Advances in benzyne chemistry: Catalytic generation and hexadehydro-Diels-Alder reaction

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TJD Group Meeting

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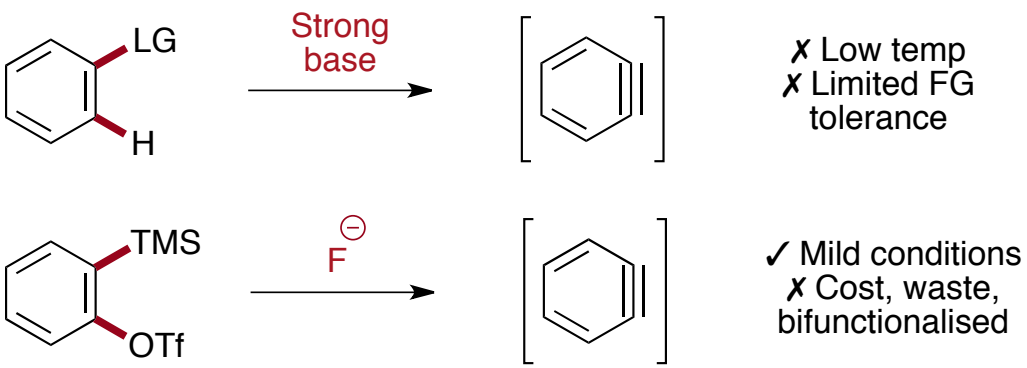
UNIVERSITY OF OXFORD

Catalytic benzyne formation

- **Established aryne formation:**

e.g.

