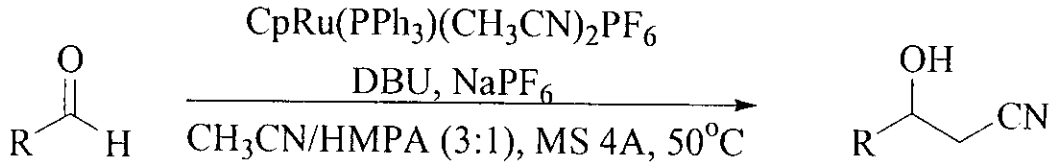
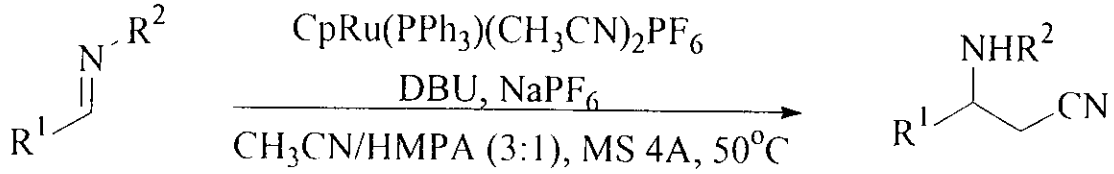
Cooperative Catalysis of a Cationic Ruthenium Complex, Amine Base, and Na Salt: Catalytic Activation of Acetonitrile as a Nucleophile

Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ASAP

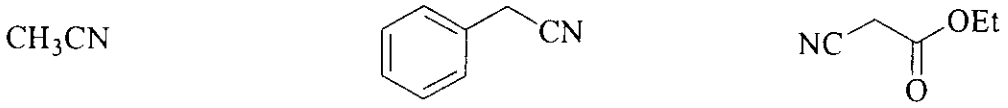




James Mignone
10/16/04

Introduction

Due to the high pK_a of simple alkylnitriles, α-cyano carbanions are usually generated from activated nitriles such as β-cyano carbonyls and α-arylnitriles.



pK_a ~31.3 pK_a~21.9 pK_a~13

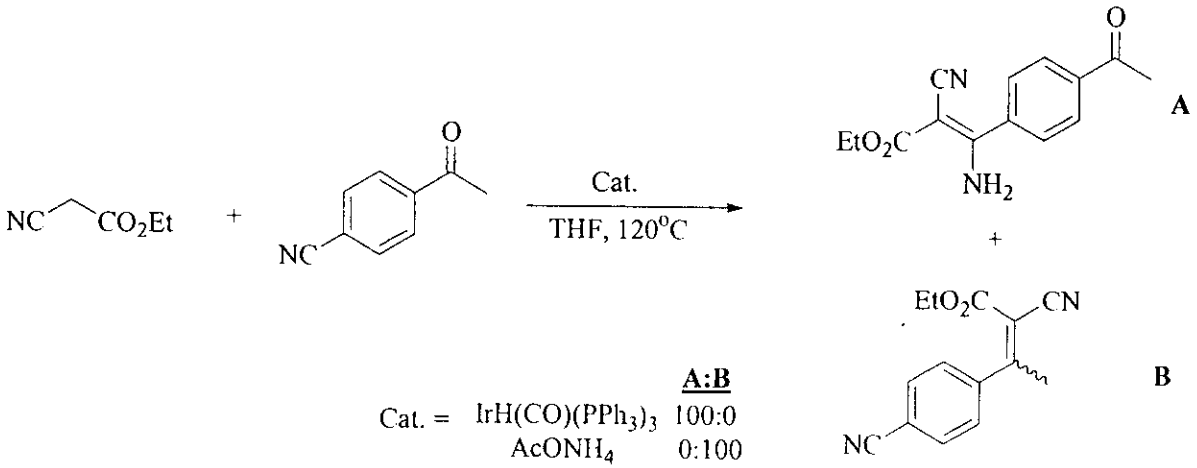
Highly basic conditions are required to generate alkynitrile nucleophiles.

Limitations:

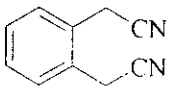
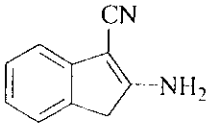
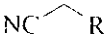
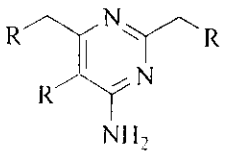
- *Chemoselective activation in a catalytic manner*
- *Substrate compatibility*
- *Undesirable side-reactions*

Most recent advances in developing milder conditions uses proazaphosphatrane base or metal tert-butoxide as a catalyst – condition are still highly basic.

