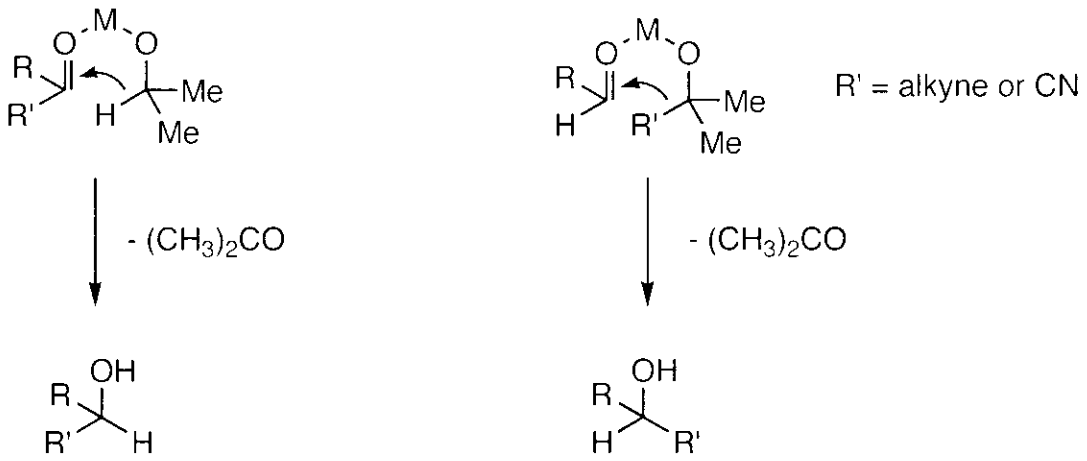
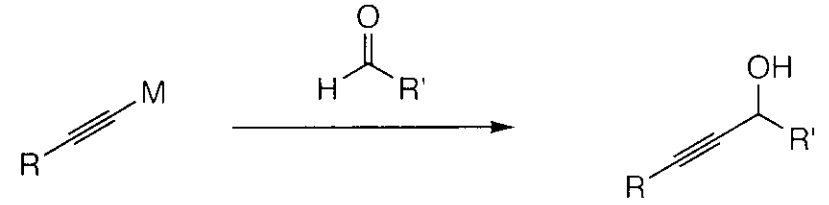
Meerwein-Ponndorf-Verley alkynylation of aldehydes: Essential modification of aluminum alkoxides for rate acceleration and asymmetric synthesis.

Ooi, T.; Miura, T.; Ohmatsu, K.; Saito, A.; Maruoka, K.
Org. Biomol. Chem. **2004**, *2*, 3312-3319.



