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An Organocascade Kinetic Resolution

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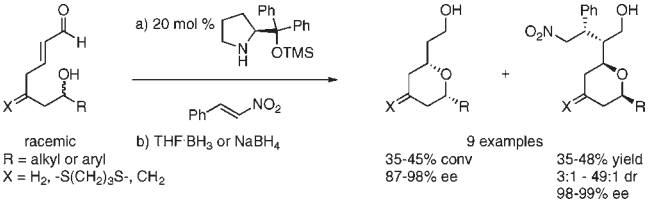
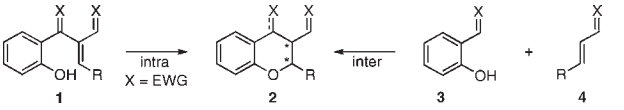
ABSTRACT



Products of a novel iminium-catalyzed oxa-Michael addition undergo a kinetic resolution by a subsequent enamine-catalyzed intermolecular reaction. This is a rare example of kinetic resolution by enamine catalysis and the first organocascade kinetic resolution. This resolution produces enantioenriched 2,6-*cis*-tetrahydropyrans and, notably, cascade products with absolute and relative configurations normally not observed using this diphenyl prolinol silyl ether. This resolution thus provides new insight into asymmetric induction in reactions employing this catalyst.

Efficient enantioselective oxa-Michael additions of alcohols are complicated by their reversibility, which can lead to low yields and selectivities.[1] Organocatalytic oxa-Michael additions of alcohols have relied primarily on two strategies to overcome this issue and as a result, with few exceptions,[2,4e,5b,6f,6l] generate structures of type **2** (Scheme 1). *Intra*molecular oxa-Michael additions (i.e., of **1**) catalyzed by chiral phosphoric acid,[2] guanidine,[3] cinchona alkaloid,[4] and thiourea[5] organocatalysts generate products in high yields, because the equilibrium of these reactions lies largely to the right. Only a few examples were both highly diastereo- and enantioselective.[2,4g,5]

Scheme 1. Organocatalytic Oxa-Michael Additions of Alcohols



Alternatively, by tethering a nucleophilic alcohol to an electrophilic center, as in **3**, *inter*molecular oxa-Michael additions are followed by intramolecular reactions, leading to cascade products in high yields and selectivities by a combination of iminium and enamine catalysis.[6] We sought to develop the enantioselective oxa-Michael

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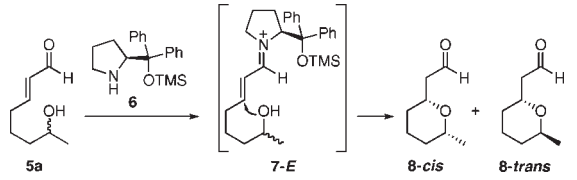
addition depicted in Table 1 (**5a**→**8-*cis*** and **-*trans***). If successful, this transformation would be the first example of a highly selective iminium-catalyzed Michael addition of an alcohol that was not part of a cascade reaction.[7] Moreover, it would provide a new, green chemical method for accessing enantioenriched 2,6-*cis*- *and trans*-tetrahydropyrans, both of which are prevalent in natural products. During studies toward this new oxa-Michael reaction, an unanticipated organocascade kinetic resolution was observed and is described herein.

Table 1. Development of a Novel Oxa-Michael Addition[a]



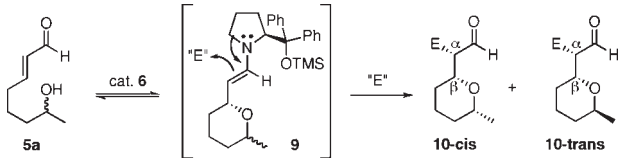
entry	cat.	time (min)	yield[b] (%)	dr[c] (*cis*/*trans*)	% ee[d] (*cis*)	% ee[d] (*trans*)
1	Et_3N	45	–			
2	–	45	–			
3	**6**	1	44	54/46	68	95
4	**6**	5	68	59/41	57	96
5	**6**	10	70	62/38	46	96
6	**6**	45	70	82/18	17	89
7	**6**[e]	20	80	62/38	52	>99
8[f]	**6**	180	73	63/37	53	>99

