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Double asymmetric synthesis: faster reactions are more selective and a model to estimate relative rate

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Supporting Information

Table of Contents.

1. Equations used in this study.

1a. *Calculation of the selectivity factor s as a function of C and ee_1 (equation 1).*

V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237-6240.
H. B. Kagan and J.-C. Fiaud, Kinetic Resolution. *Top. Stereochem.,* 1988, **18**, 249-330.

$$k_{fast}/k_{slow} = s = \frac{\ln[(1-C)(1-ee_1)]}{\ln[(1-C)(1+ee_1)]} \quad \text{(eq. 1)}$$

1b. *Calculation of the diastereofacial selectivities (equations 2 and 3).*

S. El-Baba, J.-C. Poulin and H. B. Kagan, *Tetrahedron*, 1984, **40**, 4275-4284.
H. B. Kagan, *Tetrahedron*, 2001, **57**, 2449-2468. [Note - eq. 3 is given incorrectly in the second of these references].

$$[R,R']/[R,S'] = dr[(1 + ee_2)/(1 + ee_3)] \quad \text{(eq. 2)}$$

$$[S,S']/[S,R'] = dr[(1 - ee_2)/(1 - ee_3)] \quad \text{(eq. 3)}$$

1c. *Mass balance check (equation 4).*

S. El-Baba, J.-C. Poulin and H. B. Kagan, *Tetrahedron*, 1984, **40**, 4275-4284.

$$Y = x_1 ee_1 + x_2 ee_2 + x_3 ee_3 \quad \text{(eq. 4)}$$

1d. *Horeau equation (equation 5).*

J. P. Guetté and A. Horeau, *Bull. Soc. Chim. Fr.*, 1967, 1747.

$$x_2 ee_2 + x_3 ee_3 = 0 \text{ when } C = 1 \quad \text{(eq. 5)}$$

1e. *Basis of double asymmetric synthesis (equations 6 and 7).*

S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem. Int. Ed. Engl.,* 1985, **24**, 1-30.

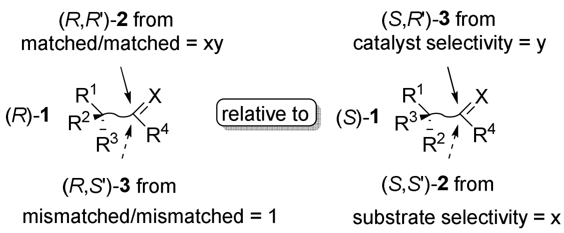
$$\Delta\Delta G^{\ddagger}\text{ (matched)} = \Delta\Delta G_1^{\ddagger} + \Delta\Delta G_2^{\ddagger} + \Delta G_{12}^{\ddagger} \quad \text{(eq. 6)}$$

$$\Delta\Delta G^{\ddagger}\text{ (mismatched)} = \Delta\Delta G_1^{\ddagger} - \Delta\Delta G_2^{\ddagger} + \Delta G'^{\ddagger}_{12} \quad \text{(eq. 7)}$$

1f. *Calculation of s_{est} and s_{pred} (equation 8).*

This work.

From the following model for the addition of YH:



$$s = \frac{k_{R,R'} + k_{R,S'}}{k_{S,S'} + k_{S,R'}} = \frac{k_{\text{matched}}}{k_{\text{mismatched}}} \simeq \frac{xy + 1}{x + y} \quad \text{(eq. 8)}$$

x = substrate dr (x : 1)   y = catalyst er (y : 1)

Use of $x = x_{est}$ and $y = y_{est}$ give s_{est}
Use of $x = x_{pred}$ and $y = y_{pred} = s_{pred}$

1g. *Derivation of equations 9 and 10.*
This work. From the model in section 1f (above):

x = substrate selectivity

y = catalyst selectivity

xy = ratio of matched/matched vs. mismatched/mismatched = (*R*,*R’*)/(*R*,*S’*) = a

x/y = (*S*,*S’*)/(*S*,*R’*) = b

Therefore:

y = a/x = a/by (as x = by), so y^2 = a/b, and y = squareroot of a/b = y_{est} (y_{est} being the value of y derived in this way).

Similarly:

x = a/y = x_{est} = a/y_{est} (x_{est} being the value of x derived in this way).

1h. *Determination of the ratio $dr_{matched}/dr_{mismatched}$ (equation 11).*

Ratio of selectivities = y^2 (where y < x)

Ratio of selectivities = x^2 (where y > x)

Proof as:

Two ratios: x : 1 (substrate selectivity) and y: 1 (catalyst selectivity)

As before (see 1f) relative rates as: *R*,*R’* = xy, *R*,*S’* = 1, *S*,*R’* = y, *S*,*S’* = x.

dr' = xy and dr'' = x/y where y < x Therefore dr'/ dr'' = xy divided by x/y = xy^2/x = y^2.

Or

dr' = xy and dr'' = y/x where y > x Therefore dr'/ dr'' = xy divided by y/x = yx^2/y = x^2.

1i. *Calculation x_{pred} (equation 12).*
This work.

$$x_{pred} = \frac{k_{R,R'} + k_{S,S'}}{k_{R,S'} + k_{S,R'}} \quad \text{eq. 12}$$

where $k_{R,R'}$, $k_{S,R'}$ and $k_{S,S'}$ are the relative rate values with $k_{R,S'}$ =1

1j. ***Calculation of conversion as a function of dr, ee_1, ee_2 and ee_3.***
H. B. Kagan, *Tetrahedron*, 2001, **57**, 2449-2468.

$C = [(1 + dr)ee_1]/[dr(ee_1 - ee_2) + ee_1 - ee_3]$ (eq. 13)

1k. ***Determination of C as a function of s and ee_1.***
G. Balavoine, A. Moradpour and H. B. Kagan, *J. Am. Chem. Soc.,* 1974, **96**, 5152-5158.

As decribed in this paper *C* may be determined as a function of ee_1 and *s* as:

$$C = 1 - \frac{1}{2}\left[\left(\frac{1 + ee_1}{1 - ee_1}\right)^{\frac{1}{2} - \frac{1}{g}} + \left(\frac{1 + ee_1}{1 - ee_1}\right)^{-\frac{1}{2} - \frac{1}{g}}\right] \quad \text{where } g = 2\frac{s - 1}{s + 1}$$

Alternatively, as derived from eq. 1:

$$C = 1 - \frac{(1 - ee_1)^{1/(s-1)}}{(1 + ee_1)^{s/(s-1)}}$$

1l. ***Calculation of the reaction mixture composition.***
Knowing *C* for a given value of *s* and ee_1 can then calculate (where *R* is the fast reacting enantiomer)

% major enantiomer (*S*) of recovered starting material = $\%sm_{major}$ =
$(1 - C) \times ((ee_1 \times 100)+100)/2$

% minor enantiomer (*R*) of recovered starting material = $\%sm_{minor}$ =
$((1 - C) \times 100) - \%sm_{major}$

% of the major reacted (*R*) enantiomer = $\%prod_{major}$ =
$50 - \%sm_{minor}$

% of the minor reacted (*S*) enantiomer = $\%prod_{minor}$ =
$50 - \%sm_{major}$

And then knowing the [*R*,*R*']/[*R*,*S*'] and [*S*,*S*']/[*S*,*R*'] ratios:

% R,R' diastereoisomer = %[R,R']

$$= \frac{[R,R']/[R,S']}{[R,R']/[R,S'] + 1} \quad \times \%\text{prod}_{major}$$

% R,S' diastereoisomer = %[R,S']

$$= \frac{1}{[R,R']/[R,S'] + 1} \quad \times \%\text{prod}_{major}$$

% S,S' diastereoisomer = %[S,S']

$$= \frac{1}{[S,R']/[S,S'] + 1} \quad \times \%\text{prod}_{minor}$$

% S,R' diastereoisomer = %[S,S']

$$= \frac{[S,R']/[S,S']}{[S,R']/[S,S'] + 1} \quad \times \%\text{prod}_{minor}$$

Therefore

$$ee_2 = \frac{\%[R,R'] - \%[S,S']}{\%[R,R'] + \%[S,S']} \qquad ee_3 = \frac{\%[S,R'] - \%[R,S']}{\%[S,R'] + \%[R,S']} \qquad dr = \frac{\%[R,R'] + \%[S,S']}{\%[S,R'] + \%[R,S']}$$

2. Examples used in Scheme 3, Table 1, and additional examples, including the determination of y_{pred}.

Each example is of a different substrate/catalyst combination. Where a paper reports two of more examples of the same substrate/catalyst combination, just one example is listed. Examples with Y (equation 4) outside of the range -0.05 to 0.05 are not included *unless* the percentage conversion was recalculated using equation 13 with reported values of dr, ee_1, ee_2 and ee_3, as determined by HPLC (and for which as a consequence Y = 0). The stereochemical descriptor (*R*/*S*) of the product is that of the enantiomer of the starting material from which it it derived. In most cases this is the correct stereochemical descriptor for the product, but if not this is noted. By extension, the sign of the ee of the product is positive if derived from the *R* enantiomer of the starting material, and -ve if derived from the *S* enantiomer of the starting material. For the determination of s_{pred} the value of y_{pred} used was determined from the ee value resulting from application of the same or similar catalyst/reaction conditions on a closely related prochiral substrate. This example is given after each reaction/set of reactions.

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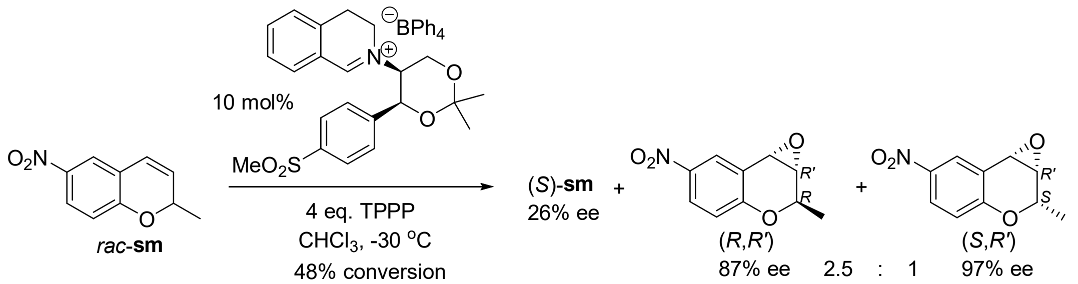
P. C. B. Page, L. F. Appleby, Y. Chan, D. P. Day, B. R. Buckley, A. M. Z. Slawin, S. M. Allin and M. J. McKenzie, *J. Org. Chem*., 2013, **78**, 8074-8082.

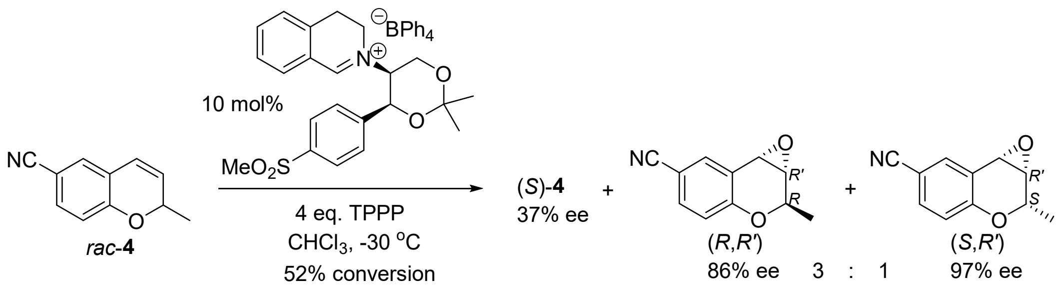
Scheme S1. **Example 1.** From Table 3, entry 1.



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mismatched}$	$dr_{matched}/dr_{mismatched}$
0.52 (-0.26)	0.343 (0.87)	0.137 (-0.97)	0.03	156	0.17	5.1	30.7	2.7	4.4	2.4	2.3	26

Relative rate: [*R*,*R*'] = 156, [*S*,*R*'] = 60, [*R*,*S*'] = 1, [*S*,*S*'] = 9.9. Value of y_{pred} = 16.

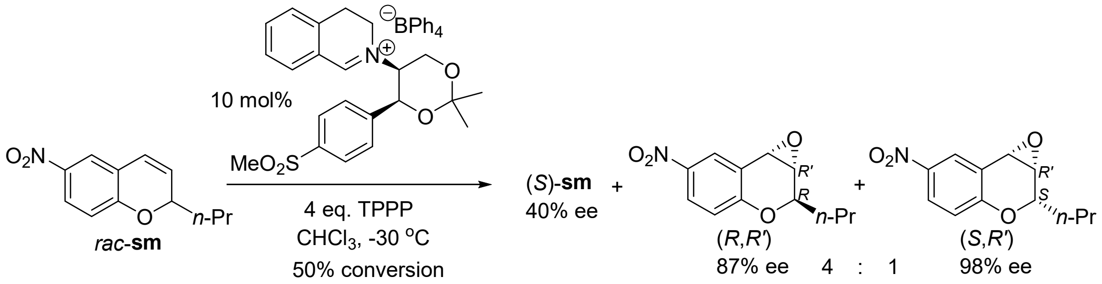
Scheme S2. **Example 2.** From Table 3, entry 2 (example used in manuscript – Scheme 3).



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R'*]/[*R*,*S'*]	[*S*,*S'*]/[*S*,*R'*]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mismatched}$	$dr_{matched}/dr_{mis-matched}$
0.48 (-0.37)	0.39 (0.86)	0.13 (-0.97)	0.03	186	0.21	6.3	29.5	3.7	5.2	3.5	2.9	40

Relative rate: [*R*,*R'*] = 186, [*S*,*R'*] = 53, [*R*,*S'*] = 1, [*S*,*S'*] = 11. Value of y_{pred} = 66.

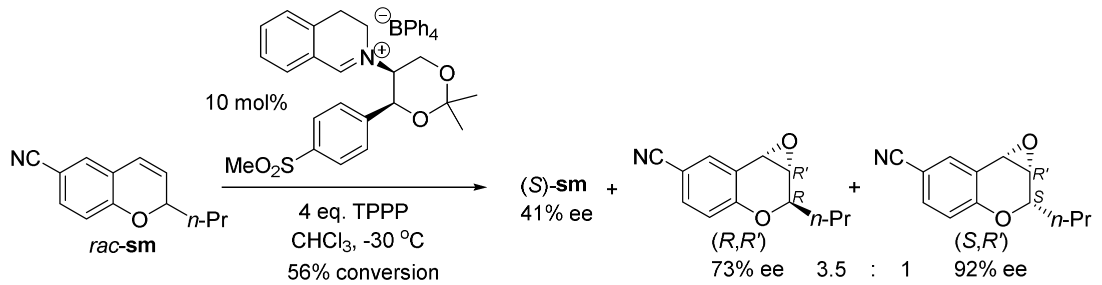
Scheme S3. **Example 3.** From Table 3, entry 3.



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R'*]/[*R*,*S'*]	[*S*,*S'*]/[*S*,*R'*]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mismatched}$	$dr_{matched}/dr_{mis-matched}$
0.50 (-0.40)	0.40 (0.87)	0.10 (-0.98)	0.05	374	0.26	9.9	37.7	4.5	7.9	3.5	3.4	98

Relative rate: [*R*,*R'*] = 374, [*S*,*R'*] = 88, [*R*,*S'*] = 1, [*S*,*S'*] = 23. Value of y_{pred} = 16.

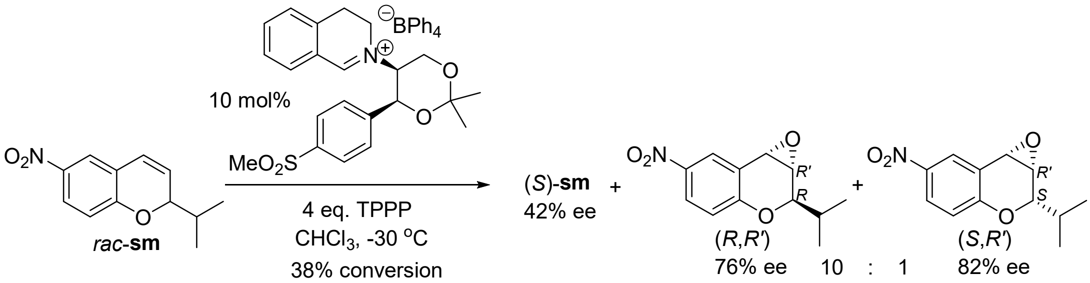
Scheme S4. **Example 4.** From Table 3, entry 4.



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R'*]/[*R*,*S'*]	[*S*,*S'*]/[*S*,*R'*]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mismatched}$	$dr_{matched}/dr_{mis-matched}$
0.44 (-0.41)	0.436 (0.73)	0.124 (-0.92)	0.02	76	0.49	6.1	12.4	4.4	4.2	4.2	2.8	38

Relative rate: [*R*,*R'*] = 76, [*S*,*R'*] =18, [*R*,*S'*] = 1, [*S*,*S'*] = 9. Value of y_{pred} = 66.

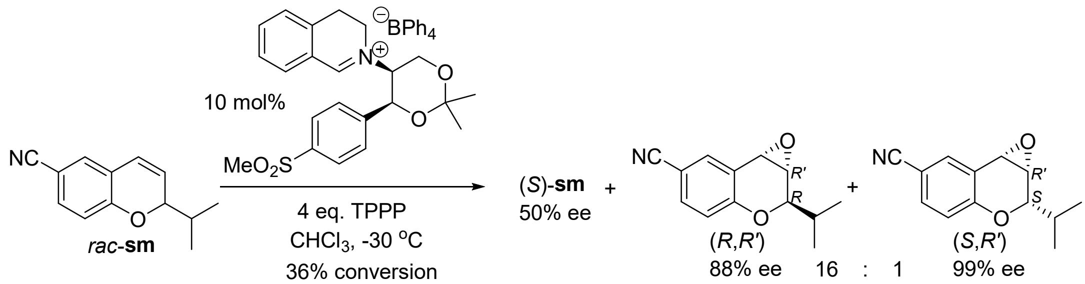
Scheme S5. **Example 5.** From Table 3, entry 7.



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*′]/ [*R*,*S*′]	[*S*,*S*′]/ [*S*,*R*′]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis\text{-}matched}$	$dr_{matched}/dr_{mis\text{-}matched}$
0.62 (-0.42)	0.345 (0.76)	0.035 (-0.82)	-0.03	96	1.3	11.2	8.6	16.5	4.9	8.1	8.0	74

Relative rate: [*R*,*R*′] = 96, [*S*,*R*′] = 5.3, [*R*,*S*′] = 1, [*S*,*S*′] = 6.9. Value of y_{pred} = 16.

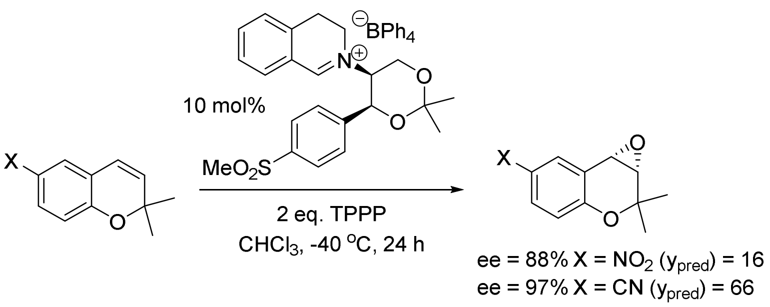
Scheme S6. **Example 6.** From Table 3, entry 8.



