C–H Activation

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Highly Linear Selective Cobalt-Catalyzed Addition of Aryl Imines to Styrenes: Reversing Intrinsic Regioselectivity by Ligand Elaboration**

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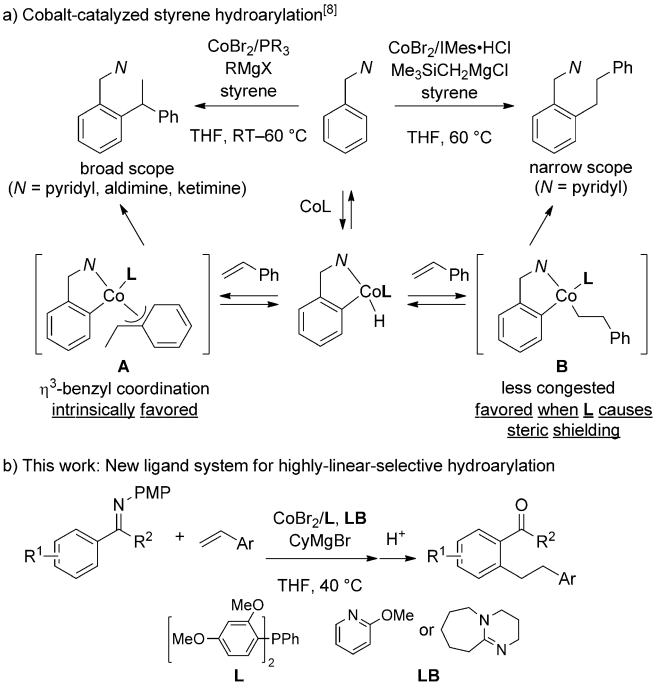
Abstract: *Highly linear selective, imine-directed hydroarylation of styrene has been achieved with cobalt-based catalytic systems featuring bis(2,4-dimethoxyphenyl)(phenyl)phosphine and either 2-methoxypyridine or DBU as a ligand and a Lewis base additive, respectively, thus affording a variety of 1,2-diarylethanes (bibenzyls) in good yields under mild reaction conditions. The triarylphosphine controls the regioselectivity, while the Lewis base significantly accelerates the reaction. Ligand screening and deuterium-labeling studies provide implications about the roles of the ligand and the Lewis base in the crucial C–C reductive elimination step.*

Control of regioselectivity in olefin functionalization reactions has been a subject of fundamental and practical interest in homogeneous catalysis.[1,2] Among such reactions is transition-metal-catalyzed addition of an arene C–H bond across styrene (hydroarylation), which can lead to branched or linear adducts. Besides Friedel–Crafts-type hydroarylation reactions which invariably lead to branched adducts,[3] various examples of styrene hydroarylation by transition-metal-mediated arene C–H activation, which selectively affords either linear or branched adducts, have been reported.[4,5] Nevertheless, the ability to achieve regiodivergence in this class of reaction, that is, to transform the same arene substrate into either of the two regioisomers by subtle modification of the catalyst or ligand structure, has been relatively limited,[5d,6,7] regardless of the presence of both 1,1-diarylethane and 1,2-diarylethane in bioactive molecules.

As one of the rare examples of regiodivergent styrene hydroarylation, we previously reported branched- and linear-selective addition of 2-arylpyridine to styrene using cobalt/phosphine (PCy_3) and cobalt/N-heterocyclic carbene (IMes) catalysts, respectively (Scheme 1a).[8a] To rationalize the regiodivergence, a common catalytic cycle involving reversible C–H oxidative addition, reversible and competitive styrene insertion leading to the branched and linear intermediates **A** and **B**, respectively, and regioselectivity-determining reductive elimination was proposed. The branched selectivity with the Co/PCy_3 catalyst was ascribed to η^3-benzyl coordination in the branched pathway,[9] while the sterically shielding nature of the IMes ligand was speculated to be the origin of the linear selectivity. A recent computational study by Fu et al. supported these speculations and suggested intrinsic preference of cobalt catalysts toward the branched selectivity.[10] Indeed, the scope of the branched-selective addition has been extended to aryl aldimines and ketimines by simple modification of the cobalt/phosphine system.[8b,c] Herein, we report on our effort to push the limit of regiodivergence in cobalt catalysis, which has led to a significant expansion of the scope of linear-selective styrene hydroarylation. Thus, with the carefully optimized ligand [bis(2,4-dimethoxyphenyl)(phenyl)phosphine] and Lewis base additive (2-methoxypyridine or DBU), highly linear selective addition of aryl ketimines to styrenes is achieved at a mild temperature (Scheme 1b).