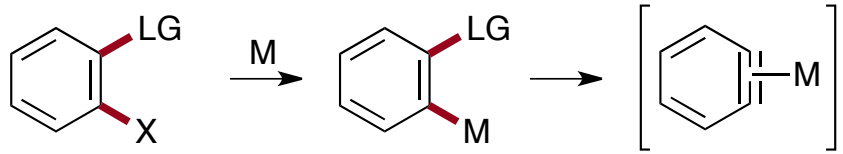


- **2 examples of catalytic aryne formation with metals.**

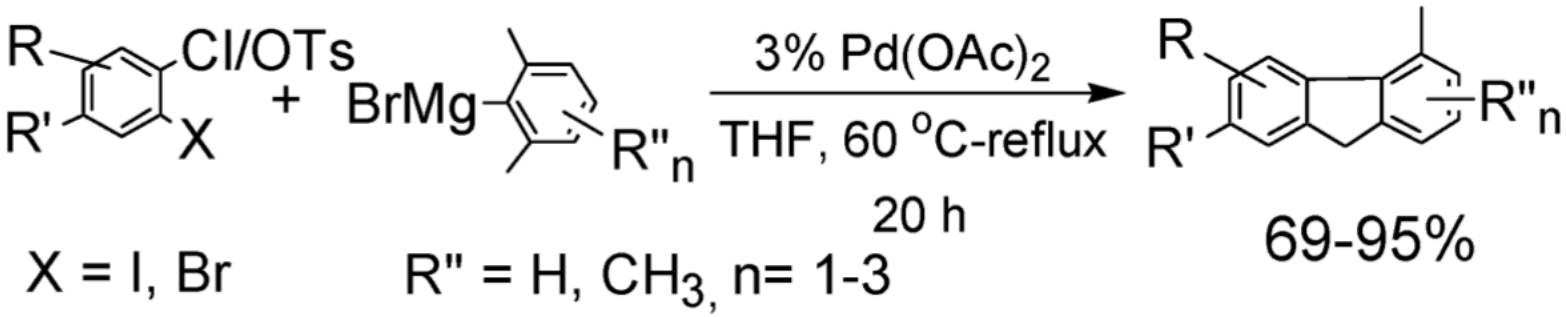
Catalytic benzyne formation

- **Example 1:**

Oxidative addition / ortho-elimination

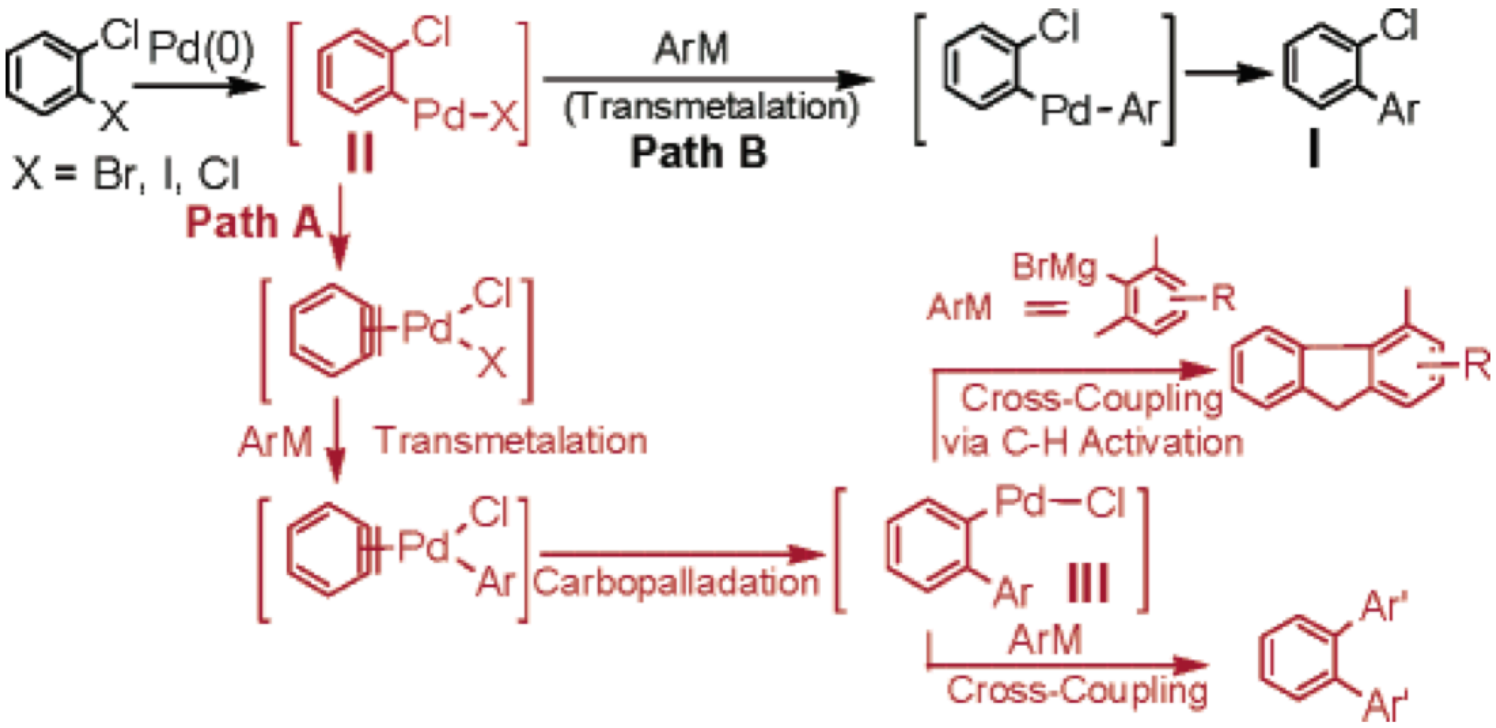


From 1,2-dihaloarenes: C.-G. Dong & Q.-S. Hu, *Org. Lett.* **2006**, *8*, 5057.



Catalytic benzyne formation

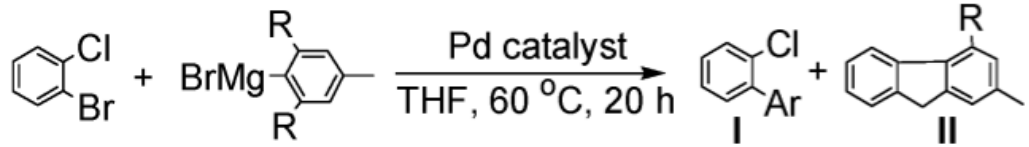
- **Example 1:** Pd must be associated with aryne, thus beneficial w.r.t. *o*-silylaryl triflate + catalytic Pd.

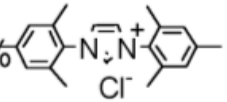


Path A *vs.* Path B?

