JOC Article

Efficient Solvent-Free Selective Monoalkylation of Arylacetonitriles with Mono-, Bis-, and Tris-primary Alcohols Catalyzed by a Cp*Ir Complex

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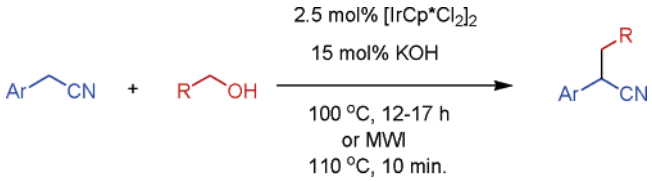

Our objectives were to develop catalytic atom-economic processes accessing and/or incorporating versatile functionality using aryl/heteroaryl acetonitriles as substrates. We report essentially solvent-free $[Cp^*IrCl_2]_2$ catalyzed redox neutral processes whereby substituted acetonitriles react with primary alcohols to deliver monosubstituted aryl/heteroaryl acetonitriles in excellent yield. We further demonstrate that such processes can be achieved by conventional or microwave heating and that bis- and tris-primary alcohols are also processed efficiently.

Introduction

The application of metal nucleophiles, catalytically generated in situ, to C−C bond forming processes is a subject of continued interest.[1] The catalytic activation of arylacetonitriles as nucleophiles has been reported earlier by our group[2] and by Murahashi et al.[3] The importance of α-alkylated nitriles lies in their potential as versatile building blocks for the construction of amides, carboxylic acids, ketones, heterocycles, and biologically active compounds.[4,5] Alkylated nitriles are traditionally synthesized using stoichiometric amounts of inorganic bases and alkyl halides.[6] Major drawbacks with this method are the toxicity of the alkylating agents, the concurrent formation of undesirable waste salts, and the potential for dialkylated byproducts.[7]

Direct catalytic alkylation with alcohols is an attractive green chemistry solution[8] that generates only water as a byproduct. Recently, Kaneda et al. reported a novel Ru-grafted hydrotalcite (Ru/HT) possessing both active Ru^{4+} species and surface base sites as a multifunctional heterogeneous catalyst for the monoalkylation of arylacetonitriles with alcohols.[9] Using transfer hydrogenation methodology, Cho et al. reported the direct α-alkylation of ketones with alcohols, using a Ru catalyst, to afford saturated alcohols via the α-alkylated ketone.[10] The same reaction can be performed in the presence of a sacrificial hydro-

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gen acceptor, such as 1-dodecene, when α-alkylated ketones are obtained.[11] More recently, Ishii et al. reported the selective direct α-alkylation of ketones with alcohols using an $[Ir(cod)Cl]_2/PPh_3/KOH$ system,[12] and Williams et al. reported indirect Wittig reactions with alcohols using $[Ir(cod)Cl]_2$[13] or a ruthenium N-heterocyclic carbene complex[14] and variants of aldol condensation.[15] Microwave assisted reactions have in recent years received much attention because of their enhanced reaction rates and greater selectivity.[16] Generally, the reactions can be run in a solvent as a homogeneous or heterogeneous mixture or without solvent.[17] Solvent-free conditions on solid supports such as silica gel, alumina, or clays were originally developed to avoid potential hazards of uncontrolled microwave heating of flammable, toxic, and volatile organic liquids.[18]

Herein, we report our findings on the selective monoalkylation of arylacetonitriles (1 mol equiv) with primary alcohols (1.5 or 3 mol equiv), and no additional solvent, under the influence of catalytic amounts of $[IrCp^*Cl_2]_2$ and KOH at 100 °C to afford α-alkylated arylacetonitriles in high yield. Also reported is the beneficial application of microwave irradiation that results in a notable rate acceleration of the alkylation cascade. This method provides a useful green route to α-alkylated arylacetonitriles with H_2O as the only byproduct.

