

Regioselectivity-Switchable Hydroarylation of Styrenes

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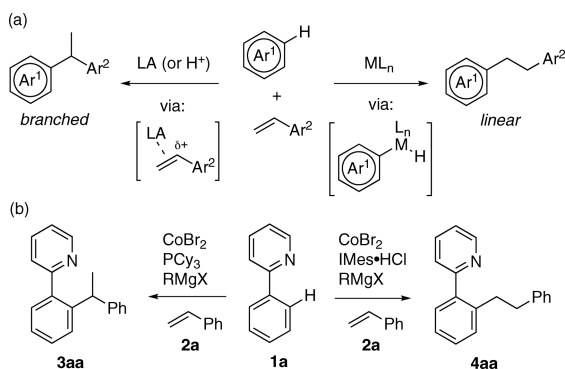
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Abstract: Cobalt–phosphine and cobalt–carbene catalysts have been developed for the hydroarylation of styrenes via chelation-assisted C–H bond activation, to afford branched and linear addition products, respectively, in a highly regioselective fashion. Deuterium-labeling experiments suggested a mechanism involving reversible C–H bond cleavage and olefin insertion steps and reductive elimination as the rate- and regioselectivity-determining step.

The addition of aromatic C–H bonds to styrenes offers a straightforward method for the synthesis of 1,1-(branched) and 1,2-(linear) diarylethane derivatives, which are structural motifs often found in biologically active compounds. There are two known major types of reactions that can be used to achieve such transformations, namely, Friedel–Crafts type alkylation by Lewis (or Brønsted) acid catalysis¹ and hydroarylation through C–H bond activation by transition metal catalysts (Scheme 1a).^{2,3} The two types of hydroarylation reactions are characterized by different substrate scopes and regioselectivities. The former reaction takes place only with electron-rich arenes and selectively affords the branched adducts because of the positive charge on the α -position of styrene that develops upon Lewis acid coordination. On the other hand, the latter reaction usually requires a directing group or other electronic perturbations (e.g., electron-poor heteroarenes) on the arene and preferentially affords the linear adduct due to the steric factors during the insertion of the C=C bond into the M–H bond, with only a few exceptions.⁴ Here we report on cobalt-catalyzed, chelation-assisted hydroarylation reactions of styrenes, which uniquely allow for switching of the branched/linear regioselectivity by ligand control (Scheme 1b).

Scheme 1. Hydroarylation Reactions to Styrenes



We recently reported on hydroarylation reactions of internal alkynes through chelation-assisted or heteroatom-directed C–H bond activation by cobalt–phosphine–Grignard ternary catalytic systems.^{5,6} As a natural extension of this chemistry we became

interested in the hydroarylation of olefins, including styrenes. Thus we set out to explore catalytic systems for the addition of 2-phenylpyridine **1a** to styrene **2a** (1.2 equiv). Selected data of the screening experiments are summarized in Table 1. A cobalt catalyst generated from CoBr₂ (10 mol %), PCy₃ (10 mol %), and *t*BuCH₂MgBr (100 mol %) or Me₃SiCH₂MgCl (80 mol %) effected the hydroarylation reaction in THF at 60 °C to afford a branched product **3aa** in 68% or 81% yield, respectively, with high regioselectivity (*b/l* = 98:2) (entries 1 and 2). The loading of the cobalt catalyst could be reduced to 5 mol % (entry 3). Other monodentate phosphine ligands such as Buchwald's biaryl phosphines also afforded the branched product **3aa** albeit in much lower yields. The choice and the amount of Grignard reagent were also critical. The use of other Grignard reagents as well as the reduction of the amount of *t*BuCH₂MgBr or Me₃SiCH₂MgCl resulted in much lower yields (see Table S1 in the Supporting Information).

To our surprise, when the reaction in entry 1 was performed using IMes•HCl (1,3-dimesitylimidazolium chloride), a precursor of an *N*-heterocyclic carbene (NHC) ligand, instead of PCy₃, a near complete switch of the regioselectivity was observed (entry 4).⁷ Thus the reaction afforded the linear adduct **4aa** in 84% yield with a regioselectivity of 97:3. The reaction with the NHC ligand was rather sensitive to the Grignard reagent and almost stopped when Me₃SiCH₂MgCl was used (entry 5). The use of other common NHC precursors afforded only small amounts of the hydroarylation products (see Table S2).