[a] Reaction conditions: **5a** (1 equiv), cat. (10 mol %), $PhCO_2H$ (10 mol %), toluene (0.4 M), 0 °C. [b] Yield of corresponding alcohol generated by in situ reduction. [c] Dr of corresponding alcohols determined by ^1H NMR. [d] % ee of *para*-nitrobenzoate derivative of corresponding alcohol determined by chiral phase HPLC. [e] 5 mol % **6** and 5 mol % $PhCO_2H$ used. [f] Reaction run at −30 °C.

This intramolecular oxa-Michael addition was not base- or acid-catalyzed but was rapidly iminium-catalyzed (entries 1 and 2 vs 3−8). By stopping this reaction at various time points (entries 3−6), two trends became apparent. First, the *trans*-tetrahydropyran product can be obtained in excellent ee. Second, although the initial oxa-Michael addition is selective, a plot of these data revealed that **8-*trans*** converts to ***epi*-8-*cis*** over time, which erodes both the *trans*/*cis* ratio and the ee of **8-*cis***.[8] Extensive optimizations[8] revealed that lower catalyst loadings (5 mol %) and temperatures (−30 °C) led to the highest yield and ee >99% of the *trans*-product (entries 7 and 8). Thus, although it is possible to stop this reaction at a time point at which the *trans*-product can be isolated in high yield and ee, at all time points, and even at incomplete conversions (entries 3 and 4), the *trans*/*cis* ratio was <1.

We wondered whether it would be possible to trap enamine intermediate **9** (Scheme 2) with an external electrophile ("E") to prevent retro-oxa-Michael addition and, in turn, the conversion of **8-*trans*** to ***epi*-8-*cis***. As alluded to earlier, it is a common practice to trap enamine intermediates arising from oxa-Michael additions by subsequent *intra*molecular reactions, as occurs when an oxa-Michael donor is tethered to an electrophilic center, as in **3**.[6] Trapping enamine intermediates arising from oxa-Michael additions using *inter*molecular reactions has not been reported and would generate *cis*- and *trans*-tetrahydropyran cascade products **10-*cis*** and **-*trans***, with a *syn* relationship between substituents at the α- and β-positions.

Scheme 2. Cascade by Enamine-Catalyzed *Inter*molecular Reaction



Using β-nitrostyrene (**11**) as the external electrophile, and a 5 mol % catalyst loading at −30 °C, trace conversion was observed (entry 1, Table 2). When the catalyst loading was increased, an unanticipated kinetic resolution was observed (entry 2). The enamine-catalyzed intermolecular reaction was slower than the retro-oxa-Michael, as **8-*trans*** had completely converted to ***epi*-8-*cis***, resulting in a racemic intermediate, ***rac*-8-*cis***. Thus, no *trans*-tetrahydropyran cascade product was observed. One enantiomer, ***epi*-8-*cis***, underwent an enamine-catalyzed intermolecular Michael addition to furnish cascade product **12**, with an *anti* relationship between its α- and β-substituents, in 42% conversion (maximum theoretical conversion = 50%), 9:1 dr, and 99% ee. The other enantiomer, **8-*cis***, underwent the subsequent enamine-catalyzed intermolecular Michael addition at a considerably retarded rate (only 11% conversion) and could be recovered in 90% ee. This kinetic resolution is highly solvent-dependent. In THF, neither enantiomer of ***rac*-8-*cis*** underwent the enamine-catalyzed intermolecular Michael addition, whereas in $CHCl_3$ both enantiomers did (entries 3 and 4).

A variety of different substrates underwent a kinetic resolution using these conditions (Scheme 3). In all cases a small amount of cascade product arising from **8-*cis*** was generated; however, alcohols **13** and **14** were produced, following an in situ reduction, in generally good to excellent yields and selectivities. Regardless of the steric bulk of the R group, products were obtained in excellent yield and selectivity (compounds **a**−**d**). Other reactive functional groups and adjacent heteroatoms were also well tolerated, as was an sp^2 hybridized R group (compounds **e**−**g**).

