DOI: 10.1002/adsc.201000070

A Thiourea-Oxazoline Library with Axial Chirality: Ligand Synthesis and Studies of the Palladium-Catalyzed Enantioselective Bis(methoxycarbonylation) of Terminal Olefins

Ying-Xiang Gao,[a] Le Chang,[a] Hang Shi,[a] Bo Liang,[a] Kittiya Wongkhan,[b] Duangduan Chaiyaveij,[b] Andrei S. Batsanov,[b] Todd B. Marder,[b,*] Chuang-Chuang Li,[a,*] Zhen Yang,[a,*] and Yong Huang[a,*]

[a] Laboratory of Chemical Genomics, Shenzhen Graduate School of Peking University, Shenzhen 518055, People's Republic of China, and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), College of Chemistry, Peking University, Beijing 100871, People's Republic of China
Fax: (+86)-755-2603-5326; e-mail: huangyong@szpku.edu.cn, zyang@pku.edu.cn, chuangli@pku.edu.cn

[b] Department of Chemistry, Durham University, South Road, Durham DH1 3 LE, United Kingdom
Fax: (+44)-191-384-4737; e-mail: todd.marder@durham.ac.uk

Received: January 28, 2010; Published online: August 16, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000070.

Abstract: We report herein the synthesis of novel chiral S,N-heterobidentate thiourea-oxazoline ligands and their application to palladium-catalyzed enantioselective bis(methoxycarbonylation)s of terminal olefins under mild conditions. Copper salts were found to play multiple roles in this reaction. Substituted 2-phenylsuccinates were obtained in >90% yield and up to 84% *ee* under optimized conditions.

Keywords: asymmetric catalysis; catalyst design; enantioselectivity; palladium; thiourea-oxazoline library

Introduction

Thioureas have emerged as an important class of ligands for transition metal-catalyzed reactions in recent years.[1–5] A number of coupling reactions catalyzed by palladium-thiourea complexes have been reported. Their advantages over traditional phosphine ligands include robust air stability and resistance to oxidation, which is important in oxidative catalytic processes, easy electronic tuning and sometimes orthogonal chemoselectivities. Bis(methoxycarbonylation) reactions have long been an efficient method to install two ester groups across a carbon-carbon double bond. Since the initial discovery by Heck in 1972,[6] several palladium-catalyzed asymmetric processes have been reported.[7] However, this reaction has had limited applications in the synthesis of complex scaffolds, partially due to poor mechanistic understanding and few reliable methodologies to ensure high yields and enantioselectivities. Styrenes are among the most challenging substrates due to their inclination to polymerize rapidly under transition metal catalysis. In fact, styrenes and CO can be co-polymerized using Pd catalysts containing nitrogen ligands such as 2,2′-bipyridyl and 1,10-phenanthroline.[7a,8] Diphosphine ligands were reported to catalyze monomethoxycarbonylations with various degrees of regioselectivity (linear *vs.* branched), depending on the electronic nature of the ligand.[7i]

We recently reported[4h] that a chiral thiourea-oxazoline **1** (Figure 1) was a highly efficient ligand for palladium-catalyzed bis(methoxycarbonylation) of

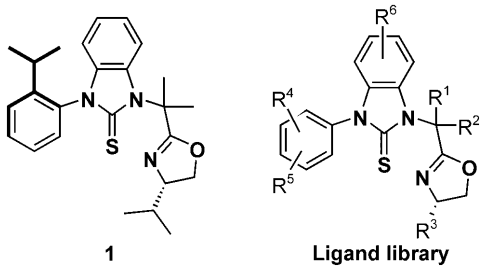
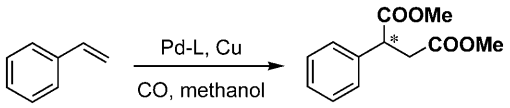


Figure 1. Thiourea-oxazoline ligands.



Scheme 1. Palladium-catalyzed bis(methoxycarbonylation) of styrene.

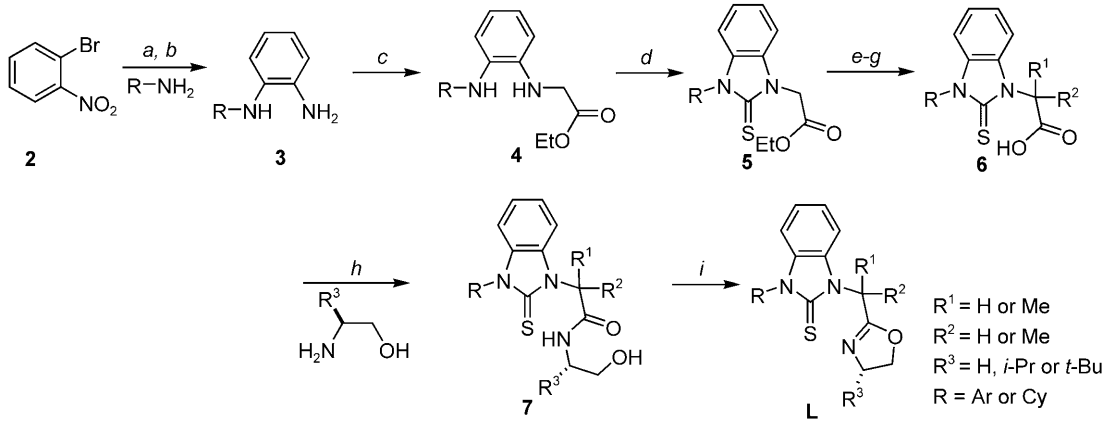
styrenes (Scheme 1). High yields and moderate *ee*s were observed with various styrenes under ambient temperature and pressure of CO. Of particular interest was our observation that atropoisomerism at the N–C_{aryl} bond appeared to be more important in determining enantioselectivity than the chiral oxazoline moiety. Importantly, both experimental and theoretical studies indicated that the barrier to rotation around the N–C_{aryl} bond was quite large, and thus the two diastereomers were readily separated and were configurationally stable even at temperatures over 100 °C With this in mind, we turned our attention to the design of alternative ligands which would also possess atropoismers, and in which a group larger than the *ortho*-isopropyl moiety would protrude into the coordination sphere of the palladium center, with the idea that this would improve enantioselectivity in the catalytic reaction. We also wished to confirm our theory by examining a larger library of ligands with and without the atropoisomerisation issue.

In addition, our recent studies showed that rigorous purification of CuCl was required in order to maintain decent enantioselectivities using ligand **1**. Commercial CuCl from various source consistently produced 10–20% lower *ee*s. In this paper, we report the synthesis of a small library of novel chiral S,N-heterobidentate thiourea-oxazoline ligands (Figure 1) and their application in palladium-catalyzed asymmetric bis(methoxycarbonylation) reactions of terminal olefins. We describe herein the synthesis of the chiral ligand library, single-crystal studies of a palladium-ligand complex and a detailed investigation of optimized reaction conditions. A more robust anthracene-substituted bidentate thiourea-oxazoline was developed in accord with the hypothesis that increased bulk near the palladium center would enhance *ee*s. Using this ligand, reactions could be carried out at 0 °C in the presence of commercial CuCl and a silver salt, giving up to quantitative yield of the desired product and up to 84% *ee* using styrene as substrate.