Activation of α-C-H Bonds and the CN Triple bond of Nitriles Using an Ir Catalyst

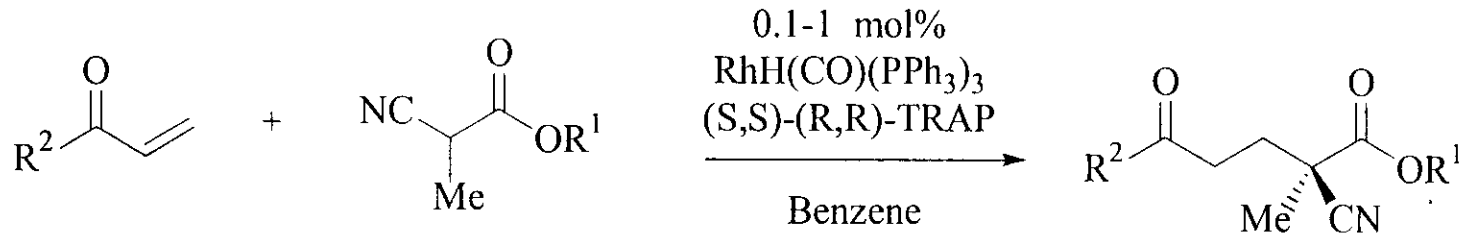


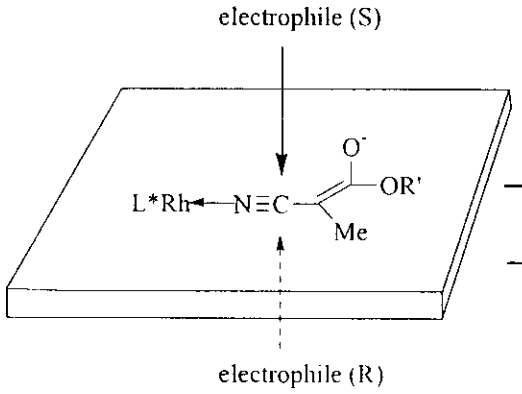
Cat. =		A:B
	$IrH(CO)(PPh_3)_3$	100:0
	$AcONH_4$	0:100

Nucleophile/ Electrophile	Product	Yield
		76%
		R = H: 37% Ph: 87%

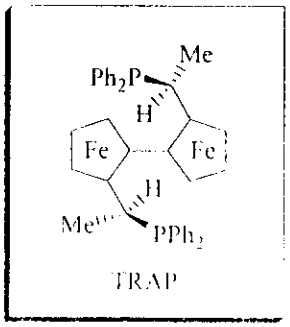
Takaya,H.; Naota, T.; Shun-Ichi, M. *J. Am. Chem. Soc.* **1998**, *120*, 4244.

