Recent Reviews:

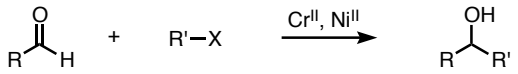
Lumbroso, A.; Cooke, M. L.; Breit, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 1890–1932.

Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407–2424.

Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1045.

- Coupling of an alkenyl halide or triflate wtih an aldehyde mediated by Cr(II) was first reported in 1977 and was found later to be initiated by a *catalytic amount* of $NiCl_2$.

Generalized Reaction Scheme:

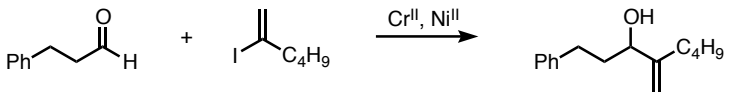


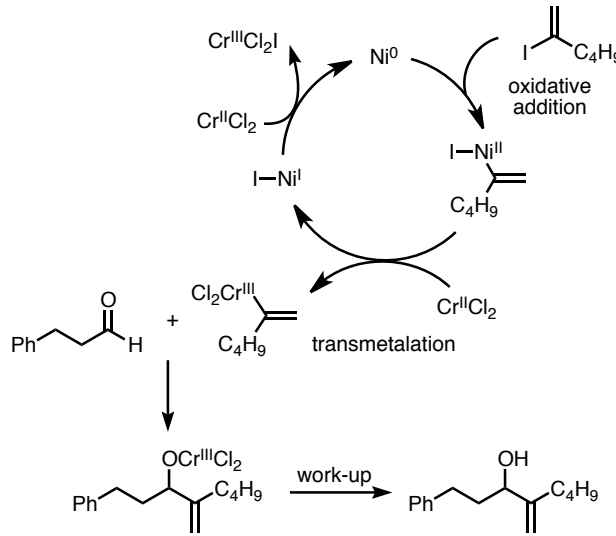
Typically:

- R' = allyl, aryl, alkenyl, alkynyl, propargyl
- X = Cl, Br, I, OSO_2CF_3, phosphonate
- metal = Cr, Ni (sometimes Co)

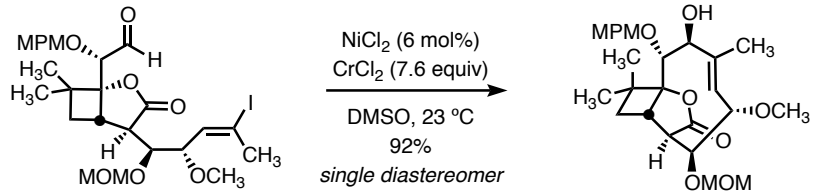
Mechanism:

- A specific example:

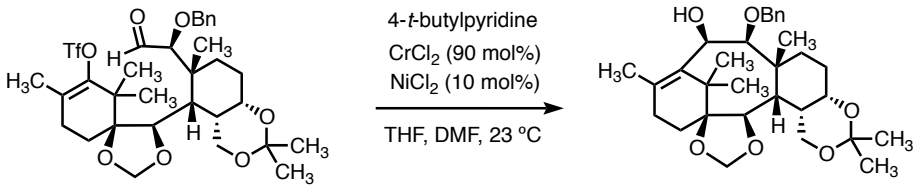




- super-stoichiometric amounts of Cr^{II} reagents are generally employed.
- aldehydes react markedly faster and with complete selectivity in the presence of ketones.
- because of the low basicity of organochromium reagents, the reaction is compatible with an array of functional groups.
- Examples:

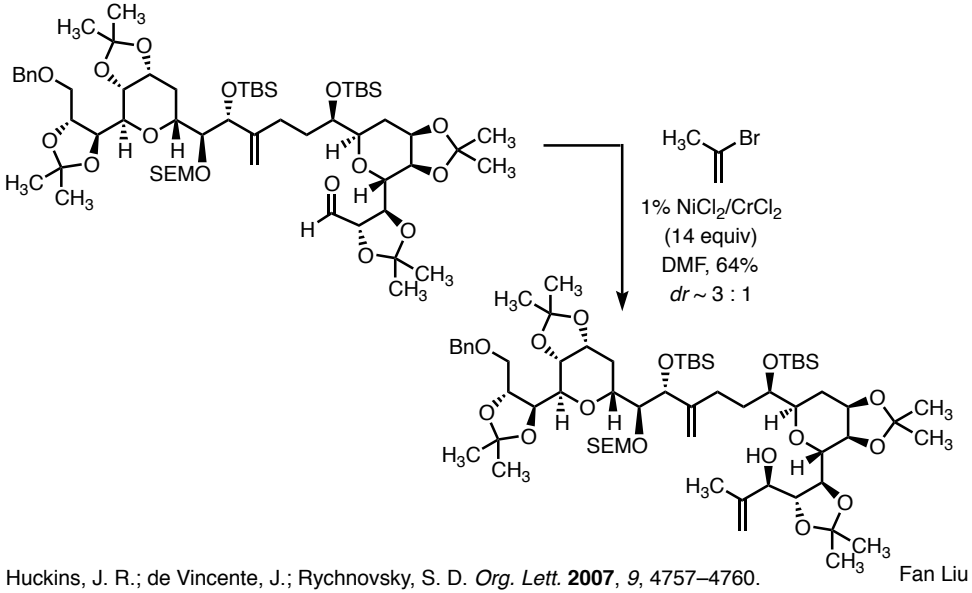


Takao, K.; Hayakawa, N.; Yamada, R.; Yamaguchi, T.; Morita, U.; Kawasaki, S.; Tadano, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3426–3429.



Product was not formed in the absence of 4-*t*-butylpyridine.

Stamos, D. P.; Sheng, X. C.; Chen, S. S.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6355–6358.



Huckins, J. R.; de Vincente, J.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4757–4760.

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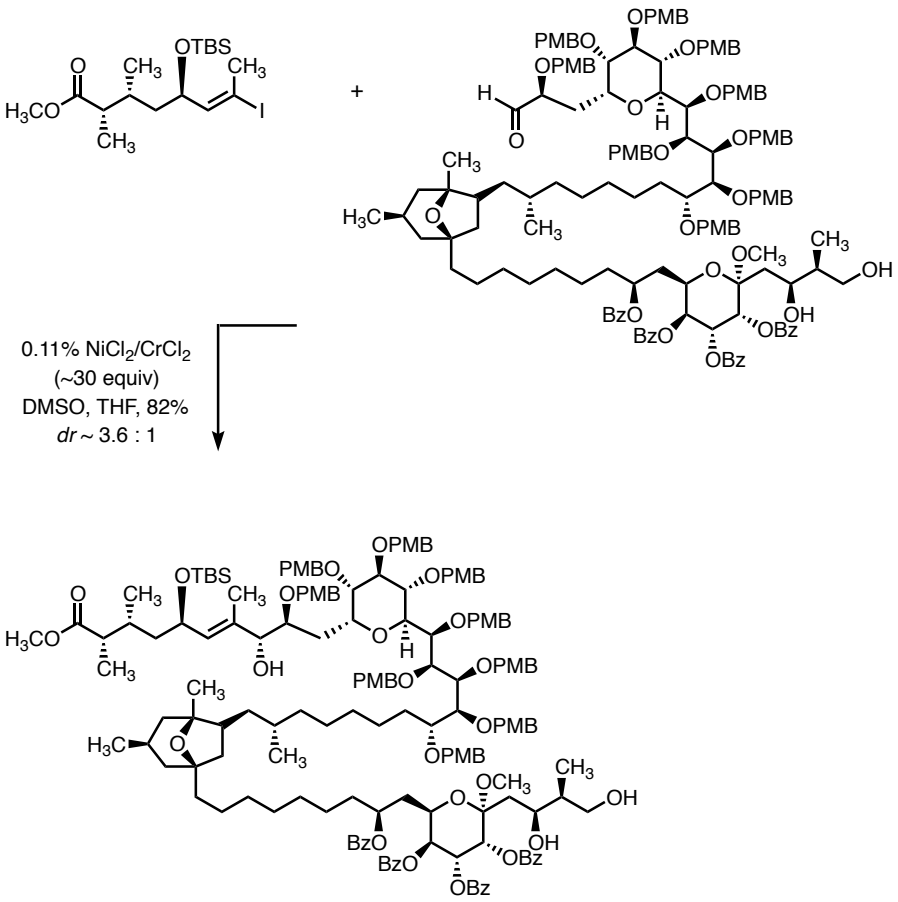
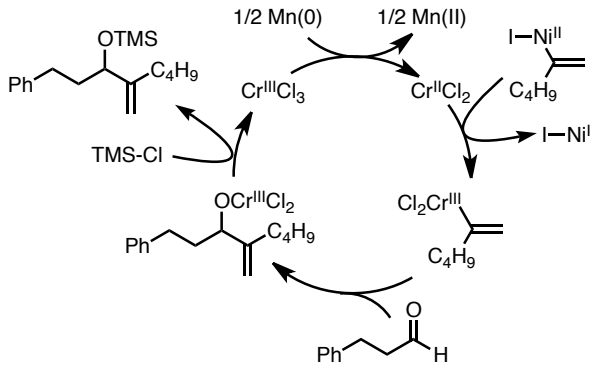
• Synthesis of a palytoxin intermediate:



