Enantioselective Synthesis of Cyclic Enol Ethers and All-Carbon Quaternary Stereogenic Centers Through Catalytic Asymmetric Ring-Closing Metathesis

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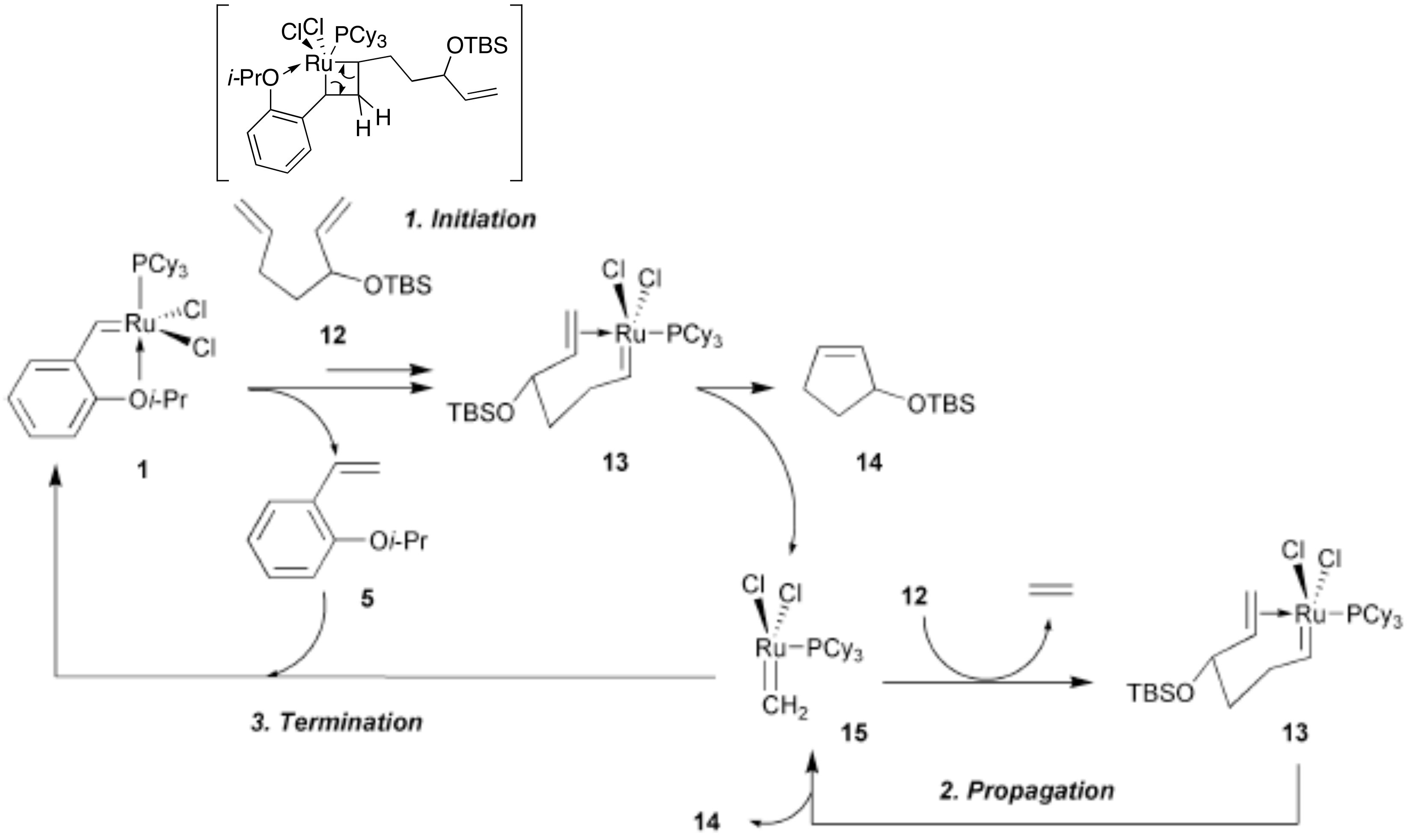
J. Am. Chem. Soc., ASAP, ja058428r

Adam Hoye
Wipf Group
4-1-06

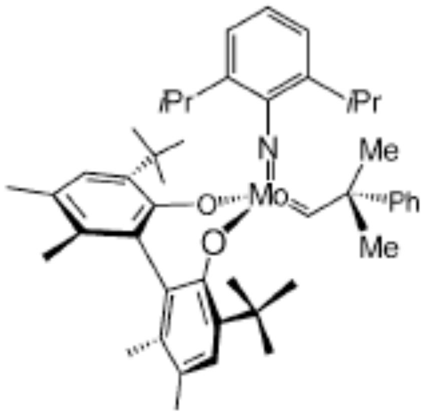
Ring Closing Metathesis (RCM)