Results and Discussion

Using alcohol as a hydrogen donor results in the formation of an intermediate aldehyde that is incorporated into the cascade via a Knoevenagel[19] condensation with the arylacetonitrile **1**, followed by transfer hydrogenation, to afford monoalkylated nitrile products **3** (Scheme 1). The use of $[IrCp^*Cl_2]_2$ as an efficient catalyst in a number of organic transformations involving transfer hydrogenation methodology has recently been reported by Fujita and Yamaguchi.[20]

A range of bases was surveyed (Table 1) for the reaction of phenylacetonitrile **1a** with benzyl alcohol **2a**.

The reaction of **1a** with **2a** in the presence of K_2CO_3 and Cs_2CO_3 (15 mol %) afforded less than 10% conversion to **3a** (Table 1, entries 1 and 2). When a stronger base, potassium *t*-butoxide, was used, the alkylation was similarly inefficient and gave **3a** with less than a 10% conversion (Table 1, entry 3). The low conversion in the latter case is probably due to inhibition of the dehydrogenation step due to a steric blockade of the Ir by coordinated *t*-butoxide.

SCHEME 1

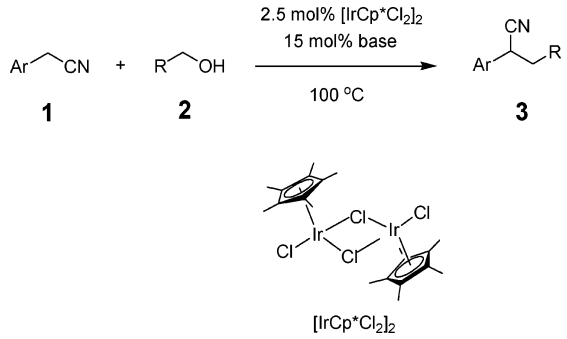
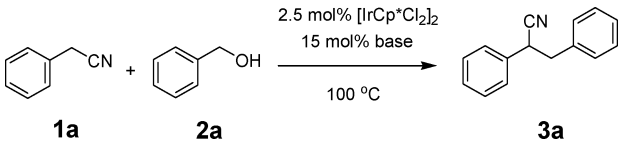


TABLE 1. Catalytic Alkylation of Phenylacetonitrile 1a with Benzyl Alcohol 2a Using $[IrCp^*Cl_2]_2$ and Different Bases[a]

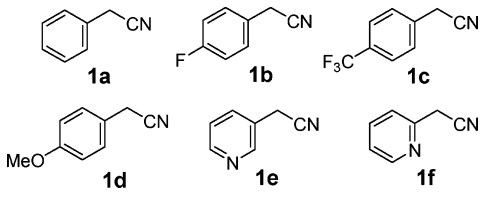


entry	base	**3a** (%)[b]
1	K_2CO_3	<10
2	Cs_2CO_3	<10
3	KO^tBu	<10
4	NaOH	84
5	**KOH**	>**99**
6	CsOH	95
7	Et_3N	0
8	DABCO	0

[a] **1a** (1 mmol) was reacted with **2a** (3 mmol) under the influence of $[Cp^*IrCl_2]_2$ (2.5 mol %) and base (15 mol %) at 100 °C for 13 h. [b] Conversion estimated by ^1H NMR spectroscopy based on **1a**.

KOH proved to be the most successful base of those screened affording a >99% conversion (Table 1, entry 5). Triethylamine and DABCO did not result in alkylation (Table 1, entries 7 and 8). The same result was observed when the reaction was performed in the absence of a base.

On the basis of these results, a variety of arylacetonitriles **1a**−**f** containing both electron-withdrawing and -donating groups was successfully alkylated with benzyl alcohol **2a** in high yield (Table 2) under the optimized conditions.



Heteroarylacetonitriles such as 3-pyridylacetonitrile **1e** and 2-pyridylacetonitrile **1f** were also efficiently alkylated with **2a** affording **3e**,**f** (Table 2, entries 5 and 6) in 88 and 89% yield, respectively.

The scope of this reaction was further examined using arylacetonitrile **1e** with a range of aromatic, heteroaromatic, and aliphatic alcohols (Table 3).

