Claire Coleman Current Lit. July 24 2004

Ligand-, Copper-, and Amine-Free Sonogashira Reaction of Aryl Iodides and Bromides with Terminal Alkynes

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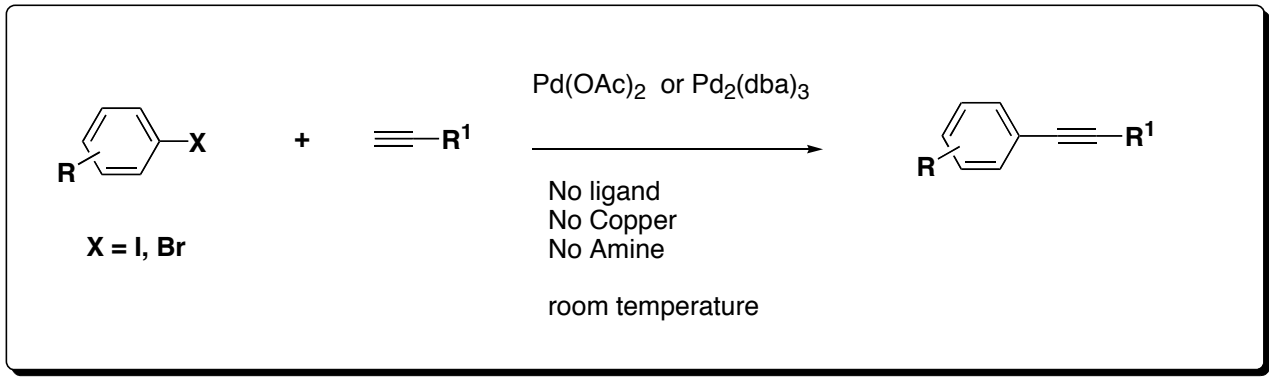
Department of Chemistry, Gilman Hall, Iowa State University



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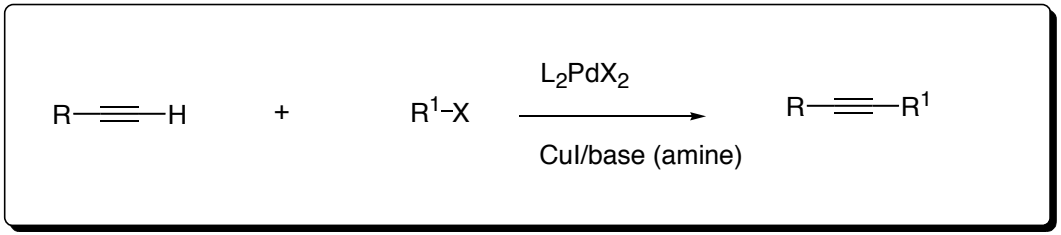
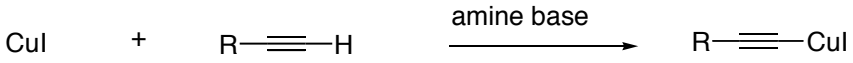
The Sonogashira Coupling



Overall elimination of HX. Occurs via organocuprates:



Sonogashira *et al*, *Tett. Lett* **1975**, 4467**.**

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Uses of the Sonogashira Coupling

Extensively used in organic synthesis

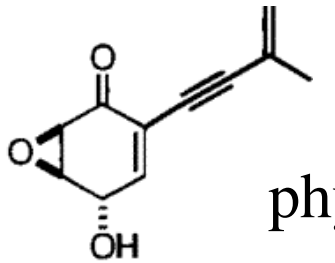
Liquid Crystalline materials

Conducting Polymers

Natural Product Synthesis

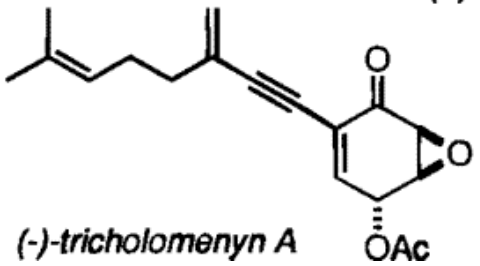
The Sonogashia Reaction is often the key step in Natural Product Synthesis

