substituted styrenes. (5) Low ee values were obtained when F-, Cl-, and Br-substituted styrenes (entries 6−8) were used as substrates as compared with the value obtained with the EtO-, MeO-, and Me-substituted styrene (entries 1−3). (6) *o*-Methyl-substituted styrenes (entries 4 and 5) gave lower ee values compared with styrenes lacking an *ortho* substituent

Table 5. Ligand 4b Based Pd-Catalyzed Bis(methoxycarbonylation) of Terminal Alkenes[a]



entry	starting material	product	time	yield[b]	ee [c]
1	 **1**	 **28b**	52h	96%	57%
2	 **19a**	 **29b**	52h	90%	61%
3	 **20a**	 **30b**	52h	96%	61%
4	 **24a**	 **31b**	52h	95%	55%

[a] Reaction conditions: styrene (1.0 mmol), $[PdCl(C_3H_5)]_2$ (0.015 mmol), ligand **4b** (0.06 mmol), and CuCl (0.2 mmol) in MeOH (4.0 mL) at 20 °C under a balloon pressure of CO and O_2 (ca. 4:1). [b] Isolated yield after silica gel chromatography. [c] The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OJ-H).

(entries 1−3), presumably because of a steric interaction between the methyl group and the ligand, which disfavors the ligand differentiation.

We then tested the carbonylative reaction with **4b** as the ligand. Especially interesting is the fact that the selected substituted styrenes gave the same high yields of products but with opposite enantioselectivity as compared with those generated using ligand **4a** (see the Supporting Information for details). For example, 4-methoxy- and 4-methylstyrenes (Table 5, entries 2 and 3) gave 61% ee vs 65% ee in the opposite sense using **4a** (Table 4, entries 2 and 3). This suggests that a significant influence on the stereochemical outcome of these reactions is the orientation of the 2-$^{i}PrC_6H_4$ ring, in addition to the oxazoline moiety. However, for styrene, the ee was slightly lower using **4b**, (65%) than with **4a** (75%), whereas, for 4-chlorostyrene, the ee was slightly higher using **4b**, (55%) vs **4a** (46%). In these latter cases, both atropoisomerism and the chirality of the oxazoline must be exerting an effect, and it seems that the former is predominant.

Conclusions

In summary, we have developed a route to synthesize a new class of S,N-ligands, and the structures of the first such ligand and its atropoisomeric $PdCl_2$ complexes were determined by single-crystal X-ray diffraction. In a preliminary study of its application in the Pd-catalyzed bis(methoxycarbonylation) of terminal olefins *at room temperature, under a balloon pressure of CO with O_2 as the oxidant*, we obtained excellent yields in all but one case and moderate ee. The catalyst has been generated in situ via premixing of the ligand with a Pd(II) precursor. Preliminary studies suggest that the catalyst precursor is probably a 1:1 Pd/L species, such as the above structurally characterized complex $PdCl_2$/**4a**. Thus, the advantage of using 2 equiv of ligand probably results from more efficient complex formation at room temperature in the short premixing time. This avoids catalysis by any uncomplexed $PdCl_2$ itself, which leads to racemic product and the formation of Pd black. Current efforts are directed toward catalysis using isolated Pd complexes of the ligands, such as $PdCl_2$/**4a** and $PdCl_2$/**4b**, to carry out mechanistic studies and to further explorations of the coordination chemistry of these novel thiourea−oxazoline ligands. In

