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Cobalt-Catalyzed, N–H Imine-Directed Hydroarylation of Styrenes

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Supporting Information Placeholder

ABSTRACT: A cobalt-catalyzed, N–H imine-directed hydroarylation reaction of styrenes is reported. A variety of diaryl and aryl alkyl N–H imines participated in the reaction to afford the corresponding branched adducts in good yield and regioselectivity. Interestingly, unsymmetrical diaryl imines with modest electronic biases reacted regioselectively at one of the aryl rings. Furthermore, the branched selectivity was reversed for substrates bearing a secondary directing group or a bulky pivaloyl N–H imine.

The addition of an arene C–H bond across an alkene (hydroarylation) through transition metal-catalyzed C–H activation represents a regioselective and atom-economical synthetic approach to alkylated arenes.¹ In particular, hydroarylation of styrenes has attracted much attention for the challenge in controlling the regioselectivity of the addition (branched vs. linear)² as well as for the relevance of the product scaffold, 1,1-diarylethane or 1,2-diarylethane, to bioactive compounds.³ Since the pioneering work of the Murai group on the ruthenium-catalyzed ketone-directed hydroarylation that displayed moderate linear selectivity,⁴ significant progress has been made in the regiocontrol of styrene hydroarylation. Thus, highly linear- and/or branched-selective styrene hydroarylation reactions using transition metals such as ruthenium,⁵ rhodium,⁶ cobalt,⁷ iridium,⁸ iron,⁹ and nickel¹⁰ have been reported.¹¹

Over the last several years, our group has developed cobalt-catalyzed hydroarylation reactions of styrenes directed by pyridine and N-aryl imine functional groups (Scheme 1a and 1b).^{7a–e} These studies have revealed that cobalt catalysts supported by electronically and sterically less biased monophosphine ligands generally show branched selectivity, while electronic and steric tuning of the catalyst by a bulky N-heterocyclic carbene (IMes) or a triarylphosphine bearing *ortho*-methoxy groups (**L1**) may reverse the regioselectivity to give linear products. As a part of our effort in broadening the scope of cobalt-catalyzed C–H functionalization,¹² in the present study, we explore the styrene hydroarylation using an N–H imine as a directing group.^{13,14} Under cobalt–triarylphosphine catalysis, a variety of diaryl and aryl alkyl N–H imines underwent branched-selective hydroarylation of styrene derivatives in good yield and regioselectivity. Most notably, the reaction of an unsymmetrical diaryl N–H imine resulted in selective alkylation of

one of the aryl rings regardless of their modest electronic and steric difference (Scheme 1c). It was also notable that the branched selectivity was reversed for substrates bearing a secondary directing group or a bulky pivaloyl N–H imine.

Scheme 1. Cobalt-Catalyzed Directed Hydroarylation of Styrene

The present study commenced with screening of reaction conditions for the addition of benzophenone N–H imine (**1a**) to styrene (**2a**, 1.5 equiv), performed in the presence of a cobalt salt (10 mol %), a triarylphosphine (20 mol %), and $t\text{-BuCH}_2\text{MgBr}$ (50

mol %) in THF at room temperature. Using CoBr₂ and PPh₃, the reaction afforded the monoalkylation product **3aa** in a moderate yield with exclusive branched selectivity, accompanied by a trace amount of the dialkylation product **4aa** (Table 1, entry 1). Upon screening of triarylphosphine ligands, P(3-ClC₆H₄)₃ emerged as a better ligand in terms of the yield and the selectivity for monoalkylation (entries 2-6). The cobalt source had dramatic influence on the catalytic activity. While the reaction became sluggish using CoCl₂ or CoI₂ (entries 7 and 8), the use of Co(acac)₂ or Co(acac)₃ led to apparently higher catalytic activity with an increased amount of the dialkylation product (entries 9 and 10). In terms of the selectivity toward monoalkylation, Co(acac)₂ was identified as the optimal cobalt source, affording **3aa** in an isolated yield of 76% (71% on 1 mmol scale).