(+)-bromoxone



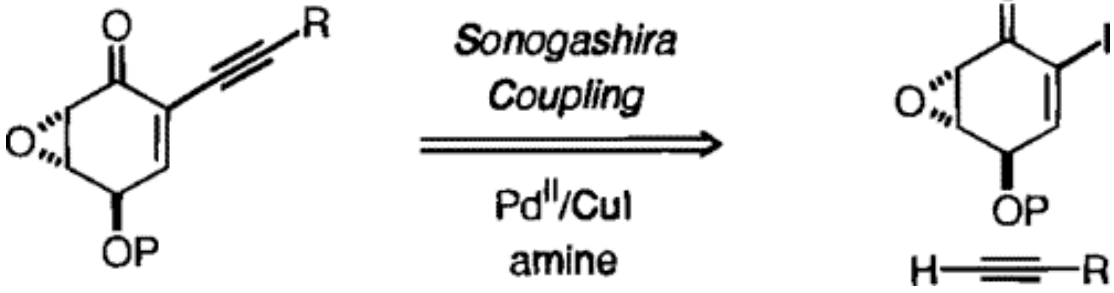
(+)-harveynone

phytotoxin



(-)-tricholomenyn A

Anti-mitotic



J. Org. Chem, **1997**, *62*, 1582.

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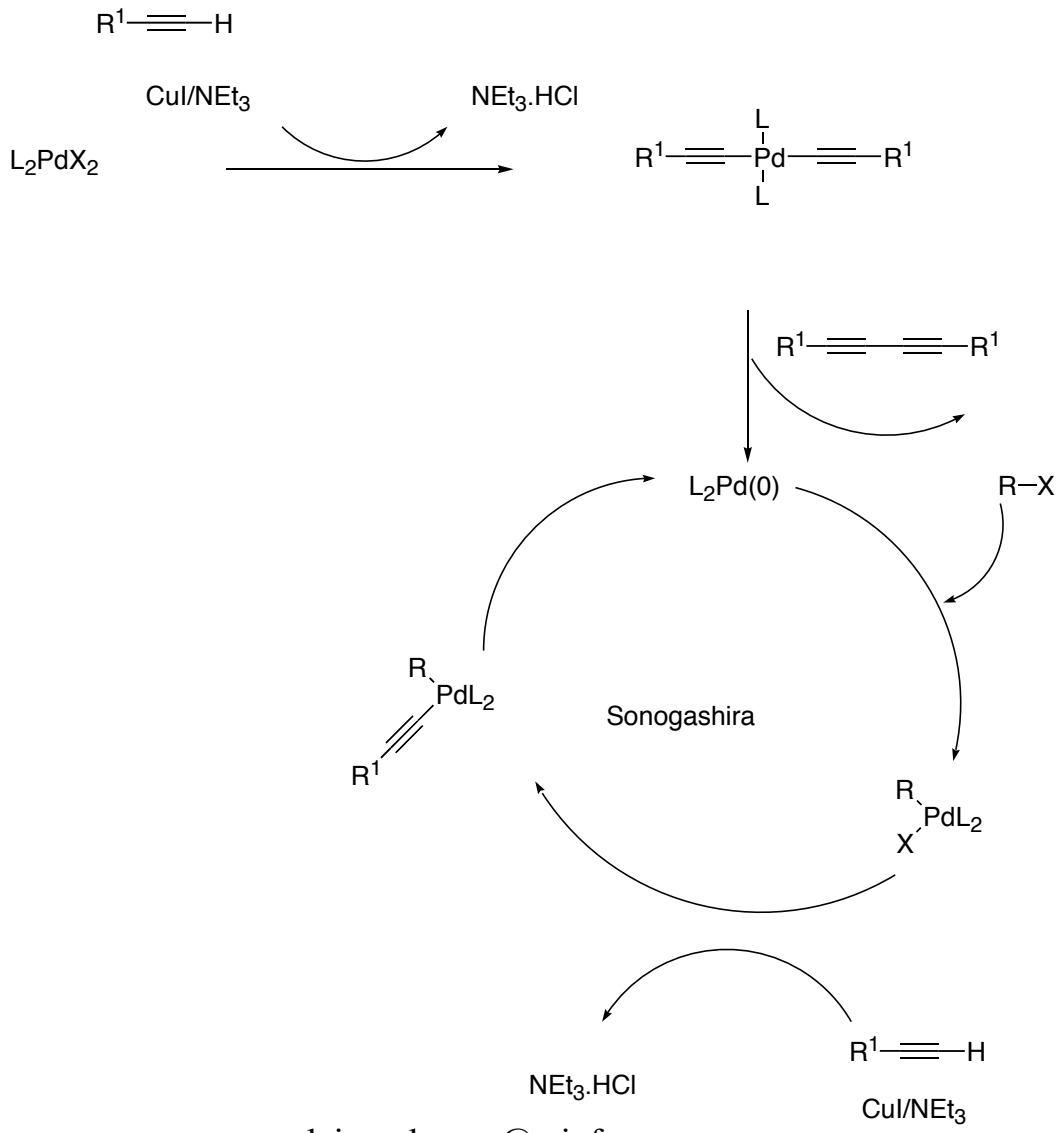
The Catalytic Cycle



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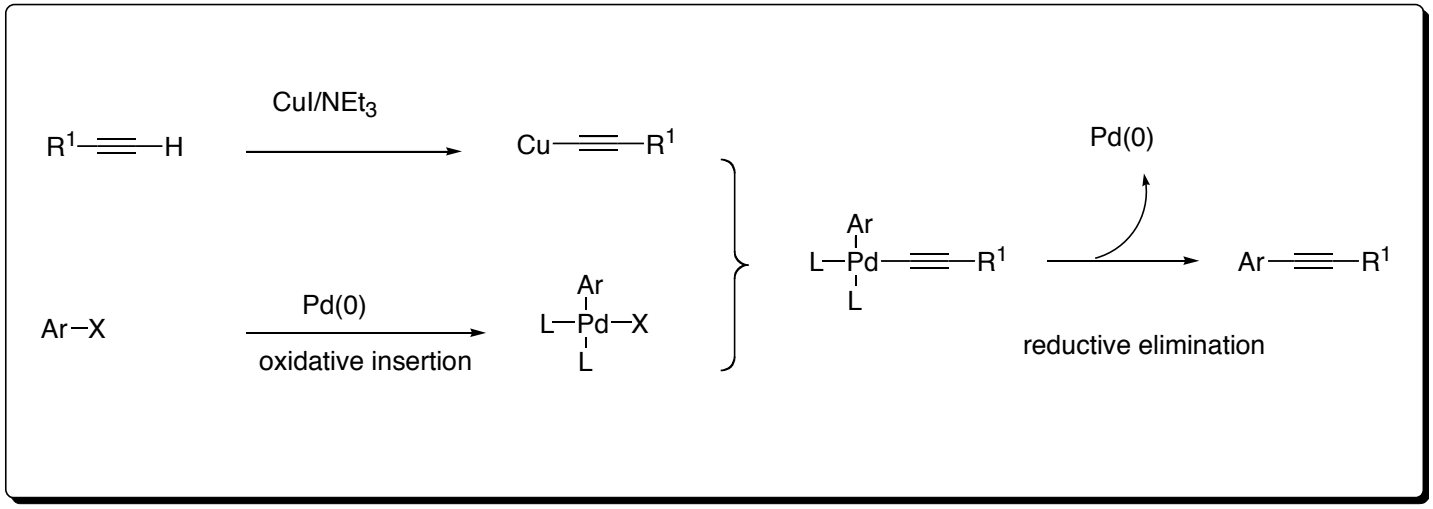
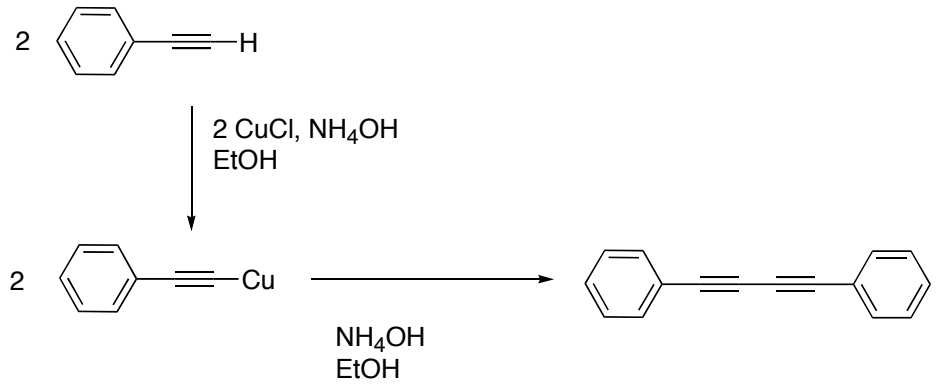
The Catalytic Cycle



