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Cooperative Catalysis of a Cationic Ruthenium Complex, Amine Base, and Na Salt: Catalytic Activation of Acetonitrile as a Nucleophile

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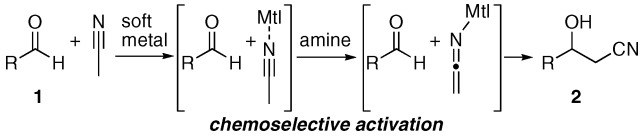
The in situ catalytic generation of metal nucleophiles and their integration into a C−C bond-forming process is a topic of sustained interest.[1] Although there have been notable advances during the past 5 years using ketones as substrates,[2c,d] the use of substrates with the oxidation state of carboxylic acid is limited.[2a,b] α-Cyano carbanions are widely used as often as enolates in organic synthesis; however, catalytic activation of nitriles as nucleophiles has been limited to active nitriles such as β-cyano carbonyls (pK_a ∼ 13[3a]) and α-arylnitriles (pK_a ∼ 21.9[3a]),[4,5] mainly due to the high pK_a (31.3[3a]) of simple alkylnitriles.[5] The in situ generation of nucleophiles from alkylnitriles requires highly basic conditions, which places a severe limitation on chemoselective activation in a catalytic manner.[5] Basicity and substrate compatibility are problematic in the direct addition of alkylnitriles to carbonyl compounds; strongly basic conditions cause undesirable reactions, whereas deprotonation fails with a weak base. Recent advances in this regard have been made using a proazaphosphatrane base (pK_a of its conjugate acid: ∼34[3b])[6] or metal *tert*-butoxide[7] as the catalyst. The reaction conditions are still highly basic, however, and in the case of the proazaphosphatrane base 2.2 equiv of Mg salt is necessary to prevent concomitant dehydration.[6] Thus, there remains much room to develop milder reaction conditions. Herein, we report the direct addition of acetonitrile to aldehydes and imines with a catalytic triad of a cationic Ru complex, usual amine base, and $NaPF_6$.

In search of a mild catalytic system, we planned to use soft Lewis acidic metals for chemoselective activation of simple alkylnitriles in the presence of carbonyl compounds. We hypothesized that soft Lewis acids[8] would lower the pK_a of alkylnitrile enough to be deprotonated by common amine bases (Scheme 1).[9] Screening of

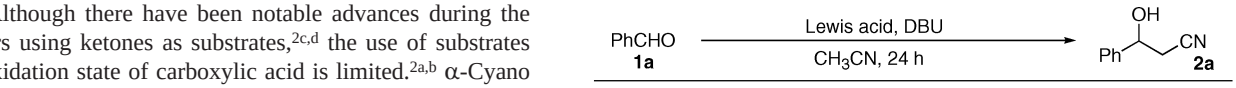
Scheme 1. Chemoselective Activation of Nitrile in the Presence of Carbonyl Compounds



various soft Lewis acids and amines revealed that some cationic soft Lewis acids effected the deprotonation of acetonitrile in the presence of DBU and promoted the addition to afford **2a** (Table 1). Among them, the best activity was obtained with cationic ruthenium complex $CpRu(CH_3CN)_3PF_6$,[10] affording **2a** in 23% yield. With the mono PPh_3 complex **3**, the reaction proceeded in a catalytic manner based on Ru (entries 6, 7). The use of 4 Å MS and HMPA further improved the conversion to 84%, although 2 equiv of DBU remained essential even at 50 °C (entry 8 vs 9). With 10 mol % $NaPF_6$, the reaction reached completion with 5 mol % DBU and Ru complex (entry 10). The combination of Ru, DBU, and $NaPF_6$ is essential (entries 11, 12).[11]

The optimized conditions were applicable to various aldehydes with 2.5−5 mol % Ru complex **3** (Table 2). The reaction with either

