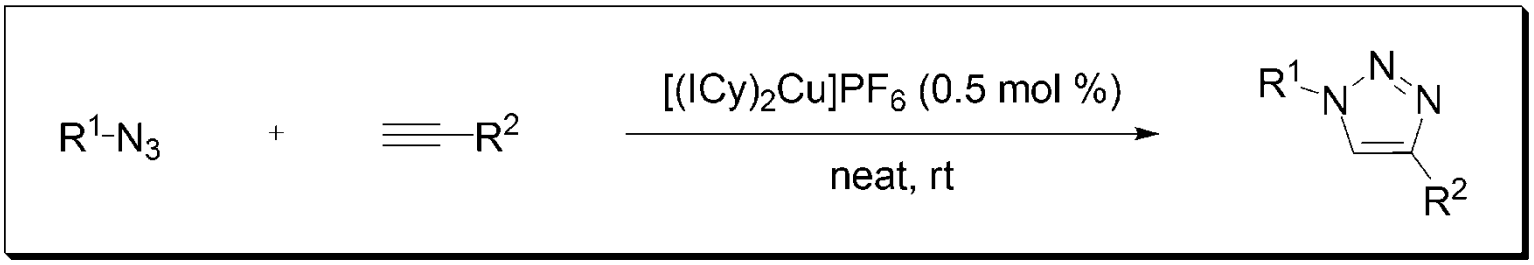
$[(NHC)_2Cu]X$ Complexes as Efficient Catalysts for Azide-Alkyne Click Chemistry at Low Catalyst Loadings

Silvia Diez-Gonzalez* and Steven P. Nolan*

Angewandte Chemie Int. Ed. **2008**, Early Veiw



Nolan Griggs
Current Literature Report - 10-18-2008

Click Chemistry - Overview

Overall Goal: "... to develop an expanding set of powerful, selective, and modular "blocks" that work reliably in both small- and large scale applications."

The criteria for an effective "click" reaction:

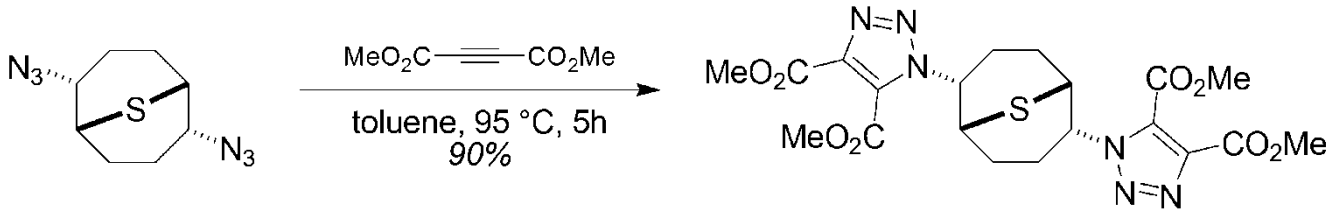
- Modular
- Wide in scope
- Very high yielding
- Generates easily removed, inoffensive byproducts
- Stereospecific (but not necessarily enantioselective)
- Simple reaction conditions (not sensitive to O_2 or H_2O)
- Uses readily available starting materials
- Run neat (or in a benign solvent such as H_2O)
- Simple product purification - no chromatography (i.e. crystallization, distillation, etc.)

To achieve these required characteristics, there must be a high thermodynamic driving force (usually > 20 kcal/mol).

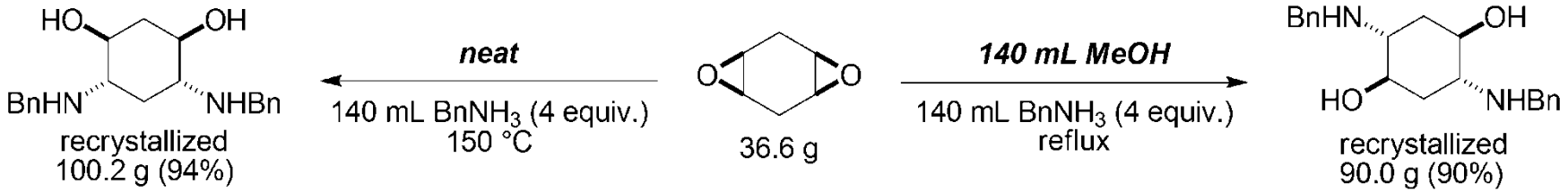
Reveiw: Sharpless, K.B.; Finn, M.G.; Kolb, H.C. *Angew Chem. Int. Ed.* **2001**, 40, 2004-2021.

