Pharmacia & Upjohn

Palladium Chemistry on Solid-Phase: Application to Small Organic Compounds and Natural Compounds Libraries

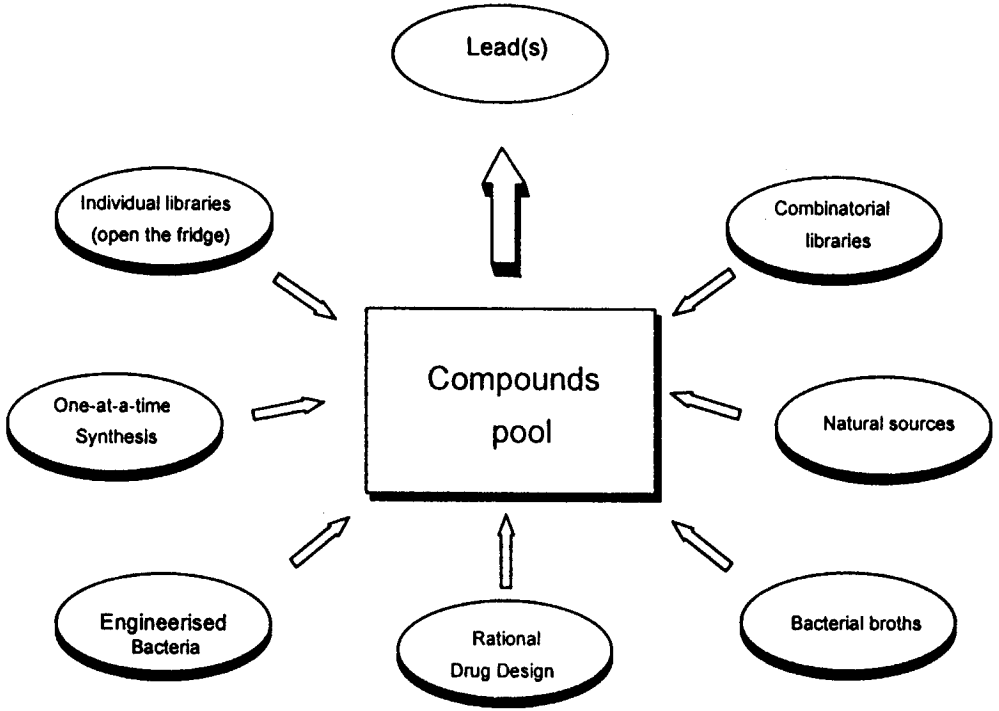
Background

Methodologies

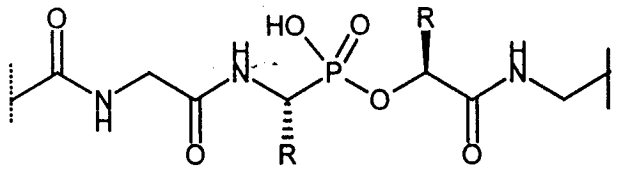
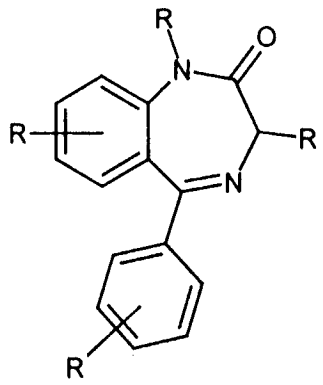
Chemistry Studies

Library Synthesis & Analysis

Current approaches to drug discovery



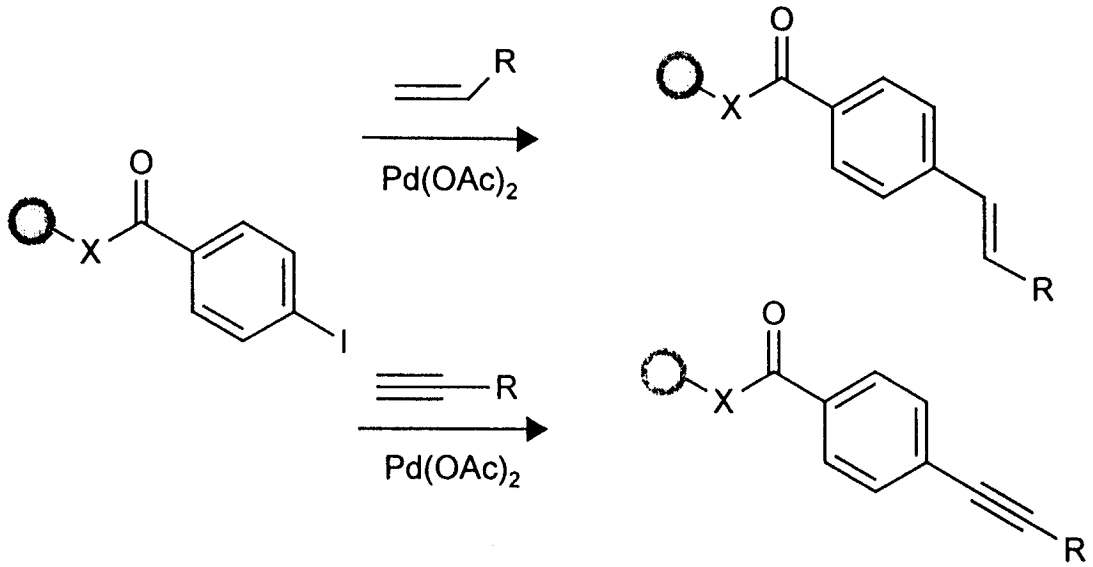
Chemistry & Methodologies.