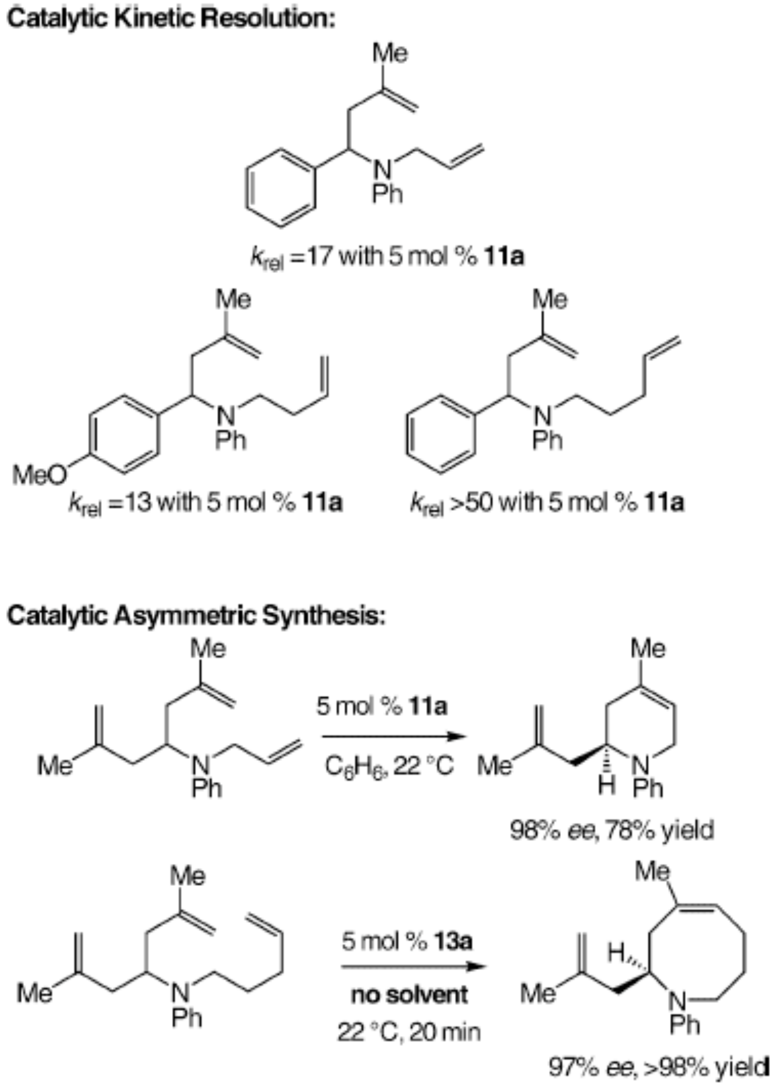
Asymmetric RCM

-Chiral substrate, achiral catalyst (common)