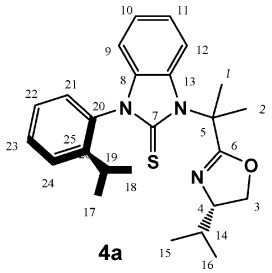
addition, we are examining alternative Pd precursors which will allow even more efficient in situ catalyst generation. Importantly, although the chiral oxazoline moiety is required to separate and isolate the two atropisomers of these ligands, in the case of **4a,b**, it would appear that the configuration of the 2-^{i}PrC_6H_4 ring exerts a considerable influence on the stereochemical outcome of the catalytic reactions. This suggests that improved ee values may result from changing the 2-^{i}Pr substituent or from the use other bulky aromatic ring systems which would also display atropoisomerism, and studies to evaluate this hypothesis are in progress. Likewise, changing the ^{i}Pr substituent on the oxazoline may allow the two effects to work together more effectively. In view of the excellent catalytic activity of the system under very mild conditions, the promising ee values obtained to date, and the exceptional potential for tuning the steric and electronic properties of this novel type of S,N-ligand, we are currently developing more concise synthetic approaches to construct a library of such ligands and are carrying out detailed experimental and theoretical studies to develop a better mechanistic understanding of the catalytic process.

Experimental Section

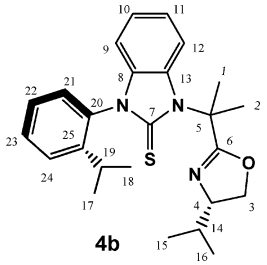
Synthesis of 1-[1-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-1-methylethyl]-3-(2-isopropylphenyl)-1,3-dihydrobenzoimidazole-2-thiones 4a and 4b. To a stirred solution of compound **17** (see the Supporting Information for its synthesis) (1.98 g, 4.5 mmol, 1 equiv) in dry THF (60 mL) was added the Burgess reagent (1.28 g, 5.4 mmol, 1.2 equiv) at room temperature under nitrogen, and the reaction mixture was stirred at 70 °C for ca. 1 h. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (hexane:CH_2Cl_2:ethyl acetate = 10:10:1) on silica gel to give ligands **4a** (0.76 g) and **4b** (0.76 g) in 80% overall yield.

Assignments of the NMR spectroscopic data for the free ligands and their $PdCl_2$ complexes was based on a series of 2D NMR studies.

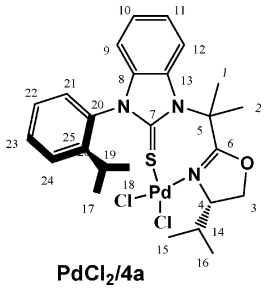
Characterization Data for 4a. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.63 (d, J_{H-H} = 9 Hz, H12), 7.51 (m, H23, H24), 7.23 (m, H22), 7.14 (m, H11, H21), 7.08 (t, J_{H-H} = 8 Hz, H10), 6.62 (d, J_{H-H} = 8 Hz, H9), 4.20 (m, H3), 3.98 (m, H3′), 3.93 (m, H4), 2.51 (m, H19), 2.26 (s, H1), 2.19 (s, H2), 1.77 (m, H14), 1.19 (d, J_{H-H} = 7 Hz, H17), 0.98 (d, J_{H-H} = 7 Hz, H18), 0.94 (d, J_{H-H} = 7 Hz, H15), 0.87 (d, J_{H-H} = 7 Hz, H16). ^{13}C{^{1}H} NMR (100 MHz): δ 171.6 (C7), 168.8 (C6), 147.8 (C25), 134.4 (C8), 133.7 (C20), 132.4 (C13), 130.0 (C24), 129.1 (C11), 127.3 (C23), 127.1 (C22), 122.6 (C10), 122.6 (C21), 112.1 (C12), 109.8 (C9), 72.5 (C4), 70.8 (C3), 62.5 (C5), 32.5 (C14), 28.3 (C1), 28.3 (C19), 25.9 (C2), 23.7 (C17), 23.0 (C18), 18.9 (C15), 18.2 (C16). Mp: 125 °C. HRMS (EI): *m*/*z* calcd for $C_{25}H_{31}N_3OS$ (M^+) 422.2221, found 422.2262.