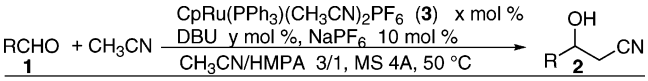
Table 1. Direct Addition of Acetonitrile with Soft Lewis Acids and DBU



entry	Lewis acid	(mol %)	DBU (mol %)	MS4A	$NaPF_6$ (mol %)	temp (°C)	yield (%)
1	none	0	200	−	0	rt	0
2	Pd $(CH_3CN)_4(BF_4)_2$	50	200	−	0	rt	11
3	$Cu(CH_3CN)_4PF_6$	50	200	−	0	rt	0
4[a]	$Ag(CH_3CN)_4BF_4$	50	200	−	0	rt	14
5	$CpRu(CH_3CN)_3PF_6$	50	200	−	0	rt	23
6	$CpRu(PPh_3)(CH_3CN)_2PF_6$ **3**	50	200	−	0	rt	63
7	$CpRu(PPh_3)(CH_3CN)_2PF_6$ **3**	10	200	−	0	rt	40
8[b]	$CpRu(PPh_3)(CH_3CN)_2PF_6$ **3**	10	200	+	0	50	84
9[b]	$CpRu(PPh_3)(CH_3CN)_2PF_6$ **3**	5	5	+	0	50	46
10[b]	$CpRu(PPh_3)(CH_3CN)_2PF_6$ **3**	5	5	+	10	50	93
11[b]	$CpRu(PPh_3)(CH_3CN)_2PF_6$ **3**	5	0	+	10	50	0
12[b]	none	0	5	+	10	50	0

[a] Reaction was performed in the dark. [b] HMPA was used as a cosolvent.

Table 2. Direct Addition of Acetonitrile to Aldehydes Catalyzed by $CpRu(PPh_3)(CH_3CN)_2PF_6$ (3), DBU, and $NaPF_6$



entry	aldehyde R =		**3** x =	DBU y =	time (h)	yield (%)
1	Ph	**1a**	5	5	24	93
2	Ph	**1a**	2.5	2.5	24	91
3	*p*-Cl-C_6H_4	**1b**	5	5	24	93
4	*p*-F-C_6H_4	**1c**	5	5	24	91
5	*p*-(CO_2Me)-C_6H_4	**1d**	5	5	24	82
6	*p*-CH_3-C_6H_4	**1e**	5	5	48	82
7	*m*-MeO-C_6H_4	**1f**	5	5	24	88
8	2-naphthyl	**1g**	5	5	40	92
9	(*E*)-cinnam	**1h**	5	5	36	84
10		**1i**	5	5	48	77
11	*c*-hex	**1j**	5	10	48	82

electron-withdrawing or -donating substituents proceeded smoothly to afford **2** in high yield. Ester functionality survived intact under these conditions (entry 5). The reaction with α,β-unsaturated aldehyde **1h** proceeded in a 1,2-fashion (entry 9). Sterically demanding α,α-disubstituted aldehyde **1i** afforded the desired product in good yield (entry 10). Base-sensitive aliphatic aldehyde **1j** provided the desired product in 82% yield without self-condensation.[12] The scope of the present catalysis was further broadened to imines (Table 3). Either *N*-Boc- or *N*-diphenylphosphinoyl(Dpp) imines **4** were successfully transformed into β-amino nitriles **5** in good yield. To the best of our knowledge, this is the first example of direct catalytic addition of acetonitrile itself to imines.

In the present catalysis, all three catalyst components, Ru complex, DBU, and $NaPF_6$, were essential (Table 1, entries 9−12). To gain insight into the role of the catalytic triad, we performed

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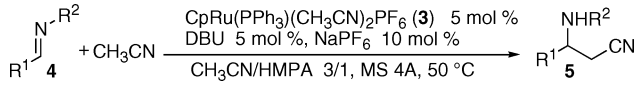
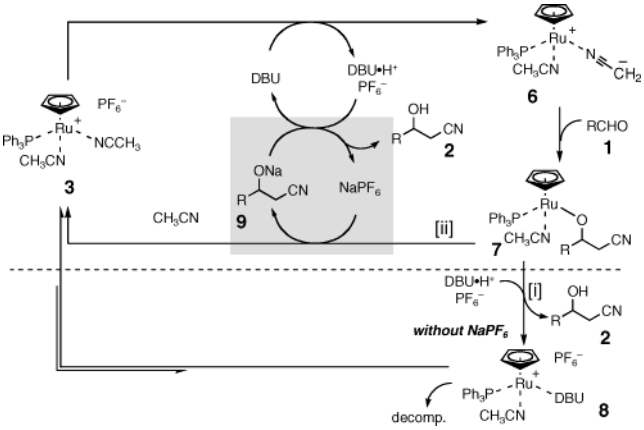
Table 3. Direct Addition of Acetonitrile to Imines Catalyzed by $CpRu(PPh_3)(CH_3CN)_2PF_6$ (**3**), DBU, and $NaPF_6$



