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Cobalt-catalyzed Branched-selective Addition of Aromatic Ketimines to Styrenes under Room-temperature Conditions

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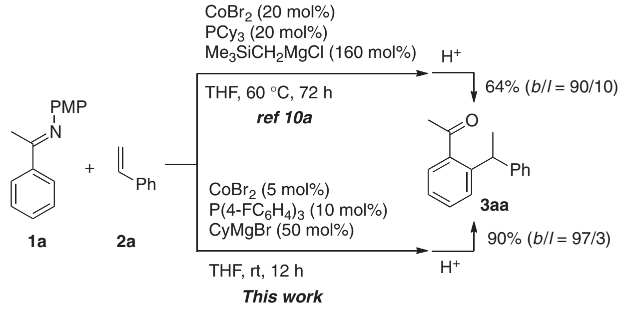
An improved cobalt-based catalytic system has been developed for the branched-selective addition of aromatic ketimines to styrenes. With an appropriate combination of triarylphosphine and the Grignard reagent, the reaction takes place smoothly at room temperature to afford 1,1-diarylethane derivatives with high regioselectivity.

Given the importance of 1,1-diarylalkane skeletons in pharmacologically active compounds,[1] methods for their efficient construction have attracted increasing interest in recent years. Among various approaches,[2–6] addition of an aromatic compound to the α-position of a styrene derivative (i.e., branched-selective styrene hydroarylation) is attractive because of the perfect atom economy and the ready availability of the starting materials.[7–10] Such transformations can be achieved either through activation of the styrene C=C bond with a Lewis acid[8] or through activation of the aromatic C–H bond with a low-valent transition-metal catalyst.[9–11] While these two types of reactions can potentially serve as complementary methods, the scope of the latter type of reaction has been relatively limited, because transition-metal-catalyzed styrene hydroarylation often exhibits selectivity toward the linear 1,2-diarylethane rather than 1,1-diarylethane.[12,13] Recently, we developed cobalt–phosphine catalytic systems for the branched-selective addition of 2-arylpyridines and aromatic aldimines to styrenes.[10] Unfortunately, these catalytic systems showed only modest activity in the reaction of an aromatic ketimine. By reinvestigation of the reaction conditions, we have now established a significantly improved catalytic system that allows for the desired transformation under mild conditions with a broad substrate scope, which is reported herein.



Scheme 1. Addition of ketimine **1a** to styrene **2a**.

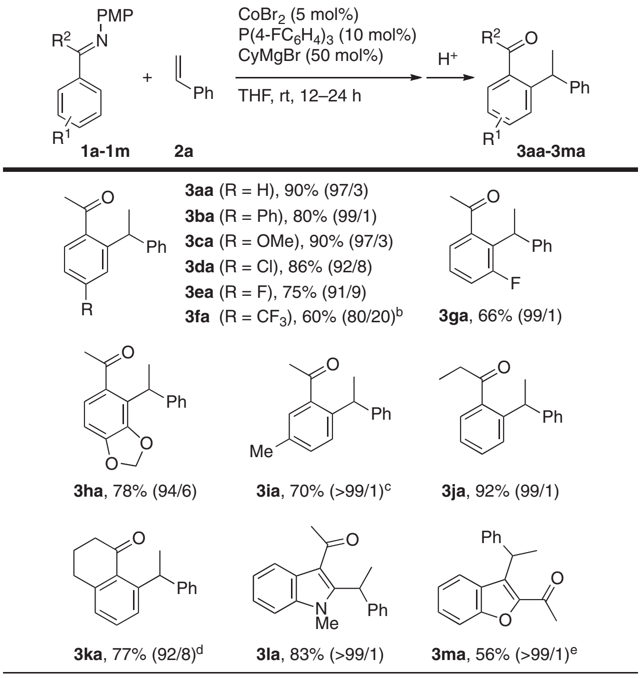
Table 1. Optimization of the addition of **1a** to **2a**[a]