The alkylation of **1e** with a variety of benzyl alcohols substituted by electron donating or withdrawing groups when carried out under conventional heating or microwave conditions gave similar yields, while under the latter conditions, the reaction rate was vastly accelerated. Microwave irradiation was per-

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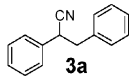
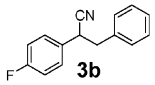
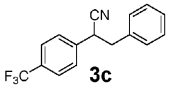
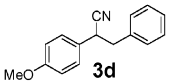
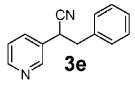
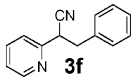
TABLE 2. Catalytic Alkylation of Various Arylacetonitriles with Benzyl Alcohol 2a Using [IrCp*Cl$_2$]$_2$ and KOH[a]

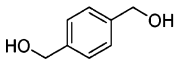
Entry	Nitrile	Product	*T* (h)	Yield (%)[b]
1	**1a**	 **3a**	13	88
2	**1b**	 **3b**	13	92
3	**1c**	 **3c**	13	88
4	**1d**	 **3d**	16	93
5	**1e**	 **3e**	12	88
6	**1f**	 **3f**	12	89

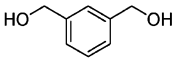
[a] The reaction was carried out at 100 °C with arylacetonitrile (1 mmol), benzyl alcohol (3 mmol), [Cp*IrCl$_2$]$_2$ (2.5 mol %), and KOH (15 mol %). [b] Isolated yield.

formed at 300 W using a CEM Discover Focused Microwave Synthesis System.

To emphasize that all electronic combinations of nitriles and alcohols can be utilized in the catalytic alkylation cascade, the arylacetonitriles **1a** (neutral) and **1d** (electron-rich) were alkylated with electron-rich/-poor benzyl alcohols **2b**,**d** and the aliphatic alcohol **2m** (Table 4).

The catalytic alkylation cascade also proved successful in alkylating bis- and tris-alcohols, such as **2n**−**p**, affording the expected products in good to high yield (Table 5, entries 1−5). In the case of 4-methoxyphenylacetonitrile, traditional heating at 100 °C for 15 h was used due to incomplete conversion to product under the standard microwave irradiation conditions (Table 5, entry 2).


2n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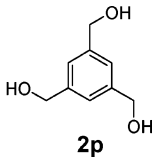
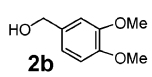
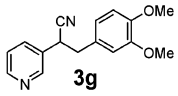
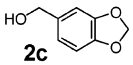
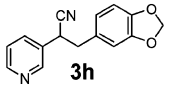
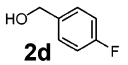
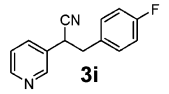
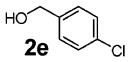
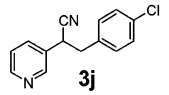
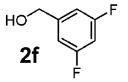
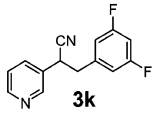
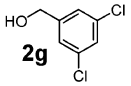
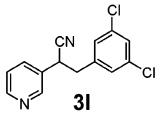
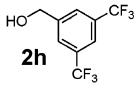
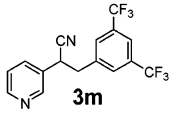
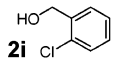
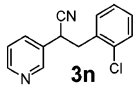
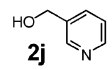
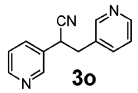
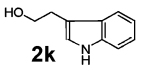
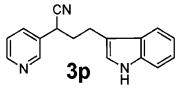
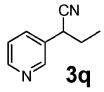
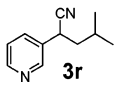

2p

The precise nature of the active catalyst and the reaction mechanism are still uncertain. However, Scheme 2 is in accord with our previous work[2] and involves three key sequential steps: (i) dehydrogenation of the primary alcohol **2** to the corresponding aldehyde **5** and a metal hydride **6**; (ii) activation of the arylacetonitrile **1** by the coordinated catalyst acting as a Lewis acid followed by deprotonation by a base. The resultant nucleophile undergoes subsequently a Knoevenagel condensation with the in situ formed aldehyde **5**, giving the arylacrylonitrile **7**; and (iii) hydrogenation of the arylacrylonitrile **7** by the metal hydride **6** to afford the monoalkylated arylacetonitrile **3**. The reaction is selective for the monoalkylated product, as in the second Knoevenagel condensation there is no proton α to the -OH group to be eliminated as water.