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*′]/ [*R*,*S*′]	[*S*,*S*′]/ [*S*,*R*′]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis\text{-}matched}$	$dr_{matched}/dr_{mis\text{-}matched}$
0.64 (-0.50)	0.339 (0.88)	0.021 (-0.99)	-0.04	3035	0.97	54	56	55	28	30	28	2954

Relative rate: [*R*,*R*′] = 3035, [*S*,*R*′] =55, [*R*,*S*′] = 1, [*S*,*S*′] = 54. Value of y_{pred} = 66.

Scheme S7. Estimation of y_{pred}. P. C. B. Page, B. R. Buckley, H. Heaney and A. J. Blacker, *Org. Lett.*, 2005, **7**, 375-377.



No examples available of epoxidation of the corresponding benzopyran without the two methyl substituents.

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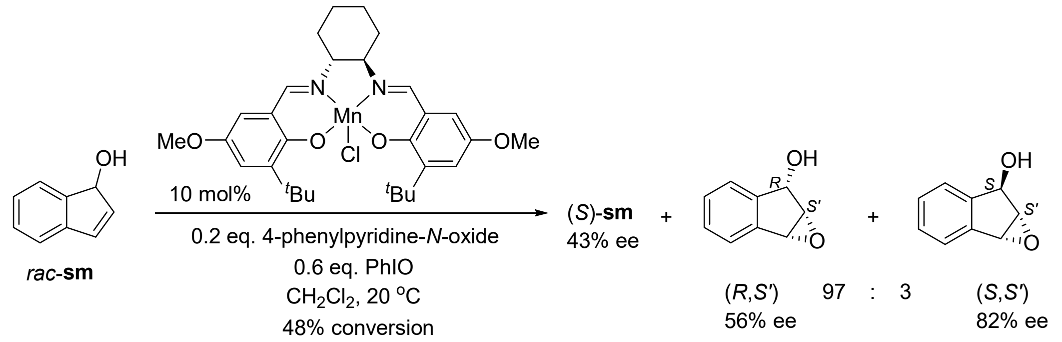
W. Adam, H.-U. Humpf, K. J. Roschmann and C. R. Saha-Möller, *J. Org. Chem*., 2001, **66**, 5796-5800.

From Table 1, entry 3**.** Example not used as Y = 0.09.

Scheme S8. **Example 7.** From Table 1, entry 4.



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*′]/ [*R*,*S*′]	[*S*,*S*′]/ [*S*,*R*′]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis\text{-}matched}$	$dr_{matched}/dr_{mis\text{-}matched}$
0.52 (-0.43)	0.466 (0.56)	0.014 (-0.82)	0.03	0.0035 (288)	0.12 (8.1)	48.2	6.0	39.9	5.3	10	4.1	36

Relative rate: [*R*,*R*′] = 1, [*S*,*R*′] = 63, [*R*,*S*′] = 288, [*S*,*S*′] = 7.8. Value of y_{predc} = 13.

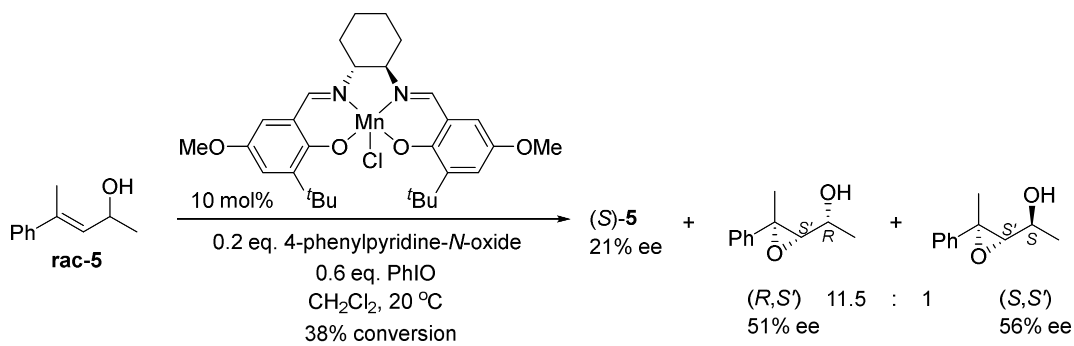
The *R* and *S* configurations of the product refer to that of the starting material and not the correct *R* and *S* configurations of the product. The reaction displayed a chemoselectivity of 86 : 14, the minor alternative reaction being -OH to C=O oxidation.

From Table 1, entry 5. Example not used as poor chemoselectivity (55% oxidation).

From Table 1, entry 5. Example not used as poor chemoselectivity (57% oxidation).

From Table 1, entry 9. Example not used as Y = 0.07.

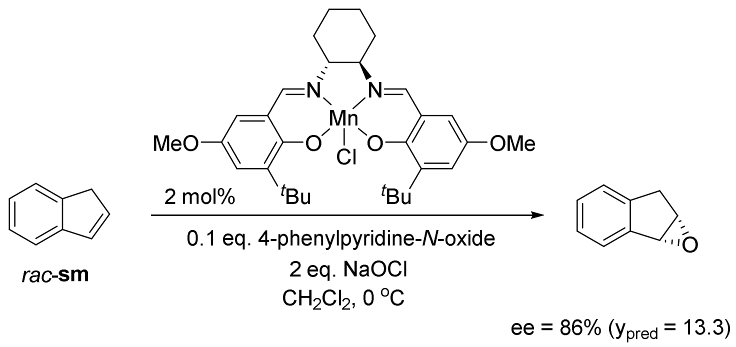
Scheme S9. **Example 8.** From Table 1, entry 10 (example used in manuscript – Table 1, entry 1).



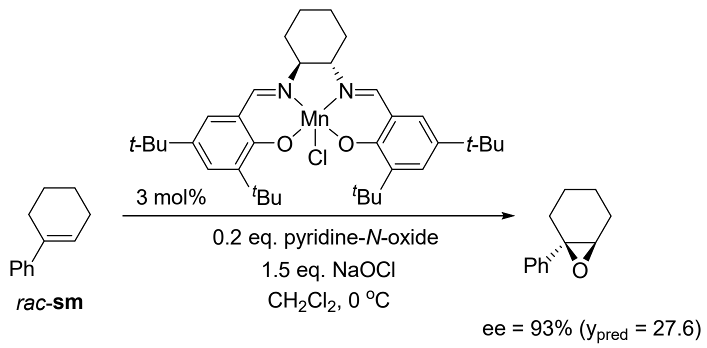
x_1 (ee$_1$)	x_2 (ee$_2$)	x_3 (ee$_3$)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.62 (-0.21)	0.35 (0.51)	0.03 (-0.56)	0.03	0.025 (40)	0.27 (3.5)	12.1	3.3	11.7	2.7	8.3	2.5	11

Relative rate: [*R*,*R*'] = 1, [*S*,*R*'] = 13, [*R*,*S*'] = 40, [*S*,*S*'] = 3.5. Value of y_{pred} = 28.

Scheme S10. Estimation of y_{pred}. P. J. Pospisil, D. H. Carsten and E. N. Jacobsen, *Chem. Eur., J.* 1996, **2**, 974-980.



Scheme S11. Estimation of y_{pred}. B. D. Brandes and E. N. Jacobsen, *J. Org. Chem*. 1994, **59**, 4378-4380.



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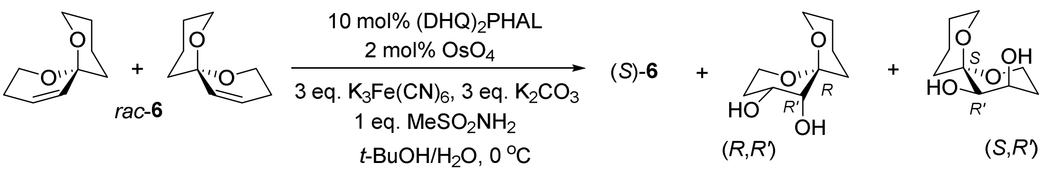
M. A. Brimble and A. D. Johnston, *Tetrahedron: Asymmetry*, 1997, **8**, 1661-1676.

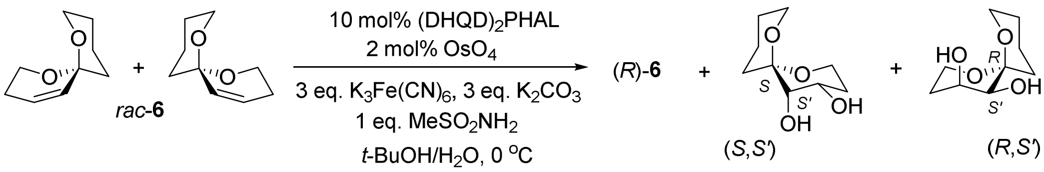
Scheme S12. **Example 9**. Table 1, entries 1-4 (entry 4, example used in manuscript – Table 1, entry 2).



Entry	x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*′]/[*R*,*S*′]	[*S*,*S*′]/[*S*,*R*′]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
1 (18 h)	0.892 (-0.046)	0.102 (0.663)	0.006 (-0.598)	0.02	70	3.6	15.9	4.4	12.3	3.5	1.8	2.3	20
2 (42 h)	0.881 (-0.068)	0.113 (0.657)	0.006 (-0.637)	0.01	86	4.0	18.4	4.7	16.7	3.8	1.8	3.2	22
3 (113 h)	0.772 (-0.187)	0.273 (0.623)	0.015 (-0.706)	0.02	100	4.0	20.1	5.0	17.4	4.0	1.8	3.2	25
4 (257 h)	0.523 (-0.404)	0.449 (0.519)	0.028 (-0.820)	0.00	135	4.2	23.9	5.7	20.8	4.6	1.9	3.8	32

Relative rate (entry 4): [*R*,*R*′] = 135, [*S*,*R*′] = 6.9, [*R*,*S*′] = 1, [*S*,*S*′] = 29. Value of y_{pred} = 2.

Scheme S13. **Example 10**. Table 1, entry 5.

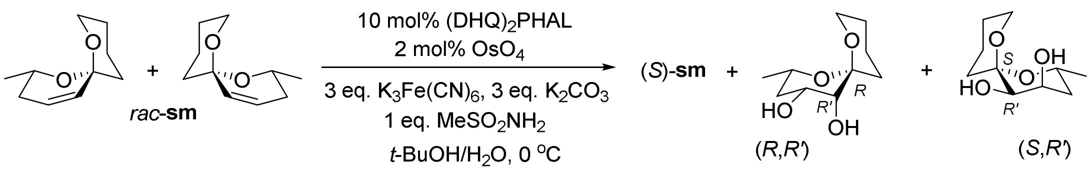


Entry	x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*′]/[*R*,*S*′]	[*S*,*S*′]/[*S*,*R*′]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
5 (18 h)	0.249 (0.673)	0.656 (-0.461)	0.095 (0.857)	-0.05	2.0	71	11.9	5.9	9.4	4.0	1.7	2.9	35

Relative rate: [*R*,*R*′] = 17 , [*S*,*R*′] = 1, [*R*,*S*′] = 8.3, [*S*,*S*′] = 71. Value of y_{pred} = 2.

Other entries not used as a) entry 2 has Y = 0.06, and for entries 2-4 the ee of the starting material *decreases* with conversion.

Scheme S14. **Example 11**. Table 2, entries 1-4

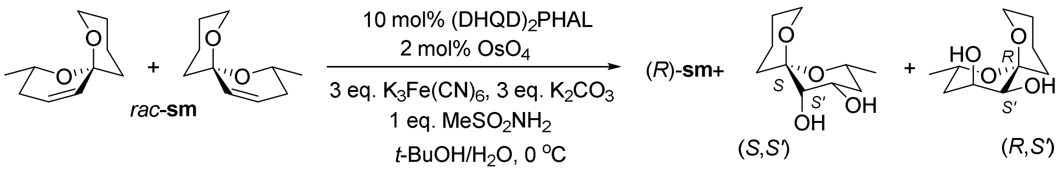


Entry	x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*′]/[*R*,*S*′]	[*S*,*S*′]/[*S*,*R*′]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
1 (18 h)	0.944 (-0.023)	0.052 (0.747)	0.004 (-0.552)	0.01	51	2,1	10.4	4.9	8.1	3.4	1.7	2.3	24
4 (257 h)	0.615 (-0.356)	0.361 (0.638)	0.024 (-0.802)	-0.01	124	3.0	19.4	6.4	20.1	4.9	1.9	5.1	41

Relative rate (entry 4): [*R*,*R*′] = 124, [*S*,*R*′] = 6.1, [*R*,*S*′] = 1, [*S*,*S*′] = 18. Value of y_{pred} = 2.

Entry 2 not used (Y = 0.09), entry 3 not used (Y = 0.11).

Scheme S15. **Example 12**. Table 2, entries 5-8

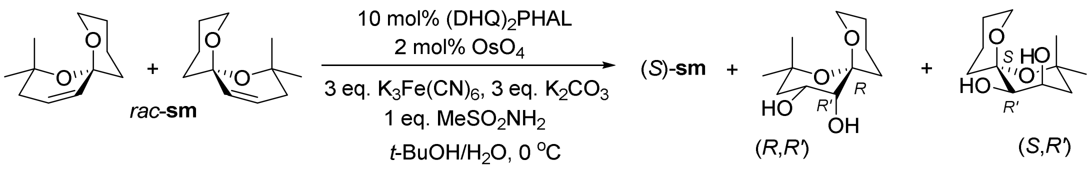


Entry	x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
5 (18 h)	0.939 (0.026)	0.054 (-0.709)	0.007 (0.645)	0.01	1.4	37	7.1	5.2	6.0	3.1	1.6	2.4	27
8 (257 h)	0.537 (0.369)	0.417 (-0.558)	0.046 (0.823)	0.00	2.2	80	13.2	6.0	11.7	4.2	1.8	3.5	36

Relative rate (entry 8): [*R*,*R*'] = 16, [*S*,*R*'] = 1, [*R*,*S*'] = 7.2, [*S*,*S*'] = 80. Value of y_{pred} = 2.

Entry 6 not used (Y = 0.12), entry 7 not used (Y = 0.07).

Scheme S16. **Example 13**. Table 3, entries 1-4

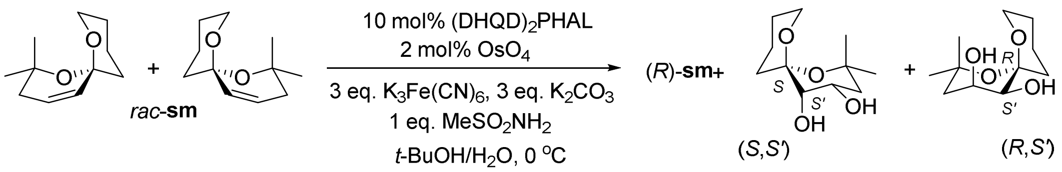


Entry	x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
1 (18 h)	0.904 (-0.016)	0.089 (0.619)	0.007 (-0.481)	0.04	40	3.3	11.4	3.5	7.9	2.7	1.7	1.4	24
3 (113 h)	0.708 (-0.101)	0.274 (0.427)	0.018 (-0.501)	0.04	44	5.8	15.9	2.7	14.0	2.4	1.8	1.8	8

Relative rate (entry 3): [*R*,*R*'] = 44, [*S*,*R*'] = 3.6, [*R*,*S*'] = 1, [*S*,*S*'] = 21. Value of y_{pred} = 2.

Entry 2 not used (Y = 0.07), entry 4 not used (Y = 0.09).

Scheme S17. **Example 14.** Table 3, entries 5-8.

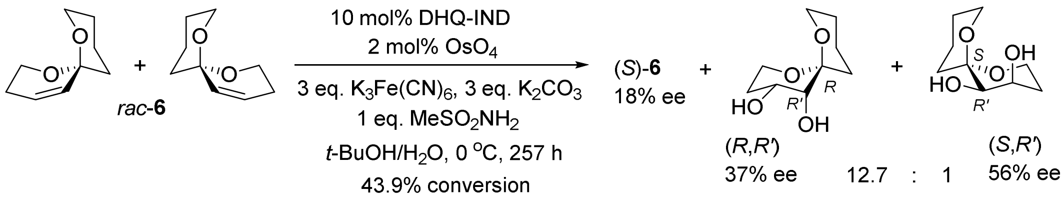


Entry	x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/[*R*,*S*']	[*S*,*S*']/[*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis\text{-}matched}$	$dr_{matched}/dr_{mis\text{-}matched}$
5 (18 h)	0.937 (0.006)	0.061 (-0.348)	0.002 (0.519)	-0.01	13	85	33.5	2.6	25.0	2.4	1.9	1.2	7

Relative rate: [*R*,*R*'] = 67, [*S*,*R*'] = 1, [*R*,*S*'] = 5.1, [*S*,*S*'] = 86. Value of y_{pred} = 2.

Entry 6 not used as s < 1.1 (1.03). Entry 7 not used (Y = 0.06), entry 8 not used (Y = 0.07).

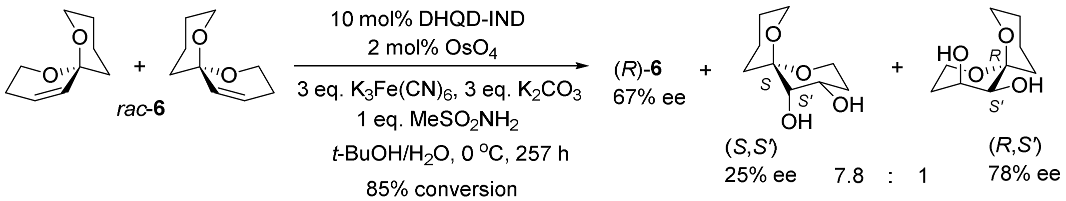
Scheme S18. **Example 15.** Table 4, entry 1.



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/[*R*,*S*']	[*S*,*S*']/[*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis\text{-}matched}$	$dr_{matched}/dr_{mis\text{-}matched}$
0.561 (-0.18)	0.407 (0.37)	0.032 (-0.56)	0.03	40	5.1	14.3	2.8	12.8	2.4	3.1	1.9	8

Relative rate: [*R*,*R*'] = 40, [*S*,*R*'] = 3.5, [*R*,*S*'] = 1, [*S*,*S*'] = 18. Value of y_{pred} = 4.

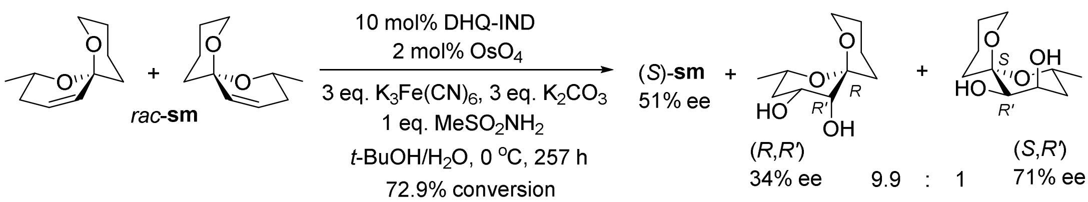
Scheme S19. **Example 16.** Table 4, entry 2.