Entry	Ligand	RMgX	Yield/% (*b*/*l*)[b]
1[c]	PCy$_3$	Me$_3$SiCH$_2$MgCl	64 (90/10)[d]
2[e,f]	P(*p*-Tol)$_3$	Me$_3$SiCH$_2$MgCl	46 (98/2)
3[e,f]	P(4-FC$_6$H$_4$)$_3$	Me$_3$SiCH$_2$MgCl	61 (99/1)
4[f]	P(4-FC$_6$H$_4$)$_3$	Me$_3$SiCH$_2$MgCl	83 (99/1)
5	P(4-FC$_6$H$_4$)$_3$	*t*-BuCH$_2$MgBr	77 (97/3)[d]
6	P(4-FC$_6$H$_4$)$_3$	BuMgBr	70 (97/3)
7	P(4-FC$_6$H$_4$)$_3$	*i*-PrMgBr	28 (97/3)
8[f]	P(4-FC$_6$H$_4$)$_3$	CyMgBr	90 (97/3)[d]
9	PPh$_3$	CyMgBr	77 (97/3)
10[f]	P(*p*-Tol)$_3$	CyMgBr	64 (97/3)
11	P(4-MeOC$_6$H$_4$)$_3$	CyMgBr	81 (97/3)
12	P(4-ClC$_6$H$_4$)$_3$	CyMgBr	37 (92/8)
13	P(4-CF$_3$C$_6$H$_4$)$_3$	CyMgBr	17 (76/24)
14	P(*o*-Tol)$_3$	CyMgBr	63 (94/6)
15	P(2-MeOC$_6$H$_4$)$_3$	CyMgBr	27 (7/93)

[a] Unless otherwise noted, the reaction was performed using **1a** (0.3 mmol), **2a** (0.45 mmol), CoBr$_2$ (5 mol %), ligand (10 mol %), Grignard reagent (50 mol %) in THF at room temperature for 24 h. [b] Determined by ^{1}H NMR. [c] The reaction was performed with 20 mol % each of CoBr$_2$ and PCy$_3$ and 160 mol % of Me$_3$SiCH$_2$MgCl at 60 °C for 72 h. The data taken from ref 10a. [d] Isolated yield. [e] The reaction was performed with 10 mol % of CoBr$_2$, 20 mol % of ligand, and 50 mol % of Me$_3$SiCH$_2$MgCl at 40 °C (ref 10b). [f] The reaction time was 12 h.

Scheme 1 and Table 1 illustrate the significant improvement made for the reaction of acetophenone ketimine **1a** and styrene **2a**. As reported previously,[10a] the reaction with the CoBr$_2$–PCy$_3$–Me$_3$SiCH$_2$MgCl system, which was developed for 2-arylpyridines, was sluggish even with a high catalyst loading (20 mol %) and at an elevated temperature (60 °C), affording the product **3aa** in moderate yield (Scheme 1 (top) and Table 1, Entry 1). The CoBr$_2$–P(*p*-Tol)$_3$–Me$_3$SiCH$_2$MgCl system (10 mol %),[10b] which was optimized for aromatic aldimines, also met with limited success (Entry 2), while the use of P(4-FC$_6$H$_4$)$_3$ instead of P(*p*-Tol)$_3$ improved the reaction (Entry 3). The reaction with a lower catalyst loading of 5 mol % at room temperature led to further improvement, affording **3aa** in 83% yield with a branched/linear (*b*/*l*) ratio of 99:1 (Entry 4). Throughout examination of Grignard reagents other than Me$_3$SiCH$_2$MgCl (Entries 5–8), the highest yield of 90% was achieved using cyclohexylmagnesium bromide (CyMgBr; Scheme 1 bottom and Entry 8). P(4-FC$_6$H$_4$)$_3$ was confirmed to be the best ligand, as other triarylphosphine ligands gave poorer results under otherwise identical conditions (Entries 9–15). Interestingly, the use of P(2-MeOC$_6$H$_4$)$_3$ resulted in reversal of the regioselectivity with a *b*/*l* ratio of 7:93, albeit in a low yield (Entry 15), whereas another *ortho*-substituted phosphine, P(*o*-Tol)$_3$, did not change the regioselectivity (Entry 14).