Results and Discussion

Synthesis of the Ligand Library and Initial Screening Results

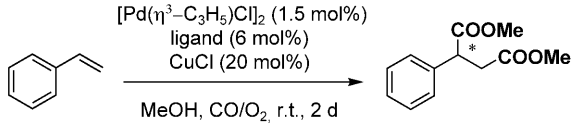
The general synthetic route to prepare the ligand library is shown in Scheme 2. Thus, 1-bromo-2-nitrobenzene **2** was coupled with the appropriate primary amines under Buchwald–Hartwig conditions,[4h,9] and the nitro group was hydrogenated to give the corresponding diamine **3**. Alkylation using ethyl bromoacetate resulted in ester **4**. Thiourea formation was accomplished using previously described conditions with thiophosgene[4d,h] in the presence of $NaHCO_3$. Thiourea-ester **5** could undergo stepwise mono- or bismethylation using LiHMDS/MeI by controlling the reaction temperature and reagent stoichiometry. Attempts to access the *gem*-dimethyl analogue through direct alkylation using ethyl 2-bromo-2-methylpropanoate gave unsatisfactory results. Hydrolysis,[10,4h] amide cou-



a: $Pd(OAc)_2$, rac-BINAP, Cs_2CO_3, toluene, 115 °C; *b*: H_2, Pd/C;
c: $BrCH_2COOEt$, K_2CO_3, KI (cat.), THF, reflux; *d*: $CSCl_2$, $NaHCO_3$, THF, 50 °C;
e: LHMDS, MeI, THF, –78 °C; *f*: LHMDS, MeI, THF, –50 °C; *g*: *t*-BuOK, H_2O, THF, r.t.;
h: EDC•HCl, CH_2Cl_2, r.t.; *i*: Burgess reagent, THF, 70 °C.

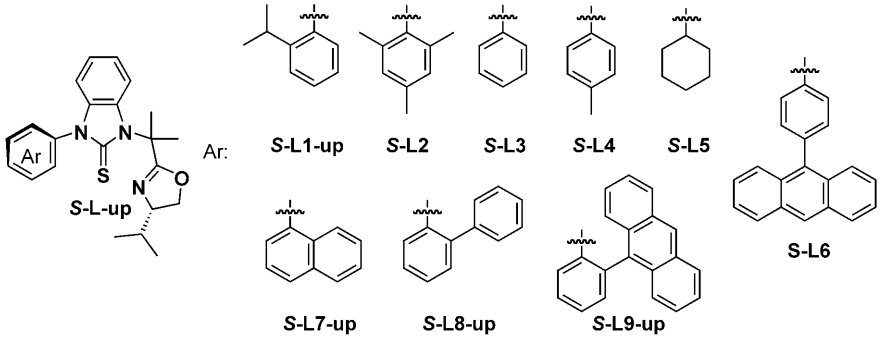
Scheme 2. General route for the synthesis of thiourea-oxazoline ligands.

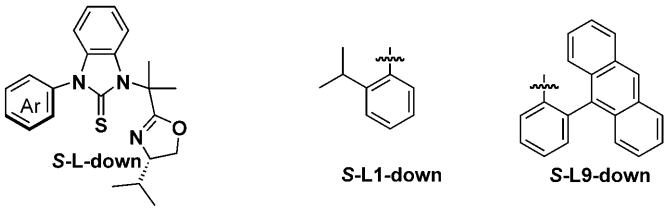
Table 1. Ligands varying left N-substitution and their catalytic activities.



Ligand	Yield [%][a]	*ee* [%][b]	Ligand	Yield [%][a]	*ee* [%][b]
***S*-L2**	90	51	***S*-L8-up**	90	65
***S*-L3**	98	51	***S*-L1-up**	95	75
***S*-L4**	98	45	***S*-L1-down**	96	–57
***S*-L5**	15	18	***S*-L9-up**	97	76
***S*-L6**	88	46	***S*-L9-down**	95	–69
***S*-L7-up**	90	70			

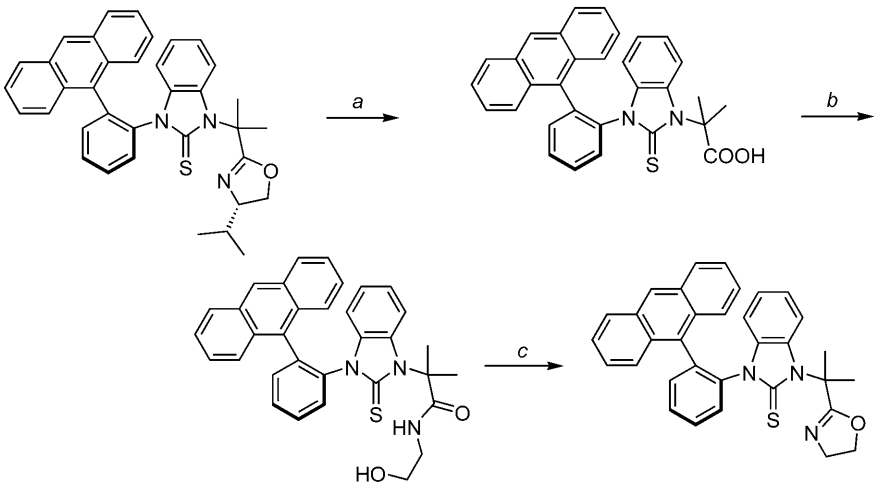
[a] Isolated yield after silica gel chromatography.
[b] Determined by chiral HPLC (Daicel Chiralcel OD-H).





pling, followed by oxazoline ring closure using the Burgess reagent[11,4h] proceeded smoothly to give ligands **L**.

The ligands containing varying "left side" aromatic (or, in one case, cyclohexyl) N-substitution and the catalytic results derived therefrom are summarized in Table 1. Using 1.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as the Pd source, ligand L, and CuCl (20 mol%), most reactions proceeded smoothly at room temperature, under atmospheric pressure of oxygen and CO (1/4 ratio), although they normally took 2 days to reach completion. It was evident that N-aryl substitution was required to maintain catalytic reactivity and enantioselectivity. Thus, the cyclohexyl substituted ligand ***S*-L5** gave sluggish, and non-selective reactions, resulting in only 15% isolated yield, with 18% *ee*. The stereogenic center of the oxazoline generated approximately 50% facial selectivity (ligand **L2–L6**). For *ortho*-substituted phenyl rings, two separable atropoisomers exist as a result of restricted C–N bond rotation. The effect of the two independent stereocenters was examined. Bulky *ortho*-substituents were among the best in terms of enantioselectivity. Using an *ortho*-9-anthracenyl substituted ligand ***S*-L9-up**, 97% yield and 76% *ee* were obtained. Noticeably, this ligand was proven to be more robust than the previous ***S*-L1-up** ligand, which required freshly purified CuCl. Various commercial samples of CuCl gave very consistent results, together with ***S*-L9-up**. It is especially interesting that the seemingly more remote atropic chirality overruled that of the oxazoline moiety in a mis-matched case, generating enantioselectivities merely 18% and 6% lower for ***S*-L1-down** and ***S*-L9-down**, respectively. The absolute configuration of the newly generated



a: 3 N HCl, 95 °C; 43%. *b*: EDC, HOBt, DMAP, TEA, CH_2Cl_2, H_2N⌒OH, r.t.; 59%.
c: Burgess reagent, THF, 70 °C, 65%.

Scheme 3. Synthesis of unsubstituted oxazoline ligands.

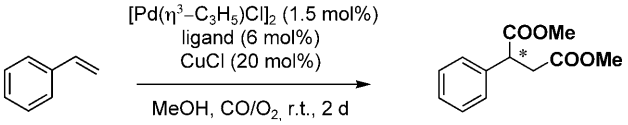
stereocenter in the product was the opposite to those generated using ***S*-L1-up** and ***S*-L9-up**.