Scheme 1. Cobalt-catalyzed, nitrogen-directed hydroarylation of styrenes. PMP = *para*-methoxyphenyl, THF = tetrahydrofuran.

The addition of the acetophenone imine **1a** to styrene (**2a**) was studied as a model reaction for ligand screening (Scheme 2). As reported previously, by using $CoBr_2$ (5 mol%), *para*-substituted triarylphosphine (10 mol%), and CyMgBr (50 mol%), this reaction gives the branched adduct **3aa′** at room temperature with high regioselectivity.[8c] Contrary to our expectation, sterically crowded tris(2,6-diethylphenyl)phosphine (**L1**) and tri(2-ethylphenyl)phos-

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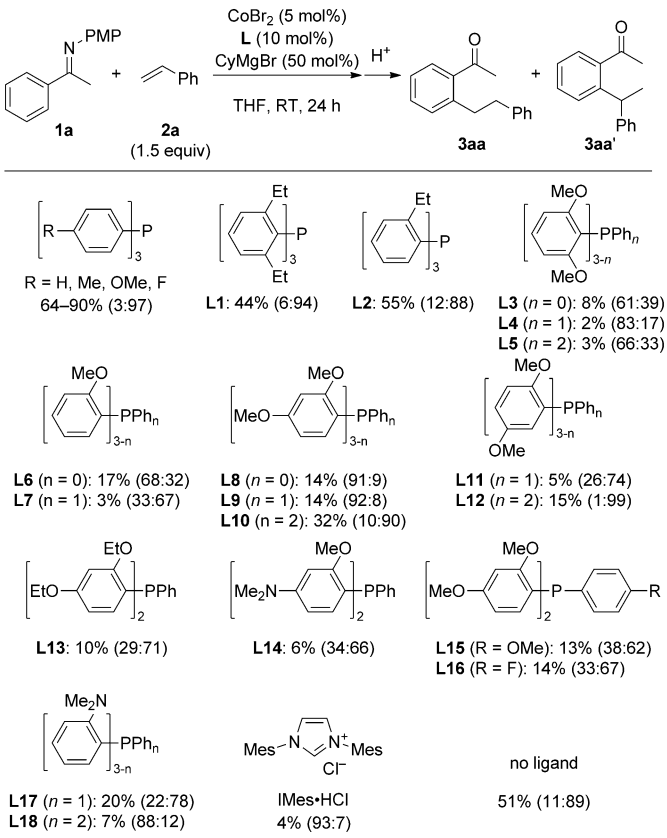
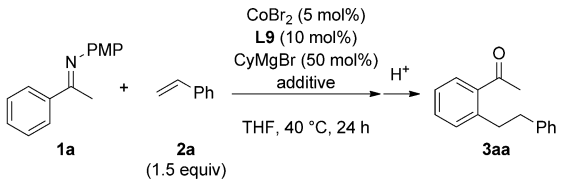


Scheme 2. Ligand screening. The reaction was performed on a 0.3 mmol scale. The yield was determined by GC using *n*-tridecane as an internal standard.

phine (**L2**) did not alter the regioselectivity, while maintaining modest catalytic activity. Notably, triarylphosphines bearing different numbers of 2,6-dimethoxyphenyl groups (**L3**–**L5**) significantly reduced the catalytic activity but reversed the regioselectivity (l/b = 83:17–61:39). Upon examination of several triarylphosphines bearing 2-methoxyaryl groups (**L6**–**L10**), an l/b ratio exceeding 90:10 was achieved with **L8** and **L9** bearing three and two, respectively, 2,4-dimethoxyphenyl groups. Subsequent screening experiments revealed significant influence of subtle changes in the ligand structure. The 2,5-dimethoxyphenyl analogues of **L8** and **L9** (**L11** and **L12**), the ethoxy analogue of **L9** (**L13**), and the 4-dimethylamino analogue of **L9** (**L14**) all exhibited branched selectivity. Even changing the phenyl group of **L9** to the 4-methoxyphenyl or 4-fluorophenyl group reversed the regioselectivity (see **L15** and **L16**). Among other ligands examined, only 2-dimethylaminophenyl(diphenyl)phosphine **L18** exhibited linear selectivity close to 9:1. As expected, the IMes ligand showed high linear selectivity but with very low catalytic activity. Note also that the reaction proceeded even without a ligand with an l/b ratio of 11:89.