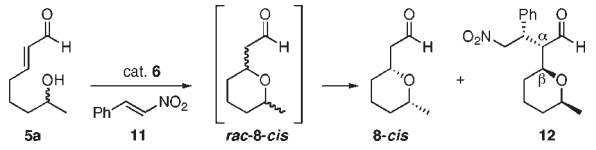
(7) (a) For a nonhighly selective version, see: Díez, D.; Núñez, M.-G.; Benéitez, A.; Moro, R.-F.; Marcos, I. S.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Synlett* **2009**, 390–394. (b) For a version using peroxyalcohols, see: Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134–8135.

(8) See Supporting Information for full details.

(9) Substrates **5h** and **5i** could not be synthesized in uncyclized form and were, thus, subjected to cascade reaction conditions as the corresponding racemic *cis*-tetrahydropyrans.

Importantly, substrates that generate tetrahydropyrans with substitution at the 4-position are amenable to this kinetic resolution.[9] Tetrahydropyran products with a dithiane ring at the 4-position were generated in good ee, but with a slightly lower dr (compound **h**). A reaction with a substrate producing tetrahydropyrans with an olefin at the 4-position could be readily scaled up to a 1.1 g scale (compound **i**).

Table 2. An Organocascade Kinetic Resolution[a]



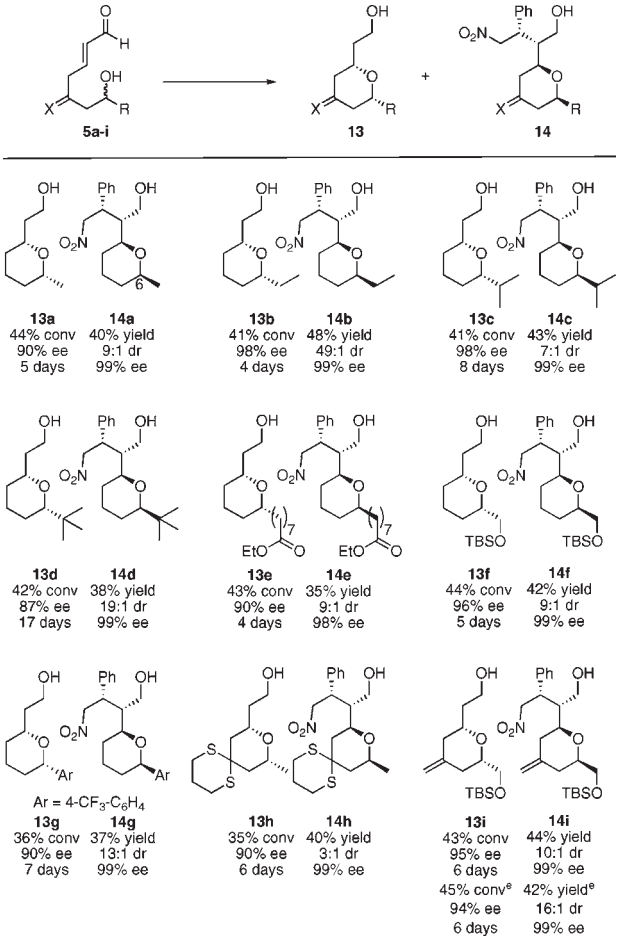
entry	solvent	% conv[b] (**8**-*cis*)	% ee[c] (**8**-*cis*)	% conv[b,d] (**12**)	dr[b] (**12**)	% ee[d,e] (**12**)
1[f]	toluene	–	N/A	–	N/A	N/A
2	toluene	45	90	42(11)	9:1	99 (nd)
3	THF	69	0	–	N/A	N/A
4	$CHCl_3$	–	N/A	39 (38)	2:1	99 (99)

[a] Reaction conditions: **5a** (1 equiv), **11** (2 equiv), **6** (20 mol %), $PhCO_2H$ (20 mol %), solvent (0.4 M), −30 °C. [b] Determined by ^1H NMR of crude reaction mixture. [c] % ee of *para*-nitrobenzoate derivative of corresponding alcohol determined by chiral phase HPLC. [d] Number in parentheses is for cascade product derived from **8**-*cis*. [e] % ee of corresponding alcohol determined by chiral phase HPLC. [f] 5 mol % **6** and 5 mol % $PhCO_2H$ used.