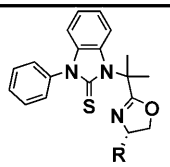
The chiral center on the oxazoline moiety was also modified in an attempt to find a synergetic/additive effect in a matched scenario. The simple unsubstituted oxazoline ligand was prepared using the route shown in Scheme 3, following separation of the atropoisomers. Other analogues bearing various chiral centers on the oxazoline were also synthesized. Cleavage of the oxazoline ring under acid conditions resulted in the formation of the *gem*-dimethyl amino acid.[12] Standard peptide coupling using HOBt/EDC with ethanolamine afforded the hydroxylamide. Treatment with the Burgess reagent led to the final thiourea-oxazoline ligand.

Generally, the size of the R group on the oxazoline moiety did not have a significant effect on the enantioselectivity of the bis(methoxycarbonylation). This is consistent with the atropic chirality being the main element dictating asymmetric induction. Nevertheless, bulky *i*-Pr and *t*-Bu ligands consistently led to superior yields and *ee*s (Table 2).

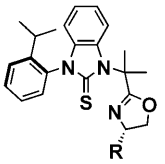
The bidentate nature of these thiourea-oxazoline ligands necessitates a quick survey of the bite angle between thiourea and oxazoline lone pairs. One way to modify this angle is to remove methyl groups from the side chain. **L10** was obtained as two diastereoisomers, assigned as ***S*-L10-*R*** and ***S*-L10-*S***. Theoretically, there are four stereoisomers for ***S*-L11** (***S*-L11-*R*-up**, ***S*-L11-*S*-up**, ***S*-L11-*R*-down** and ***S*-L11-*S*-down**, respectively), however, only two (***S*-L11-*R*-up** and ***S*-L11-*S*-down**) were separated by silica gel chromatography. The other two decomposed readily during work-up and purification, probably due to the presence of an imine α-proton that leads to decomposition or epimerization.

Table 2. Impact of chiral centers on the oxazoline moiety.

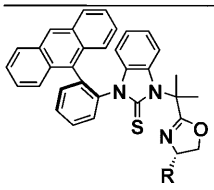




R	Yield [%]	*ee* [%]
Bn	90	34
Ph	60	48
i-Pr	98	51



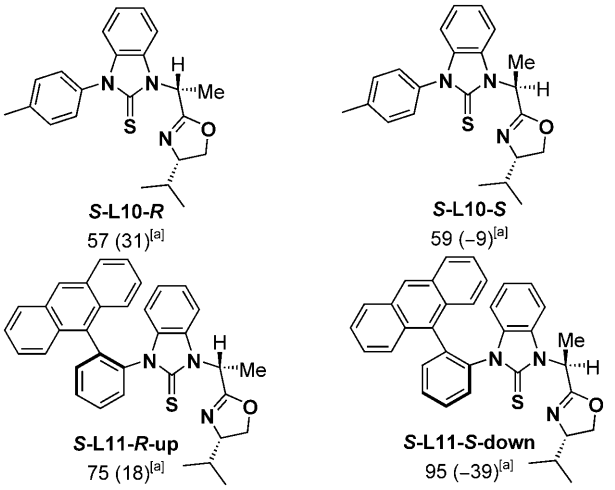
R	Yield [%]	*ee* [%]
i-Pr	95	75
t-Bu	90	78
	90	62



R	Yield [%]	*ee* [%]
H	88	65
i-Pr	97	76
gem-di-Me	95	63

Unfortunately, the mono-methylated ligands performed worse than the *gem*-dimethyl scaffolds, and the reactions were very slow. In fact, the bis(methoxycarbonylation) did not occur using the standard 1:2 Pd/**L** ratio. A Pd/**L** ratio of 1:1 generated partial conversion and poor enantioselectivity. This suggested that mono-methylated oxazolines were poor chelating ligands for palladium and that a significant portion of

Table 3. Bis(methoxycarbonylation) using mono-methylated ligands.



[a] Isolated yield after silica gel chromatography. Number in parathesis is *ee*, determined by chiral HPLC (Daicel Chiralcel OD-H).

the bis(methoxycarbonylation) may proceeded *via* a ligand-free Pd(II) species (Table 3).

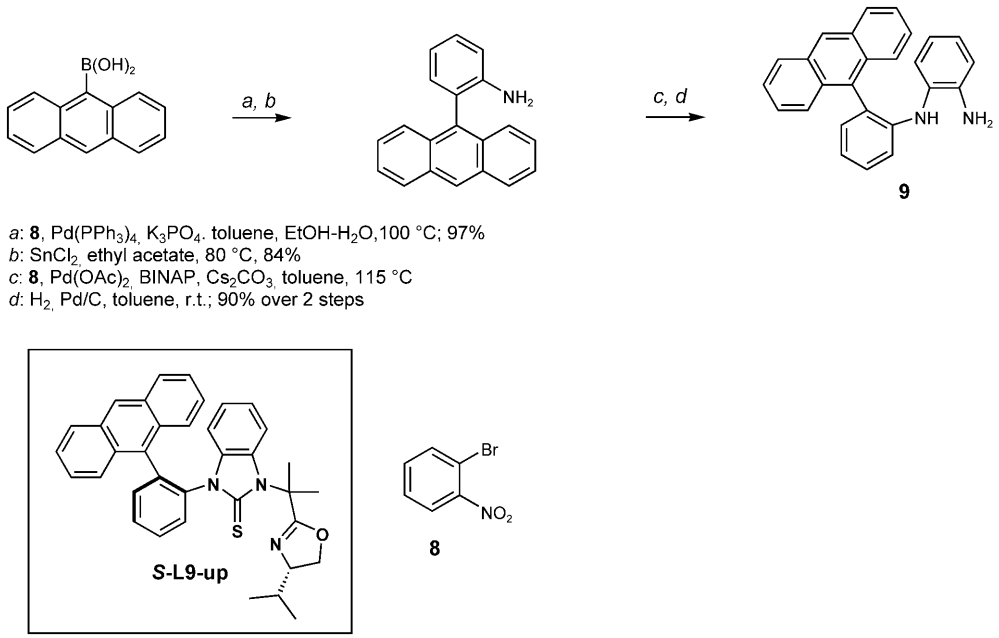
Reaction Condition Studies using *S*-L9-up

The quick ligand library survey helped us to locate the most promising ligand, ***S*-L9-up**. The corresponding synthetic starting material *N*-1-(2-(anthracen-9-yl)phenyl)benzene-1,2-diamine **9** (see Scheme 2 for steps beyond **9**) was prepared according to Scheme 4. ***S*-L9** was obtained as a 1:1 mixture of atropic isomers, which was resolved *via* silica gel column chromatography to give ***S*-L9-up** and ***S*-L9-down**. ***S*-L9-up** turned out to be the matched combination of the atropic chirality and the stereogenic center on the oxazoline. In CH_2Cl_2 at room temperature, it forms very cleanly a monomeric complex with $PdCl_2$, which was characterized by X-ray diffraction.

Various alcohols and mixed solvents were screened and the results are listed in Table 4. Bulkier alcohols resulted in slow (Table 4, entry 2) or even no (entries 3 and 4) reaction. No product was detected when diethylamine was used as the nucleophile (Table 4, entry 5). MeOH proved to be the most reactive nucleophile, and the effect of co-solvents was also examined. Although addition of chloroform improved enantioselectivity slightly, the reaction rate dropped significantly.

