Lewis Acid-Promoted Imine Synthesis by the Insertion of Isocyanides into C–H Bonds of Electron-Rich Aromatic Compounds

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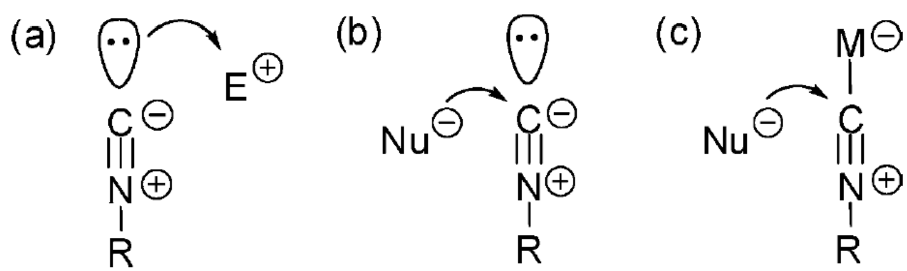
Chatani, N. *et al.*, *Org. Lett.* **2007**, *9*, 3351-3353

Ambiphilic Reactivity of Isocyanides

isocyanides

- Isocyanides possess unique reactivity due to the presence of a formally divalent carbon atom

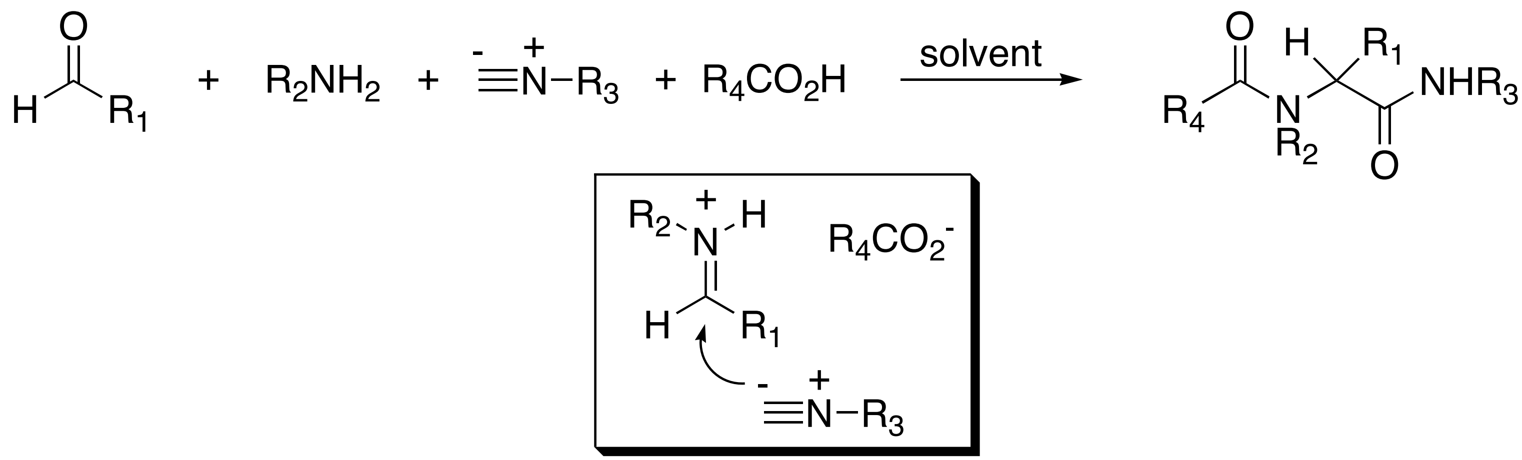


- Nucleophilic reactions dominate; electrophilic reactions commonly observed with strong nuclephiles