Problem-Side Reaction

In the presence of Cu(I) cocatalyst------Glaser type oxidative dimerisation of the alkyne



To address this several reports described Copper free Sonogashira Couplings

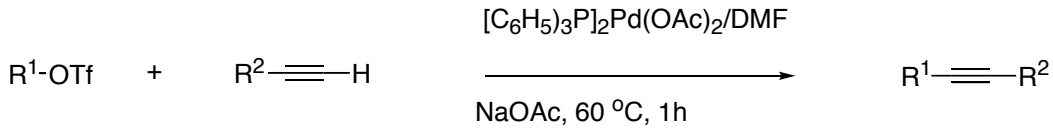
Ideally a ligandless, copperless and amine free process would improve Sonogashira couplings by

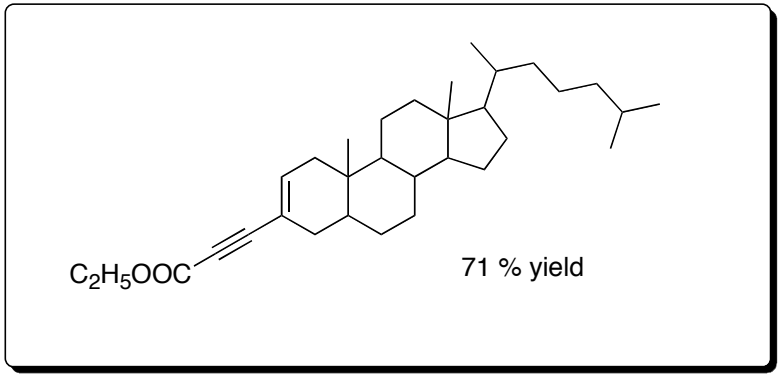
Cheaper: Avoid the use of expensive and sensitive ligands

Enviromentally Friendly: No disposal of large quantities of amines for industrial purposes

Higher Yields: Avoid Glasier dimerisations

Coupling of Enol Triflates with Terminal Alkynes under Copper Free conditions





Using phosphine ligated palladium precursor
2 examples that were copper and amine free

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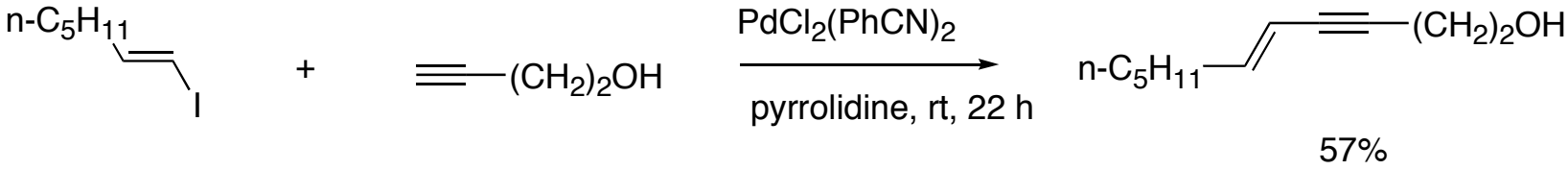
Cacci et al Synthesis, **1986**, 320.

Phosphine and Copper Free Sonogashira Coupling

Coupling of a vinyl iodide and terminal alkyne 1 example



But still required amine

Linstrumelle *et al, Tett Lett*, **1993**, 6403

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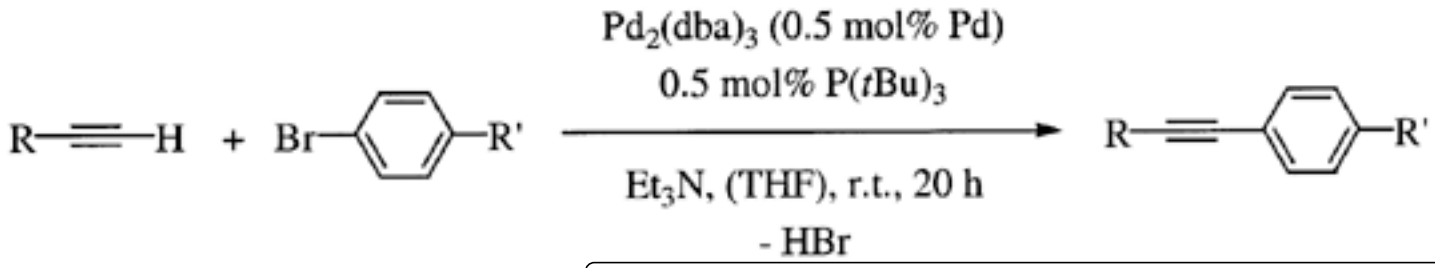
Copper free, Palladium catalysed Sonogashira reaction of aryl bromides with terminal alkynes at rt.



