JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

pubs.acs.org/JACS

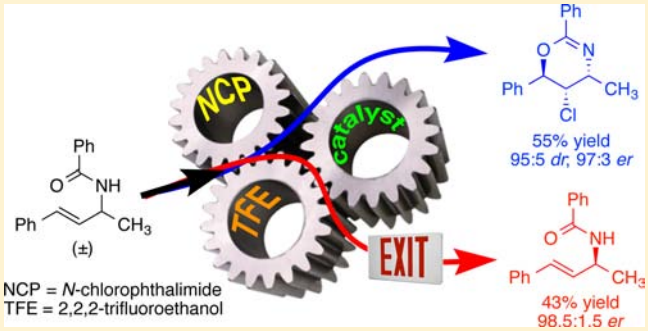
Kinetic Resolution of Unsaturated Amides in a Chlorocyclization Reaction: Concomitant Enantiomer Differentiation and Face Selective Alkene Chlorination by a Single Catalyst

Arvind Jaganathan, Richard J. Staples, and Babak Borhan*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States

Supporting Information

ABSTRACT: The first example of a kinetic resolution via chlorofunctionalization of olefins is reported. The enantiomers of racemic unsaturated amides were found to have different hydrogen-bonding affinities for chiral Lewis bases in numerous solvents. This interaction was exploited in developing a kinetic resolution of racemic unsaturated amides via halocyclization. The same catalyst serves to both "sense chirality" in the substrate as well as mediate a highly face-selective chlorine delivery onto the olefin functionality, resulting in stereotriad products in up to 99:1 *dr* and up to 98.5:1.5 *er*. The selectivity factors were typically greater than 50 to allow for the simultaneous synthesis of both the products and unreacted substrates in highly enantioenriched form at yields approaching 50%. The reaction employs catalytic amounts (≤0.50 mol %) of a commercially available and recyclable organocatalyst.



INTRODUCTION

Nature relies on enzyme catalysis to effect formidable reactions with astonishing efficiency. The remarkable chemo- and stereospecificity of enzymatic reactions leads to rapid generation of complex architectures from simple precursors. Key to the success of these reactions is the extensive preorganization of the substrate into reactive conformations, as well as a multitude of covalent and/or noncovalent substrate-enzyme interactions. The combined effect of differential entropy and enthalpy modulations serve to distinguish between numerous reaction pathways that would have all been equally accessible in the absence of the enzyme.[1] Efforts by synthetic chemists to develop small-molecule catalysts that mimic enzymes have led to a better appreciation for the power of enzyme catalysis, as well as the development of novel chemistry (examples include the polyene cascade reactions that generate terpenes, the putative cascade cyclization reactions that yield polyheterocyclic natural products, and products of the polyketide biosynthesis, to name a few).[2] But despite these advances, biasing reactions exclusively into one of the multitude of available reaction pathways remains a daunting challenge within the realm of small-molecule catalysis; this is especially true when many of these pathways are energetically accessible under reaction conditions. Unlike enzymes, small molecule catalysts do not enjoy large decreases in the differential entropy and enthalpy of activation for mediating reactions.[3] Nonetheless, small-molecule catalysts are generally more promiscuous in terms of substrate specificity and are easily manipulated by means of modular syntheses. Consequently, the pursuit to discover catalysts that are capable of mimicking enzymes by reducing the available reaction pathways for any given reaction is a worthwhile endeavor.

Advances in synthetic chemistry have led to robust "chemical" equivalents for numerous reactions that are traditionally perceived as the domain of enzyme catalysis. Arguably, the most mimicked of these transformations is the kinetic resolution of racemic mixtures, whereby an enzyme can selectively function on one of two enantiomers.[4] The interest in developing kinetic resolutions goes beyond the academic interest of enabling proposals or validations of theoretically predicted "molecular-recognition" phenomena; they often serve as a practical means for the synthesis of enantioenriched molecules. Jacobsen and co-workers have elegantly summarized the criteria for an "ideal kinetic resolution".[5] The numerous requirements include the ready availability of the catalyst and substrates, paucity of methods to access the desired chiral molecules using alternate methods, the cost of the catalyst, substrate scope, and practical ease in recovery of products and catalysts. Our lab recently had the occasion to examine the possibility of a double stereoselection by an organocatalyst in the context of an asymmetric alkene halogenation reaction.[6] In our prior studies, we had demonstrated that unsaturated amides can be subjected to a highly enantioselective chlorocyclization reaction to afford corresponding dihydro-oxazine heterocycles with excellent stereoselectivities (Figure 1a, typically greater than 97.5:2.5 *er*).[7,8] These findings indicated that in the presence of the chiral catalyst the two diastereomeric transition