TABLE 3. Catalytic Alkylation of 1e with Various Alcohols Using [IrCp*Cl$_2$]$_2$ and KOH under Traditional Heating[a] versus Microwave Irradiation (MWI)[b]

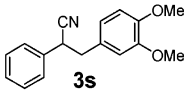
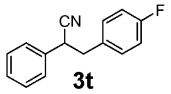
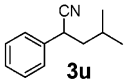
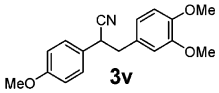
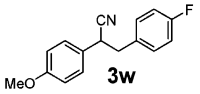
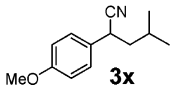
Entry	Alcohol	Product	Yield (%)[c]	MWI Yield (%)[c]
1	 **2b**	 **3g**	86	82
2	 **2c**	 **3h**	90	86
3	 **2d**	 **3i**	89	89
4	 **2e**	 **3j**	87	85
5	 **2f**	 **3k**	82	86
6	 **2g**	 **3l**	85	87
7	 **2h**	 **3m**	78	75
8	 **2i**	 **3n**	88	84
9	 **2j**	 **3o**	84	81
10	 **2k**	 **3p**	77	67[d]
11	 **2l**	 **3q**	90	88
12	 **2m**	 **3r**	80	87

[a] The reaction was carried out with **1e** (1 mmol), alcohol (1.5 or 3 mmol), [Cp*IrCl$_2$]$_2$ (2.5 mol %), and KOH (15 mol %) at 100 °C for 12−17 h. [b] The reaction was carried out in a microwave reactor with **1e** (1 mmol), alcohol (1.5 or 3 mmol), [Cp*IrCl$_2$]$_2$ (2.5 mol %), and KOH (15 mol %) at 110 °C for 10 min. [c] Isolated yield. [d] Dioxane (1.0 mL) was used as cosolvent.

Conclusion

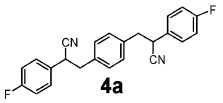
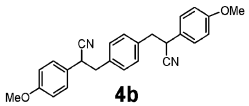
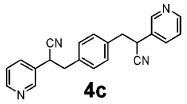
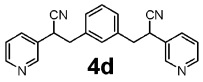
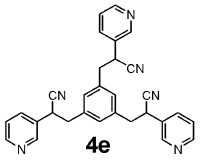
A convenient and highly effective catalytic system has been developed for the selective monoalkylation of arylacetonitriles with a wide range of aromatic, heteroaromatic, and aliphatic alcohols. Alkylation of bis- and tris-primary alcohols also pro-

TABLE 4. Catalytic Alkylation of 1a,d with Alcohols 2b,d,m Using $[IrCp^*Cl_2]_2$ and KOH[a]

Entry	Nitrile	Alcohol	Product	Yield (%)[b]
1	**1a**	**2b**	 **3s**	91
2	**1a**	**2d**	 **3t**	84
3	**1a**	**2m**	 **3u**	76[c]
4	**1d**	**2b**	 **3v**	88
5	**1d**	**2d**	 **3w**	85
6	**1d**	**2m**	 **3x**	93[c]

[a] The reaction was performed using arylacetonitrile (1 mmol), alcohol (3 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), and KOH (15 mol %) at 100 °C for 14 h. [b] Isolated yield. [c] 1 mL of alcohol was used as solvent.

