Organic & Biomolecular Chemistry

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Open Access Article. Published on 19 April 2013. Downloaded on 11/5/2025 9:13:32 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 3432

Received 9th April 2013,
Accepted 10th April 2013

DOI: 10.1039/c3ob40709h

www.rsc.org/obc

Elucidating absolute configuration of unsaturated alcohols *via* enantioselective acylation reactions†

Christina M. LeGay, Colton G. Boudreau and Darren J. Derksen*

Enantioselective nucleophilic acylation catalysis provides a simple method of determining absolute configuration for unsaturated alcohols. Extension of this technique to natural products and synthetic compounds, as well as current limitations of this approach, are also described.

The absolute configuration of a chemical compound is generally of considerable importance for biological activity. One of the most commonly used methods for determining the configuration of small molecules is the Mosher ester analysis utilising diastereomeric esters that introduce anisotropic magnetic shielding in a predictable fashion.[1,2] Despite the undeniable utility of the advanced Mosher method, some of the practical limitations of this technique are the comparatively high cost of the reagents that are typically used in excess (particularly the acyl chlorides) and the requirement that the esters are stable and isolable. Recent work from the group of Rychnovsky has demonstrated that asymmetric catalysis can be used to elucidate absolute configuration.[3] The use of asymmetric catalysis recognizes that the well-established field of kinetic resolution, mediated by non-enzymatic acylation catalysts, is a closely related process to determining configuration with respect to the rates of reaction between enantiomers and diastereomers (Fig. 1). As a kinetic resolution utilises a racemic mixture of starting materials and a chiral catalyst to react enantioselectively with one component of a mixture (Fig. 1, A and B, or C and D), the configuration of an unknown chiral secondary alcohol can similarly be elucidated by comparing the rates of reaction mediated by enantiomeric catalysts (Fig. 1, A and C, or B and D). Although this strategy is expected to be general across asymmetric acylation catalysts capable of kinetic resolutions,[3,4] the commercial availability and extensive precedent for Fu's 'planar-chiral' DMAP derivatives[5,6]

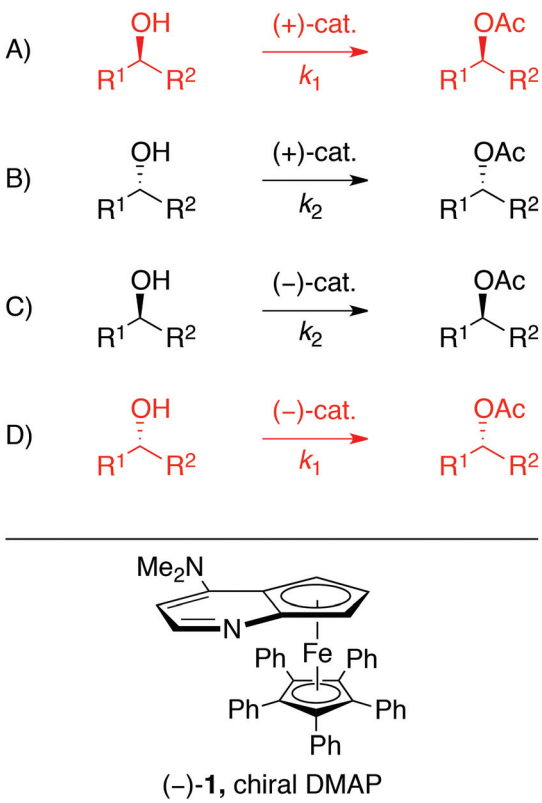


Fig. 1 Top: Enantiomeric processes proceed with the same rate (red = k_1, black = k_2). Kinetic resolution reactions employ racemic starting materials and an enantioselective catalyst (A and B or C and D) while determination of configuration can be achieved by comparing the rate of reaction between the unknown secondary carbinol and enantiomeric catalysts. (A and C or B and D). Bottom: Fu's commercially available 'planar-chiral' DMAP, (–)-DMAP-C_5Ph_5.

suggested these catalysts would be the most attractive to chemists likely to employ this technique. Although the initial costs of the chiral DMAP catalysts is comparable to the MTPA acids required for Mosher ester analysis, the iron catalysts can be easily recovered using routine silica chromatography and recycled in later experiments.[7] As the selectivity factors for

Department of Chemistry, St. Francis Xavier University, Physical Sciences Complex, 5009 Chapel Square, Antigonish, NS B2G 2W5, Canada. E-mail: dderksen@stfx.ca; Fax: +1-902-867-2414; Tel: +1-902-867-3918

†Electronic supplementary information (ESI) available: General experimental procedures and sample spectra for the acylation of (*S*)-(–)-1-phenylethanol. See DOI: 10.1039/c3ob40709h

This journal is © The Royal Society of Chemistry 2013

Open Access Article. Published on 19 April 2013. Downloaded on 11/5/2025 9:13:32 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

many unsaturated substrates have already been determined for catalyst-mediated kinetic resolutions, we focused on applying this methodology to chiral, unsaturated secondary alcohols. Using (*S*)-(−)-1-phenylethanol (**2**) as a model system, we observed the (+)-chiral DMAP mediated reaction to proceed more rapidly than the corresponding reaction with the (−)-catalyst when monitored by ^{1}H-NMR spectroscopy, as expected (Fig. 2).