-Achiral substrate, chiral catalyst

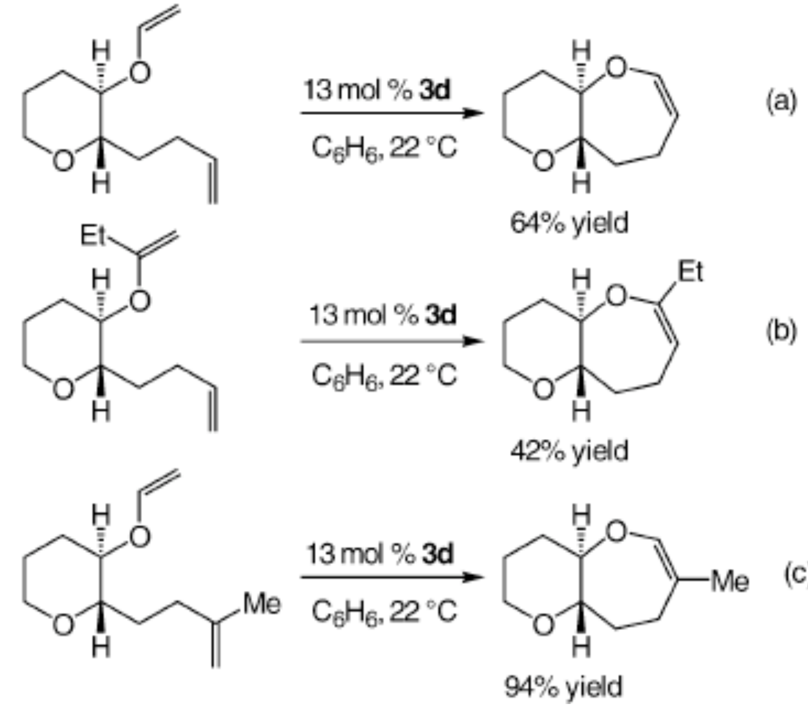


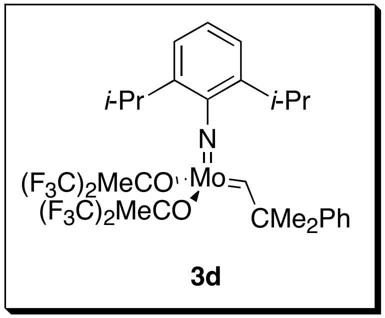
11a [14]