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/[*R*,*S*']	[*S*,*S*']/[*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis\text{-}matched}$	$dr_{matched}/dr_{mis\text{-}matched}$
0.15 (0.67)	0.753 (-0.25)	0.097 (0.78)	0.01	3.3	44	12.0	3.7	10.2	2.9	3.8	2.2	14

Relative rate: [*R*,*R*'] = 16, [*S*,*R*'] = 1, [*R*,*S*'] = 4.9 , [*S*,*S*'] = 44. Value of y_{pred} = 6.

Scheme S20. **Example 17.** Table 4, entry 3.



x_1 (ee$_1$)	x_2 (ee$_2$)	x_3 (ee$_3$)	Y	[*R*,*R*′]/ [*R*,*S*′]	[*S*,*S*′]/ [*S*,*R*′]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.271 (-0.51)	0.662 (0.34)	0.067 (-0.71)	0.04	46	3.8	13.2	3.5	11.7	2.8	3	2.3	12

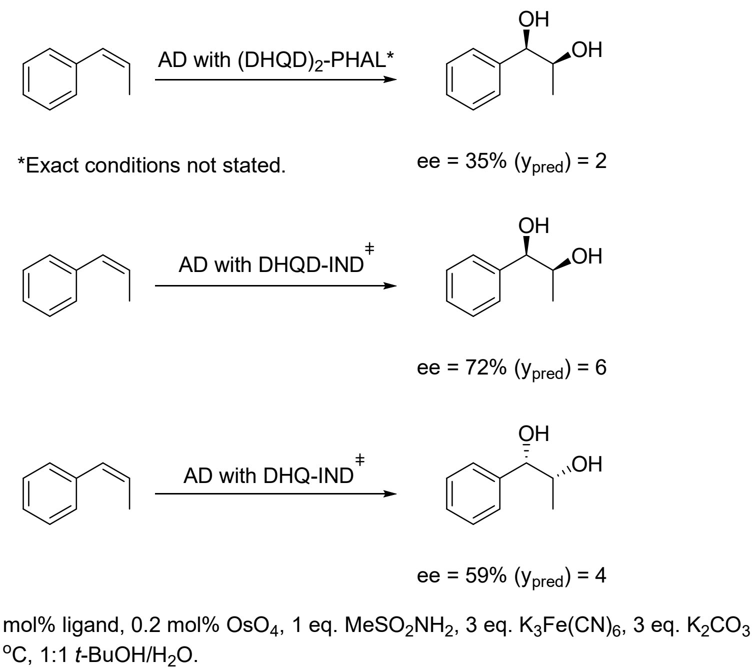
Relative rate: [*R*,*R*′] = 46, [*S*,*R*′] = 4.3, [*R*,*S*′] = 1, [*S*,*S*′] = 16. Value of y_{pred} = 4.

Table 4, entry 4 not used (Y = 0.12).

Table 4, entry 5 not used (Y = 0.17).

Table 4, entry 6 not used (Y = 0.06).

Scheme S21. Estimation of y_{pred}. L. Wang and K. B. Sharpless, *J. Am. Chem. Soc.*, 1992, **114**, 7568-7570.



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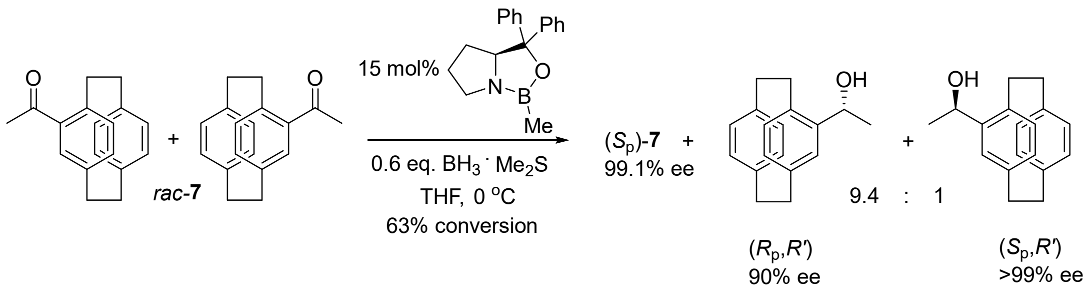
P. Dorizon, C. Martin, J.-C. Daran, J.-C. Fiaud and H. B. Kagan, *Tetrahedron: Asymmetry*, 2001, **12**, 2625-2630.
Scheme S22. Example 18. Table 2, entry 2 (example used in manuscript – Table 1, entry 3).

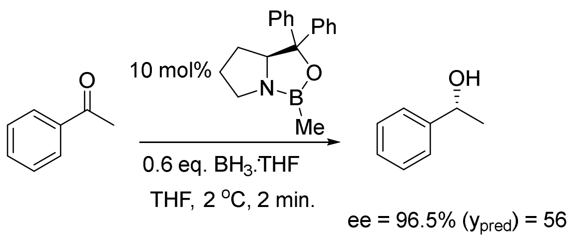


x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R'*]/ [*R*,*S'*]	[*S*,*S'*]/ [*S*,*R'*]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.37 (-0.991)	0.57 (0.74)	0.06 (-0.99)	0.00	1653	1.2	45.3	36.5	42.1	20	24	19	1332

Relative rate: [*R*,*R'*] = 1653, [*S*,*R'*] = 39, [*R*,*S'*] = 1, [*S*,*S'*] = 49. Value of y_{pred} = 56.

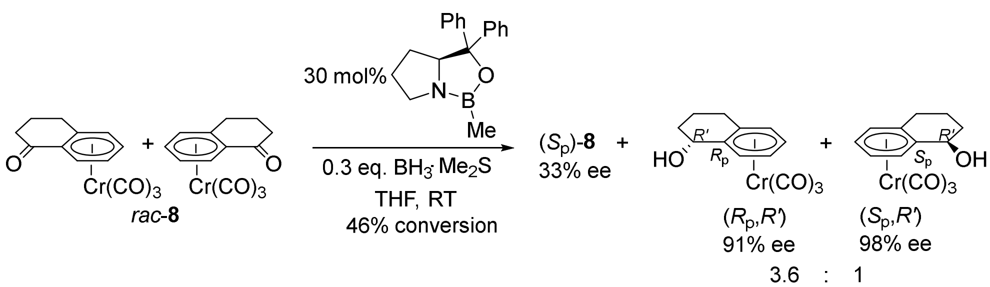
A conversion of 63% was calculated using eq. 13. With the literature conversion of 59% Y = -0.07. Such is the sensitivity of the value of *s* to conversion that this resulted in the literature value of 27 changing to a value of 19. This is one of nine examples of this reaction in this manuscript for which the ee values of all three components of the kinetic resolution are reported.

Scheme S23. Estimation of y_{pred}. E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925-7926.



H.-G. Schmalz and H. Jope, *Tetrahedron*, 1998, **54**, 3457-3464.

Scheme S24. **Example 19.** Table 1, entry 1 (example used in manuscript - Table 1, entry 4).

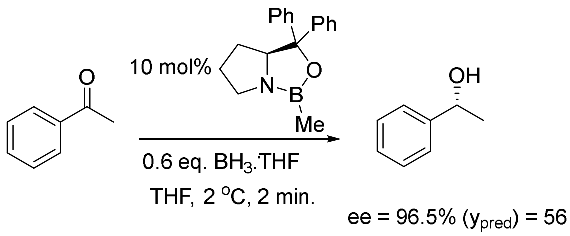


x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.54 (-0.33)	0.36 (0.91)	0.10 (-0.98)	0.05	344	0.16	7.5	45.8	3.7	6.5	3.5	3.1	56

Relative rate: [*R*,*R*'] = 344, [*S*,*R*'] = 96, [*R*,*S*'] = 1, [*S*,*S*'] = 16. Value of y_{pred} = 56.

This is one of four examples of this reaction in this manuscript for which the ee values of all three components of the kinetic resolution are reported.

Scheme S25. Estimation of y_{pred}. E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925-7926



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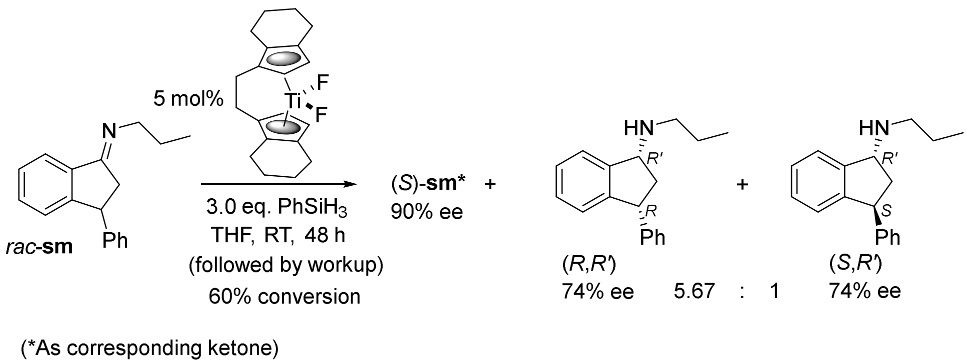
J. Yun and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 767-774.

Scheme S26. **Example 20.** Table 1, entry 3.



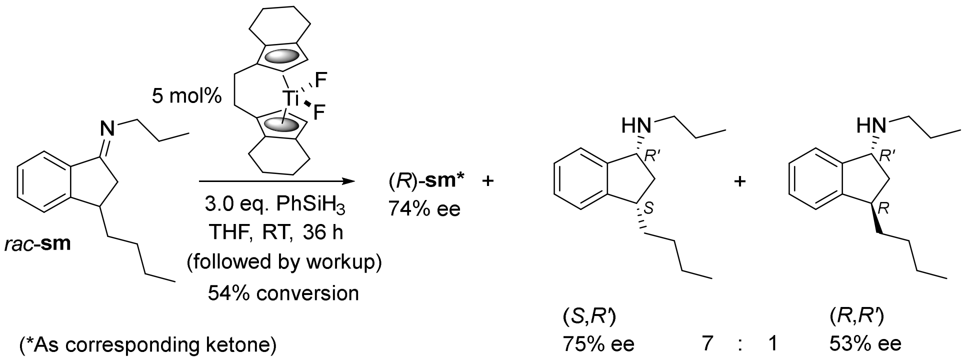
x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.40 (-0.90)	0.51 (0.74)	0.09 (-0.74)	-0.05	38	0.85	5.7	6.7	14.1	3.1	11	11.7	32

Relative rate: [*R*,*R*'] = 38, [*S*,*R*'] = 1.8, [*R*,*S*'] = 1, [*S*,*S*'] = 1.52. Value of y_{pred} = 49.

The configuration of the minor product diastereisomer assigned using Y (-0.05), as Y = 0.08 for the alternative (*R*,*S*') outcome.

One other example with this substrate catalyst combination.

Scheme S27. **Example 21.** Table 1, entry 5.



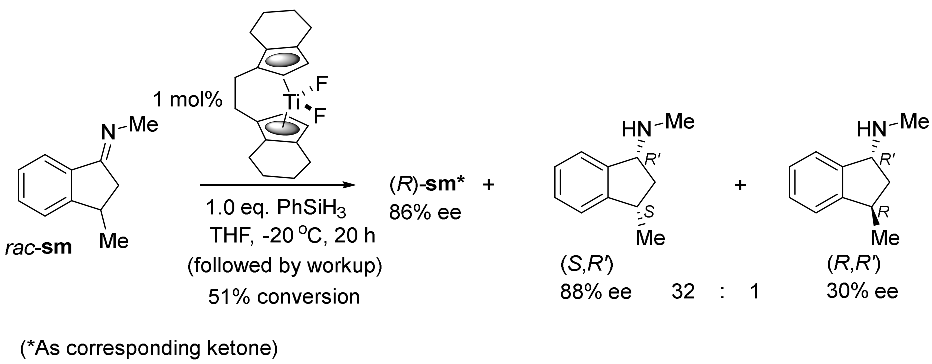
x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	s = $k_{matched}$/ $k_{mis\text{-}matched}$	$dr_{matched}$/ $dr_{mis\text{-}matched}$
0.46 (0.74)	0.473 (-0.75)	0.068 (0.53)	0.02	0.85 (1.14)	0.038 (26)	5.5	4.8	11.9	2.6	9.6	9.5	23

Relative rate: [*R*,*R*'] = 1.3, [*S*,*R*'] = 26, [*R*,*S*'] = 1.5, [*S*,*S*'] = 1. Value of y_{pred} = 49.

The configuration of the minor product diastereisomer assigned using Y (0.02), as Y = -0.05 for the alternative (*S*,*S*') outcome.

One other example with this substrate catalyst combination.

Scheme S28. **Example 22.** Table 2, entry 3.



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	s = $k_{matched}$/ $k_{mis\text{-}matched}$	$dr_{matched}$/ $dr_{mis\text{-}matched}$
0.49 (0.86)	0.495 (-0.88)	0.015 (0.30)	-0.01	0.34 (3.0)	0.012 (87)	16.1	5.4	51	4.1	25	29	29

Relative rate: [*R*,*R*'] = 0.76, [*S*,*R*'] = 87, [*R*,*S*'] = 2.28, [*S*,*S*'] = 1. Value of y_{pred} = 49.

The configuration of the minor product diastereisomer assigned using Y (-0.01), as Y = -0.02 for the alternative (*S*,*S*') outcome.

Three other examples with this substrate catalyst combination run at 15 °C, 0 °C and -30 °C. Two of these below.

At 15 °C (Table 2, entry 1)

x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*′]/[*R*,*S*′]	[*S*,*S*′]/[*S*,*R*′]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.43 (0.92)	0.533 (-0.77)	0.037 (0.42)	0.00	0.43 (2.33)	0.023 (44)	10.1	4.3	25.9	3.1	17	17.6	19

Relative rate: [*R*,*R*′] = 0.77, [*S*,*R*′] = 44, [*R*,*S*′] = 1.79, [*S*,*S*′] = 1. Value of y_{pred} = 49.

The configuration of the minor product diastereisomer assigned using Y (0.00), as Y = -0.03 for the alternative (*S*,*S*′) outcome.

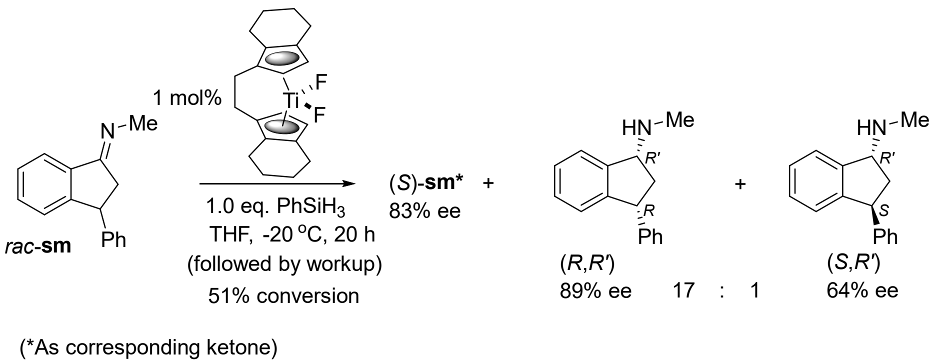
At 0 °C (Table 2, entry 2)

x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*′]/[*R*,*S*′]	[*S*,*S*′]/[*S*,*R*′]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.45 (0.93)	0.523 (-0.83)	0.027 (0.41)	0.00	0.43 (2.34)	0.017 (60)	11.8	5.1	35.4	3.6	21	24.5	26

Relative rate: [*R*,*R*′] = 0.75, [*S*,*R*′] = 60, [*R*,*S*′] = 1.74, [*S*,*S*′] = 1. Value of y_{pred} = 49.

The configuration of the minor product diastereisomer assigned using Y (0.00), as Y = -0.03 for the alternative (*S*,*S*′) outcome.

Scheme S29. **Example 23.** Table 2, entry 5.



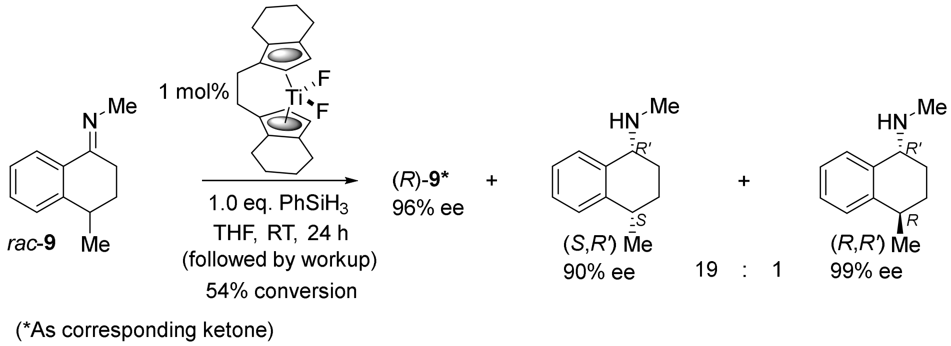
x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*′]/[*R*,*S*′]	[*S*,*S*′]/[*S*,*R*′]	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.49 (-0.83)	0.482 (0.89)	0.028 (-0.64)	0.00	90	1.15	10.2	8.8	32.3	4.8	20	22.8	78

Relative rate: [*R*,*R*′] = 90, [*S*,*R*′] = 1.86, [*R*,*S*′] = 1, [*S*,*S*′] = 2.15. Value of y_{pred} = 49.

The configuration of the minor product diastereisomer assigned using Y (0.00), as Y = 0.04 for the alternative (*R*,*S*′) outcome.

One other example with this substrate catalyst combination.

Scheme S30. **Example 24.** Table 3, entry 1 (example used in manuscript - Table 1, entry 5).

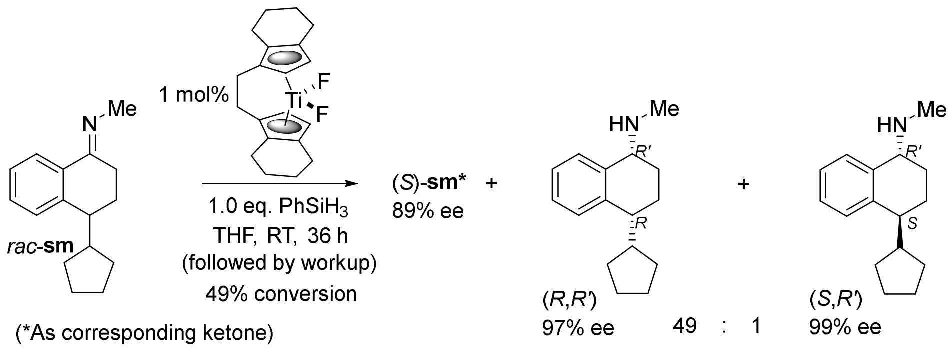


x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	s = $k_{matched}$/ $k_{mis-matched}$	$dr_{matched}$/ $dr_{mis-matched}$
0.46 (0.96)	0.513 (-0.90)	0.027 (0.99)	0.01	1.05	0.00028 (3610)	58.7	61.5	74.8	30	30	38.6	3447

Relative rate: [*R*,*R*'] = 48, [*S*,*R*'] = 3610, [*R*,*S*'] = 46, [*S*,*S*'] = 1. Value of y_{pred} = 49.