Characterization Data for 4b. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.62 (d, J_{H-H} = 8 Hz, H12), 7.52 (m, H23, H24), 7.35 (m, H22), 7.13 (m, H11, H21), 7.08 (t, J_{H-H} = 7 Hz, H10), 6.62 (d, J_{H-H} = 7 Hz, H9), 4.23 (t, J_{H-H} = 9 Hz, H3), 3.90 (m, H3, H4), 2.50 (m, H19), 2.24 (s, H1), 2.20 (s, H2), 1.78 (m, H14), 1.18 (d, J_{H-H} = 7 Hz, H17), 0.99 (d, J_{H-H} = 7 Hz, H18), 0.96 (d, J_{H-H} = 7 Hz, H15), 0.86 (d, J_{H-H} = 7 Hz, H16). ^{13}C{^{1}H} NMR (125 MHz): δ 171.6 (C7), 168.9 (C6), 147.7 (C25), 134.4 (C8), 133.7 (C20), 132.4 (C13), 130.0 (C24), 129.2 (C11), 127.3 (C23), 127.0 (C22), 122.6 (C10), 122.5 (C21), 112.1 (C12), 109.7 (C9), 72.8 (C4), 71.0 (C3), 62.5 (C5), 32.5 (C14), 28.3 (C19), 27.2 (C1), 26.9 (C2), 23.6 (C17), 23.1 (C18), 19.1 (C15), 18.4 (C16). Mp: 110 °C. HRMS (EI): *m*/*z* calcd for $C_{25}H_{31}N_3OS$ (M^+) 422.2221, found 422.2263.



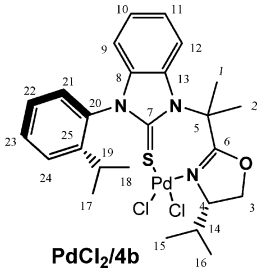
Synthesis and Characterization of $PdCl_2$/4a. To a solution of **4a** (213 mg, 0.05 mmol) in MeOH (4 mL) was added $Pd(PhCN)_2Cl_2$ (197 mg, 0.05 mmol). The reaction mixture was heated to reflux at 50 °C for 4 h. The solvent was removed on a rotary evaporator. The residue was dissolved in CH_2Cl_2, and then Et_2O was added to precipitate the product as an orange solid, which was collected by filtration, washed with Et_2O (3×), and then dried in vacuo. The single crystal for X-ray diffraction was grown via slow evaporation of a solution in CH_2Cl_2/MeOH (50:50). Yield: 274 mg, 92%. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.99 (d, J_{H-H} = 8 Hz, H12), 7.63 (m, H23, H24), 7.44 (m, H22), 7.34 (t, J_{H-H} = 8 Hz, H11), 7.31 (t, J_{H-H} = 8 Hz, H10), 6.93 (d, J_{H-H} = 8 Hz, H21) 6.83 (d, J_{H-H} = 8 Hz, H9), 4.87 (m, H4), 4.46 (t, J_{H-H} = 9 Hz, H3), 4.24 (t, J_{H-H} = 9 Hz, H3′), 3.38 (s, H1), 3.10 (m, H14), 2.55 (s, H2), 2.33 (m, H19), 1.27 (d, J_{H-H} = 7 Hz, H17), 1.00 (d, J_{H-H} = 7 Hz, H18), 0.87 (d, J_{H-H} = 7 Hz, H15), 0.75 (d, J_{H-H} = 7 Hz, H16). ^{13}C{^{1}H} NMR (125 MHz): δ 167.4 (C7), 163.8 (C6), 147.4 (C25), 134.1 (C8), 132.2 (C23), 131.7 (C13), 131.1 (C20), 128.2 (C24), 128.1 (C22), 127.6 (C21), 125.5 (C11), 125.3 (C10), 114.8 (C12), 111.6 (C9), 71.1 (C4), 69.2 (C3), 62.2 (C5), 30.5 (C14), 28.7 (C19), 28.6 (C1), 28.3 (*C*2), 23.9 (C18), 23.2 (C17), 18.4 (C15), 14.6 (C16).