Table 1. Addition of Benzophenone N-H Imine to Styrene^a

entry	CoX _n	ligand	yield (%) ^b	
			3aa	4aa
1	CoBr ₂	PPh ₃	38	5
2	CoBr ₂	P(4-FC ₆ H ₄) ₃	23	14
3	CoBr ₂	P(4-ClC ₆ H ₄) ₃	15	0
4	CoBr ₂	P(3-MeOC ₆ H ₄) ₃	20	0
5	CoBr ₂	P(3-FC ₆ H ₄) ₃	33	8
6	CoBr ₂	P(3-ClC ₆ H ₄) ₃	45	3
7	CoCl ₂	P(3-ClC ₆ H ₄) ₃	8	0
8	CoI ₂	P(3-ClC ₆ H ₄) ₃	26	0
9	Co(acac) ₂	P(3-ClC ₆ H ₄) ₃	76 ^c (71) ^d	9
10	Co(acac) ₃	P(3-ClC ₆ H ₄) ₃	54	21

^aThe reaction was performed using 0.3 mmol of **1a** (*c* = 0.3 M) and 0.45 mmol of **2a**. ^bDetermined by GC using *n*-tridecane as an internal standard. ^cIsolated yield. ^dIsolated yield for 1 mmol-scale reaction.

With the optimized conditions in hand, we explored the scope of N-H imine substrates for the styrene hydroarylation (Scheme 2). Various *para*-substituted benzophenone imines participated in the reaction with **2a**, affording the branched products **3ba–3fa** in good yields. Notably, unsymmetrical diaryl imines bearing phenyl and *para*-substituted (OMe, F, or SMe) phenyl groups underwent selective alkylation on the latter benzene ring (see **3ba–3da**). Furthermore, diaryl imine bearing *para*-methoxyphenyl and *para*-tolyl groups was selectively alkylated on the former aryl group (see **3ea**). These regioselectivities are remarkable when compared to other reported C–H functionalization reactions of diaryl N–H imines, where substantial electronic difference between the aryl groups (e.g., phenyl and *para*-nitrophenyl) was required to achieve

high regioselectivity.¹⁵ For diaryl imines bearing phenyl and *meta*-substituted (Me or CF₃) phenyl groups, the alkylation took place at the *ortho* position of the phenyl group (see **3ga** and **3ha**). The reaction of di(*meta*-tolyl) imine occurred at the less hindered *ortho* position to afford the branched adduct **3ia** in somewhat lower yield. Note that imine derived from bis(3,5-dimethylphenyl)methanone failed to undergo desired hydroarylation. Interestingly, a 3,4-methylenedioxy group on diaryl imine caused alkylation at the proximity of the ether functionality with a preference (4:1) for the linear alkylation product **3ja**.

Besides diaryl N–H imines, *para*-substituted phenyl butyl N–H imines also underwent smooth hydroarylation to afford, upon hydrolysis, the ketone products **3ka–3na** in good yields with moderate to good branched selectivity (*b*/*l* = 4/1 to 12/1). As was the case for **3ja**, the reaction of 3,4-methylenedioxyphenyl butyl imine proceeded with the same sense of regioselectivity of C–H cleavage and hydroarylation, affording the linear adduct **3oa** as the dominant product. An analogous result was obtained using *meta*-fluorophenyl butyl imine (see **3pa**). Meanwhile, *meta*-trifluoromethylphenyl butyl imine reacted at the less hindered *ortho* position, affording the branched product **3qa** in good yield. We also observed distinct behavior of pivalophenone N–H imine derivatives. While the reaction under the standard conditions or conditions using sterically unbiased triarylphosphines displayed poor regioselectivity (*b*/*l* = 1:1–2:1),¹³ linear selective addition was achieved using **L1** or bis(2,5-dimethoxyphenyl)(phenyl)phosphine **L2** instead of P(3-ClC₆H₄)₃ (see **3ra** and **3sa**).^{7d}

Scheme 2. Scope of Aryl N–H Imines^a

^aThe reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 9. The major regioisomer is shown with the branched/linear (b/l) ratio (determined by ¹H NMR) in the parentheses (unless indicated, the regioselectivity was higher than 20:1). ^b**L2** was used instead of P(3-ClC₆H₄)₃, and pyridine (80 mol %) was added.