Methodology	**Typical Example**
• Split-Mix	
• Parallel synthesis	

Palladium Mediated Solid-Phase reactions

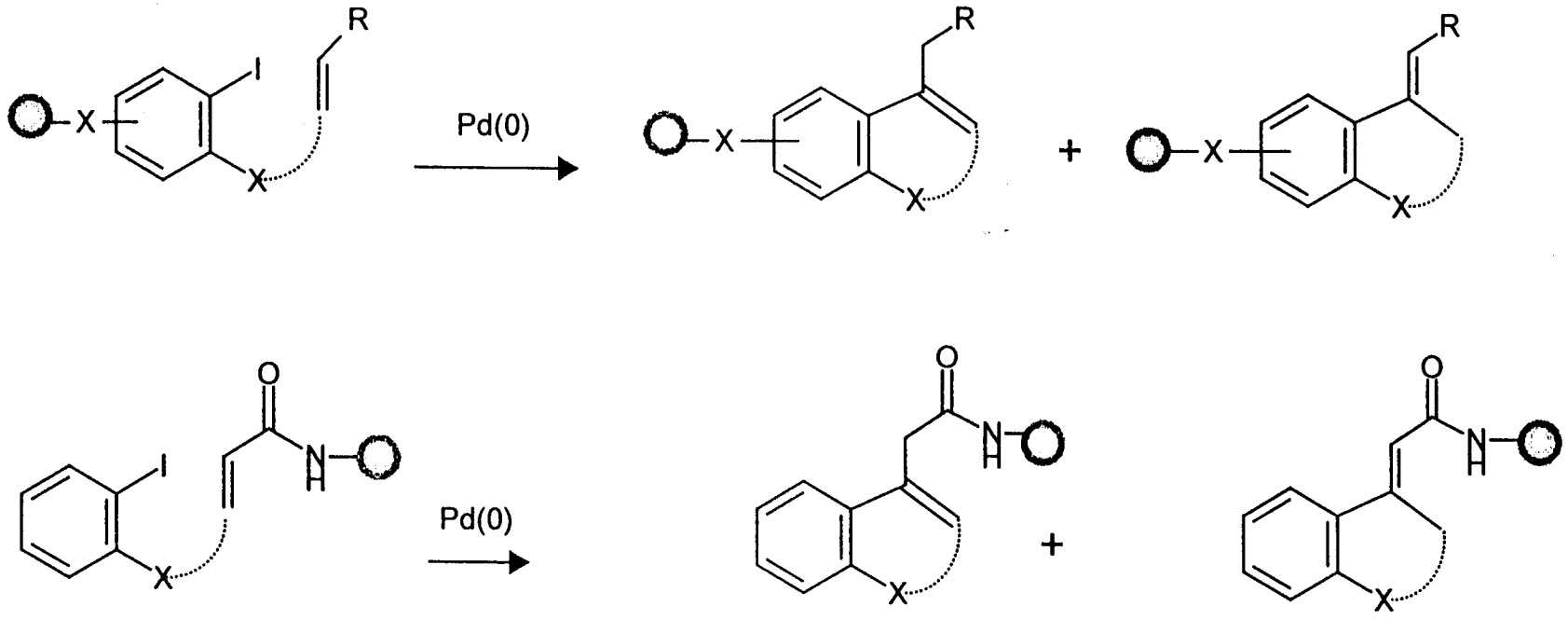
- Homogeneous palladium catalyst is a powerful tools for C-C bond formation also in solid-phase.
- The use of solid-phase linked starting materials allows the removal by simple filtration of the homogeneous palladium catalyst from the reaction mixture.
- Over the last three-four years palladium mediated reactions on solid-phase have been reported: Heck reaction , and the Stille and Suzuki coupling are good examples.

Heck Reaction in solid-phase.



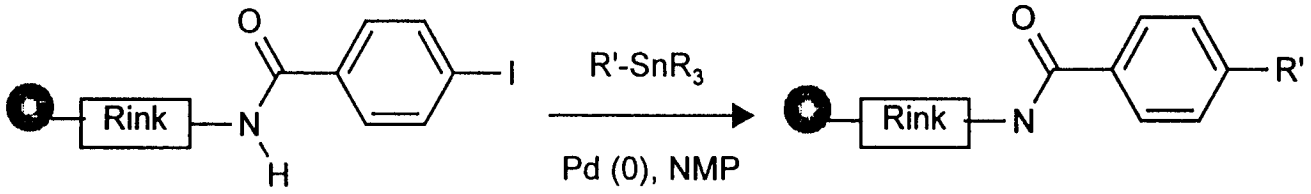
Yu, K-L.; Deshpande, M. S.; Dolatrai, V. M. *Tetrahedron Lett.* **1994**, *35*, 8919.
Hiroshige, M.; Hauske, J. R.; Zhou, P. *Tetrahedron Lett.* **1995**, *36*, 4567.

Heterocycles synthesis by intramolecular Heck Reaction

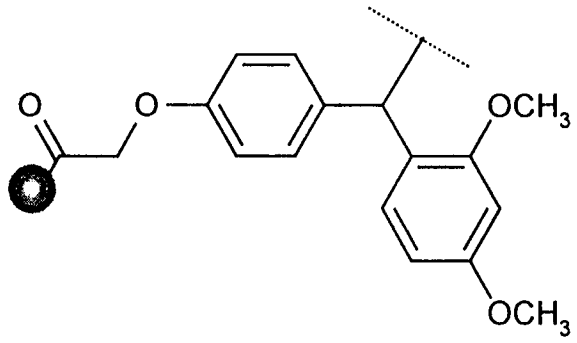


Isoquinolines: Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60,* 5748.
Indoles: Yun, W.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 7189.
Macrocycles: Hiroshige, M.; Hauske, J. R.; Zhou, P. *J. Am. Chem. Soc.* **1995**, *117*, 11590

Stille Reaction in solid-phase

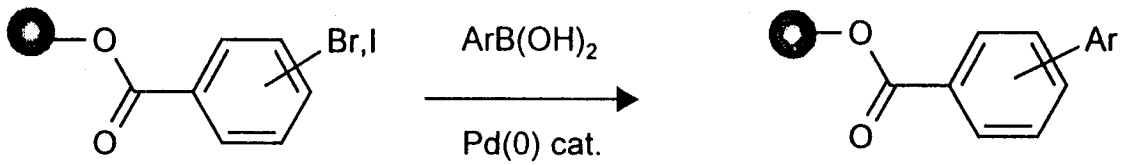


Rink = linker:

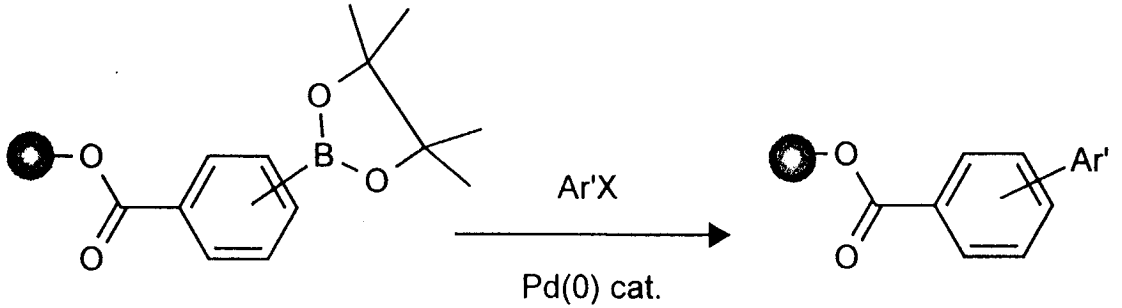


Deshpande, M. S. *Tetrahedron Lett.* **1994**, *35*, 5613.
Forman, F. W.; Sucholeiki, I. *J. Org. Chem.* **1995**, *60*, 523.
Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306.

Suzuki Coupling in Solid-phase

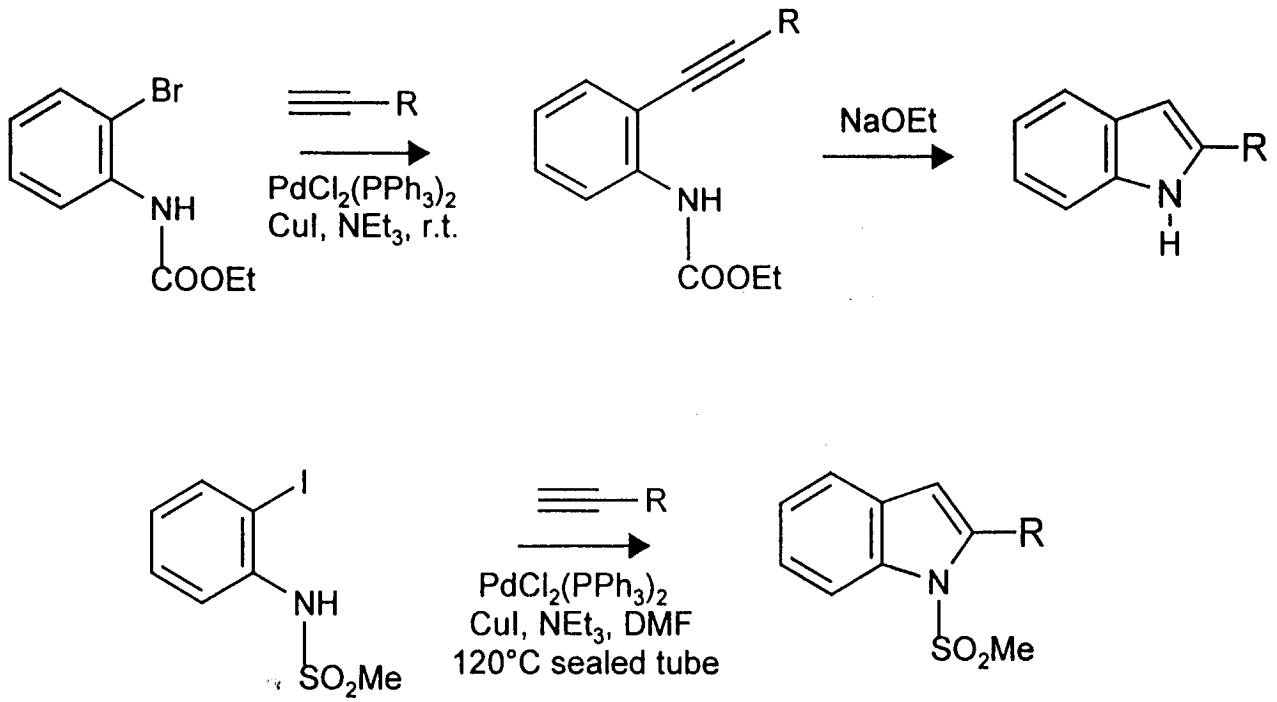


Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177.
Han, Y.; Walker, S. D.; Young, R. N. *Tetrahedron Lett.* **1996**, *37*, 2703.
Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169.



Piettre, S. R.; Baltzer, S. *Tetrahedron Lett.* **1997**, *38*, 1197.

Catalytic Castro Reaction

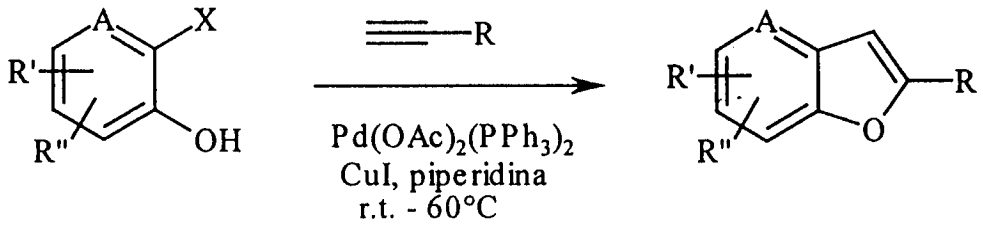


Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 31.

Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305.

Villemin, D; Goussu, D. *Heterocycles* **1989**, *29*, 1255.

Cacchi Reaction

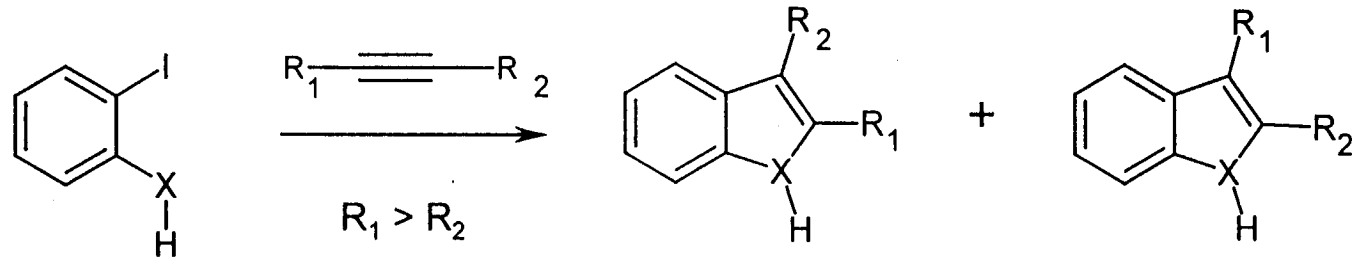


A = CH, N
X = I, Br
R' = H, 2-CH_3, 1-CHO
R'' = H, 3-OCH_3

Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 928, and references herein.