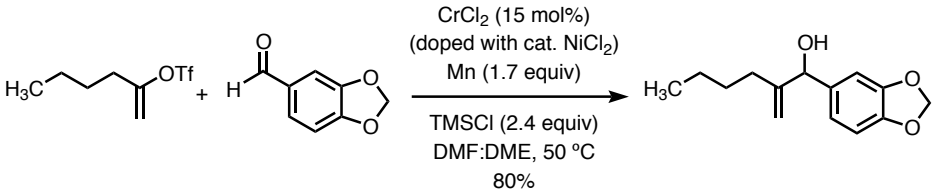
Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7525–7530.

Catalytic in Chrominium: Addition of super stoichiometric amounts of the non-toxic metal manganese allows the reaction to proceed with catalytic amounts of Cr.

• **TMSCl + Mn(0)**: TMSCl serves to liberate Cr^{III} from the product chromium alkoxide. Mn(0) reduces Cr^{III} to the catalytically active Cr^{II} species:



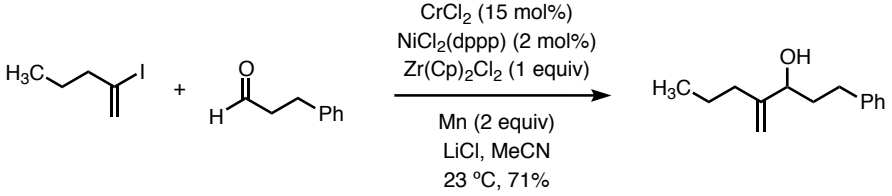
• Example:



Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357.

• **$Zr(Cp)_2Cl_2$ + Mn(0)**: use of $Zr(Cp)_2Cl_2$ in lieu of TMSCl suppresses formation of TMS enol ethers of aldehydes and increases the reaction rate.

• Example:



Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031–5033.

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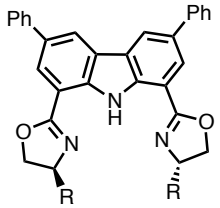
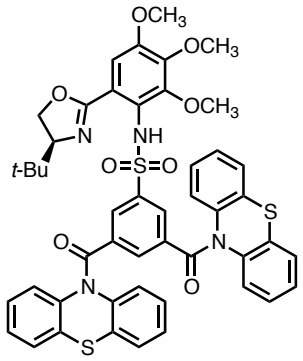
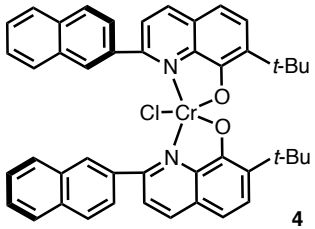
Ligand Additives: Addition of supporting ligands often accelerates the reaction. Use of chiral ligands affords enantiomerically enriched secondary alcohol products.



