Catalytic Asymmetric 1,4-Addition Reactions Using □,□-Unsaturated N-Acylpyrroles as Highly Reactive Monodentate □,□-Unsaturated Ester Surrogates

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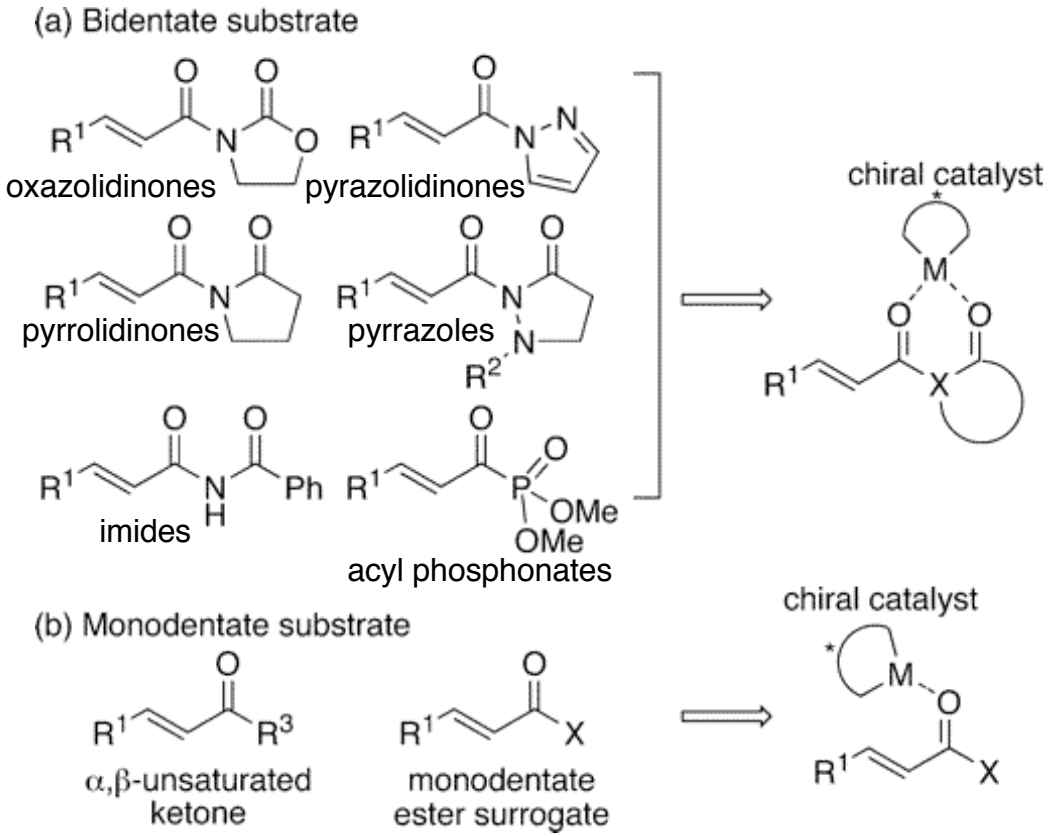
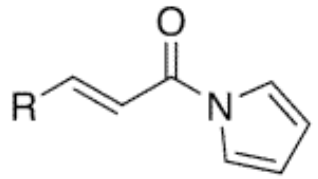
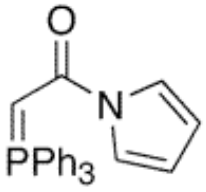
Introduction

- Catalytic asymmetric 1,4-additions to □,□-unsaturated ketones.
- For □,□-unsaturated esters lower reactivity is an issue.
- Monodentate Vs bidentate substrates.
- Objective: development of monodentate ester substitute.





1 R = aryl, alkyl, alkenyl



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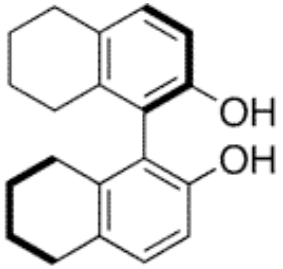
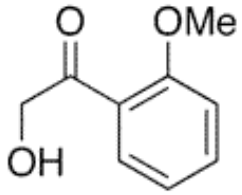