Domling, A., *Chem. Rev.* **2006**, *106*, 17-89

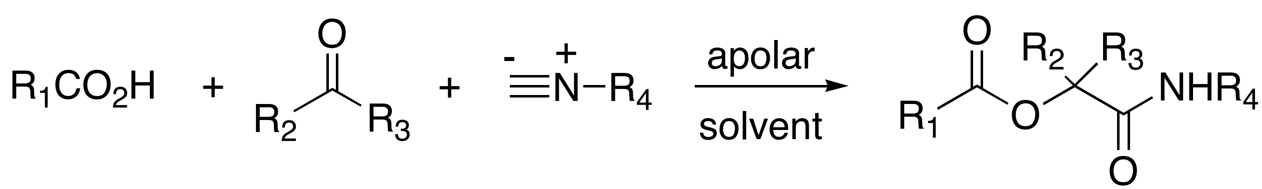
Isocyanides As Nucleophiles

Ugi Multicomponent Coupling Reaction



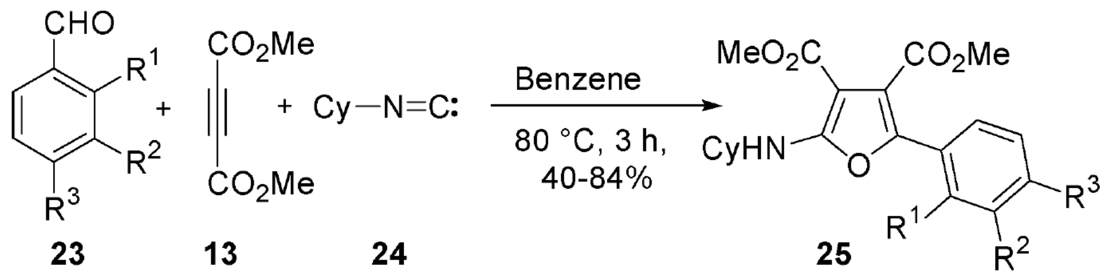
Ugi, I., *Pure Appl. Chem.* **2001**, *73*, 187-191

Passerini Reaction

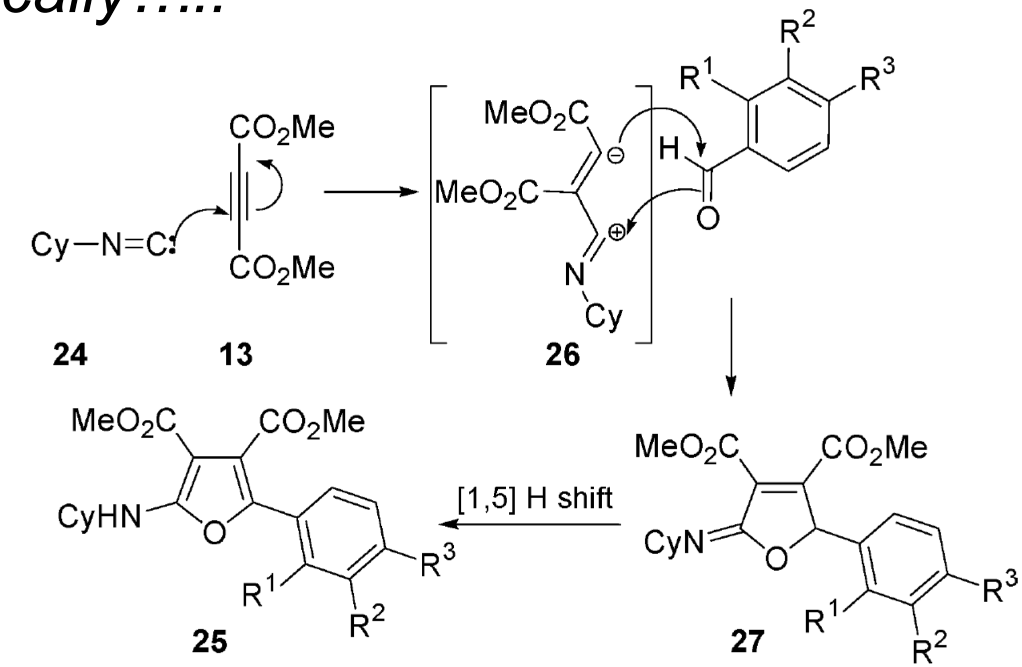


Ostaszewski, R. *et al.*, *Pure Appl. Chem.* **2003**, *75*, 413-419

Synthesis of substituted Furans

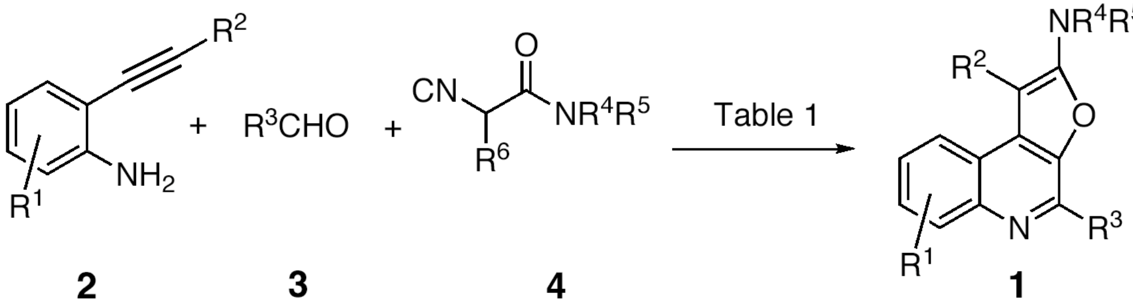


Mechanistically…..