1 R = *i*-Pr
2 R = *t*-Bu

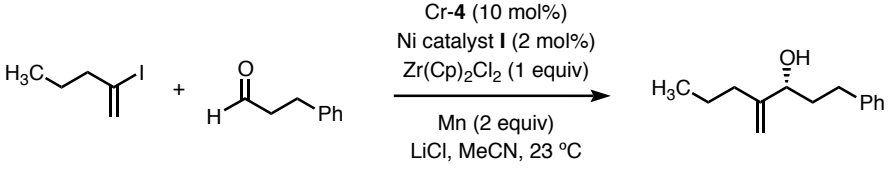


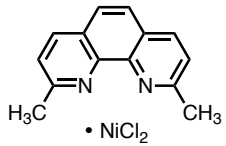
3



4

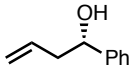
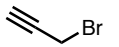
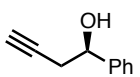
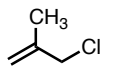
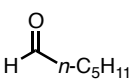
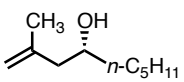
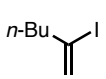
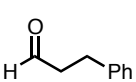
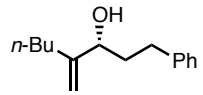
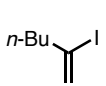
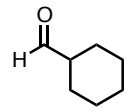
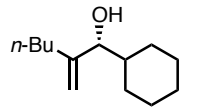
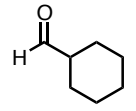
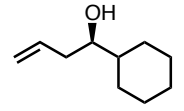
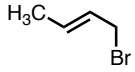
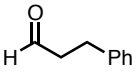
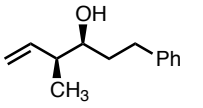
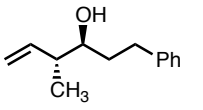
- Ligands on Ni, although not believed to be involved in the enantio-determining C–C bond-forming step, can have a dramatic influence on the enantioselectivity due to ligand scrambling:





• $NiCl_2$
I
($NiCl_2$•DMP)

Namba, K.; Cui, S.; Wang, J.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5417–5419.
Liu, X.; Li, X.; Chen, Y.; Hu, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 6136–6139.

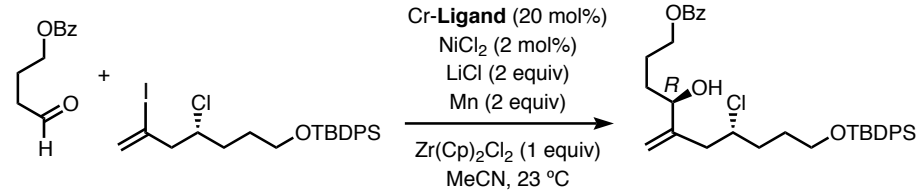
nucleophile	aldehyde	method	product	ligand (mol%)	temp (°C)	yield (%)	ee (%)
		A		1 (10)	0	89	93
		A		2 (10)	23	84	71
		A		1 (10)	23	83	96
		B		3 (10)	23	90	92
		B		3 (5)	23	–	93
		C		4 (3)	23	90	98
		C		4 (3)	23	71	94
						17	94

Method A[1]: $CrCl_2$ (10 mol%), Mn (2 equiv), DIPEA (30 mol%), TMSCl (2 equiv), THF; TBAF, THF
Method B[2]: $NiCl_2$•DMP (2 mol%), $CrCl_2$ (10 mol%), Proton Sponge (11 mol%), LiCl (2 equiv), Mn (2 equiv), $ZrCp_2Cl_2$ (1 equiv), MeCN
Method C[3]: Mn (3 equiv), TESCl (1.1 equiv), DME:MeCN; TBAF, THF.