(*R*)-H_8-BINOL **3**



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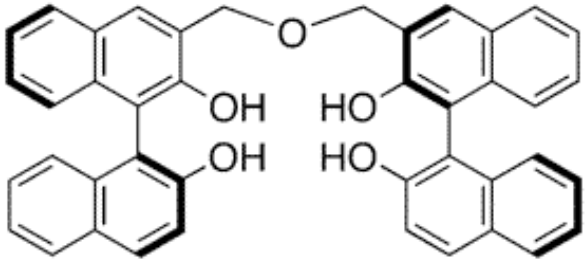
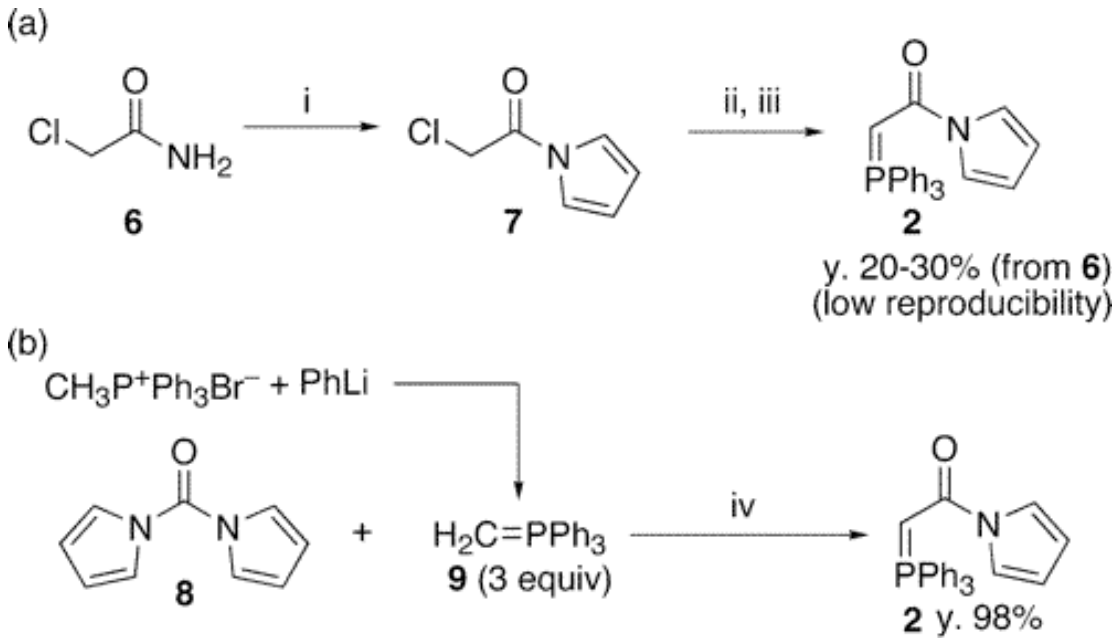


(*S*,*S*)-linked-BINOL **5**

Preparation of Ylide 2



Conditions: (i) 2,5-dimethoxytetrahydrofuran, AcOH, 100 C; (ii) PPh_3, toluene, 100 C; (iii) 2 M aq NaOH, CH_2Cl_2/H_2O; (iv) THF/Et_2O, -78 to 25 C.

Proposed catalytic cycle for the epoxidation promoted by Ln-Binol complex.

- Ln-Binol complex favors monodentate coordination.
- Not applicable for α,β-unsaturated esters.
- Bidentate substrates, oxazolidinone, carboxylic acid imidazolide and α,β-unsaturated morpholinyl amide: not practical results.
- Poor conversion;
- High catalyst loading;
- Explosive TBHP;
- Unstable, low soluble and difficult to prepare substrates.

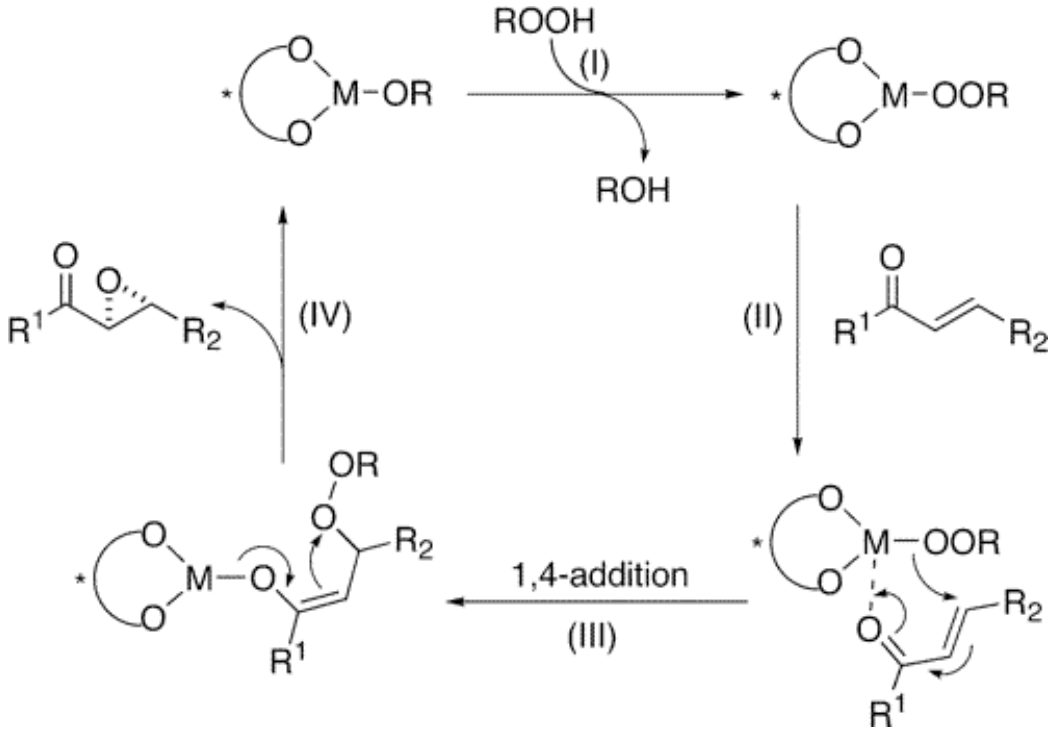
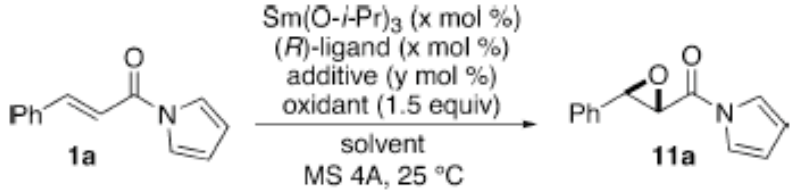


