Asymmetric addition of complex nucleophiles – towards the Taxol core

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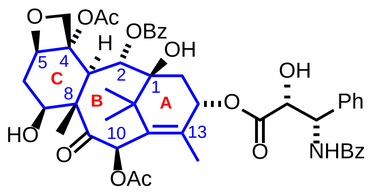
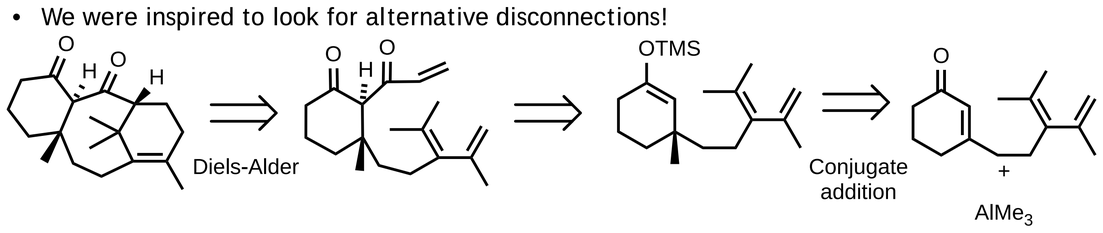
1 Taxol core: prior art



Taxol (with core highlighted)

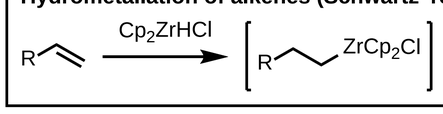
- Taxol is structurally complex and is thus a useful benchmark for evaluating new synthetic methods.
- Baran and co workers [1] synthesised the core (Taxadiene) in 2012.
- Their route efficiency came from two tactics
  1. Intramolecular Diels-Alder reaction (IMDA) to form the AB ring system. [2]
  2. Catalytic asymmetric conjugate addition to set the quaternary stereocenter at C8. [3]

- We were inspired to look for alternative disconnections!

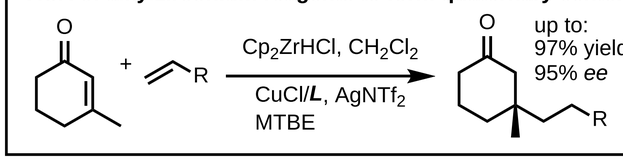


2 Asymmetric conjugate addition (ACA)

Hydrometallation of alkenes (Schwartz' reagent)



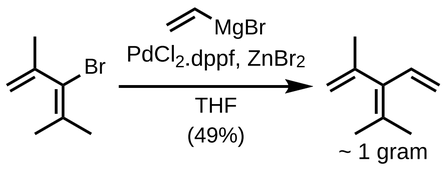
ACA of alkylzirconium reagents to form quaternary centers



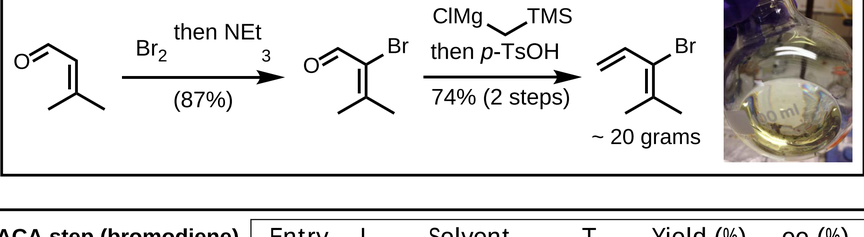
- Alkenes can be used as nucleophiles in ACA reactions via their hydrometallated form. [4]
- A variety of products containing tertiary or quaternary stereocenters can be accessed from either cyclic or acyclic enones. [5]
- Yields and enantioselectivities are usually high (see quaternary center formation above [6]).
- Functional groups are tolerated: protected alcohols, aromatic rings, halogens etc
- Reactions don't require cryogenic temperatures (compared to when using traditional organometallic reagents).

3 Early approaches

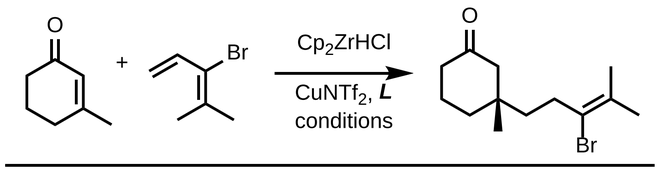
Triene synthesis



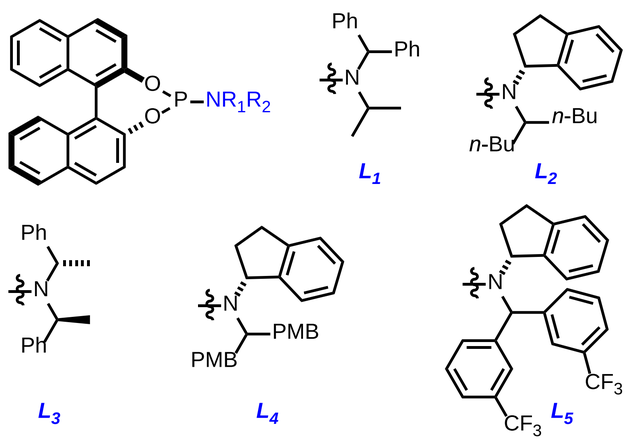
Bromodiene [7] synthesis



Optimisation of ACA step (bromodiene)



