The kinetic resolution of allylic alcohols by a non-enzymatic acylation catalyst; application to natural product synthesis†

Stéphane Bellemin-Laponnaz, Jennifer Tweddell, J. Craig Ruble, Frank M. Breitling and Gregory C. Fu*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139 USA. E-mail: gcf@mit.edu

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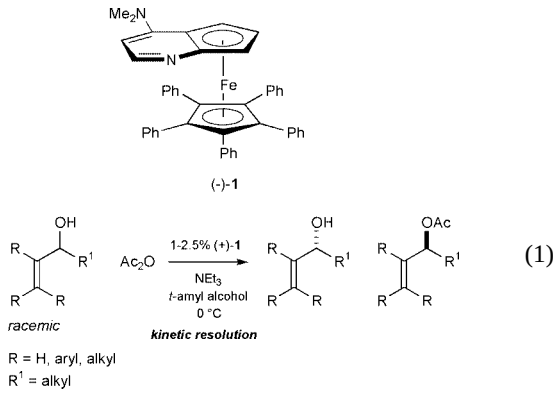
A planar-chiral DMAP derivative is shown to serve as an effective catalyst for the kinetic resolution of allylic alcohols; to illustrate its practical utility, the catalyst is applied to the resolution of two alcohols that have been employed as intermediates in recent natural product total syntheses.

During the mid-1990s, Evans *et al.*[1] and Vedejs and Chen[2] reported the first stoichiometric chiral acylating agents that are effective for the kinetic resolution of alcohols [selectivity factor (*s*) > 10],[3] work that marked an important first step in the development of non-enzyme-based methods for enantioselective acylation.[4] Soon thereafter, the groups of Vedejs,[5] Oriyama,[6] Fuji,[7] Miller[8] and ourselves[9] described the first chiral non-enzymatic acylation *catalysts* that are effective for the kinetic resolution of alcohols. With regard to substrate scope, the generality that has been reported to date follows the order: arylalkylcarbinols[10] > cycloalkanols[11] > propargylic alcohols[12] > allylic alcohols.[13]

Our work on catalytic enantioselective acylation has focused on the application of planar-chiral DMAP derivative **1** to the kinetic resolution of arylalkylcarbinols and of propargylic alcohols.[9] In addition, we observed in a 1997 study that we could resolve two *allylic* alcohols with good selectivity.[9a,14] Herein, we report a systematic investigation of the kinetic resolution of allylic alcohols by catalyst **1** [eqn. (1)], establishing fairly broad substrate scope and applying the method to two alcohols that have served as key building blocks in recent natural product syntheses.

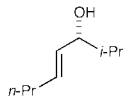
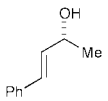
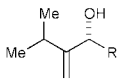
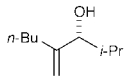
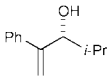
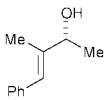
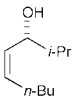
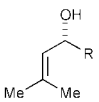
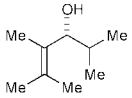


(1)

We have found that catalyst **1** can effect the kinetic resolution of most families of allylic alcohols with good selectivity [Table 1; 1.0–2.5% (+)-**1**, Ac_2O, NEt_3, *t*-amyl alcohol, 0 °C]. Allylic alcohols that do not possess a substituent either geminal or *cis* to the hydroxy-bearing group are usually resolved with modest selectivity (entry 1). A notable exception to this generalization occurs when there is a phenyl group in the *trans* position, in which case the selectivity factor increases dramatically (entry 2).

Allylic alcohols that possess a substituent geminal to the hydroxy-bearing group are usually resolved effectively by catalyst **1** (entries 3–8); again, the presence of a phenyl substituent in the *trans* position leads to substantially improved enantioselection (entry 9 *vs.* entries 3–8). Similarly, kinetic resolutions of allylic alcohols that possess a substituent *cis* to the hydroxy-bearing group generally proceed with good selectivity (entries 10–12). Furthermore, tetrasubstituted allylic alcohols are acylated with high stereoselection (entry 13).