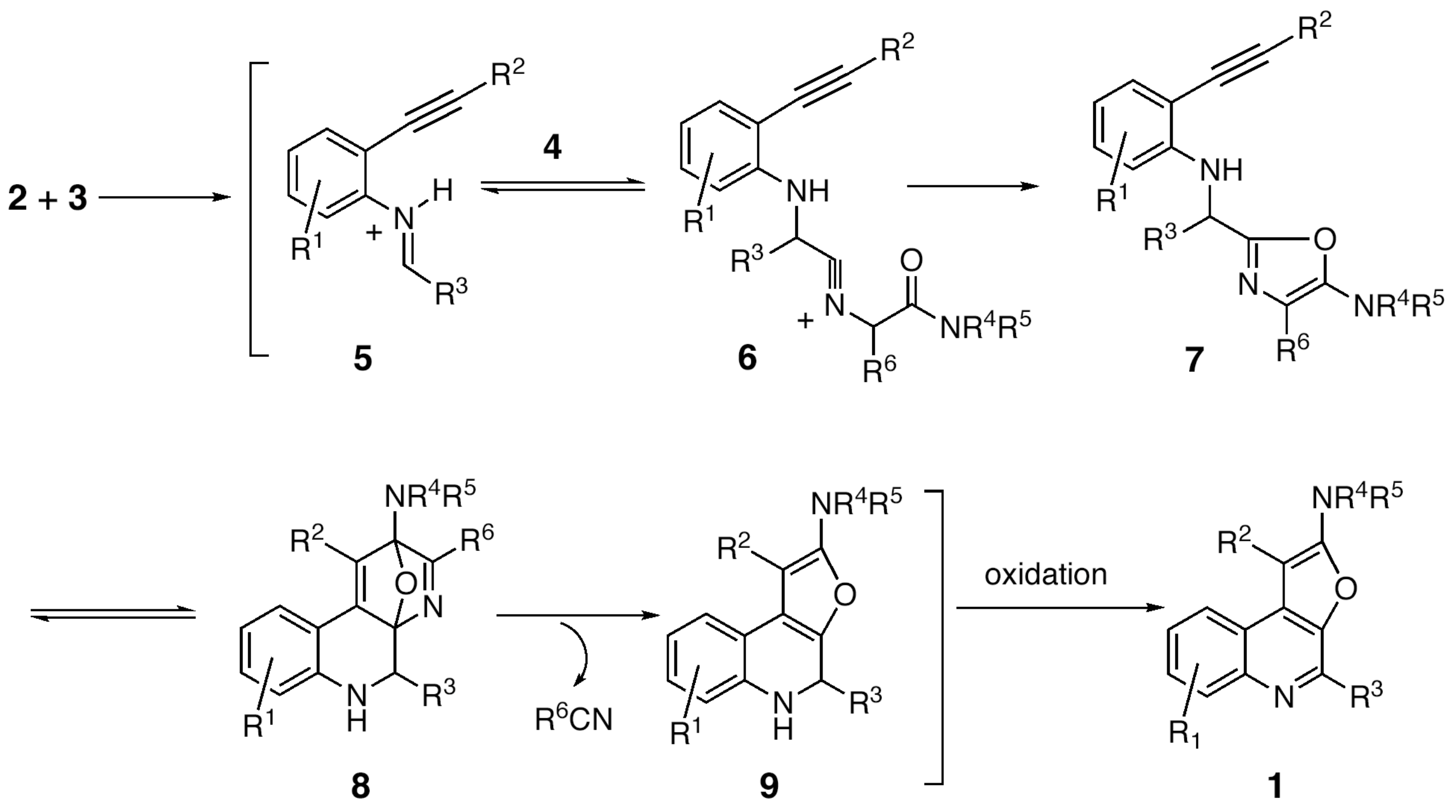


Nair, V.; Vinod, A. U., *Chem. Commun.* **2000**, 1019-1020

Synthesis of Highly Substituted Furo[2,3-c]quinolines



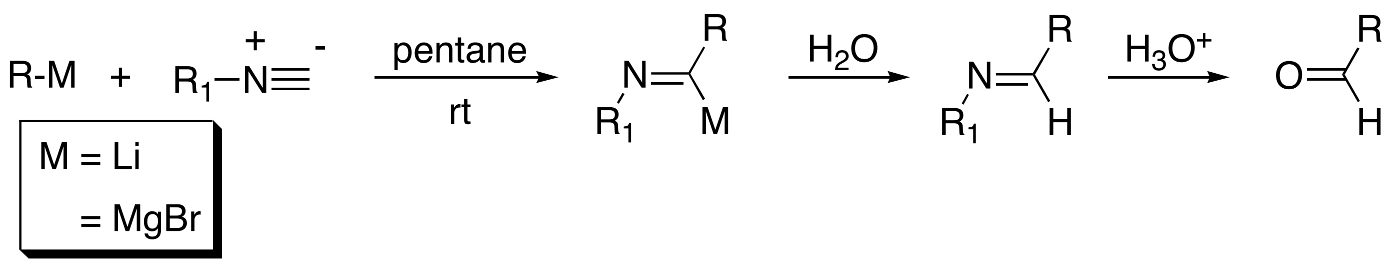
0.1 M in toluene
RT to reflux, 15 h



Zhu, J.; Fayol, A., *Angew. Chem. Int. Ed.* **2002**, 41, 3633-3635

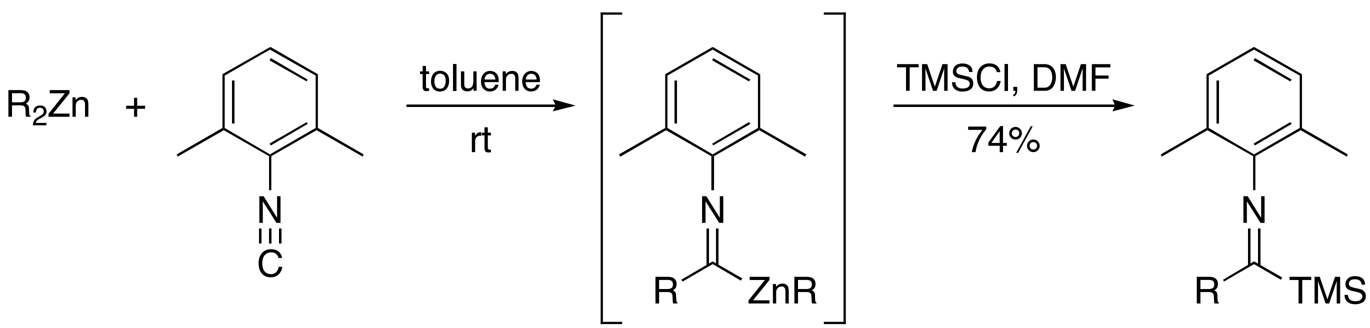
Isocyanides As Electrophiles

Addition of Alkyl Lithium and Alkyl Grignard Reagents



Walborsky, H. M. *et al.*, *J. Org. Chem.* **1974**, *39*, 600-604

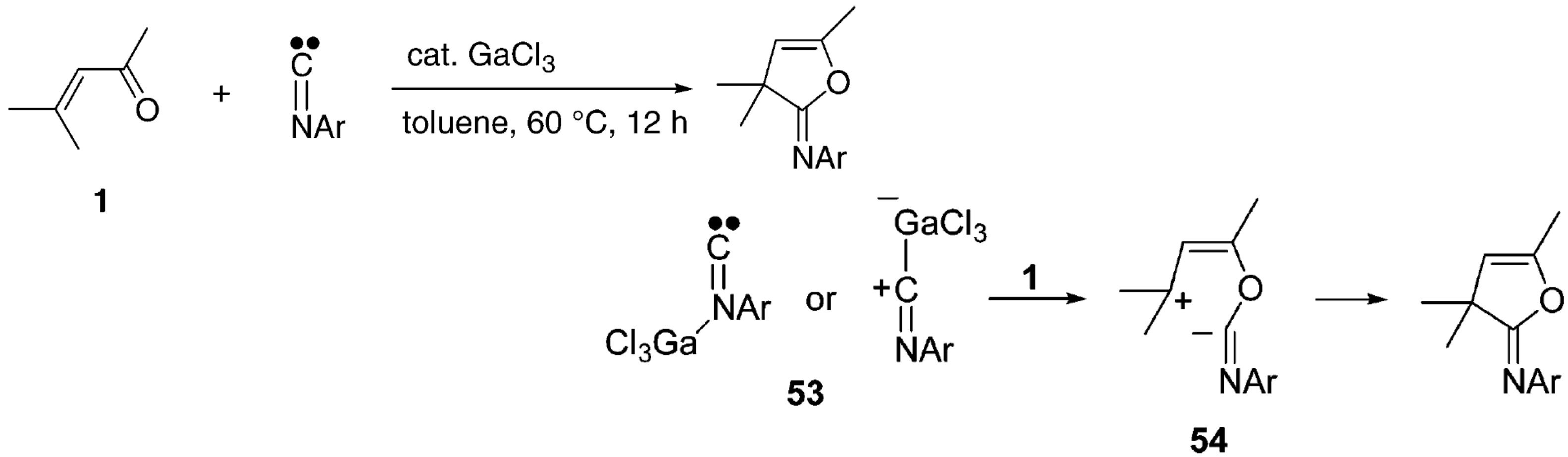
Addition of Dialkyl Zinc Reagents



Ito, Y. *et al.*, *J. Org. Chem.* **1988**, *53*, 4158-4159

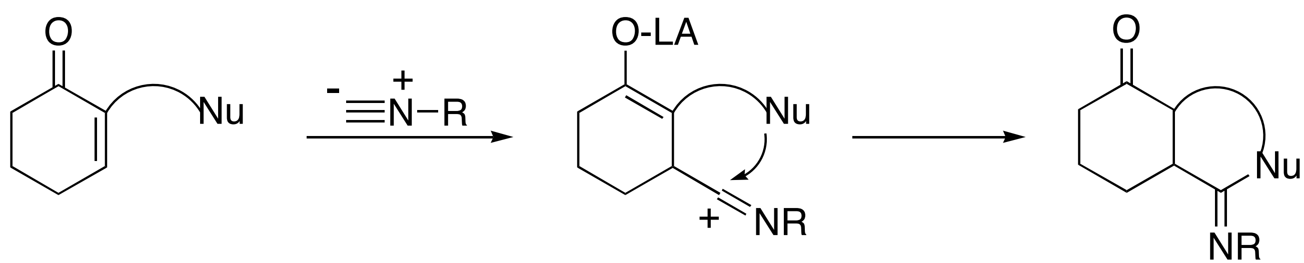
Isocyanides As Electrophiles

