Organocatalytic Acylative Kinetic Resolution of Acyclic Tertiary Alcohols

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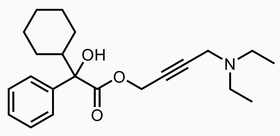
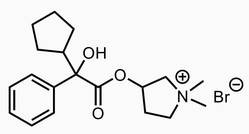
Introduction

Chiral acyclic tertiary alcohols are commonly present in bioactive compounds. Although the synthesis and isolation of enantiopure chiral acyclic tertiary alcohols has attracted much attention in the past decade, it still remains challenging.

Voriconazole

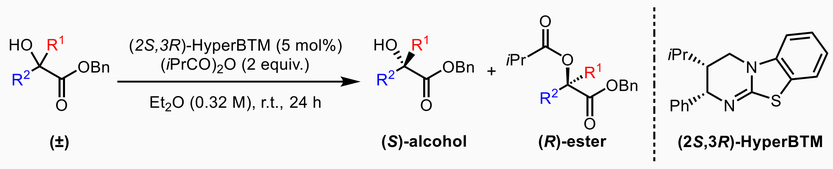


Oxybutynin



Glycopyrronium bromide

Asymmetric direct 1,2-addition of nucleophiles into carbonyls is the most popular synthetic route for obtaining highly enantioenriched acyclic tertiary alcohols.[1] While kinetic resolution (KR) serves as a powerful tool when a racemate can be easily obtained but asymmetric synthesis proves challenging, only limited cases of organocatalytic kinetic resolution of acyclic tertiary alcohol have been reported to date.[2] This poster discribes an operationally simple, highly enantioselective isothiourea-catalysed acylative KR of acyclic tertiary alcohols, allowing access to highly enantioenriched compounds (*ee* up to > 99:1) with *s* factor up to > 500.[3]



Kinetic Resolution (KR)

KR allows separation of enantiomers in a racemate, and can only happen when the rate constant *(k)* for each enantiomer is different in a given reaction, i.e. $k_R \neq k_S$.

$$SM_R + SM_S \xrightarrow[k_R >> k_S]{\text{Cat*}} P_R + SM_S \quad \text{both enantioenriched}$$

Selectivity factor, *s*, is defined as the relative rate constants of a pair of enantiomers in a KR , and is determined using Kagan's equations. Selectivity factor *(s)* is used to compared the effectiveness of a KR.