Received: July 15, 2013
Published: September 3, 2013

   dx.doi.org/10.1021/ja407241d | *J. Am. Chem. Soc.* 2013, 135, 14806−14813

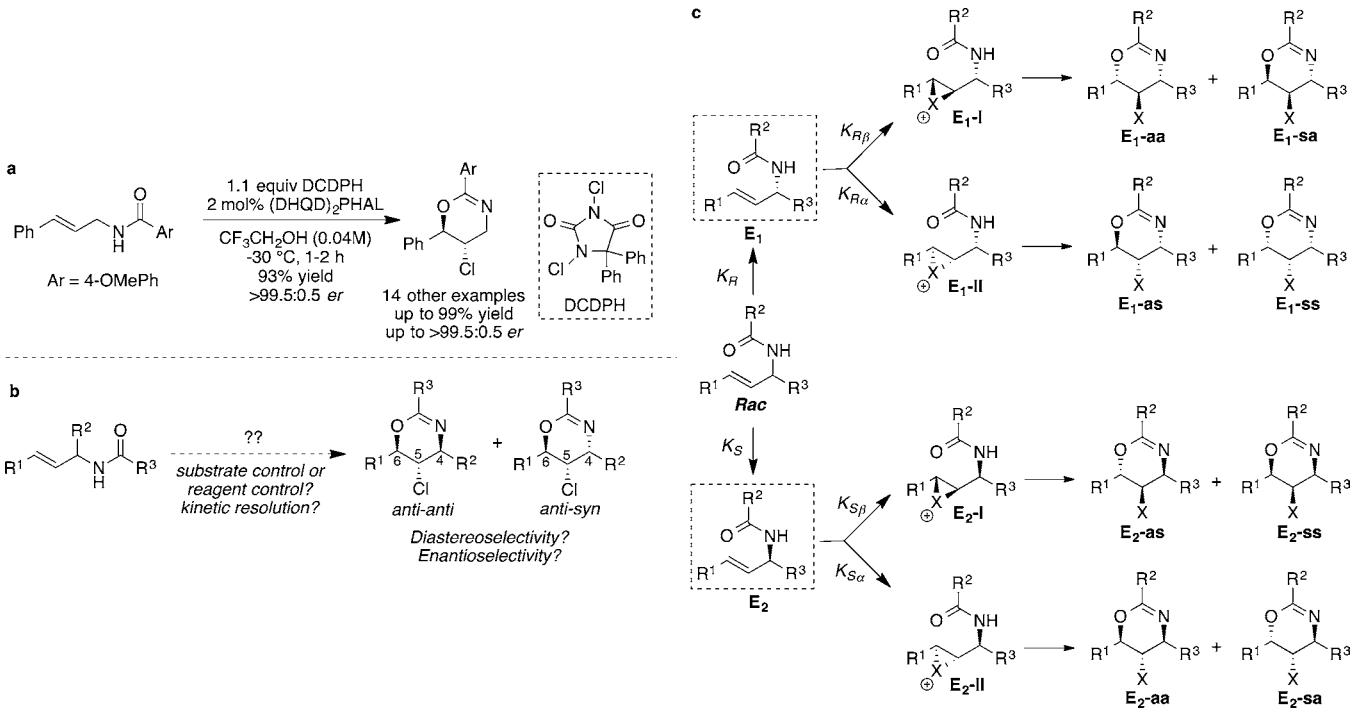


Figure 1. Enantioselective chlorocyclization of unsaturated amides. (a) Previous work. (b) Proposed stereoselective chlorocyclization of racemic unsaturated amides: Reagent or substrate control may predominate. (c) Mechanistic possibilities for the transformation: two distinct stereoselective steps can lead to a kinetic resolution of substrate leading to the diastereo- and enantioselective synthesis of stereotriad products.

states are sufficiently well differentiated energetically to allow for high levels of enantioinduction.