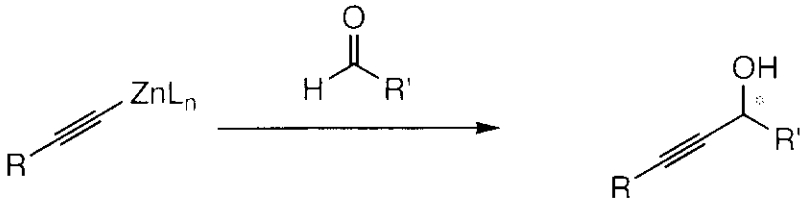
Synthesis of alkynols: other methods

- Classical



M = Li or Mg

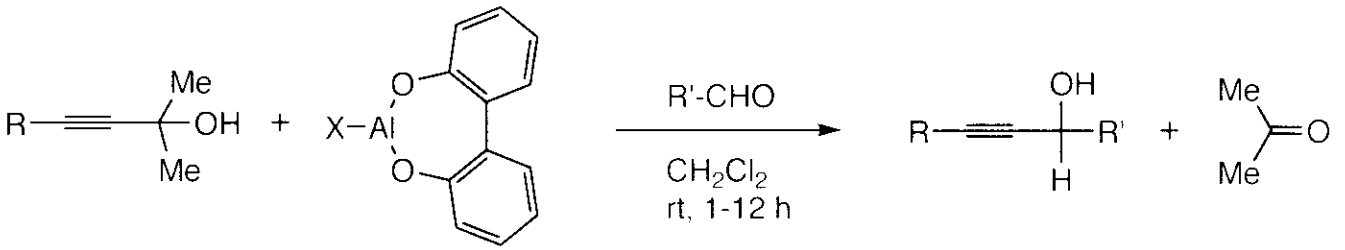
- Modern asymmetric variants



Carreira: $Zn(OTf)_2$, N-methylephedrine

Pu: $Zn(Et)_2$, BINOL, Ti(O*i*-Pr)4

First report of MPV alkynylation

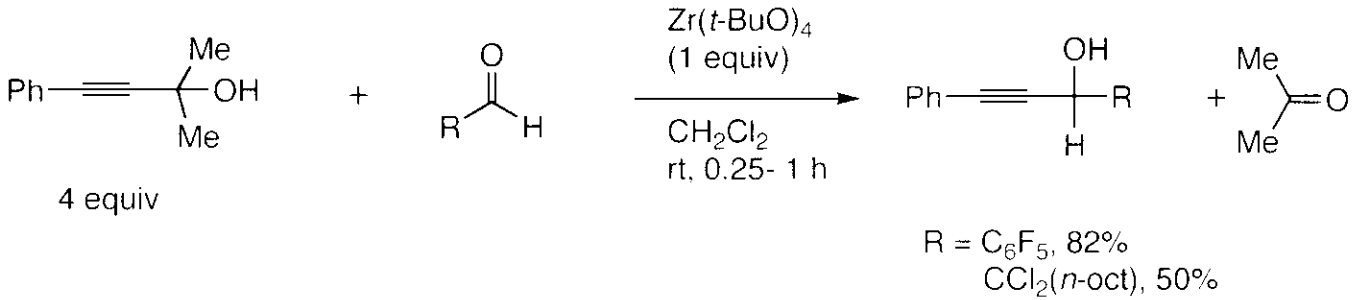


R = Ph, CH=CHPh X = Me or O*t*-Bu R' = CHCl(*n*-Oct)
CCl_2(*n*-Oct)
CCl_3
CBr_3
C_6F_5
CCPh

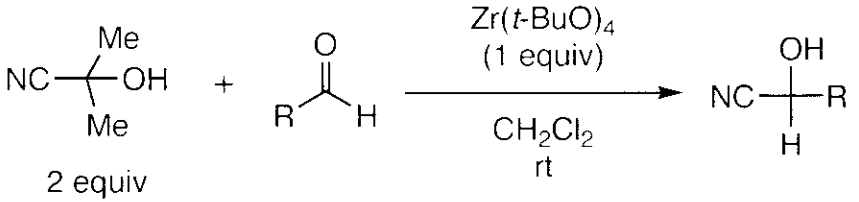
- Yields: 40 - 99%
- 3 catalytic (10 - 20 mol %) examples were reported.
- Cyanation also reported.

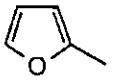
Ooi, T.; Miura, T.; Maruoka, K. *J. Am. Chem. Soc.* **1998**, *120*, 10790-10791