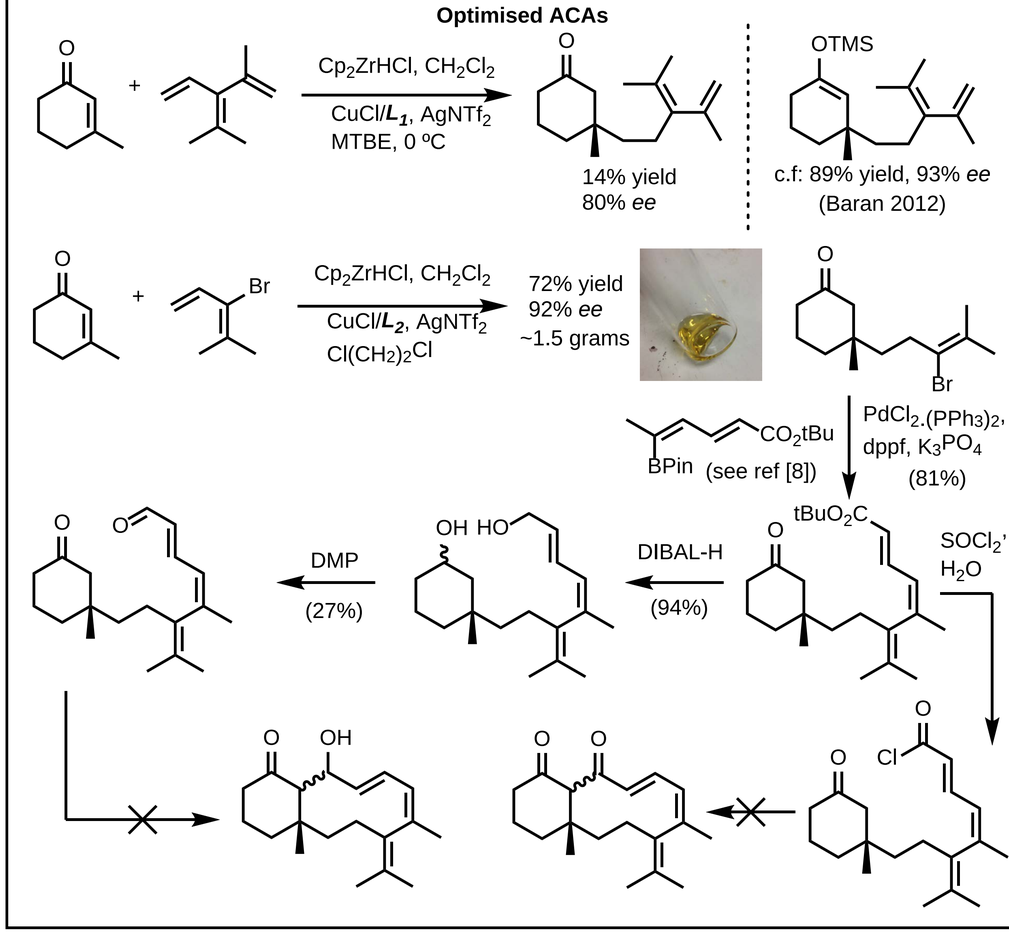
L:



Entry	L	Solvent	T	Yield (%)	ee (%)
1	1	MTBE	RT	70	6
2	3	MTBE	RT	63	18
3	4	MTBE	RT	42	64
4	5	MTBE	RT	49	86
5	2	MTBE	RT	81	82
6	2	$ClCH_2CH_2Cl$	RT	45	90
7	2	PhMe	RT	70	84
8	2	2-Me-THF	RT	77	76
9	2	Et_2O	RT	49	80
10	2	$CHCl_3$	RT	54	88
11	2	CH_2Cl_2	RT	37	84
12	2	o-$PhCl_2$	RT	36	88
13	2	$ClCH_2CH_2Cl$	0 °C	39	92
14	2	PhMe	0 °C	44	14
15[1]	2	PhMe	RT	48	60
16[2]	2	PhMe	RT	71	88
17[3]	2	PhMe	RT	66	90