enantiometric excess

$$ee = \frac{[R] - [S]}{[R] + [S]}$$

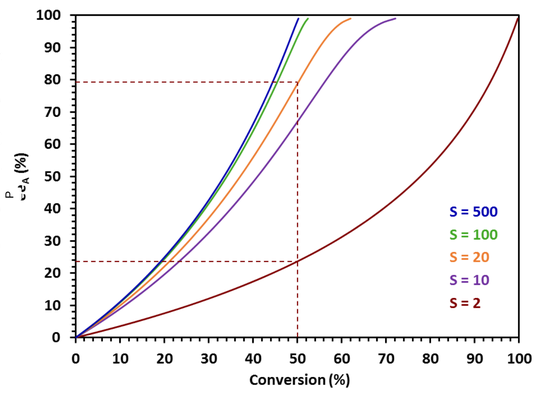
conversion

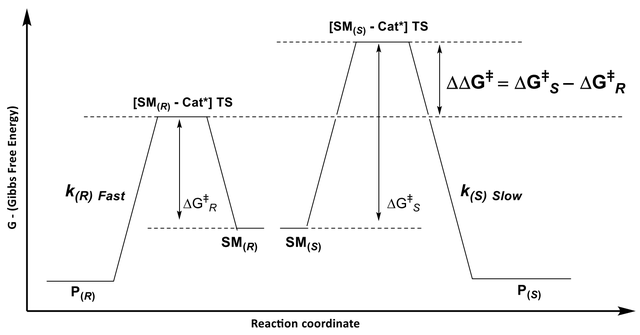
$$c = \frac{ee_{SM}}{ee_{SM} + ee_P}$$

selectivity factor

$$s = k_{rel} = \frac{k_{fast}}{k_{slow}} = e^{\Delta\Delta G^{\ddagger} / RT}$$

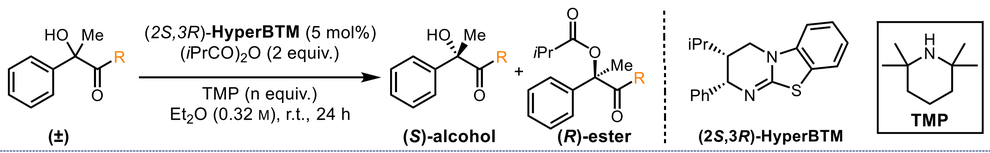
Starting from a racemate, two enantiomers of the starting material (SM) react with the same chiral species, generating two diastereoisomeric TS with an energy differecne of $\Delta\Delta G^{\ddagger}$. A larger $\Delta\Delta G^{\ddagger}$ indicates a larger difference in the *k* of the two enantiomers, hence a bigger *s*, a more efficient KR.

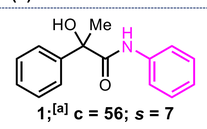




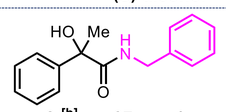
ee_{SM} increases while ee_p decreases over the course of the reaction. In order to have a good compromise between the yield and the enantiopurity of the isolated products, the conversion of the reaction is normally adjusted to ~50% in this project

Optimisation – Carbonyl Group Screening

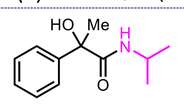




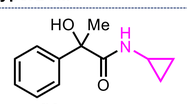
1;[a] **c = 56; *s* = 7**
alc: 85:15; 40%
est: 78:22; 52%



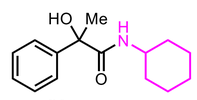
2;[b] **c = 37; *s* = 4**
alc: 64.5:35.5; 60%
est: 75:25; 33%



3;[b] **c = 15; *s* = 2**
alc: 53:47; 81%
est: 66:34; 10%

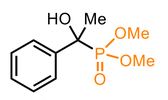


4;[b] **c = 33; *s* = 4**
alc: 63:37; 63%
est: 76:24; 30%

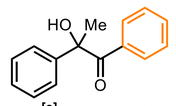


5;[b] **c = 12; *s* = 2**
alc: 52:48; 76%
est: 38:62; 10%

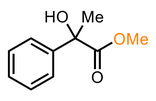
6;[c] **R = Me, c = 0**
7;[c] **R = OMe,c = 0**



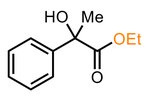
8;[d] **c = 17; s = 1**
alc: 51.5:48.5; 65%
est: 57.5:42.5; 12%



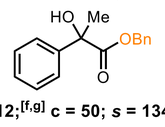
9;[e] **c < 2; *s* = 9**
alc: 50.5:49.5; 90%
est: 90:10; 1%



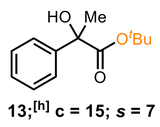
10;* c = 41; *s* = 66
alc: 84:16; 43%
est: 97:3; 39%



11; c = 32; *s* = 62
alc: 72,5:27.5; 60%
est: 98:2; 25%



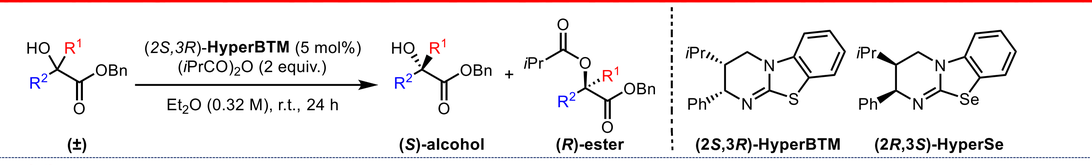
12;[f,g] **c = 50; *s* = 134**
alc: 98:2; 45%
est: 97:3; 46%