Larock Reaction

Synthesis of Indoles and Benzofurans 2,3-disubstituted.



1 **2** **3**

The reaction is reported to be regioselective, in fact only the most sterically hindered **2** (R_1>R_2, X = N) is reported.

Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.
Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.

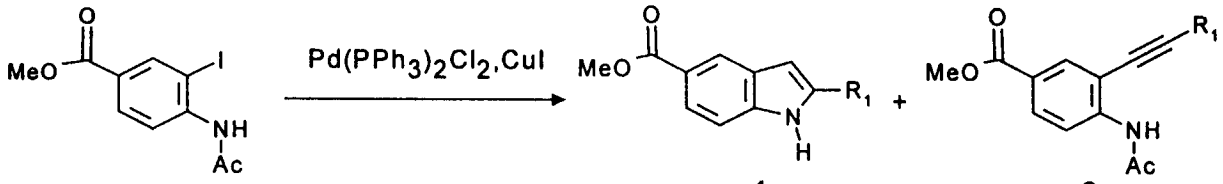
Solid-phase chemistry requirements towards libraries construction

- Synthetic strategy
  - Avoid protection deprotection sequences, or functional groups transformations.
  - Avoid heterogeneous reactions. The reactants must be kept in solution to be washed out at the end of the reaction.
  - High yields in each step (>90%)
- Critical issues
  - High temperatures (>100°C)
  - Low temperatures (< -50°C)
  - Strong acidic and basic conditions.

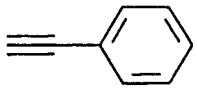
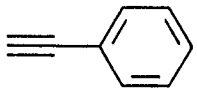
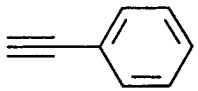
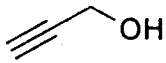
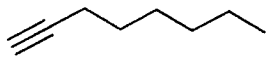
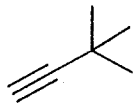
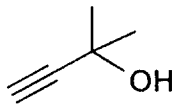
Castro and Larock reactions drawbacks for libraries construction

- 1. Reaction conditions not useful for solid-phase automated synthesis:
  - Heterogeneous reaction.
  - High temperatures in sealed tubes.
  - Strong bases for the cyclisation step.
  - Long times.
- 2. Limited in scope:
  - No substitution on the aromatic ring.
  - Only simple alkynes have been used.
- 3. Low yields.

Studies on the Castro reaction in solution

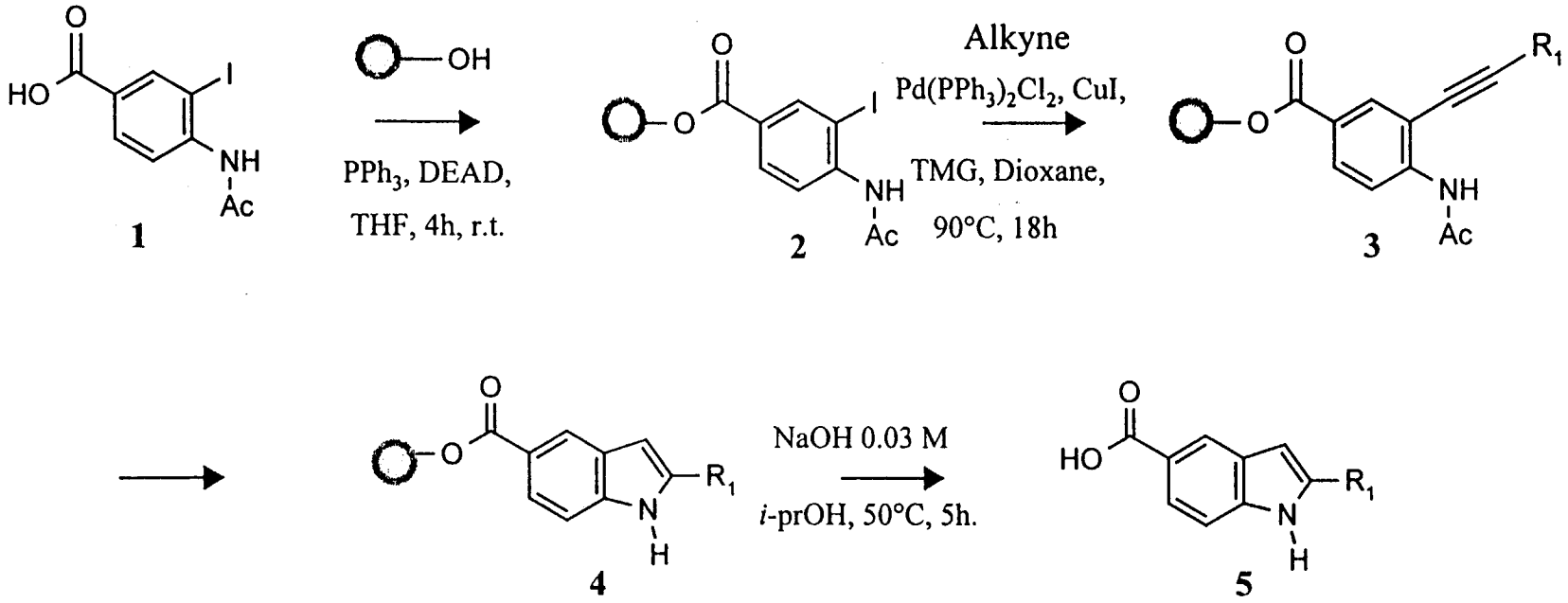


1 2

Entry	Alkyne	T	Conversion	Ratio **1/2** (Y%)
1		r.t	> 99%	0:100 (93)
2		60	>99%	45:55 (95)
3		80	>99%	100:0 (95)
4		80	> 99%	100:0 (60)[a]
5		80	> 99%	100:0 (84)
6		80	> 99%	0:100 (84)
7		80	> 99%	0:100 (55)

