Secondary Benzylation with Benzyl Alcohols Catalyzed by A High-Valent Heterobimetallic Ir-Sn Complex

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 $\begin{array}{c} R \\ Ar \\ \hline OH \end{array} + Y-H \\ \hline \begin{array}{c} [Ir_2(COD)_2(SnCl_3)_2(Cl)_2(\mu-Cl)_2] (1 \text{ mol}\%) \\ \hline DCE, 30-80 \ ^{\circ}C \end{array} \\ \hline Ar \\ \hline Y \\ \hline R = Me, -CH_{2^-}, -CHBr_2, allyl; Ar = aryl, thienyl \\ Y-H = Arene, Heteroarene, N, S, O Nucleophiles \end{array}$

A highly efficient secondary benzylation procedure has been demonstrated using a high-valent heterobimetallic complex $[Ir_2(COD)_2(SnCl_3)_2(Cl)_2(\mu-Cl)_2]$ **1** as the catalyst in 1,2-dichloroethane to afford the corresponding benzylated products in moderate to excellent yields. The reaction was performed not only with carbon nucleophiles (arenes and heteroarenes) but also with oxygen (alcohol), nitrogen (amide and sulfonamide), and sulfur (thiol) nucleophiles. Mechanistic investigation showed the intermediacy of the ether in this reaction. An electrophilic mechanism is proposed from Hammett correlation.

Even after 125 years since its discovery, Friedel-Crafts alkylation (FCA) remains a fundamental tool toward the construction of various organic architectures of pharmaceutical and industrial relevance.¹ Within the FCA domain, there has been multi-prong development in the area of alkylation of arenes and heteroarenes. Tuning a FCA catalyst to deliver high turnover frequency (TOF), substrate and alkylating agent selectivity, and environment friendliness has truly become a never-ending (hence, ever-young) exercise. Toward this pursuit, the resurgence/ evolution of d- and f-block metal catalysts (either simple salts or designer complexes) is quite breathtaking.² Our continuing success in dual-reagent catalysis involving transition metal and tin as the partners³ led us to propose a new bimetallic catalysis concept for the alkylation of arenes.⁴ According to this proposal, a high-valent bimetallic scaffold III could be generated by the oxidative addition of a main group (possibly Si, Sn, In) halide or surrogate II across a low-valent late transition metal organometallic partner I (Scheme 1). Indeed the oxidative addition reaction of Si-X and Sn-X across low-valent late transition metal complexes to generate the corresponding silvl metal or stanna metal motifs is well-known.⁵

One may note that scaffold **III** bears interesting features for potential application within a cooperative catalysis regime. These

SCHEME 1. Generating High-Valent Heterobimetallic Motif

$$[Tm^{p}] + Mgm-X \xrightarrow{Ox. Addn.} X-[Tm^{p+2}]-Mgm$$

$$I \qquad III \qquad III$$

SCHEME 2. Preparation of Catalyst 1



features include (i) a high-valent and soft electrophilic transition metal center (Tm) for the activation of soft nucleophiles such as a π -system, (ii) a hard Lewis acidic main group metal center (Mgm) for the activation of substrates having hard donor atoms, and (iii) close proximity of Tm and Mgm centers for proximal binding and subsequent coupling between different organic substrates.

We present here a successful demonstration of the above concept for the secondary benzylation of a variety of carbon (arenes and heteroarenes), oxygen (alcohol), nitrogen (amide and sulfonamide), and sulfur (thiol) nucleophiles with secondary benzyl alcohol derivatives employing a novel high-valent iridium—tin heterobimetallic catalyst, namely, $[Ir_2(COD)_2-(SnCl_3)_2(Cl)_2(\mu-Cl)_2]$ **1**. In this regard, one may note that there are only a few successful reports of secondary alkylation directly from corresponding alcohols (having β -H atom) as the alkylating agents.⁶

Complex 1 was easily obtained by the reaction of $[Ir(COD)-(\mu-Cl)]_2$ in dichloromethane with SnCl₄ (2 equiv) in benzene at room temperature followed by slow crystallization (Scheme 2). The structure of 1 has been unambiguously established by X-ray crystal structure analysis (Figure 1).

