



CaC₂/TBAF: Application in Sonogashira Coupling Reaction

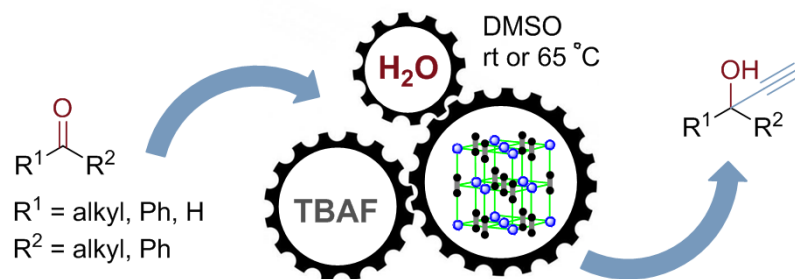
Abolfazl Hosseini

9.10.2015

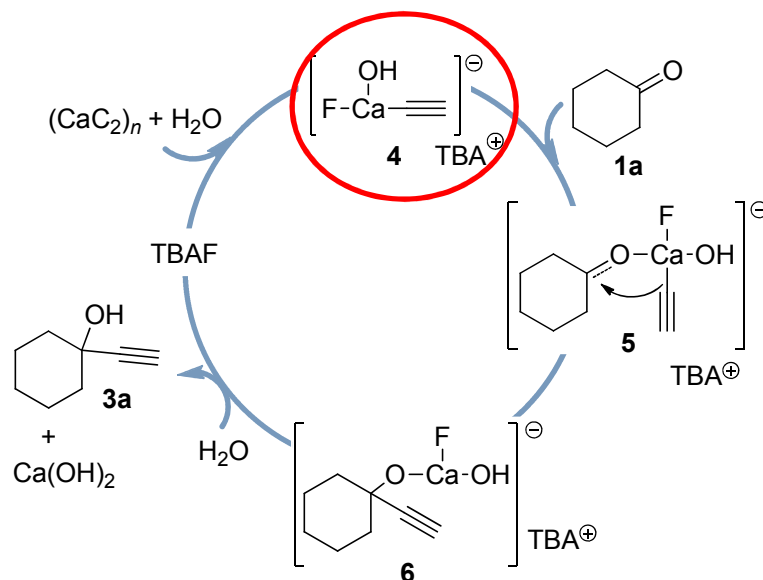
Institut für Organische Chemie Giessen

Previous work:

Fluoride-assisted activation of calcium carbide: A simple method for the ethynylation of aldehydes and ketones

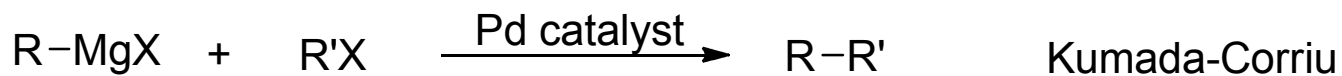
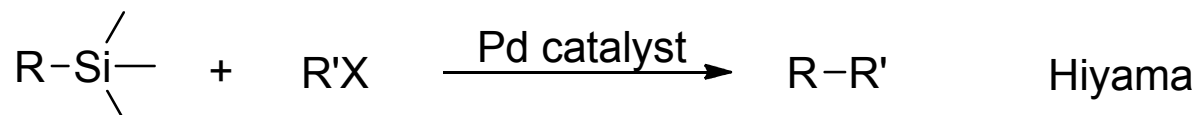


Suggested mechanism for the fluorine catalyzed ethynylation of aldehydes and ketones with CaC_2



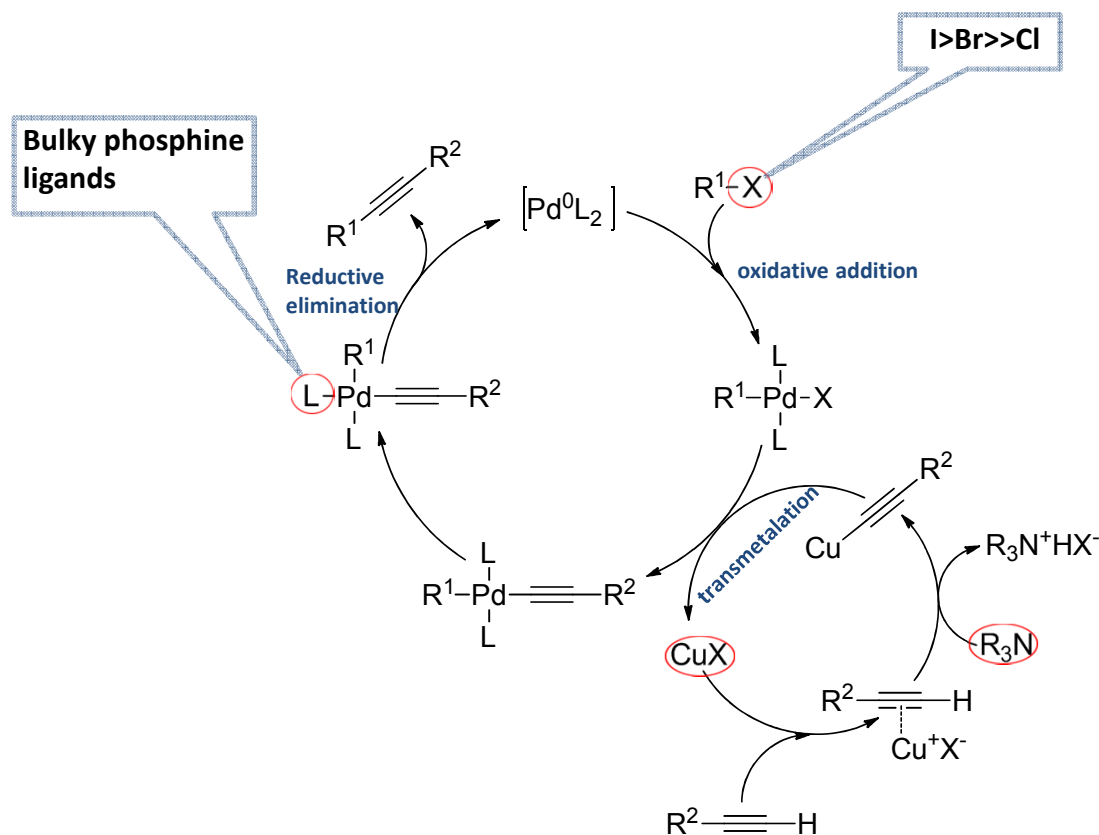
Ref: Hosseini, A.; Seidel, D.; Miska, A.; Schreiner, P. R. *Org. Lett.* **2015**, 17, 2808.