Activation with Lewis Acids: s-cis ketones



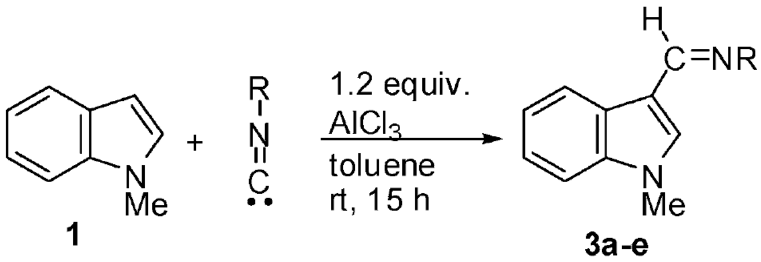
Chatani, N. *et al.*, *J. Am. Chem. Soc.* **2005**, *127*, 761-766

Activation with Lewis Acids: s-trans ketones



Winkler, J. D.; Asselin, S. M., *Org. Lett.* **2006**, *8*, 3975-3977

Initial Experiments

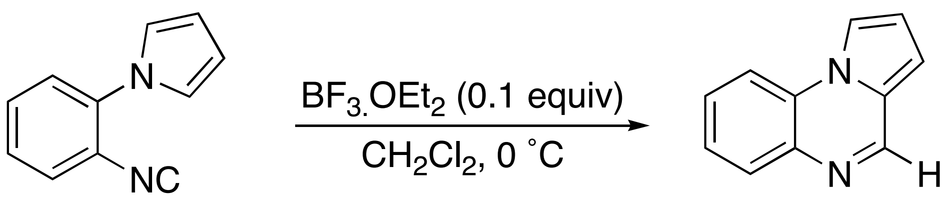


R = 2,6-$Me_2C_6H_3$ (**2a**)	88%
3,5-$Me_2C_6H_3$ (**2b**)	68%
4-$MeOC_6H_4$ (**2c**)	79%
4-ClC_6H_4 (**2d**)	64%
benzyl (**2e**)	82%

1 + **2a** —(lewis acid / PhMe, rt)→ **3a**

entry	lewis acid	yield (%)
1	$BF_3.OEt_2$	68
2	$GaCl_3$	86
3	$In(OTf)_3$	90

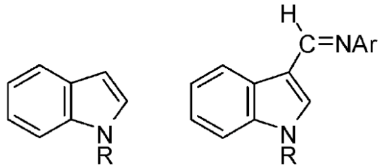
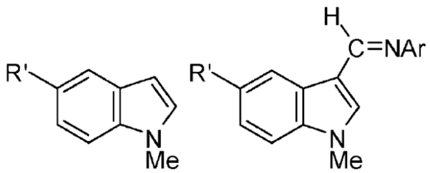
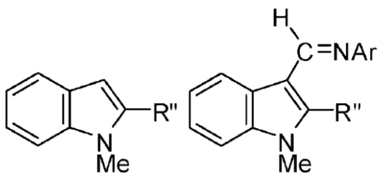