Table 1. Cobalt-Catalyzed Reaction of 2-Phenylpyridine **1a** and Styrene **2a**^a

Entry	Ligand (mol %)	RMgX (mol %)	Yield (3aa : 4aa) ^b
1	PCy ₃ (10)	<i>t</i> BuCH ₂ MgBr (100)	68% (98:2)
2	PCy ₃ (10)	Me ₃ SiCH ₂ MgCl (80)	81% (98:2)
3	PCy ₃ (5)	Me ₃ SiCH ₂ MgCl (50)	88% (96:4) ^d
4	IMes•HCl (10)	<i>t</i> BuCH ₂ MgBr (100)	84% (3:97) ^d
5	IMes•HCl (10)	Me ₃ SiCH ₂ MgCl (100)	3% (<1:99)

^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), CoBr₂ (10 mol %), ligand, RMgX, THF (0.3 M), 60 °C, 12 h. ^b Determined by GC using *n*-tridecane as an internal standard. ^c 5 mol % of CoBr₂ were used. ^d Isolated yields.

The above two catalytic systems were applicable to a variety of arylpyridine derivatives (Table 2). The substrates bearing electron-donating substituents at the 4- or 3-positions, under Co–PCy₃ and Co–IMes catalyzed conditions, reacted with styrene to afford the corresponding branched and linear products, respectively, in moderate to good yields with a regioselectivity greater than 90:10 (entries 1–4). The 3-substituted substrates underwent C–C bond formation exclusively at the less hindered position (entries 3 and 4). A slight decrease in the regioselectivity was observed with a 4-fluoro substituent (entry 5). With a highly electron-withdrawing CF₃ group, the regioselectivity of the Co–PCy₃ catalysis decreased to 79:21 (entry 6). Moreover, the Co–IMes catalysis afforded the branched

product as the major product with a regioselectivity of 85:15. These observations suggest that the reaction pathways to the branched and linear products are competing with each other (vide infra), and the competition is affected not only by the ligand but also by the electronic nature of the substrate. It was also notable that the presence of a 2-methyl group completely stopped the Co-PCy₃ catalysis but did not interfere with the Co-IMes catalysis (entry 7). On the other hand, steric hindrance at the pyridyl ring did not interfere with the reaction (entry 8).

Table 2. Cobalt-Catalyzed Addition of 2-Arylpyridine Derivatives to Styrene^a

Entry	Substrate	Product (yield, branched:linear ratio) ^b	
		Co-PCy ₃ catalysis	Co-IMes catalysis
1	1b (R = 4-OMe)	3ba (82%, 96:4)	4ba (74%, 2:98)
2	1c (R = 4-NMe ₂)	3ca (46%, >99:1)	4ca (53%, 1:99)
3	1d (R = 3-Me)	3da (67%, 97:3) ^c	4da (86%, 2:98)
4	1e (R = 3-OMe)	3ea (67%, >99:1)	4ea (58%, 7:93)
5	1f (R = 4-F)	3fa (83%, 85:15)	4fa (82%, 14:86) ^d
6	1g (R = 4-CF ₃)	3ga (31%, 79:21)	4ga (81%, 85:15)
7	1h (R = 2-Me)	3ha (N.R.)	4ha (81%, 1:99) ^e
8	1i (R = 2-Me, 4-OMe)	3ia (78%, >99:1)	4ia (81%, <1:99)

^a The reaction was performed with 0.3 mmol of the arene and 0.36 mmol of styrene. Co-PCy₃ catalysis: CoBr₂ (10 mol %), PCy₃ (10 mol %), Me₃SiCH₂MgBr (80 mol %), 40–80 °C, 12–72 h; Co-IMes catalysis: CoBr₂ (10 mol %), IMes•HCl (10 mol %), *t*BuCH₂MgBr (100 mol %), 40–80 °C, 12–72 h. For detailed conditions for each substrate, see Supporting Information. ^b Isolated yield. Regioselectivity was determined by ¹H NMR or GC. N.R. = No reaction. ^c *t*BuCH₂MgBr was used instead of Me₃SiCH₂MgCl. ^d Dialkylated product was obtained in 18% yield. ^e Loadings of CoBr₂, the ligand, and the Grignard reagent were doubled.