Cross coupling reactions



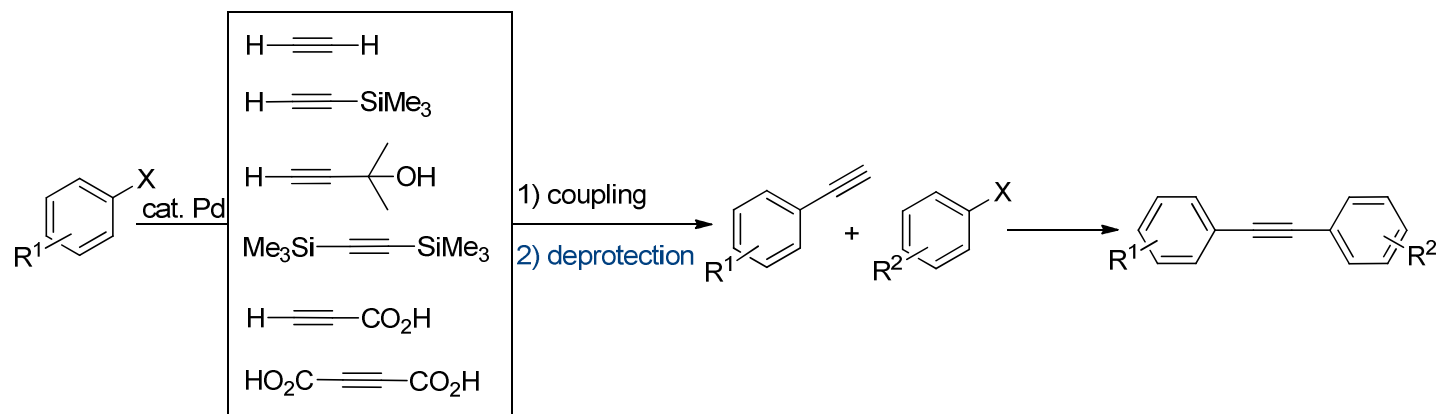
Sonogashira coupling reaction

First reported in 1975 by Sonogashira.

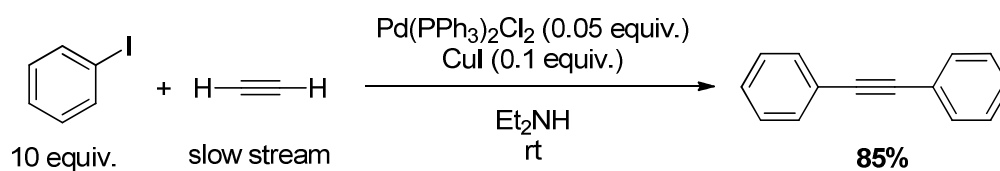


- (1) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.* **1975**, 16, 4467. (2) Fauvarque, J. F.; Pfluger, F.; Troupel, M. *J. Organomet. Chem.* **1981**, 208, 419.
 (3) Amatore, C.; Pfluger, F. *Organometallics* **1990**, 9, 2276. (4) Portnoy, M.; Milstein, D. *Organometallics* **1993**, 12, 1665.

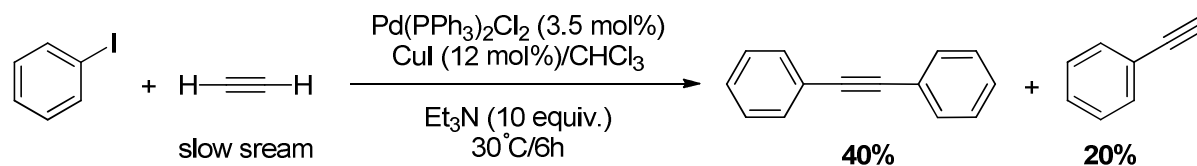
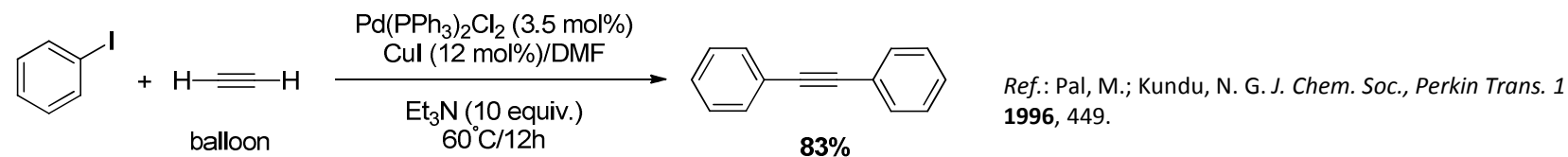
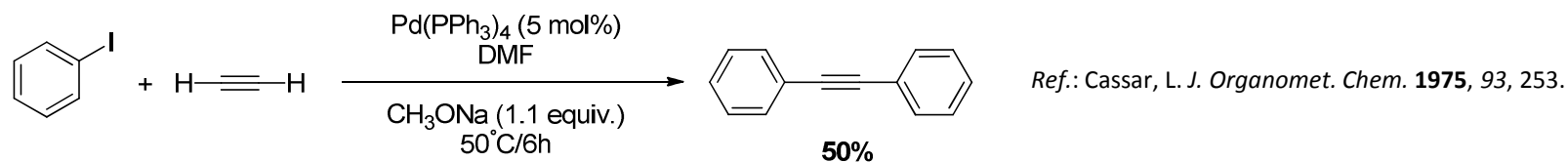
Synthesis of symmetrical and unsymmetrical diarylalkynes