Alternative Synthesis of $PdCl_2$/4a. To a solution of **4a** (10.7 mg, 0.026 mmol) in CD_2Cl_2 (1 mL) was added $Pd(PhCN)_2Cl_2$ (10.3 mg, 0.026 mmol). The solution was transferred to an NMR tube, and the reaction was shown to be complete and quantitative within 2 min at room temperature, as evidenced by ^{1}H NMR spectroscopy. The sample was transferred to a small round-bottom flask using CH_2Cl_2, and the combined solution was evaporated to dryness on a rotary evaporator. The solid sample was then dried in vacuo for 3 h and was shown to contain 1 equiv of benzonitrile of crystallization by elemental analysis. Anal. Calcd for $C_{25}H_{31}Cl_2N_3OPdS{\cdot}C_6H_5CN$: C, 54.75; H, 5.17; N, 7.98. Found: C, 54.47; H, 5.12; N, 7.94.

Synthesis and Characterization of $PdCl_2$/4b. The same procedure and scale were employed as for $PdCl_2$/**4a**, but using **4b** in place of **4a**. Yield: 270 mg, 90%. ^{1}H NMR (500 MHz, CD_2Cl_2):

δ 7.99 (d, J_{H-H} = 9 Hz, H12), 7.63 (m, H23, H24), 7.45 (t, J_{H-H} = 9 Hz, H22), 7.35 (t, J_{H-H} = 9 Hz, H11), 7.29 (t, J_{H-H} = 9 Hz, H10), 7.17 (d, J_{H-H} = 9 Hz, H21) 6.81 (d, J_{H-H} = 9 Hz, H9), 4.88 (m, H3), 3.98 (m, H4), 4.5 (t, J_{H-H} = 9 Hz, H3), 4.28 (t, J_{H-H} = 9 Hz, H3′), 3.37 (s, H1), 3.03 (m, H14), 2.54 (s, H2), 2.28 (m, H19), 1.24 (d, J_{H-H} = 7 Hz, H17), 0.98 (d, J_{H-H} = 7 Hz, H18), 0.92 (d, J_{H-H} = 7 Hz, H15), 0.85 (d, J_{H-H} = 7 Hz, H16). $^{13}C\{^1H\}$ NMR (125 MHz): δ 167.7 (C7), 163.9 (C6), 146.4 (C25), 134.1 (C8), 132.2 (C13), 131.8 (C24), 130.8 (C20), 128.6 (C21), 128.2 (C22), 128.1 (C23), 125.4 (C10), 125.1 (C11), 114.9 (C12), 111.4 (C9), 71.1 (C4), 69.2 (C3), 62.0 (C5), 30.3 (C14), 29.2 (C1), 28.5 (C2), 28.5 (C19), 24.1 (C17), 23.5 (C18), 18.6 (C15), 15.1 (C16). Anal. Calcd for $C_{25}H_{31}Cl_2N_3OPdS$: C, 50.13; H, 5.22; N, 7.02. Found: C, 49.83; H, 5.13; N, 6.50.



Alternative Synthesis of $PdCl_2$/4b. Compound $PdCl_2$/**4b** was synthesized by the same procedure as for $PdCl_2$/**4a** using **4b** (11.0 mg, 0.026 mmol) in CD_2Cl_2 (1 mL), to which was added $Pd(PhCN)_2Cl_2$ (10.4 mg, 0.026 mmol). The reaction was complete and conversion quantitative within 2 min at room temperature, as evidenced by ^1H NMR spectroscopy.

General Procedure for the Pd-Catalyzed Asymmetric Bis-(methoxycarbonylation) of Terminal Olefins. To a solution of MeOH (4.0 mL) in an oven-dried Schlenk tube were added $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5.5 mg, 0.015 mmol), ligand **4a** or **4b** (25.3 mg, 0.06 mmol), and CuCl (20 mg, 0.2 mmol), and the mixture was stirred at 20 °C for 30 min under nitrogen. To this solution was added the appropriate terminal olefin (1.0 mmol) via syringe, and the mixture was stirred at 20 °C under a balloon pressure of CO and O_2 (ca. 4:1) for an additional 52 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (hexane:ethyl acetate = 8:1) on silica gel to give the corresponding products (see the Supporting Information for the syntheses of products **18b**−**31b**).