Catalytic benzyne formation

- **Example 1:**



entry	R	catalyst	conversion (%)	ratio (%) [b] I	ratio (%) [b] II
1	CH_3	1.5% $Pd_2(dba)_3$ + 6% Ph_3P	99	69	31
2	CH_3	1.5% $Pd_2(dba)_3$ + 6% Cy_3P	99	91	9
3	CH_3	1.5% $Pd_2(dba)_3$ + 6% *t*-Bu_3P	99	90	10
4	CH_3	3% $Pd(PPh_3)_4$	99	88	12
5	CH_3	1.5% $Pd_2(dba)_3$ + 6% 	22	99	<1
6	CH_3	1.5% $Pd_2(dba)_3$ + 3% DPPE, DPPB or BINAP	5-27	99	<1
7	CH_3	1.5% $Pd_2(dba)_3$ or 3% $Pd(PhCN)_2Cl_2$ or 3% $Pd(OAc)_2$	99	<3	>97
8	CH_3	None	0	-	-
9	H	1.5% $Pd_2(dba)_3$ + 6% *t*-Bu_3P	99	93	7 [c]
10	H	3% $Pd(OAc)_2$	99	48	52 [c]

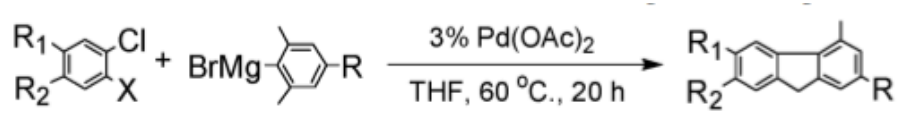
[a] Reaction conditions: 1-bromo-2-chlorobenzene (1.0 equiv), Grignard reagent (2.5 equiv), THF (2 mL). [b] Ratio based on ^1H NMR. [c] 4,4″-Dimethyl-(1,1′,2′,1″)-terphenyl was the product.

I = product from pathway B (i.e. transmetallation then reductive elimination).

II = product from pathway A (i.e. *via* benzyne intermediate then C_{sp3}-H activation).

Catalytic benzyne formation

- **Example 1:** Substrate scope



entry	dihalide	BrMg-R	product	yield(%)[b,c]
1	Cl, Br	BrMg		95
2	Cl, Br	BrMg		86
3	Cl, Br	BrMg		89
4	Cl, I	BrMg		93
5	Cl, I	BrMg		92
6	Cl, Br	BrMg	/ (77:23) [e]	84 [d]
7	Cl, Br	BrMg	/ (80:20) [e]	89 [d]
8	MeO, Cl, Br	BrMg, MeO	/ MeO (78:22) [e]	86
9	Cl, I	BrMg	/ (85:15) [e]	82
10	Cl, Cl	BrMg		61[f]

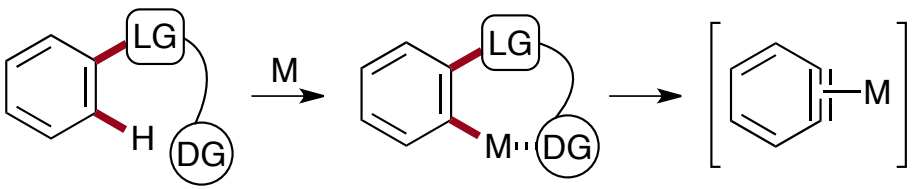
[a] Reaction conditions (not optimized): dihalide (1.0 equiv), Grignard reagent (2.5 equiv), $Pd(OAc)_2$ (3%), THF (2 mL). [b] Isolated yields. [c] 2-Chlorobiaryls were observed in less than 5% yields. [d] 1.5% $Pd_2(dba)_3$ as catalyst. [e] Ratio based on ^1H NMR. [f] Refluxing, 40 h, 16% 2-chloro-2′,4′,6′-trimethylbiphenyl was observed.