Click Chemistry - Common Examples

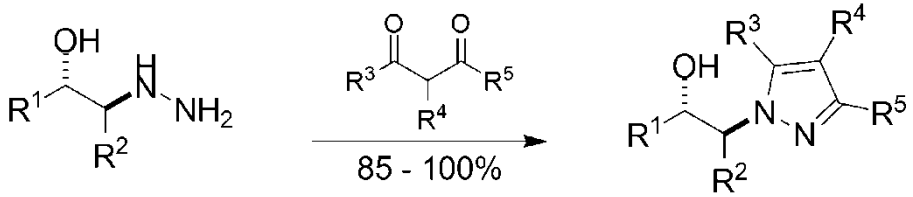
- Cycloadditions of unsaturated species - 1,3-dipolar cycloadditions, Diels - Alder



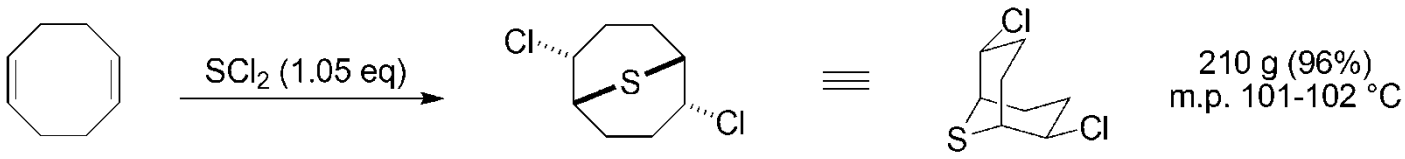
- Nucleophilic substitution chemistry - particularly ring-opening of strained heterocyclic electrophiles



- "Non-aldol" carbonyl chemistry - formation of ureas, aromatic heterocycles, oxime ethers, hydrazones



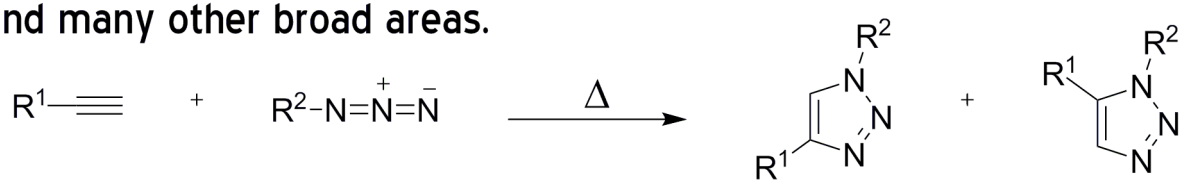
- Additions to C-C multiple bonds - epoxidation, aziridination, dihydroxylation, Michael additions of Nu-H reagents



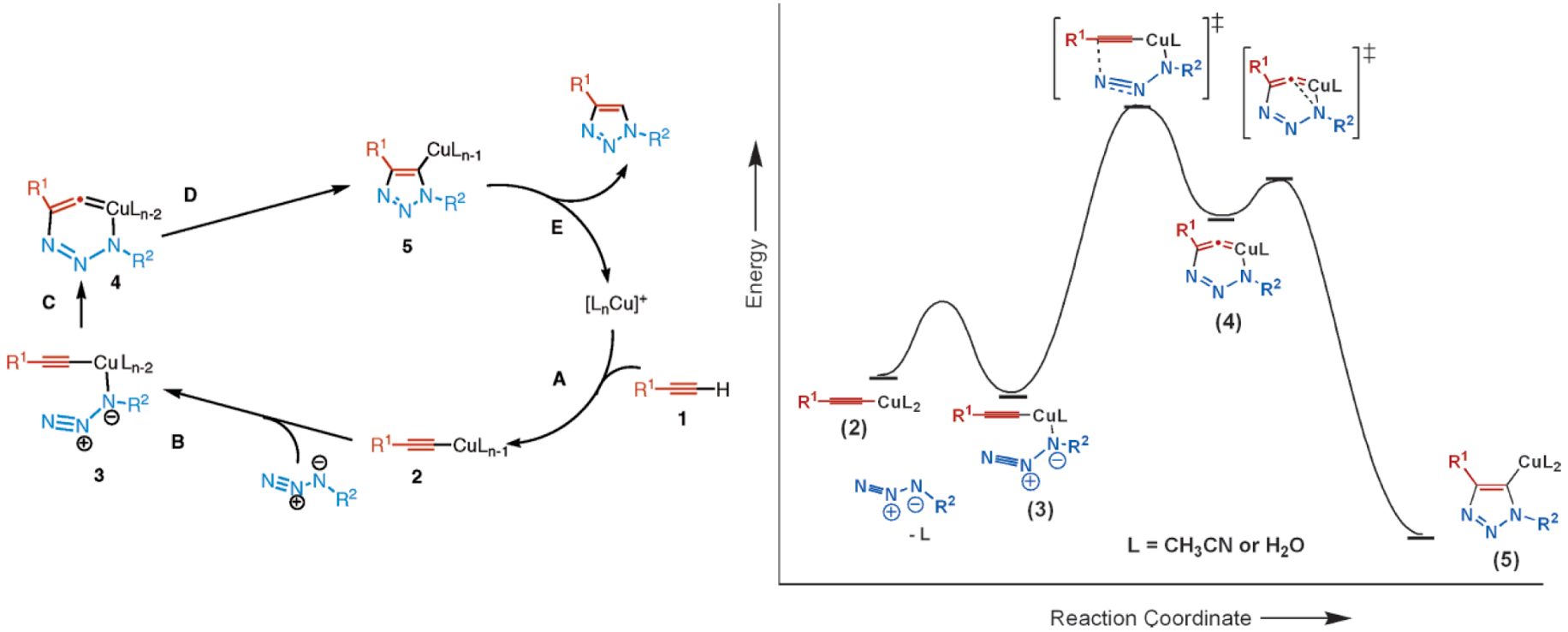
Sharpless et al. J. Org. Chem. 2001, 66, 4386-4392