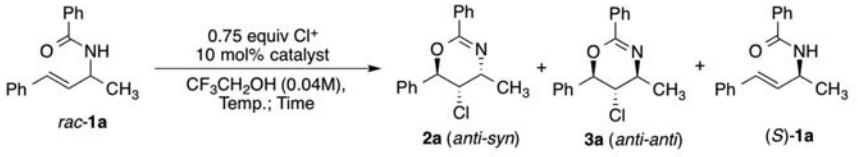
Nonetheless, in the presence of pre-existing chirality in the substrate (Figure 1b), the challenge of controlling the absolute stereochemistry of products is compounded by the additional requirement of controlling the relative stereochemistry of the two newly created stereocenters. Furthermore, the propensity of chloronium ions to readily isomerize to the corresponding carbocations[9] followed subsequently by a "syn" or "anti" capture of the carbocation by the pendant amide nucleophile results in two additional diastereomeric transition states. The capacity to achieve the required level of selectivity with the catalyst system was in doubt, until recent mechanistic studies with an analogous reaction system, which demonstrated the ability of the catalytic complex to not only dictate face selectivity of chlorenium transfer, but also exquisitely control the stereochemistry of cyclization.[10] The capability to control the stereochemical outcome of two independent events by the same catalytic system piqued our interest in challenging this system to further stereodifferentiate a racemic substrate as a result of preferential binding, much like that in enzymatic systems.

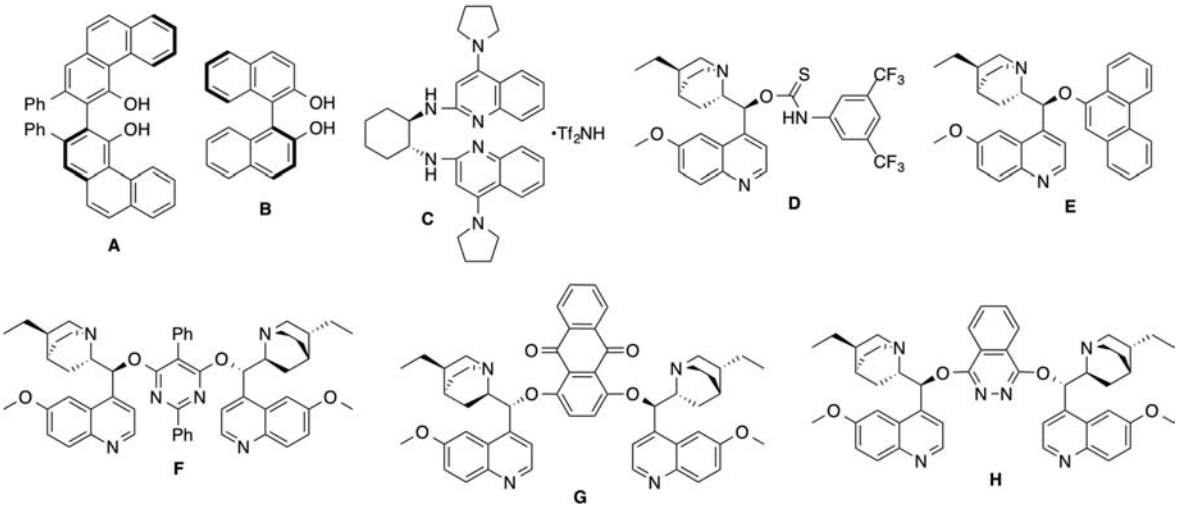
The chlorocyclization of a generic chiral amide, such as the one depicted in Figure 1c, can yield eight distinct stereoisomeric products **E$_1$-aa** to **E$_2$-sa** in the presence of a chiral catalyst. Preliminary studies revealed that there was no evidence of the "syn" opening pathway for both the noncatalyzed or the catalyzed chlorocyclization of racemic substrates (i.e., **E$_1$-sa** to **E$_2$-sa**, which would arise from a "syn" opening were not detected in the reaction). Also, there was no inherent bias for the pathways that lead to the anti-syn (**E$_1$-as** + **E$_2$-as**) and the anti-anti (**E$_1$-aa** + **E$_2$-aa**) diastereomers at ambient temperature (noncatalyzed reactions had an anti-syn:anti-anti ratio of ~60:40; see the Supporting Information, SI). We were intrigued by the possibility of using a single chiral catalyst that could promote the formation of predominantly one diastereomer of the product with high enantioselectivity. In order to meet this challenge, the catalyst must serve to "sense chirality" of the substrate in the first stage and enable highly face selective chlorenium delivery to the "matched" catalyst-bound substrate in the second stage. If the catalyst can selectively accelerate the reaction of one of the two enantiomers (i.e., promote a kinetic resolution of the racemate), then only two of the four pathways will be accessible. The two remaining pathways are defined by the face selectivity in the chlorenium delivery to the olefin moiety. If the same catalyst could further enable a highly face selective chlorenium delivery to the fast reacting enantiomer of the substrate, then one would expect a single stereoisomer of the cyclized product. It is evident that high levels of stereoselection at two stages must operate in concert to enable a diastereoselective kinetic resolution. This enzyme-like catalysis will be manifested as a kinetic resolution of the racemate that also leads to stereotriad products with high diastereoselectivity.