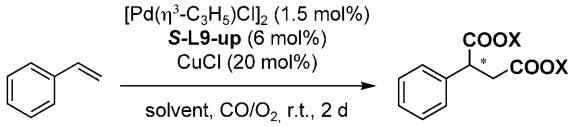
Presumably, the function of CuCl was to regenerate Pd(II) through oxidation, similar to that of $CuCl_2$ in the traditional Wacker oxidation.[13] The use of molecular oxygen avoided the need for a stoichiometric amount of CuCl, thanks to its facile oxidation of Cu(I) to Cu(II). However, to our surprise, $CuCl_2$ itself did not promote bis(methoxycarbonylation) in our system. Furthermore, a stoichiometric amount of Pd(II), as both *in situ* generated or pre-formed thiourea-oxazoline complexes, failed to promote bis(methoxycarbonylation) in the absence of CuCl and oxygen (Scheme 5).

This is very strong evidence that copper did not simply act as an oxidant. It is our hypothesis that



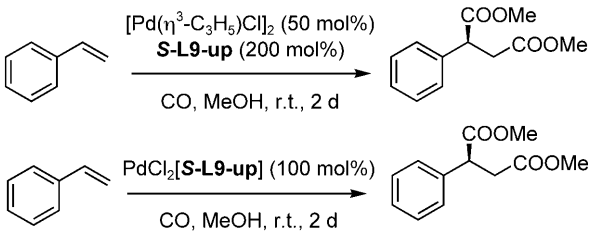
Scheme 4. Synthesis of thiourea-oxazoline ligand ***S*-L9**.

Table 4. Pd-catalyzed carbonylation in different solvents.



Entry	Solvent	Ratio	Yield [%][a]	*ee* [%][b]	Entry	Solvent	Ratio	Yield [%][a]	*ee* [%][b]
1	MeOH	/	97	76	12	CH_3CN/MeOH	1/1	17[d]	63
2	EtOH	/	27[c]	70	13	AcOH/MeOH	1/1	5[d]	63
3	*i*PrOH	/	NR	/	14	DCE/MeOH	1/1	NR	/
4	*t*BuOH	/	NR	/	15	DCM/MeOH	1/1	99	76
5	Et_2NH	/	NR	/	16	$CHCl_3$/MeOH	1/1	94	77
6	THF/MeOH	1/1	88	69	17	$CHCl_3$/MeOH	2/1	81[e]	79
7	dioxane/MeOH	1/1	98	59	18	$CHCl_3$/MeOH	4/1	66[e]	78
8	DMF/MeOH	1/1	39[d]	60	19	toluene/MeOH	1/1	92	75
9	DMSO/MeOH	1/1	5[d]	/	20	bezene/MeOH	1/1	82	73
10	NMP/MeOH	1/1	77[d]	60	21	xylene/MeOH	1/1	98	73
11	acetone/MeOH	1/1	>99[d]	67	22	$CHCl_3$/toluene/MeOH	1/1/1	81[e]	79

[a] Isolated yield after silica gel chromatography. Number in parathesis is *ee*, determined by chiral HPLC (Daicel Chiralcel OD-H).[a] Isolated yield after silica gel chromatography.
[b] Determined by HPLC analysis (Daicel Chiralcel OD-H).
[c] Incomplete conversion after 2 d.
[d] Conversion determined by GC-MS with biphenyl as external reference after 2 d.
[e] Incomplete conversion after 64 h.

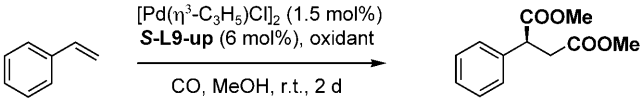


Scheme 5. Bis(methoxycarbonylation) reaction with a stoichiometric amount of Pd(II).

CuCl participates in carbon-metal bond forming and breaking processes during the catalytic cycle. To understand better the role of copper, various "oxidants" were examined in lieu of CuCl. The results are listed in Table 5. None of the metal and organic oxidants we examined catalyzed the bis(methoxycarbonylation) of styrene, except for Cu(I) salts.

Although chloride counter ion was not required, we did observe a mild "Cl" effect (Table 6). Cu(OTf) was as effective for bis(methoxycarbonylation) under standard conditions. It was later found that palladium catalysts bearing Cl were required in order to perform efficiently. No reaction was observed using $Pd(OAc)_2$. On the other hand, the reaction employing CuCl/$Pd(OAc)_2$ in combination proceeded smoothly. Addition of various inert chloride sources did not improve the reaction. The reaction rate correlated strongly with the amount of CuCl used. The reactions acceler-

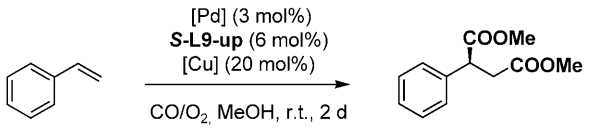
Table 5. Effect of various "oxidants."



Entry	Oxidant	M [mol%]	Yield [%][a]	*ee* [%][b]
1	$CuCl/O_2$	20	97	75
2	$CuBr/O_2$	20	62	76
3	CuI/O_2	20	NR	/
4	$(CuOTf)_2C_6H_6/O_2$	20	82	72
5	$FeCl_3/O_2$	20	NR	/
6	$Fe(acac)_3/O_2$	20	NR	/
7	$CoCl_2/O_2$	20	NR	/
8	DDQ	100	NR	/
9	$PhI(OAc)_2$	100	NR	/
10	$PhI(CF_3COO)_2$	100	NR	/

[a] Isolated yield after silica gel chromatography.
[b] Determined by chiral HPLC (Daicel Chiralcel OD-H).

Table 6. Effect of chloride ion.



Entry	[Pd]	[Cu]	Yield [%][a]	*ee* [%][b]
1	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	CuCl	97	75
2	$Pd(OAc)_2$	CuCl	83	77
3	$PdCl_2$	CuCl	94	73
4	$PdCl_2(CH_3CN)_2$	CuCl	98	76
5	$PdCl_2(PhCN)_2$	CuCl	94	77
6	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	$(CuOTf)_2C_6H_6$	82	72
7	$Pd(OAc)_2$	$(CuOTf)_2C_6H_6$	NR	/
8	$PdCl_2$	$(CuOTf)_2C_6H_6$	86	74
9	$PdCl_2(CH_3CN)_2$	$(CuOTf)_2C_6H_6$	94	73
10	$PdCl_2(PhCN)$	$(CuOTf)_2C_6H_6$	85	73

[a] Isolated yield after silica gel chromatography.
[b] Determined by chiral HPLC (Daicel Chiralcel OD-H).[a] Isolated yield after silica gel chromatography.
[b] Determined by HPLC analysis (Daicel Chiralcel OD-H).

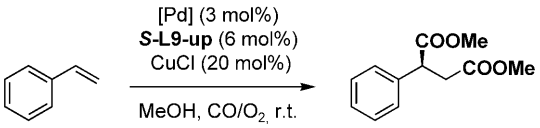
ated significantly with 20 mol% or more of CuCl. The reaction using CuCl alone, in the absence of any palladium catalyst did not proceed.

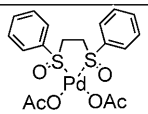
Bis(methoxycarbonylation) is normally a Pd(II)-catalyzed reaction. The electronic nature of palladium should play a very important role in catalyst reactivity. We discovered at quite an early stage that the background reaction, using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ without any ligand, proceeded almost as fast as the "catalyzed" version (Table 7, entries 1A and 1B). This made it very difficult to develop a highly enantioselective reaction. In order to find a distinct rate gap between the background and ligand-assisted pathways, various Pd species were examined and reaction progress was closely monitored.

Bis(methoxycarbonylation) did not occur under Pd-free conditions, indicating that both palladium and copper are required. Cationic Pd(II) generally gave a faster reaction, compared with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, accompanied by suppressed background ligand-free competition. In particular, reactions using 3 mol% $PdCl_2(CH_3CN)_2$ were able to reach complete conversion within 8 h, and thus this was chosen as the standard palladium catalyst precursor for the following studies. We note that Pd(0), in the form of $Pd_2(dba)_3$ (Table 7, entry 4 A), was also an effective catalyst precursor in the presence of ligand ***S*-L9-up**.