1,3-dipolar Huisgen Cycloaddition

- Most widely used "click" reaction. Found applications in drug discovery, materials science, biotechnology, and many other broad areas.



- In 2002, it was found that regioselectivity could be controlled through the use of Cu(I) salts.[1] In 2004, DFT studies gave further insight into the mechanism.[2]

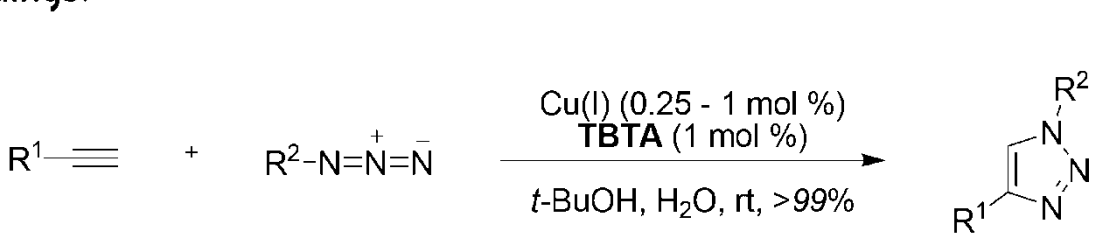


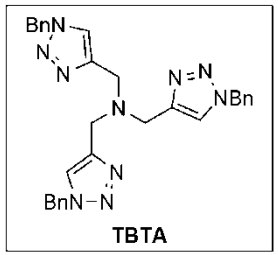
1. Sharpless, K.B. et al. *Angew. Chem. Int. Ed.* **2002**, 41(14), 2596.
2. Sharpless, K.B. et al. *J. Am. Chem. Soc.* **2004**, 127, 210.

Cu(I)-ligand Studies on the Huisgen Cycloaddition

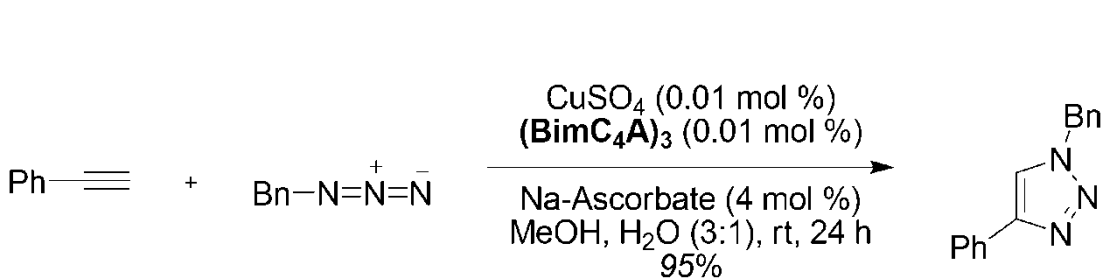
- The main benefit of having a ligand on copper would be stabilizing the oxidation state of copper throughout the reaction, thus allowing for lower catalyst loadings and cleaner reactions.