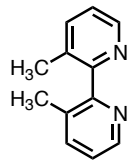
[1]Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140–1141.; Inoue, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 2977–2980.
[2]Namba, K.; Cui, S.; Wang, J.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5417–5419.
[3]Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, 128, 2554–2555.

Fan Liu

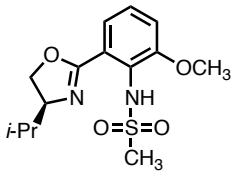
• catalysts can override inherent selectivities of the substrate:



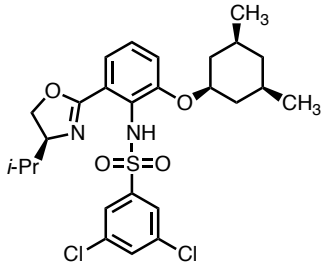
Ligands	*dr* (*S* : *R*)
3,3'-dimethyl-2,2'-dipyridine	1.2 : 1
(*S*)-**5**	1 : 8.0
(*R*)-**5**	8.1 : 1
(*S*)-**6**	1 : 15
(*R*)-**6**	16 : 1
(*S*)-**7**	1 : 21
(*R*)-**7**	24 : 1



3,3'-dimethyl-2,2'-dipyridine



5



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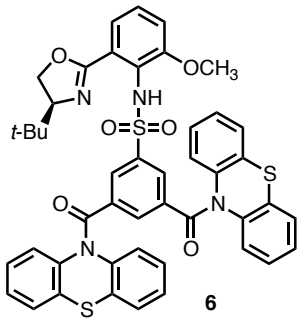
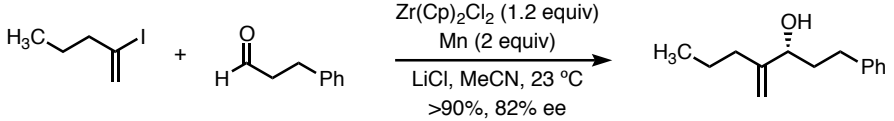
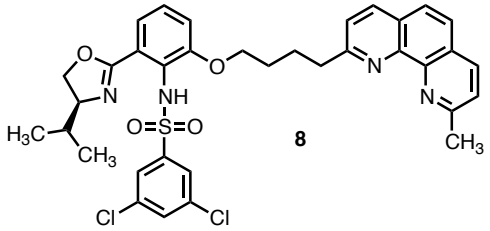


6

Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15387–15393.

• Ligand **8** contains binding sites for both Ni and Cr and dramatically lowers the catalyst loading required for asymmetric addition.

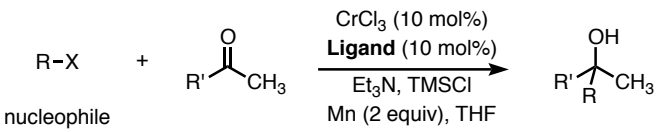


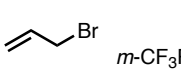
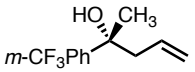
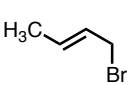
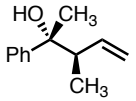
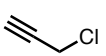
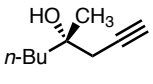
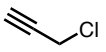
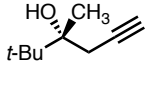
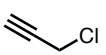
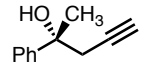


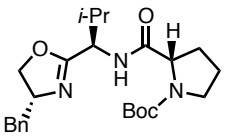
8

Liu, X.; Henderson, J.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 16678–16680.
Peng, J.; Kishi, Y. *Org. Lett.* **2012**, *14*, 86–89.