An interesting observation was made when the ligand/catalyst ratio was altered. As shown in Table 8,

Table 7. Pd-catalyzed carbonylation using different palladium precursors with or without ligand ***S*-L9-up**.



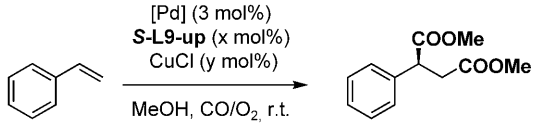
Entry[a]	[Pd]	Conversion [%][b] 4 h	8 h	16 h	30 h	*ee* [%][c]
1A	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	9	42	98	>99	75
1B		18	30	63	93	/
2A	PdI_2	0	0	5	15	73
2B		6	28	67	69	/
3A	$PdCl_2(CH_3CN)_2$	61	94	>99	>99	73
3B		1	6	30	49	/
4A	Pd_2dba_3	18	35	70	90	75
4B		0	0	15	40	/
5A	$[Pd(CH_3CN)_4](BF_4)_2$	53	80	>99	>99	76
5B		2	6	39	55	/
6A	$(NH_4)_2PdCl_4$	7	29	82	92	76
6B		0	0	5	14	/
7A	$Pd(NO_3)_2 \cdot xH_2O$	44	75	>99	>99	75
7B		0	0	4	12	/
8A	$Pd(NH_3)_4PdCl_4$	4	13	70	83	76
8B		0	2	14	42	/
9A	$Pd(acac)_2$	25	66	>99	>99	74
9B		4	9	33	60	/
10A		16	39	92	>99	76
10B		0	2	12	24	/

[a] A: ***S*-L9-up** was added. B: Blank reaction without ligand.
[b] Determined by GC-MS using biphenyl as external reference.
[c] Determined by HPLC analysis (Phenomenex Lux 5u Cellulose-2).

the reaction rate dropped significantly when the ratio of (Pd + Cu)/L was less than 1/1 (Table 8, entries 1–4). The reaction did not proceed when the ratio of (Pd + Cu)/L was 1/2 or less (Table 8, entry 4). On the other hand, with a large excess of copper, the ligand/Pd ratio alone did not affect the reaction to any extent (Table 8, entries 5–8). This is a strong indication that thiourea-oxazolines are actually a poison to copper. Presumably, by complexing with copper, the ligand effectively shuts down the activity of copper. Unfortunately, attempts to isolate a copper-ligand complex have as yet been unsuccessful. Further studies are currently under way.

The standard reaction conditions employ dry methanol. A small amount of water did not affect the bis(methoxycarbonylation) to a great extent. When the water concentration was increased to 10 equivalents with respect to substrates, the reaction became slower (Table 9). Any amount of water beyond 10 equivalents significantly inhibited the bis(methoxycarbonyla-

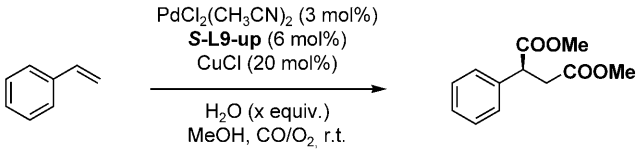
Table 8. Efferct of the metal ligand ratio.



Entry	*x* [mol%]	*y* [mol%]	Yield [%]	*ee* [%][a]
1[b]	3	3	81[d]	72
2[b]	6	3	29[d]	73
3[b]	9	3	23[d]	73
4[b]	12	3	–[d,e]	72
5[c]	3	20	99[f]	72
6[c]	4.5	20	98[f]	74
7[c]	6	20	99[f]	75
8[c]	9	20	90[f]	76

[a] Determined by HPLC analysis (Daicel Chiralcel OD-H).
[b] $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was used.
[c] $PdCl_2(CH_3CN)_2$ was used.
[d] Reaction time over 4 days. Isolated yield after silic gel chromatography.
[e] Less than 10% yield.
[f] Reaction time is 16 h. Conversion determined by GC-MS.

Table 9. Effect of water.



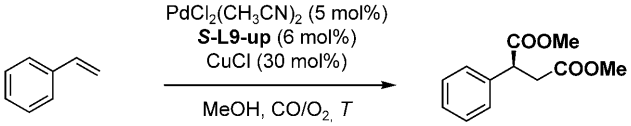
x	Conversion [%][a]				*ee* [%][b]
	4 h	8 h	16 h	30 h	
0	6	30	76	89	74
1	16	35	82	90	75
2	7	31	68	77	75
5	14	24	77	80	75
10	3	12	54	72	75

[a] Conversion determined by GC-MS.
[b] Determined by HPLC analysis (Daicel Chiralcel OD-H).

tion). These results confirmed that commercial grade methanol can be used without distillation.

We have shown that CuCl plays an additional role beyond simply that of an oxidant for these reactions. It has been reported that CuCl can absorb CO in organic solvents.[14] It may also act as a CO shuttle to facilitate CO transfer to palladium, and ultimately to substrates. *N,N,N′,N′*-Tetramethylethylenediamine is known to stabilize copper-carbonyl complexes. The

Table 10. Reaction at lower temperatures.



T	Conversion [%][a]				*ee* [%][b]
	8 h	16 h	30 h	72 h	
–20 °C	0	0	0	1	/
0 °C	1	7	9	24	79

[a] Determined by GC-MS.
[b] Determined by HPLC analysis (Phenomenex Lux 5u Cellulose-2).

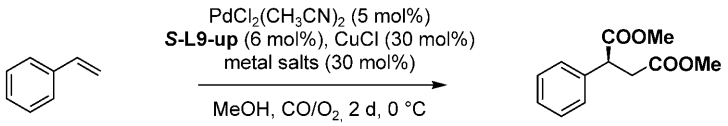
N-containing bases TMEDA and pyridine were tested, and they shut down the bis(methoxycarbonylation) almost completely, possibly due to strong coordination to palladium. Addition of Brønsted acids did not lead to noticeable improvement either. After we improved the reaction rate from *ca.* 48 h to within 8 h, a logical solution to the moderate enantioselectivity would be carrying out the reactions at low temperatures. To our surprise, 20 °C below room temperature led to an extremely slow reaction, not consistent with the kinetics law expected (Table 10). Several factors could potentially contribute to this loss of reactivity at low temperature, such as poor solubility of metal complexes, inefficient absorption of CO by copper, etc.

Fortunately, addition of another metal salt, especially silver salts, with moderate redox potential helped to resurrect the bis(methoxycarbonylation) at 0 °C (Table 11). It is not clear what the role of the silver salt is. Control experiments under chloride-free conditions yielded trace amounts of product. This suggested that silver did not simply act as a chloride scavenger, as it often does in other reactions[15]. After screening a variety of metal salts, we found that silver triflate was able to promote bis(methoxy-carbonylation) at 0 °C with good conversion and over 80% *ee*.

Various substituted styrenes were examined using ***S*-L9-up** under the optimized protocol (Table 12). For most of the substituted styrenes, yields were good to excellent. The substrates bearing electron-donating groups on the phenyl rings resulted in faster reactions and generally higher *ee* values than those containing electron-withdrawing groups. It was noticed that electron-deficient styrenes were particularly sensitive to polymerization under the reaction conditions. The reactions were generally much slower. ***S*-L9-up** failed to induce appreciable level of enantioselectivities using non-styrene type alkene substrates.

***S*-L9-up** forms clean monomeric complex with $PdCl_2$ in methylene chloride (see Figure 2 for crystal

Table 11. Effect of metal salts on reaction at 0 °C.