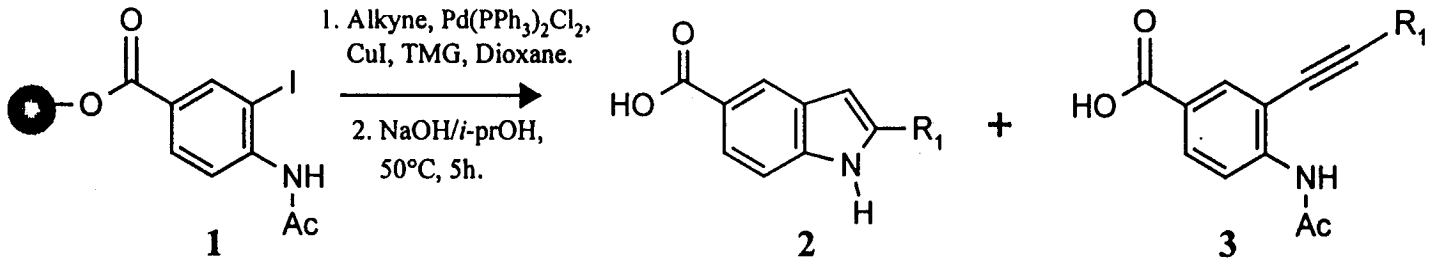
a) N, O acyl migration. b) Unsubstituted indole 2-carboxylate.

Study of the Castro Reaction in Solid Phase

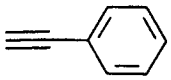
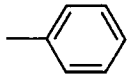
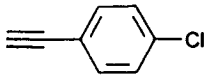
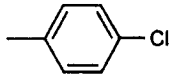
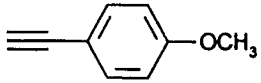
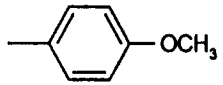
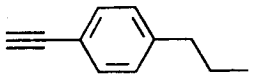
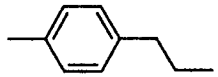
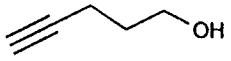
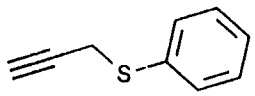
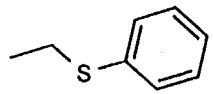
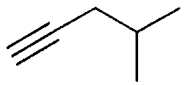
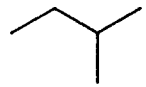


Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307

The Castro reaction in solid phase

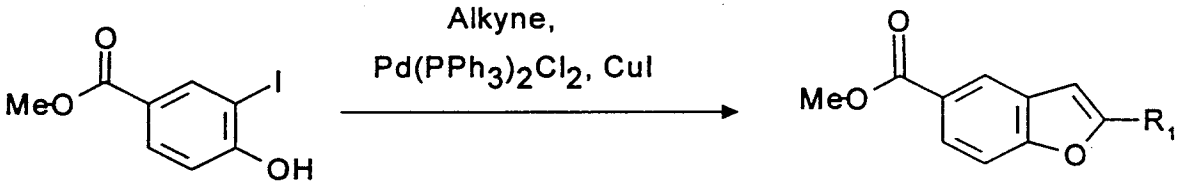


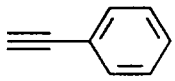
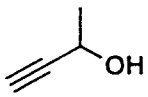
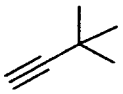
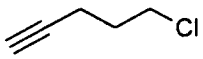
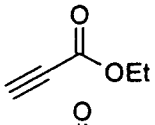
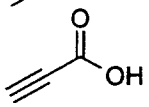
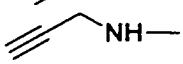
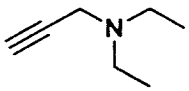
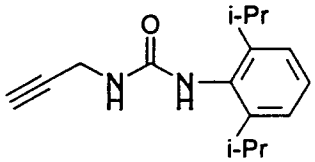
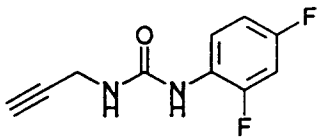
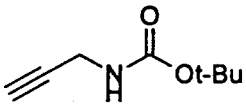
100 mg of TG-OH, 24 hours reaction, 50 eq alkyne, 5-10 μmoles of product

Entry	Alkyne	Ratio **2/3**[a]	R_1	Assay (%)[b]	Conversion (Overall Yields **2** + **3**)[c]
1		96:4		83	> 99% (72%)
2		> 99:1		81	> 99% (52%)
3		> 99:1		85	> 99% (48%)
4		> 99:1		87	> 99% (55%)
5		99:1		> 90	> 99% (95%)
6		> 99:1		78	> 99% (81%)
7		92:8		94	> 99% (82%)

a)Determined by HPLC. b) Normalised HPLC area. c)Yields evaluated by quantitative HPLC against standards.