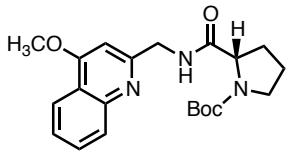
• Ligands for the enantioselective allylation and propargylation of ketones have been developed:



nucleophile	product	ligand	temp (°C)	yield (%)	ee (%)
		9	0	63	91
		9	0	69	88 (*anti*) 70 (*syn*)
		10[a]	25	70	70
		10[a]	25	86	96
		10[a]	25	75	92



9



10

[a]1 equiv of LiCl was added.

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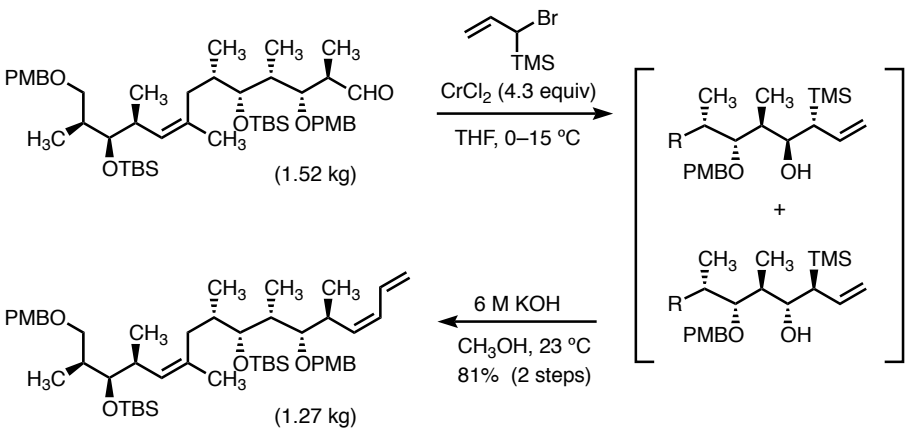
- Examples in synthesis:

- A one-pot NHK-Peterson elimination strategy was used for the large-scale synthesis of the anticancer marine natural product discodermolide:



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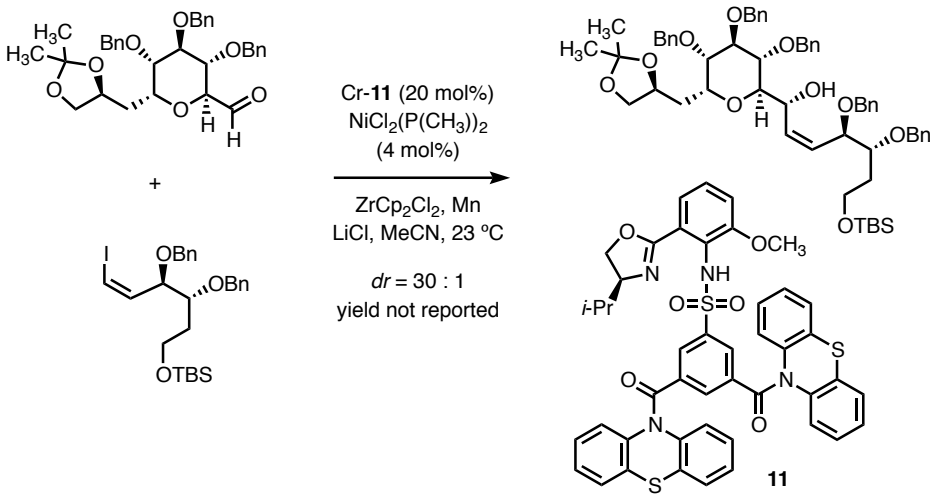