No CuI as cocatalyst

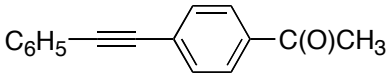
0.5 mol-%palladium and ligand

triethylamine as base

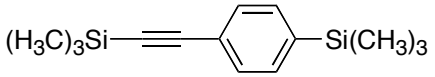
Air sensitive and pyrophoric $P(t\text{-}Bu)_3$

Herrmann, *Eur. J. Org. Chem.*, **2000**, 3679

employing Et_3N as solvent

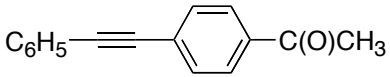


99%
TON 200

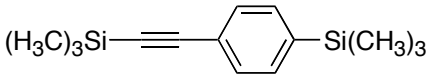


100 %
TON 200

1.5 eqv. Et_3N, THF as solvent



79%
TON 158



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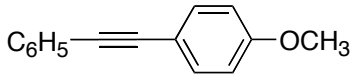
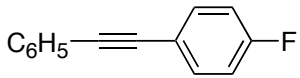
TON 198

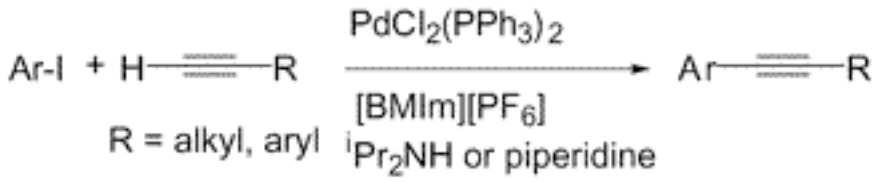


42%
TON 84



71%
TON 142

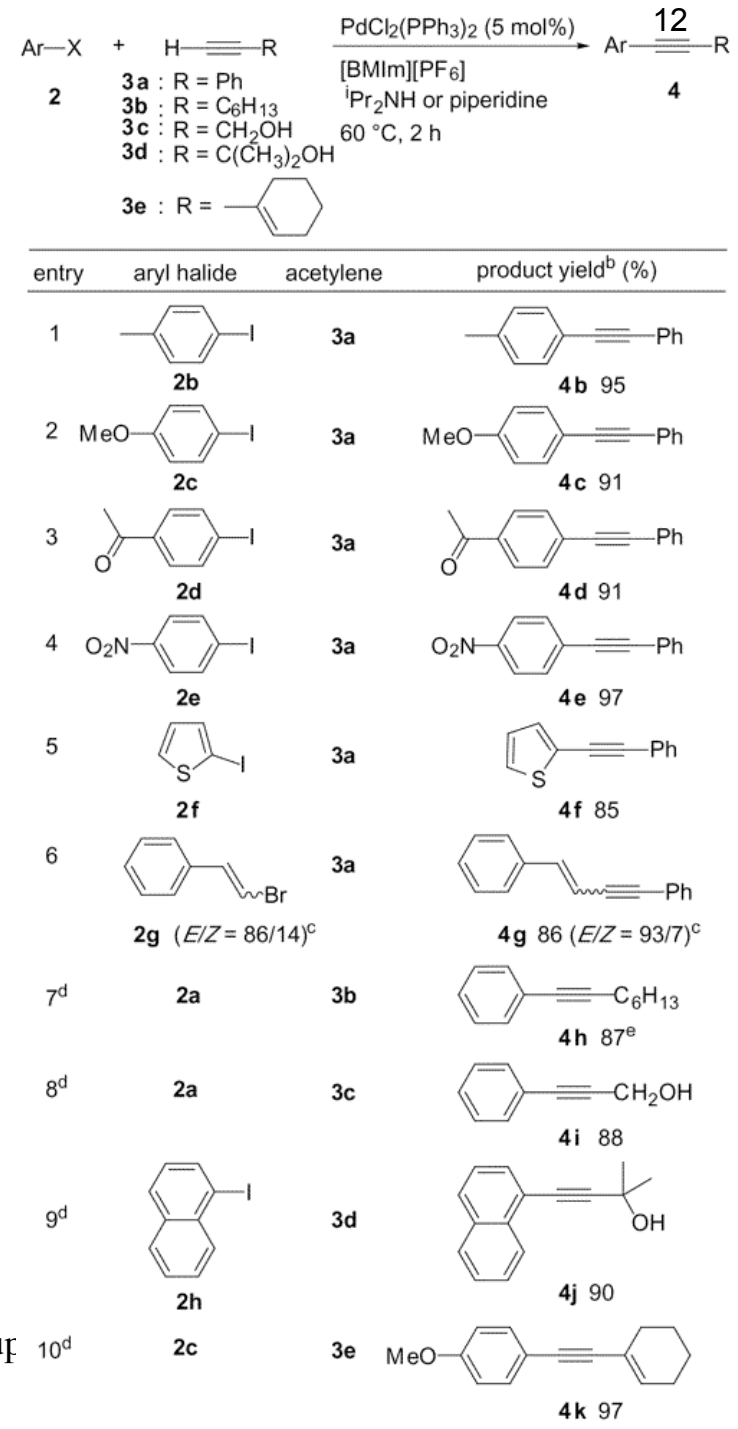
Copper free Sonogashira Coupling Of aryl iodides in Ionic Liquids



Extracted products with hexane from catalyst

Washed ionic layer with water to remove Ammonium salts

Ionic liquid with Pd catalyst could be reused



Ryu, *Org. Lett*, *2002*, 1691.

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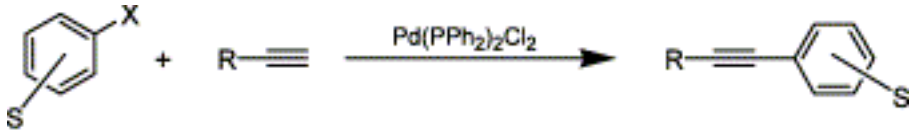
Copper free Sonogashira Couplings of aryl iodides and activated aryl bromides

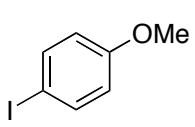
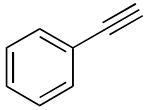
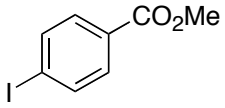
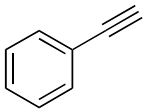
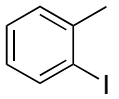
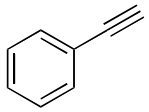
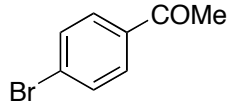
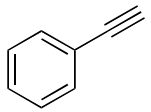
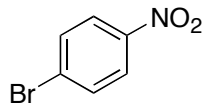
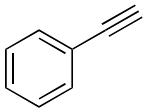