The configuration of the minor product diastereisomer assigned using Y (0.01), as Y = -0.05 for the alternative (*S*,*S*') outcome.

Scheme S31. **Example 25.** Table 3, entry 5.



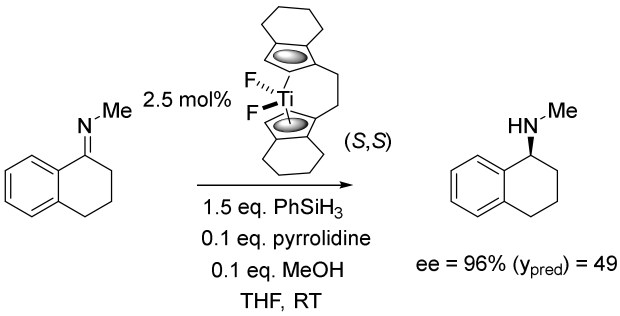
x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	s = $k_{matched}$/ $k_{mis-matched}$	$dr_{matched}$/ $dr_{mis-matched}$
0.51 (-0.89)	0.4802 (0.97)	0.0098 (-0.99)	0.00	9653	0.74 (1.35)	84.4	114	135	49	36	78	7131

Relative rate: [*R*,*R*'] = 9653, [*S*,*R*'] = 71, [*R*,*S*'] = 1, [*S*,*S*'] = 52. Value of y_{pred} = 49.

The configuration of the minor product diastereisomer assigned using Y (0.00), as Y = 0.02 for the alternative (*R*,*S*') outcome.

One other example with this substrate catalyst combination.

Scheme S32. Estimation of y_{pred}. X. Verdaguer, U. E. W. Lange, M. T. Reding and S. J. Buchwald, *J. Am. Chem. Soc*. 1996, **118**, 6784-6785.



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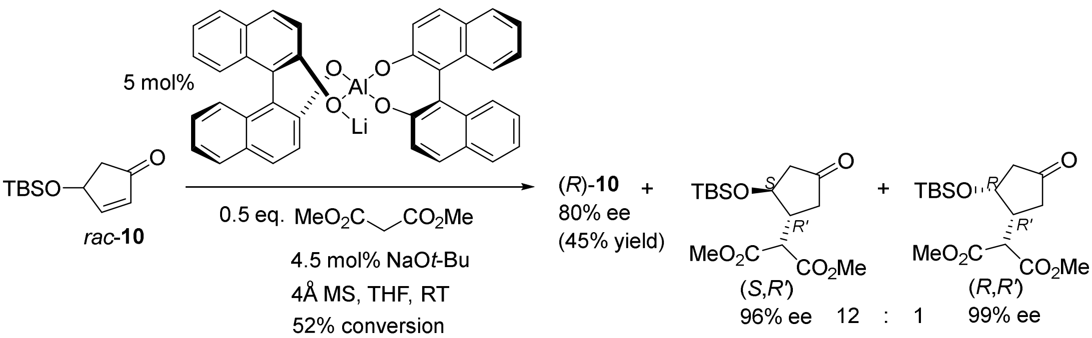
H. Mihara, Y. Sohtome, S. Matsunaga and M. Shibasaki, *Chem. Asian J.,* 2008, **3**, 359-366.

Scheme S33. **Example 26.** Table 3, entry 1, and Scheme 3 (example used in manuscript – Table 1, entry 6).

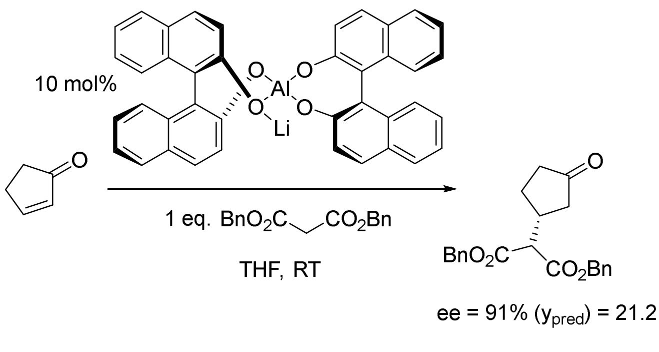


x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis\text{-}matched}$	$dr_{matched}/dr_{mis\text{-}matched}$
0.48 (0.80)	0.48 (-0.96)	0.04 (0.99)	-0.04	4.1	0.0004 (2352)	23.8	98.7	20.0	19	10	16	567

Relative rate: [*R*,*R*'] = 118, [*S*,*R*'] = 2352, [*R*,*S*'] = 29 , [*S*,*S*'] = 1. Value of y_{pred} = 21.

Five further examples with this substrate catalyst combination.

Scheme S34. Estimation of y_{pred}. T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date and M. Shibasaki, *Angew. Chem., Int. Ed. Engl.,* 1996, **35**, 104-106.



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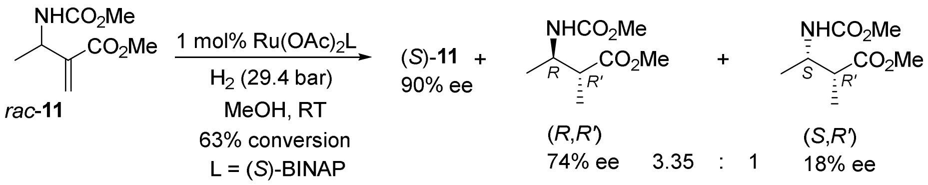
M. Takagi and K. Yamamoto, *Tetrahedron*, 1991, **47**, 8869-8882.

Scheme S35. **Example 27.** Table 4, entry 2 (example used in manuscript – Table 1, entry 7).

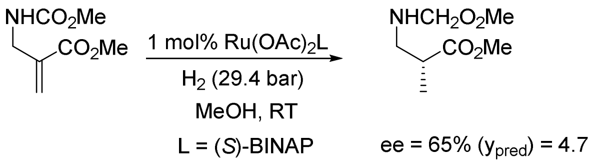


x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.37 (-0.90)	0.485 (0.74)	0.145 (-0.18)	0.00	7.1	0.74 (1.36)	2.3	3.1	5.0	1.5	2.5	9.4	5.2

Relative rate: [*R*,*R*'] = 19.3, [*S*,*R*'] = 1.4, [*R*,*S*'] = 2.7 , [*S*,*S*'] = 1. Value of y_{pred} = 4.7.

Conversion used = 63% (from eq. 11) rather than value of 68% (for which Y = 0.07).

Scheme S36. Estimation of y_{pred}. Same publication.



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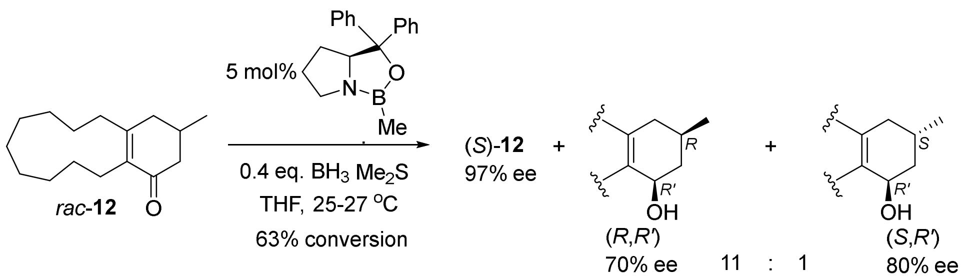
C. Fehr, J. Galindo and O. Etter, *Eur. J. Org. Chem.*, 2004, 1953-1957.

Scheme S37. **Example 28.** Scheme 2 (example used in manuscript – Table 1, entry 8)

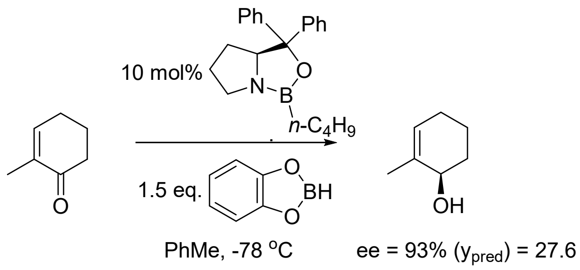


x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.368 (-0.97)	0.579 (0.70)	0.053 (-0.80)	0.01	93	1.82	13.0	7.1	28.8	4.7	14	14	51

Relative rate: [R,R'] = 93, [S,R'] = 2.4, [R,S'] = 1 , [S,S'] = 4.3. Value of y_{pred} = 28.

The values of x_1, x_2 and x_3 determined from the percentage yield values of 35%, 55% and 5% given for (*S*)-**13**, (*R*,*R*)-product and (*S*,*R'*)-product respectively, corrected to 100%. The configuration of the minor product diastereisomer confirmed using Y (0.01), as Y = 0.09 for the alternative (*R*,*S'*) outcome.

Scheme S38. Estimation of y_{pred}. E. J. Corey and R. K. Bakshi, *Tetrahedron Lett.,* 1990, **31**, 611-614.



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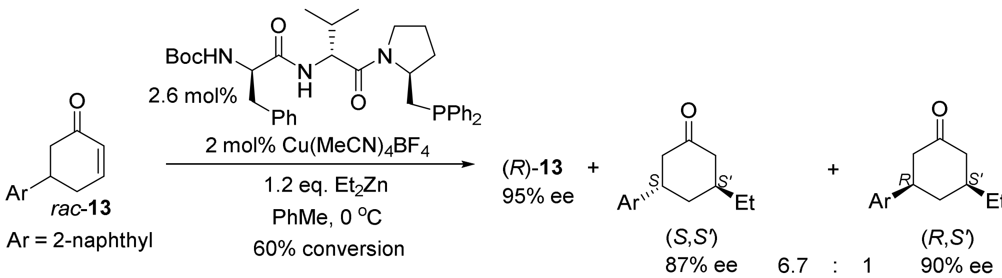
T. Soeta, K. Selim, M. Kuriyama and K. Tomioka, *Tetrahedron*, 2007, **63**, 6573-6576.

Scheme S39. **Example 29.** Table 1, entry 5 (example used in manuscript - Table 1, entry 9).

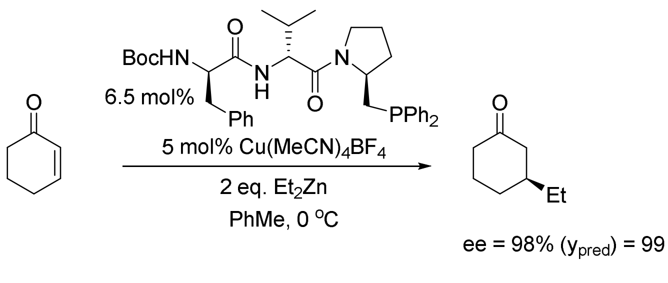


x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[R,R']/ [R,S']	[S,S']/ [S,R']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis\text{-}matched}$	$dr_{matched}/dr_{mis\text{-}matched}$
0.400 (0.95)	0.522 (-0.87)	0.078 (0.90)	0.00	0.46 (2.2)	125	7.6	16.5	19.7	5.2	16	16	57

Relative rate: [R,R'] = 2.5 , [S,R'] = 1, [R,S'] = 5.5 , [S,S'] = 125. Value of y_{pred} = 99.

Conversion used = 60% (from eq. 11). Using the yield values quoted (33% for (*R*)-**13** and 64% for the two product diastereoisomers), adjusted to 100%, gave Y = -0.25.

Scheme S40. Estimation of y_{pred}. T. Soeta, K. Selim, M. Kuriyama and K. Tomioka, *Adv. Synth. Catal.*, 2007, **349**, 629-635.



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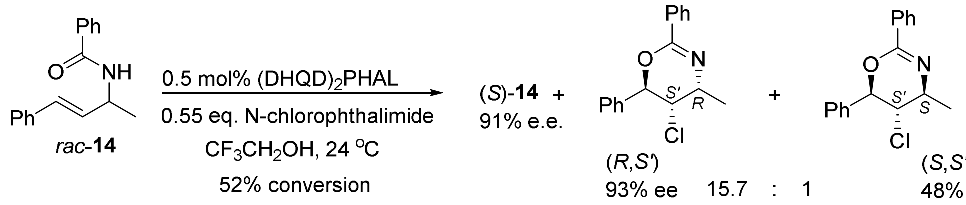
A. Jaganathan, R. J. Staples and B. Borhan, *J. Am. Chem. Soc.*, 2013, **135**, 14806-14813.

Scheme S41. **Example 30.** Table 1, entry 12 (example used in manuscript - Table 1, entry 10).



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.480 (-0.91)	0.489 (0.93)	0.031 (-0.48)	0.00	0.017 (58.5)	1.34	6.6	8.9	30.5	3.8	26	36	44

Relative rate: [*R*,*R*'] = 1.4 , [*S*,*R*'] = 1, [*R*,*S*'] = 83 , [*S*,*S*'] = 1.34.Value of y_{pred} = 199.

Conversion used = 52% (from eq. 13). Using the quoted conversion value of 48% (Y = -0.07).

This is one of several examples with this catalyst/substrate/reagent combination with differing catalyst loading (3 mol% to 0.01 mol%), and in two cases with an alternative Cl^+ source (NCS and DCDMH). Other catalysts employed gave much reduced level of selectivity.

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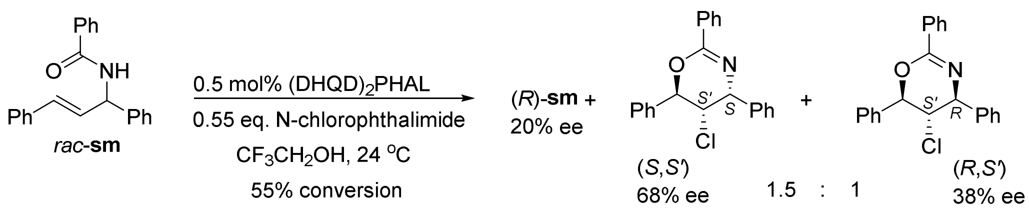
Scheme S42. Example 31. Table 2, entry 14.



x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.45 (0.20)	0.33 (-0.68)	0.22 (0.38)	-0.05	0.35 (2.9)	4.1	1.2	3.4	1.5	1.1	1.5	1.7	1.4

Relative rate: [*R*,*R*'] = 1, [*S*,*R*'] = 1.3 , [*R*,*S*'] = 2.9, [*S*,*S*'] = 5.2. Value of y_{pred} = 199.

The *S* and *R* configurations of the product refer to that of the starting enantiomers from which they are derived, and not the correct *R* and *S* configurations of the product.

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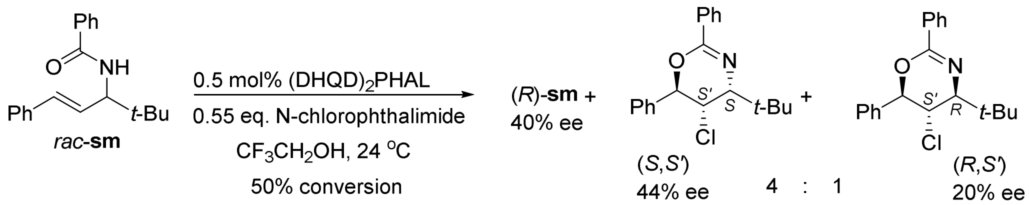
Scheme S43. **Example 32.** Table 2, entry 15.

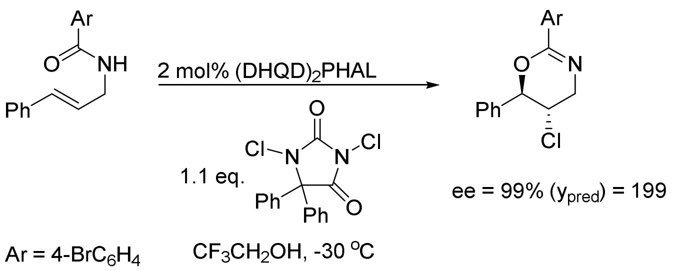


x_1 (ee_1)	x_2 (ee_2)	x_3 (ee_3)	Y	[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis\text{-}matched}$	$dr_{matched}/dr_{mis\text{-}matched}$
0.400 (0.40)	0.400 (-0.44)	0.100 (0.20)	0.04	1.9	7.2	3.7	2.0	4.8	1.5	4.6	3.4	4

Relative rate: [*R*,*R*'] = 1.9, [*S*,*R*'] = 1.2 , [*R*,*S*'] = 1, [*S*,*S*'] = 8.5. Value of y_{pred} = 199.

The *S* and *R* configurations of the product refer to that of the starting enantiomers from which they are derived, and not the correct *R* and *S* configurations of the product.

Scheme S44. Estimation of y_{pred}. A. Jaganathan, A. Garzan, D. C. Whitehead, R. J. Staples and B. Borhan, *Angew. Chem. Int. Ed.,* 2011, **50**, 2593-2596.



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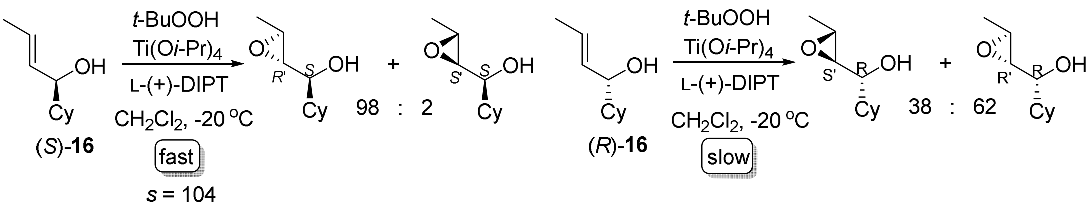
3. Examples used in Table 2, and additional examples, including the determination of y_{pred}.

V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237-6240.

Scheme S45. **Example 33.** Table 1, entry 2 (example used in manuscript - Table 2, entry 1).

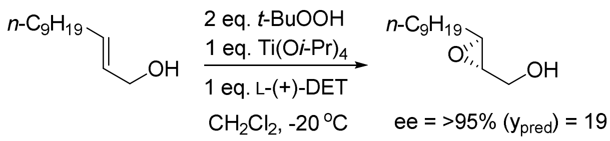


[*R*,*R*']/ [*R*,*S*']*	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}*	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
1.63	0.02 (50)	5.5	8.9	38	4	13	105	30

Relative rate: [*R*,*R*'] = 1.6, [*S*,*R*'] = 271 , [*R*,*S*'] = 1, [*S*,*S*'] = 5.5. Value of y_{pred} = 19.

*Diastereoselectivity measured in the early stages of the reaction = 32 : 1

Scheme S46. Estimation of y_{pred}. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5976-5978.