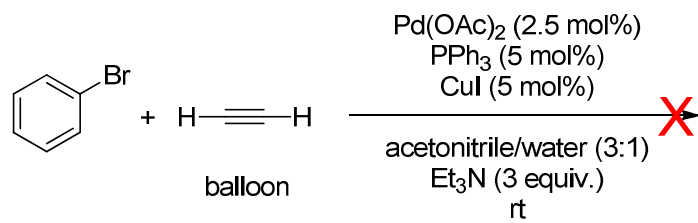
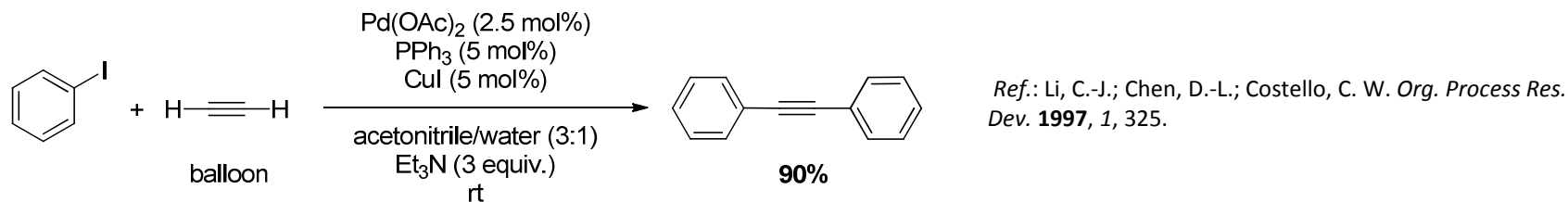
Literature survey on the use of acetylene gas in Sonogashira coupling reaction

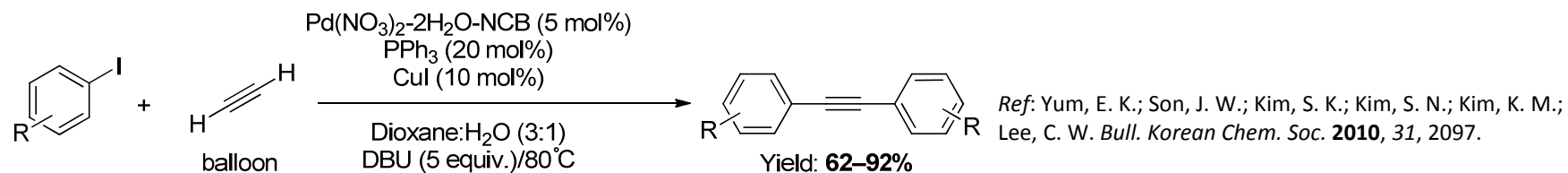


Ref.: Sonogashira, K.; Tohda, Y.; Hagira, N.
Tetrahedron Lett. **1975**, 4467.



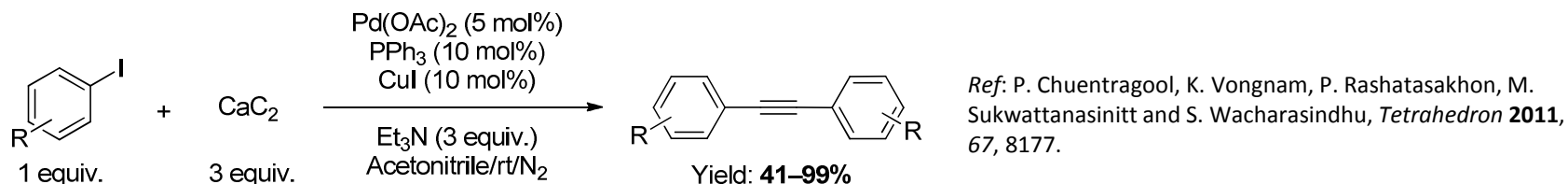
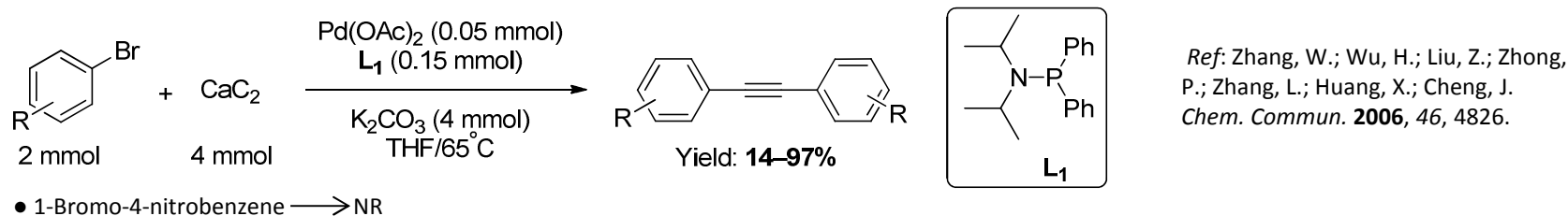
The reaction was also moisture sensitive, no product being isolated in the presence of 5% water.