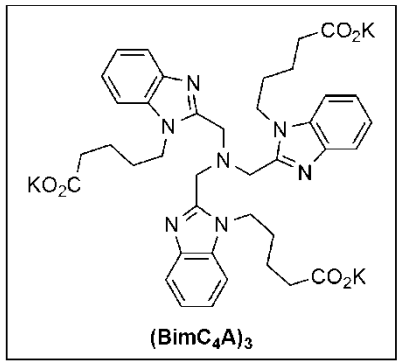
- Several well-defined catalyst systems have been developed with some interest in lower catalyst loadings:



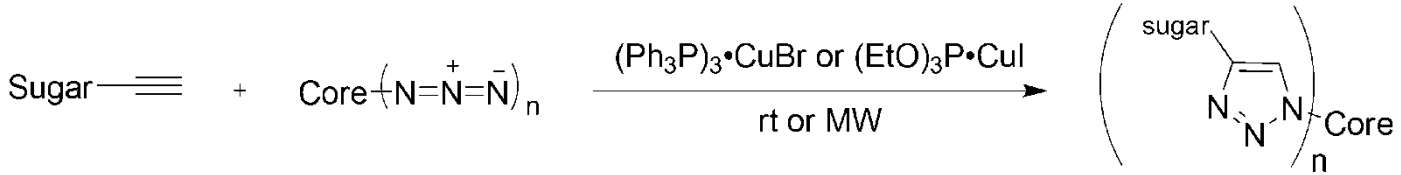


Sharpless K.B. et al. *Org. Lett.* **2004**, 6(17), 2853.



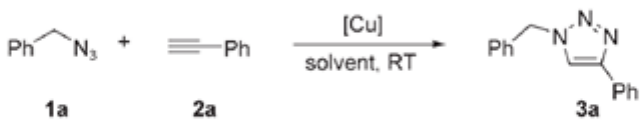


Finn, M.G. et al. *J. Am. Chem. Soc* **2007**, 129, 12696.



Santoyo-Gonzalez et al. *Org. Lett.* **2003**, 5(11), 1951.

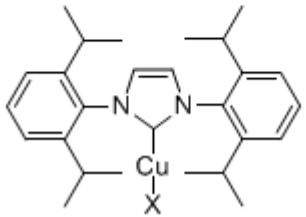
Use of (NHC)CuX Catalysts



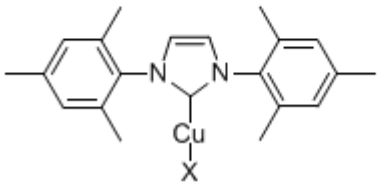
1a 2a 3a

Entry	[Cu] (mol%)	Solvent [mL]	t [h]	Yield [%]
1	[(IPr)CuCl] (5)	water/*t*BuOH (3)	18	18
2	[(IMes)CuCl] (5)	water/*t*BuOH (3)	18	65
3	[(SIMes)CuCl] (5)	water/*t*BuOH (3)	18	93
4	[(SIMes)CuBr] (5)	water/*t*BuOH (3)	9	95
5	[(SIMes)CuBr] (5)	water (1)	0.5	98
6	[(SIMes)CuBr] (0.8)	neat	0.3	98
7	CuBr	neat	1	0

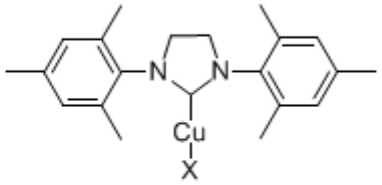
[a] Isolated yields are the average of at least two runs.



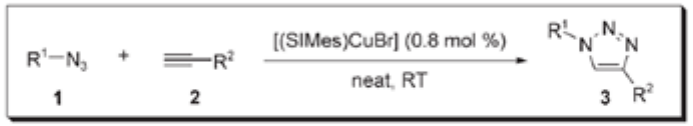
(IPr)CuCl



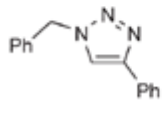
(IMes)CuCl



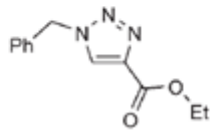
(SIMes)CuCl



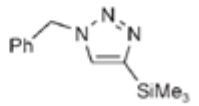
1 2 3



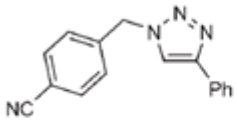
3a, 20 min, 98%



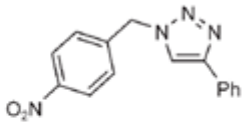
3b, 2 h, 91%



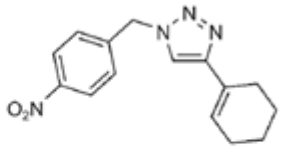
3c, 45 min, 98%[a]