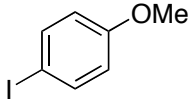
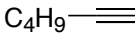
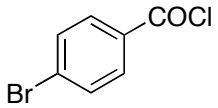
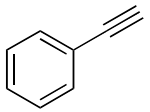
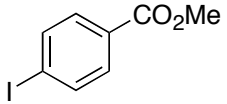
X = Br, I, S = substituent, R = Ph, Me_3Si, C_4H_9

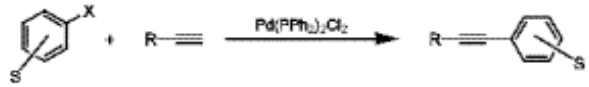
Using $Pd(PPh_2)Cl_2$

0.5 to 4 mol%

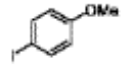
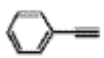
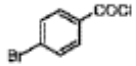
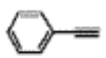
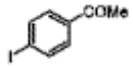
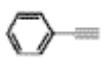
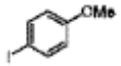
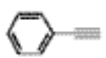
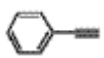
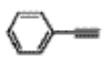
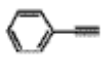
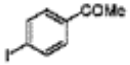
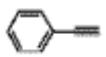
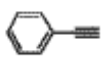
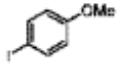
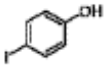
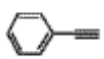
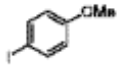
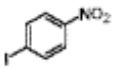
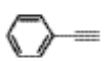
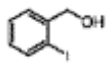
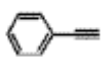
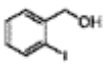
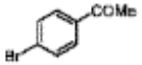
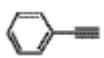
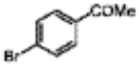
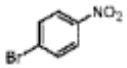
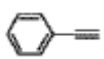
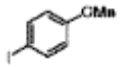
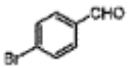
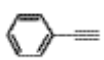
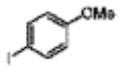
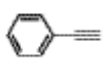
Piperidine as base

Aryl halide	Alkyne	Product Yield %
		91
		93
		0
		94
		90

Aryl halide	Alkyne	Product Yield %
		96
		99
		99



X = Br, I, S = substituent, R = Ph, Me_3Si, C_4H_9

Entry	Aryl halide	Alkyne	Yield (%)	Entry	Aryl halide	Alkyne	Yield (%)
1			91[b]	12			99[c]
2			93[b]	13			79[d]
3			94[b]	14			72[d]
4			0[b]	15			96[d]
5			96[b]	16		Me_3Si—	99[e]
6			92[b]	17		C_4H_9—	96[e]
7			99[b]	18		Me_3Si—	99[c]
8			99[b]	19		Me_3Si—	40[e]
9			94[c]	20		Me_3Si—	75[f]
10			90[c]	21		Me_3Si—	28[d]
11			74[c]	22			99[f]

a) Reactions were run using 1 mmol aryl halide, 1 mmol phenylacetylene, 3 mmol piperidine. The reaction mixture was placed in a pre-heated oil bath at 70 °C and held there for the allotted time

b) 2 mol % $Pd(PPh_3)_2Cl_2$ reaction time of 10 min

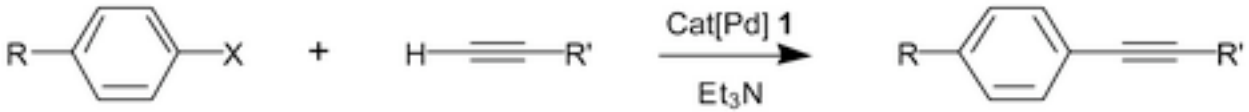
c) 4 mol % $Pd(PPh_3)_2Cl_2$ reaction time of 10 min

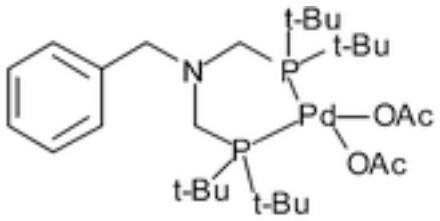
d) 0.5 mol % $Pd(PPh_3)_2Cl_2$ reaction time of 20 min

e) 2 mol % $Pd(PPh_3)_2Cl_2$ reaction time of 10 min

f) Run on 10 mmol scale. 2 mol % $Pd(PPh_3)_2Cl_2$ reaction time of 10 min.

Copper free Palladium catalyst for reaction with aryl halides





1

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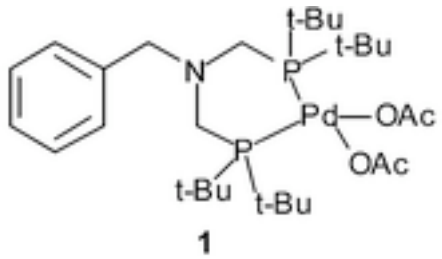
Have to synthesise the ligand, but works with some aryl chlorides



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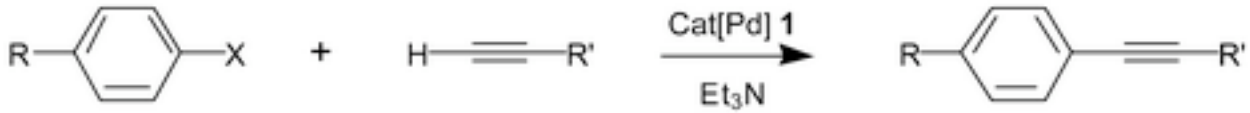
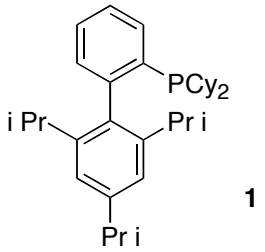