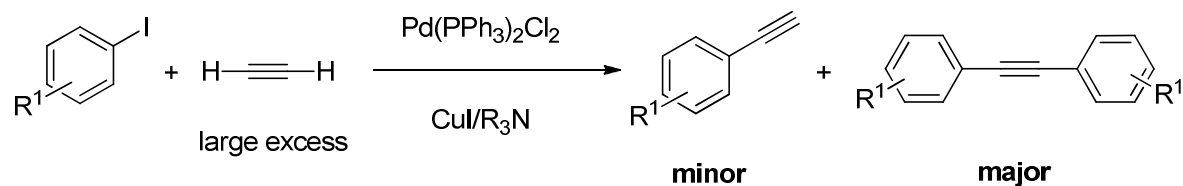
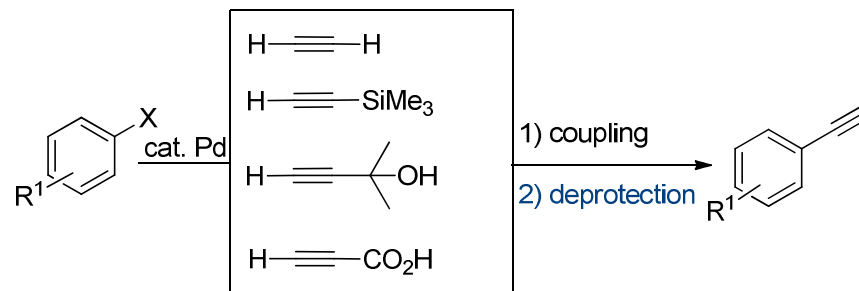
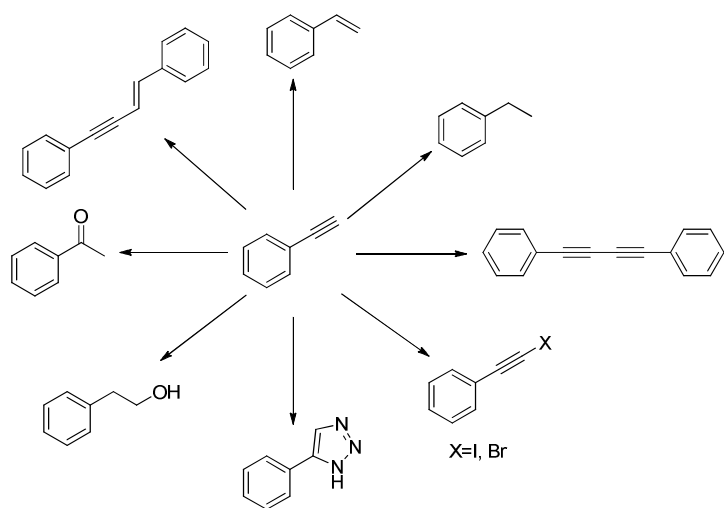


NCB: nano-sized carbon balls as acetylene gas absorbent

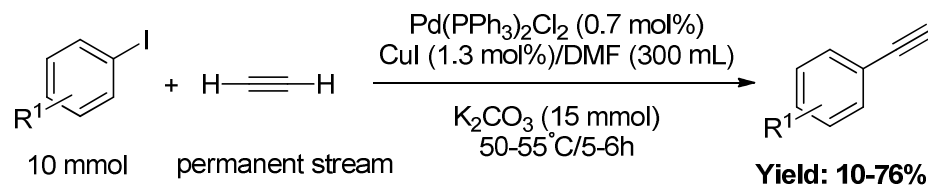
Literature survey on the use of calcium carbide in Sonogashira coupling reaction



- The reaction of bromobenzene or triflate gave no desired product and only a small amount of starting material could be recovered along with unidentified complex mixtures. In the case of the tosylate, only a trace amount of the target compound diphenylethyne was isolated along with an almost quantitative recovery of starting material.
- K_2CO_3 was ineffective base in this reaction and afforded 16 and 0% of desired product in MeOH and THF, respectively.

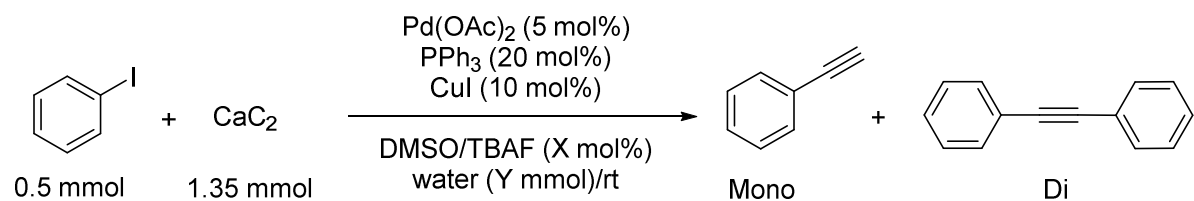


Ref: Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.



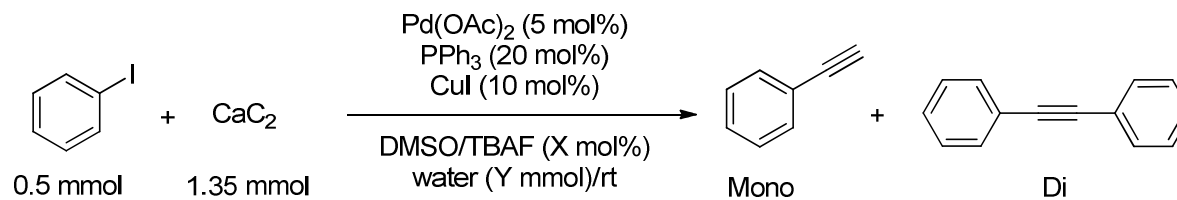
Ref: Vasilevsky, S. F.; Klayatskaya, S. V.; Elguero, J. *Tetrahedron* **2004**, 60, 6685.

work up: 1500 mL water; 900 mL ether was used



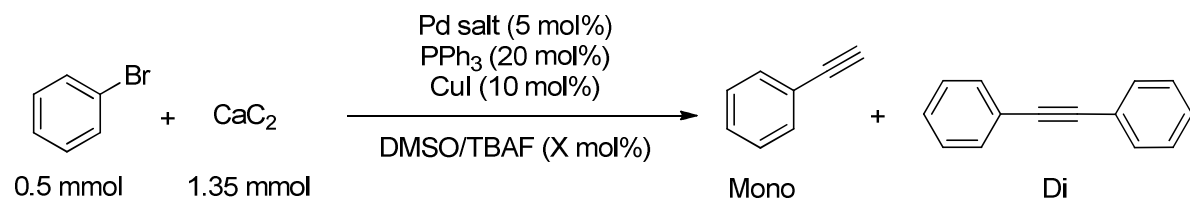
Entry	TBAF (mol %)	Total water (mmol)	GC-MS, 4h			GC-MS, 20h		
			Mono	Di	Total	Mono	Di	Total
1	5	—	5%	78%	83%	2%	98%	100%^a
2	10	—	5%	25%	30%	6%	93%	99%
3	15	—	6%	32%	38%	1%	99%	100%
4	20	—	8%	16%	24%	8%	92%	100%
5	5	2.2	2%	—	2%	47%	14%	61%
6	5	1.1	15%	85%	100%			
7	15	1.1	13%	4%	17%	21%	79%	100%
8	20	1.1	9%	—	9%	30%	70%	100%

^a after 7h.