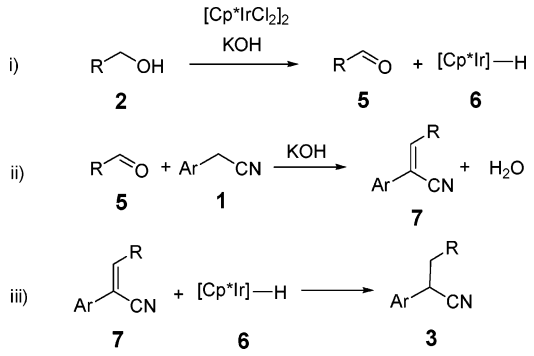
TABLE 5. Catalytic Alkylation of 1b,d,e with Bis- and Tris-alcohol 2n,o,p Using $[IrCp^*Cl_2]_2$ and KOH[a]

Entry	Nitrile	Alcohol	Product	MWI Yield (%)[b]
1	**1b**	**2n**	 **4a**	74
2	**1d**	**2n**	 **4b**	71[c]
3	**1e**	**2n**	 **4c**	86
4	**1e**	**2o**	 **4d**	62
5	**1e**	**2p**	 **4e**	72[d]

[a] The reaction was carried out in a microwave reactor with nitrile (1.1 mmol), alcohol (0.5 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), and KOH (15 mol %) at 110 °C for 10 min. [b] Isolated yield. [c] Reaction carried out using traditional heating at 100 °C for 15 h. [d] The reaction was carried out in a microwave reactor with nitrile (1.1 mmol), alcohol (0.33 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), and KOH (15 mol %) at 110 °C for 10 min.

ceeded efficiently. It was further demonstrated that such processes can be achieved either by conventional or microwave heating. Utilization of microwave irradiation resulted in a notable rate acceleration. In addition, this green catalytic hydrogen transfer cascade is highly atom-economic and produces H_2O as the only byproduct.

SCHEME 2[a]



[a] (i) Dehydrogenation of the primary alcohol **2** to the corresponding aldehyde **5** and a metal hydride **6**; (ii) activation of the arylacetonitrile **1** by the coordinated catalyst acting as a Lewis acid followed by deprotonation by a base. The resultant nucleophile undergoes subsequently a Knoevenagel condensation with the in situ formed aldehyde **5** giving the arylacrylonitrile **7**; (iii) hydrogenation of the arylacrylonitrile **7** by the metal hydride **6** to afford the monoalkylated arylacetonitrile **3**. The reaction is selective for the monoalkylated product, as in the second Knoevenagel condensation there is no proton α to the -OH group to be eliminated as water.

Experimental Procedures

General. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. For ^1H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Chemical shifts (δ) are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS). Mass spectrometric data (MS) were obtained by electrospray ionization (ESI) or electron ionization (EI). For preparative scale chromatography, silica gel (60 Å particle size 35−70 μm) was used. Infrared spectra were recorded either as a thin film on sodium chloride plates or using the solid attachments. Thin films were prepared by the evaporation of a solution of the compound in chloroform. Melting points are uncorrected.

(A) General Procedure for the $[IrCp^*Cl_2]_2$ Catalyzed Alkylation Cascade of Nitriles (1a−f) by Alcohols (2a−o). A mixture of nitrile (1 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol % based on nitrile), KOH (15 mol %), and alcohol (1.5 or 3.0 mmol) was flushed with nitrogen. The reaction mixture was then magnetically stirred in a Schlenk tube at 100 °C for 12−17 h. The progression of the reaction was monitored by TLC. After the reaction was complete, the crude mixture was analyzed by ^{1}HNMR and thereafter purified by column chromatography eluting with diethyl ether, diethyl ether/petroleum, or methanol/diethyl ether.

2,3-Diphenylpropanenitrile (3a). Prepared by the general procedure A from phenylacetonitrile (0.117 g, 1.00 mmol), KOH (9 mg, 0.152 mmol), $[IrCp^*Cl_2]_2$ (0.020 g, 0.025 mmol), and benzyl alcohol (0.324 g, 3.00 mmol). Work-up followed by column chromatography eluting with a 1:9 v/v ether/petroleum ether gave **3a** (0.182 g, 88%) as colorless plates, mp 53−55 °C (lit.[21] 54 °C); (Found: C, 87.10; H, 6.20; N, 7.00; $C_{15}H_{13}N$ requires: C, 86.92; H, 6.32; N, 6.76%); ν_{max} (film) 2236 (CN stretching) cm^{-1}; *m*/*z* (EI, %) 207 (M^+, 12), 116 ($PhCHCN^+$, 5), 91 ($PhCH_2^+$), 100); δ_H (300 MHz, $CDCl_3$); 7.48−7.29 (m, 8H), 7.26−7.19 (m, 2H), 4.07 (dd, 1H, J = 8.2 and 6.7 Hz), 3.27 (dd, 1H, J = 13.6 and 8.2 Hz), and 3.20 (dd, 1H, J = 13.6 and 6.7 Hz); δ_C (75.5 MHz, $CDCl_3$); 136.8 (C),