Control studies on secondary benzylation were performed using 1-phenylethanol 2 as the representative alcohol and *o*-xylene as the arene in the presence of 1 mol % of catalyst 1and in 1,2-dichloroethane as the solvent (Scheme 3). Each

(4) For a preliminary report, please see: Choudhury, J.; Podder, S.; Roy, S. J. Am. Chem. Soc. 2005, 127, 6162.

^{(1) (}a) Olah, G. A. Friedel Crafts and Related Reactions; Wiley-Interscience: New York, 1964; Vol. II, Part I. (b) Olah, G. A. A Life of Magic Chemistry. Autobiographical Reflections of a Nobel Prize Winner; Wiley-Interscience: New York, 2001. (c) Roberts, R. M.; Khalaf, A. A. Friedel-Crafts Alkylation Chemistry. A Century of Discovery; Marcel Dekker: New York, 1984.

⁽²⁾ For overview, see: (a) Lewis Acids in Organic Synthesis; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vols. 1 and 2. (b) Kobayashi, S. In Stimulating Concepts in Chemistry; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, Germany, 2000; pp 3–12. (c) Corma, A.; Garcia, H. Chem. Rev. 2003, 103, 4307. (d) Bandini, M.; Melloni, A.; Umani-Ronchi, A. Angew. Chem., Int. Ed. 2004, 43, 550. (e) Fürstner, A.; Voigtländer, D.; Schrader, W.; Giebel, D.; Reetz, M. T. Org. Lett. 2001, 3, 417. (f) Dyker, G.; Hildebrandt, D.; Liu, J.; Merz, K. Angew. Chem., Int. Ed. 2003, 42, 4399. (g) Mertins, K.; Jovel, I.; Kischel, J.; Zapf, A.; Beller, M. Angew. Chem., Int. Ed. 2005, 44, 238. (h) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. Angew. Chem., Int. Ed. 2005, 44, 3913.

^{(3) (}a) Sinha, P.; Roy, S. *Organometallics* **2004**, *23*, 67. (b) Banerjee, M.; Roy, S. *Org. Lett.* **2004**, *6*, 2137. (c) Banerjee, M.; Roy, S. *J. Mol. Catal. A: Chem.* **2006**, *246*, 231.

^{(5) (}a) Corey, J. Y.; Braddock-Wilking, J. Chem. Rev. 1999, 99, 175.
(b) Janzen, M. C.; Jennings, H. A.; Puddephatt, R. J. Organometallics 2001, 20, 4100. (c) Mark, S. H.; William, L. W.; John, H. N. Chem. Rev. 1989, 89, 11.

^{(6) (}a) Yamauchi, T.; Hattori, K.; Mizutaki, S.; Tamaki, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3617. (b) Kotsuki, H.; Ohishi, T.; Inoue, M. *Synlett* **1998**, 255. (c) Kotsuki, H.; Ohishi, T.; Inoue, M.; Kojima, T. *Synthesis* **1999**, *4*, 603. (d) Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. J. Org. Chem. **2003**, *68*, 9340.



FIGURE 1. ORTEP of catalyst **1** with 50% thermal ellipsoids (H atoms are excluded for clarity).

SCHEME 3. Secondary Benzylation: Control Studies with Alcohol 2 and *o*-Xylene



reaction was monitored for a 12 h period. When the reaction was conducted at room temperature, much of the alcohol remained unreacted. Also the targeted benzylation product did not form; instead, dibenzylether **3** was obtained in ca. 19% GC yield. Reaction at 50 °C led to the formation of benzylation product **4** along with dibenzylether **3** in ca. 25 and 36% yields, respectively. Gratifyingly, a 100% conversion of alcohol to **4** was observed at 80 °C, and the isolated yield of **4** was 89%. A similar reaction, but with alcohol/arene ratio as 1:1.2, afforded product **4** in 85% yield after 16 h. We also noted that this reaction does not require inert atmosphere and can be performed in an air atmosphere as well without comprising product yield.