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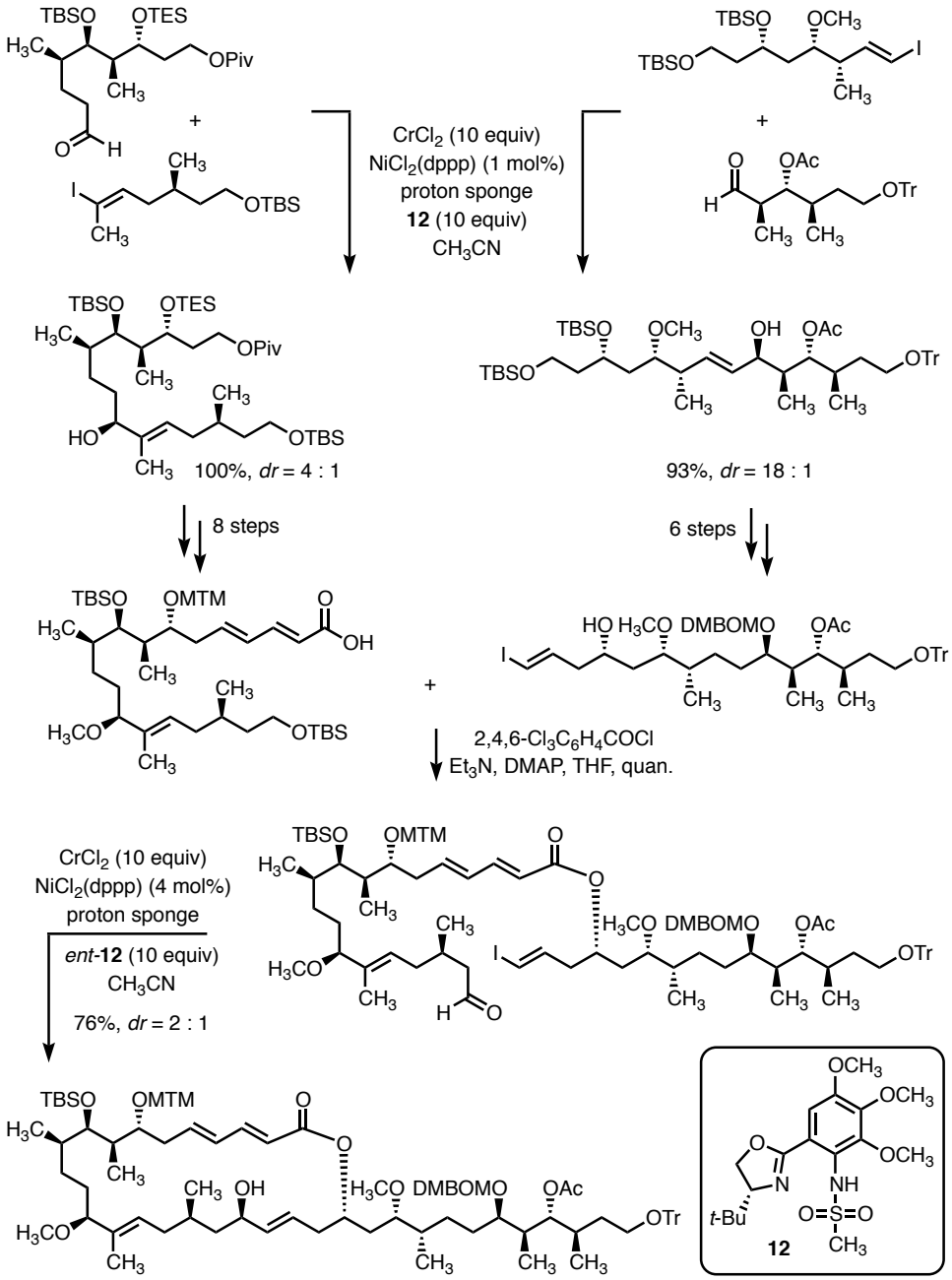

Kobayashi, K.; Fujii, Y.; Hayakawa, I.; Kigoshi, H. *Org. Lett.* **2011**, *13*, 900–903.
Kobayashi, K.; Fujii, Y.; Hirayama, Y.; Kobayashi, S.; Hayakawa, I.; Kigoshi, H. *Org. Lett.* **2012**, *14*, 1290–1293.