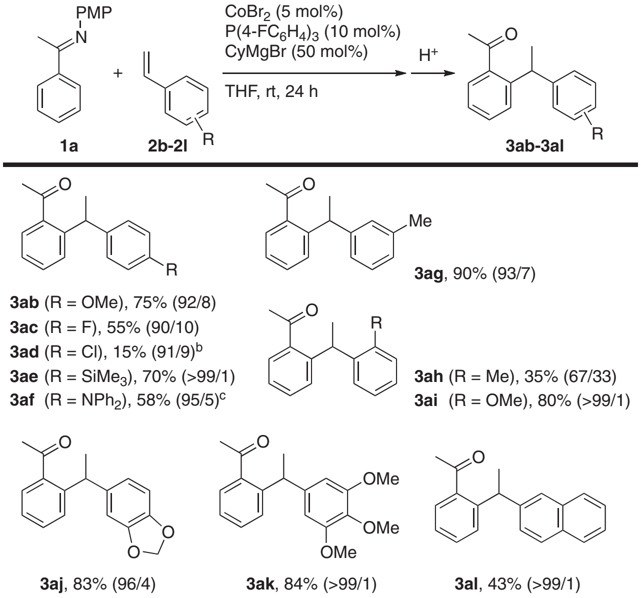
Table 2. Addition of various ketimines to styrene **2a**[a]



3aa (R = H), 90% (97/3)
3ba (R = Ph), 80% (99/1)
3ca (R = OMe), 90% (97/3)
3da (R = Cl), 86% (92/8)
3ea (R = F), 75% (91/9)
3fa (R = CF_3), 60% (80/20)[b]
3ga, 66% (99/1)
3ha, 78% (94/6)
3ia, 70% (>99/1)[c]
3ja, 92% (99/1)
3ka, 77% (92/8)[d]
3la, 83% (>99/1)
3ma, 56% (>99/1)[e]

[a] The reaction was performed on a 0.3 mmol scale. The yield refers to the isolated yield. The *b*/*l* ratio determined by ^{1}H NMR is shown in parentheses. See Supporting Information for experimental details.[15] [b] The reaction was performed using P(*p*-Tol)$_3$ and Me_3SiCH_2MgCl instead of $P(4-FC_6H_4)_3$ and CyMgBr, respectively, for 48 h. [c] The reaction time was 36 h. [d] The *b*/*l* ratio was determined by GC. [e] The reaction time was 28 h.

Table 3. Addition of ketimine **1a** to various styrene derivatives[a]



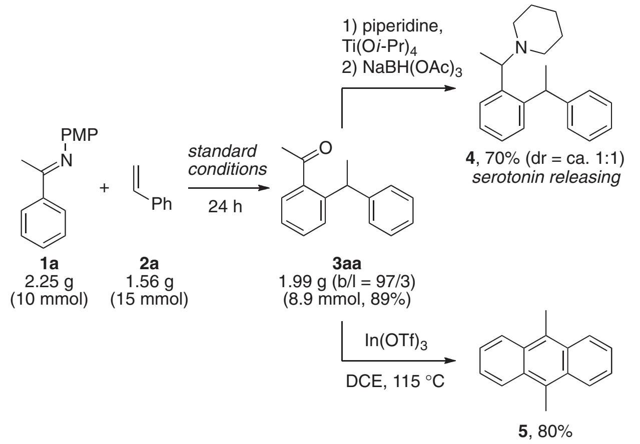
3ab (R = OMe), 75% (92/8)
3ac (R = F), 55% (90/10)
3ad (R = Cl), 15% (91/9)[b]
3ae (R = $SiMe_3$), 70% (>99/1)
3af (R = NPh_2), 58% (95/5)[c]
3ag, 90% (93/7)
3ah (R = Me), 35% (67/33)
3ai (R = OMe), 80% (>99/1)
3aj, 83% (96/4)
3ak, 84% (>99/1)
3al, 43% (>99/1)

[a] The reaction was performed on a 0.3 mmol scale. The yield refers to the isolated yield. The *b*/*l* ratio determined by ^{1}H NMR is shown in parentheses. See Supporting Information for experimental details.[15] [b] Obtained as a mixture with dechlorinated product (i.e., **3aa**, ratio = 10:1). [c] 100 mol % of CyMgBr was used.