Upon further optimization using **L9**, we found that the addition of an appropriate Lewis base significantly enhances the reaction efficiency without deteriorating the linear selectivity (Table 1). Among pyridine derivatives, 2-methoxypyridine was particularly effective (entries 1–4). Using 4 equivalents of 2-methoxypyridine, the product **3aa** was

Table 1: Effect of additives.[a]



Entry	Additive (mol%)	Yield [%][b]	l/b[c]
1	none	40	92:8
2	pyridine (80)	54	93:7
3	DMAP (80)	32	89:11
4	2-methoxypyridine (80)	70	95:5
5	2-methoxypyridine (200)	80	94:6
6	2-methoxypyridine (400)	91[d]	97:3
7[e]	2-methoxypyridine (80)	70	4:96
8	DBU (80)	91	93:7
9	DMPU (80)	63	97:3
10	TMEDA (80)	38	88:12

[a] The reaction was performed on a 0.3 mmol scale. [b] Determined by ^{1}H NMR spectroscopy or GC. [c] Linear-to-branched ratio determined by ^{1}H NMR spectroscopy or GC. [d] Yield of isolated product. [e] **L9** was omitted. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-(*N*,*N*-dimethyl)pyridine, DMPU = 1,3-dimethyltetrahydro-2-pyrimidinone, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

obtained in 91% yield upon isolation, with an l/b ratio of 97:3 (entry 6). The use of 2-methoxypyridine in the absence of **L9** resulted in high branched selectivity (entry 7), thus demonstrating that **L9** plays a decisive role in the linear selectivity. Examination of other Lewis bases identified DBU as another effective additive (91% yield, l/b = 93:7; entry 8).

By using the Co/**L9**/2-methoxypyridine catalytic system, the reaction of imines derived from substituted acetophenones, except for some *meta*-substituted derivatives (see below), with styrene afforded the corresponding 1,2-diarylethanes **3aa**–**ga** in moderate to good yields with l/b ratios of 90:10 or greater (Figure 1). The imine derived from 3′-methylacetophenone reacted exclusively at the less hindered

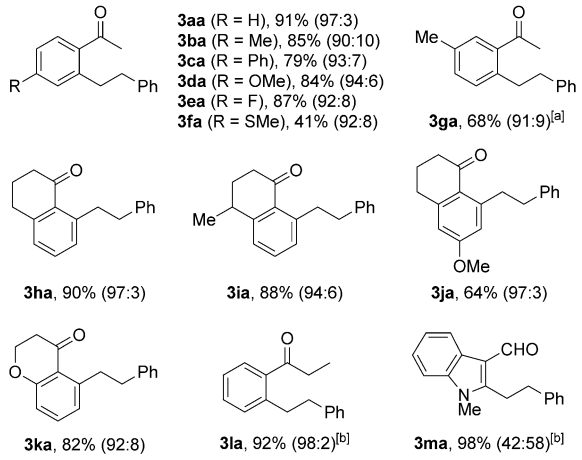
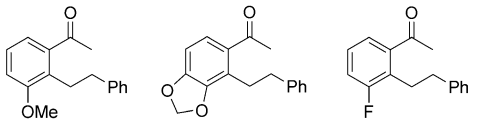


Figure 1. 1,2-Diarylethanes obtained from various imines and styrene under the reaction conditions in Table 1, entry 6. The linear-to-branched ratio is shown within parentheses. [a] The reaction time was 48 h. [b] DBU (80 mol%) was used instead of 2-methoxypyridine.

position (**3ga**). Imines prepared from tetralone derivatives and 4-chromanone also afforded the desired 1,2-diarylethanes **3ha–ka**. While the performance of the Co/**L9**/2-methoxypyridine system was moderate for a propiophenone-derived imine (72% yield, l/b = 81:19), the Co/**L9**/DBU system (Table 1, entry 8) significantly improved the reaction (**3la**). The reaction of 3-iminoindole was smooth but poorly regioselective, regardless of the catalytic system used (**3ma**; Figure 1).