Table 1 Reactions conditions, conversions and turnover numbers (TON) for the Sonogashira coupling of aryl halides with alkynes using **1** as the sole catalyst[a]

Entry	X	R	R′	Temperature/°C	Catalyst **1** (mol%)	React. time	Conv. (%)[b]	TON
1	I	H	C_6H_5	80	1	15 min	100	100
2	I	H	C_6H_5	25	1	30 min	100	100
3	I	H	C_6H_5	−20	1	1 d	70	70
4	I	H	C_6H_5	−40	1	2 d	51	51
5	I	H	$Si(CH_3)_3$	25	1	8 h	76	76
6	I	H	C_6H_5	80	0.5	15 min	100	200
7	I	H	C_6H_5	80	0.1	2 h	100	1000
8	I	H	C_6H_5	80	0.01	1 d	87	8700
9	I	H	C_6H_5	80	0.001	7 d	71	71000
10	Br	H	C_6H_5	80	1	20 min	100	100
11	Br	H	C_6H_5	25	1	1 h	100	100
12	Br	Me	C_6H_5	80	1	3 h	96	96
13	Br	H	$Si(CH_3)_3$	25	1	15 h	54	54
14	Cl	H	C_6H_5	80	1	50 min	4	4
15	Cl	H	C_6H_5	25	1	3 h	9	9
16	Cl	H	$Si(CH_3)_3$	25	1	2 d	5	5
17	Cl	CN	C_6H_5	80	1	5 d	13	13
18	Cl	F	C_6H_5	80	1	5 d	14	14
19	Cl	$COOCH_3$	C_6H_5	25	1	3 d	15	15
20	Cl	$COOCH_3$	C_6H_5	80	2	3 d	30	30
21	Cl	$COOCH_3$	C_6H_5	40	1	3 d	22	22

[a] *Reaction conditions*: aryl halide (2 mmol), alkyne (3 mmol), Et_3N (6 mL). [b] Unoptimized isolated yield.

Coupling of aryl Chlorides and Aryl tsoylates with terminal alkynes using a bulky phosphine ligand under copper and amine free conditions



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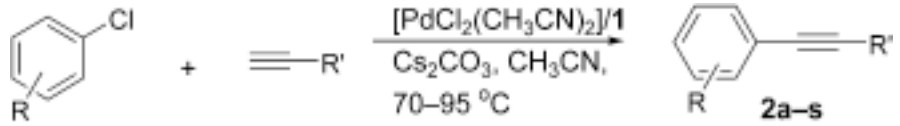

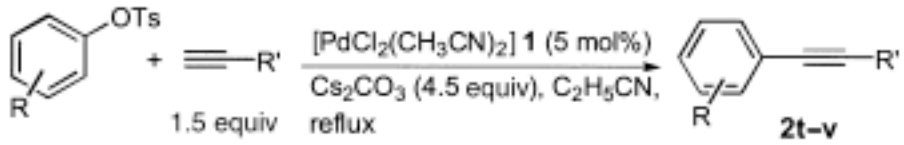

Buchwald, *Angewandte, Int. Ed.*, **2003**, *42*, 5993.

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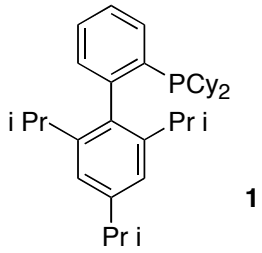
Coupling of aryl Chlorides and Aryl tsoylates with terminal alkynes using a bulky phosphine ligand under copper and amine free conditions



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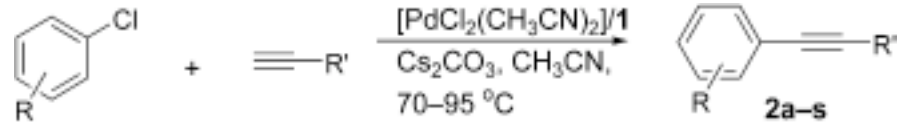

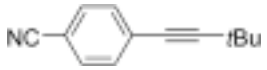

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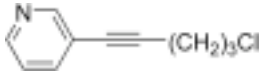

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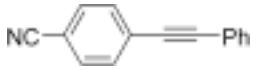

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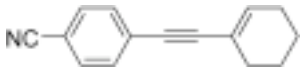

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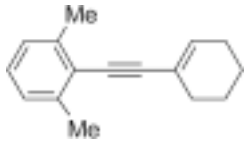

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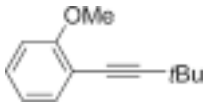

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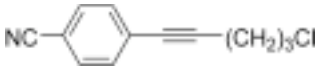

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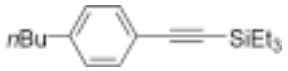

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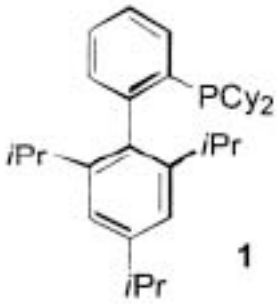
First report of Sonogashira couplings of aryl tsoylates



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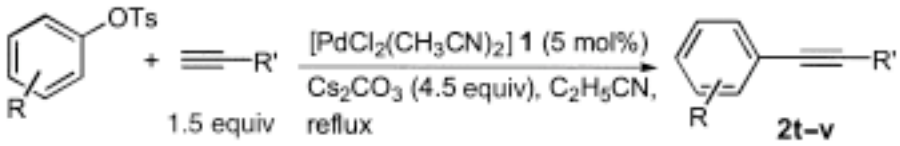
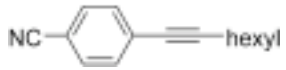
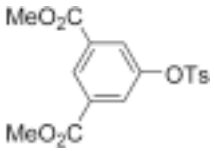
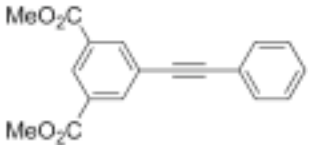
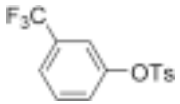
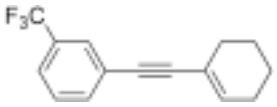