The absolute configuration of **13a** was established by comparison of data for a known compound.[8] The absolute configuration of **14a** at the 6-position of the tetrahydropyran was established by running this organocascade reaction with the pure *R* and pure *S* enantiomers of **5a**.[8] The configurations of the remaining stereocenters in **14a** were established by X-ray crystallography of its *para*-nitrobenzoate derivative.[8]

Our working stereochemical model for this organocascade kinetic resolution is illustrated in Scheme 4. Racemic alcohol **5a** reacts with catalyst **6** to form *E*-iminium **7**-***E***. The hydroxyl group approaches from the face opposite the bulky groups of the catalyst, generating oxa-Michael products **8**-***trans*** and **8**-***cis***. Oxa-Michael product **8**-***trans*** is highly unstable because one of the substituents must occupy an axial position on the tetrahydropyran ring. Therefore, **8**-***trans*** undergoes a rapid retro-oxa-Michael/oxa-Michael addition to generate the thermodynamically favored, all-equatorial ***epi*-8**-***cis***. Although we could not isolate **8**-***trans*** to test the mechanism of the retro-oxa-Michael, we know that, in the forward direction, the oxa-Michael addition is iminium-catalyzed (and, as mentioned, not simply base- or acid-catalyzed) and that nucleophiles reacting with iminium ions formed from catalyst **6** generally approach from the face opposite the bulky groups of this catalyst. It is therefore possible that conversion of **8**-***trans*** to ***epi*-8**-***cis*** may occur via a high energy *Z*-iminium species **7**-***Z***.[10]

Scheme 3. A General Organocascade Kinetic Resolution[a−d]



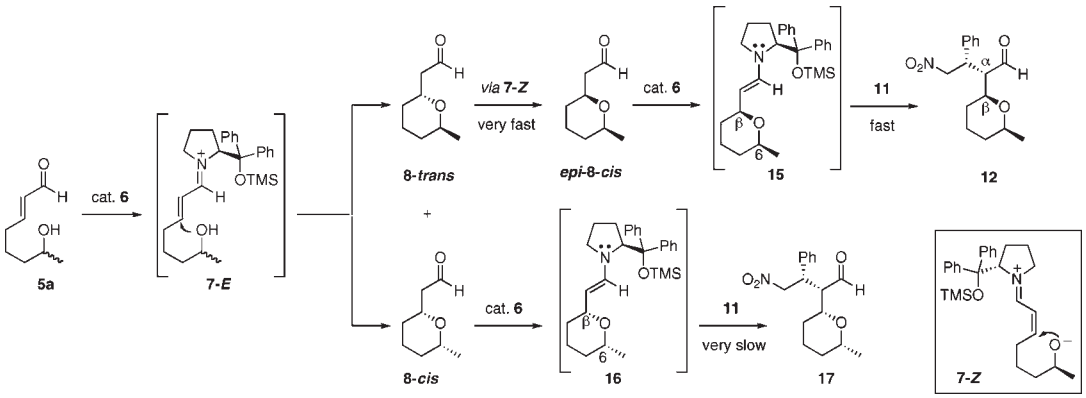
[a] Reaction conditions: **5a** (0.44 mmol), **11** (0.88 mmol), **6** (0.088 mmol), $PhCO_2H$ (0.088 mmol), toluene (1.1 mL), −30 °C, then THF·BH_3 (1 M in THF, 0.5 mL) or $NaBH_4$ (2 mmol), MeOH (4.4 mL). [b] Conv and dr determined by ^1H NMR. [c] Yield = yield of isolated product. [d] Ee's of alcohol or of *para*-nitrobenzoate derivative of alcohol determined by chiral phase HPLC. [e] Reaction run on 4 mmol scale.