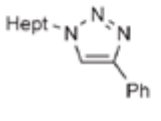
3d, 30 min, 93%



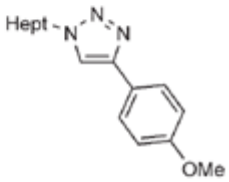
3e, 45 min, 89%



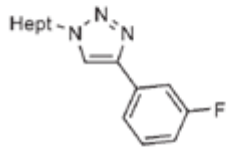
3f, 1.5 h, 93%



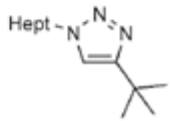
3g, 25 min, 93%



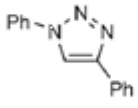
3h, 15 min, 93%



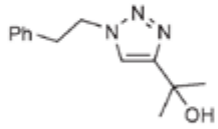
3i, 10 min, 89%



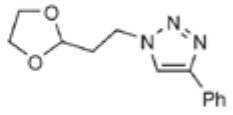
3j, 5 h, 95%[b]



3k, 1.5 h, 86%



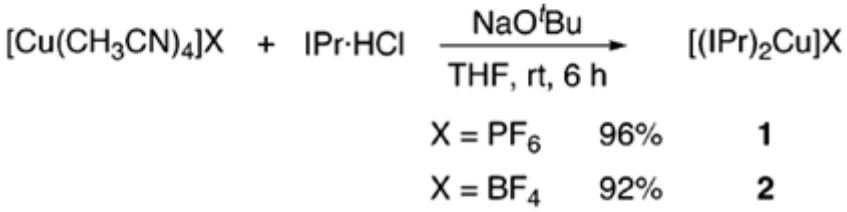
3l, 4 h, 94%[b]

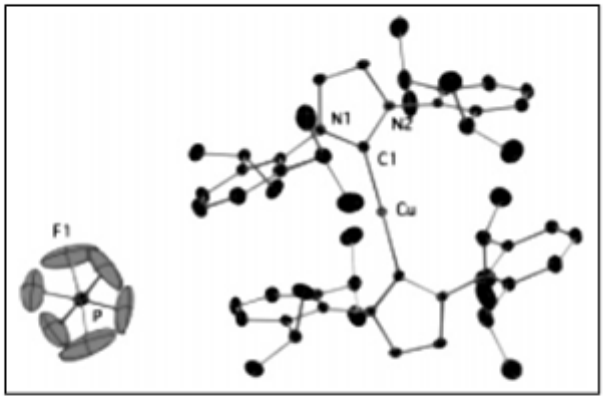


3m, 1 h, 92%

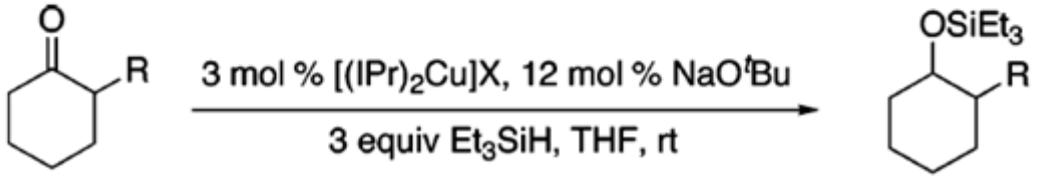
Nolan, S.P. et al. *Chem Eur. J.* **2006**, 12, 7558-7564.

New Cationic Copper (I) Complexes: $[(NHC)_2Cu]X$





$[(IPr)_2Cu]PF_6$, 1

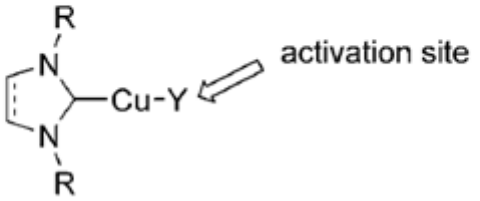


		R = H	R = Me
$[(IPr)_2Cu]\ PF_6$	**1**	2 h, 97%	6 h, 92% (*trans:cis* = 90:10)
$[(IPr)_2Cu]\ BF_4$	**2**	0.5 h, 98%	3 h, 90% (*trans:cis* = 85:15)

- Showed increased activity for the hydrosilation of carbonyl compounds to previous catalysts of type (NHC)CuX.

Nolan S.P. et al *Organometallics* **2006**, 25, 2355.