Imines bearing a *meta*-alkoxy or *meta*-fluoro substituent (**1n–p**) behaved very differently (Figure 2). These imines underwent regioselective C–H activation at the position proximal to the alkoxy group or the fluorine atom, as expected from previous studies by us[8,11,12] and Ackermann



additive	**3na**	**3oa**	**3pa**
2-methoxypyridine	28% (18:82)[a]	68% (27:73)	69% (30:70)
DBU	23% (67:33)[a]	74% (58:42)	72% (89:11)

Figure 2. 1,2-Diarylethanes obtained from *meta*-alkoxy or *meta*-fluoro imines and styrene under the reaction conditions in Table 1, entry 6 (2-methoxypyridine as the additive) or entry 8 (DBU as the additive). The linear-to-branched ratio is shown within parentheses. [a] The yield was determined by ^{1}H NMR spectroscopy.

et al.,[13] but afforded the 1,2-diarylethanes **3na–pa** as minor products, with l/b ratios of approximately 2:8 to 3:7. Notably, the use of DBU instead of 2-methoxypyridine had a sizable effect on the regioselectivity (l/b ratios = ca. 6:4–9:1).

As summarized in Figure 3, various *para*, *meta*, *ortho*, and multisubstituted styrenes participated in the reaction with **1a** to afford the corresponding 1,2-diarylethanes **3ab–ap** in good yields with high regioselectivities (90:10 or greater), except for the case of 4-phenylstyrene (**3ag**; l/b = 75:25). The reaction of 2-vinylbenzofuran took place sluggishly with poor regioselectivity (**3aq**; 8%, l/b = 39:61). The reaction of 2-vinylnaphthalene was even more sluggish (2%, l/b = 38:62 with the DBU system; data not shown). The reason for such poor reactivities remains unclear at this moment.

To gain insight into the reaction pathway, the reaction of the deuterated imine [D]$_5$-**1a** and 4-methoxystyrene (**2e**) was examined (Table 2). The reaction under the standard conditions (6 h) afforded the linear product in 79% yield with substantial decrease in the deuteration rate of the *ortho* position (C1) and significant deuterium incorporation into both the methylene moieties (C2 and C3; entry 1). Along with this, substantial H/D scrambling between the *ortho* positions (C4) of the recovered imine and the recovered styrene (C5 and C6) was observed. A similar yield and H/D scrambling patterns were obtained using DBU as the additive (entry 2). While the reaction in the absence of additive was sluggish as expected, the degree of H/D scrambling between the recovered starting materials was substantial (entry 3). The reaction at 0°C resulted in an apparent decrease in the product yield and the

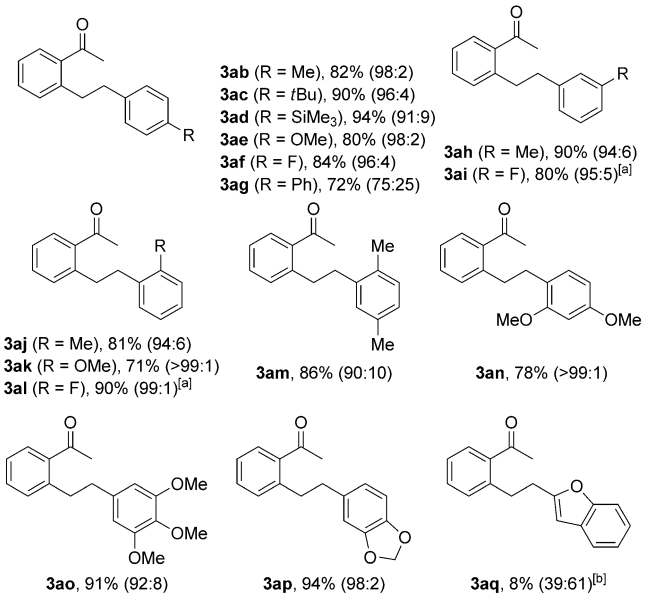
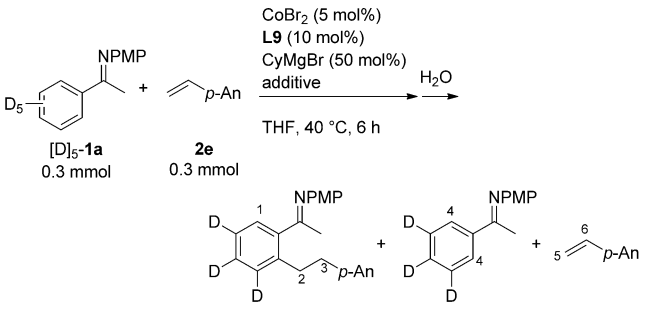


Figure 3. 1,2-Diarylethanes obtained from **1a** and various styrenes under the reaction conditions in Table 1, entry 6. The linear-to-branched ratio is shown within parentheses. [a] DBU (80 mol%) was used instead of 2-methoxypyridine. The reaction time was 48 h. [b] Determined by ^{1}H NMR spectroscopy.