Rh-Catalyzed Asymmetric Michael Addition of α–Cyano Carboxylates



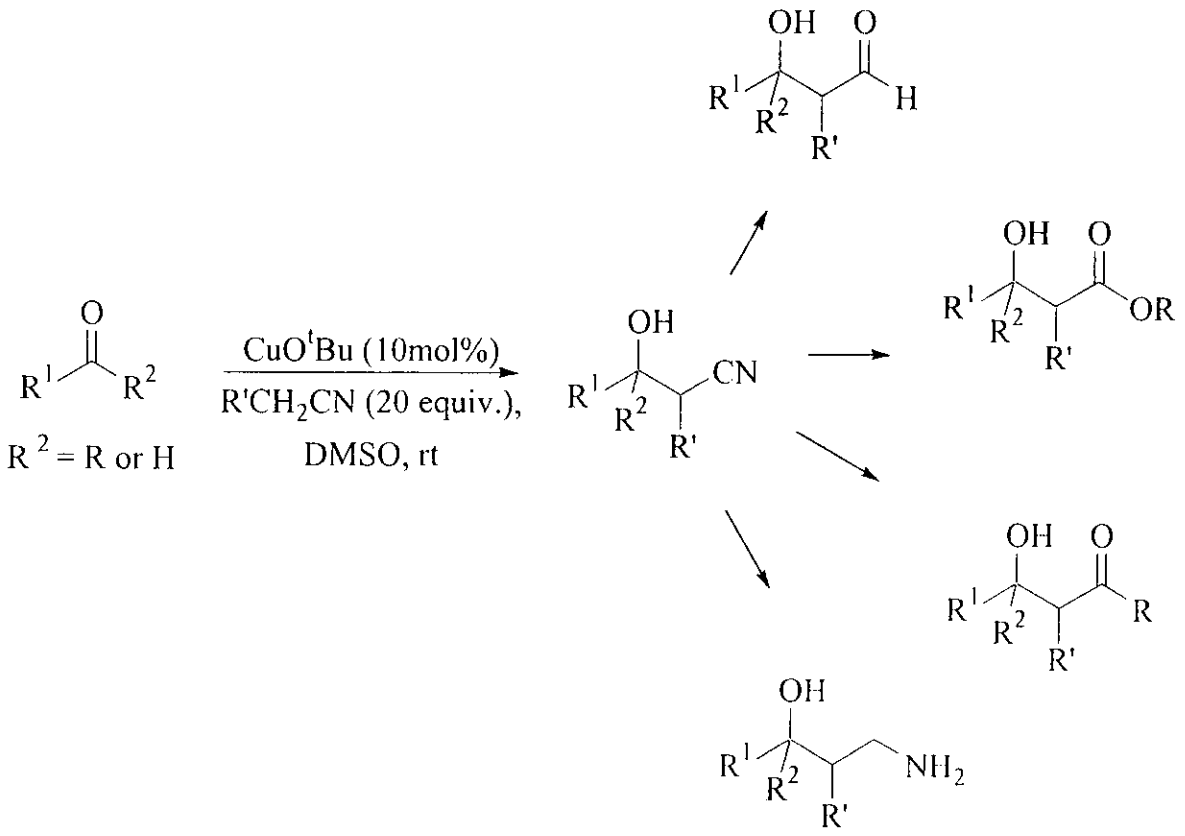


entry	2, R^2	1, R^1	temp, °C	addition time, h[b]	time, h[c]	product (3–9) yield, %[d]	ee, %[e]	config[f]
1	Me (2a)	Me (1a)	5	*i*	10	99 (3a)	72	*R*
2	Me (2a)	Et (1b)	5	*i*	10	95 (3b)	81	*R*
3	Me (2a)	*i*-Pr (1c)	5	*i*	10	99 (3c)	84	*R*
4	Me (2a)	*i*-Pr (1c)	3	*i*	10	97 (3c)	86	*R*
5	Me (2a)	*t*-Bu (1d)	5	*i*	10	95 (3d)	81	*R*
6	Et (2b)	*i*-Pr (1c)	3	*i*	10	98 (4)	85	*R*
7	Ph (2c)	*i*-Pr (1c)	5	1.5	2	95 (5)[g]	83[h]	*R*
8	4-MeOPh (2d)	*i*-Pr (1c)	3	1.5	2	99 (6)[g]	89[h]	*R*
9	2-MeOPh (2e)	*i*-Pr (1c)	3	1.5	2.5	98 (7)[g]	86[h]	*R*
10	4-ClPh (2f)	*i*-Pr (1c)	3	4	4.5	98 (8)[g]	85[h]	*R*
11	H (2g)	*i*-Pr (1c)	3	2.5	3.5	88 (9)[g]	87	*R*
12[h]	H (2g)	*i*-Pr (1c)	3	6	7	89 (9)	84	*R*



Sawamura, M.; Hamashima, H.; Ito, I. *J. Am. Chem. Soc.* **1992**, *114*, 8295.

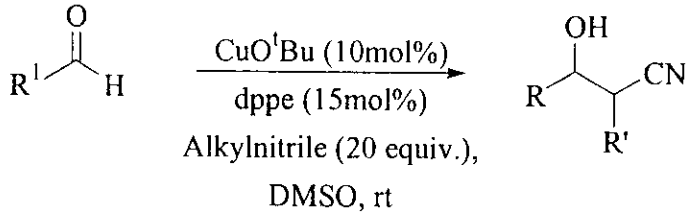
Direct Catalytic Aldol-Type Reactions Using RCH_2CN

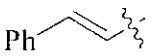
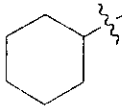


Cyanomethylation of carbonyl compounds is a surrogate ester enolate reaction generating β–hydroxy nitriles which can be converted to useful building blocks.

Suto, Y.; Kunagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org.Lett.* **2003**, *17*, 3147.