Next we examined the benzylation of other arenes as the C-nucleophiles with various secondary benzyl alcohol derivatives in DCE at 80 °C. For convenience, the alcohol/arene ratio was kept at 1:5, and the corresponding benzylated products were isolated in moderate to good yields (Table 1). The reactions of toluene and 1-methylnaphthalene with alcohol 2 gave the corresponding benzylated products 12 and 13 in 77 and 54% yields, respectively, as a mixture of two isomers. In both cases, the *o:p* ratio was 15:85 (vide ¹H NMR). Other secondary benzyl alcohol derivatives such as alcohol 5 and 6 produced the corresponding benzylated products 14 and 15 in good yields. The reaction of alcohol 7 with 1-methoxynaphthalene afforded 16 in 93% yield. Similar reaction of 7 with *p*-cresol and anisole yielded 17 and 18 in 55 and 52% yields, respectively, along with 1,2-dihydronaphthalene (unestimated).

The present alkylation reaction could also be applied to heteroarenes (Table 2). The reactions with heteroarenes were performed at 30–80 °C, and the benzylated products were obtained in moderate to excellent yields. The reaction of 2, 5, and 9 with thiophene and 2-methylthiophene afforded the benzylated thiophenes 20, 21, and 22 in 65–78% yields as a mixture of regioisomers at the 2- and 3-positions. With benzo-[*b*]thiophene, 1-phenylethanol 2 gave the corresponding benzylated product 23 as a single isomer in 81% isolated yield. Due to its low boiling point, furan was used in excess (20 equiv with respect to alcohol), and the reaction was conducted at room temperature. The reaction resulted in both 2-alkylated and 2,5bisalkylated furans 24 and 25 in 78 and 10% isolated yields.

TABLE 1. Reaction of Benzylic Alcohols with Arenes Catalyzed by 1^a

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entry	arene	alcohol	no.	time (h)	product	no.	yield (%)
1	o-Xylene	OH Me	2	12	Me Me Me	4	89
2 ^b	Toluene	OH Me	2	12	Me	12	77
3 ^{e,d}	1-Methyl Naphthalene	OH Me	2	12	Me	13	54
4°	Anisole	OH	5	0.5	Сулования и страна и Сулования и страна и с	14	97
5°	1-Methoxy Naphthalene	Me Br H	6	3	Me Br H Br	15	83
6 ^{c,f}	1-Methoxy Naphthalene	OH	7	0.5	OMe	16	93
7 ^{c.g}	p-Cresol	OH	7	5	Me HO	17	55 ^b
8 ⁱ	Anisole	OH	7	4	OMe	18	52 ^b
9°	<i>o-</i> Chloro Phenol	OH Me	8	24	Me Me OH	19	57

^{*a*} Unless otherwise mentioned, reaction conditions: alcohol (0.25 mmol), arene (1.25 mmol), cat **1** (0.0025 mmol), solvent DCE (1 mL), 80 °C. ^{*b*} Ratio of o:p = 15:85. ^{*c*} Arene (0.3 mmol). ^{*d*} Ratio of o:p = 15:85. ^{*e*} Ratio of o:p = 15:85. ^{*f*} Ratio of o:p = 16:84. ^{*s*} Ratio of o:p = 8:92. ^{*h*} Along with 1,2-dihydronaphthalene. ^{*i*} Ratio of o:p = 18:82.

The reaction of 2,5-dimethylfuran with alcohol **11** was complete in 10 min and afforded the alkylated product **26** in 87% yield. The reaction of alcohol **9** with benzo[b]furan gave the desired product **27** in good yield and as a single isomer.