Entry	Metal salt	Conversion [%][a]	*ee* [%][b]	Entry	Metal salt	Conversion [%][a]	*ee* [%][b]
1	$CuCl_2$	15	78	9	$AgOOCCF_3$	25	/[c]
2	Fe_3O_4	43	79	10	AgO	9	80
3	$FeCl_3$	0	/[c]	11	AgOTf	88	81
4	$Fe(acac)_3$	20	78	12	Ag_2O	38	80
5	$CoCl_2$	25	78	13	AgF	0	/[c]
6	AgCl	62	80	14	AgBr	26	76
7	$AgNO_3$	62	80	15	AgI	29	74
8	Ag_2CO_3	9	/[c]	16	Salen-Co(II)[d]	10	/[c]

[a] Determined by GC-MS with biphenyl as external reference.
[b] Determined by HPLC analysis (Phenomenex Lux 5u Cellulose-2).
[c] The *ee* was not determined.
[d] (1*R*,2*R*)-(−)-1,2-Cyclohexanediamino-*N,N′*-bis(3,5-di-*tert*-butylsalicylidene)cobalt(II).

structure). The Pd complex adopts a square planar geometry with a severely biased steric environment. The bulky anthracene substituent overwhelmingly blocks a significant portion of the space above the palladium square planar. At the same time, one of the *gem*-methyl groups is pointing inwards to the palladium center. This combination may block the left pathway in Figure 3. The bottom half of the left aniline aromatic ring and *i*-Pr group on the oxazoline, effectively shield the lower part of the palladium square plane. Since the oxazoline ring is noticeably bent downward in the X-ray structure of the palladium-thiourea complex, we speculate that this only leaves an open channel between the axial *gem*-methyl and *i*-Pr group on the oxazoline to accommodate the steric demands of the phenyl moiety of the incoming styrene (Figure 3, pathway on the right).

This hypothesis predicts an *S* absolute stereochemistry, which is consistent with the experimental observations.[16] However, we note that the mechanism of the carboxylation process including the role of copper and other additives is not yet well understood, and it is clear that more detailed mechanistic studies are needed to understand fully the rather complex facial differentiation process.

Conclusions

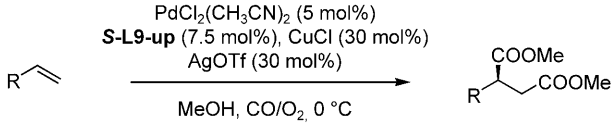
Systematic studies revealed several interesting features of the palladium thiourea-oxazoline-catalyzed asymmetric bis(methoxycarbonylation) of styrenes. Structure-selectivity relationships (SSR) and structure-reactivity relationships (SRR) led to a more robust and more selective ligand, namely ***S*-L9-up**. Chemically labile styrenes were bis(methoxycarbonylated) under very mild conditions in high yields and respectable enantioselectivities. The delicate catalytic system required an additional metal salt, AgOTf, to work properly at low temperatures. Further studies on more reactive and selective ligands, and to obtain a deeper mechanistic understanding of the bis(methoxycarbonylation) catalytic cycle, are currently under way and will be reported in due course.

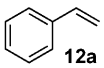
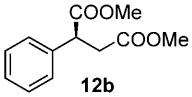
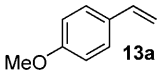
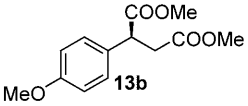
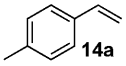
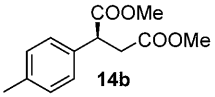
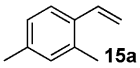
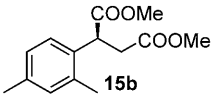
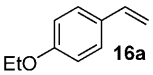
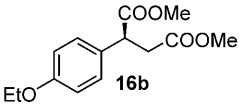
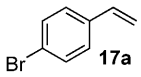
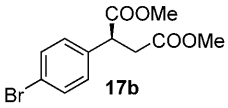
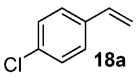
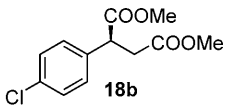
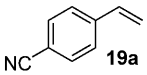
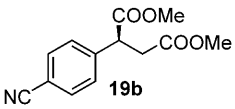
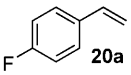
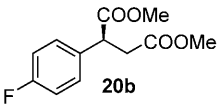
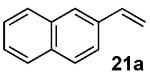
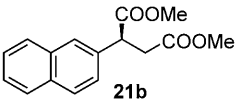
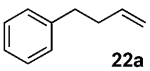
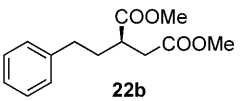
Experimental Section

General Remarks

All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Unless otherwise indicated, chemicals were purchased commercially, and used without further purification. Anhydrous THF was distilled from sodium-benzophenone, and dichloromethane was distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Tsingdao silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Brüker Advance 300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz), Brüker Advance 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz), Varian Inova 300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz), Varian Inova 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz), or Varian Inova 700 (^{1}H: 700 MHz, ^{13}C: 175 MHz) spectrometers and calibrated using residual un-

Table 12. Ligand ***S*-L9-up**-based Pd-catalyzed bis(methoxycarbonylation) of terminal alkenes.



Entry	Substrate	Product	Time	Yield [%][a]	*ee* [%][b]
1	 **12a**	 **12b**	60 h	85	84
2	 **13a**	 **13b**	60 h	88	76
3	 **14a**	 **14b**	60 h	82	79
4	 **15a**	 **15b**	60 h	83	68
5	 **16a**	 **16b**	60 h	78	76
6	 **17a**	 **17b**	4 d	75	64
7	 **18a**	 **18b**	4 d	88	64
8[c]	 **19a**	 **19b**	48 h	84	45
9	 **20a**	 **20b**	4 d	85	67
10	 **21a**	 **21b**	4 d	82	76
11[c]	 **22a**	 **22b**	48 h	92	21

[a] Isolated yield after silic gel chromatography.
[b] Determined by HPLC analysis (Phenomenex Lux 5u Cellulose-2).
[c] The reaction was run at room temperature.

deuterated solvent as an internal reference. Assignments of the NMR spectroscopic data were based on a series of 2D NMR studies. Mass spectrometric data were obtained using ABI QSTAR Elite mass spectrometer using ESI (electrospray ionization), ZAB-HS (EI, 70 eV) spectrometer or Thermo LTQFT mass spectrometer (for ESI/HR-MS-ESI). Melting points were obtained using a Sanyo Gallenkamp apparatus, and are uncorrected. The enantiomeric excesses of the products were determined by HPLC analysis on an Agilent 1100 HPLC or Agilent 1200 HPLC using a Diacel Chiralcel OD-H (Daicel, 4.6×250 mm) or OJ-H (Daicel, 4.6× 250 mm) column or Phenomenex Lux 5u Cellulose-2