Table 2. Catalytic Asymmetric Epoxidation Reaction of α,β-Unsaturated *N*-Acylpyrrole **1a**



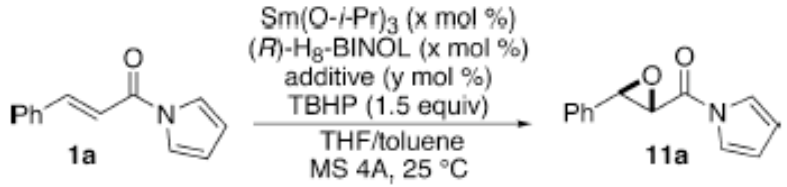
entry	$Sm(O\text{-}i\text{-}Pr)_3$ (x mol %)	ligand (x mol %)	additive (y mol %)	solvent	oxidant[a]	time (h)	yield[b] (%)	ee[c] (%)
1	10	BINOL (10)	$Ph_3As(O)$ (10)	THF	TBHP	0.5	93	94
2	5	BINOL (5)	$Ph_3As(O)$ (5)	THF	TBHP	0.5	85	96
3	5	H_8-BINOL (5)	$Ph_3As(O)$ (5)	THF	TBHP	0.5	94	99
4	5	H_8-BINOL(5)	$Ph_3P(O)$ (15)	THF	TBHP	0.5	84	94
5	5	H_8-BINOL (5)	$Ph_3P(O)$ (50)	THF	TBHP	0.5	88	98
6	5	H_8-BINOL(5)	$Ph_3P(O)$ (100)	THF	TBHP	0.5	85	97
7	5	H_8-BINOL (5)	$Ph_3P(O)$ (15)	THF/toluene	TBHP	0.4	85	96
8	5	H_8-BINOL(5)	$Ph_3P(O)$ (50)	THF/toluene	TBHP	0.5	92	99
9	5	H_8-BINOL (5)	$Ph_3P(O)$ (100)	THF/toluene	TBHP	0.2	97	99
10	5	H_8-BINOL(5)	$Ph_3P(O)$ (100)	THF/toluene	CMHP	0.2	91	>99.5

[a] TBHP in decane or CMHP in toluene was used. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

First tunning:

- Ligand: H8-BINOL 5 mol%;
- Lanthanide: $Sm(O\text{-}i\text{-}Pr)_3$ 5 mol%;
- Additive: $Ph_3P(O)$ 100 mol%;
- Oxidant: TBHP or CMHP
- Solvent: THF/toluene.

Table 3. Trials to Reduce Catalyst Loading in Catalytic Asymmetric Epoxidation Reaction of α,β-Unsaturated *N*-Acylpyrrole **1**



entry	$Sm(O\text{-}i\text{-}Pr)_3$ (x mol %)	H_8-BINOL (x mol %)	additive (y mol %)	MS 4 Å (mg/mmol of **1a**)	concn of [**1a**] (M)	time (h)	yield[a] (%)	ee[b] (%)
1[c]	5	5	$Ph_3P(O)$ (100)	1000	0.1	0.2	97	99
2[c]	1	1	$Ph_3P(O)$ (100)	500	1	0.3	94	99
3[d]	0.5	0.5	$Ph_3P(O)$ (100)	250	1	0.6	100	97
4[d]	0.2	0.2	$Ph_3P(O)$ (100)	100	2	1	99	97
5[d]	0.1	0.1	$Ph_3P(O)$ (100)	100	2	2	90	96
6[d]	0.1	0.1	$Ph_3As(O)$ (0.1)	100	3	0.6	100	99
7[d]	0.05	0.05	$Ph_3As(O)$ (0.05)	100	3	1	100	98
8[d]	0.02	0.02	$Ph_3As(O)$ (0.02)	100	3	1.5	94	99

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] TBHP in decane was used. [d] Anhydrous TBHP in toluene (dried with MS 4A) was used.