Entry	TBAF (mol %)	water (mmol) ^a	Conv., 4h			Conv., 20h		
			Mono	Di	Total	Mono	Di	Total
1	1	—	2%	54%	56%	—	100%	100%
2	2	—	2%	52%	54%	—	100%	100%
3	1	1.1	9%	6%	15%	9%	91%	100%
4	2	1.1	14%	86%	100%			

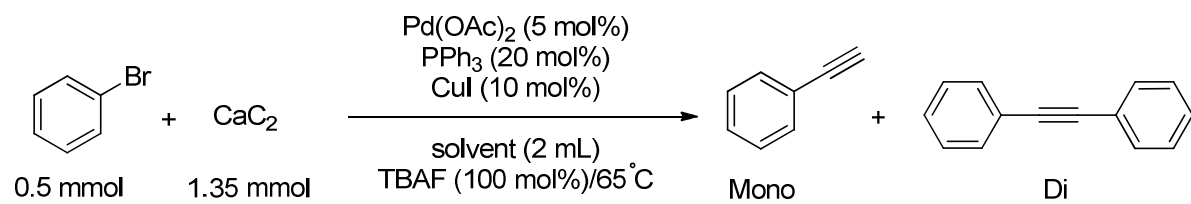
^a Total amount of water (from TBAF•3 H₂O and added water).



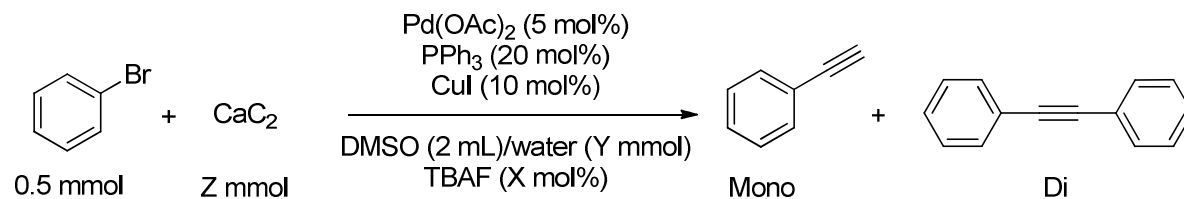
Entry	TBAF (mol %)	Pd salt	Temp. (°C)	Conv., 18h			Conv., 22h		
				Mono	Di	Total	Mono	Di	Total
1	1	Pd(OAc) ₂	rt	—	—	—			
2	5	Pd(OAc) ₂	rt	—	—	—			
3	1	Pd(OAc) ₂	60	trace	—	trace			
4	5	Pd(OAc) ₂	60	trace	—	trace			
5	10	Pd(OAc) ₂	120	—	3%	3%	4%	57%	61% ^b
6 ^a	10	Pd(PPh ₃) ₂ Cl ₂	120	—	4%	4%	8%	16%	24% ^b
7	100	Pd(OAc) ₂	rt	trace	—	trace			
8	100	Pd(OAc) ₂	65	12%	62%	74%	13%	62%	75%

^a without adding PPh₃.

^b After 18h, extra TBAF was added, totally reached to 50 mol%. The time is accounted when extra TBAF was added.

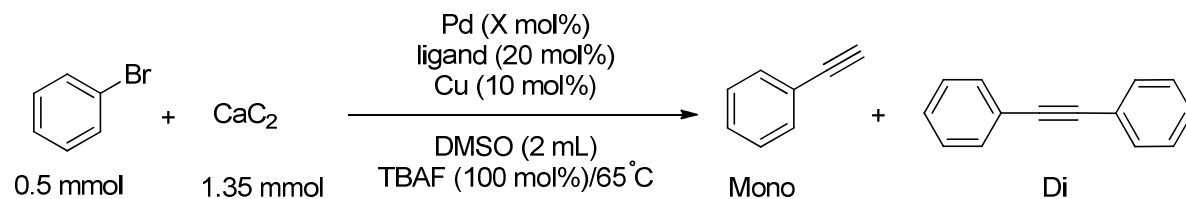


Entry	Solvent	Conv., 20h		
		Mono	Di	Total
1	DMSO	13%	62%	75% ^a
2	THF	—	17%	17%
3	Toluene	—	31%	31%
4	Dioxane	2%	58%	60%
5	NMP	12%	57%	69%
^a after 22h.				