Title Paper: Inception and Catalyst Screen

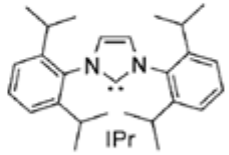


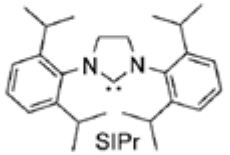
activation site

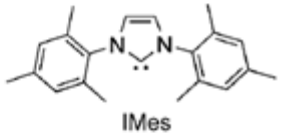
ketone hydrosilylation ⇨ Y = Cl, Y = NHC — Ref. 14, Ref. 13 — improved performance

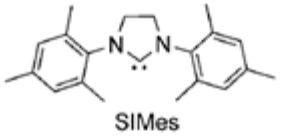
[3+2] cycloaddition ⇨ Y= Cl, Br, Y = NHC — Ref. 9, this study — ?

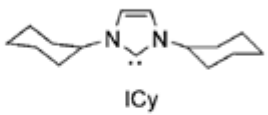
NHC =

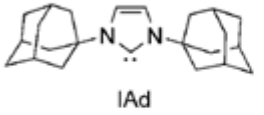


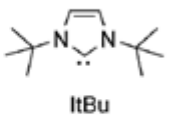


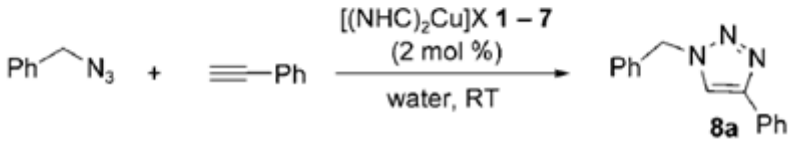






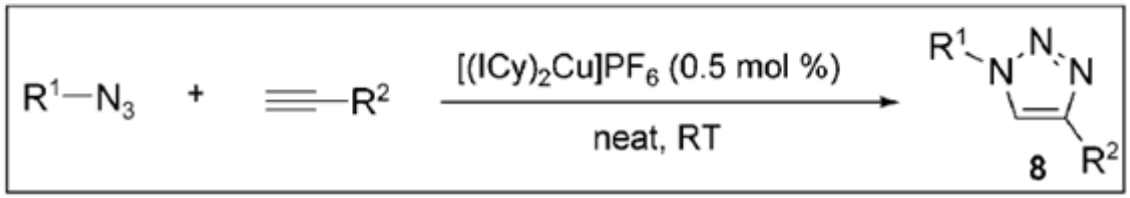


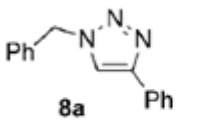




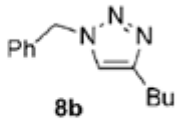
$[(NHC)_2Cu]PF_6$		t [h]	Conv. [%][a]	$[(NHC)_2Cu]BF_4$		t [h]	Conv. [%][a]
$[(IPr)_2Cu]PF_6$	**1a**	18	71	$[(IPr)_2Cu]BF_4$	**1b**	8	100
$[(SIPr)_2Cu]PF_6$	**2a**	5	100	$[(SIPr)_2Cu]BF_4$	**2b**	5	100
$[(IMes)_2Cu]PF_6$	**3a**	6	100	$[(IMes)_2Cu]BF_4$	**3b**	6	100
$[(SIMes)_2Cu]PF_6$	**4a**	18	5	$[(SIMes)_2Cu]BF_4$	**4b**	18	13
$[(ICy)_2Cu]PF_6$	**5a**	1.5	99	$[(ICy)_2Cu]BF_4$	**5b**	5	95
$[(IAd)_2Cu]PF_6$	**6a**	5	100	$[(IAd)_2Cu]BF_4$	**6b**	3	100
$[(ItBu)_2Cu]PF_6$	**7a**	18	76	$[(ItBu)_2Cu]BF_4$	**7b**	18	35