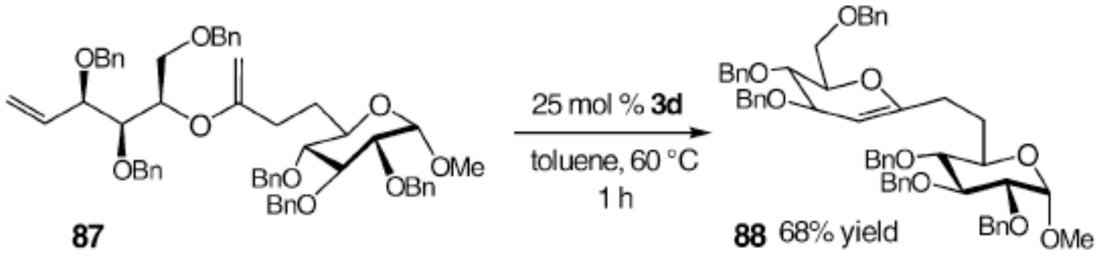


Schrock, R. R.; Hoveyda, A. H.; *Angew. Chem. Int. Ed.*, **2003**, *42*, 4592

Enol Ethers in RCM



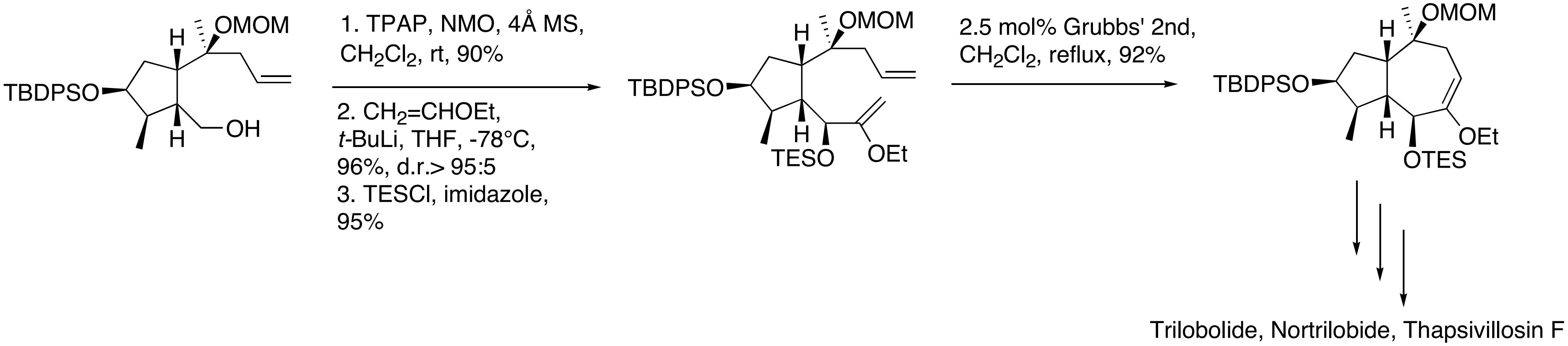




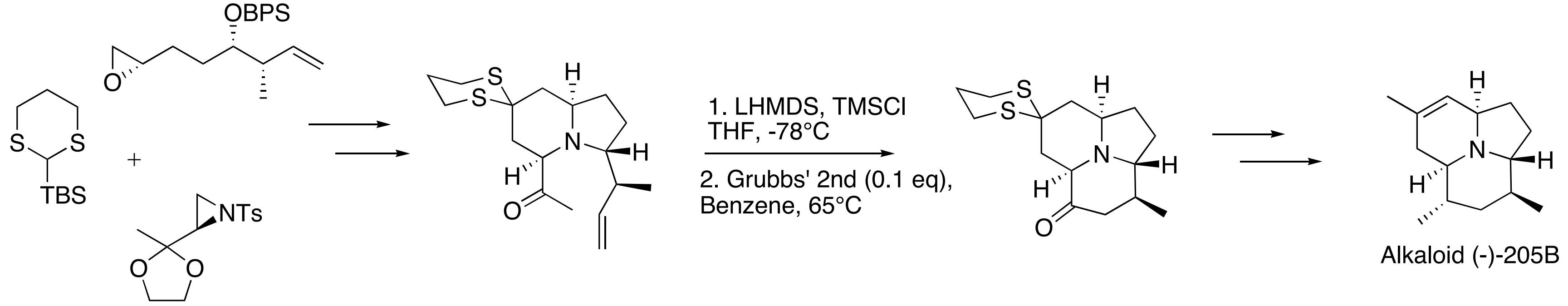
- Poor initiation with Ru-based catalysts observed in some cases

Schrock, R. R.; Hoveyda, A. H.; *Angew. Chem. Int. Ed.*, **2003**, *42*, 4592

Enol Ether Metathesis in Natural Product Synthesis

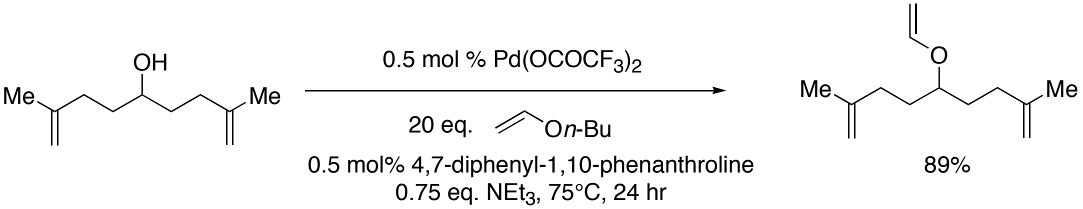


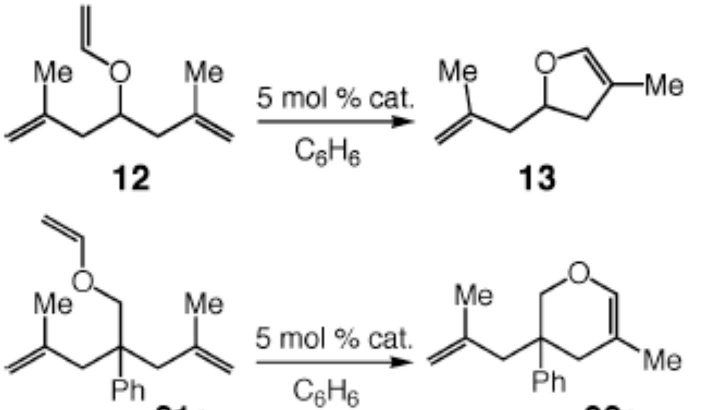
Oliver, S. F.; Högenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V.; *Angew. Chem. Int. Ed.* **2003**, *42*, 5996



Kin, D.-S.; Smith, A. B.; *Org. Lett.* **2005**, *7*, 3247

Preliminary Enol Ether RCM Reactions

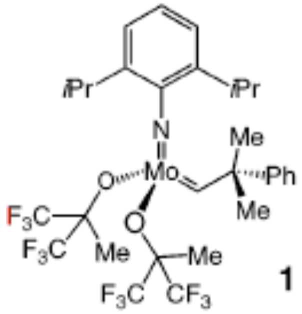




12 **13**

21a **22a**

entry	catalyst	temp (°C)	time (h)	conv (%)^b
1	**1**	22	3	>98
2	**2**	22	14	<2
3	**2**	65	1	88
4	**11**	22	14	5
5	**11**	65	1	19^c
7	**1**	22	1	86
8	**2**	22	1	92
9	**11**	22	17	47
10	**11**	65	1	>98



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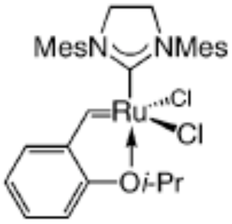

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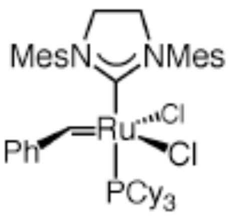