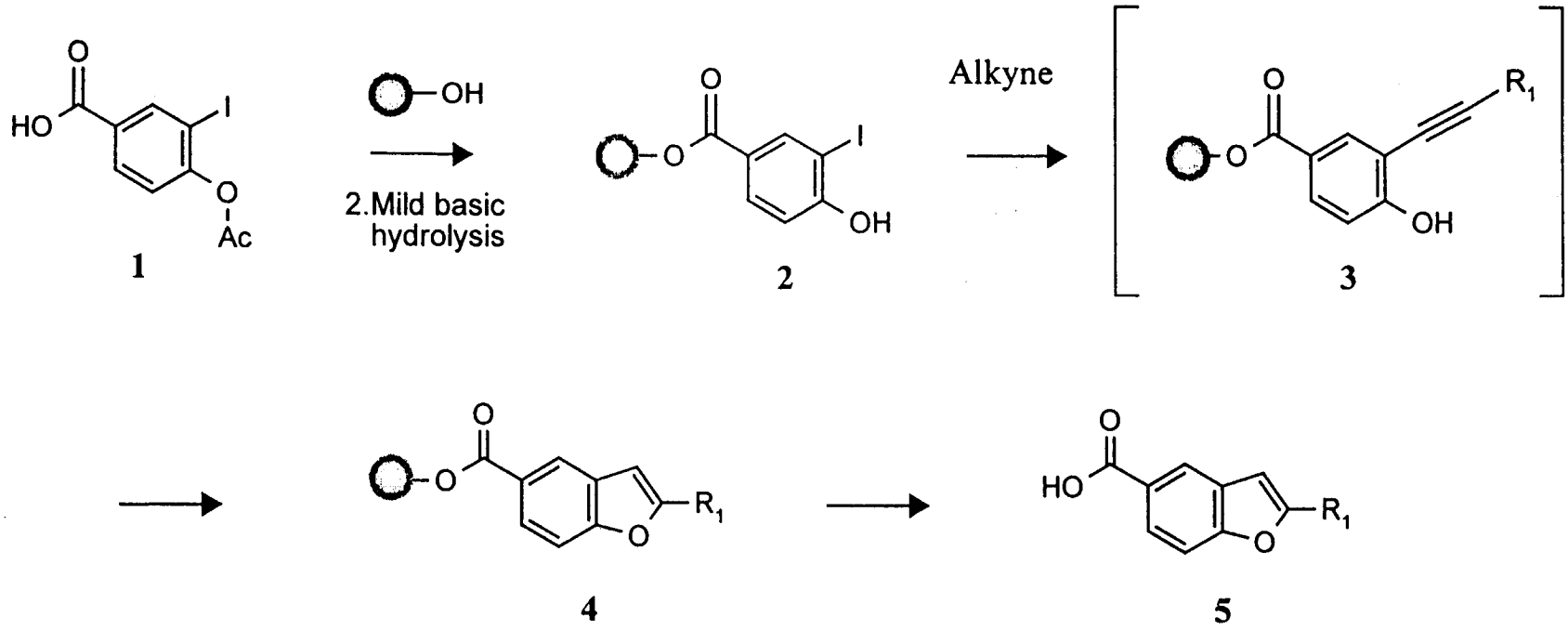
Studies on the Cacchi reaction in solution.



Entry	Alkyne	Conversion	Yield (%)[a]
1		>99%	75
2		>99%	65
3		>99%	65
4		>99%	77
5		-	-
6		>99%	65
7		>99%	42
8		>99%	67
9		>99%	76
10		>99%	60
11		>99%	77

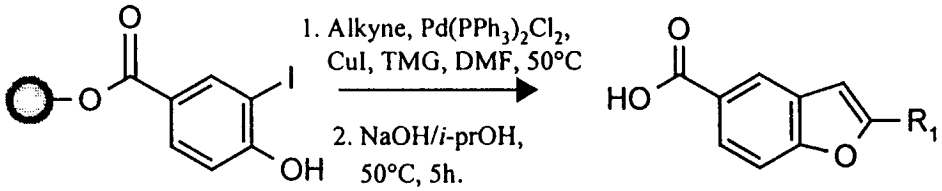
a) Crystallized products.

Studies of the Cacchi reaction in solid-phase



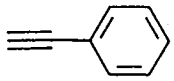
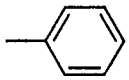
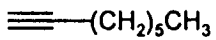
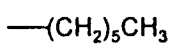
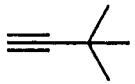
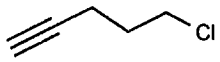
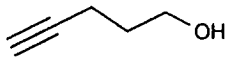
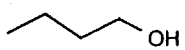
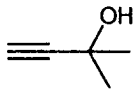
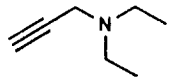
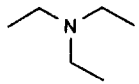
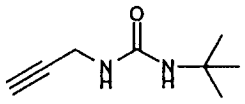
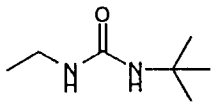
Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311

Cacchi Reaction in solid-phase



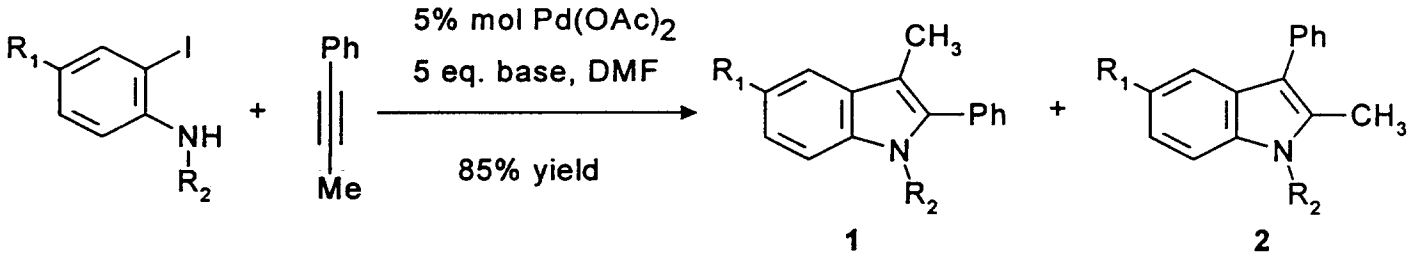
1 **2**

100 mg of TG-OH, 24 hours reaction, 50 eq alkyne, 5-10 µmoles of product

Entry	Alkyne	R_1	Assay (%)[a]	Conversion (Overall Yields)[b]
1			89	> 99% (71%)
2			89	> 99% (53%)
3			94	> 99% (40%)
4			71	> 99% (61%)
5			86	> 99% (55%)
6			89	> 99% (65%)
7			88	> 99% (42%)
8			85	> 99% (52%)

a) Normalised HPLC area. b) Determined by HPLC against standards .