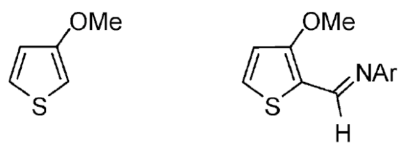
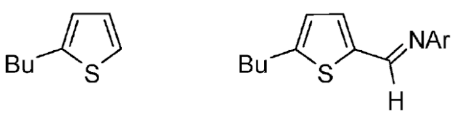
- A formal insertion of the isocyanide into the aromatic C-H bond
- Group 13 elements: excellent promoters
- Intermolecular reaction is unprecedented



Kobayashi, K., *et al.*, *Chem. Lett.* **1998**, 9, 551-552

Chatani, N. *et al.*, *Org. Lett.* **2007**, *9*, 3351-3353

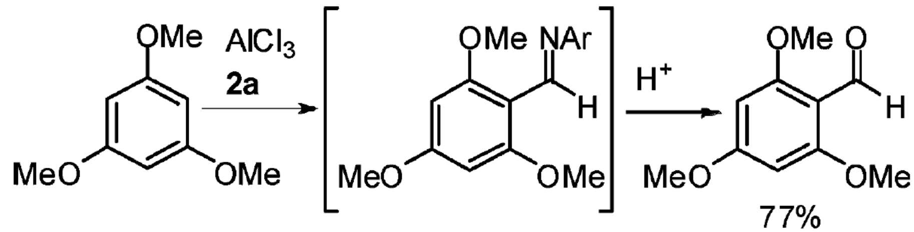
Substrate Scope

entry	aromatics / product[b]		yield (%)[c]	
1		R = Me	88	
2		R = CH_2Ph	81	
3		R = 4-MeC_6H_4	93	
4		R = H	78	
5		R' = Me	76	
6		R' = Ph	73	
7		R' = OMe	80	
8		R' = Br	89	
9		R' = CO_2Me	83	
10[d]		R" = Me	85	run at 60 ˚C
11		R" = Ph	92	
12			84[e]	+ 3-subst. isomer (6%)
13			78	
14[d]			82	run at 60 ˚C