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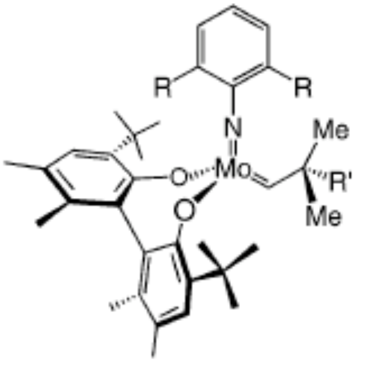
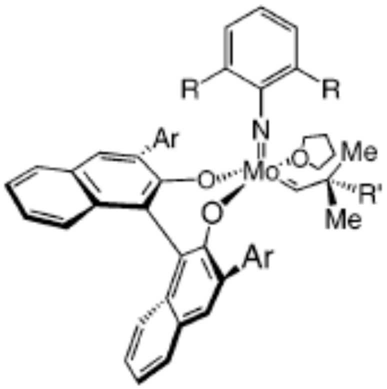
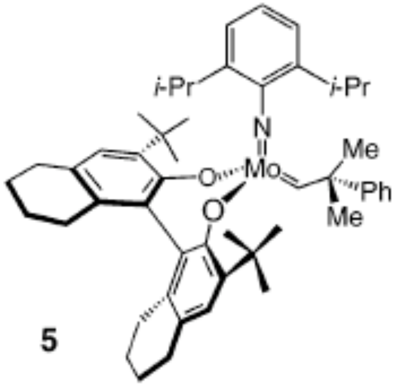
Catalyst Screening



3a R = *i*-Pr R' = Ph
3b R = Me R' = Ph
3c R = Cl R' = Me



4a R = *i*-Pr R' = Ph



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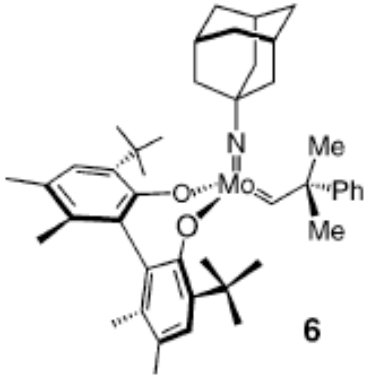

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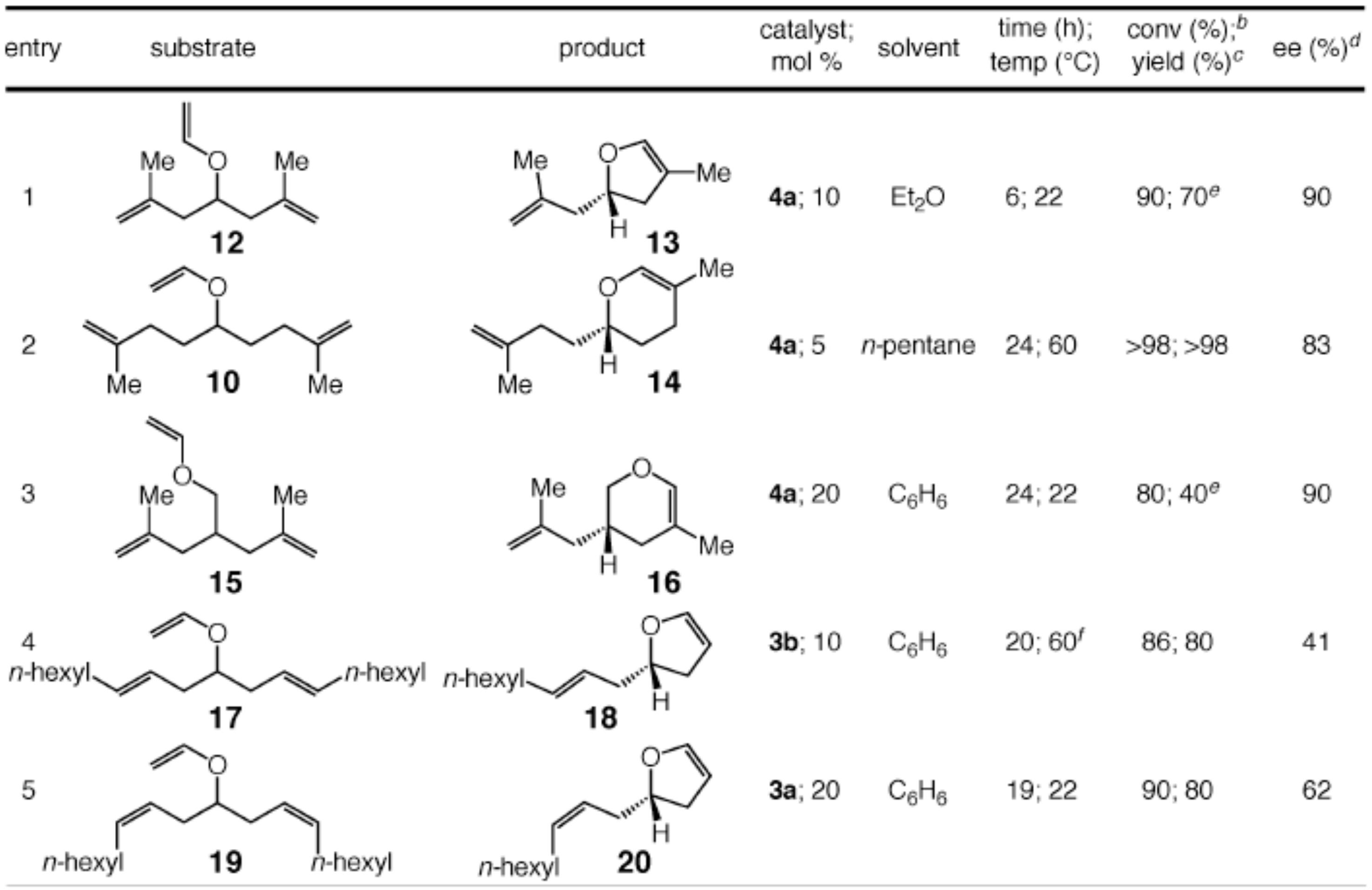
-Ru-based complexes did not promote RCM of desired enol ether substrates