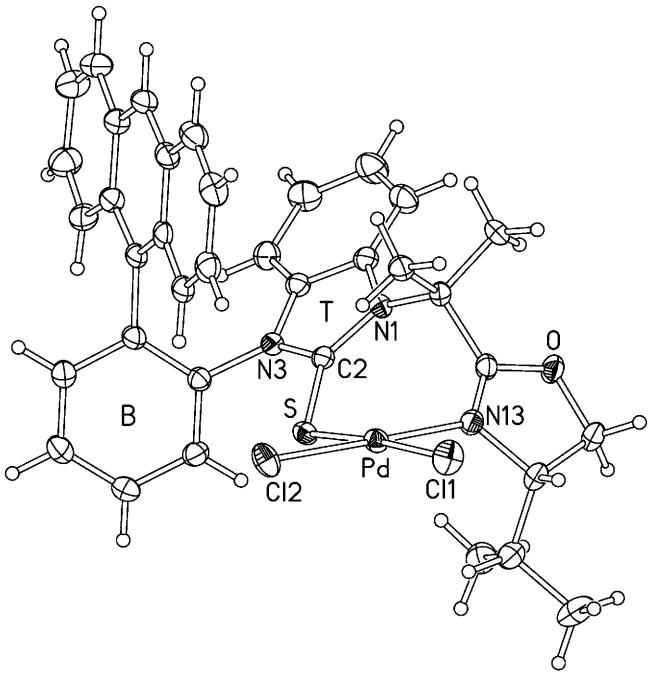


Figure 2. X-ray molecular structure of $PdCl_2$/***S*-L9-up** (thermal ellipsoids at 50% probability). The Pd atom has a distorted square-planar coordination. Selected bond distances: Pd–Cl(1) 2.3090(6), Pd–Cl(2) 2.3039(6), Pd–S 2.2833(6) and Pd–N(13) 2.007(7) Å. Dihedral angles between planes: benzothiourea (*T*)/benzene (*B*) 72°, *B*/anthracenyl 73°, *T*/Pd-coordination plane (*M*) 40°, *M*/oxazoline 54°. The asymmetric unit also contains 4 molecules of $CDCl_3$. Crystallographic data (excluding structure factors) for $PdCl_2$/***S*-L9-up**·4 $CDCl_3$ have been deposited with the Cambridge Crystallographic Data Centre as CCDC 766369. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44)-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

column (4.6×250 mm) and UV/CD detectors. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet.

General Procedure for the Pd-Catalyzed Asymmetric Bis(methoxycarbonylation)s of Terminal Olefins (Table 12)

A mixture of $PdCl_2(CH_3CN)_2$ (13 mg, 0.050 mmol), ligand ***S*-L9-up** (42 mg, 0.075 mmol), CuCl (30 mg, 0.30 mmol) and 8 mL MeOH was stirred at room temperature under a balloon pressure of CO and O_2 (*ca* 4:1) until a clear solution was formed. Then, AgOTf (77 mg, 0.30 mmol) was added at 0 °C, followed by substrate (1.0 mmol). The reaction mixture was stirred at 0 °C (Table 12, entries 1–5, 6, 7, 9, 10) or at room temperature (Table 12, entries 8, 11) for the indicated time. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, hexanes/EtOAc = 10/1) to give the product (see the Supporting Information for the syntheses of products **13b**–**22b**).

Compound 12b: Product **12b** was obtained in 85% yield with 84% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.34 (m, 5H), 4.08–4.13 (m, 1H), 3.68 (s, 3H), 3.64 (s, 3H), 3.17–3.26 (m, 1H), 2.64–2.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 171.9, 137.6, 128.8, 127.6, 127.6, 52.3, 51.8, 46.9, 37.5; HR-MS (EI): *m/z* = 222.0894, calcd for $C_{12}H_{14}O_4$ [M^+]: 222.0892; HPLC (Phenomenex Lux 5u Cellulose-2, hexane/*i*-PrOH = 80/20, 0.6 mL min^{-1}, 230 nm, 30 °C): t_r (major) = 10.0 min, t_r (minor) = 12.1 min.

Acknowledgements

This work was supported by grants of the National Science and Technology Major Project "Development of key technologies for the combinatorial synthesis of privileged scaffolds" (2009ZX09501-012), the National Science Foundation of China (20325208 and 20521202) and Nanshan Science & Technology (NANKEPING2007005). T.B.M. and Z.Y. thank the Royal Society for an International Joint Project Grant. T.B.M. thanks the EPSRC (UK) for an Overseas Research Travel Grant and the Royal Society of Chemistry for a Journals Grant for International Authors. K.W. and D.C. thank the Royal Thai Government for postgraduate scholarships.

References

[1] a) G. P. Chiusoli, C. Venturello, S. Merzoni, *Chem. Ind.* **1968**, 977; b) G. P. Chiusoli, M. Costa, P. Pergreffi, S.

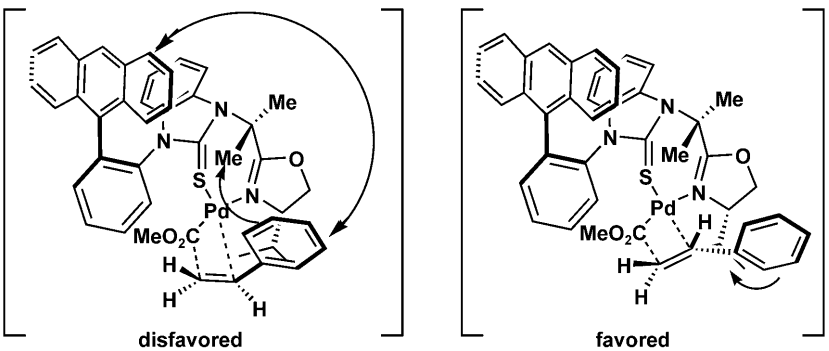


Figure 3. Proposed explanation for facial differentiation.

Reverberi, G. Salerno, *Gazz. Chim. Ital.* **1985**, *115*, 691; c) B. Gabriele, G. Salerno, M. Costa, G. P. Chiusoli, *J. Organomet. Chem.* **1995**, *503*, 21.

[2] a) F. Touchard, P. Gamez, F. Fache, M. Lemaire, *Tetrahedron Lett.* **1997**, *38*, 2275; b) F. Touchard, M. Bernard, F. Fache, F. Delbecq, V. Guiral, P. Sautet, M. Lemaire, *J. Organomet. Chem.* **1998**, *567*, 133; c) F. Touchard, M. Bernard, F. Fache, M. Lemaire, *J. Mol. Catal. A: Chem.* **1999**, *140*, 1; d) M. L. Tommasino, C. Thomazeau, F. Touchard, M. Lemaire, *Tetrahedron: Asymmetry* **1999**, *10*, 1813; e) F. Touchard, F. Fache, M. Lemaire, *Eur. J. Org. Chem.* **2000**, 3787; f) C. Saluzzo, R. ter Halle, F. Touchard, F. Fache, E. Schulz, M. Lemaire, *J. Organomet. Chem.* **2000**, *603*, 30; g) J. A. J. Breuzard, M. L. Tommasino, F. Touchard, M. Lemaire, M. C. Bonnet, *J. Mol. Catal. A: Chem.* **2000**, *156*, 223; h) C. Saluzzo, M. Lemaire, *Adv. Synth. Catal.* **2002**, *344*, 915; i) R. Abdallah, J. A. J. Breuzard, M. C. Bonnet, M. Lemaire, *J. Mol. Catal. A: Chem.* **2006**, *249*, 218.

[3] T. Y. Zhang, M. J. Allen, *Tetrahedron Lett.* **1999**, *40*, 5813.