NB: 2-Haloaryl tosylates also suitable substrates

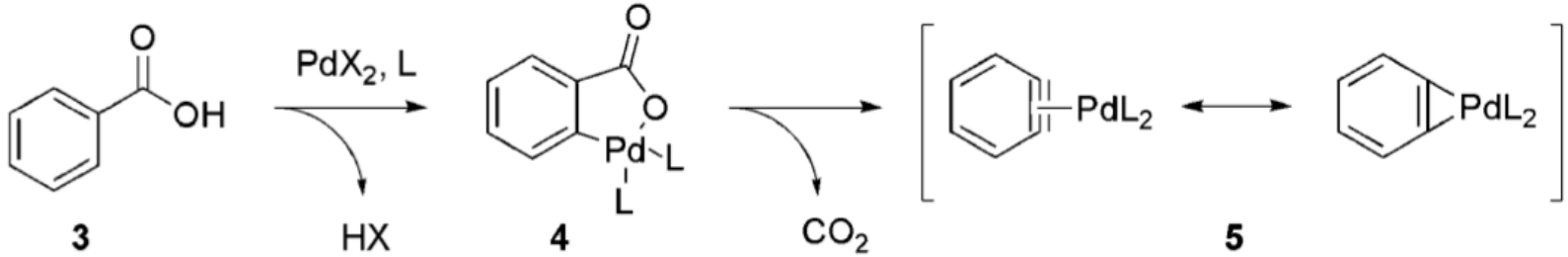
Catalytic benzyne formation

- **Example 2:**

Directed C-H metalation / ortho elimination



From benzoic acid: A. A. Cant, L. Roberts & M. F. Greaney, *Chem. Commun.* **2010**, *46*, 8671.

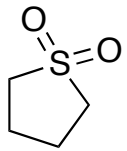


Pd-bound aryne for further C-C and C-X bond formation

Catalytic benzyne formation

- **Example 2:** Optimisation

Various oxidants, solvents, ligands



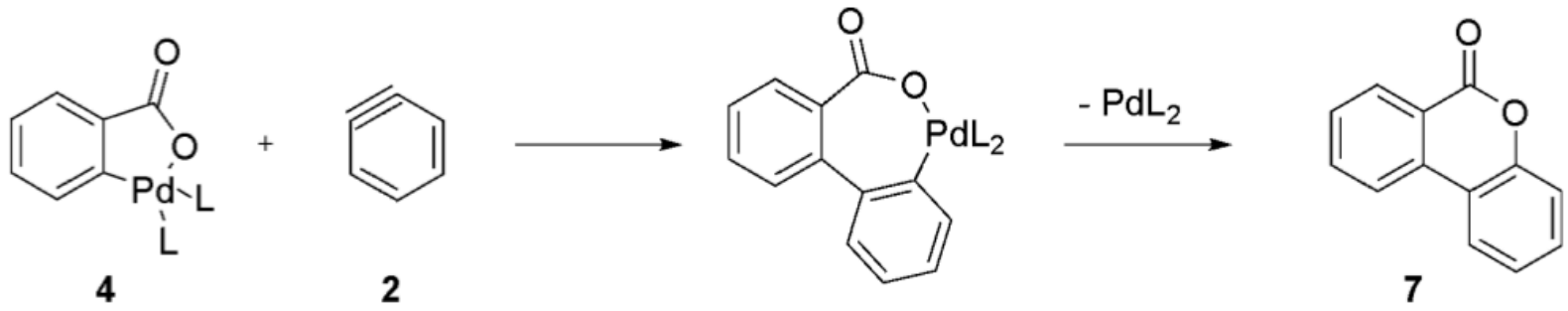
sulfolane

Entry	Oxidant	Solvent	Ligand	Yield[a] (%)
1	Air	DMF	dppb	0
2	Ag_2CO_3	DMF	dppb	0
3	Benzoquinone	DMF	dppb	0
4	$Cu(OAc)_2$ (1 equiv.)	DMF	dppb	4
5	$Cu(OAc)_2$ (1 equiv.)	DMF	phen	7
6	$Cu(OAc)_2$ (1 equiv.)	DMF[c]	phen	13
7	$Cu(OAc)_2$ (0.75 equiv.)	DMF[c]	phen	20
8	$Cu(OAc)_2$ (0.5 equiv.)	DMF[c]	phen	17[b]
9	$Cu(OAc)_2$ (0.75 equiv.)	Sulfolane[c]	phen	37
10	$Cu(OAc)_2$ (0.75 equiv.)	Sulfolane[c]	phen	13
11	$Cu(OAc)_2$ (0.75 equiv.)	Sulfolane[d]	phen	47[e]

Reaction conditions: solvent (0.5 mL), $Pd(OAc)_2$ (10 mol %), ligand (10 mol %) and benzoic acid (111 mg, 0.9 mmol) were sonicated together for 1 min. K_2HPO_4 (2 equiv.), TBAB (1 equiv.), 4 Å MS, and oxidant were then added and the reaction was heated to 150 °C for 16 h, open to air.[a] Yields determined by GC with triphenylene as external standard. [b] No sonication. [c] 1.5 mL of solvent used. [d] 2.5 mL of solvent used. [e] Isolated yield; dppb = diphenylphosphinobutane; phen = 1,10-phenanthroline.