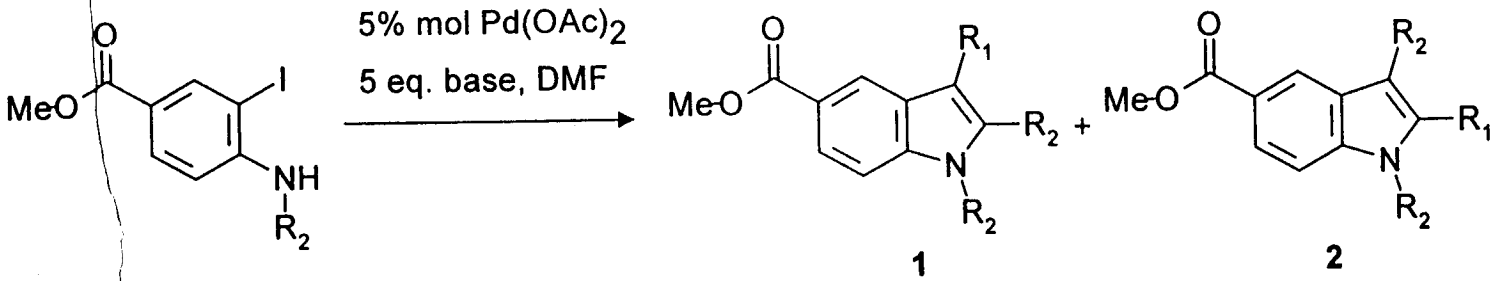
Larock synthesis of indoles
Reaction study.

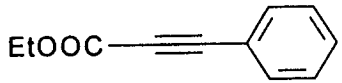
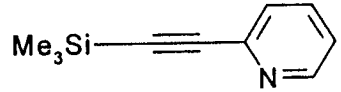
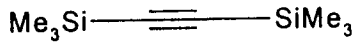
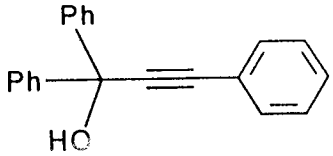


Entry	R_1	R_2	Base	Additive	T°C	Conv.	Ratio **1/2**[a]
1	H	H	KOAc	LiCl	100	> 99%	82/18
2	H	H	KOAc	-	100	> 99%	84/16
3	H	Ac	KOAc	LiCl	100	> 99%	81/19
4	COOMe	H	KOAc	LiCl	100	> 99%	78/22
5	COOMe	H	KOAc	LiCl	80	> 99%	83/17
6	COOMe	Ac	KOAc	LiCl	100	> 99%	82/18
7	COOMe	Ac	KOAc	-	100	> 99%	81/19
8	COOMe	H	TMG	-	100	nr	-
9	COOMe	H	TMG	LiCl	100	nr	-
10	COOMe	Ac	TMG	-	100	nr	-
11	COOMe	Ac	TMG	LiCl	100	> 99%	73/27
12	COOMe	H	TMG	DPPF	100	> 99%	87/13
13	COOMe	H	TMG	TPP	100	> 99%	87/13
14	COOMe	H	NBu_4OAc	-	100	> 99%	92/8

a) Evaluated by GC.

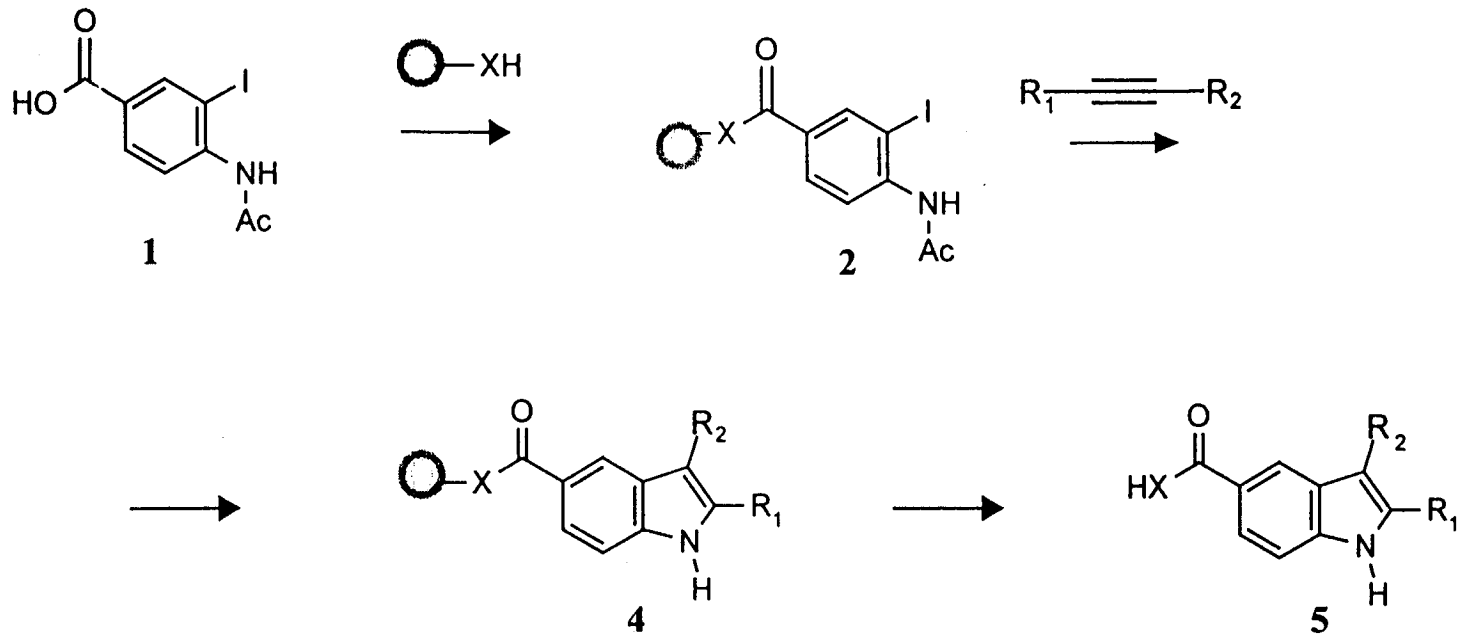
Extending the scope of the Larock reaction



Entry	R_1	Alkyne	Conversion	Ratio 1/2	Yield (%)
1	Ac		> 99%	70/30	78
2	Ac		> 99%	85/15	70
3	H		90%	1/99	36[a]
4	H		>99%	mix[b]	-
5	H		>99%	60/40	-
6	H		> 99%	50/50	40