$Zr(t\text{-}BuO)_4$ Promoted MPV Alkynylation and Cyanation of Aldehydes



R = C_6F_5, 82%
$CCl_2(n\text{-oct})$, 50%

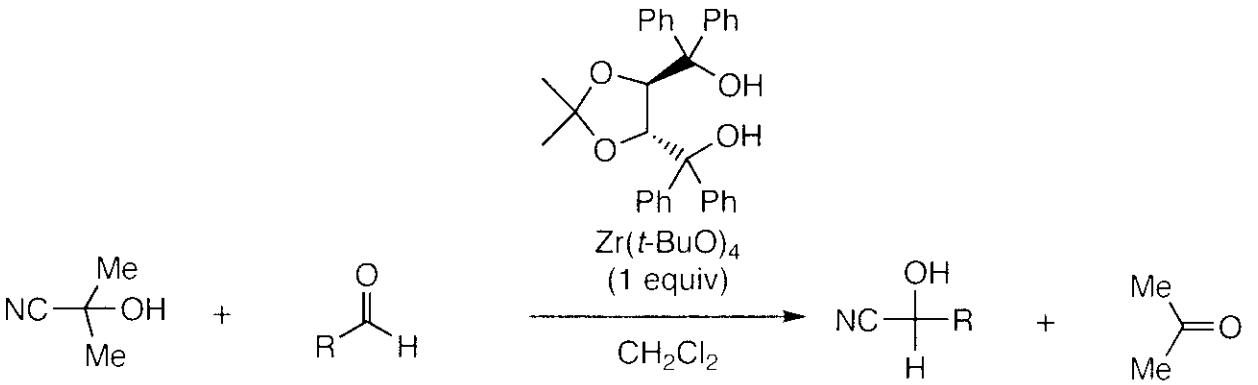


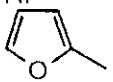
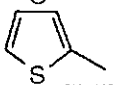
Entry	Aldehyde (R)	Reaction time (h)	Product	Yield (%)[a]
1	C_6F_5	0.1	**5a**	90
2	Ph	0.5	**5b**	93
3	*o*-Cl-C_6H_4	0.5	**5c**	76
4	*p*-NO_2-C_6H_4	0.5	**5d**	82
5	*p*-MeO-C_6H_4	5	**5e**	91
6	α-Np	2	**5f**	91
7	$Ph(CH_2)_2$	1	**5g**	96
8	$CH_3(CH_2)_6$	0.5	**5h**	91
9		0.5	**5i**	82

[a] Isolated yield.

Ooi, T.; Takaya, K.; Miura, T.; Maruoka, K. *SynLett.* **2000**, 69-71.
Ooi, T.; Miura, T.; Takaya, K.; Ichikawa, H; Maruoka, K. *Tetrahedron,* **2001**, *57*, 867-873.

Asymmetric Cyanation

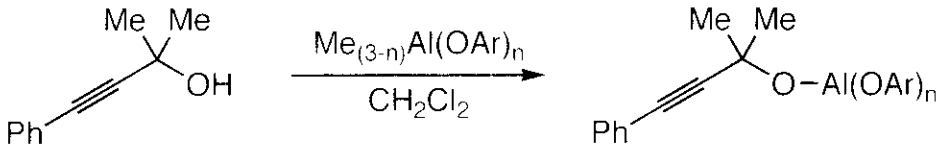


Entry	Aldehyde (R)	Condition (°C, h)	Product	Yield (%)[a]	ee (%)[b] (config)[c]
1	$Ph(CH_2)_2$	−40, 7.5	**5g**	63	85 (*R*)
2		−40, 7.5		80	80 (*R*)[d]
3		−78, 7.5		32	91 (*R*)
4	$CH_3(CH_2)_8$	−40, 5	**5j**	63	84 (*R*)
5	*c*-Hex	−40, 5	**5k**	55	79 (*R*)
6	*t*-Bu	−40, 5	**5l**	36	72 (*R*)
7	$PhCH_2$	−40, 5	**5m**	47	59 (*R*)
8	Ph	−40, 18	**5b**	45	63 (*R*)
9		−40, 18	**5i**	30	61 (*R*)
10		−40, 18	**5n**	28	54 (*R*)
11	*trans*-PhCH=CH	−40, 18	**5o**	25	29 (*R*)

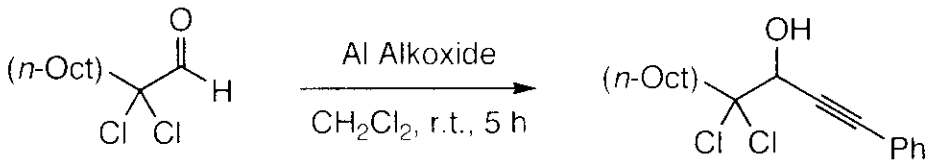
[a] Isolated yield of acetate.
[b] Enantiomeric excesses were determined by GC analysis of the corresponding acetates with chiral column (GL SCIENCE CP-CHIRASIL-DEX CB).
[c] Absolute configurations were determined by comparison of optical rotations of cyanohydrins with literature values.
[d] 4 equiv. of acetone cyanohydrin was used.

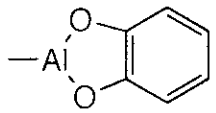
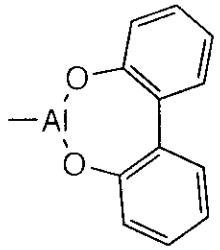
Ooi, T.; Miura, T.; Takaya, K.; Ichikawa, H; Maruoka, K. *Tetrahedron*, **2001**, *57*, 867-873.