Direct Catalytic Addition of Alkylnitriles



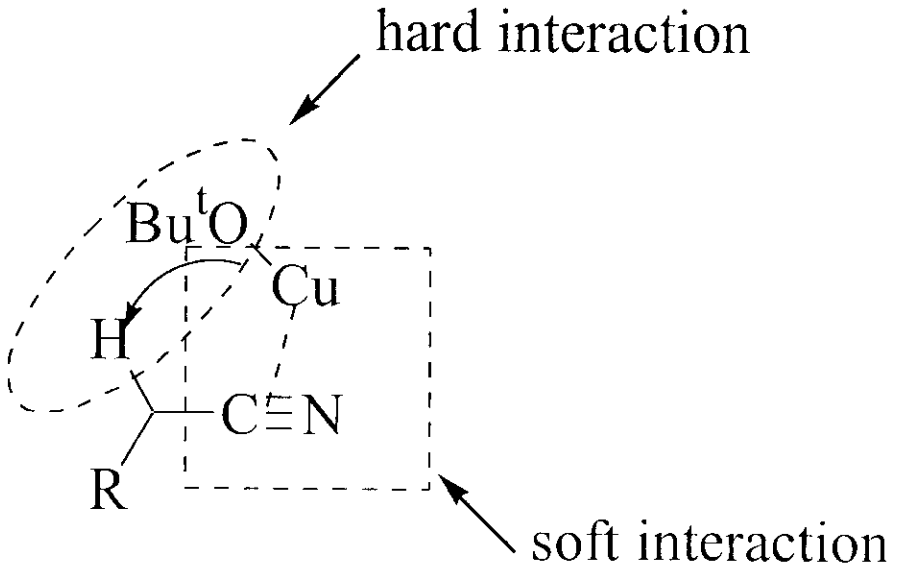
entry	R^1	alkylnitrile	yield(%)
1	C_6H_5	CH_3CN	95
2	C_6H_5	CH_3CN	81
3		CH_3CN	78
4		CH_3CN	71
5	C_6H_5	CH_3CH_2CN	90
6	C_6H_5	$CH_3CH_2CH_2CN$	76

← ~1.5:1 d.r. for other alkylnitriles

Aromatic aldehydes, α,β-unstaurated aldehydes and aliphatic aldehydes work well.

Suto, Y.; Kunagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org.Lett.* **2003**, *17*, 3147.