ArOTs	PRODUCT	
		73%
		62%
		78%

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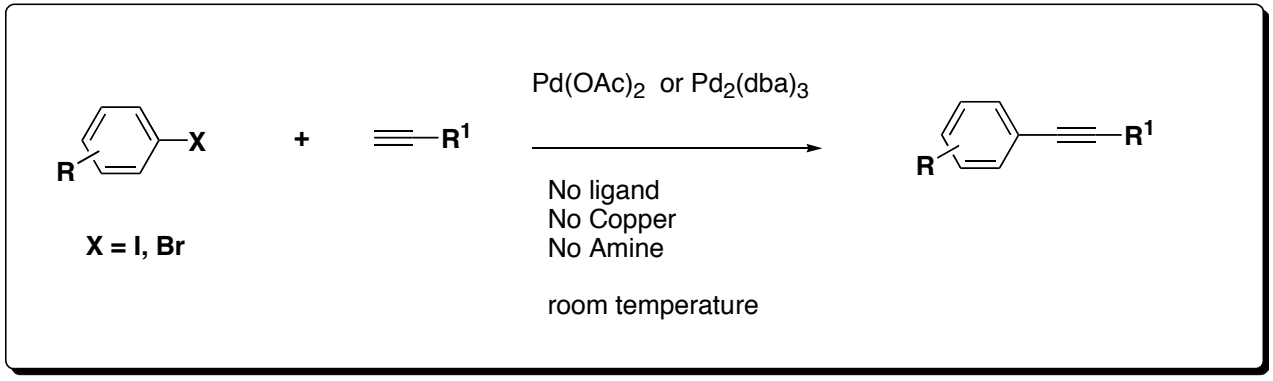
First report of a ligand, copper and amine free Sonogashira coupling at rt

Employing $Pd(Oac)_2$ or $Pd_2(dba)_3$ as catalyst

Tetrabutylammonium acetate as the base

For reaction of aryl iodides and bromides with terminal alkynes



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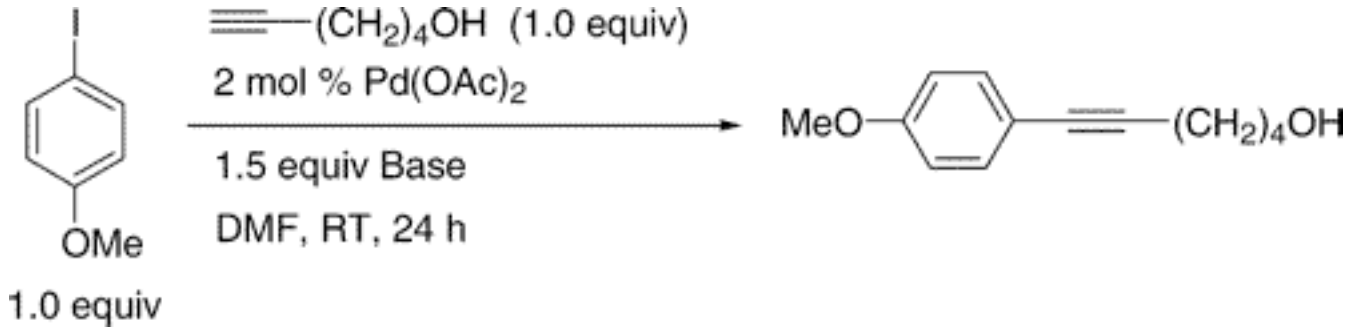
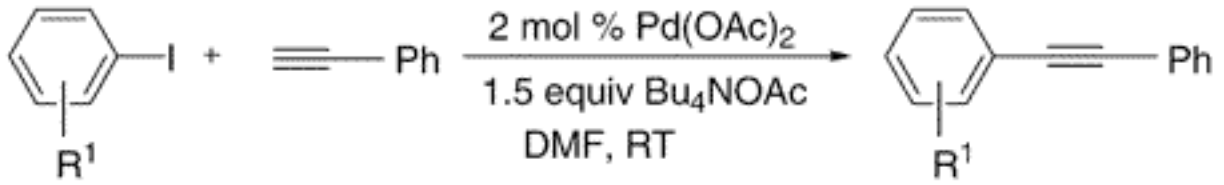
Initial goal--finding a suitable base

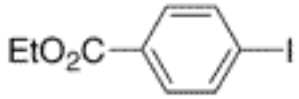
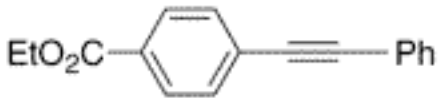
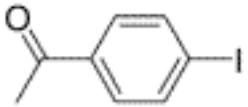
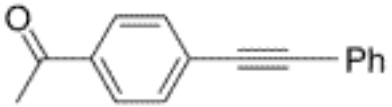
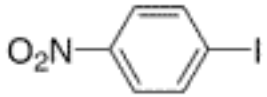
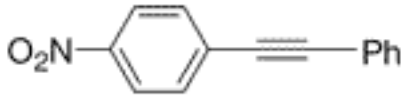
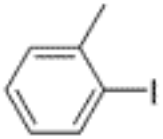
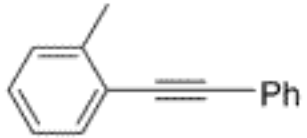
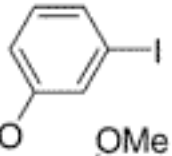
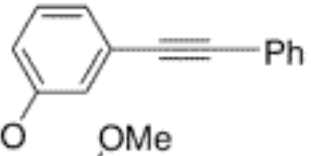
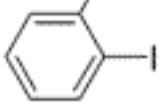
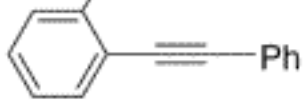
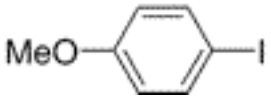
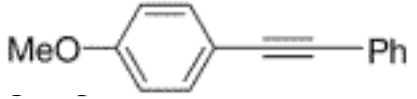