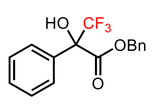
13;[h] **c = 15; *s* = 7**
alc: 56.5:43.5; 78%
est: -:-; 11%

s and *c* determined by HPLC analysis; * absolute configuration determined by comparison of optical rotation to literature; [a] 2 equiv. of TMP; [b] 10 equiv. of TMP; [c] 10 mol% (2*S*,3*R*)-HyperBTM at 50 °C; [d] 20 mol% (2*S*,3*R*)-HyperBTM, 4 equiv. $(MeCO)_2O$, 6 equiv. NEt_3, in CH_2Cl_2 (0.16 M) at r.t. over 72h; [e] *er* of ester determined by chiral HPLC analysis of reaction crude; [f] 1.02 g (4 mmol) scale gave *s* = 115 at c = 50%; [g] 2 mol% (2*R*,3*S*)-HyperSe with 1 equiv. $(iPrCO)_2O$, opposite enantioselectivity, *s* = 107 at c = 49%; [h] *s* calculated using c from ^{1}H NMR spectrum of reaction crude

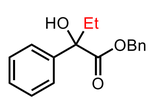
Substrate Scope



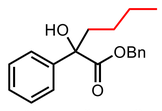
1. Me variation



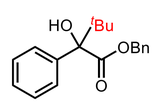
14; c = 26; *s* = 5
14;[a] **c = 48; *s* = 8**
alc: 79:21; 38%
est: 82:18; 41%



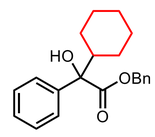
15; c < 2; *s* = 16
15;[a,b,c] **c = 58; *s* =8**
alc: 89:11; 38%
est: 78:22; 40%



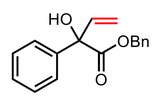
16; c < 2; *s* = 9
16;[a,b,c] **c = 58; *s* = 7**
alc: 87:13; 35%
est: 77:23; 50%



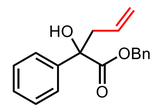
17;[d] **c = 0**



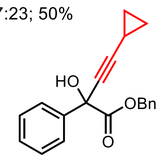
18;[d] **c = 0**



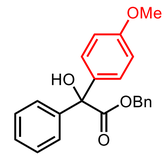
19; c = 32; *s* = 22
19;[a] **c = 45; *s* = 19**
alc: 84:16; 40%
est: 91:9; 41%



20; c = 6; *s* = 9
20;[c] **c = 42; *s* = 9**
alc: 76:24; 54%
est: 85:15; 37%

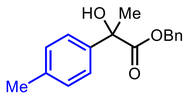


21;[e] **c = 47; *s* = 6**
alc: 76:24; 45%
est: 79.5:20.5; 40%

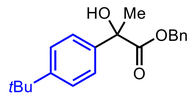


22; c = 16; *s* = 1.4
alc: 51.5:48.5; 81%
est: 57:43; 10%

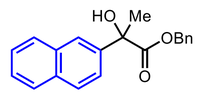
2. Aromatic Ph variation



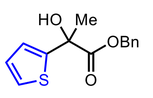
23; c = 50; *s* = 71
alc: 95:5; 45%
est: 96:4; 45%



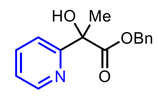
24; c = 49; *s* = 140
alc: 96:4; 37%
est: 97.5:2.5; 39%



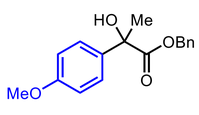
25; c = 52; *s* =74
alc: 98:2; 41%
est: 95:5; 41%