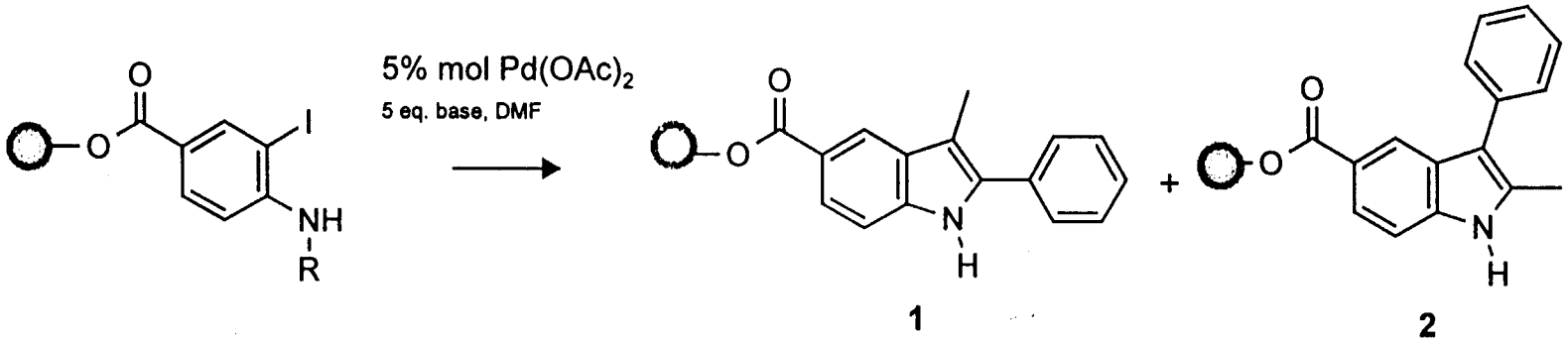
a) Desilylated product b) Mixtures of sylylated and desylylated products.

Larock reaction on solid-phase



X = NH: Zhang, H. -C.; Brumfield, K. K.; Maryanoff, B. E. *Tetrahedron Lett.* **1997**, *38*, 2493

Expanding the indoles library with the Larock reaction.

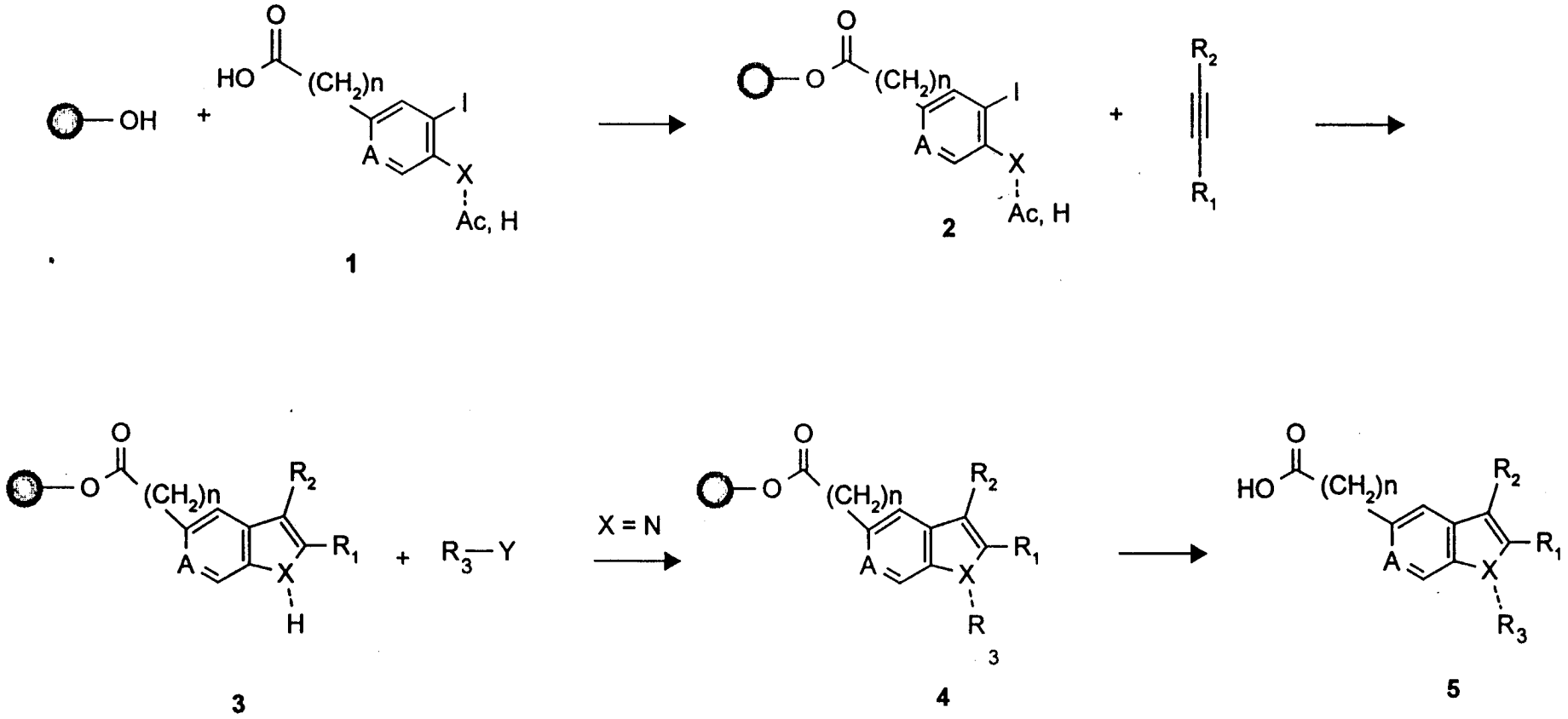


100 mg of resin, 24 hours reaction, 50 eq phenyl propyne, DMF or DMA.

Entry	R	Base	T °C	Conversion	Ratio 1/2
1	Ac	KOAc	100	>99%	83/17
2	Ac	K_2CO_3	80	>99%	78/22
3	Ac	Bu_4NOAc	80	-[a)]	-
4	H	K_2CO_3	80	>99%	80/20
5	H	Bu_4NOAc	80	-[a)]	-
6	Ac	TMG[b)]	90	>99%	79/21
7	H	TMG[b)]	90	0	-

a) Mixture of products. b) $PdCl_2(PPh_3)_2$

Synthetic Scheme for the indoles and benzofurans Libraries Construction



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