Kinetic resolution via alkene halofunctionalization is captivating for many reasons. First, the products are stereotriads (with two new stereocenters being created in the process) adorned with numerous functional handles for further elaboration. Resolutions that create additional stereocenters in the products are relatively rare and are challenging due to the additional requirement of controlling the product diastereoselectivity.[11] Second, the kinetic resolution would necessitate the discovery of an intermolecular catalyst-substrate interaction that will serve to "sense" chirality of racemic amides. Finally, a kinetic resolution via chlorofunctionalization of olefins was an unrealized transformation prior to this work.[8e,x,12] It must be emphasized that high face selectivity in the delivery of a halenium ion on to the olefin moiety is neither a necessary nor

dx.doi.org/10.1021/ja407241d | J. Am. Chem. Soc. 2013, 135, 14806−14813

Table 1. Catalyst Screen for Kinetic Resolution in the Chlorocyclization of Unsaturated Amides





entry	catalyst (equiv)	temp/time(°C/h)	Cl+ source	conv.[a] (%)	dr[b] (2a:3a)	er[c] (2a)	er[c] (3a)	er[c] (S)-1a
1	none	4/4.5	DCDMH	42	65:35			
2	0.1 **A**	4/4.5	DCDMH	44	71:29	53:47 (*ent*-**2a**)	51:49	54:46
3	0.1 **B**	4/4.5	DCDMH	47	70:30	51:49	50:50	50:50
4	0.1 **C**	4/4.5	DCDMH	28	66:34	51:49	50:50	50:50
5	0.1 **D**	4/4.5	DCDMH	69	44:56	57:43	53:47	55:45
6	0.1 **E**	−30/1	DCDMH	49	24:76	54:46 (*ent*-**2a**)	70:30 (*ent*-**3a**)	52:48
7	0.1 **F**	−30/1	DCDMH	56	22:78	62:38 (*ent*-**2a**)	52:48	53:47
8	0.1 **G**	−30/1	DCDMH	60	18:82	62:38	60:40	59:41
9	0.1 **H**	−30/1	DCDMH	61	92:8	94:6	98:2	97:3
10[d,e]	0.03 **H**	24/1	NCS	53	96:4	97:3	90:10	97:3
11[d,e]	0.03 **H**	24/1	NCP	55	95:5	97:3	92:8	98.5:1.5
12[d,e]	0.005 **H**	24/0.17	NCP	48	94:6	96.5:3.5	74:26	95.5:4.5
13[d,e]	0.0025 **H**	0/1	NCP	49	94.5:5.5	98:2	72:28	93:7
14[d,e]	0.0001 **H**	0/1	NCP	28	94:6	98.5:1.5	58:42	68:32
15[d,e]	quasi-*ent*-**H**	24/1	NCP	55	94:6	97:3 (*ent*-**2a**)	91:9 (*ent*-**3a**)	98:2 (*R*)-**1a**

[a]Based on calibrated GC yield of unreacted olefin using undecane as internal standard (see SI). [b]Determined by GC analysis. [c]Determined by chiral HPLC. [d]Reaction concentration was 0.10 M. [e]0.55 equiv of chlorenium source was used.

a sufficient condition for achieving an efficient resolution. The crucial requirement is for the chiral catalyst to sufficiently differentiate the reaction rates of the two enantiomers of the racemate. The face selectivity merely dictates the diastereoselectivity of the cyclized products.