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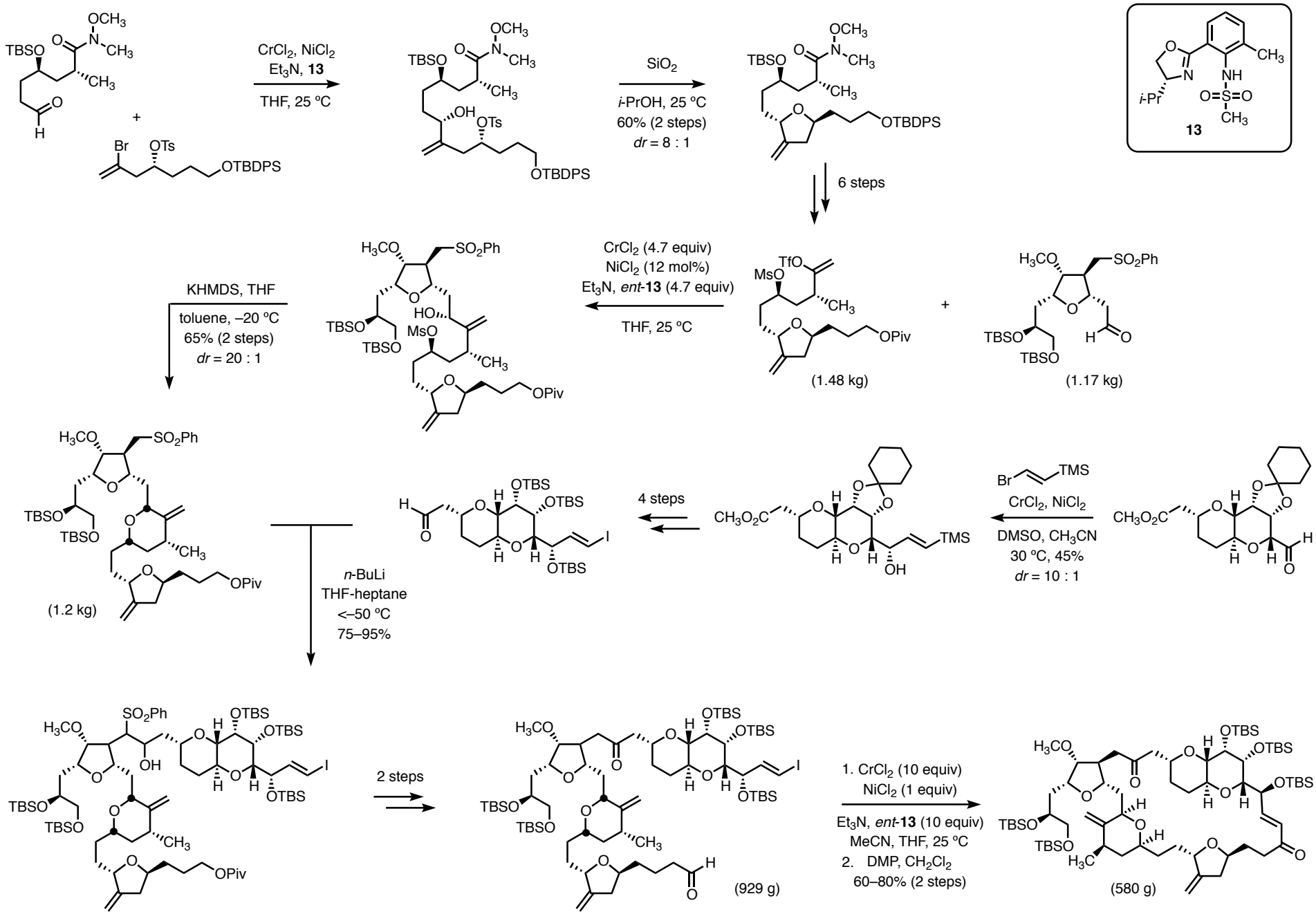
• Application to the synthesis of the anticancer drug Halaven®:



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