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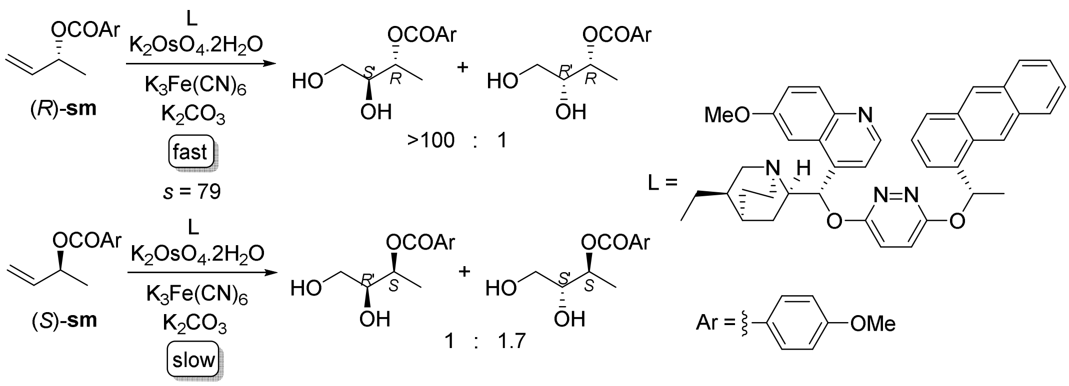
E. J. Corey, M. C. Noe and A. Guzman-Perez, *J. Am. Chem. Soc.,* 1995, **117**, 10817-10824.

Scheme S47. **Example 34.** Table 3, entries 1 and 2.

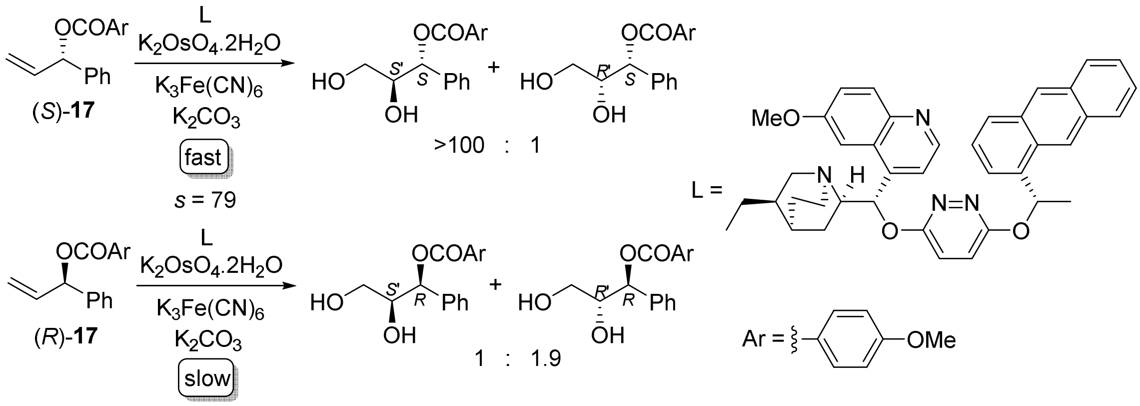


[*R*,*R*']/ [*R*,*S*']*	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.01 (100)	1.7	7.7	13	24	5	11	20	59

(*100 : 1 used for >100 : 1).

Relative rate: [*R*,*R'*] = 1, [*S*,*R'*] = 1.9 , [*R*,*S'*] = 100, [*S*,*S'*] = 3.2. Value of y_{pred} = 19.

Scheme S48. **Example 35.** Table 3, entries 3 and 4 (example used in manuscript - Table 2, entry 2).



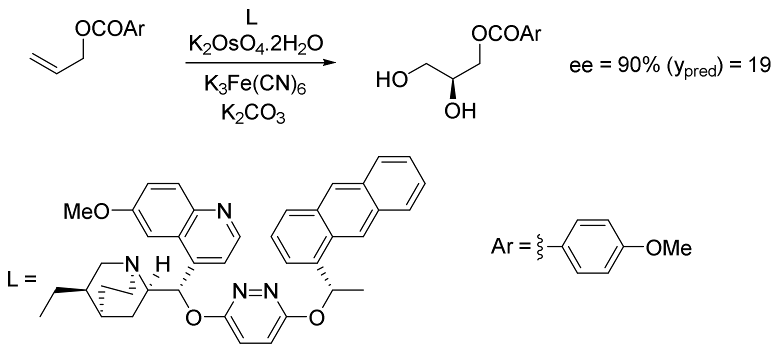
[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']*	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
1.9	100	7.3	13.7	55	5	14	79	53

(*100 : 1 used for >100 : 1).

Relative rate: [*R*,*R'*] = 1.9, [*S*,*R'*] = 2.3 , [*R*,*S'*] = 1, [*S*,*S'*] = 226. Value of y_{pred} = 19.

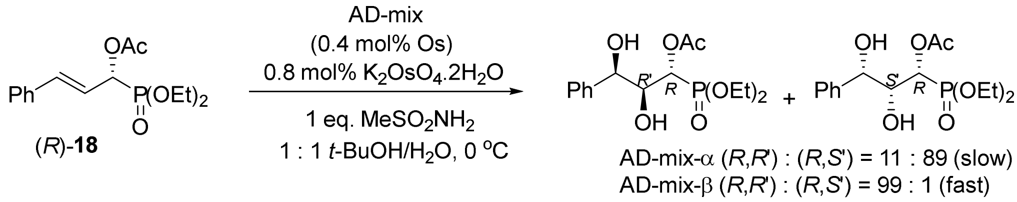
The *S* and *R* configurations of the product refer to that of the starting enantiomers from which they are derived, and not the correct *R* and *S* configurations of the product.

Scheme S49. Estimation of y_{pred}. Same publication.



T. Yokomatsu, T. Yamagishi, T. Sada, K. Suemune and S. Shibuya, *Tetrahedron*, 1998, **54**, 781-790.

Scheme S50. **Example 36.** Table 1, entries 2 and 3 (example used in manuscript - Table 2, entry 3).



Kinetic resolution with *rac*-**18**
AD-mix-α s = 4.9 (S fast)
AD-mix-β s = 15.6 (R fast)

Using s from AD-mix-β.

[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	S_{est}	S_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
99*	0.124# (8.1)	3.5	28.3	61	3	24	16	12

*Value from AD-mix-β. #Value from AD-mix-α.

Relative rate: [*R*,*R*'] = 140, [*S*,*R*'] = 8.1 , [*R*,*S*'] = 1.4, [*S*,*S*'] = 1. Value of y_{pred} = 39.

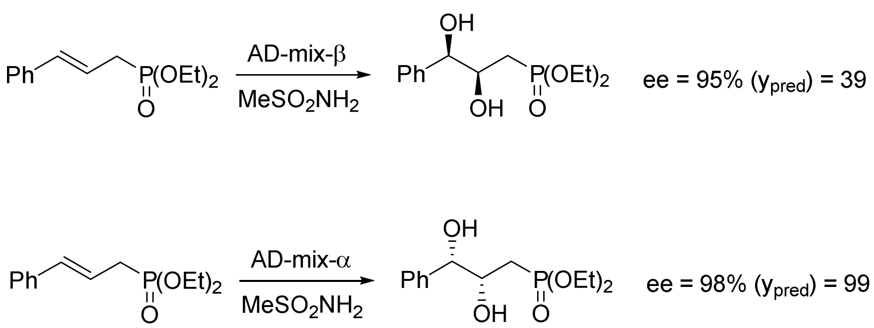
Using s from AD-mix-α.

[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	S_{est}	S_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.124# (8.1)	99*	3.5	28.3	36	3	26	5	12

*Value from AD-mix-β. #Value from AD-mix-α.

Relative rate: [*R*,*R*'] = 2.3, [*S*,*R*'] = 1 , [*R*,*S*'] = 18.2, [*S*,*S*'] = 99. Value of y_{pred} = 99.

Scheme S51. Estimation of y_{pred}. Same publication.



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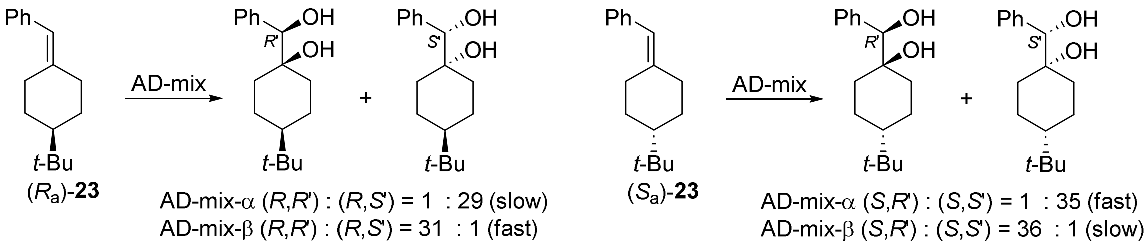
M. S. VanNieuwenhze and K. B. Sharpless, *J. Am. Chem. Soc.,* 1993, **115**, 7864-7865.

Scheme S52. **Example 37.**

(example used in manuscript - Table 2, entry 4).



Kinetic resolution with *rac*-**23** AD-mix-α s = 5.0 (S_a fast) AD-mix-β s = 9.7 (R_a fast)

For AD-mix-β.

[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
31	0.028 (36)	0.93	33	7.4	0.96	6	9.7	0.9

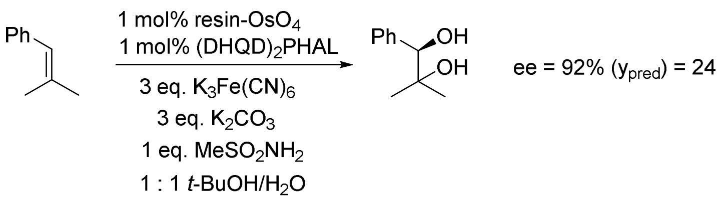
Relative rate: [*R*,*R*'] = 348, [*S*,*R*'] = 36 , [*R*,*S*'] = 11, [*S*,*S*'] = 1. Value of y_{pred} = 24.

For AD-mix-α.

[*R*,*R*']/ [*R*,*S*']	[*S*,*S*']/ [*S*,*R*']	x_{est}	y_{est}	x_{pred}	s_{est}	s_{pred}	$s = k_{matched}/k_{mis-matched}$	$dr_{matched}/dr_{mis-matched}$
0.034 (29)	35	1.1	32	4.4	1.1	4	5.0	1.2

Relative rate: [*R*,*R*'] = 1, [*S*,*R*'] = 4.1 , [*R*,*S*'] = 29, [*S*,*S*'] = 146. Value of y_{pred} = 24.

Scheme S53. Estimation of y_{pred}. B. M. Choudary, N. S. Chowdari, K. Jyothi and M. L. Kantam, *J. Am. Chem. Soc.*, 2002, **124**, 5341-5349.



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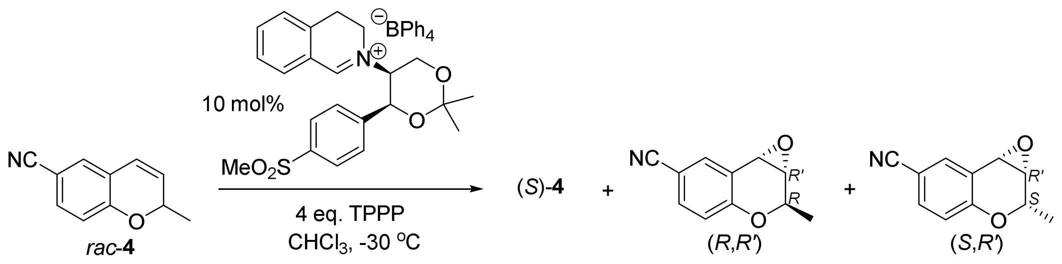
4. Graphical representation of the predicted reaction progress of the example given in Scheme 3.

Scheme S54.



Prediction of the progress of the reaction described in Table 1, example 1 based on *s* = 2.9, [*R*,*R*']/[*R*,*S*'] = 186 and [*S*,*S*']/[*S*,*R*'] = 0.21.

Figure S1. (a) Change in ee with conversion.

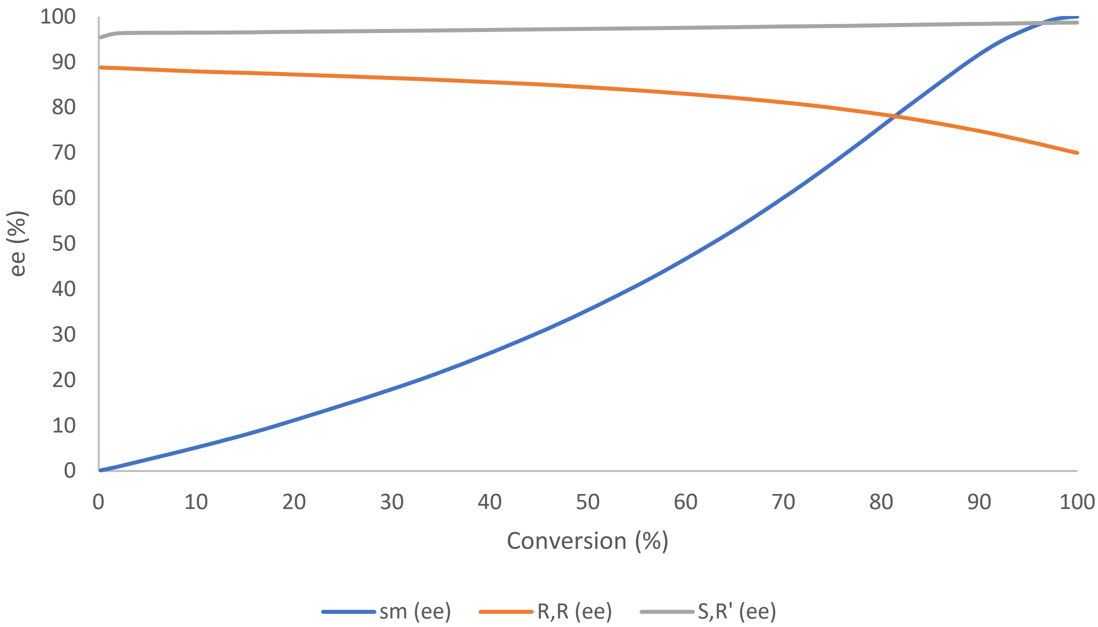


Figure S2. (b) Change in dr ([*R*,*R*'] + [*S*,*S*'])/([*R*,*S*'] + [*S*,*R*']) with conversion (Starting dr = 3.7. Final dr = 1.4).

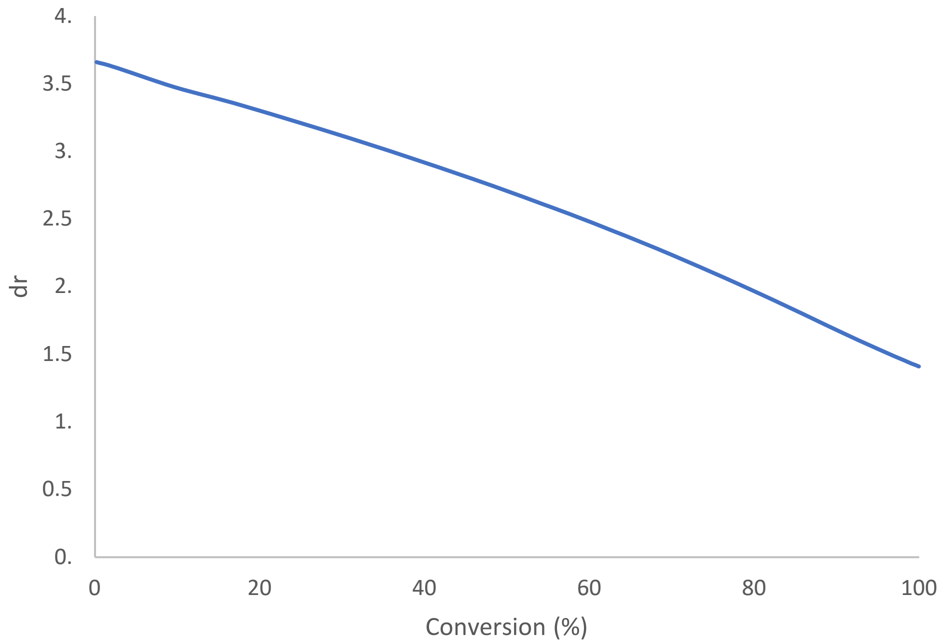


Figure S3. Prediction of the progress of the reaction with s = 2.9 and [*R*,*R*']/[*R*,*S*'] = 1/[*S*,*S*']/[*S*,*R*'] = 4.76 and [*S*,*S*']/[*S*,*R*'] = 1/[*R*,*R*']/[*R*,*S*'] = 0.0054 (*i.e.* the alternative scenario where the more selective reaction is slower).

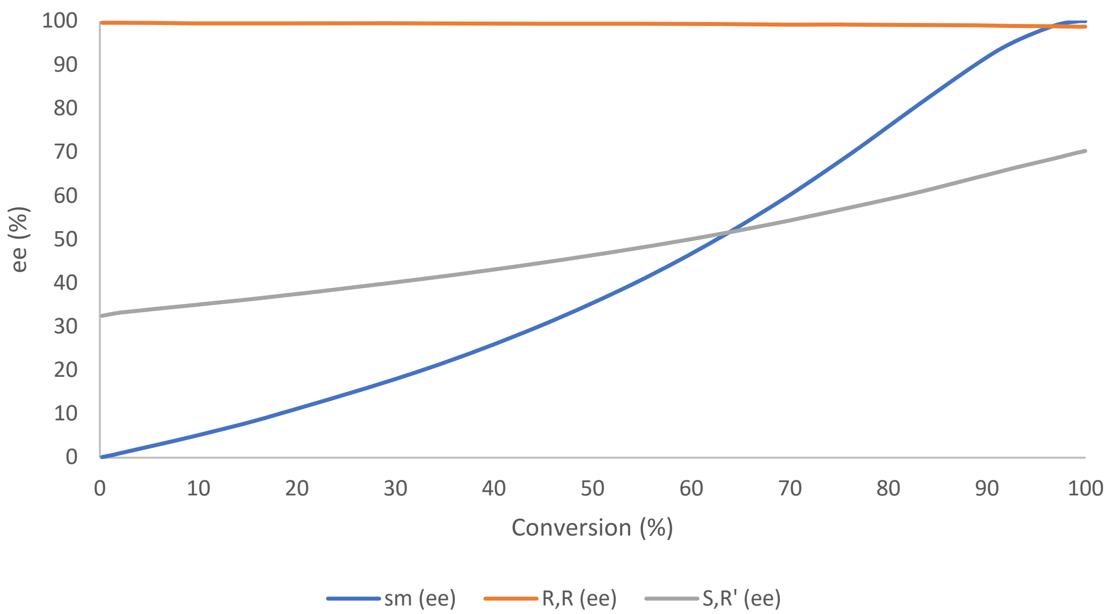
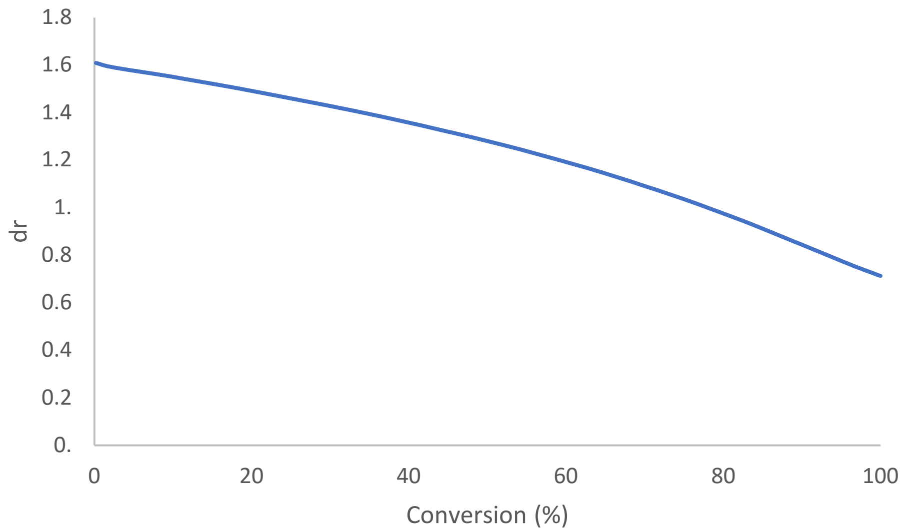


Figure S4. (b) Corresponding change in dr ([*R*,*R*'] + [*S*,*S*'])/([*R*,*S*'] + [*S*,*R*']) with conversion (Starting dr = 1.61. Final dr = 0.71).