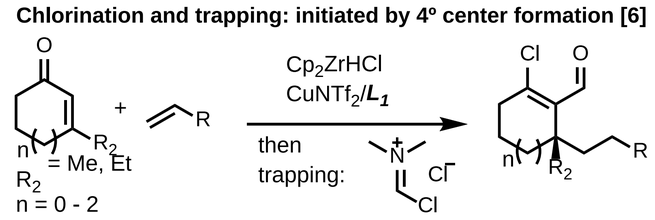
[1] 3 mL "solvent", 0.25 mL CH_2Cl_2. [2] 2 mL "solvent", 0.5 mL CH_2Cl_2. [3] 2 mL "solvent", 1 mL CH_2Cl_2

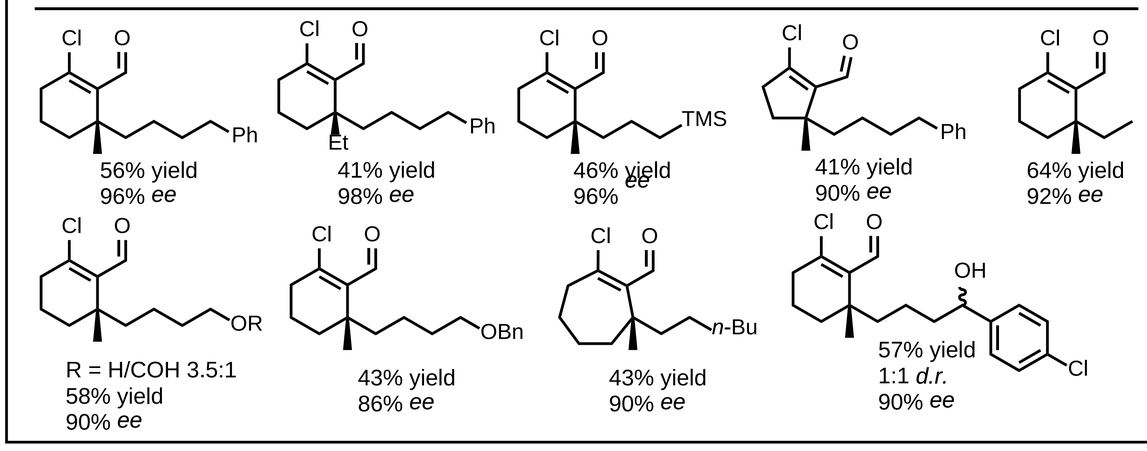
Optimised ACAs



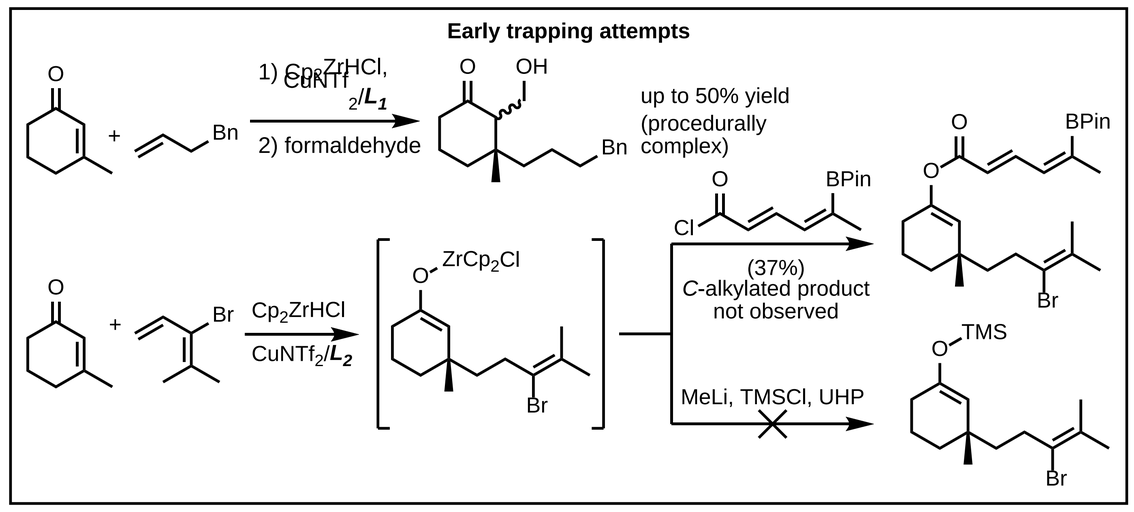
4 Tandem ACA/trapping reactions

Chlorination and trapping: initiated by 4º center formation [6]