Ar = 2,6-dimethylphenyl

> Heterocycle (1.0 mmole)
> Isocyanide (1.2 mmole)
> $AlCl_3$ (1.2 mmole),
> toluene, rt, 15 h

Scheme 2



- $AlCl_3$-mediated insertion exhibits a wide substrate scope
- Electron withdrawing groups on indole: *not* tolerated

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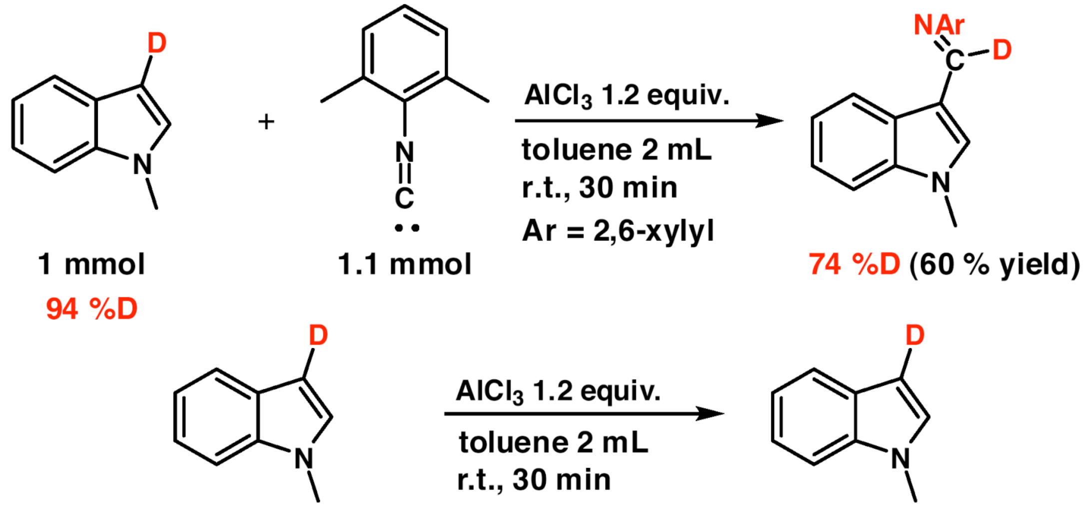
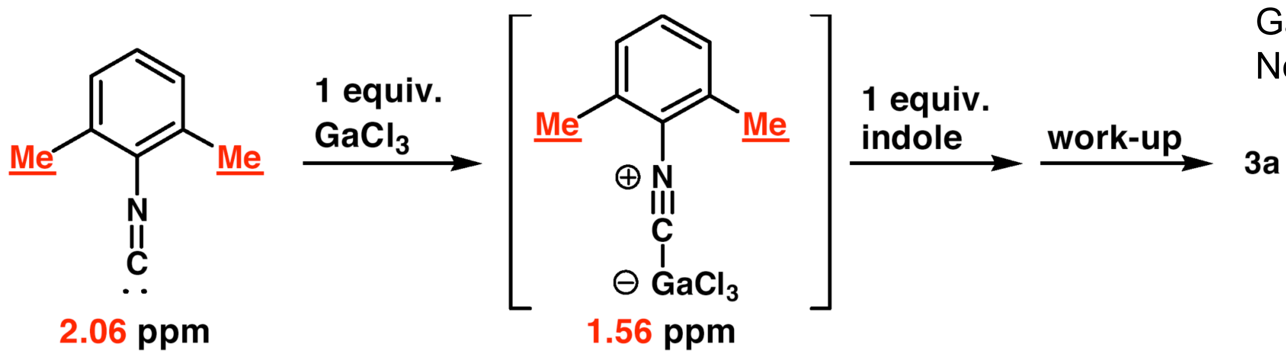
Labeling Experiments