Ligand acceleration of MPV alkynylation catalysts



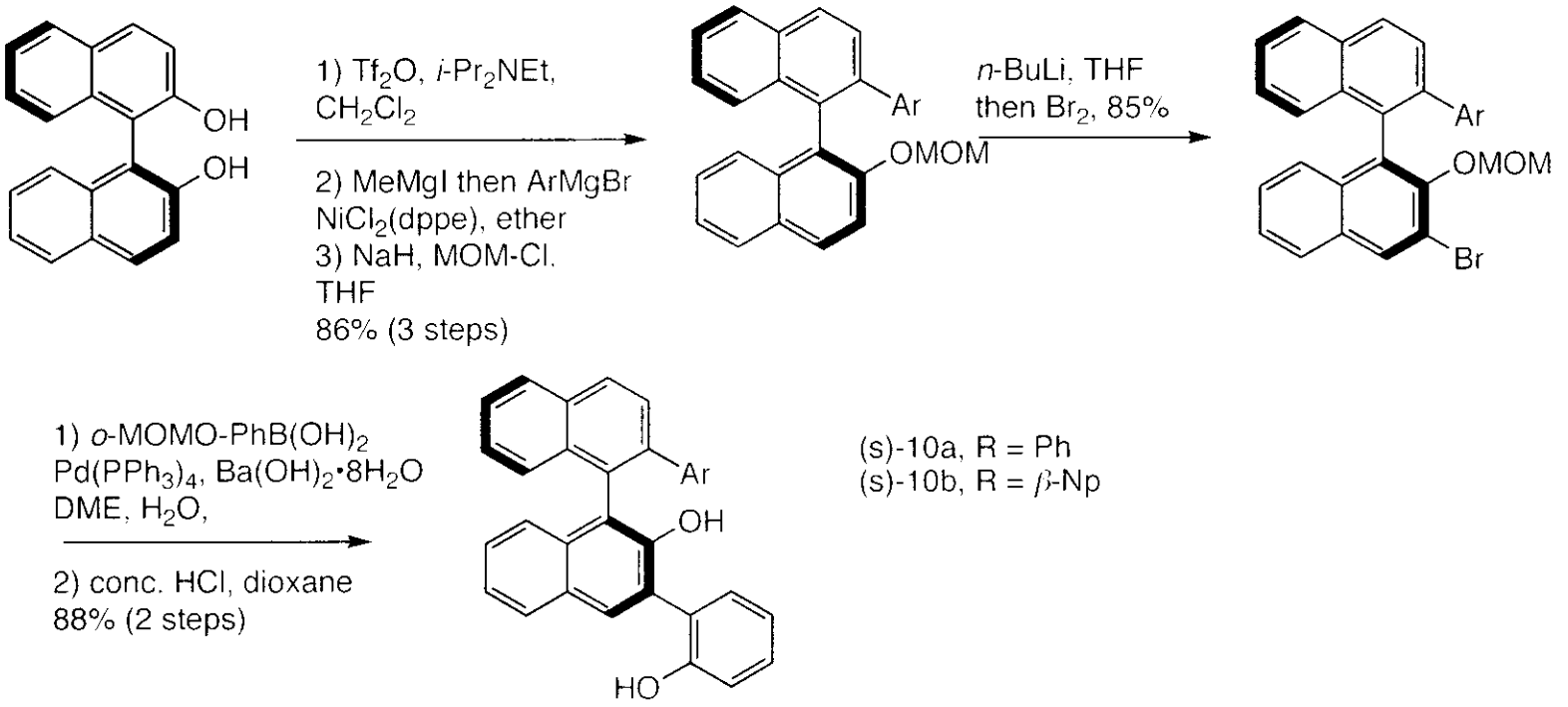
Al Alkoxide



Al(OPh)	0%
Al(OPh)2	16%
	20%
	53%

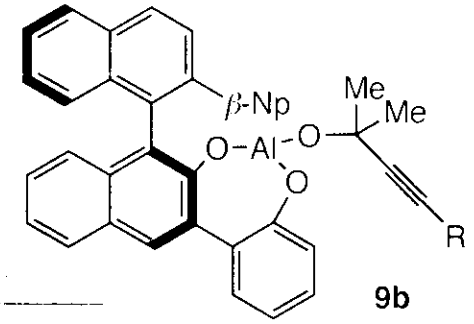
Ooi, T.; Miura, T; Ohmatsu, K.; Saito, A.; Maruoka, K. *Org. Biomol. Chem.* **2004**, *2*, 3312-3319.