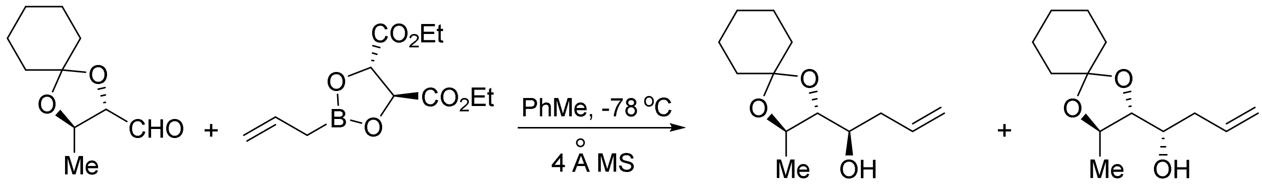


5. Examples of the determination of s_{est} from dr values in a matched/mismatched double asymmetric synthesis.

Example 1. Data from: W. R. Roush, L. K. Hoong, M. A. J. Palmer, J. A. Straub and A. D. Palkowitz, *J. Org. Chem.*, 1990, **55**, 4117-4126.

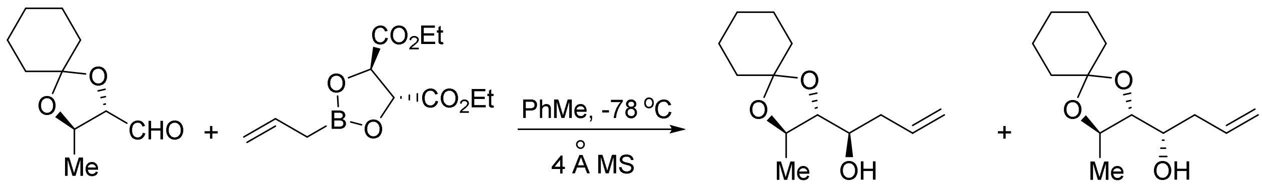
Scheme S55.

Matched



300 : 1

Mismatched



27 : 73

$a = 300/1 = 300$. $b = 27/73 = 0.37$

$y_{est} = \sqrt{(a/b)} = 28.5 \quad x_{est} = a/y_{est} = 10.5$

$$s_{est} = \frac{x_{est}y_{est} + 1}{x_{est} + y_{est}} = 7.7$$

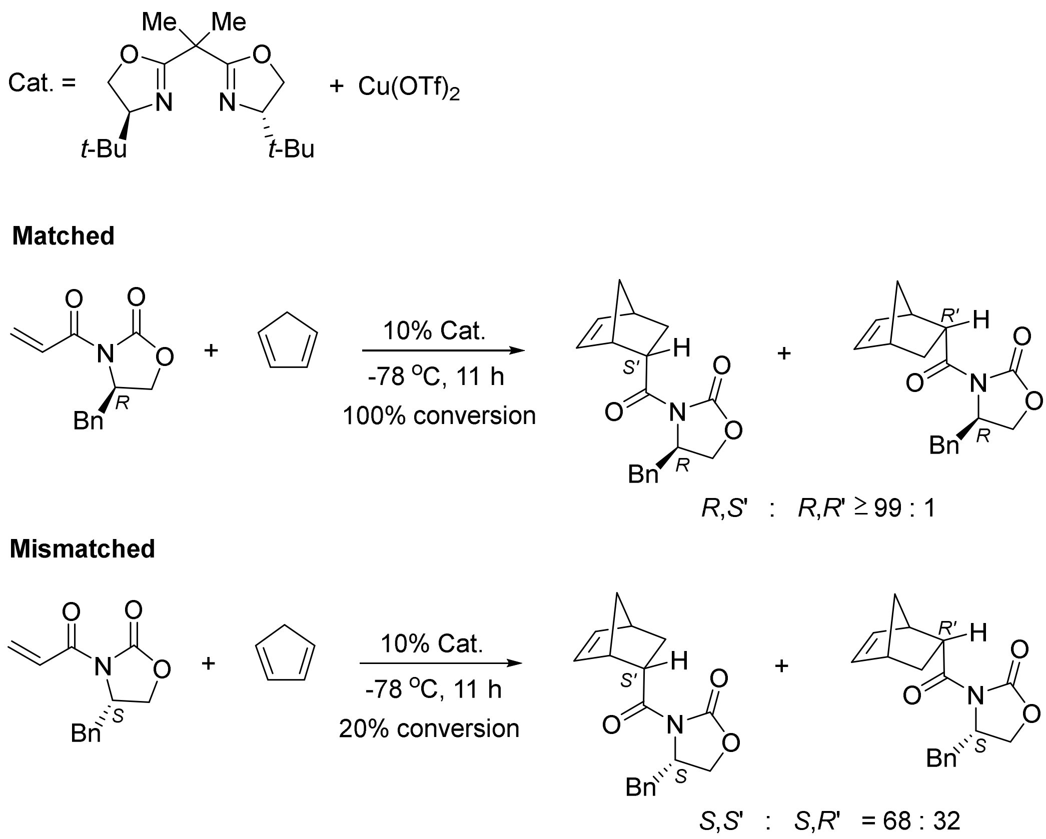
i.e. an estimate of the rate difference of the fast (matched) reaction relative to the slow (mismatched) reaction.

The catalyst selectivity term y_{est} is the same as the *average diasterefacial selectivity* of a chiral reagent proposed by Roush in the paper from which this example is taken.* For this reaction this was expressed as 93% de [*i.e.* the same as (28.5-1)/(28.5+1) x 100].

*Calculated from the average of the two $\Delta\Delta G^{\ddagger}$ values for the matched and mismatched reactions.

Example 2. Data from: D. A. Evans, S. J. Miller and T. Lectka, *J. Am. Chem. Soc.*, 1993, **115**, 6460-6461.

Scheme S56.



$a = [R,S']/[R,R'] = 99$

$b = [S,R']/[S,S'] = 32/68 = 0.47$

$y_{est} = \sqrt{(a/b)} = 14.5 \qquad x_{est} = a/y_{est} = 6.8$

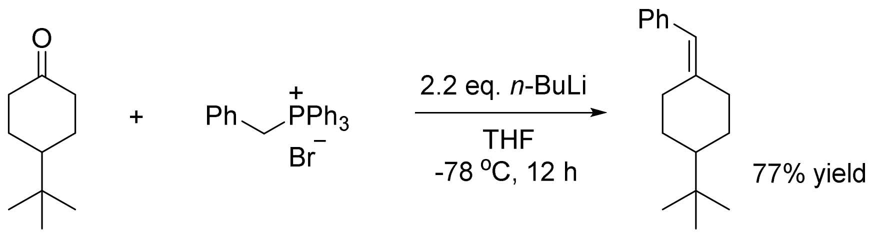
$s_{est} = \dfrac{x_{est}y_{est} + 1}{x_{est} + y_{est}} = 4.7$ *i.e.* an estimate of the rate difference of the fast (matched) reaction relative to the slow (mismatched) reaction.

This 5 fold estimated difference in rate is in approxiamate agreement with the conversion values of 100% and 20% noted for the matched and mismatched reactions, respectively. In this paper it is noted that in the mismatched example the cycloadduct is derived from a catalyst-dominated rather than a substrate-dominated process. This is now captured in the catalyst selectivity term y_{est} = 14.5 *vs*. the substrate selectivity term x_{est} = 6.8.

6. Additional experimental details, NMR spectra and HPLC chromatographs

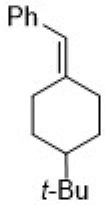
Method for the synthesis of *rac*-23.

Scheme S57.



A solution of *n*-BuLi (8.55 mL, 21.4 mmol, 2.5 M in hexanes, 2.2 eq.) was added slowly to a cooled vigorously stirred white suspension of benzyltriphenylphosphonium bromide (8.43 g, 19.45 mmol, 2.0 eq.) in THF (80 mL) at -78 °C. The resulting deep red solution was stirred at -78 °C for 10 mins, the cooling bath removed, and then stirred at RT for 1 h. Afterwards, the reaction mixture was cooled to -78 °C for 10 mins followed by the addition of a solution of 4-*tert*-butylcyclohexanone (1.50 g, 9.72 mmol, 1.0 eq.) in THF (20 mL) at -78 °C. The reaction mixture was allowed to warm up to RT and stirred for 12 h at RT. Upon completion (TLC), the mixture was quenched with saturated aqueous solution of ammonium chloride (60 mL) and extracted with ethyl acetate (80 mL). The organic layer was washed with water (50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography using 1% ethyl acetate in hexanes to give *rac*-**23** (1.71 g, 7.49 mmol, 77%) as a colourless oil.

Figure S5. **23** ^{1}H NMR ($CDCl_3$, 500 MHz)



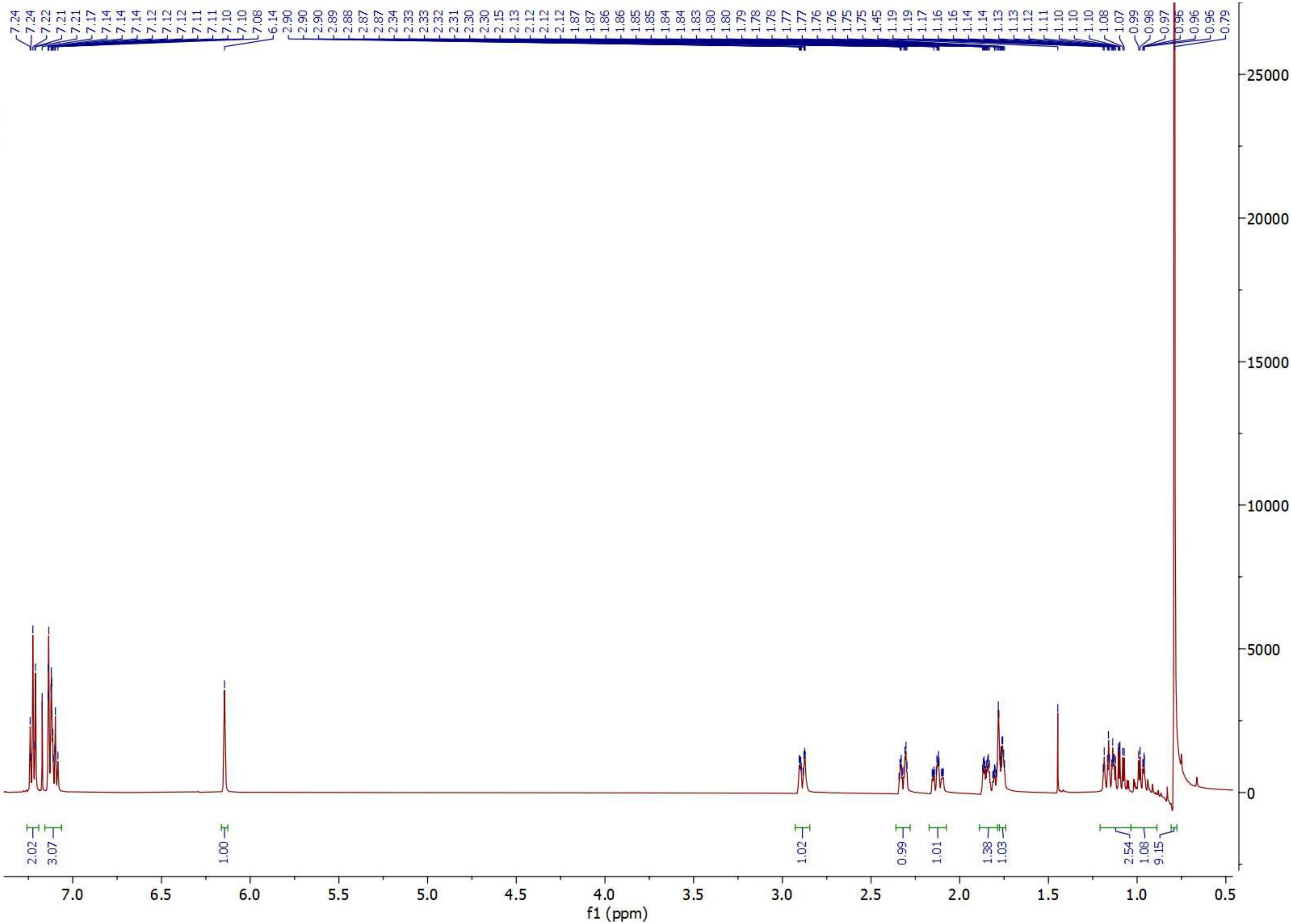
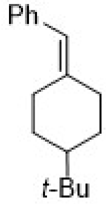


Figure S6. **23** ^{13}C NMR ($CDCl_3$, 125 MHz)



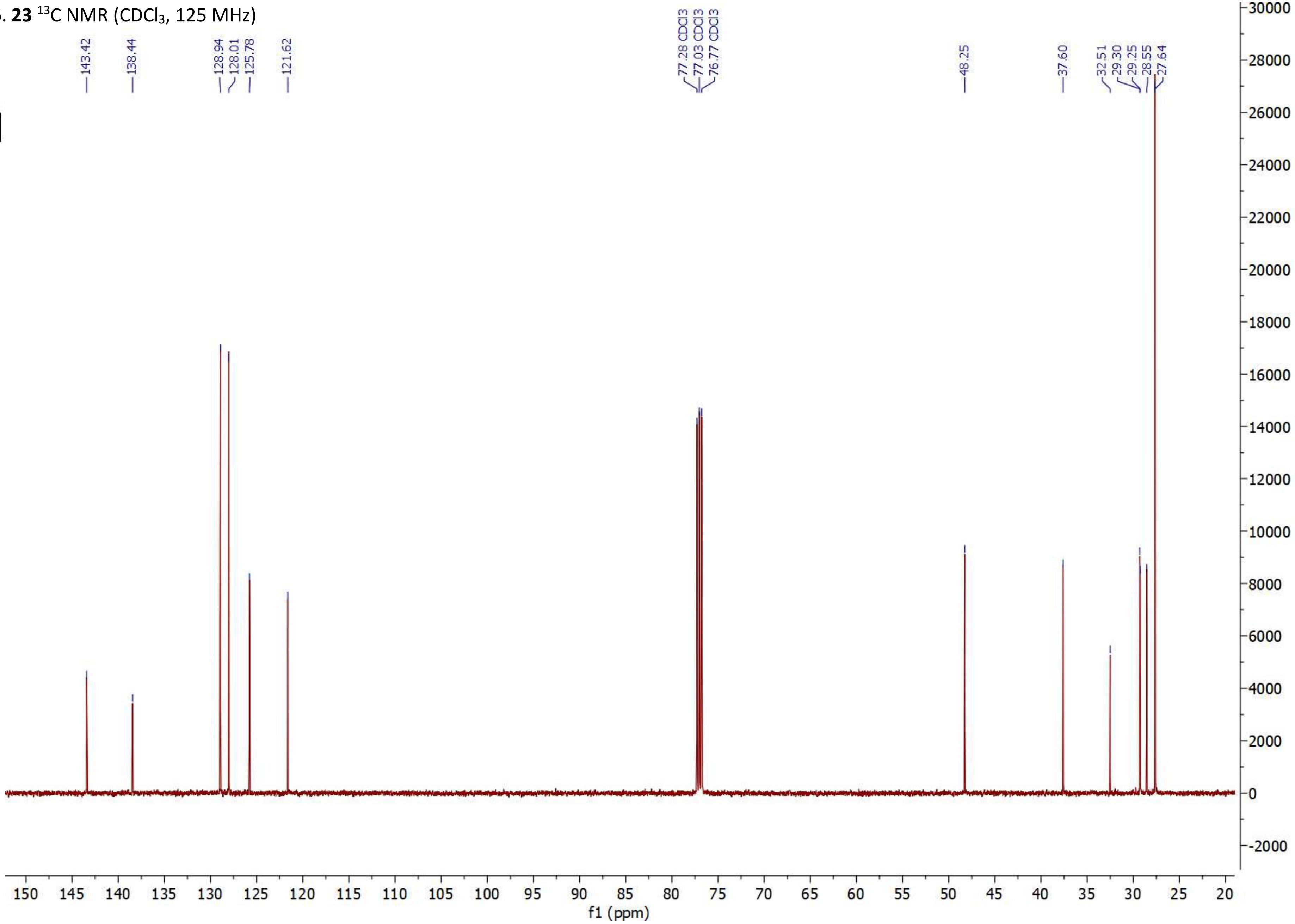


Figure S7. **24** ^{1}H NMR ($CDCl_3$, 400 MHz)

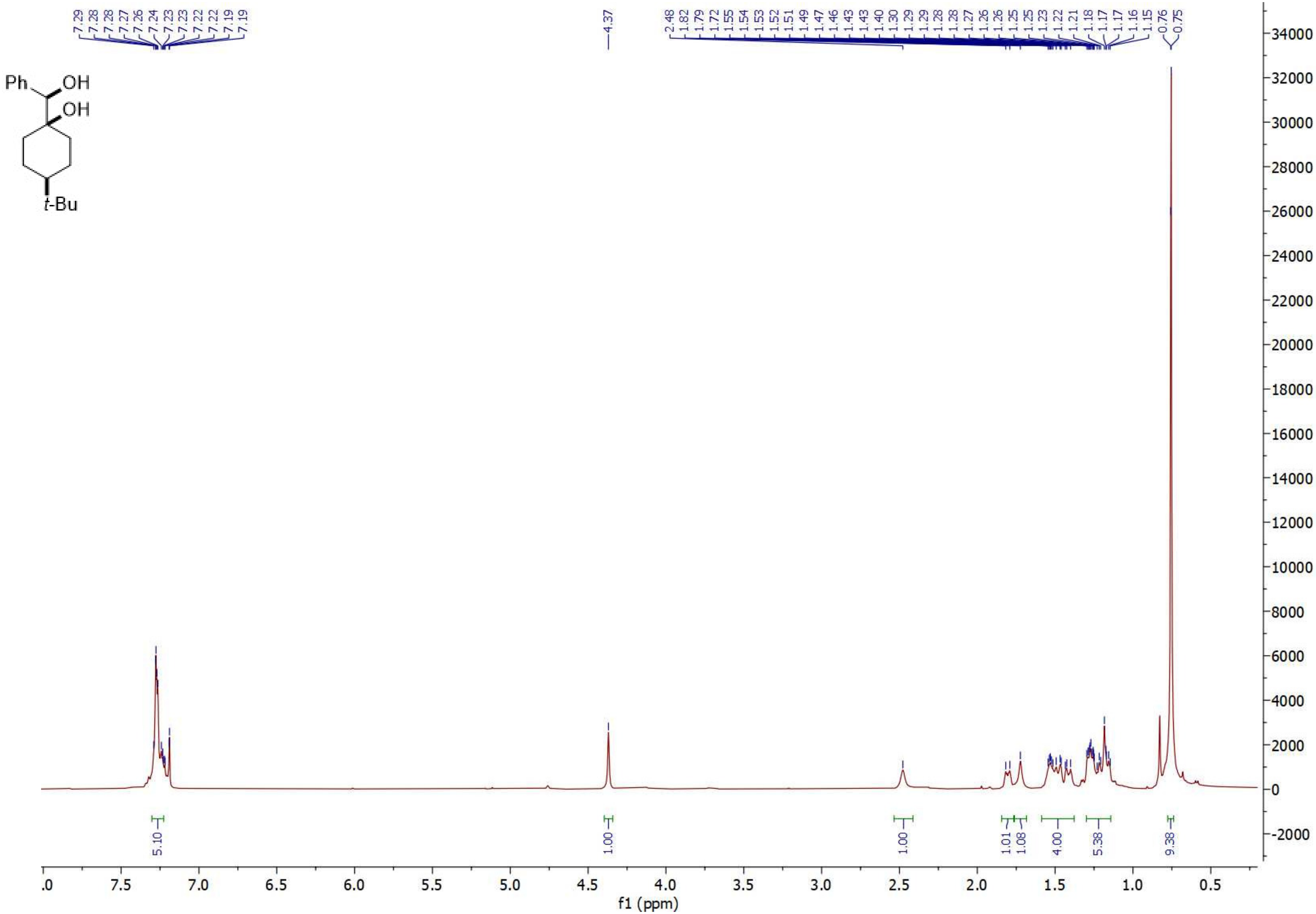


Figure S8. **24** ^{13}C NMR ($CDCl_3$, 100 MHz)