Table 3 summarizes the addition reactions of **1a** to various styrene derivatives. Styrenes bearing electron-donating or neutral substituents generally performed well for both of the catalytic systems in terms of efficiency and regioselectivity (>90:10) (entries 1–5), except that a methyl group at the 2-position slowed the Co-PCy₃ catalysis. Some of the Co-IMes catalyzed reactions were accompanied by small amounts (5–13%) of dialkylated products. Note that α-methylstyrene failed to react under the Co-PCy₃ catalysis, while the Co-IMes catalysis gave its linear adduct in 26% yield (data not shown). The reactions of fluorine-substituted styrenes were relatively sluggish and required a higher catalyst loading (20 mol %) in some cases, yet afforded the products in reasonable yields with high regioselectivity (>90:10), except 2-fluorostyrene, which failed to participate in the reaction under the Co-PCy₃ catalysis (entries 6–8). The Co-IMes catalysis of 2-vinylnaphthalene resulted in a significant decrease in the regioselectivity (*b/l* = 39:61), while perfect regioselectivity was achieved with the Co-PCy₃ catalysis (entry 9). Aliphatic olefins such as *tert*-butylethylene exclusively afforded the linear product in low yield regardless of the catalytic system (entry 10).

The addition of an aromatic imine to styrene was also achieved (Scheme 2), while the reaction was sluggish and required a higher

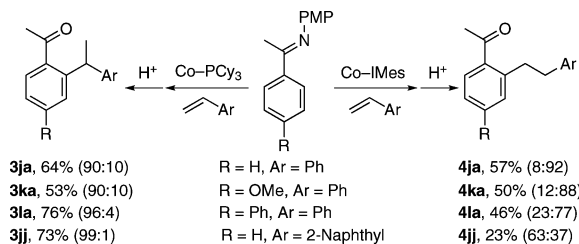
Table 3. Cobalt-Catalyzed Addition of 2-Phenylpyridine to Various Styrene Derivatives^a

Entry	R	Yield (3:4) ^b	
		Co-PCy ₃ catalysis	Co-IMes catalysis
1	4-MeC ₆ H ₄ (2b)	93% (>99:1)	69% (1:99) ^c
2	3-MeC ₆ H ₄ (2c)	87% (99:1)	60% (6:94) ^c
3	2-MeC ₆ H ₄ (2d)	34% (92:8) ^d	78% (<1:99) ^c
4	4-PhC ₆ H ₄ (2e)	80% (99:1)	72% (9:91)
5	4-MeOC ₆ H ₄ (2f)	68% (99:1)	74% (10:90)
6	4-FC ₆ H ₄ (2g)	86% (94:6) ^d	69% (2:98)
7	3-FC ₆ H ₄ (2h)	66% (>99:1) ^d	62% (7:93) ^d
8	2-FC ₆ H ₄ (2i)	N.R.	84% (2:98) ^c
9	2-Naphthyl (2j)	88% (>99:1)	68% (39:61)
10	<i>t</i> Bu (2k)	7% (<1:99)	39% (<1:99) ^c

^a The reaction was performed on a 0.3 mmol scale. Co-PCy₃ catalysis: CoBr₂ (10 mol %), PCy₃ (10 mol %), Me₃SiCH₂MgBr (80 mol %), 60 °C, 12–52 h; Co-IMes catalysis: CoBr₂ (10 mol %), IMes•HCl (10 mol %), *t*BuCH₂MgBr (100 mol %), 60 °C, 12–48 h. ^b Isolated yield. Regioselectivity was determined by ¹H NMR or GC. N.R. = No reaction. ^c Dialkylated products (5–13%) were obtained. ^d Loadings of CoBr₂, the ligand, and the Grignard reagent were doubled.

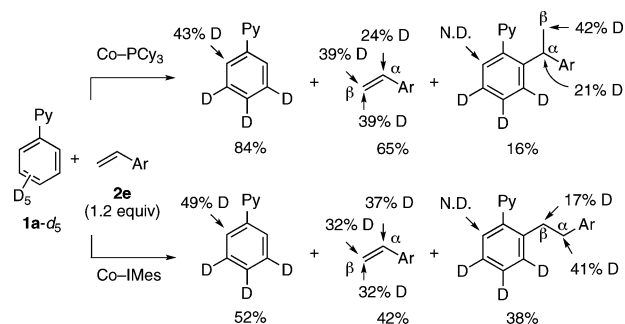
catalyst loading (20 mol %). The Co-PCy₃ catalysis, followed by acidic hydrolysis, afforded the branched ketone products in moderate to good yields with high regioselectivity. On the other hand, the Co-IMes catalysis was sensitive to the nature of both the imine and olefin, resulting in varying yields and regioselectivities. Note that the C=N bond of the imine remained untouched under the present reaction conditions.