To demonstrate the simplicity of implementing this methodology, we investigated the use of the most basic chromatography-coupled analysis, thin-layer chromatography (TLC). Although the experiment utilises only qualitative results, the relative rates of acylation can be easily observed for (*S*)-1-phenylethanol acylation (s-factor 43, 0 °C, *t*-amyl alcohol[6]) and are consistent with the result determined by ^{1}H-NMR spectroscopy in $CDCl_3$.[8] It is important to note that the TLC approach is not suitable for all substrates as lower selectivity factors produce results that appear ambiguous to the unaided eye. This is the case with 3-butyn-2-ol (Fig. 2) where TLC is insufficient to compare the relative rates of reaction while ^{1}H-NMR spectroscopy is able to differentiate between the rates of reaction mediated by enantiomeric catalysts.

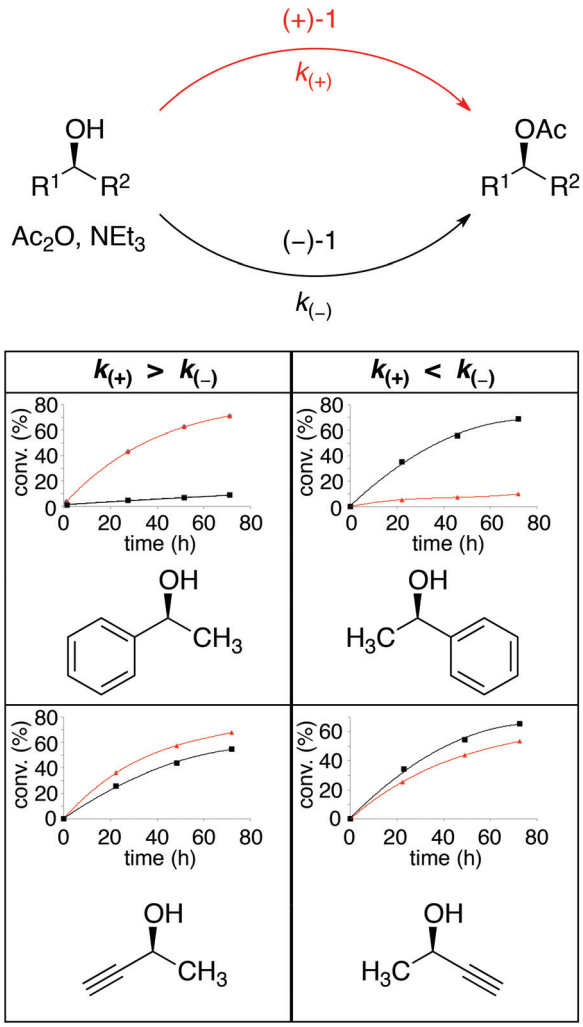
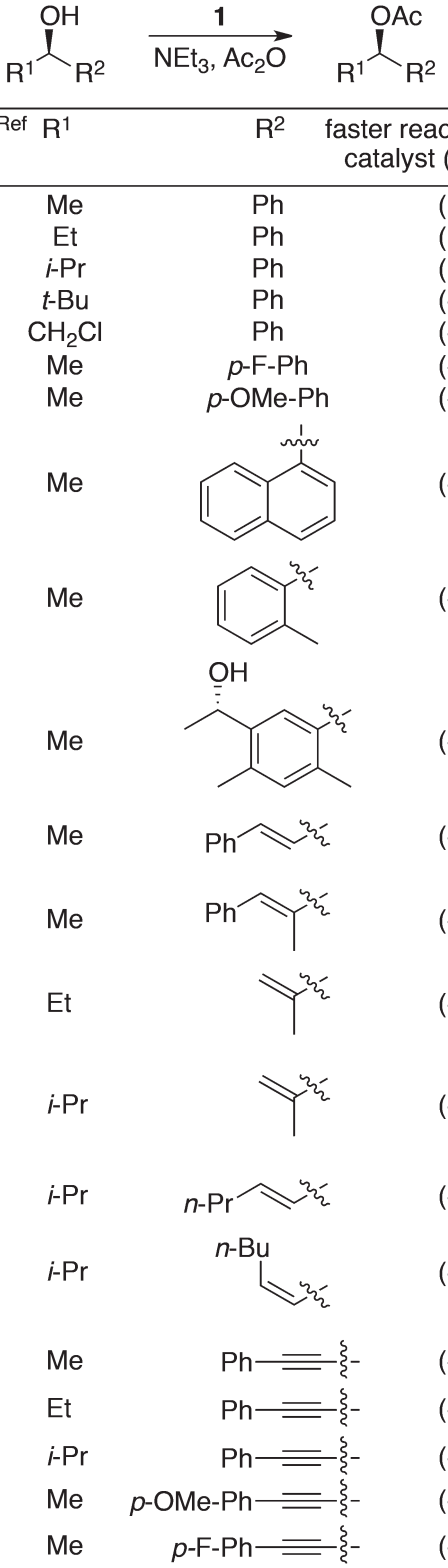