Catalytic benzyne formation

- **Example 2:** side product with excess $Cu(OAc)_2$



25 % yield of dibenzopyranone **7** with 2.0 equiv $Cu(OAc)_2$ & *tert*-butyl X-Phos as ligand.

Catalytic benzyne formation

- **Example 2:**

- High product selectivity.

- *meta*-Benzoic acids must proceed *via* aryne **2a** as same products as *para*-SM.

- Product isomers match those from conventional aryne precursors.

- *ortho*-SM typically ineffective.

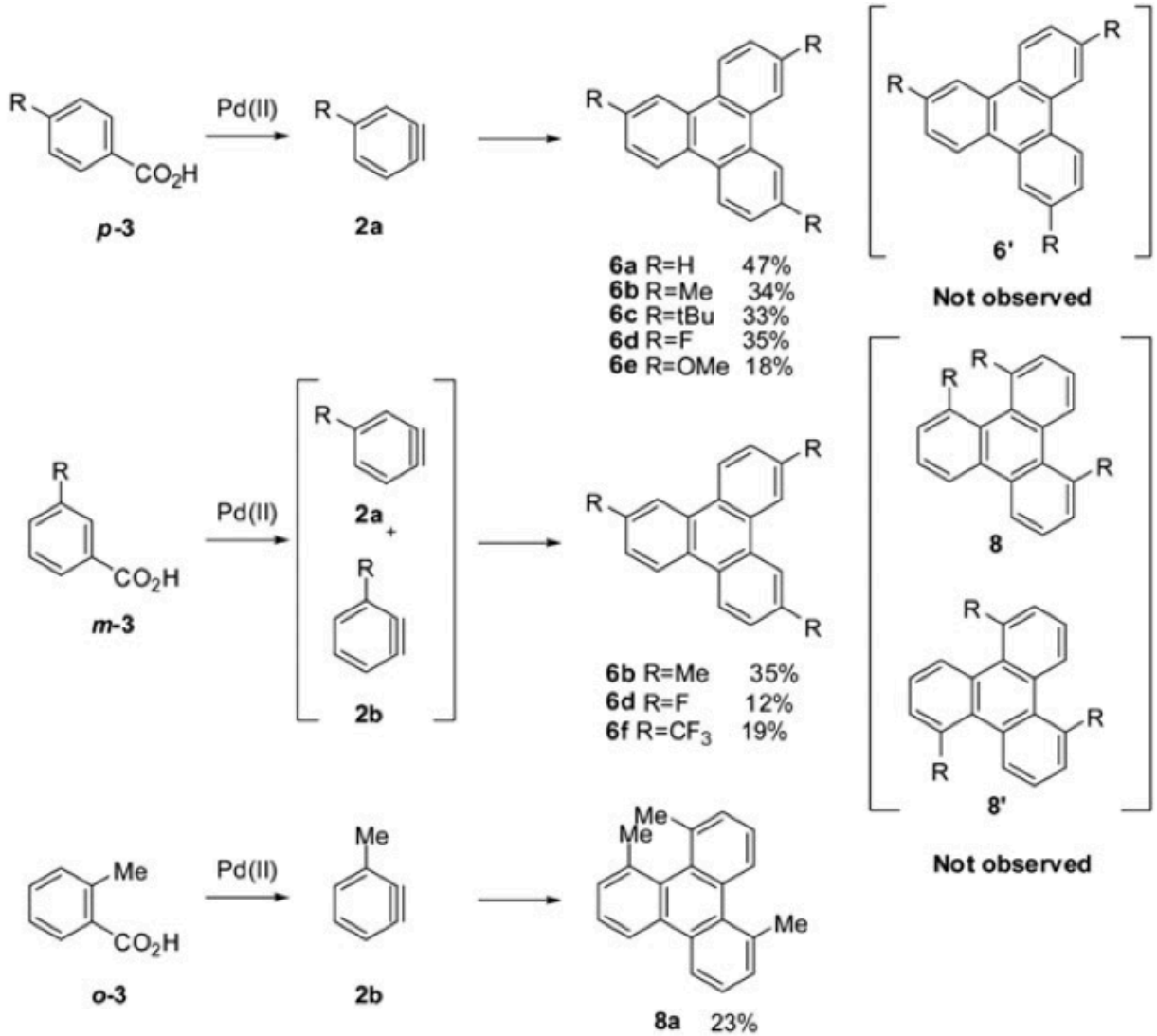


Fig. 3 Monosubstituted benzoic acid trimerisation. Conditions as in Table 1.