(21) Barbry, D.; Pasquier, C.; Faven, C. *Synth. Commun.* **1995**, *25*, *19*, 3007.

135.7 (C), 129.7 (2 × CH), 129.5 (2 × CH), 129.1 (2 × CH), 128.7 (CH), 128.0 (2 × CH), 127.9 (CH), 120.9 (C), 42.7 (CH_2), and 40.2 (CH).

(B) General Procedure for the [IrCp*Cl$_2$]$_2$ Catalyzed Alkylation Cascade of Nitriles (1b,e) by Alcohols (2b−p) under Microwave Irradiation. A mixture of nitrile (1 mmol), [IrCp*Cl$_2$]$_2$ (2.5 mol % based on nitrile), KOH (15 mol %), and alcohol (1.5 or 3 mmol) was loaded and sealed under air in a microwave tube. The reaction mixture was then magnetically stirred under microwave irradiation (300 W, sealed reaction vessel) for 10 min (hold time) at 110 °C. The reaction temperature was controlled and monitored using the built-in standard temperature control system for the system, which consists of a noncontact infrared sensor located in the instrument cavity. The crude reaction mixture was analyzed by ^{1}HNMR and thereafter purified by column chromatography eluting with diethyl ether, diethyl ether/petroleum, or methanol/diethyl ether.

3-(3,4-Dimethoxyphenyl)-2-(pyridin-3-yl)propanenitrile (3g). Prepared by general procedures A and B from 3-pyridylacetonitrile (0.118 g, 1.0 mmol), KOH (9 mg, 0.152 mmol), [IrCp*Cl$_2$]$_2$ (0.020 g, 0.025 mmol), and 3,4-dimethoxybenzyl alcohol (0.504 g, 3.0 mmol). Work-up followed by column chromatography eluting with diethyl ether gave **3g** (0.230 g, 86% from A and 0.219 g, 82% from B) as colorless plates, mp 55−57 °C; (Found: C, 71.35; H, 5.85; N, 10.45; $C_{16}H_{16}N_2O_2$ requires: C, 71.62; H, 6.01; N, 10.44%); ν_{max} (solid) 2244 (CN stretching) cm^{-1}; *m*/*z* (ESI, %) 269 (M + 1, 55); δ_H (300 MHz, $CDCl_3$); 8.58 (dd, 1H, J = 4.7 and 1.4 Hz), 8.47 (d, 1H, J = 2.3 Hz), 7.55 (dt, 1H, J = 7.9 and 1.8 Hz), 7.29 (dd, 1H, J = 7.9 and 4.7 Hz), 6.78 (d, 1H, J = 8.2 Hz), 6.65 (dd, 1H, J = 8.2 and 2.0 Hz), 6.56 (d, 1H, J = 2.0 Hz), 4.07 (app. t, 1H, J = 7.0 Hz), 3.85 (s, 3H), 3.78 (s, 3H), 3.17 (dd, 1H, J = 13.6 and 7.4 Hz), and 3.10 (dd, 1H, J = 13.6 and 6.7 Hz); δ_C (75.5 MHz, $CDCl_3$); 149.9 (CH), 149.3 (C), 149.2 (CH), 148.9 (C), 135.5 (CH), 131.5 (C), 128.1 (C), 124.0 (CH), 122.0 (CH), 120.0 (C), 112.9 (CH), 111.7 (CH), 56.2 (2 × CH_3), 41.7 (CH_2), and 37.7 (CH).

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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