- H at C-3 is transferred to the imino carbon in the product

^{1}H-NMR experiment with $GaCl_3$



$GaCl_3$: more soluble in Non-polar solvents

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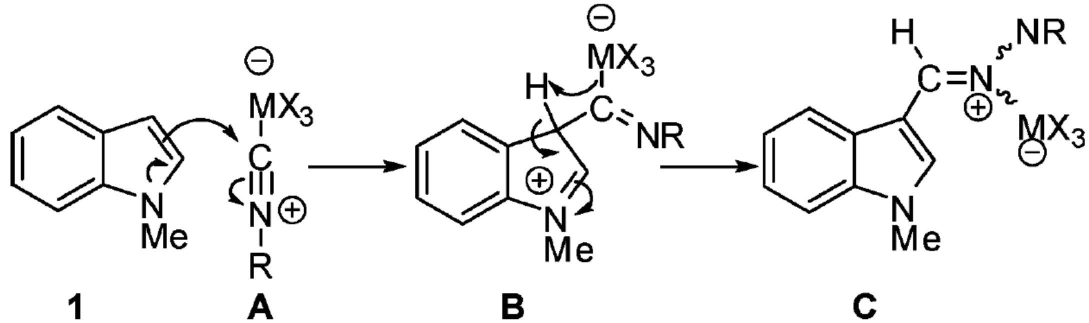
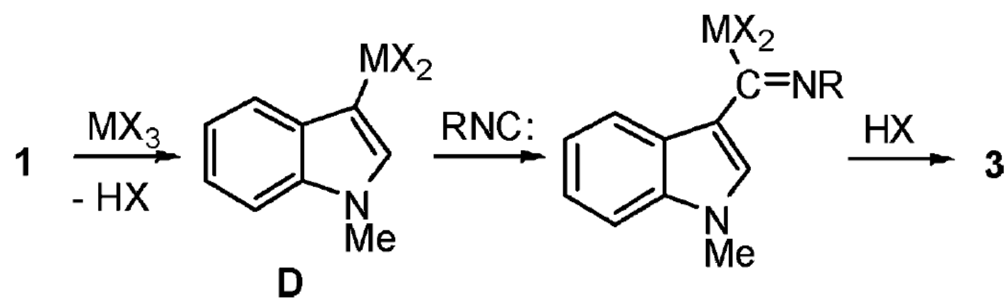
Proposed Mechanism

Scheme 3



Nucleophilic attack of the indole onto LA-activated isocyanide
Rearomatization *via* deprotonation and protonolysis of C-M bond

Alternative Mechanism



- Treatment of a solution of indole + isonitrile with LA: no interaction between indole and LA

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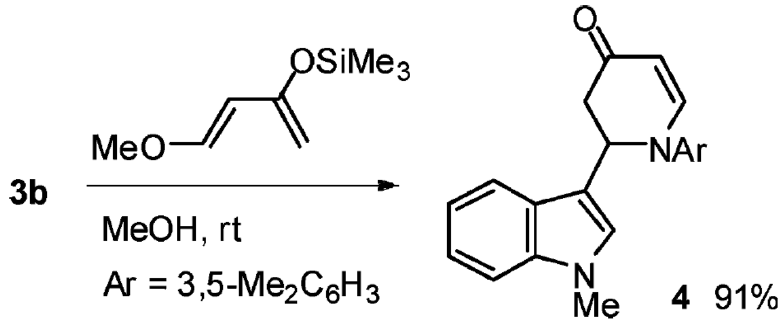
Further Structural Elaboration

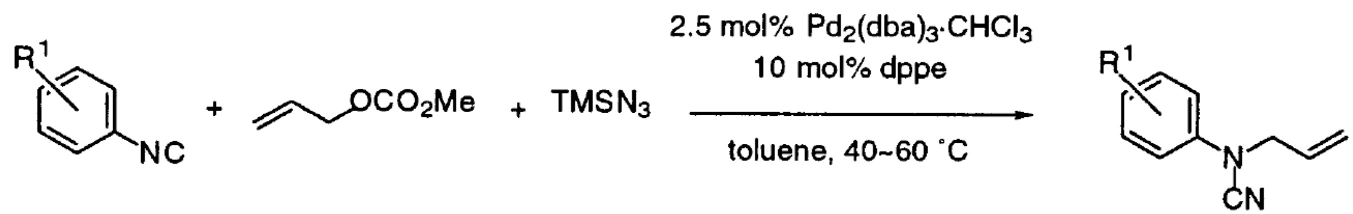


Conclusions

- A novel protocol for the α-addition of isocyanides to aromatic compounds promoted by inexpensive LAs has been developed
- This method provides a direct and practical access to a wide variety of imines via aromatic C-H bond functionalization
- Ongoing research seeks to explore this new isocyanide insertion process into other chemical bonds