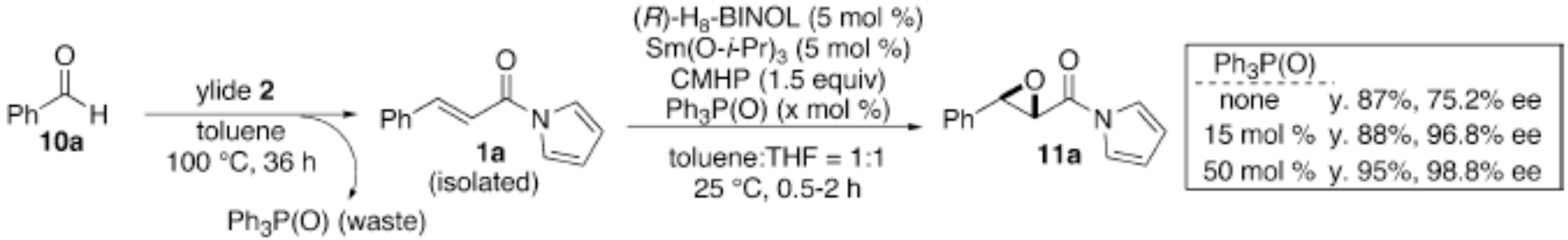
Second tunning:

- H8-BINOL/$Sm(O\text{-}i\text{-}Pr)_3$ as low as 0.1, 0.05 and 0.02 mol%;
- Keep the catalyst concentration within 1-5mM for best *ee*'s;
- Practical aspects for large scale: reduced MS amounts, catalytic loading.
- Catalytic $Ph_3As{=}O$; equimolar $Ph_3P{=}O$.

Sequential Wittig Olefinaton-Catalytic Asymmetric Epoxidation

(A) One-pot Sequential Wittig-Catalytic Asymmetric Epoxidation Process

(B) Step-by-step Wittig-Catalytic Asymmetric Epoxidation Process



Scheme 3. Catalytic Asymmetric Epoxidation of *Z*-α,β-Unsaturated *N*-Acylpyrrole

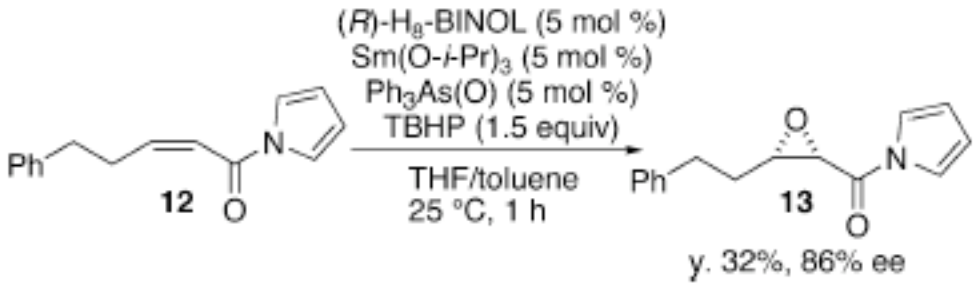
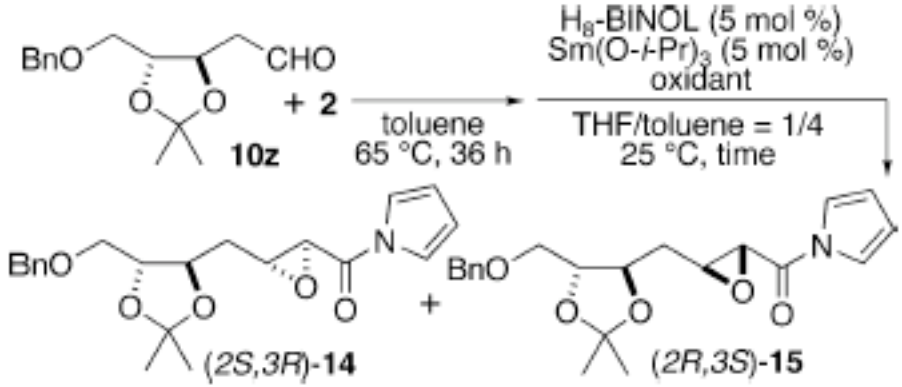