Fig. 2 Consistent with literature precedent, if $k_{(+)} > k_{(-)}$, R^1 = unsaturated, R^2 = alkyl. If $k_{(+)} < k_{(-)}$, R^1 = alkyl, R^2 = unsaturated. Top: 1-phenylethanol, bottom: 3-butyn-2-ol. Solvent $CDCl_3$, monitored by ^{1}H-NMR spectroscopy.



Entry[Ref]	R^1	R^2	faster reacting catalyst (**1**)
1[6]	Me	Ph	(−)
2[9]	Et	Ph	(−)
3[9]	*i*-Pr	Ph	(−)
4[9]	*t*-Bu	Ph	(−)
5[9]	CH_2Cl	Ph	(−)
6[9]	Me	*p*-F-Ph	(−)
7[9]	Me	*p*-OMe-Ph	(−)
8[9]	Me		(−)
9[6]	Me		(−)
10[6]	Me	OH	(−)
11[7]	Me	Ph	(−)
12[7]	Me	Ph	(−)
13[7]	Et		(−)
14[7]	*i*-Pr		(−)
15[7]	*i*-Pr	*n*-Pr	(−)
16[7]	*i*-Pr	*n*-Bu	(−)
17[10]	Me	Ph	(−)
18[10]	Et	Ph	(−)
19[10]	*i*-Pr	Ph	(−)
20[10]	Me	*p*-OMe-Ph	(−)
21[10]	Me	*p*-F-Ph	(−)

Fig. 3 Literature precedent for enantioselective acylation reactions mediated by catalyst **1**.[6,7,9,10]

Open Access Article. Published on 19 April 2013. Downloaded on 11/5/2025 9:13:32 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

However, given the simplicity and sensitivity of the TLC approach, we have found that it is suitable to attempt the TLC method first, and then proceed to a more quantitative analysis method as required.

Although this kinetics-based approach is ideal for compounds where direct precedent exists in the kinetic resolution literature (Fig. 3), a predictive model for characterization of novel chiral compounds is the end goal of this research. By review of our data and the available literature utilising the ferrocene-derived chiral DMAP catalysts (Fig. 3), an apparent trend is observed: if the rate of acylation for (+)-DMAP-C_5Ph_5 is greater than for (–)-DMAP-C_5Ph_5, R^1 (Fig. 2) contains an unsaturated moiety while R^2 is an alkyl substituent. Similarly, if the rate of acylation for (–)-DMAP-C_5Ph_5 is greater than for (+)-DMAP-C_5Ph_5, R^1 (Fig. 2) contains the alkyl substituent while R^2 is unsaturated.

Based on our research interest in natural products, we investigated the use of this methodology on the natural alkaloid (–)-lobeline[11] (**2**) and a sidechain protected analogue of chloramphenicol (**3**, Fig. 4). The current limitation of the TLC-based approach is demonstrated with (–)-lobeline as the relatively low selectivity between acylation catalysts does not allow the configuration to be unambiguously determined; ^{1}H-NMR spectroscopy revealed modest selectivity consistent with the proposed model. By comparison, the enantioselective acylation selectivity for chloramphenicol derivative (**3**) is sufficiently high that the correct configuration could be readily deduced by monitoring the reactions by TLC or ^{1}H-NMR spectroscopy.[8] With the further development and commercial availability of highly selective acylation catalysts, we expect the scope of this methodology will continue to increase due to its simplicity and ability to produce rapid results.