With the $CoBr_2$–$P(4-FC_6H_4)_3$–CyMgBr catalytic system in hand,[14] we first explored the reaction of a variety of aryl ketimines with styrene (Table 2). Imines bearing electron-donating and neutral substituents at the *para*-position afforded the desired products in good yield with high branched selectivity (**3aa**–**3ca**). On the other hand, *para*-chloro and -fluoro substituents slightly lowered the regioselectivity (**3da** and **3ea**). A *para*-trifluoromethyl group made the reaction under the standard conditions rather sluggish, presumably because it slowed the reductive elimination step.[10a] Reasonable conversion was achieved by changing the ligand and the Grignard reagent to P(*p*-Tol)$_3$ and Me_3SiCH_2MgCl, respectively, albeit with much reduced regioselectivity (**3fa**). As has been observed for other cobalt-catalyzed C–H functionalization reactions,[10b,16,17] the fluorine atom and methylenedioxy group at the *meta*-position directed the reaction to take place at their proximal positions (**3ga** and **3ha**), while an imine bearing a *meta*-methyl group expectedly reacted at the less hindered position (**3ia**). Imines derived from propiophenone and tetralone smoothly participated in the reaction to afford the corresponding adducts **3ja** and **3ka** in good yield with high branched selectivity. Heteroaryl imines were also amenable to the present hydroarylation reaction, as demonstrated by the formation of functionalized indole **3la** and benzofuran **3ma** with perfect (>99/1) regioselectivity. Note that the present catalytic system was also applicable to aromatic aldimines derived from 1-naphthaldehyde and *o*-tolualdehyde, exclusively affording the corresponding branched adducts in 79 and 72% yields, respectively (data not shown).

The scope of styrene derivatives was next explored (Table 3). Styrenes bearing *para*-methoxy, -fluoro, -trimethylsilyl, and -diphenylamino groups participated in the reaction with imine **1a** to afford the corresponding branched adducts in moderate-to-good yield (**3ab**, **3ac**, **3ae**, and **3af**). In contrast, *p*-chlorostyrene reacted sluggishly to afford the adduct **3ad** in poor yield, which was accompanied by a small amount of dechlorination product (i.e., **3aa**). An *ortho*-methyl group on styrene made the reaction rather sluggish and significantly reduced the regioselectivity (**3ah**), while *o*-methoxystyrene smoothly participated in the reaction to afford the adduct **3ai** with perfect regioselectivity. Polyalkoxystyrenes and 2-vinylnaphthalene also afforded the desired branched adducts **3aj**–**3al** with excellent regioselectivity. Note that the present catalytic system also allowed (linear) for the ortho-alkylation of **1a** with vinyltrimethylsilane, norbornene, and *n*-hexene, albeit in a low yield for the last case (75, 91, and 15% yields, respectively; data not shown).[18]

The present hydroarylation reaction is scalable enough to allow for further transformation of the 1,1-diarylethane product (Scheme 2). The reaction of **1a** and **2a** could be performed on a 10 mmol scale with virtually no decrease in the yield and regioselectivity. Reductive amination of the acetyl group of the hydroarylation product **3aa** with piperidine afforded the product **4** in 70% yield (as a 1:1 mixture of diastereomers), which is among a series of related compounds with potential serotonin releasing activity.[19] The diarylethane **3aa** was also amenable to



Scheme 2. Gram-scale hydroarylation and futher transformations.

indium-catalyzed dehydrative cyclization,[20] affording 9,10-dimethylanthracene (**5**) in 80% yield. Thus, with the present catalytic system for ketimine hydroarylation and the previously reported system for aldimine hydroarylation, the combination of cobalt-catalyzed styrene hydroarylation and dehydrative cyclization now offers convenient two-step routes to anthracenes and related polycyclic aromatic hydrocarbons.

In summary, we have developed a $CoBr_2$–$P(4\text{-}FC_6H_4)_3$–CyMgBr catalytic system for the highly branched selective addition of aromatic ketimines to styrenes under room-temperature conditions. Further improvement of the catalytic system, mechanistic studies, and synthetic applications are currently underway. The development of a linear-selective catalyst through steric and electronic tuning of the phosphine ligand is also a subject of further studies.

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