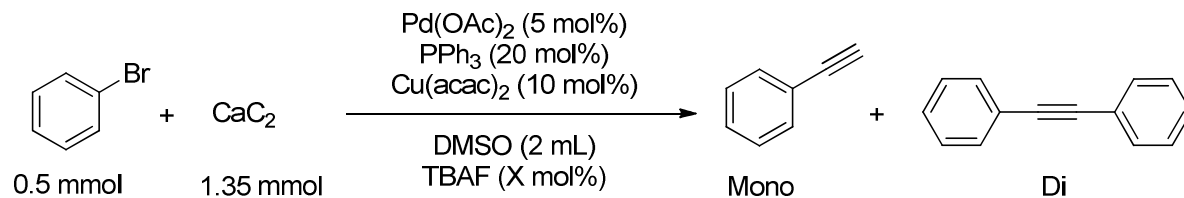


Entry	CaC ₂ (mmol)	TBAF (mol %)	Water (mmol) ^a	Temp. (°C)	Conv.				Conv.			
					Time (h)	Mono	Di	Total	Time (h)	Mono	Di	Total
1	2.7	100	—	65	20	28%	47%	75%				
2	2.7	100	2.5	65	20	35%	37%	72%				
3	1.35	100	1.2	65	20	8%	52%	60%				
4	1.35	100	—	90	3	5%	62%	67%	24	trace	80%	80%
5	2.7	100	—	90	3	9%	40%	49%	24	—	65%	65%
6	2.7	100	2.5	90	3	6%	60%	66%	24	trace	68%	68%
7	4	100	—	90	3	8%	55%	63%	24	—	72%	72%
8	1.35	50	—	65	3	2%	trace	2%	20	3%	9%	12%
9	1.35	50	1.5	65	3	3%	2%	5%	20	6%	6%	12%
10	1.35	100	—	65	3	15%	47%	62%	20	3%	74%	77%
11	0.68	100	—	65	3	6%	38%	44%	20	3%	60%	63%
12	1.35	200	—	65	3	2%	47%	49%	24	6%	85%	91%

^a Total amount of water (from TBAF•3 H₂O and added water).



#	Cu	Pd (mol%)	Ligand	Time (h)	Conv.			Time (h)	Conv.		
					Mono	Di	Total		Mono	Di	Total
1	CuI	Pd(OAc) ₂ (5)	Tri(<i>o</i> -tolyl)phosphine	3	trace	–	trace	24	4%	2%	6%
2	CuI	Pd/C (10)	PPh ₃	3	2%	trace	<3%	24	5%	2%	7%
3	Cu(acac) ₂	Pd(OAc) ₂ (5)	PPh ₃	3	18%	52%	70%	24	trace	96%	96%
4	CuCl	Pd(OAc) ₂ (5)	PPh ₃	3	17%	62%	79%	20	10%	77%	87%
5	CuBr	Pd(OAc) ₂ (5)	PPh ₃	3	15%	40%	55%	20	18%	65%	83%

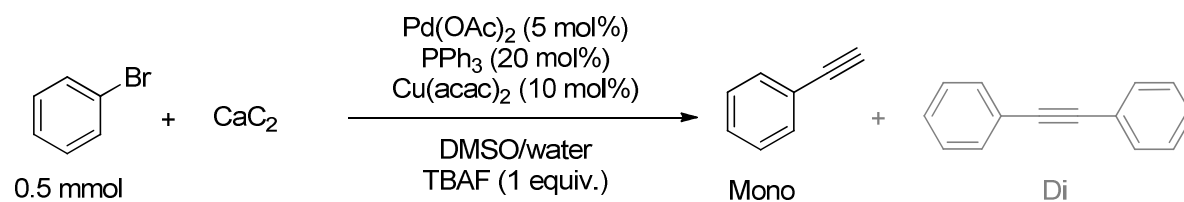


#	Pd (mol%)	TBAF (mol%)	Temp. (°C)	Conv., (3h)			Conv., (20)		
				Mono	Di	Total	Mono	Di	Total
1	Pd(OAc) ₂ (5)	100	rt	trace	–	trace	6%	3%	9%
2	Pd(OAc) ₂ (5)	50	65	12%	9%	21%	5%	46%	51%
3	–	100	65	–	–	0%	trace	–	trace

Summary results for homocoupling reaction:

- (1) Water promotes monosubstitution.
- (2) Increasing the temperature had a little effect on total conversion and decreased the mono substituted product.
- (3) Conversion was increased when higher amounts of TBAF was used.

Attempts to synthesize monosubstituted acetylenes



Entry	CaC ₂ (mmol)	Added Water (mmol)	Temp. (°C)	Conv.			Conv.				
				Time (h)	Mono	Di	Total	Time (h)	Mono	Di	Total
1	5.4	5.5	65	4	8%	—	8%	24	55%	33%	88%
2	5.4	5.5	100	4	42%	12%	54%	24	46%	8%	54%
3	5.4	5.5	40–50	16	3%	—	3%	3 ^a	9%	—	9%
4	5.4	3.9	65	4	2%	—	2%	24	39%	47%	86%
5	5.4	7.2	65	4	14%	—	14%	24	31%	60%	91%
6	4	4.2	65	4	7%	—	7%	24	31%	44%	75%
7	10.5	11	65	4	4%	—	4%	24	51%	49%	100%
8	5.4	5.5 ^b	75	5	25%	8%	33%	24	42%	24%	66%
9	5.4	11 ^b	75	—	—	—	—	24	33%	6%	39%
10 ^c	5.4	5.5	65	4	—	—	—	24	23%	5%	28%
11 ^d	5.4	5.5	65	4	—	—	—	24	—	—	—

^a after 16h, extra PPh₃ (20 mol%) was added. ^b water was added through syringe pump; ^c P(*t*-Bu)₃ was used.
^d Pd(dppe)₂(NO₃)₂ was used.

Summary:

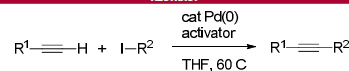
- (1) It seems that the formation of active parts take some time, higher temperature will increase the initial rate but kills the active species and stops the reaction.
- (2) 55–75 °C is an appropriate temperature rang.
- (3) PPh_3 was more effective than tri(*o*-tolyl)phosphine and $\text{P}(t\text{-Bu})_3$.
- (4) Slow reaction promotes disubstituted product.

On the effect of TBAF in coupling reactions:

Non-Sonogashira-Type
Palladium-Catalyzed Coupling Reactions
of Terminal Alkynes Assisted by
Silver(I) Oxide or Tetrabutylammonium
FluorideAtsunori Mori,* Jun Kawashima, Tomohiro Shimada, Masahiro Suguro,
Kazunori Hirabayashi, and Yasushi NishiharaChemical Resources Laboratory, Tokyo Institute of Technology, Nagatsuta,
Yokohama 226-8503, Japan
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Received June 4, 2000

ABSTRACT



Palladium-catalyzed reaction activator: TBAF. An activator furnishes various arylated or alkynylated alkynes in good to excellent yields. The similar coupling reaction is also found to proceed using tetrabutylammonium fluoride (TBAF) or tetrabutylammonium hydroxide (TBAOH) as an activator.