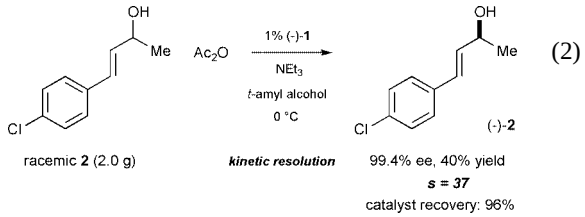
Table 1 Kinetic resolutions of allylic alcohols catalyzed by (+)-**1** (Ac_2O, NEt_3, *t*-amyl alcohol, 0 °C)

Entry	Unreacted alcohol, major enantiomer	Selectivity factor[a] (ee of unreacted alcohol)
1		**5.4** 92% ee @ 75% conv.
2		**64** 99% ee @ 54% conv.
3	R = *n*-pentyl	**4.7** 90% ee @ 77% conv.
4	R = *i*-Pr 	**10** 92% ee @ 63% conv.
5	R = Et 	**11** 93% ee @ 63% conv.
6	R = *i*-Pr	**17** 93% ee @ 58% conv.
7		**25** 94% ee @ 55% conv.
8		**14** 93% ee @ 59% conv.
9		**80** 98% ee @ 53% conv.
10		**5.3** 90% ee @73% conv.
11	R = *n*-pentyl 	**12** 97% ee @ 66% conv.
12	R = *i*-Pr	**18** 97% ee @ 60% conv.
13		**29** 99% ee @ 59% conv.

[a]The selectivity factors are the average of two runs.

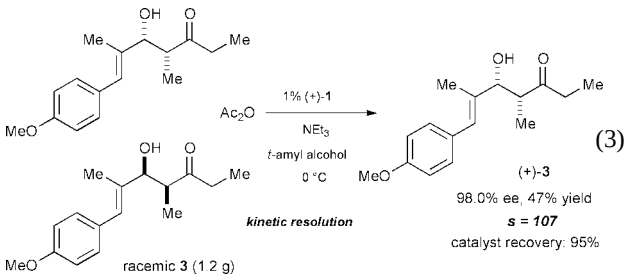
† Electronic supplementary information (ESI) available: full experimental details. See http://www.rsc.org/suppdata/cc/b0/b002041i/

In order to demonstrate the utility of this method, we have applied catalyst **1** to the kinetic resolution of two allylic alcohols that have served as key intermediates in recent natural product total syntheses. For example, Brenna *et al.* employed (−)-**2** in a 1997 synthesis of (−)-baclofen,[15] which is used as a muscle relaxant. We have determined that catalyst **1** effects the kinetic resolution of racemic **2** with a selectivity factor of 37 [eqn. (2)]. This reaction was run on a 2 g scale, exposed to air, thereby illustrating the practicality of the process. At the conclusion of the kinetic resolution, 96% of the catalyst was recovered.



(2)

Aldol adduct (+)-**3** is a key intermediate in the recent Sinha–Lerner synthesis of epothilone A,[16] an exciting new potential anti-cancer drug.[17] Adduct (+)-**3** has itself been the focus of much attention, owing to the fact that it can be generated by an aldolase antibody through kinetic resolution of racemic **3** (96% ee at 60% conversion ⇒ $s \sim 17$).[16,18] We have determined that catalyst **1** can also effect the kinetic resolution of this compound, with a selectivity factor of 107 [eqn. (3); reaction run exposed to air on a 1.2 g scale; acetylated **3**: 52% yield, 91.8% ee].[19]



(3)

In conclusion, we have established that planar-chiral DMAP derivative **1** is the most versatile non-enzymatic acylation catalyst for the kinetic resolution of allylic alcohols that has been reported to date, furnishing good selectivity for most substrates. Furthermore, we have illustrated the usefulness of this method by applying it to the kinetic resolution of two alcohols that have served as intermediates in recent natural product total syntheses.

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This paper is dedicated to the memory of John A. Osborn.

Notes and references

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11 Thirteen examples with $s > 10$: refs. 6–8.
12 Eight examples with $s > 10$: ref. 9(*d*).
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18 For commentaries, see: P. G. Schultz, *Proc. Natl. Acad. Sci. USA*, 1998, **95**, 14 590; S. Borman, *Chem. Eng. News*, Dec. 14, 1998, p. 15.
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