-For various olefin substitutions (1,1 and 1,2), only **4a** exhibited repetitive catalytic activity (i.e. it was always active)

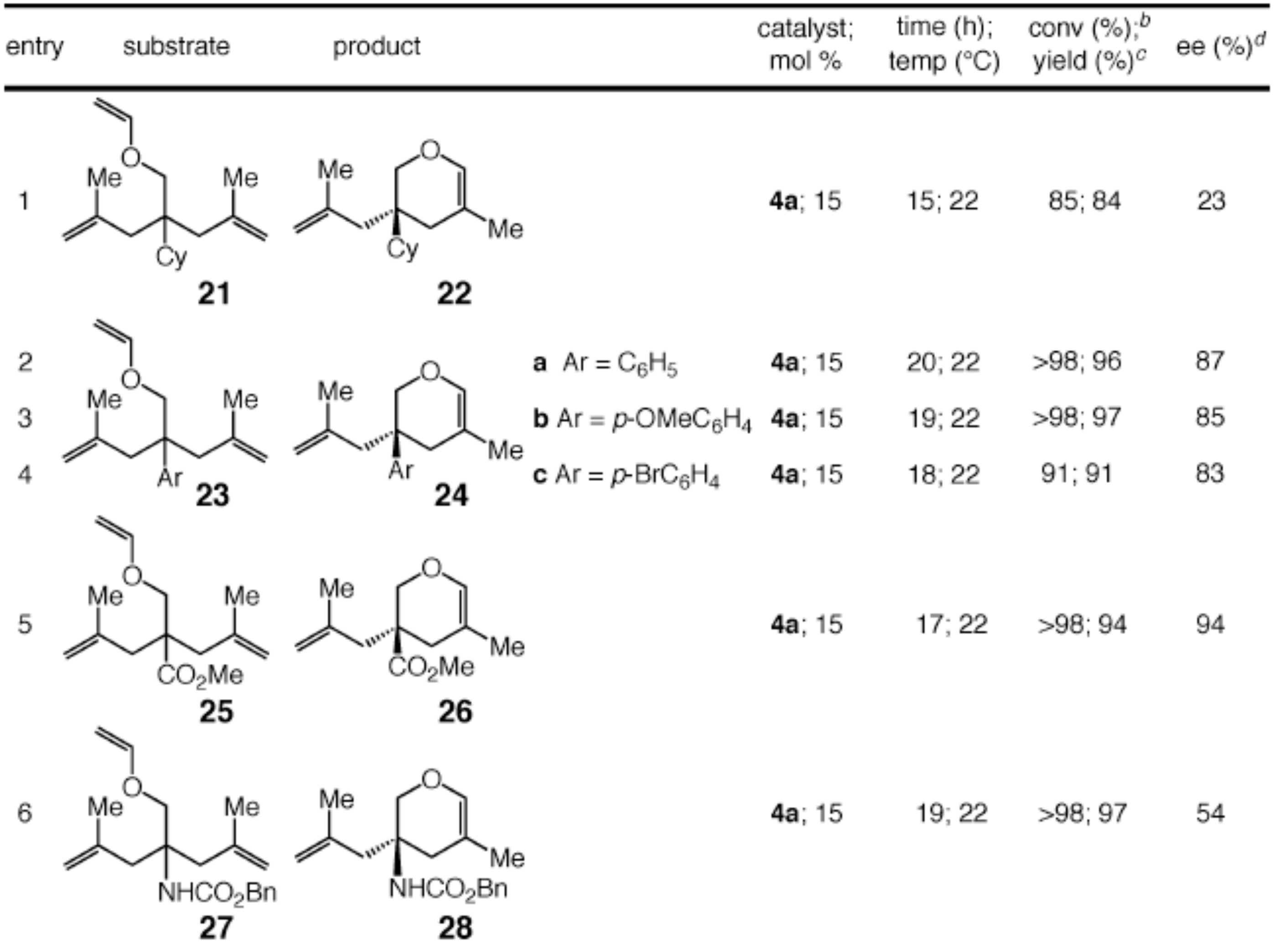
-Optical purity of RCM reactions changes dramatically between catalysts. Thus, these reactions are case specific, and the availability of structurally distinct catalysts is important in reaction optimization