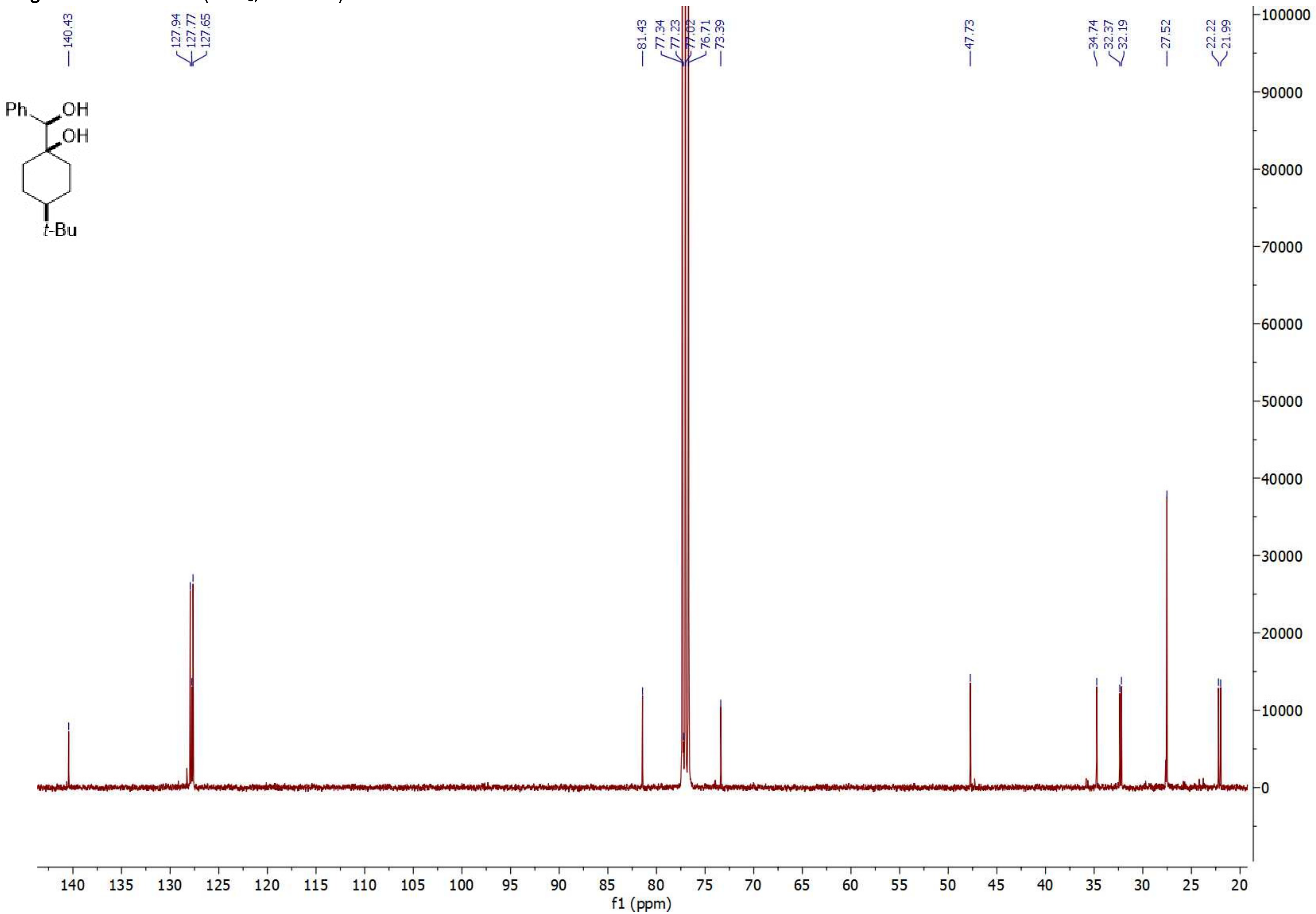
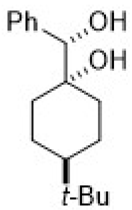


Figure S9. **25** ^{1}H NMR ($CDCl_3$, 400 MHz)



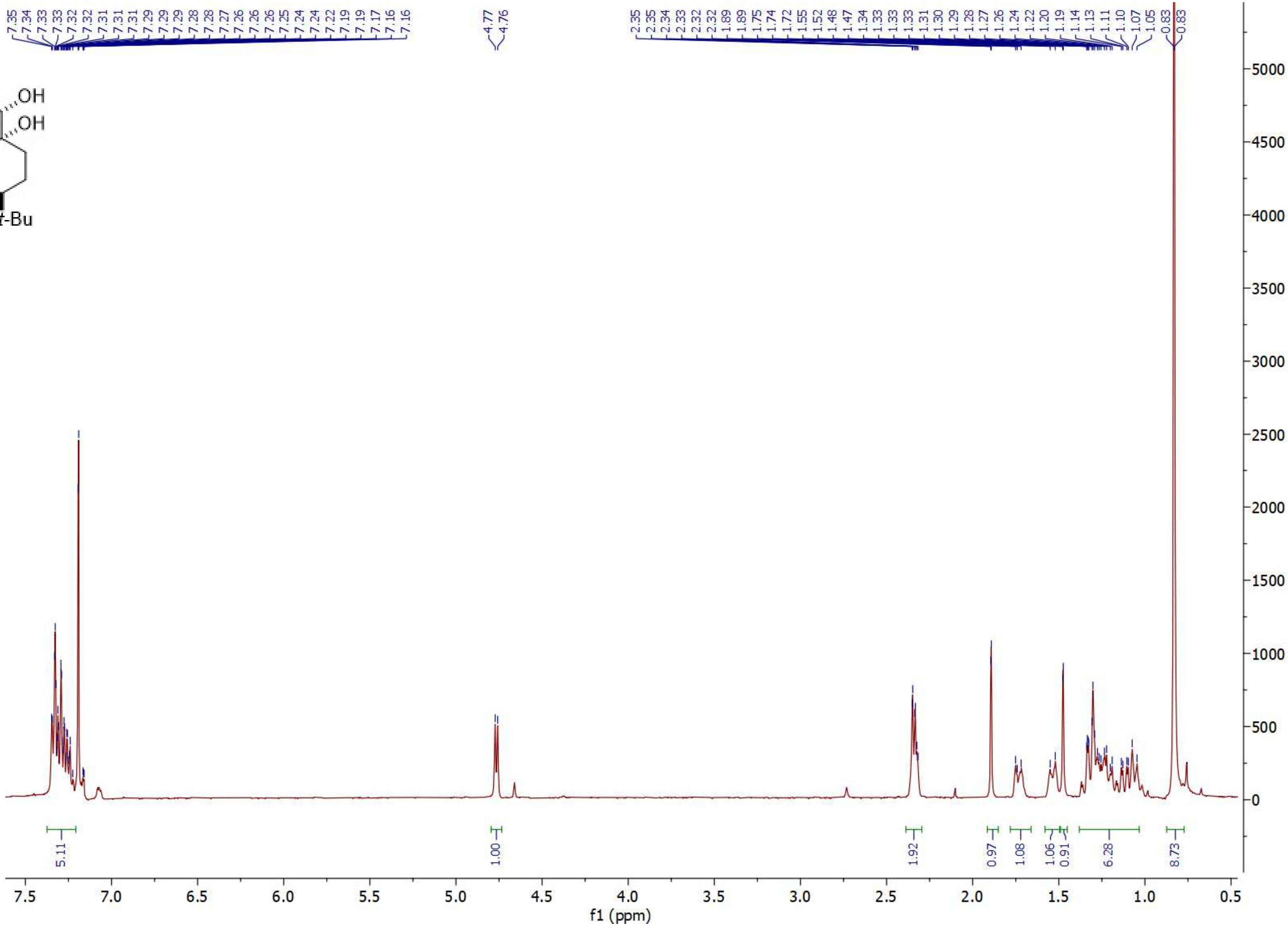


Figure S10. **25** ^{13}C NMR ($CDCl_3$, 100 MHz)

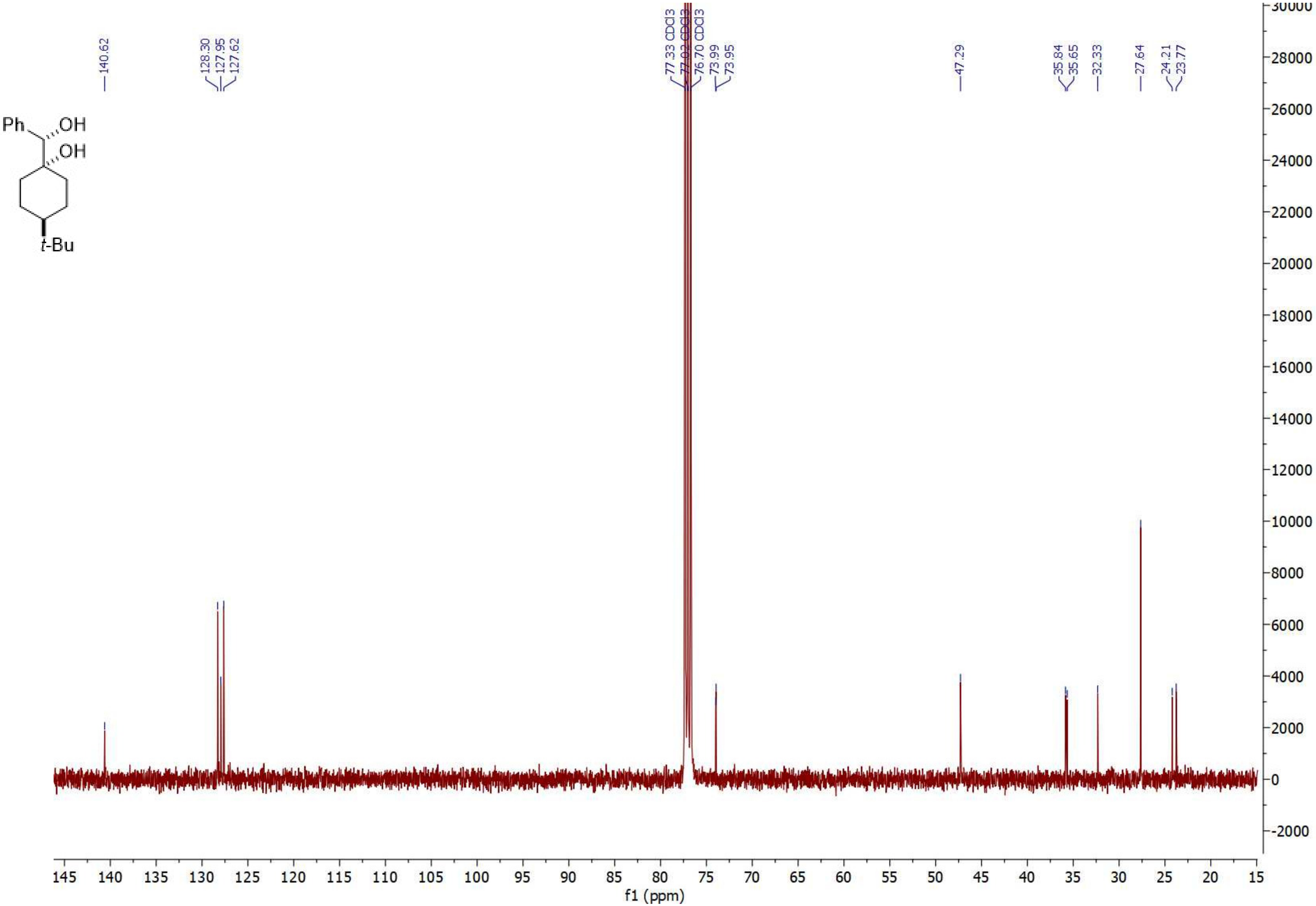


Figure S11. ^{1}H NMR ($CDCl_3$, 400 MHz)of the dihydroxylation products using quinuclidine as ligand.

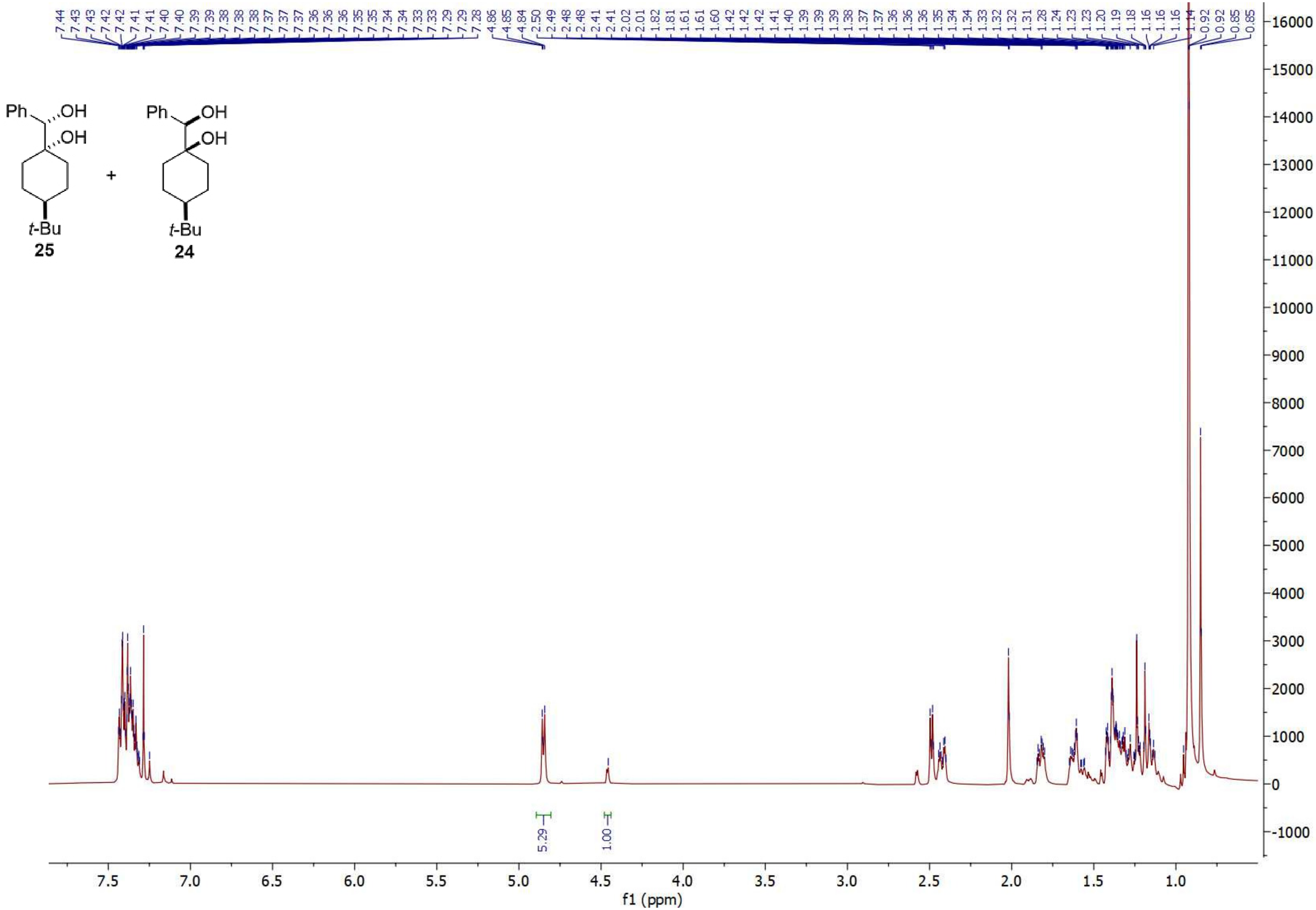
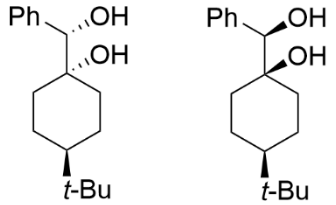


Figure S12. ^{1}H NMR ($CDCl_3$, 400 MHz) of the dihydroxylation products from (R_a)-**23** and AD-mix-α.