Asymmetric MPV alkynylation: Ligand Synthesis



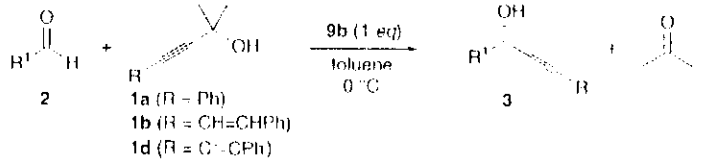
Ooi, T.; Miura, T; Ohmatsu, K.; Saito, A.; Maruoka, K. *Org. Biomol. Chem.* **2004**, *2*, 3312-3319.

Asymmetric MPV alkynylation



9b

Table 2 Asymmetric MPV alkynylation of various reactive aldehydes[a]



Entry	Aldehyde (R^1)	Alkyl source (R)	Time/h	Yield (%)[b]	ee (%)[c] (config)[d]	Product
1	$C(Br_2)(CH_2)_5CH_3$ (**2g**)	Ph	1.5	78	64[e]	**3ga**
2		Ph	1.5	88	81	**3ga**
3		CH=CHPh	1.5	82	74	**3gb**
4	$C(Br_2)(CH_2)_5CH_3$ (**2h**)	Ph	1	84	78 (*R*)	**3ha**
5		CH=CHPh	1.5	81	80	**3hb**
6	$C(Br_2)CH_2Ph$ (**2i**)	Ph	1	70	82	**3ia**
7		CH=CHPh	5	72	67	**3ib**
8	CCl_3 (**2e**)	Ph	18	85	83 (*R*)	**3ea**
9		CH=CHPh	1.5	99	85	**3eb**
10		C≡CPh	1.5	73	71	**3ed**
11	CBr_3 (**2d**)	Ph	18	87	90 (*R*)	**3da**
12		CH=CHPh	1.5	94	83	**3db**
13		C≡CPh	5	71	86	**3dd**
14	CCl_2CHPh (**2j**)	Ph	1.5	30[e]	96	**3ja**

[a] Unless otherwise noted, aldehyde **2** was treated with *in situ* generated aluminium alkoxide **9b** (1 equiv) in the presence of 1 (1 equiv) in distilled toluene at 0 °C. [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis using a following chiral column with hexane/*i*-PrOH as solvent: Daicel Chiralcel OJ for entries 1, 2, 12 and 13; Daicel Chiralcel OD for entries 3, 4, 6, 8, 10 and 11; Daicel Chiralpak AD for entries 5, 7, 9 and 14. [d] Absolute configuration was established, after conversion to the known products, by comparing the optical rotation with the literature values. See the Experimental Section. [e] With aluminium alkoxide **9a**. [f] Use of each 2 equiv of Al reagent and 1. [g] The alkynylation product **3ja** (R^1 = Ph, R = PhCH=CCl) works as a hydride source for the MPV reduction of the starting aldehyde to furnish 2-chloro-1,5-diphenyl-1-penten-4-yn-3-one and 2-chloro-3-phenyl-2-propen-1-ol as side-reaction products.

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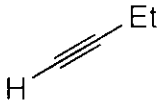
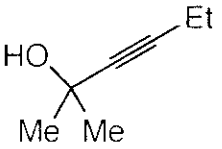
Potential advantages of the methodology:

- Volatile alkynes

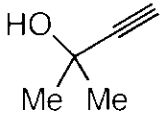


Butyne
gas at 25 °C

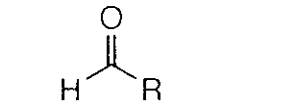


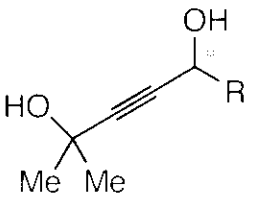
Butyne acetone adduct
bp: 144 °C / 760 torr

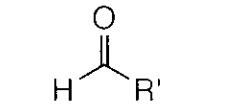
- Chemoselective alkyne linchpin strategy

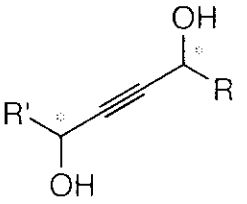


Commercially available in bulk









Conclusions:

- First enantioselective MPV-alkynylation of aldehydes (yields: 30 - 99%; ee: 64-96%).
- Catalyst generated in situ
- Reasonable reaction time (1-18 h) and temperature (0 °C)
- Substrate scope is limited.
- Not generally catalytic