Synthesis of 2-Phenylsuccinic Acid Dimethyl Ester (2). Product **2** was obtained in 95% yield with 75% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 2.64−2.71 (m, 1H), 3.17−3.26 (m, 1H), 3.64 (s, 3H), 3.68 (s, 3H), 4.08−4.13 (m, 1H), 7.25−7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.5, 46.9, 51.8, 52.3, 127.6, 127.6, 128.8, 137.6, 171.9, 173.3. HRMS (EI): *m*/*z* calcd for $C_{12}H_{14}O_4$ (M^+) 222.0892, found 222.0894. HPLC conditions: CHIRALCEL OJ-H, hexane:^{i}PrOH = 90:10, 0.8 mL/min, 230 nm, 30 °C, t_R(major) = 19.9 min, t_R(minor) = 24.8 min.

X-ray Diffraction Studies. X-ray diffraction experiments (Table 6) were carried out on Bruker three-circle diffractometers with SMART 6K (**4a**, $PdCl_2$/**4a**) or SMART 1K ($PdCl_2$/**4b**) CCD area detectors using graphite-monochromated Mo Kα radiation ($\bar{\lambda}$ = 0.71073 Å) and Cryostream (Oxford Cryosystems) open-flow N_2 cryostats. A full sphere of reciprocal space was covered with narrow-frame (0.3°) ω scans. Diffraction from $PdCl_2$/**4a** was very weak (mean $I/\sigma(I)$ = 3.9). For both $PdCl_2$/**4a** and $PdCl_2$/**4b**, reflection intensities were corrected for absorption by Gaussian integration based on crystal face indexing. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of all reflections, using SHELXTL software.[18] The absolute configurations of all three compounds were determined from anomalous scattering by the Flack method.[19]

Table 6. Crystallographic Data for the Ligand 4a and Complexes $PdCl_2$/4a and $PdCl_2$/4b

	4a	$PdCl_2$/**4a**	$PdCl_2$/**4b**
CCDC deposition no.	640924	640925	640926
empirical formula	$C_{25}H_{31}N_3OS$	$C_{25}H_{31}Cl_2N_3OPdS$	
fw	421.59	598.89	
T (K)	120	120	120
cryst size (mm)	0.28 × 0.20 × 0.17	0.16 × 0.03 × 0.02	0.42 × 0.13 × 0.01
cryst syst	monoclinic	tetragonal	orthorhombic
space group (No.)	$P2_1$ (4)	$P4_1$ (76)	$P2_12_12_1$ (19)
a (Å)	11.841(1)	9.2008(4)	9.7352(9)
b (Å)	15.138(1)	9.2008(4)	12.5655(11)
c (Å)	12.813(1)	31.348(1)	21.151(2)
β (deg)	90.95(1)	90	90
V (Å^3)	2296.4(3)	2653.8(2)	2587.3(4)
Z	4	4	4
ρ_{calcd} (g cm^{-3})	1.219	1.499	1.537
μ (mm^{-1})	0.16	1.00	1.03
max 2θ (deg)	58	55	58
no. of total reflns	29694	22405	13750
no. of unique reflns	12198, 8487[a]	6077, 3071[a]	6345, 5514[a]
R_{int}	0.092	0.152	0.038
no. of params	565	304	310
R1[a,b]	0.050	0.068	0.039
wR2[c]	0.106	0.114	0.065
max/min electron density	0.38/−0.26	1.52/−0.66	0.42/−0.65
Flack param	−0.06(5)	−0.04(5)	−0.02(3)

[a] Number of reflections with $I \geq 2\sigma(I)$. [b] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [c] $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$.

Computational Studies. Computations of the rotational barriers for interconversion of the atropoisomers **4a,b** were carried out via DFT calculations using Gaussian03.[20] The B3LYP functional was used, and the 6-31G* basis set was employed for all atoms. The IEFPCM model and UAHF radii were used to model solvent effects.

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Supporting Information Available: Full characterization data including ^1H and ^{13}C NMR spectra for the known products. This material is available free of charge via the Internet at http://pubs.acs.org.

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