Base	Yield %	
Bu_4NOAc	93, 6h	⟸
Cs_2CO_3	69	⟸
Et_3N	5	
DBU	8	
piperidine	5	
Na_2CO_3	30	

DMF was the optimum solvent

Using phenylacetylene

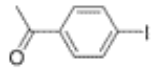
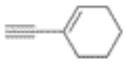
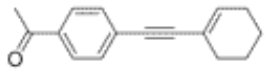
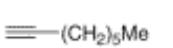
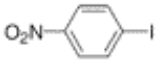
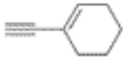
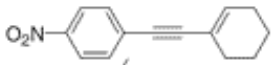
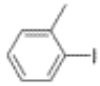
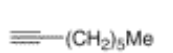
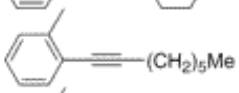
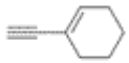
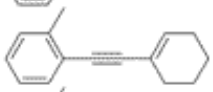
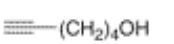
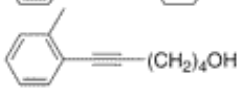
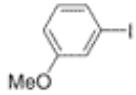
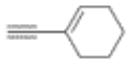
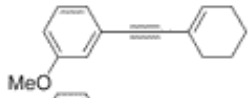
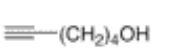
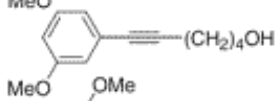
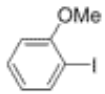
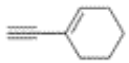
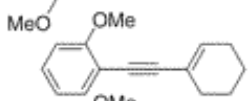
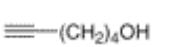
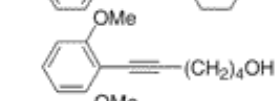
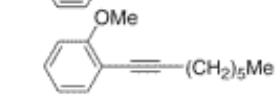
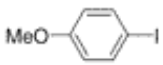
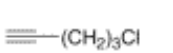
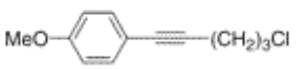
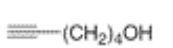
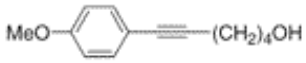
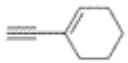
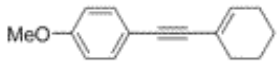
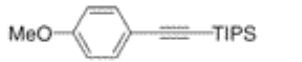


entry	aryl iodide	product	time (h)	yield (%)[a]
1			3	96[b]
2			3	97[b]
3			3	97[b]
4			6	68
5			6	73 (80)[c]
6			6	74 (79)[c]
7			6	77 (86)[c]

b = 1 mol% $Pd(OAc)_2$

[3 mol%]

Series of aliphatic Terminal alkynes

entry	aryl iodide	alkyne	product	time (h)	yield (%)[b]
1				3	90[c]
2				3	94[c]
3				3	96[c]
4				3	98[c]
5				3	97[c]
6				6	95
7				6	96
8				6	89
9				6	70 (81)[d]
10				6	85
11				6	75 (86)[d]
12				6	77 (86)[d]
13				6	93
14				6	80[e]
15				6	93
16				6	76 (84)[d]
17				6	97
18				6	87[e]

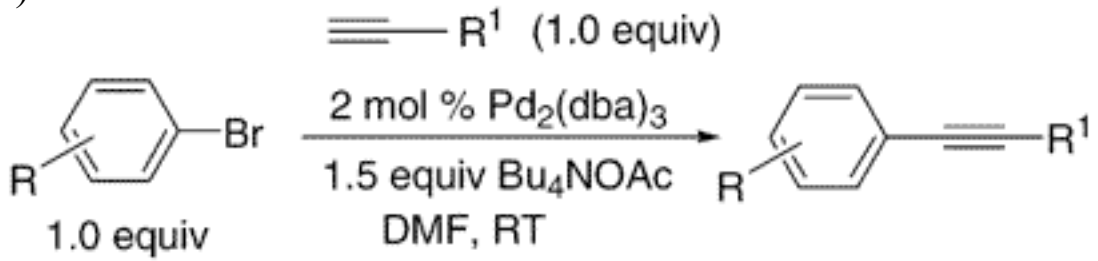
Isolated yields (average of two runs).
c 1 mol % of Pd(OAc)2
was employed.
d Parenthesized yields were obtained
with 3 mol % of Pd(OAc)2.
e Pd2(dba)3 was used in place of Pd(OAc)2.

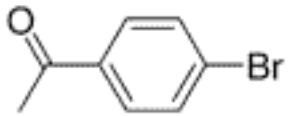
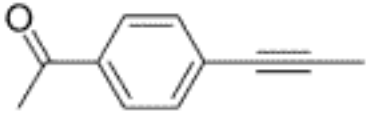
cl

a Isolated yields (average of two runs).

Aryl bromides

Electron rich were sluggish



entry	aryl bromide	product	time (h)	yield (%)[a]
1	O_2N–C$_6$H$_4$–Br	O_2N–C$_6$H$_4$–C≡C–Ph	5	86
2		O_2N–C$_6$H$_4$–C≡C–$(CH_2)_4OH$	5	92
3		O_2N–C$_6$H$_4$–C≡C–$(CH_2)_5Me$	5	91
4			5	90
5	NC–C$_6$H$_4$–Br	NC–C$_6$H$_4$–C≡C–$(CH_2)_4OH$	8	94
6		NC–C$_6$H$_4$–C≡C–TIPS	12	89
7		NC–C$_6$H$_4$–C≡C–Ph	24	70

The choice of **tetrabutylammonium acetate** as the base is important

Authors unsure of its role but suggest

It removes the most acidic hydrogen in the alkyne
May facilitate reduction of $Pd(Oac)_2$ to a catalytically active Pd(0) species

Stabilises the oxidative addition adduct
ArPd(II)X (12 e^- unstable complex)

$[ArPd(II)X_3]^{2-}2Bu_4N^+$ (16 e^-)

Conclusion

The first Ligand, Copper and Amine free Sonogashira coupling was described

Future benefits

Useful for key steps in natural product synthesis
Enviromentally useful for industry