Catalytic benzyne formation

- **Example 2:** with alkyne.

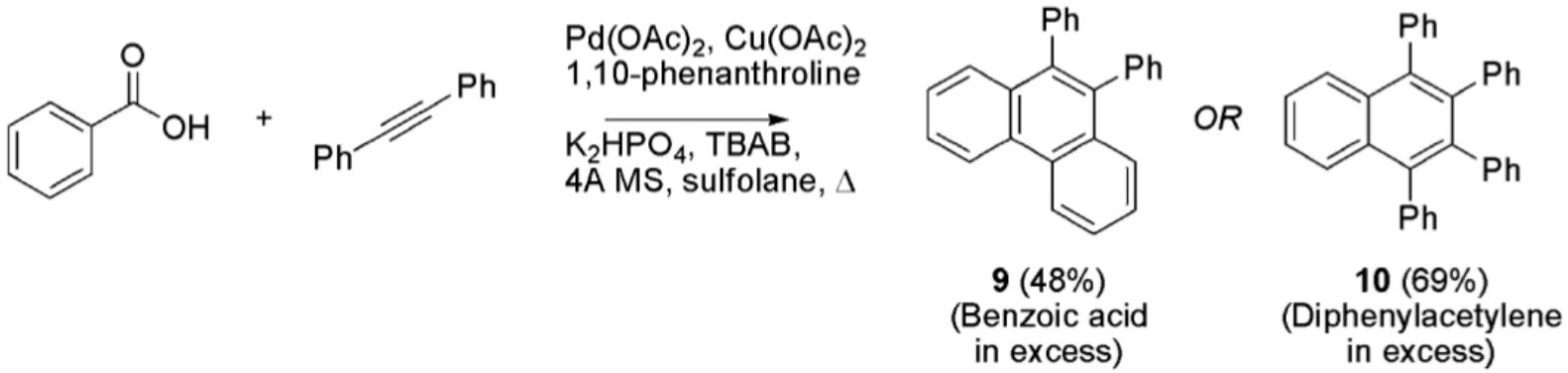
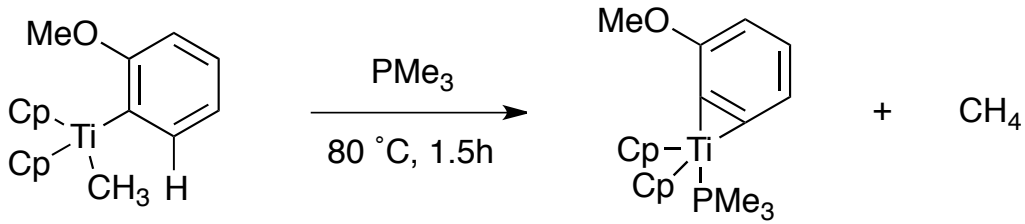
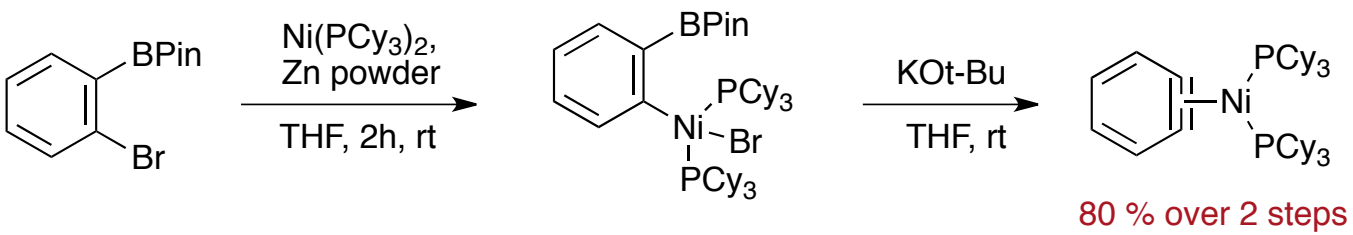


Fig. 4 Naphthalene and phenanthrene synthesis from benzoic acid.