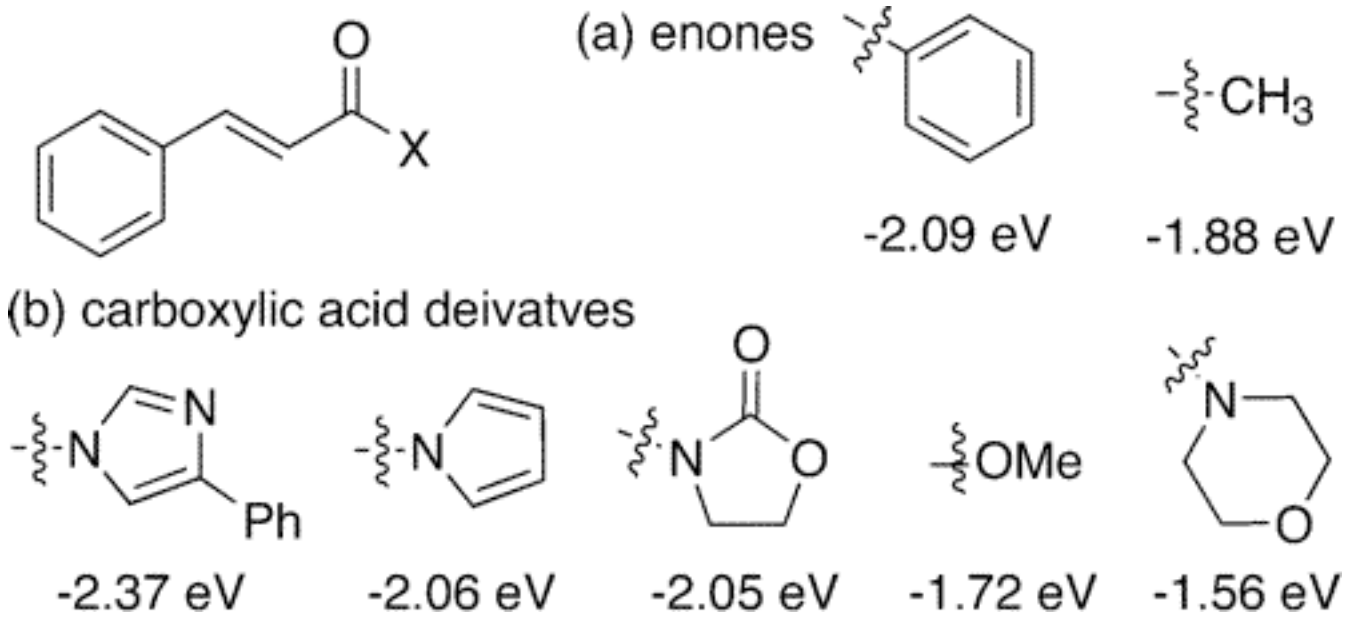
Table 5. Sequential Wittig–Catalytic Asymmetric Epoxidation Reaction with Chiral Aldehyde



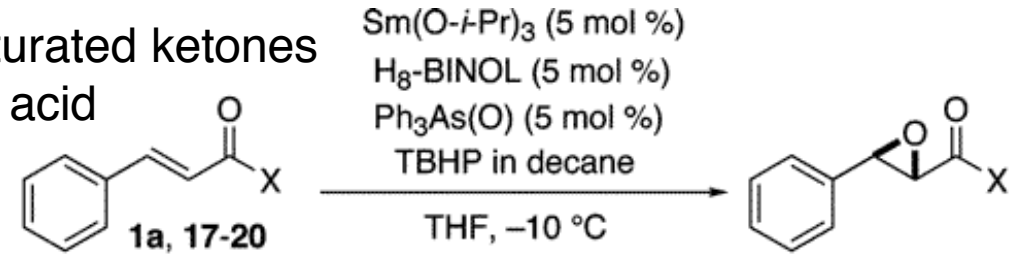
entry	ligand	time (h)	oxidant	yield[a] (%)	dr[b] (14/15)
1	(*R*)-H8-BINOL	0.7	CMHP	80	>99/1
2	(*S*)-H8-BINOL	0.9	CMHP	60	1/56
3	(*S*)-H8-BINOL	0.7	TBHP	78	1/36

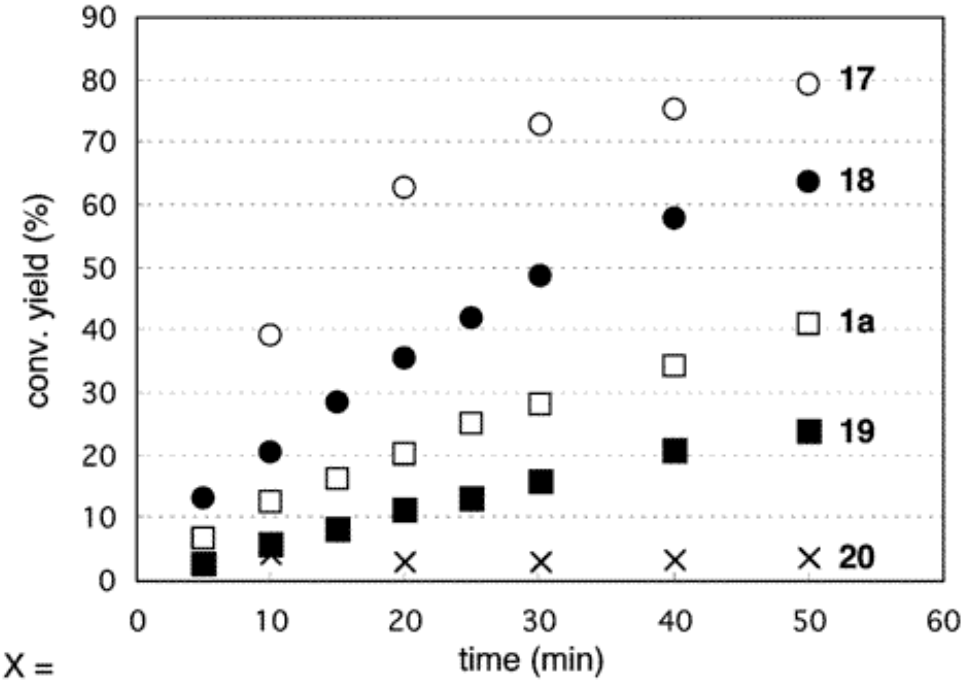
[a] Isolated yield. [b] Determined by HPLC analysis.