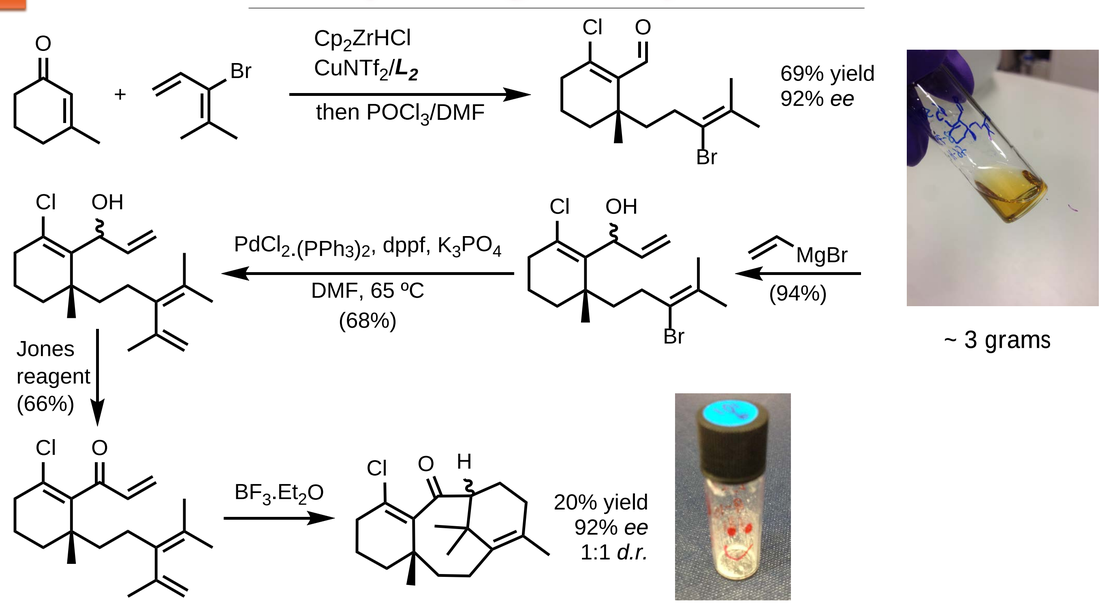




Early trapping attempts

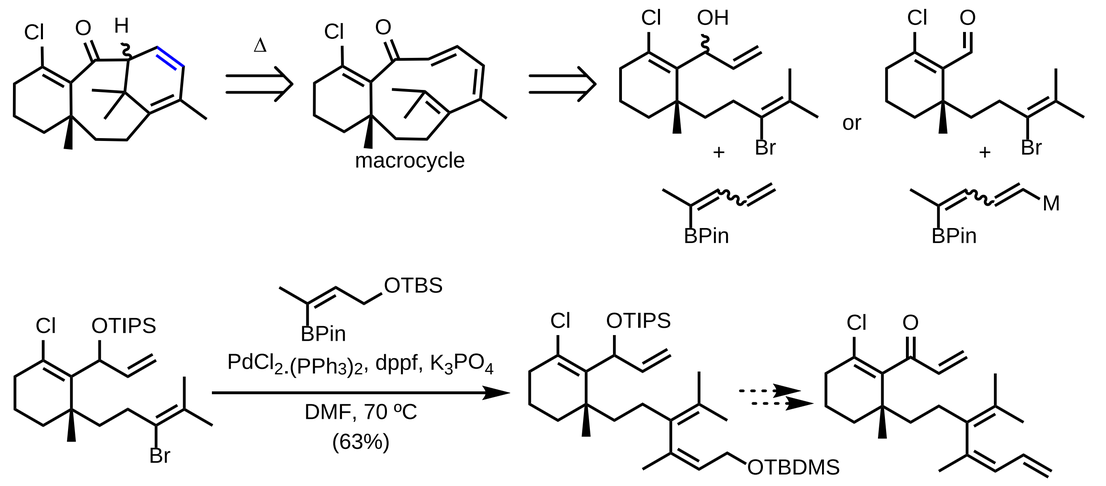


5 Completing the synthesis



~ 3 grams

6 Future work



References:
[1] Nat. Chem. 2011, 4, 21. **[2]a** J. Chem. Soc Perkin Trans. 1 1986, 1303. **b** Tetrahedron Lett. 1994, 35, 1317–1320. **c** J. Org. Chem. 2000, 65, 7865–7869. **[3]** Chem. Eur. J. 2007, 13, 9647–9662. **[4]a** Nat. Chem. 2012, 4, 649–654. **b** Chem. Sci. 2018, 9, 2628–2632. **[5]** The inquisitive reader is referred to the publications list on the Fletcher group website. **[6]** Angew. Chem. Int. Ed. 2013, 52, 7995 **[7]** First reported in J. Org. Chem. 2005, 70, 3871 **[8]** Prepared according to literature procedure: J. Am. Chem. Soc. 2006, 128, 5338.