Hypothesis on Deprotonation

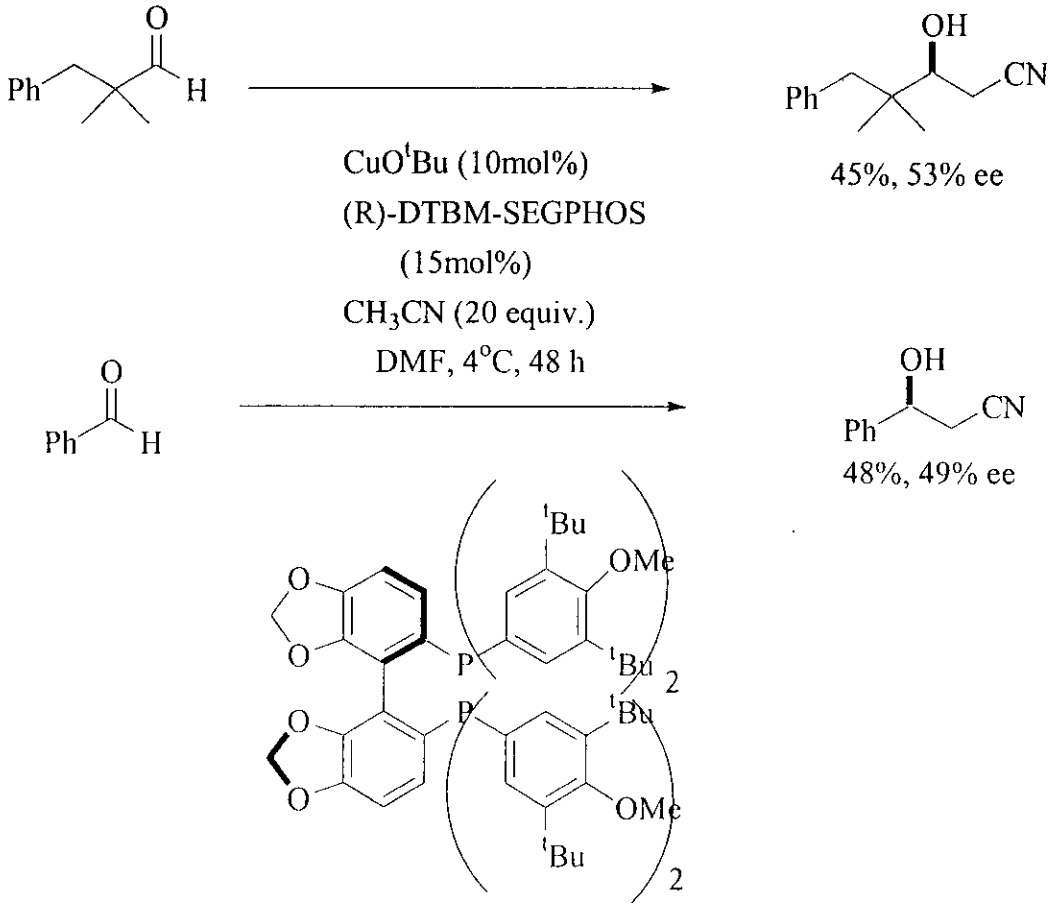


The soft interaction between Cu and the nitrile polarizes the α-carbon-hydrogen bond of the alkylnitrile and thus acidifies the α-proton.

The hard alkoxide then attacks the hard α-proton.

Suto, Y.; Kunagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org.Lett.* **2003**, *17*, 3147.

Direct Catalytic Enantioselective Cyanomethylation of Aldehydes

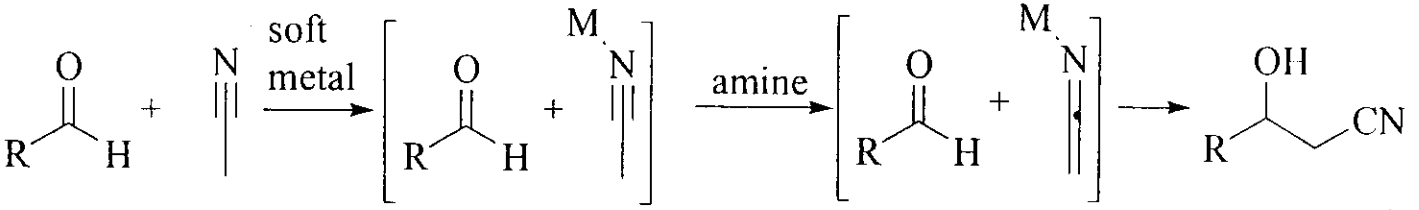


(R)-DTBM-SEGPHOS

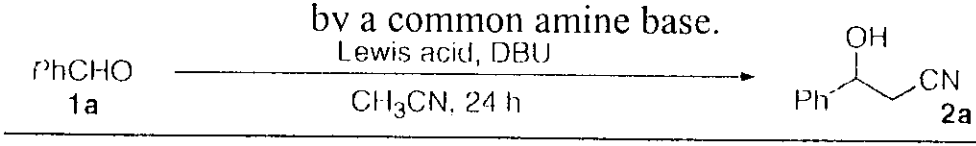
First example of cat. enantioselective cyanomethylatin of aldehydes.

Suto, Y.; Kunagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org.Lett.* 2003, *17*, 3147.

Chemoselective Activation of Nitrile in the Presence of Carbonyl Compounds / Soft Lewis Acid Screen



Goal is to use a soft Lewis Acid to lower the pK_a of the alkynitrile enough to be deprotonated by a common amine base.



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

Entry 10 afforded best results—combination of Ru, DBU and $NaPF_6$ is essential.

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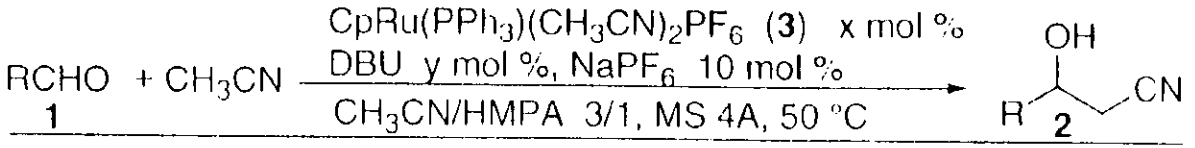
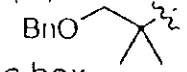
Direct Addition of Acetonitrile to Aldehydes Catalyzed by $CpRu(PPh_3)(CH_3CN)_2PF_6$, DBU and $NaPF_6$



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/donating substituents, ester functionality, α,β-unsaturated ,α,α-disubstituted and base-sensitive aldehydes proceeded in high yields.