Electronic properties of □,□-unsaturated N-acylpyrrole

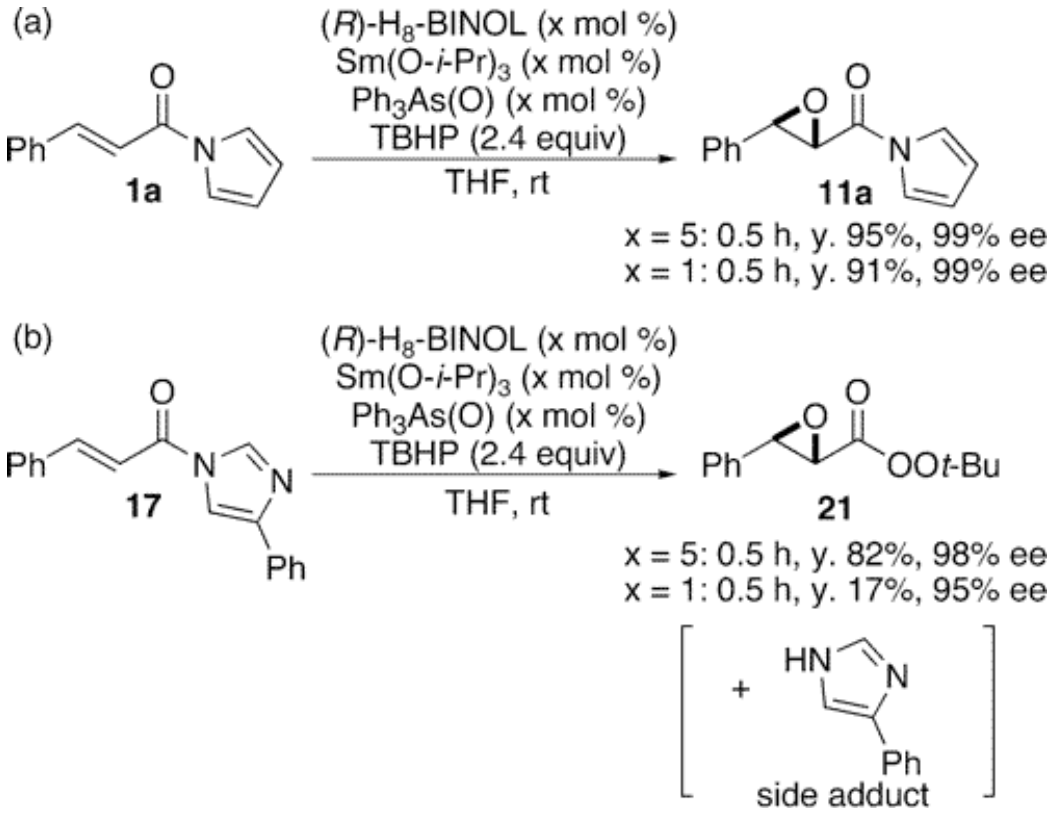


Epoxidation profile of □,□-unsaturated ketones and □,□-unsaturated carboxylic acid derivatives.