Reaction Scope

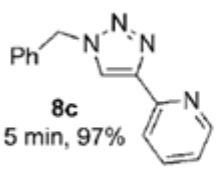




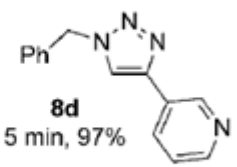
8a
5 min, 99%



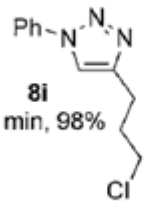
8b
45 min, 93%



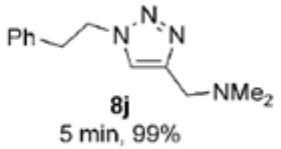
8c
5 min, 97%



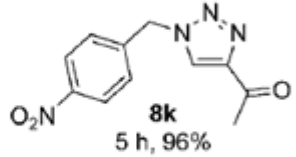
8d
5 min, 97%



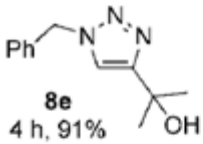
8i
25 min, 98%



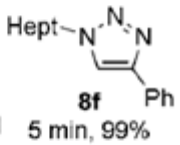
8j
5 min, 99%



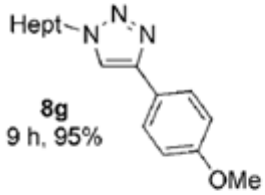
8k
5 h, 96%



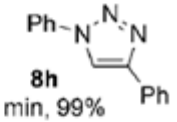
8e
4 h, 91%



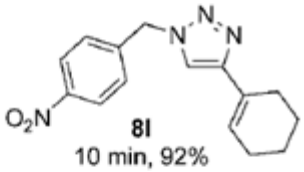
8f
5 min, 99%



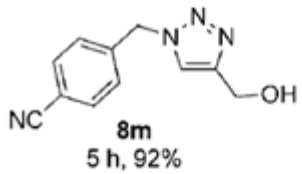
8g
9 h, 95%



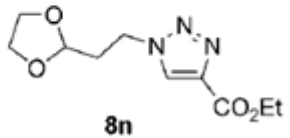
8h
5 min, 99%



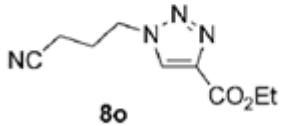
8l
10 min, 92%



8m
5 h, 92%

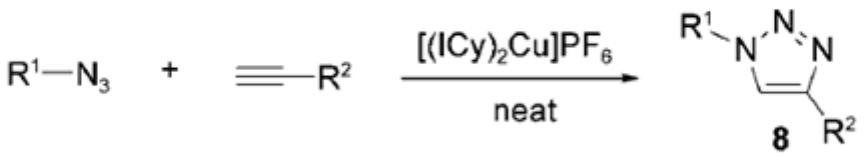


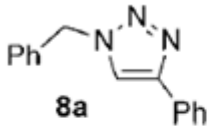
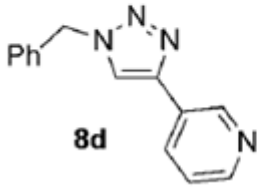
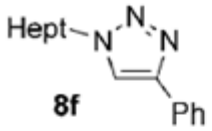
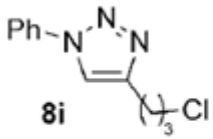
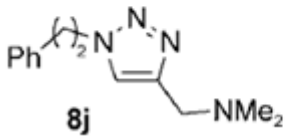
8n
7 h, 96%