To explore the generality of the reaction further, we briefly examined the reactions of alcohols **2** and **8** with representative nitrogen, oxygen, and sulfur nucleophiles (Table 3). The reaction of alcohol **2** with aniline and *N*,*N*-dimethylaniline led to the formation of complex mixtures. However, less nucleophilic substrates such as sulfonamide or amide were amenable for the transformation. Thus, reaction of **2** with benzene sulfonamide afforded the corresponding benzylated product **28** in 84% yield after 1 h. The reaction of benzamide was comparatively slower and after 3 h provided the benzylated product **29** in 50% yield along with unreacted amide. Facile reaction of **2** with 1-propanethiol as the S-nucleophile resulted in the formation of the desired product **30** in 95% isolated yield. Similar reaction of **2** with ethanol as the O-nucleophile was examined, and the desired ether **31** was obtained in 89% isolated yield.

To obtain an insight into the reaction pathway, we monitored the reaction of 1-phenylethanol **2** with *o*-xylene in presence of catalyst **1** (0.75 mol %) in 1,2-dichloroethane at 80 °C for 14

TABLE 2. Reaction of Benzylic Alcohols with Heteroarenes Catalyzed by 1^a



^{*a*} Unless otherwise mentioned, reaction conditions: alcohol (0.25 mmol), heteroarene (1.25 mmol), cat **1** (0.0025 mmol), solvent DCE (1 mL), 50 °C. ^{*b*} **2**:**3** = 80:20. ^{*c*} **2**:**3** = 85:15. ^{*d*} Heteroarene (0.5 mmol). ^{*e*} **2**:**3** = 85: 15. ^{*f*} **2**:**3** = 80:20. ^{*s*} Room temperature. ^{*h*} Heteroarene (5 mmol). ^{*i*} At 80 °C.

h by gas chromatography analysis and plotted the time evolution of the reactant and products. As indicated in Figure 2, in the first part of the reaction, ether **3** was formed more rapidly than benzylated product **4**. The formation of ether was maximal at 3 h. Subsequently, the yield of **3** decreased, and the yield of the benzylated product **4** increased. The above observation suggests possible intermediacy of ether in the present alkylation reaction. Indeed, in a separate experiment, by using ether **3** as the alkylating agent and *o*-xylene as the arene partner, we could obtain the benzylated product **4** in 92% isolated yield. Similar observation was also noticed in the metal triflate catalyzed benzylation reaction.^{6d}

One may note that, under Brønsted or Lewis acid catalyzed conditions, secondary benzyl alcohols having a β -H atom tend to form corresponding olefins. Formation of styrene from 1-phenylethanol under such conditions is particularly noteworthy.⁷ Since metal-catalyzed hydroarylation of olefins is well-known,⁸ we sought to clarify whether styrene is a plausible intermediate in our case. To test this hypothesis, the reaction of styrene with *o*-xylene was conducted in DCE at 80 °C in the presence of catalyst 1 (1 mol %) and was monitored for 12 h. We observed that a majority of the styrene remained unreacted, and alkylated product 4 was formed in <10% GC yield. A hydroarylation pathway is therefore ruled out.



FIGURE 2. Time evolution of ether **3** and product **4** in the reaction of alcohol **2** with *o*-xylene catalyzed by **1** at 80 °C.

Finally, to test the likelihood of an electrophilic secondary benzylation mechanism, we wished to subject the reaction to Hammett analysis to determine the reaction constant, that is, the ρ value.⁹ This was attempted by the kinetic analysis (details in the Supporting Information) using gas chromatography for the reaction of thiophene with five different para-substituted secondary benzyl alcohols, $p-R-C_6H_4-CH(Me)OH$, 8 (R = Me), 2 (R = H), 32 (R = F), 33 (R = Br), and 9 (R = Cl), at 45 °C. The data for the first 20% conversion fit nicely into pseudo-first-order rate plots, from which rate constants (k) are evaluated (Table 4). As shown in Figure 3, the relative rate constant $log(k_R/k_H)$ values linearly correlated with Hammett substituent constants (σ_p). From the plot, Hammett reaction constant ρ was found to be moderately negative (-2.21). The moderate negative Hammett reaction constant ρ (lying between -2 and -4) supports an electrophilic pathway in the present secondary benzylation reaction. It also indicates the possibility of generation of weak positive charge (δ +) at the benzylic center of the alcohol due to the coordination with the alcoholic OH group to the Sn center of the complex. In other words, the absence of a large negative Hammett reaction constant ρ is indicative of the absence of a "distinct" free benzylic cation in our system.⁹