Scheme 2. Addition of Aryl Imines^a



^a The reaction was performed with 0.3 mmol of the imine and 0.36 mmol of the olefin. PMP = *p*-Methoxyphenyl. Co-PCy₃ catalysis: CoBr₂ (20 mol %), PCy₃ (20 mol %), Me₃SiCH₂MgBr (160 mol %), 60 °C, 72 h; Co-IMes catalysis: CoBr₂ (20 mol %), IMes•HCl (20 mol %), *t*BuCH₂MgBr (200 mol %), 60 °C, 72 h. In parentheses is shown the *b/l* ratio.

To gain insight into the reaction mechanism, deuterium-labeling experiments were performed (Scheme 3). Thus, the reactions of **1a-d**₅ with 4-vinylbiphenyl **2e** under the Co-PCy₃ and Co-IMes catalyzed conditions were stopped at an early stage. ¹H NMR analysis of the recovered starting materials and the hydroarylation products revealed extensive H/D scrambling between **1a-d**₅ and **2e** prior to product formation. Thus we observed a significant decrease in the deuterium content at the *ortho* position of **1a-d**₅ and a considerable degree of deuterium incorporation into the α- and β-positions of **2e** in both of the catalytic systems. As a natural consequence of this the products bore deuterium atoms at both the α- and β-positions. Note that, under the Co-PCy₃ catalysis, the deuterium content was higher at the β-position than at the α-position and that this trend was reversed for the Co-IMes catalysis.

Scheme 3. Deuterium-Labeling Experiments^a

^a Py = 2-pyridyl; Ar = 4-PhC₆H₄. Co-PCy₃ catalysis: CoBr₂ (10 mol %), PCy₃ (10 mol %), Me₃SiCH₂MgCl (80 mol %), 60 °C, 1 h; Co-IMes catalysis: CoBr₂ (10 mol %), IMes·HCl (10 mol %), *t*BuCH₂MgBr (100 mol %), 60 °C, 30 min. Deuterium incorporation was determined by ¹H NMR analysis. N.D. = Not determined due to overlapping peaks.

We consider that the present hydroarylation reactions proceed via the following steps: (1) chelation-assisted oxidative addition of the C–H bond to the cobalt center,^{5,8} (2) insertion of styrene into the Co–H bond, and (3) reductive elimination of the resulting aryl(1-phenylethyl)cobalt or aryl(2-phenylethyl)cobalt intermediate. On the basis of the necessity of a larger amount of the Grignard reagent than required for the reduction of Co^{II} to Co⁰, we speculate that organocobalt(0)ate species are involved as the reactive species.^{5,6,9} The observation of H/D scrambling suggests that the C–H bond cleavage and olefin insertion steps are reversible and that the two insertion pathways are competing in both the Co–PCy₃ and Co–IMes systems. Thus the reductive elimination would be the rate- and regioselectivity-determining step. We speculate that the thermodynamic preference for benzylcobalt species^{4d,10} governs the branched selectivity for the Co–PCy₃ catalysis, while the preference of the cobalt center to avoid steric repulsion gives rise to the linear selectivity in the Co–IMes catalysis.¹¹ Substituents on the arene and styrene substrates should also affect the two competing pathways (e.g., Table 2, entry 6).

In summary, we have developed cobalt-catalyzed, chelation-assisted hydroarylation reactions of styrenes. The ligand-controlled regioselectivity switch of the present level is very rare in hydroarylation reactions reported thus far.¹² In light of the orthogonal scope and selectivity of the Lewis acid and transition metal catalyzed hydroarylation reactions,^{1–4} the branched selectivity with the Co–PCy₃ catalysis is particularly attractive. The use of the inexpensive cobalt catalysts and the relatively mild reaction conditions are also notable features of the reaction.¹³ Extension of this chemistry to more diverse aromatic and olefinic substrates, including asymmetric catalysis, could have a major impact on the synthesis of substituted benzene derivatives.

Acknowledgment. We thank the National Research Foundation, Singapore (NRF-RF2009-05 to N.Y.) and Nanyang Technological University for generous financial support.

Supporting Information Available: Details of experimental procedures and physical properties of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA108809U