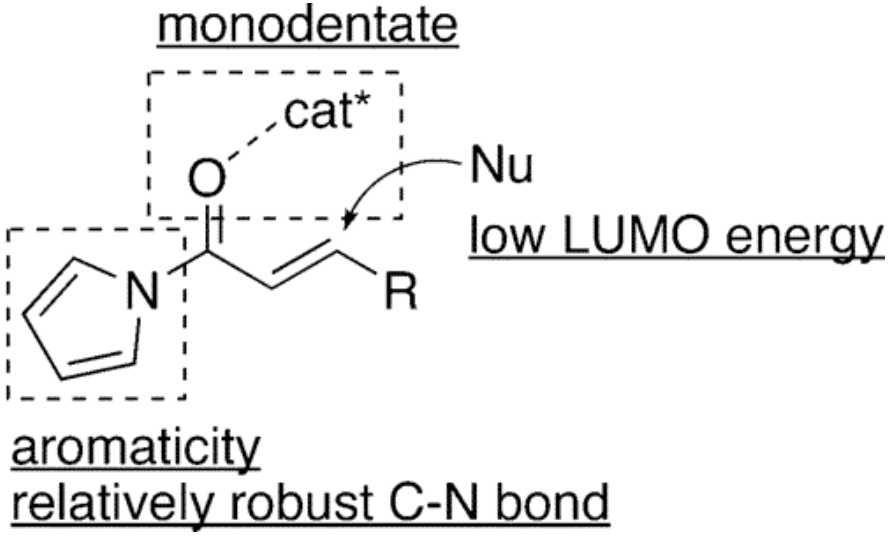




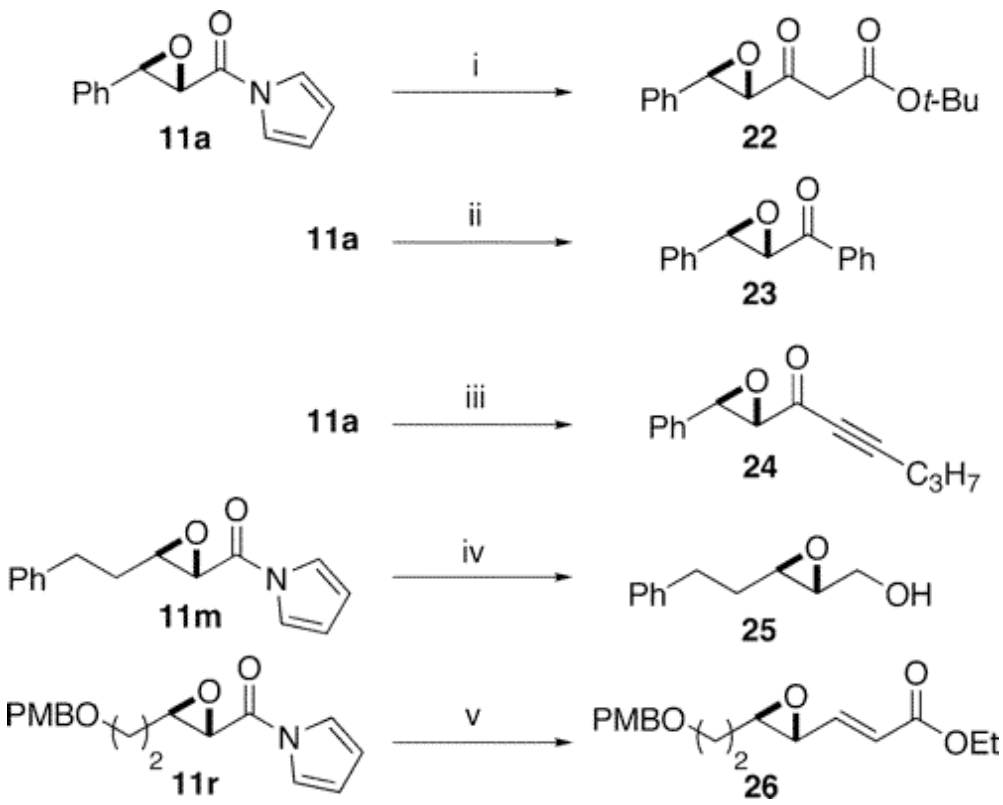
• Imidazoline **17** > phenyl enone **18** > N-acyl pyrrole **1a** > methyl enone **19** >> amide **20**.



Scheme 4. Catalytic Asymmetric Epoxidation Reaction of (a) Unsaturated *N*-Acylpyrrole **1a** and (b) *N*-Acylimidazolide **17** with 5 and 1 Mol % Sm Catalyst

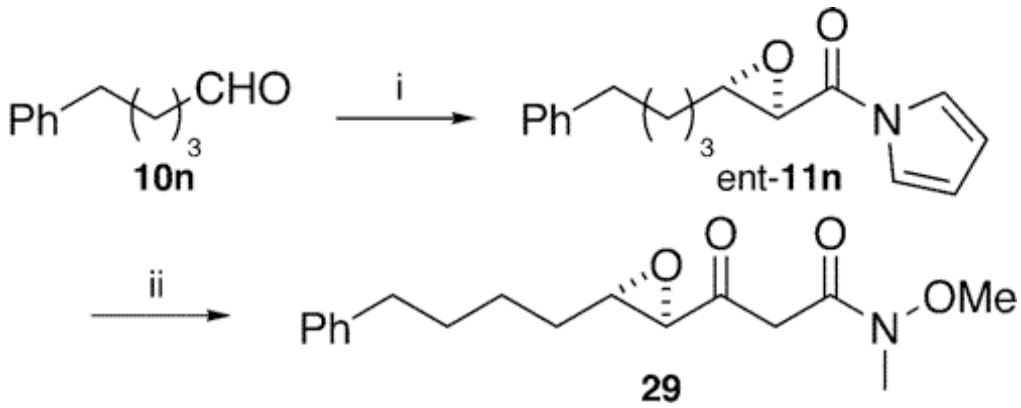


Better solubility then the N-acylimidazolide **17**.