RESULTS AND DISCUSSION

Reaction Optimization. The development of the kinetic resolution began with the evaluation of the inherent diastereoselectivity of this transformation in the absence of any catalyst (i.e., mapping the substrate control). Marginal preference for the formation of **2a** was observed (entry 1, Table 1; **2a**:**3a** varied from 60:40 to 70:30 depending on the chlorenium source employed; see SI for results with other chlorenium sources). This was followed by the evaluation of numerous organocatalysts at 10 mol % catalyst loading and incomplete conversions in order to determine whether (a) substrate control could be significantly amplified or overridden and (b) if competent catalysts for a kinetic resolution could be identified.

Our studies commenced with the evaluation of numerous hydrogen-bonding catalysts such as BINOL and its derivatives in the hope that they may preferentially associate with one enantiomer of the substrate.[13] However, the results with catalysts **A** and **B** were disappointing (entries 2 and 3, Table 1). This was followed by the evaluation of other catalysts that have shown promise in enantioselective alkene halogenation reactions in recent years. The bis-amidine derived Bronsted acid catalyst **C** pioneered by Johnston and co-workers[8d] and the thiocarbamate catalyst **D** analogous to those used by Yeung's group[8ab] also proved ineffective in resolving the racemic substrate (entries 4 and 5, Table 1). Reactions **A**−**D** did not exhibit rate acceleration, little to no enantioselectivity, and similar diastereoselectivity as the noncatalyzed reaction. Better results were obtained when cinchona alkaloid derived chiral Lewis bases were screened. Four catalysts (catalysts **E**-**H**) that

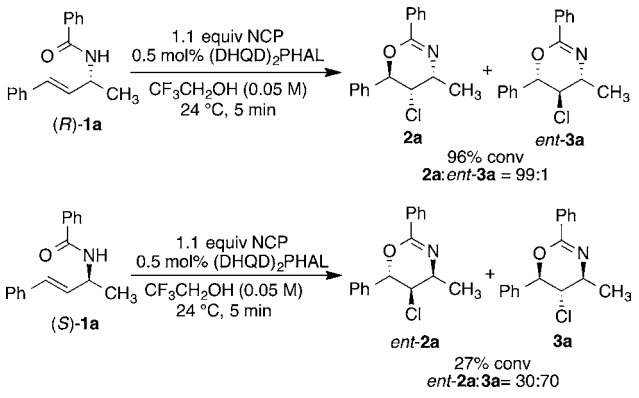
dx.doi.org/10.1021/ja407241d | J. Am. Chem. Soc. 2013, 135, 14806−14813

significantly altered the substrate control (and thereby confirmed their participation in the stereodetermining step)[14] were identified. Catalysts **E**, **F**, and **G** gave the anti-anti diastereomer **3a** as the predominant diastereomer (entries 6−8, Table 1). But despite overriding substrate control, the enantioselectivities of the cyclized products and the unreacted olefin were poor with all three catalysts; i.e., these catalysts were neither competent in resolving the racemic substrate nor capable of imparting face selectivity of the chlorenium ion delivery to the olefin. In sharp contrast, catalyst **H** ($(DHQD)_2PHAL$) served to significantly amplify the substrate control by affording **2a** as the major diastereomer (**2a**:**3a** = 92:8, entry 9, Table 1). More importantly, when the reaction was stopped at 61% conversion, the major diastereomer **2a** was isolated in 94:6 *er* and the unreacted olefin was highly enriched in the *S*-enantiomer (97:3 *er*).[15] While tremendous rate acceleration was observed with all four catalysts, only $(DHQD)_2PHAL$ was identified as a competent catalyst for kinetic resolution. Stoichiometric NMR experiments revealed that $(DHQD)_2PHAL$ was likely behaving as a hydrogen bonding catalyst to promote the kinetic resolution (vide infra).