Intermediates **8**-***cis*** and ***epi*-8**-***cis*** can react with catalyst **6** to form enamines **16** and **15**, respectively. In enamine **15**, the bulky groups of the catalyst and the substituents at the β- and 6-positions all block the top face of the enamine. These synergistic blocking effects evidently result in rapid reaction with an electrophile that approaches from the bottom face of the enamine, generating cascade product **12**. In enamine **16**, the bulky groups of the catalyst shield the top face of the enamine, while the substituents at the β- and 6-positions shield the bottom face. These opposing blocking effects may account for the relative unreactivity of enamine **16**.

Thus, formation of ***epi*-8**-***cis***, which effectively arises from the approach of the alcohol from the same face as the bulky groups of the catalyst in iminium species **7**-***E***, is disfavored in the initial oxa-Michael addition, in accord with the accepted model for asymmetric induction of

(10) *Z*-Iminium species have been invoked in olefin isomerizations; for example, see: Yang, J. W.; Fonseca, M. T. H.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108–110.

Scheme 4. Proposed Mechanism of Organocascade Kinetic Resolution



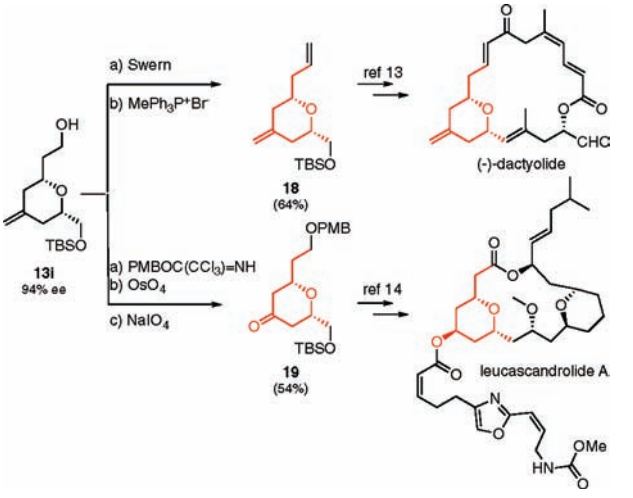
catalyst **6**. However, ***epi*-8-*cis*** is *matched* for the subsequent enamine-catalyzed intermolecular reaction. This is indicative of a more complex relationship between the role of steric influences of the substrate and that of the catalyst (discussed in the preceding paragraph) in asymmetric induction in reactions catalyzed by **6** than has previously been proposed. Notably, this also results in the formation of cascade products, **12**, with the opposite absolute (i.e., *S* configuration at the β-position) and relative (i.e., *anti* relationship between α- and β-substituents) configuration to those of cascade products normally arising from use of catalyst **6**.

Moreover, this is a rare example of a kinetic resolution by enamine catalysis. While there are many examples of the use of enamine/iminium catalysis in dynamic kinetic asymmetric transformations,[11] there are only isolated examples of their use in kinetic resolutions.[12]

The products of this kinetic resolution are synthetically useful. Alcohol **13i** was readily transformed into intermediates in the total syntheses of two complex natural products, as outlined in Scheme 5.[13,14]

In conclusion, we have developed an organocascade kinetic resolution, which provides access to enantioenriched, functionalized tetrahydropyrans. The organocascade is initiated by a novel oxa-Michael addition that is highly selective but rapidly reversible. In a rare demonstration of the use of enamine catalysis in a kinetic resolution, an *inter*molecular reaction has, for the first time, been used to resolve racemic oxa-Michael adducts. The experimental (i.e., solvent dependency) and stereochemical insights

Scheme 5. Synthetic Utility of Resolved Oxa-Michael Adducts



presented herein may facilitate the broader application of enamine catalysis in kinetic resolutions, as well as other new applications of these catalysts. Further investigations into this, and related, organocascade kinetic resolutions are presently underway, and results will be reported in due course.

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Supporting Information Available. General experimental conditions and full characterization data for compounds **5a**–**i**, **13a**–**i**, **14a**–**i**, **18**, **19**, and the corresponding alcohols of ***8-cis*** and ***-trans***. This material is available free of charge via the Internet at http://pubs.acs.org.

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