Enantioselective Synthesis by Mo-catalyzed ARCM



entry	substrate	product	catalyst; mol %	solvent	time (h); temp (°C)	conv (%);[b] yield (%)[c]	ee (%)[d]
1	**12**	**13**	**4a**; 10	Et_2O	6; 22	90; 70[e]	90
2	**10**	**14**	**4a**; 5	*n*-pentane	24; 60	>98; >98	83
3	**15**	**16**	**4a**; 20	C_6H_6	24; 22	80; 40[e]	90
4	**17**	**18**	**3b**; 10	C_6H_6	20; 60[f]	86; 80	41
5	**19**	**20**	**3a**; 20	C_6H_6	19; 22	90; 80	62

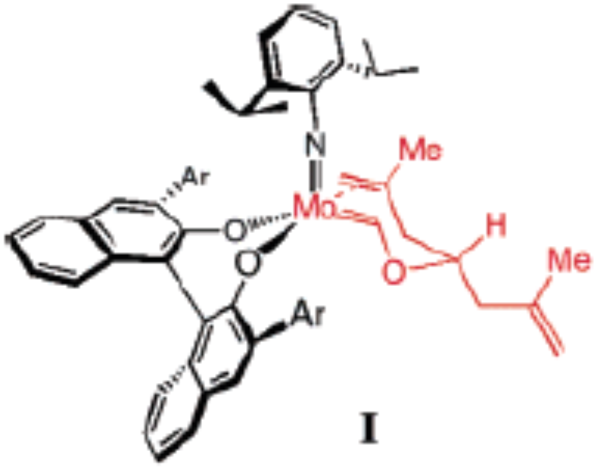
Quaternary Carbon Stereogenic Center Formation



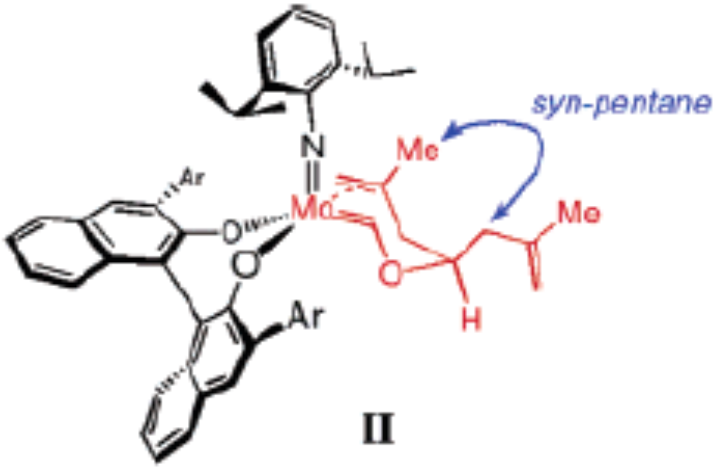
entry	substrate	product		**catalyst**; mol %	time (h); temp (°C)	conv (%);[b] yield (%)[c]	ee (%)[d]
1	**21**	**22**		**4a**; 15	15; 22	85; 84	23
2	**23**	**24**	**a** Ar = C_6H_5	**4a**; 15	20; 22	>98; 96	87
3			**b** Ar = *p*-OMeC_6H_4	**4a**; 15	19; 22	>98; 97	85
4			**c** Ar = *p*-BrC_6H_4	**4a**; 15	18; 22	91; 91	83
5	**25**	**26**		**4a**; 15	17; 22	>98; 94	94
6	**27**	**28**		**4a**; 15	19; 22	>98; 97	54

"…the first instances of efficient enantioselective synthesis of all-carbon quaternary stereogenic centers by catalytic asymmetric olefin metathesis."