Benzyne generation with stoichiometric organometallics



J. Cámpura & S. L. Buchwald, *Organometallics,* **1993**, *12*, 4182.
Cases of sigma-bond metathesis with Zr, Ta, Nb, Mo & Ru, see review:
A. M. Dyke, A. J. Hester & G. C. Lloyd-Jones, *Synthesis*, **2006**, *24*, 4093.



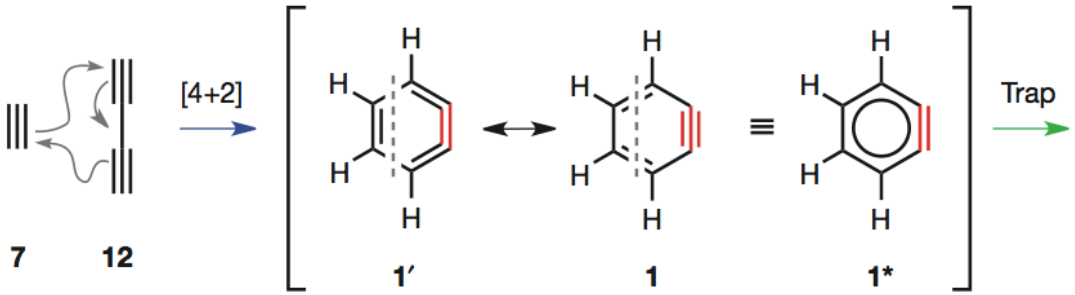
Pd analogue also stable

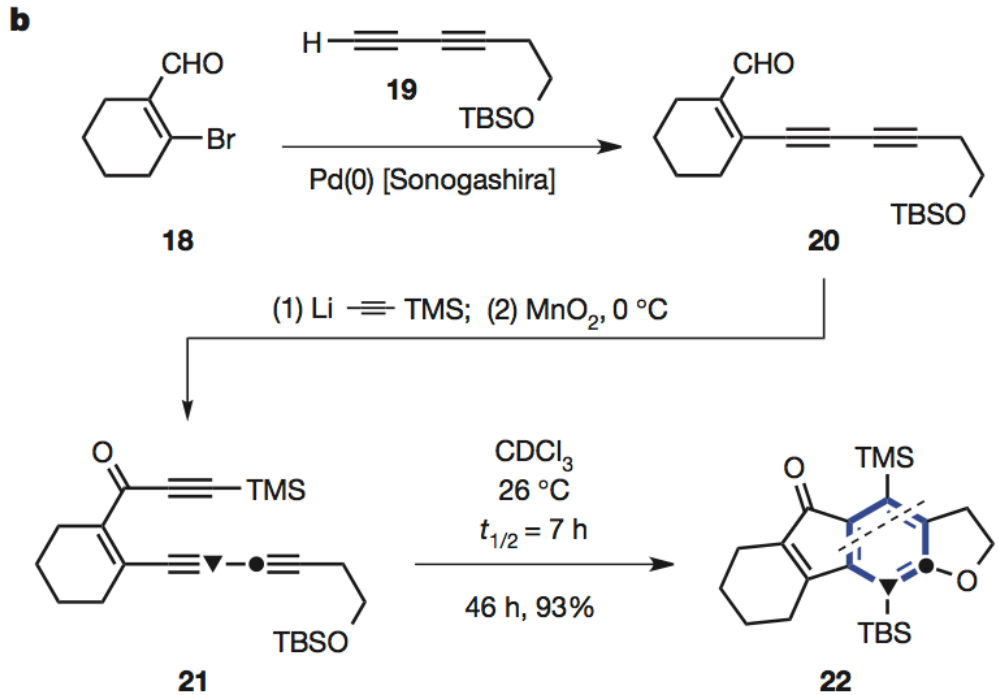
Ni(0) and Pd(0) complexes: M. Retbøll, A. J. Edwards, A. D. Rae, A. C. Willis, M. A Bennett & E. Wenger, *J. Am. Chem. Soc.* **2002**, *124*, 8348.

Metal-free benzyne generation

- **Hexahydro-Diels-Alder reaction.**

e.g.





T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby & B. P. Woods, *Nature*, **2012**, *490*, 208.