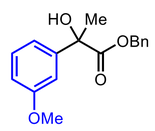
29; c = 55; *s* = 64
alc: > 99:1; 40%
est: 90.5:9.5; 49%



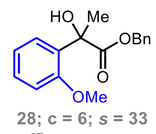
30; c = 51; *s* = 46
alc: 95:5; 47%
est: 93,5:6.5; 42%



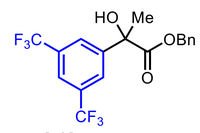
26; c = 43; *s* = 85
alc: 85.5:14.5; 49%
est: 97.5:2.5; 35%



27; c = 51; *s* = 58
alc: 96.5:3.5; 44%
est: 94.5:5.5; 47%

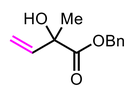


28; c = 6; *s* = 33
28;[f] **c = 35; *s* = 20**
alc: 73:27; 58%
est: 93:7; 30%

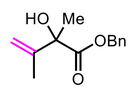


31;[g,h] **c = 63; *s* = 12**
alc: 97.5:2,5; 29%
est: -:-; 53%

3. None aromatic Ph variation



32;[g] **c = 62; *s* = 7**
alc: 91:9; 32%
est: -:-; 50%



33;* c = 39; *s* > 500
alc: 81:19; 53%
est: > 99.5:0.5; 30%

34; c = 27; *s* = 11
alc: 64.5:35.5; 61%
est: 89.5:10.5; 21%

35; c = 19; *s* = 11
35;[a] **c = 40; *s* = 24**
alc: 79:21; 50%
est: -:-; 35%

36; c = 22; *s* = 32
36;*[a] **c = 47; *s* = 19**
alc: 85:15; 44%
est: 90:10; 45%

37;[e] **c = 41; *s* = 1.5**
alc: 55:45; 48%
est: 57:43; 34%

4. Effect of the carbonyl group

38;*[b,c] **c = 50; *s* = 3**
alc: 69:31; 41%
est: 69:31; 38%

39;[b,c] **c = 12; *s* = 2**
alc: 52:48; 72%
est: 65:35; 2%

s and *c* determined by HPLC analysis; * absolute configuration determined by comparison of optical rotation to literature; [a] 2 mol% (2*R*,3*S*)-HyperSe, opposite enantioselectivity; [b] 2 equiv. of NEt_3; [c] 2 equiv. of $(MeCO)_2O$; [d] no acylation observed with DMAP; [e] 0.55 equiv. of $(iPrCO)_2O$; [f] 5 mol% (2*R*,3*S*)-HyperSe, opposite enantioselectivity; [g] *ee* of ester couldn't be determined by means of HPLC or GC analysis, *s* calculated using c from ^{1}H NMR spectrum of reaction crude; [h] 1 equiv. of $(iPrCO)_2$;

Proposed Mechanism and TS Model

Computational studies of the KR of 3-hydroxyoxindoles suggested three key interactions in the TS model: 1) the S···O interaction, which holds the acyl group *syn*-coplanar to the isothiouronium core; 2) chelation by carboxylate generated in-situ, through a non-classical C–H···O hydrogen bond; 3) C=O···isothiouronium interaction, primarily electrostatic in nature, is favoured over commonly proposed π-isothiouronium interaction.[4]

As substrate **38** and **39** has further confirmed the vital role played by the C=O···isothiouronium interaction in the enantiodiscrimination, a transition state model of this newly developed acylative KR of acyclic tertiary alcohols can be proposed. A proposed catalytic cycles is also shown below.

(a) Transition state models of KR of 3-hydroxyoxindoles

(*R*)-TS-I
slow reacting
(*R*)-enantiomer

(*S*)-TS-I
fast reacting
(*S*)-enantiomer

1) S•••O interaction
2) chelation by carboxylate
3) C=O••isothiouronium interaction

(b) Proposed transition state model of KR of acyclic tertiary alcohols

fast reacting
(*R*)-enantiomer

References

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