Further studies focused on improving some of the practical aspects of this reaction, such as the reaction temperature, concentration, and catalyst loading. The identity of the chlorenium source did not significantly influence the diastereo- and enantioselectivity of this transformation. *N*-chlorophthalimide (NCP) was eventually chosen for further studies due to the practical ease of removing the phthalimide byproduct using a basic workup as well as the consistently higher isolated yields of the cyclized products (entry 11, Table 1) (a detailed account of results with different chlorenium sources and other reaction variables' optimization can be found in the SI). Remarkably, no loss in efficiency was seen even at ambient temperatures and at higher concentrations (0.10 M) (entries 12 to 14, Table 1) while maintaining sub 1.0 mol % catalyst loadings, indicating exquisite specificity of the catalyst for the transformation of the *R* enantiomer of the substrate. The catalyst loading could be reduced to as low as 0.25 mol % (entry 13, Table 1). The quasi-enantiomeric $(DHQ)_2PHAL$ catalyst gave practically identical results favoring the opposite enantiomers of products and the recovered olefin (entry 15, Table 1).

Predictably, a clear preference was observed for the chlorocyclization of enantiomerically pure (*R*)-**1a** in comparison to (*S*)-**1a** under optimized conditions (Scheme 1). In the presence of stoichiometric amounts of *N*-chlorophthalimide and 0.50 mol % of $(DHQD)_2PHAL$, (*R*)-**1a** was almost completely consumed in 5 min to give exclusively the anti-syn diastereomer **2a** (99:1 *dr*) indicating exquisite α-face selectivity in the delivery of the chlorenium ion to the olefin of (*R*)-**1a**. Under identical conditions, (*S*)-**1a** showed only 27% conversion to product. Notably, low olefin face selectivity was seen in the chlorenium delivery still favoring the α face by a ratio of 70:30 indicating a much attenuated reagent control for (*S*)-**1a**.

Scheme 1. Observed Difference in Reagent Control by $(DHQD)_2PHAL$ in Mediating the Chlorocyclization of (*R*)-1a and (*S*)-1a



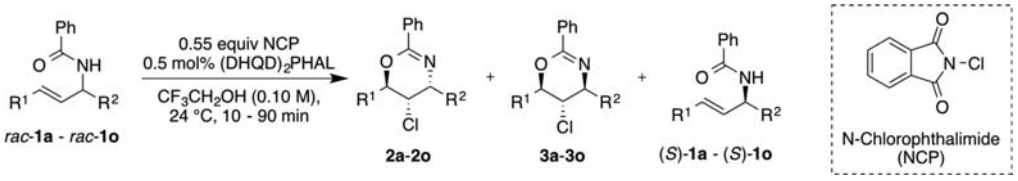
Substrate Scope. The generality of the kinetic resolution was investigated by subjecting numerous trans disubstituted allylic amides to optimized reaction conditions. As seen in Table 2, the reaction was tolerant of electronically and sterically diverse aryl substituents on the olefin. Electron deficient and halogenated aryl rings presented no difficulties, nor did substrates with ortho substituents on the aromatic ring. These substrates were resolved in comparable efficiency as the test substrate (entries 1−6, 8, and 9 Table 2). In all of these instances, the cyclized products were formed with excellent diastereoselectivity (93:7 to >99:1 *dr*) at ∼50% conversion. Furthermore, the enantioselectivity for the major diastereomer was >95:5 for most products and the unreacted substrates were isolated in >90:10 *er* for most substrates (a single crystallization was usually sufficient to upgrade the enantioselectivity to >97.5:2.5 *er*). The effect of increasing steric demand of the olefin substituent as well as the substituent at the α-carbon (i.e., the C4 and C6 substituents of the cyclized products) was then studied. Substrate **1j** with a sterically demanding naphthyl substituent was efficiently resolved (92:8 *er* for unreacted substrate at 55% conversion), albeit the diastereoselectivity of the cyclized product was poor (entry 10, 74:26 *dr*). This result indicates that the catalyst effectively discriminates the enantiomers of the racemic substrate; but a poor facial selectivity in the chlorenium delivery to the olefin leads to the diminished diastereoselectivity.