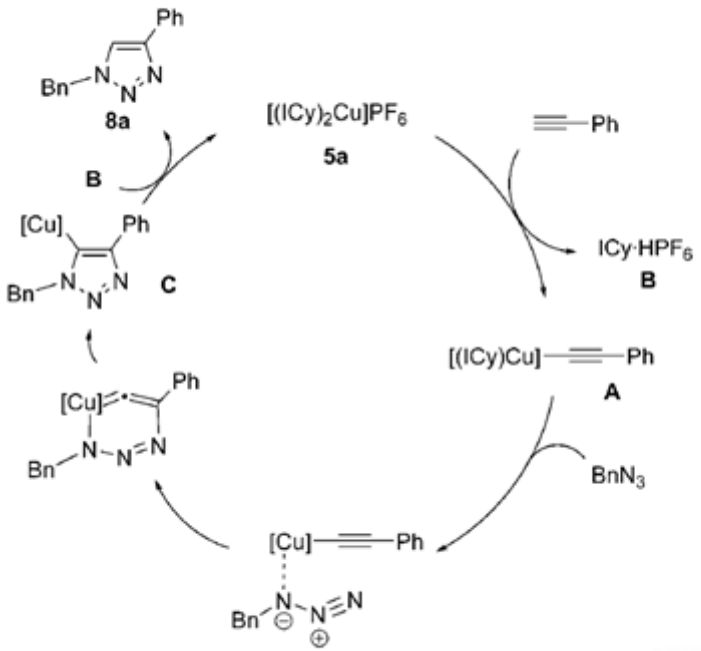
8o
7 h, 96%

Examining the Catalyst Loading



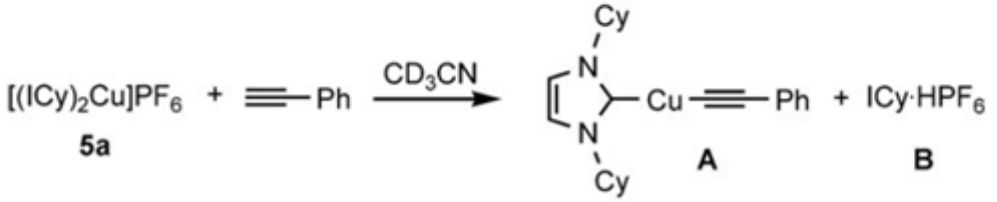
8	T [°C]	[Cu] [ppm]	t [h]	Conv. [%][a]	TON
 8a	RT	50	48	80	16000
	40	50	8	89	17800
	50	40	4	81	20250
 8d	RT	75	6	91	12133
 8f	RT	200	20	72	3600
 8i	RT	300	43	85	2833
	40	100	18	70	7000
 8j	RT	300	40	45	1500
	40	100	18	71	7100

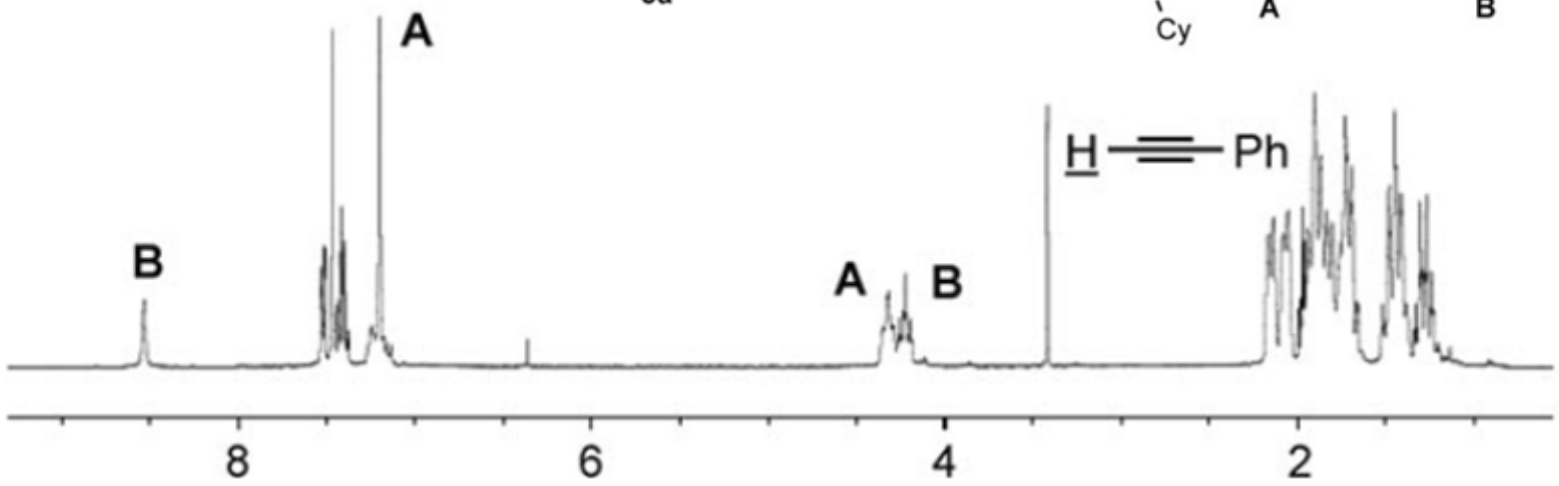
Mechanistic Considerations



Scheme 3. Postulated mechanism. Bn = benzyl.

- Both A and B were isolated and unambiguously assigned. For comparison, the analogous structures for the IPr-series were also made in a similar fashion and compared with the known data.
- Therefore, it appears one of the ligands is serving as a base in the reaction to form the requisite copper acetylide!
- When pure A and pure B were treated with one another, pure triazole product was obtained, along with the regeneration of the precatalyst.





Conclusions

- $[(NHC)_2Cu]X$ Complexes serve as efficient catalysts for azide-alkyne "Click" chemistry.
- Along with high yields, the reaction can be performed in the absence of solvent with a large reaction scope.
- In one case, catalyst loading was dropped to 40 ppm to give the product with a TON above 20,000 and a turnover frequency of 5000/h.
- Preliminary mechanistic studies indicate the role of one ligand to serve as the base for acetylenic deprotonation in the catalytic cycle.