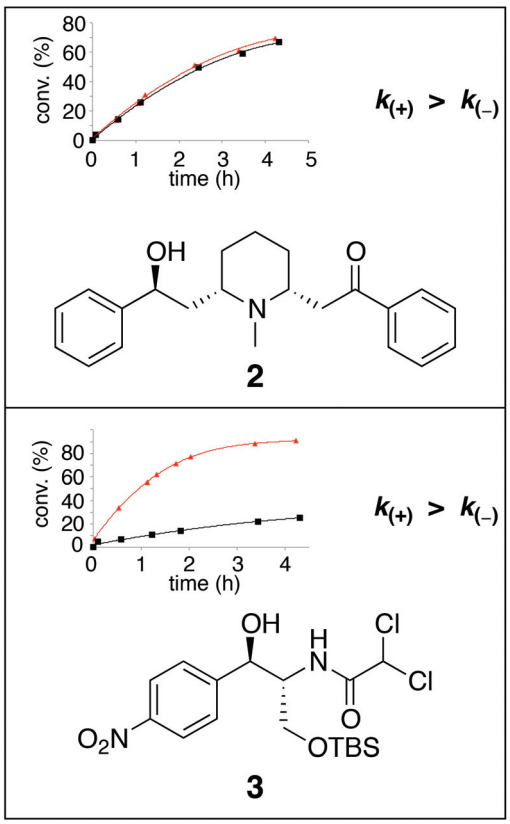


Fig. 4 Acylation of test substrates (–)-lobeline (**2**) and TBS protected chloramphenicol derivative (**3**) are consistent with proposed model (Fig. 2). Solvent $CDCl_3$, monitored by ^{1}H-NMR spectroscopy.

Conclusions

Some of the advantages of using a method based on asymmetric catalysis to determine absolute configuration are the savings realized by avoiding an excess of chiral acylating agents, and the added simplicity of analysis. With the commercial availability of all required catalysts and reagents, this kinetics-based strategy of determining configuration is readily accessible to researchers and simple to perform. With the ongoing development of new enantioselective acylating agents,[4] the availability of increasingly sensitive chromatography-coupled detection methods and development of high-resolution mass spectrometry methods,[3c] we anticipate this overall strategy will find value for determining configuration on small amounts of materials, such as that encountered in structural elucidation of natural products, and as a complementary method to Mosher ester analysis or the Rychnovsky acylation method.

We thank StFX for financial support (start-up funds and University Council for Research) and for a Summer Research Internship (CGB).

Notes and references

1 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.
2 T. R. Hoye, C. S. Jeffrey and F. Shao, *Nat. Protoc.*, 2007, **2**, 2451.
3 (*a*) A. J. Wagner, J. G. David and S. D. Rychnovsky, *Org. Lett.*, 2011, **13**, 4470; (*b*) S. M. Miller, R. A. Samame and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2012, **134**, 20318; (*c*) M. A. Perry, J. V. Trinidad and S. D. Rychnovsky, *Org. Lett.*, 2013, **15**, 472.
4 X. Li, H. Jiang, E. W. Uffman, L. Guo, Y. Zhang, X. Yang and V. B. Birman, *J. Org. Chem.*, 2012, **77**, 1722; C. E. Müller and P. R. Schreiner, *Angew. Chem., Int. Ed.*, 2011, **50**, 6012; H. Pellissier, *Adv. Synth. Catal.*, 2011, **353**, 1613; J. E. Taylor, S. D. Bull and J. M. J. Williams, *Chem. Soc. Rev.*, 2012, **41**, 2109.
5 G. C. Fu, *Acc. Chem. Res.*, 2004, **37**, 542.
6 J. C. Ruble, J. Tweddell and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 2794. Contains 6 examples of benzylic alcohols (s-factors of 12–52).

 This journal is © The Royal Society of Chemistry 2013

7 S. Bellemin-Laponnaz, J. Tweddell, J. C. Ruble, F. M. Breitling and G. C. Fu, *Chem. Commun.*, 2000, 1009. Contains 15 examples of allylic alcohols (s-factors of 4.7–107).
8 See ESI† for experimental details and results.
9 J. C. Ruble, H. A. Latham and G. C. Fu, *J. Am. Chem. Soc.*, 1997, **119**, 1492. Contains 7 examples of benzylic alcohols (s-factors 12–52) and examples of allylic alcohols (s-factors 14–22).
10 B. Tao, J. C. Ruble, D. A. Hoic and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 5091. Contains 10 examples of alkyne-containing compounds (s-factors 3.8–20).
11 F.-X. Felpin and J. Lebreton, *J. Org. Chem.*, 2002, **67**, 9192.

Open Access Article. Published on 19 April 2013. Downloaded on 11/5/2025 9:13:32 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.