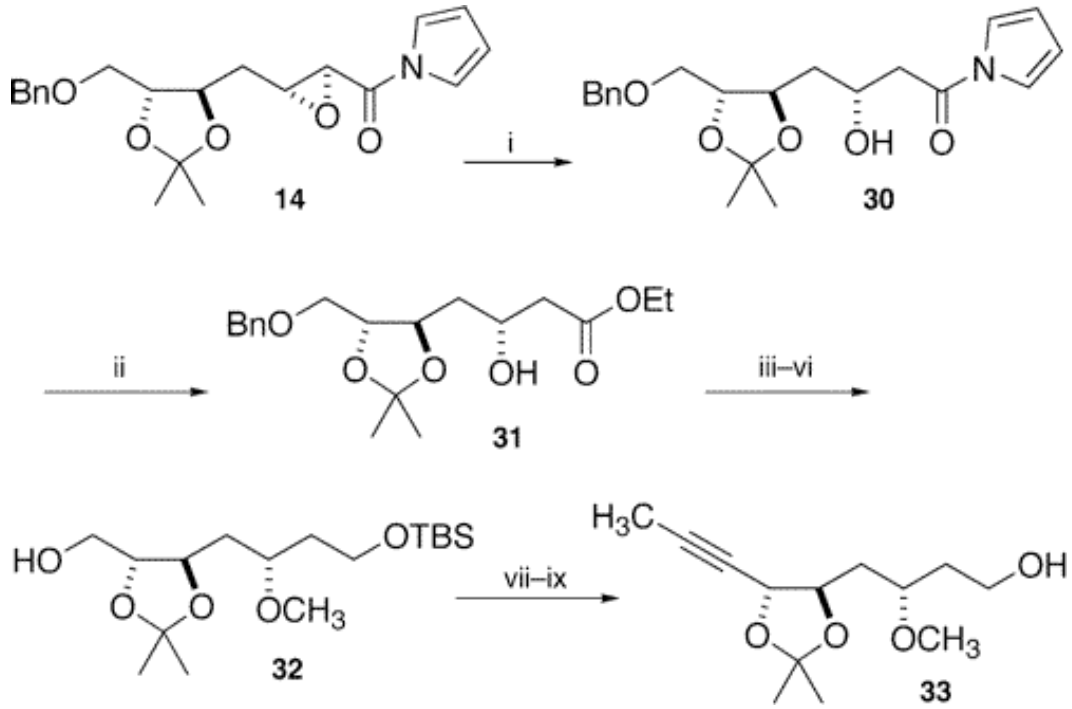
Transformations of Pyrrolyl Epoxides. Conditions: (i) *tert*-butyl acetate, BuLi, -78 C; then DBU, 25 C, (74%); (ii) PhLi, then DBU, 25 C, (88%); (iii) BuLi, 1-pentyne, -78 C, then DBU, 0 C, (84%); (iv) $LiBH_4$, 0 to 25 C; then $NaBH_4$, 25 C, (72%); (v) $LiBH_4$, 25 C, then $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, 25 C,(69%).

Transformation of Michael Adduct. Conditions: (i) EtSLi, EtOH, 25 C, 2 h, y. 96%.



Preparation of Synthetic Intermediate for Antifungal Natural Product. Conditions: (i) ylide **2**, toluene, 85 C, then Sm(O-*i*-Pr)$_3$ (5 mol %), (*S*)-H$_8$-BINOL (5 mol %), MS 4A, THF/toluene, CMHP, 25 C, 0.8 h, y. 83% (from **10n**), 96% ee; (ii) $CH_3C(O)N(OCH_3)CH_3$, LHMDS, THF, -78 C, 20 min; then DBU, CH_2Cl_2, 25 C, 40 min, y. 63% (two steps).

Synthesis of Intermediate **33** in Smith's Total Synthesis of Phorboxazole A.



(i) PhSeSePh, $NaBH_4$, 25 C (94%); (ii) EtSLi, EtOH, 25 C,(92%); (iii) CH_3I, Ag_2O, MS 3A, toluene, 45 C, (93%); (iv) $LiAlH_4$, Et_2O, 25 C,(85%); (v) TBSCl, imidazole, 25 C, (86%); (vi) H_2 $Pd(OH)_2$, $NaHCO_3$, 25 C, (96%); (vii) PCC, AcONa, MS 3A, 25 C, then $(CH_3O)_2P(O)C(N_2)COCH_3$, 25 C, (57%); (viii) BuLi, -78 C; then CH_3I, -78 C to 25 C, (91%); (ix) Bu_4N+F-, 25 C, (88%).

Conclusion

- Modentate ester surrogate □,□-unsaturated N-acylpyrrole;
- Good to excellent yields and *ee*'s for epoxidation;
- Good results for the first asymmetric Michael additions, but still limited;
- One spot transformation aldehyde to epoxide;
- Further investigations.