Much effort has been paid to the construction of organic a (co)solvent, has widely been used as a practical tool for



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Bis-Sonogashira cross-coupling: an expeditious approach to
chain, phenylene-modified 1,ω-diols†Simon Drescher,*^{a,b} Susan Becker,^a Bodo Döhner^a and Alfred Blume^aReceived 6th March 2012, Accepted 8th March 2012
DOI: 10.1039/c2ra20411h

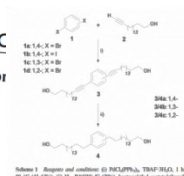
The synthesis of long-chain, phenylene-modified 1,ω-diols can be effectively performed in 60% overall yield using the bis-Sonogashira cross-coupling with 6 mol% of PdCl₂(PPh₃)₂ and tetrabutylammonium fluoride in a copper-, amine- and solvent-free setting followed by hydrogenation.

An expeditious and highly efficient method for the synthesis of long-chain 1,ω-diols is of high importance in supramolecular chemistry. Especially in the field of bipolar lipid (bipolar amphiphile) synthesis, these diols play an important role since they represent the hydrophilic end of the bipolar lipid. These bipolar molecules were

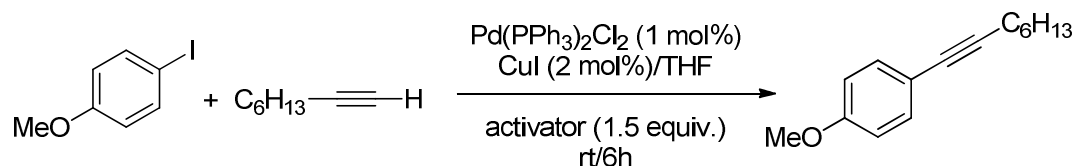
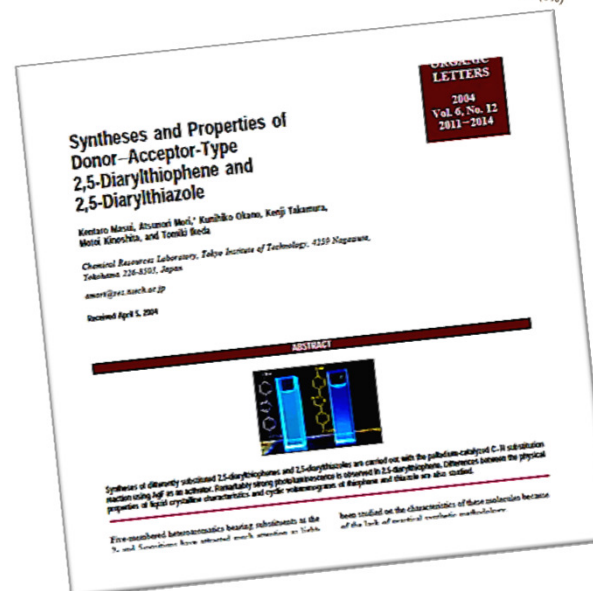
the synthesis of unsymmetrical bipolar lipids, it is a very time-consuming synthetic pathway.¹⁰ Therefore, the expeditious Sonogashira cross-coupling reaction is a rational alternative for the preparation of such phenylene-modified diols.

Sonogashira cross-coupling¹¹ is one of the most powerful and straightforward methods for the formation of carbon-carbon bonds in organic synthesis.¹² Usually, the Pd-catalyzed reaction conditions are mild, and many reactions can be carried out at ambient temperatures. However, the Sonogashira reaction often generates homocoupling products of terminal alkynes,¹³ difficult to separate from the target molecule due to similar chromatographic properties.

Dynamic Article Links



Scheme 1. Synthesis of unsymmetrical 1,ω-diols via bis-Sonogashira cross-coupling.

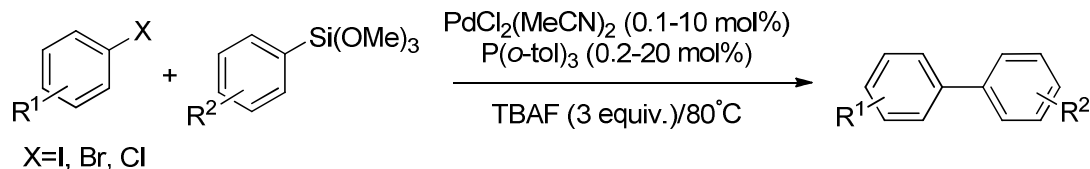


Activator: TBAF (77%), Et₃N (14%), piperidine (20%), Et₂NH (33%), ⁱPr₂NH (15%)

Ref: Mori, A.; Shimada, T.; Kondo, T.; Sekiguchi, A. *Synlett* **2001**, 649.

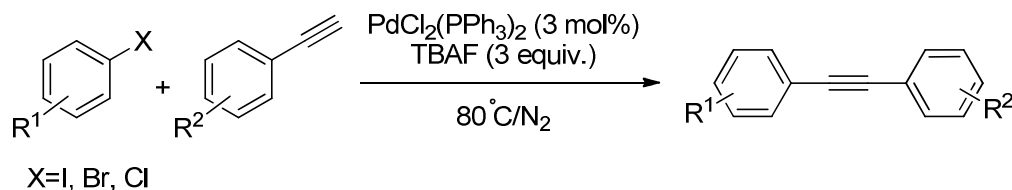
TBAF: Application in coupling reactions

Hiyama



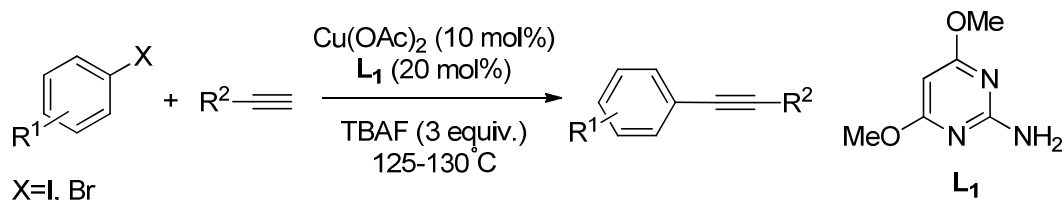
Ref: Li, J.-H.; Deng, C.-L.; Xie, Y.-X. *Synthesis* **2006**, 969.