25 7.5 : 1 **24**

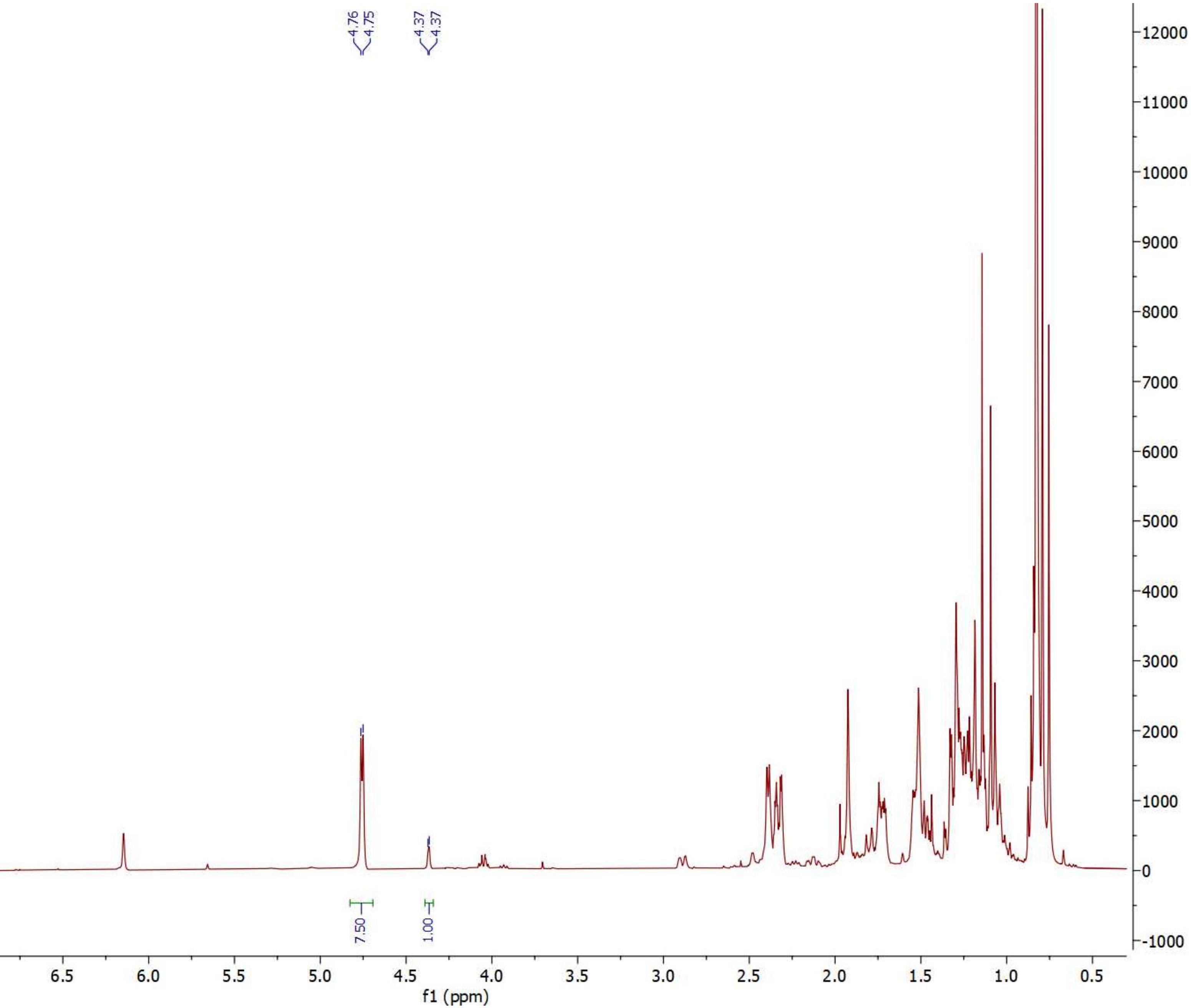
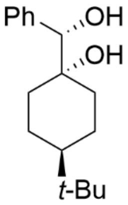
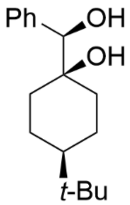


Figure S13. ^{1}H NMR ($CDCl_3$, 400 MHz) of the dihydroxylation products from (R_a)-**23** and AD-mix-β.



25

1 : 2.4



24

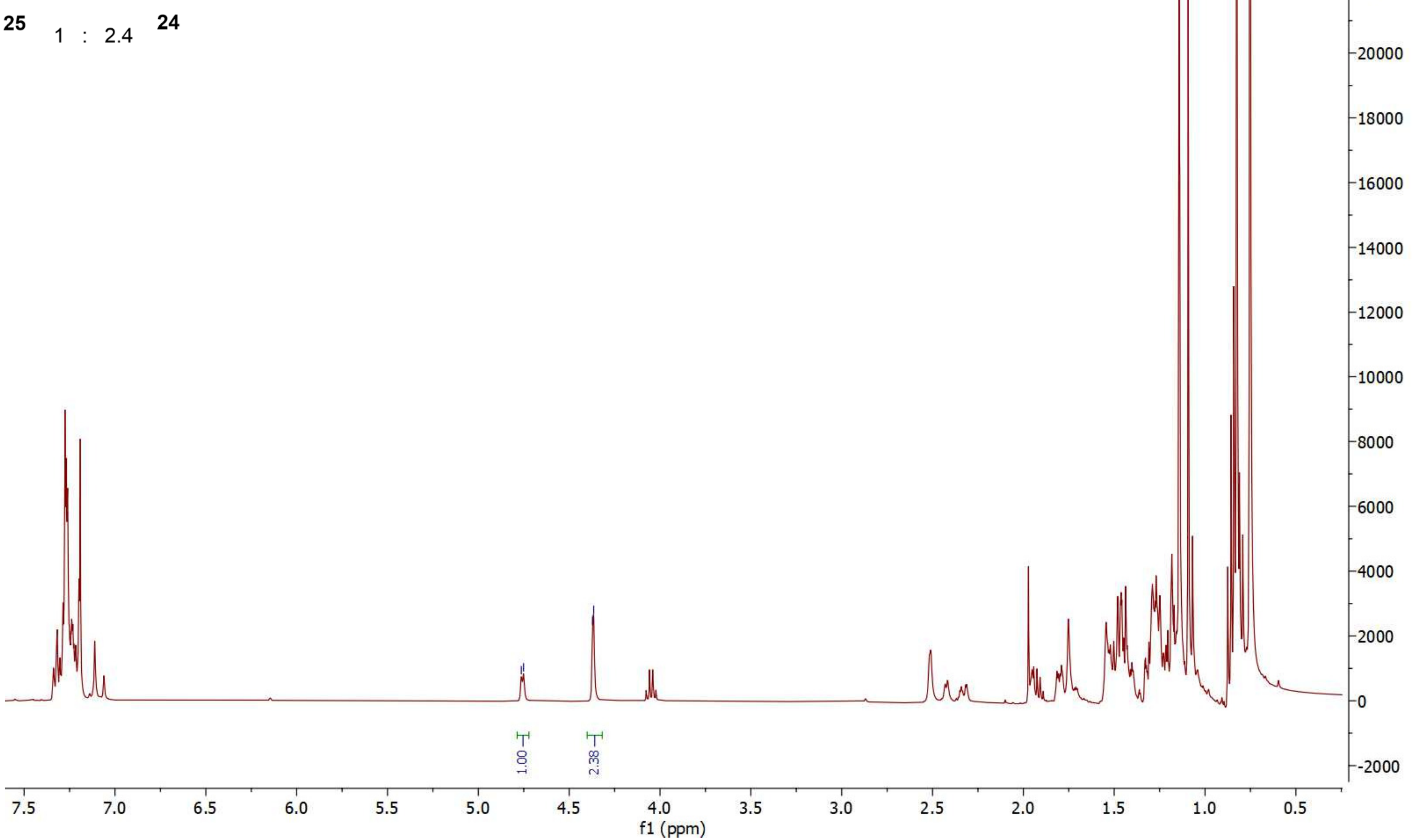
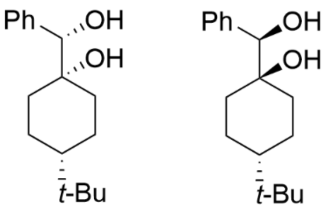


Figure S14. ^{1}H NMR ($CDCl_3$, 400 MHz) of the dihydroxylation products from (S_a)-**23** and AD-mix-α.



24 2.8 : 1 **25**

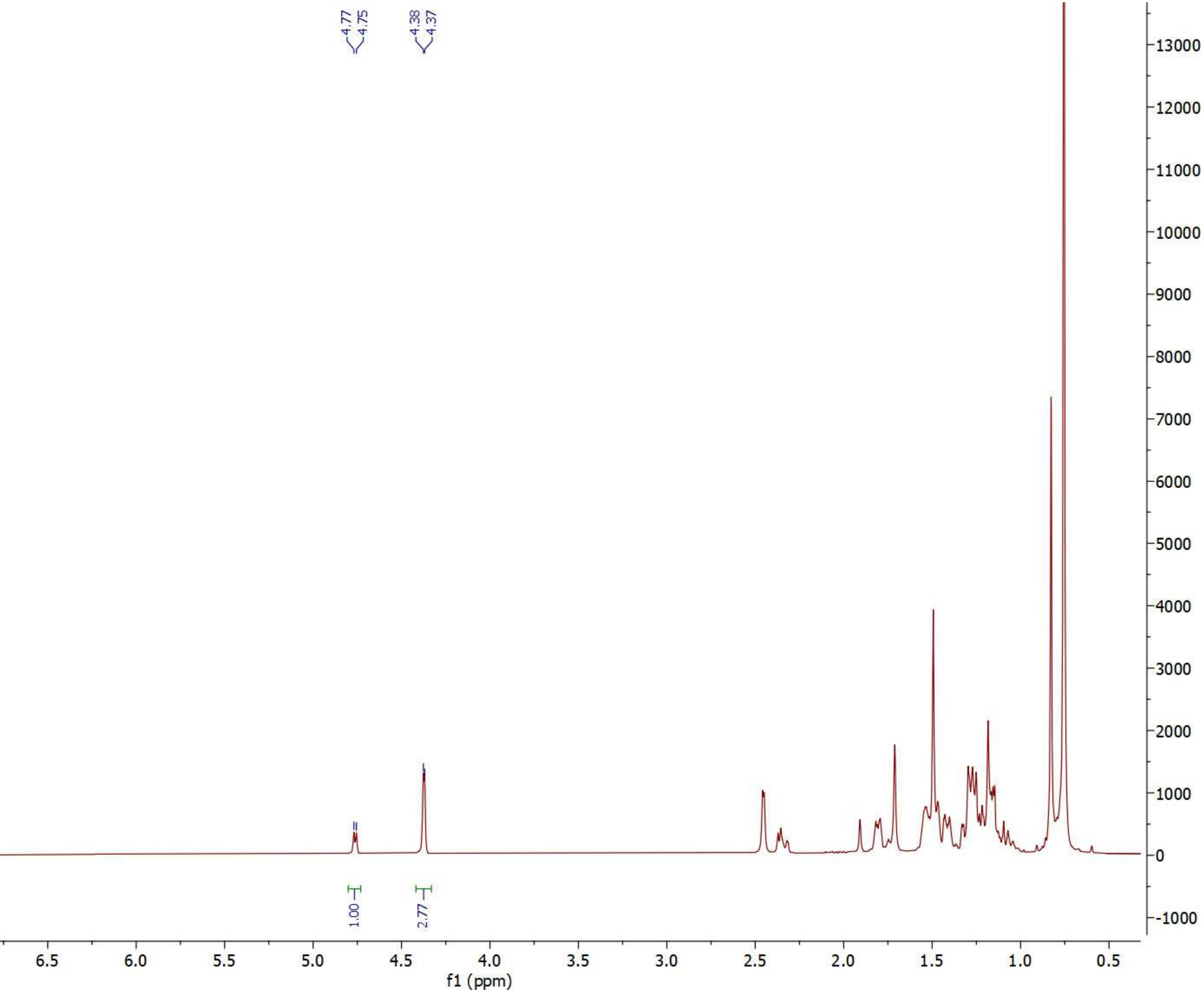
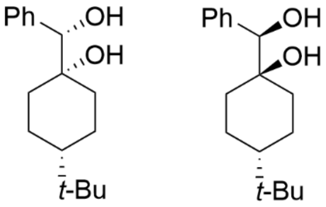
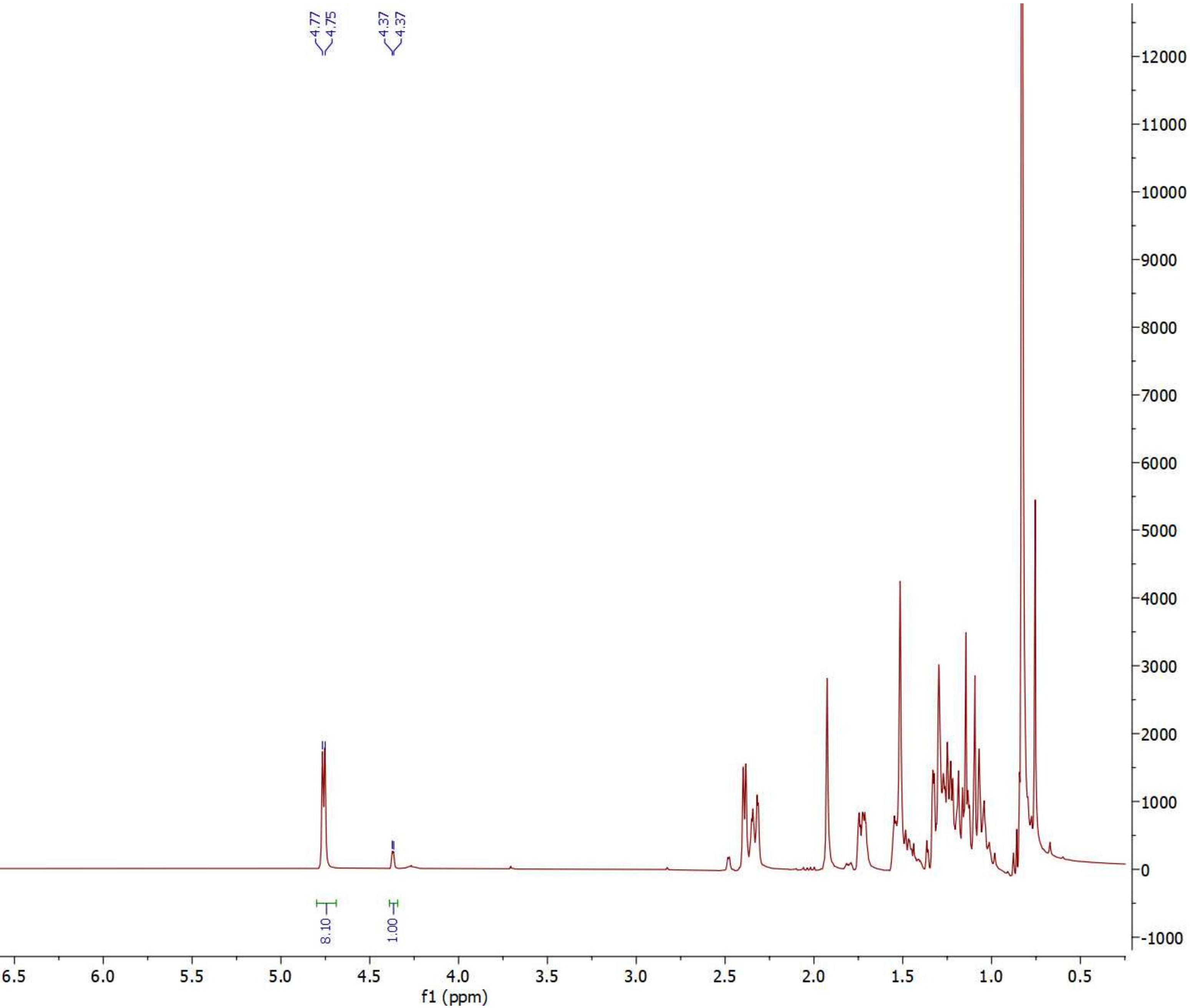


Figure S15. [1]H NMR ($CDCl_3$, 400 MHz) of the dihydroxylation products from (S_a)-**21** and AD-mix-β.

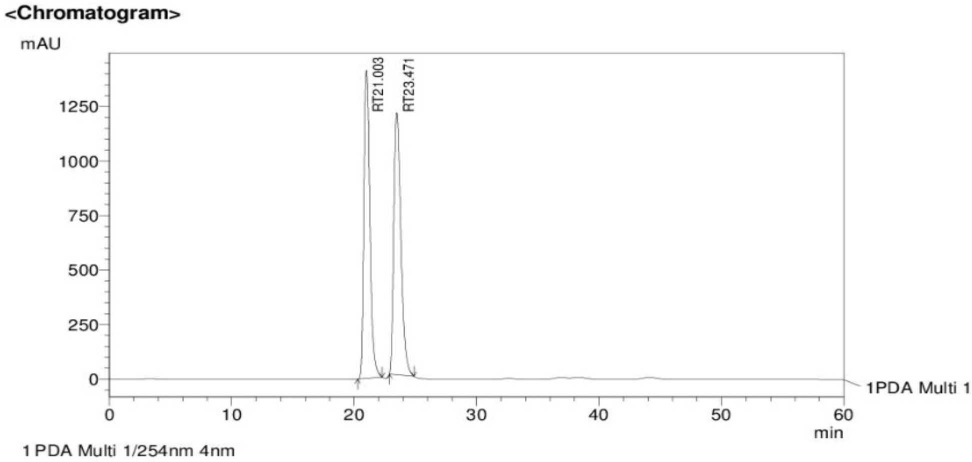


24 1 : 8.1 **25**



HPLC condition for *rac*-23: OJ-3 chiral column (*i*-PrOH:hexanes = 0.8:99.2, 0.2 mL/min, wavelength = 254 nm, 22 °C); S_a-**23** = 21.003 min and R_a-**23** = 23.471 min.

Figure S16.



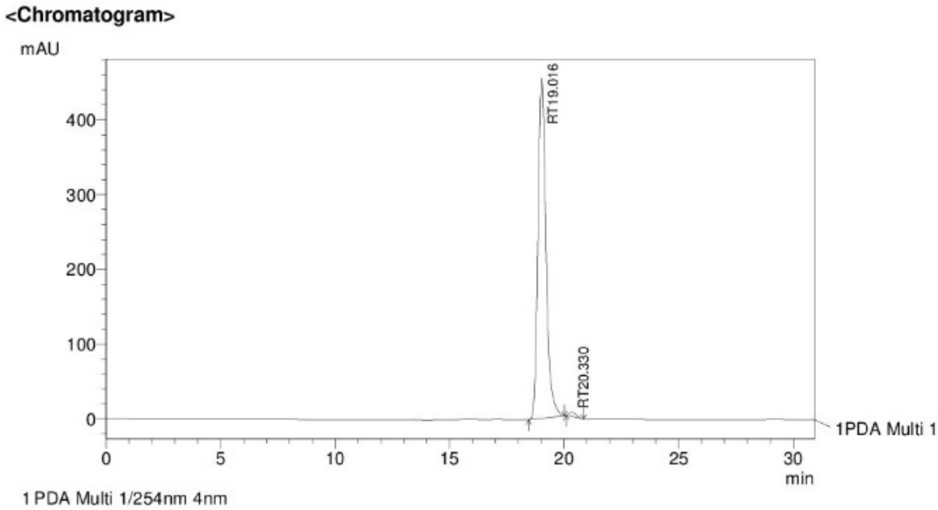
<Results>

PDA

ID#	Name	Ret. Time	Area	linimum Peak Purity Inde	Conc.	Units
1	RT21.003	21.003	48009207	Not calculated	0.000	mg/L
2	RT23.471	23.471	48700697	Not calculated	0.000	mg/L

HPLC conditions for the kinetic resolution of the product obtained using AD-mix-β: OJ-3 chiral column (*i*-PrOH:hexanes = 0.8:99.2, 0.2 mL/min, wavelength = 254 nm, 22 °C); S_a-**21** = 19.016 min (major) and R_a-**23** = 20.330 min (minor). 98% ee.

Figure S17.



<Results>

PDA

ID#	Name	Ret. Time	Area	linimum Peak Purity Inde	Conc.	Units
1	RT19.016	19.016	11090087	Not calculated	0.000	mg/L
2	RT20.330	20.330	120054	Not calculated	0.000	mg/L