In summary, we have shown a facile secondary benzylation of arenes and heteroarenes with secondary benzyl alcohol derivatives catalyzed by a high-valent Ir^{III} —Sn^{IV} complex. The benzylation reaction, which likely involves an electrophilic mechanism, was also extended to nitrogen (amide and sulfonamide), sulfur (thiol), and oxygen (alcohol) nucleophiles. The reaction mechanism includes the formation of ether as an intermediate. The new catalytic reactions presented in this note could be a meaningful addition to the existing methods using secondary benzyl alcohol derivatives having β -H for the synthesis of arylalkane derivatives.

Experimental Section

Synthesis of Substrates. All of the reactions were carried out under argon atmosphere. Solvents were dried by the usual methods

^{(7) (}a) Nishiguchi, T.; Machida, N.; Yamamoto, E. *Tetrahedron Lett.* **1987**, 28, 4565. (b) Kantam, M. L.; Santhi, P. K.; Siddiqui, M. F. *Tetrahedron Lett.* **1993**, 34, 1185. (c) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-I. J. Org. Chem. **1997**, 62, 6997. (d) Lange, J.-P.; Mesters, C. M. A. M. Appl. Catal. A: Gen. **2001**, 210, 247.

^{(8) (}a) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. J. Am. Chem. Soc. 2001, 123, 9692. (b) Dyker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L. Adv. Synth. Catal. 2003, 345, 1247. (c) Bhalla, G.; Oxgaard, J.; Goddard, W. A.; Periana, R. A. Organometallics 2005, 24, 3229. (d) Kischel, J.; Jovel, I.; Mertins, K.; Zapf, A.; Beller, M. Org. Lett. 2006, 8, 19. (e) Rueping, M.; Nachtsheim, B. J.; Scheidt, T. Org. Lett. 2006, 8, 3717.

⁽⁹⁾ Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. In Organic Chemistry; Oxford University Press: Oxford, UK, 2001; pp 1090-1100.

TABLE 3. Reaction of Benzylic Alcohols with N-, O-, and S-Nucleophiles Catalyzed by 1^a



^{*a*} Unless otherwise mentioned, reaction conditions: alcohol (0.25 mmol), nucleophile (0.25 mmol), cat **1** (0.0025 mmol), solvent DCE (1 mL), 80 °C. ^{*b*} Nucleophile (2.5 mmol).

 TABLE 4.
 Kinetic Data for the Secondary Benzylation of Thiophene with Benzylic Alcohols

entry	R	$k_{\rm R} \times 10^4 ({\rm s}^{-1})$	$k_{\rm R}/k_{\rm H}$	$\log(k_{\rm R}/k_{\rm H})$	$\sigma_{ m p}{}^+$
1	Me	4.0751	2.2022	0.3428	-0.17
2	Н	1.8505	1	0	0
3	F	1.1883	0.6421	-0.1924	0.05
4	Br	0.6050	0.3269	-0.4856	0.22
5	Cl	0.5037	0.2722	-0.5651	0.23



FIGURE 3. Hammett plot of $\log(k_R/k_H)$ versus σ_p^+ for secondary benzylation of thiophene with benzylic alcohols p-R $-C_6H_4-CH(Me)$ -OH.

and distilled before use. Secondary benzyl alcohol derivatives were prepared according to the literature procedure.¹⁰

Synthesis of Catalyst 1. To a solution of $[Ir(COD)(\mu-Cl)]_2$ (34 mg, 0.05 mmol) in dichloromethane (3 mL) was added very slowly a solution of SnCl₄ (11.7 μ L, 0.1 mmol) in benzene (200 μ L) under an argon atmosphere. The mixture was left undisturbed for 24 h. Deep red crystals were isolated from the reaction mixture, which were filtered, washed with benzene, and vacuum-dried. Yield: 97% (58 mg). Mp 241–244 °C (dec). Solubility: soluble in DMSO,

MeCN, hot methanol, benzyl alcohol; moderately soluble in acetone; insoluble in DCM, CHCl₃, benzene, toluene, and other hydrocarbons.