Sonogashira



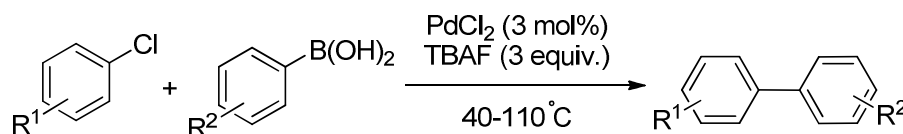
Ref: Liang, Y.; Xie, Y.-X.; Li, J.-H. *J. Org. Chem.* **2006**, 71, 379.

Sonogashira



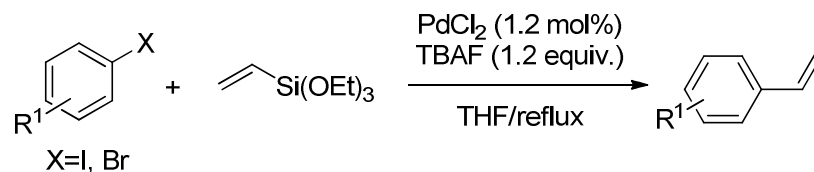
Ref: Xie, Y.-X.; Deng, C.-L.; Pi, S.-F.; Li, J.-H.; Yin, D.-L. *Chin. J. Chem.* **2006**, 24, 1290.

Suzuki–Miyaura

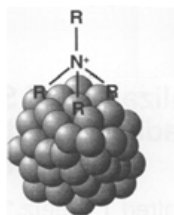


Ref: Tao, L.; Xie, Y.; Deng, C.; Li, J.-H. *Chin. J. Chem.* **2009**, 27, 1365.

Hiyama

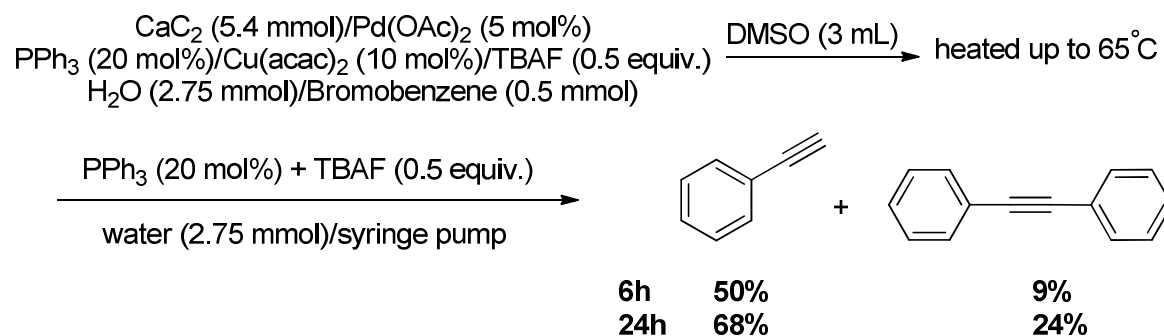


Ref: Chatterjee, T.; Dey, R.; Ranu, B. C. *New J. Chem.* **2011**, 35, 1103.

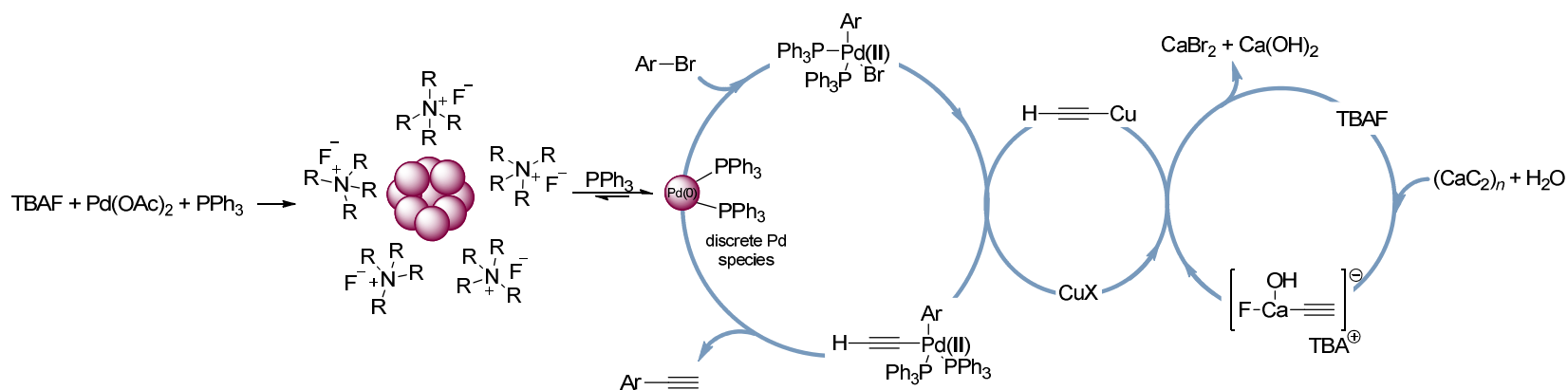


Model for the interaction of tetraalkylammonium ions with Pd clusters.

Ref. Reetz, M. T.; Helbig, H.; Quaker, S. A.; Stimming, U.; Bruer, N.; Vogel, R. *Science* **1995**, 267, 367.



Proposed mechanism





Acknowledgement

- Thanks to Professor Schreiner for his support, helpful discussions and suggestions
- The whole group for pleasant work environment

Thank You for Your Attention