The effect of increasing steric demand of the substituent at α-position of the amide had a more dramatic effect. Substrates **1k** and **1l** with conformationally flexible allyl and n-C_5H_{11} substituent, respectively, were excellent substrates for the resolution (entries 11 and 12, Table 2). Much diminished efficiency was observed when the α-substituent was a homobenzyl, phenyl, or a *t*-butyl substituent (entries 13 to 15, Table 2). Cyclization of substrates **1m**, **1n**, and **1o** required higher catalyst loadings (3.0 mol %) and longer reaction times (90 min) to reach ∼50% conversion. In the case of substrate **1n** with a C_6H_5 α-substituent, practically no resolution of the racemic substrate was seen (**1n** was recovered in 60:40 *er* at 55% conversion). The cyclization exhibited poor diastereoselectivity (**2n**/**3n** = 60:40) and the products exhibited only moderate levels of enantioselectivity (84:16 *er* for **2n** and 69:31 *er* for **3n**). Likewise, substrate **1o** with the bulky *t*Bu substituent also fared poorly. The lower reaction rates and resolution efficiency with these substrates is attributed to poor substrate-catalyst interaction due to increased steric impediments (stoichiometric substrate-catalyst NMR studies support this hypothesis; see below for discussion and the SI for the NMR studies).

NMR Analysis of Stoichiometric Substrate-Catalyst Mixtures. As outlined in Figure 1c, the first and crucial level of selectivity is defined by the catalyst's ability to preferentially accelerate (or inhibit) the reaction of one of the two enantiomers presumably via hydrogen-bonding interactions.

dx.doi.org/10.1021/ja407241d | J. Am. Chem. Soc. 2013, 135, 14806−14813

Table 2. Substrate scope for kinetic resolution *via* chlorocyclization



entry	substrate	R^1	R^2	conversion[a] (Yield of **2**+**3**)[b]	*dr* (**2**:**3**)[c]	*er* (**2a**–**2o**)[d]	*er* (**1a**–**1o**)[d]
1	**1a**	C_6H_5	CH_3	57% (55%)	95:5	97:3	98.5:1.5
2	**1b**	4-Cl–C_6H_4	CH_3	55% (54%)	95.5:4.5	96:4	99.5:0.5
3	**1c**	4-F–C_6H_4	CH_3	55% (46%)	95:5	93.5:6.5	99:1
4	**1d**	2-Cl–C_6H_4	CH_3	50% (50%)	97:3	96.5:3.5	91:9
5[e]	**1e**	3-OMe-C_6H_4	CH_3	42% (36%)	>99:1	98.5:1.5	85:15
6	**1f**	4-CF_3–C_6H_4	CH_3	55% (45%)	96:4	96:4	89:11
7[f]	**1g**	4-CH_3–C_6H_4	CH_3	54% (36%)	80:20	82:18	76:24
8	**1h**	2-CH_3–C_6H_4	CH_3	55% (52%)	93:7	96:4	97:3
9	**1i**	2-F–C_6H_4	CH_3	55% (48%)	93:7	94:6	99:1
10[f,g,h]	**1j**	1-naphthyl	CH_3	53% (44%)	74:26	ND	92:8
11	**1k**	C_6H_5	CH_2=$CHCH_2$	54% (51%)	98:2	98:2	88:12
12	**1l**	C_6H_5	*n*-C_5H_{11}	54% (49%)	97:3	94:6	92:8
13[f,g,h]	**1m**	C_6H_5	$CH_2CH_2C_6H_5$	50% (45%)	89:11	88:12 (**2m**)	77:23
14[f,g,h]	**1n**	C_6H_5	C_6H_5	55% (52%)	60:40	84:16 (**2n**)/69:31 (**3n**)	60:40
15[f,g]	**1o**	C_6H_5	*t*-Bu	50% (46%)	80:20	72:28 (**2o**) /60:40 (**3o**)	70:30

[a]Based on GC yields of the unreacted substrate using undecane as internal standard (see SI). [b]Isolated yield after column chromatography. [c]Determined by crude NMR and/or GC analysis. [d]Determined by chiral HPLC. [e]Reaction was run at −30 °C for 1 h and then at 0 °C for 2 h. [f]3.0 mol % catalyst was used. [g]Reaction time was 90 min. [h]Reaction was run in $(CF_3)_2CHOH$ to improve solubility of substrate.