Table 2: Deuterium-labeling experiments.



Entry	Additive	Yield [%][a]	^{1}H NMR integration[b]					
			C1	C2	C3	C4	C5	C6
1	2-MeOPy	79	0.41	0.93	0.96	1.26	1.43	0.70
2	DBU	82	0.36	0.85	0.92	1.11	1.22	0.63
3	none	19	0.32	0.99	0.90	1.06	1.27	0.68
4[c]	2-MeOPy	10	0.48	1.14	0.96	0.62	1.50	0.85

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Determined after separation of the crude reaction mixtures on silica gel. Signals of the methoxy groups were used as references. [c] The reaction was performed at 0°C.

degree of H/D scrambling (entry 4). These observations suggest 1) rapid and reversible C–H activation and styrene insertion irrespective of the presence or absence of the additive and 2) rate- and regioselectivity-determining reductive elimination. A possible role of the additive is to accelerate reductive elimination, while an alternative role in an off-cycle process (e.g., preventing catalyst deactivation) may not be excluded.

On the basis of the above argument, the ligand **L9** is thought to stabilize the transition state (TS) from the linear intermediate **B** and/or destabilize the TS from the branched intermediate **A** (Scheme 1 a). The results of the ligand screening (Scheme 2) suggest that the linear selectivity of **L9** cannot be simply ascribed to its steric property (**L1** and **L2**). We speculate that the 2-methoxy group of **L9** serves as a hemilabile donor to provide the linear TS (**TS B**) with extra stabilization (Figure 4). Such stabilization may not be available in the η^3-benzyl, branched TS (**TS A**) because of coordinative saturation. The irregular regioselectivity observed for the *meta*-alkoxy- and *meta*-fluoro-substituted imines (Figure 2) may be attributed to the interference of the Co–O coordination in **TS B** by the interaction of the *meta*-alkoxy or *meta*-fluoro group with the cobalt center. Note, however, that these models apparently oversimplify the subtlety of the ligand effect on the regioselectivity.

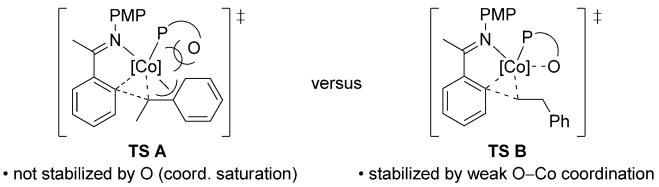
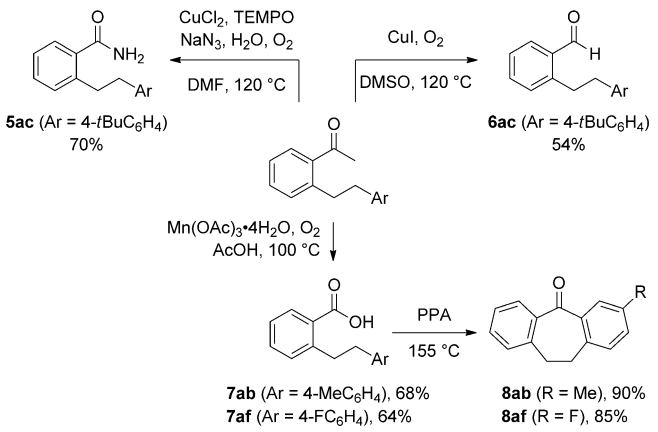


Figure 4. Hypothetical transition-state models for linear selectivity.

Recent developments in oxidation methods enable facile and selective conversion of the acetyl group of the 1,2-diarylethane product into a primary amide (**5ac**; Scheme 3),[14] a formyl (**6ac**),[15] or a carboxy (**7ab**, **7af**)[16] group under copper- or manganese-catalyzed aerobic conditions. The latter products can be converted into the 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptan-5-ones **8ab** and **8af**, featuring a core structure of pharmaceutically relevant compounds such as amitriptyline (an antidepressant).



Scheme 3. Transformations of 1,2-diarylethane products. DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, PPA = polyphosphoric acid, TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl.

In summary, we have developed new cobalt-based catalytic systems for highly linear selective addition of an aryl ketimine to styrene through careful tuning of the triarylphosphine ligand and the Lewis base additive, and thus expanded the scope of regiodivergence of cobalt-catalyzed styrene hydroarylation. The roles of the ligand and the additive in regiocontrol and acceleration of the catalysis warrant further experimental and theoretical studies.

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