¹H NMR (200 MHz, DMSO-*d*₆): δ ppm 1.71–1.79 (br m, 8H, $-CH_2$), 2.21–2.26 (br m, 8H, $-CH_2$), 4.16 (br s, 8H, =CH). ¹³C NMR (54.6 MHz, DMSO-*d*₆): δ ppm 30.7 ($-CH_2$), 54.8 (=CH), 73.6 (=CH). IR (KBr, cm⁻¹): 1329(s), 1433(s), 1469(m), 1617-(s), 2850(w), 2907(m), 2954(m), 3010(w). Far-IR (polyethylene film, cm⁻¹): [360, 336] (Sn–Cl_{sym}), 291 (m, Ir–Cl), 246 (w, Sn–Cl_{asym}). Raman (cm⁻¹): 210 (Ir–Sn), 345 (Sn–Cl). UV–vis (MeCN): (λ_{max} , nm; (log ϵ)): 360 (3.33), 413 (3.34), 425 (3.35), 466 (2.71), 481 (2.75). Anal. Calcd for C₁₆H₂₄Cl₁₀Sn₂Ir₂: C, 16.09; H, 2.01. Found: C, 15.89; H, 2.03.

General Procedure. The following typical procedure has been adopted for the synthesis of all the benzylated products.

Typical Procedure for the Benzylation of o-Xylene with 1-Phenylethanol 2 Catalyzed by [Ir₂(COD)₂(SnCl₃)₂(Cl)₂(μ -Cl)₂] 1. A 10 mL Schlenk flask equipped with a magnetic bar was charged with high-valent heterobimetallic complex, [Ir₂(COD)₂-(SnCl₃)₂(Cl)₂(µ-Cl)₂] 1 (3 mg, 0.0025 mmol), o-xylene (153 µL, 1.25 mmol), and 1,2-dichloroethane (1 mL). The flask was degassed with argon and placed into a constant temperature bath at 80 °C. After the mixture was stirred vigorously for 5 min, 1-phenylethanol 2 (30 μ L, 0.25 mmol) was added to it, and the reaction was allowed to continue at 80 °C for 12 h. After completion of the reaction, solvent was removed under reduced pressure and the mixture was subjected to column chromatography over silica gel (60-120 mesh, eluent: 60-80 °C petroleum ether) to afford the corresponding benzylated product $\hat{4}$ as colorless oil in 89% (47 mg) isolated yield. ¹H NMR (200 MHz, CDCl₃): δ ppm 1.62 (d, ³*J*(H,H) = 7.2 Hz, 3H), 2.22 (s, 6H), 4.09 (q, ${}^{3}J(H,H) = 7.2$ Hz, 1H), 6.95–7.08 (m, 3H), 7.17–7.29 (m, 5H). ¹³C NMR (54.6 MHz, CDCl₃): δ ppm 19.3, 19.8, 21.9, 44.4, 124.9, 125.9, 127.5, 128.3, 129.0, 129.6, 134.1, 136.4, 143.9, 146.7. Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.15; H, 8.87.

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Supporting Information Available: General methods, details of GC analysis and kinetics procedure, spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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^{(10) (}a) Zeynizadeh, B.; Behyar, T. *Bull. Chem. Soc. Jpn.* 2005, 78, 307.
(b) Kundu, A.; Prabhakar, S.; Vairamani, M.; Roy, S. *Organometallics* 1997, 16, 4796. (c) Das, J. P. Ph.D. Thesis, Indian Institute of Technology, Kharagpur, India, 2005.