Next, the unsymmetrical benzophenone imine **1b** was subjected to the reaction with various styrene derivatives (Scheme 3). Styrenes bearing *para*-methyl, *t*-butyl, methoxy, fluoro, chloro, methylthio, and trimethylsilyl groups afforded the branched hydroarylation products **3bb–3bh** in good yields through selective alkylation of the *para*-methoxyphenyl group, while in some cases minor branched products, which likely arose from the alkylation of the phenyl group, were observed (see **3bd–3bf**). The present catalytic system was also applicable to *meta*- and *ortho*-substituted styrenes, which afforded the corresponding branched adducts **3bi–3bo** in good yields.

Scheme 3. Addition of Benzophenone N-H Imine **1b to Various Styrenes^a**

^aThe reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 9. The b/l ratio was higher than 20:1. ^bA regioisomeric branched adduct was observed (ratio shown in the parentheses).

To gain insight into the mechanism, the reaction of decadeuterated benzophenone imine **1a-d₁₀** and 4-methoxystyrene (**2d**) was examined (Scheme 4). The desired product **3ad-d_n** was obtained in good yield with significant H/D scrambling. Thus, substantial deuterium incorporation was observed at the methyl and the methine positions, with ¹H NMR integrations of 1.13H and 0.47H, respectively. Meanwhile, the deuterium contents at the remaining three *ortho*-positions decreased significantly, as indicated by ¹H NMR integrations of 0.43H for the *ortho* position of the alkylated benzene ring and 0.69H for the *ortho* positions of the other benzene ring.

Scheme 4. Deuterium-Labeling Experiment

A plausible catalytic cycle would involve reversible oxidative addition of the *ortho* C–H bond to a low-valent cobalt species, reversible and competitive styrene insertion to give branched (**A**) or linear (**B**) intermediates, and irreversible reductive elimination (Scheme 5).¹⁶ The reversibility of the first two steps as well as the competitiveness of the two insertion pathways would account for the H/D scrambling observed in the deuterium labeling experiment. The general preference for the branched adduct may be explained by stabilizing η³-benzyl coordination involved in **A** and its reductive elimination.

Scheme 5. Proposed Catalytic Cycle

Besides the above general mechanistic picture, we are tempted to comment on the regioselectivity of the C–H cleavage and the hydroarylation in some specific cases. First, the reactions of *meta*-oxygen or fluorine-substituted imines (see **3oa'** and **3pa'**) may be rationalized in terms of secondary directing effect. Thus, the Co–O (or Co–F) interaction would not only favor C–H cleavage at its proximity^{7b,d,13} but also stabilize the linear intermediate **B** while interfering with the η^3 -benzyl coordination in the branched intermediate **A**. Second, the linear selective reaction of pivalophenone imines (see **3ra'** and **3sa'**) may be attributed to the bulky imine and the nature of **L2**. The bulkiness of the imine group would disfavor the formation of the more congested branched adduct, and the *ortho*-methoxy group of **L2** would serve as a hemilabile ligand to Co to stabilize **B**.^{7d} Lastly, the regioselectivity of C–H alkylation for unsymmetrical diaryl imines **1b–1e** is not trivial to rationalize. We suspect that the methoxy, fluoro, and methylthio groups in these substrates would cause electron-withdrawing effect on the *meta*-position to facilitate the C–H oxidative addition, while their possible role to accelerate other elementary steps could not be excluded.

The present alkylation products are amenable to further alkylation on the remaining *ortho* C–H bond with vinylsilane by our previously reported cobalt-catalyzed conditions (Scheme 6).¹³ The reaction of alkylated benzophenone imine **3ba** with vinyltrimethylsilane resulted in preferential alkylation of the unhindered phenyl group, affording the product **5** and its minor regioisomer **5'**. The reaction of alkylated aryl butyl imine **3ma** with vinylsilane furnished unsymmetrically dialkylated product **6**.

Scheme 6. Further *ortho*-Alkylation with Vinylsilane^a

^aSee the Supporting Information for detailed reaction conditions.

In summary, we have demonstrated that N–H imine serves as a directing group for room-temperature hydroarylation of styrenes under cobalt catalysis. A variety of diaryl and aryl alkyl N–H imines underwent branched-selective addition in good yield and regioselectivity. The high regioselectivity of C–H cleavage for unsymmetrical diaryl N–H imines and the substrate- and/or ligand-controlled reversal of the branched selectivity were among notable observations. The origin of the observed regioselectivities and their synthetic implications deserve further exploration.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at <http://pubs.acs.org>.

Detailed experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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