entry	R^1	R^2		time (h)	yield (%)
1[a]	Ph	Boc	**4a**	24	84
2	*o*-CH_3-C_6H_4	Boc	**4b**	12	86
3	*p*-MeO-C_6H_4	Boc	**4c**	24	91
4[a]	2-naphthyl	Boc	**4d**	48	79
5	*o*-CH_3-C_6H_4	$P(O)Ph_2$	**4e**	48	81
6	*p*-Cl-C_6H_4	$P(O)Ph_2$	**4f**	48	86

[a] Performed with 10 mol % DBU.

Scheme 2. Proposed Catalytic Cycle



mechanistic studies of the reaction with **1a**. A plausible catalytic cycle is proposed as depicted in Scheme 2. NMR and ESI-MS analysis[13] indicated that Ru coordinated predominantly to acetonitrile, rather than to **1a** or HMPA, suggesting that Ru acts as a Lewis acid to activate acetonitrile for deprotonation.[14] Acetonitrile bound to Ru in **3** was deprotonated by free DBU to afford Ru-bound metalated nitrile **6**.[15] The substantial value of the obtained kinetic isotope effect, $k_H/k_D = 5.6$, and first-order rate dependency on DBU in initial rate kinetics suggest that this step is rate-determining.[16] Subsequent 1,2-addition of metalated nitrile to **1a** proceeds rapidly to give Ru-alkoxide **7**.[16] The beneficial effect of $NaPF_6$ is explained by the following observations. ESI-MS and NMR studies[13] of DBU and **3** in CH_3CN without **1a** and $NaPF_6$ indicated that DBU can coordinate to the Ru center to afford **8**, although the equilibrium strongly favored **3** rather than **8**. On the other hand, the formation of **8** was facilitated in the presence of **1a** without $NaPF_6$, possibly because the protonation−ligand exchange between **7** and $DBUH^+ \cdot PF_6^-$ would readily afford **8** (Scheme 2, step i).[13,17] Considering the spatial arrangement of ligands in **8**, ligated DBU is positioned too far away to deprotonate intramolecularly. Thus, the accumulation of **8** decreased the concentration of free DBU available for deprotonation, resulting in a lower reaction rate and catalytic efficiency. In addition, **8** was unstable and gradually decomposed to give $Ph_3P{=}O$ and Ru black as confirmed by ^{31}P NMR. Therefore, the chemical yield was modest in the absence of $NaPF_6$. An NMR study indicated that $NaPF_6$ effectively suppressed the accumulation of **8**,[13] allowing the complete reaction with 5 mol % DBU. Taking into account a favorable hard−hard interaction between the Na cation and alkoxide,[18] $NaPF_6$ would accelerate the transformation from Ru-alkoxide **7** into complex **3** and the Na-alkoxide **9** rather than into **8** (Scheme 2, step ii). Then, **9** would be protonated with $DBUH^+ \cdot PF_6^-$ to afford **2** and regenerate $NaPF_6$. Therefore, the amount of active catalyst **3** and free DBU was sufficient to promote the reaction, resulting in higher catalyst turnover. In this system, Ru activates acetonitrile, DBU effects the deprotonation, and the Na cation transfers the resulting alkoxide, all of these working cooperatively to efficiently drive the catalytic cycle.

In conclusion, we demonstrated efficient catalytic activation of acetonitrile as a nucleophile under mild basic conditions with cooperative catalysis of a cationic Ru complex, DBU, and $NaPF_6$. Preliminary mechanistic studies suggested a role for each of the three catalytic components. Further mechanistic studies as well as exploration of the enantioselective variants are in progress.

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Supporting Information Available: Detailed experimental procedure and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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