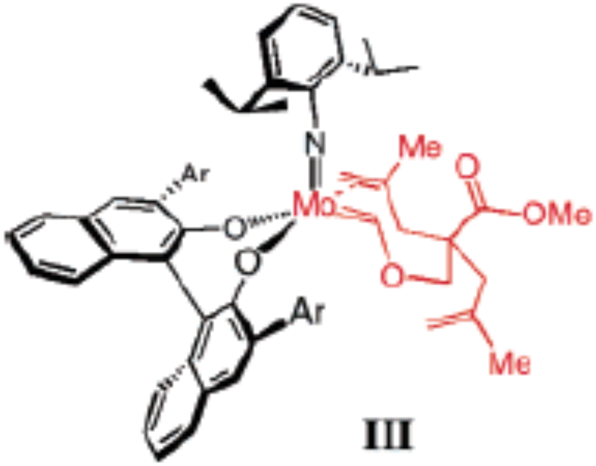
Proposed Transition States



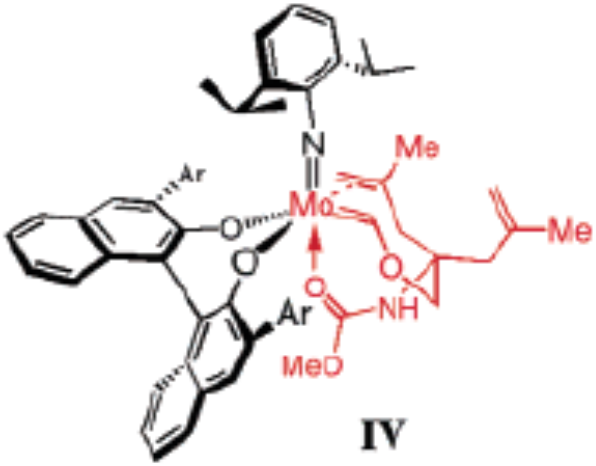
I



II

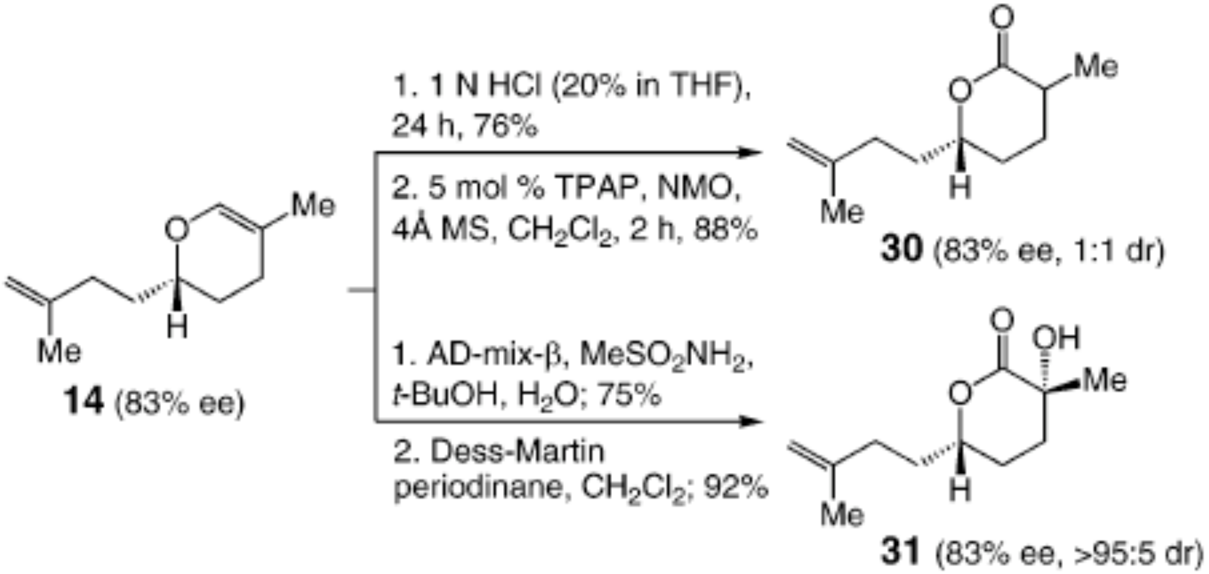


III



IV

Functionalization of Cyclic Enol Ethers



14 (83% ee)

30 (83% ee, 1:1 dr)

31 (83% ee, >95:5 dr)

Conclusions

- ACRCM has been used to efficiently form enantiomerically enriched cyclic enol ethers having quaternary stereocenters using Mo-based catalysts
- Synthetic utility of this process remains to be seen due to the substrate dependant nature of the process and need for structurally distinct chiral catalysts