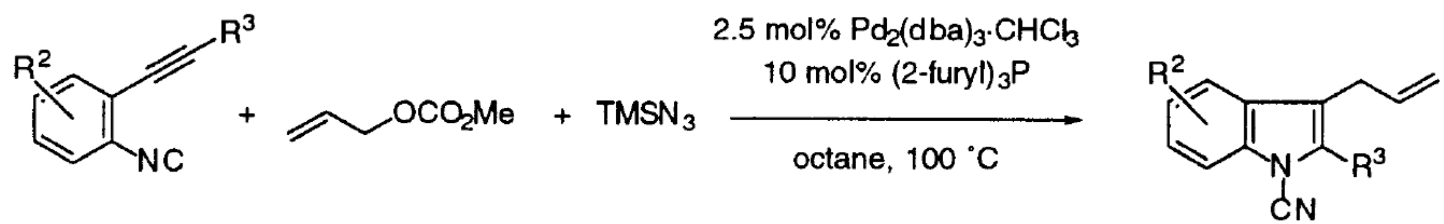
Isocyanides: Metal-Mediated MCRs

Synthesis of allyl aryl cyanamides



1 → 2

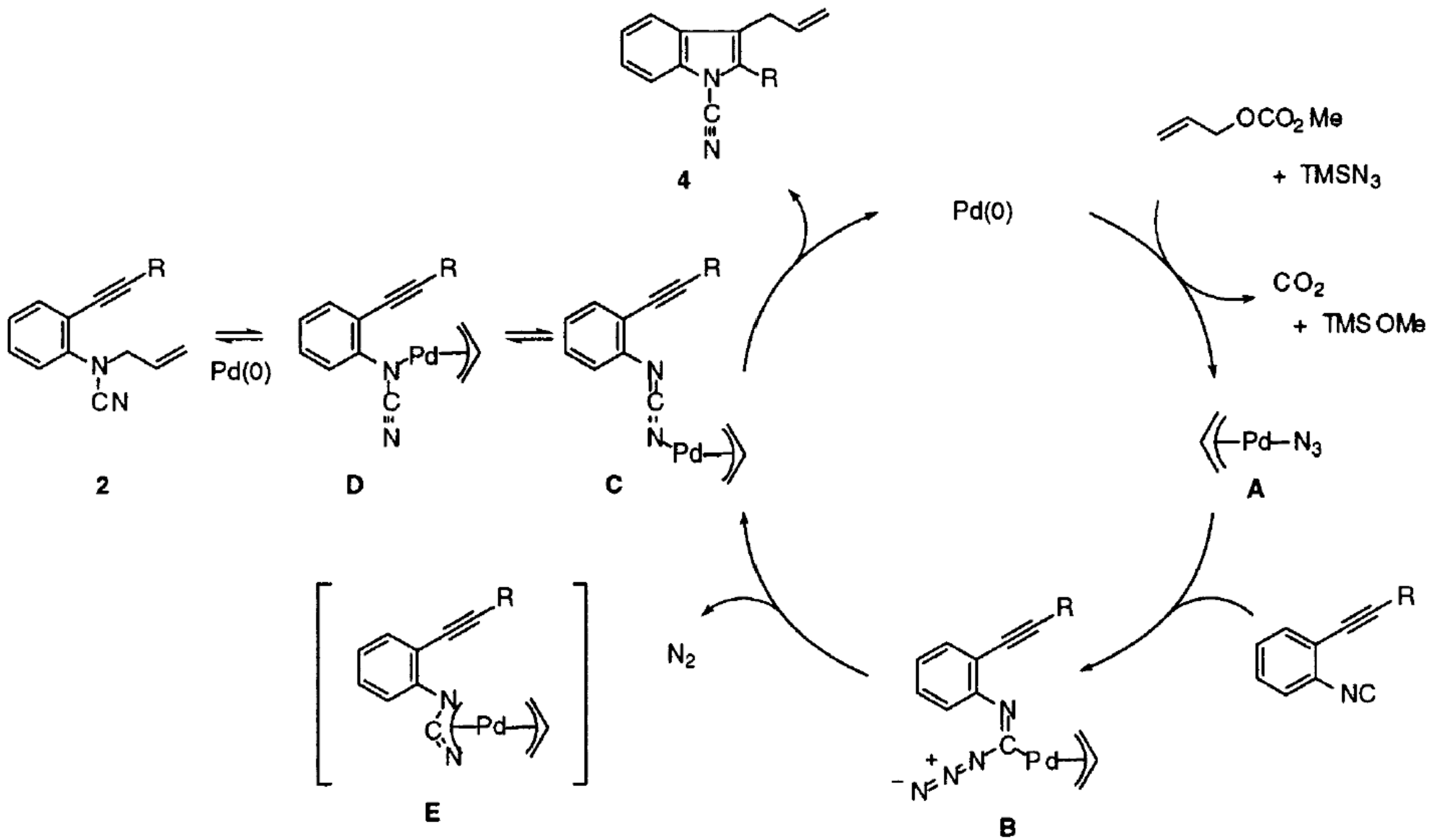
Synthesis of N-cyanoindoles



3 → 4

Kamijo, S.; Yamamoto, Y., *J. Am. Chem. Soc.* **2002**, *124*, 11940-11945

Mechanism of the formation of *N*-cyanoindoles



Kamijo, S.; Yamamoto, Y., *J. Am. Chem. Soc.* **2002**, *124*, 11940-11945