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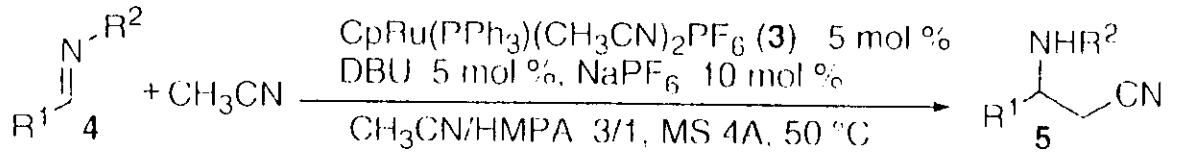
Direct Addition of Acetonitrile to Imines Catalyzed by $CpRu(PPh_3)(CH_3CN)_2PF_6$, DBU and $NaPF_6$



entry	R¹	R²		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

N-Boc and *N*-Dpp imines were transformed into β-amino nitriles in good yield.

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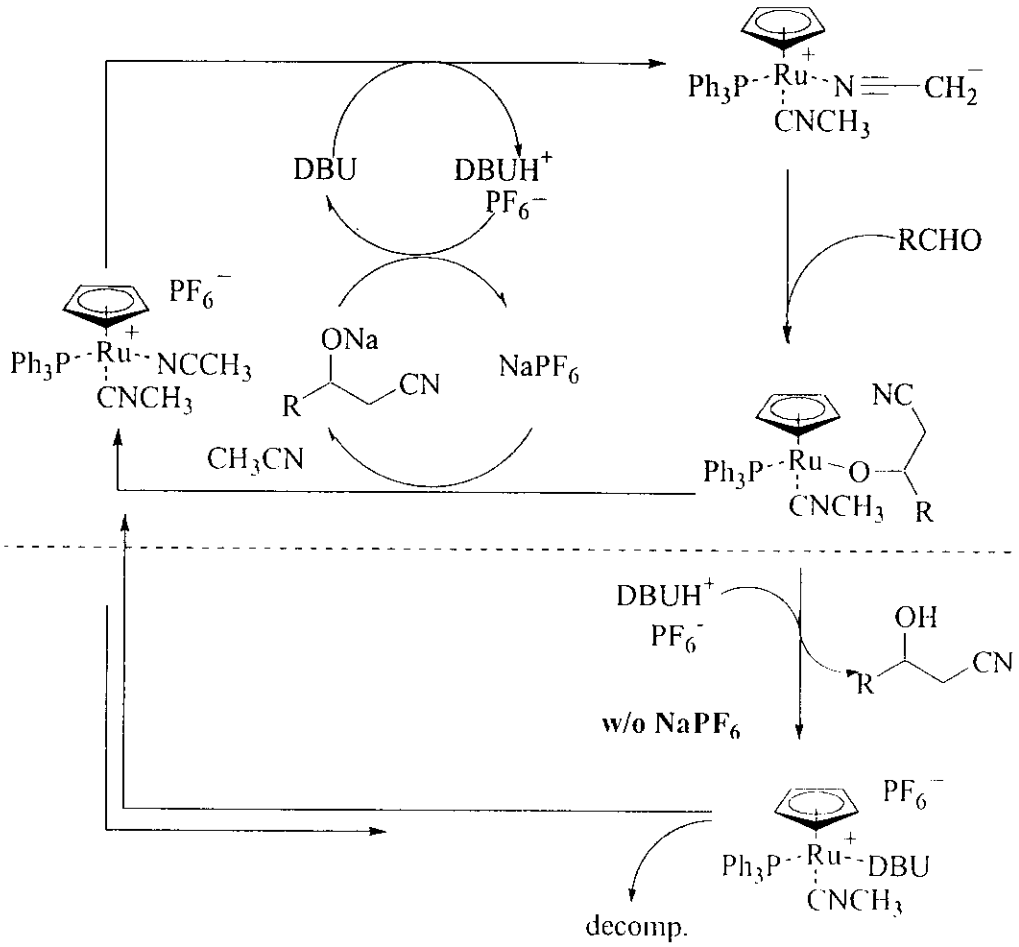
Proposed Catalytic Cycle



Kumagai,N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ASAP

Conclusion

- This paper demonstrates the direct addition of CH_3CN to aldehydes and imines via Ru complex, amine base and $NaPF_6$.

- Conditions are less harsh (less basic) relative to previous work in this area.

- Functional group compatibility.

- An enantioselective variant of this work is currently being explored along with further mechanistic studies.