[4] a) N. Yang, H. Miao, Z. Yang, *Org. Lett.* **2000**, *2*, 297; b) M. Dai, C. Wang, G. Dong, J. Xiang, Y. Luo, B. Liang, J. Chen, Z. Yang, *Eur. J. Org. Chem.* **2003**, 4346; c) M. Dai, B. Liang, C. Wang, Z. You, J. Xiang, G. Dong, J. Chen, Z. Yang, *Adv. Synth. Catal.* **2004**, *346*, 1669; d) M. Dai, B. Liang, C. Wang, J. Chen, Z. Yang, *Org. Lett.* **2004**, *6*, 221; e) Y. Tang, L. Deng, Y. Zhang, G. Dong, J. Chen, Yang, Z. *Org. Lett.* **2005**, *7*, 593; f) Y. Tang, Y. Zhang, M. Dai, T. Luo, L. Deng, J. Chen, Z. Yang, *Org. Lett.* **2005**, *7*, 885; g) Y. Tang, L. Deng, Y. Zhang, G. Dong, J. Chen, Z. Yang, *Org. Lett.* **2005**, *7*, 1657; h) B. Liang, J. Liu, Y. Gao, K. Wongkhan, D. Shu, Y. Lan, A. Li, A. Batsanov, J. Howard, T. B. Marder, J. Chen, Z. Yang, *Organometallics* **2007**, *26*, 4756; i) Y. Liu, X. Li, G. Lin, Z. Xiang, J. Xiang, M. Zhao, J. Chen, Z. Yang, *J. Org. Chem.* **2008**, *73*, 4625.

[5] a) D. Yang, Y.-C. Chen, N.-Y. Zhu, *Org. lett.* **2004**, *6*, 1577; b) W. Chen, R. Li, B. Han, B.-J. Li, Y.-C. Chen, Y. Wu, L.-S. Ding, D. Yang, *Eur. J. Org. Chem.* **2006**, 1177.

[6] a) R. F. Heck, *J. Am. Chem. Soc.* **1972**, *94*, 2712; b) D. M. Fenton, P. J. Steinwand, *J. Org. Chem.* **1972**, *37*, 2034; c) D. E. James, L. F. Hines, J. K. Stille, *J. Am. Chem. Soc.* **1976**, *98*. 1806; d) D. E. James, J. K. Stille, *J. Am. Chem. Soc.* **1976**, *98*, 1810; e) J. K. Stille, R. Divakaruni, *J. Org. Chem.* **1979**, *44*, 3474; f) G. E. Morris, D. Oakley, D. A. Pippard, D. J. H. Smith, *J. Chem. Soc. Chem. Commun.* **1987**, 410; g) D. Milstein, *Acc. Chem. Res.* **1988**, *21*, 428; h) J. Tsuji, *Synthesis* **1990**, 739; i) P. Bréchot, Y. Chauvin, D. Commereuc, L. Saussine, *Organometallics* **1990**, *9*, 235; j) S. Toda, M. Miyamoto, H. Kinoshita, K. Inomata, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3600; k) E. Drent, J. A. M. van Broekhoven, M. J. Doyle, *J. Organomet. Chem.* **1991**, *417*, 235.

[7] a) C. Pisano, S. C. A. Nefkens, G. Consiglio, *Organometallics* **1992**, *11*, 1975; b) S. C. A. Nefkens, M. Sperrle, G. Consiglio, *Angew. Chem.* **1993**, *105*, 1837; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1719; c) M. Sperrle, G. Consiglio, *J. Mol. Catal. A* **1999**, *143*, 263; d) M. Sperrle, G. Consiglio, *Chem. Ber. Recl.* **1997**, *130*, 1557; e) Y. Ukaji, M. Miyamoto, M. Mikuni, S. Takeuchi, K. Inomata, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 735; f) S. Takeuchi, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 955; g) K. Saigo, *Tetrahedron Lett.* **1998**, *39*, 7529; h) L. Wang, W. Kwok, J. Wu, R. Guo, T. T.-L. Au-Yeung, Z. Zhou, A. S. C. Chan, K.-S. Chan, *J. Mol. Catal. A* **2003**, *196*, 171; i) E. Guiu, M. Caporali, B. Muñoz, C. Müller, M. Lutz, A. L. Spek, C. Claver, P. W. N. M. van Leeuwen, *Organometallics* **2006**, *25*, 3102; j) C. Godard, B. K. Munoz, A. Ruiz, C. Claver, *Dalton Trans.* **2008**, 853.

[8] a) E. Drent, Eur. Pat. Appl. 229,408, **1986**; *Chem. Abstr.* **1991**, *108*, 6617; b) P. Corradini, C. De Rosa, A. Panunzi, G. Petrucci, P. Pino, *Chimia* **1976**, *44*, 52; c) M. Barsacchi, G. Consiglio, L. Medici, G. Petrucci, U. W. Suter, *Angew. Chem.* **1991**, *103*, 992; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 989.

[9] a) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131; b) J. F. Hartwitg, *Pure Appl. Chem.* **1999**, *71*, 1417; c) J. F. Hartwig, in: *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.: E. Negishi), Wiley-Interscience, New York, **2002**, p 1051; d) T. J. Seiders, D. W. Ward, R. H. Grubbs, *Org. Lett.* **2001**, *3*, 3225.

[10] P. G. Gassman, W. N. Schenk, *J. Org. Chem.* **1977**, *42*, 918.

[11] a) E. M. Burgess, H. R. Penton Jr. , E. A. Taylor, *J. Org. Chem.* **1973**, *38*, 26; b) P. Wipf, C. P. Miller, *Tetrahedron Lett.* **1992**, *33*, 907.

[12] A. I. Meyers, D. L. Temple Jr. , *J. Am. Chem. Soc.* **1970**, *92*, 6644.

[13] J. A. Keith, P. M. Henry, *Angew. Chem.* **2009**, *121*, 2; *Angew. Chem. Int. Ed.* **2009**, *48*, 2.

[14] M. Pasquali, C. Floriani, A. Gaetani-Manfredotti, *Inorg. Chem.* **1981**, *20*, 3382.

[15] a) I. Moritani, Y. Fujiwara, S. J. Danno, *J. Organomet. Chem.* **1971**, *27*, 279; b) A. C. Albeniz, P. Espinet, Y.-S. Lin, *Organometallics* **1995**, *14*, 2977; c) K. Karabelas, C. Westerlund, A. Hallberg, *J. Org. Chem.* **1985**, *50*, 3896; d) K. Karabelas, A. Hallberg, *J. Org. Chem.* **1986**, *51*, 5286; e) K. Karabelas, A. Hallberg, *J. Org. Chem.* **1988**, *53*, 4909; f) M. M. Abelman, T. Oh, L. E. Overman, *J. Org. Chem.* **1987**, *52*, 4130; g) T. Jeffery, *J. Chem. Soc. Chem. Commun.* **1991**, 324; h) Y. Sato, T. Honda, M. Shibasaki, *Tetrahedron Lett.* **1992**, *33*, 2593; i) Y. Sato, S. Watanabe, M. Shibasaki, *Tetrahedron Lett.* **1992**, *33*, 2589; j) A. Ashimori, L. E. Overman, *J. Org. Chem.* **1992**, *57*, 4571; k) A. Madin, L. E. Overman, *Tetrahedron Lett.* **1992**, *33*, 4859; l) H. Fukui, Y. Fukushi, S. Tahara, *Tetrahedron Lett.* **2003**, *44*, 4063; m) J. Malm, P. Björk, S. Gronowitz, A.-B. Hörnfeldt, *Tetrahedron Lett.* **1992**, *33*, 2199; n) Y. Uenishi, J.-M. Beau, R. W. Armstrong, Y. Kishi, *J. Am. Chem. Soc.* **1987**, *109*, 4756; o) H. Chen, M.-Z. Deng, *J. Org. Chem.* **2000**, *65*, 4444; p) M.-C. P. Yeh, W.-C. Tsao, Y.-J. Wang, H.-F. Pai, *Organometallics* **2007**, *26*, 4271.

[16] The absolute configuration of dimethyl 2-phenylsuccinate was determined by a comparison with the reported specific rotations: J. Lehmann, G. C. Lloyd-Jones, *Tetrahedron* **1995**, *51*, 8863, and the absolute configurations of other products were assigned accordingly.