The absolute magnitudes as well as the relative difference in the association constants (K_{aR} vs K_{aS}) of the two enantiomers with the chiral catalyst are crucial in enabling the kinetic resolution. Implicit is the assumption that only the "bound" enantiomer will react, regardless of whether it is the stronger or the weaker bound enantiomer (scenarios where the stronger bound olefin enantiomer is stereoelectronically incapable of capturing the halenium ion cannot be ruled out at this stage). Given the excellent selectivity factors even at ambient temperatures, stoichiometric mixtures of the test substrate *rac*-**1a** and catalyst $(DHQD)_2PHAL$ were evaluated by ^1H NMR in CF_3CH_2OH in order to elucidate the nature of substrate-catalyst interactions that lead to differential reaction rates for the two enantiomers (Figure 2).[16] Most of the protons of *rac*-**1a** exhibited upfield shifts suggesting an intimate association of the substrate and the catalyst. Surprisingly, a clean formation of diastereomeric complexes (in a 1:1 ratio) was seen even at ambient temperatures. With enantiomerically pure (*R*)-**1a** and (*S*)-**1a**, diastereomerically pure complexes were seen, ruling out the possibility of nonenantiospecific fluxional processes on a NMR time scale (see Figure 2a). Diminished or no diastereotopicity was observed in other deuterated solvents such as $CDCl_3$, C_6D_6, acetone-d_6, and CD_3CN (see SI for spectra). It is perhaps not surprising that other solvents fare poorly as a reaction medium.

We postulate that the quinuclidine nitrogen atoms of the chiral catalyst ($pK_a \approx 10$) are protonated in CF_3CH_2OH (pK_a of CF_3CH_2OH = 12.5; mole ratio of catalyst/$CF_3CH_2OH \geq$ 1:25,000 for reactions and ~1:1,000 for NMR studies). This hypothesis is supported by NMR studies that reveal little change in the chemical shifts of the methylene and methine protons adjacent to the quinuclidine nitrogen atoms of the catalyst before and after addition of stoichiometric quantities (2.0 equiv) of benzoic acid (see right side column in Figure 2b; methine proton H_d shows negligible shift from 3.49 ppm to 3.52 ppm after catalyst protonation. Likewise, small downfield shift is seen for the methylene protons H_e). This behavior is in sharp contrast to that seen in $CDCl_3$, where H_d and H_e have distinct chemical shifts depending on the protonation state of the catalyst. Catalyst protonation leads to significant downfield shifts of H_d and H_e (H_d shifts from 3.39 ppm to 3.52 ppm; H_e protons shift from 2.60 to 2.80 ppm to 2.94–3.20 ppm, see $CDCl_3$ column in Figure 2b). Furthermore, the chemical shifts for H_d and H_e in CF_3CH_2OH *without* the benzoic acid additive are similar to those of the *protonated* catalyst in $CDCl_3$ (3.52 ppm for H_d and 2.94–3.20 ppm for H_e); also there is no further downfield shift in the presence of stoichiometric quantities of benzoic acid in CF_3CH_2OH. These results suggest that the catalyst is protonated in CF_3CH_2OH even without an external proton source. The protonation of the quinuclidine nitrogen atoms may cause a change in the conformation of the catalyst and allow for better substrate-catalyst interactions in CF_3CH_2OH as opposed to other solvents. Although significant, catalyst protonation cannot be the only role for CF_3CH_2OH, since mere incorporation of protic additives in different solvents does not recapitulate the results with CF_3CH_2OH. Besides its enhanced acidity, CF_3CH_2OH is a good hydrogen bond donor, a weak nucleophile, a noncoordinating counteranion, and also a highly polar solvent. The latter set of features is not easily duplicated with other solvent systems. In any event, the protonated catalyst can serve as a hydrogen bond donor to bind to the amide functional group (whereas the nonprotonated catalyst can only serve as a hydrogen bond acceptor). These NMR studies support the hypothesis that stereodiscrimination likely results from asymmetric *general acid catalysis* (i.e., hydrogen-bonding catalysis) by protonated $(DHQD)_2PHAL$ in CF_3CH_2OH, although a chiral Lewis-base assisted Bronsted acid catalysis (LBBA) by CF_3CH_2OH cannot be ruled out at this stage.[17]

dx.doi.org/10.1021/ja407241d | J. Am. Chem. Soc. 2013, 135, 14806–14813

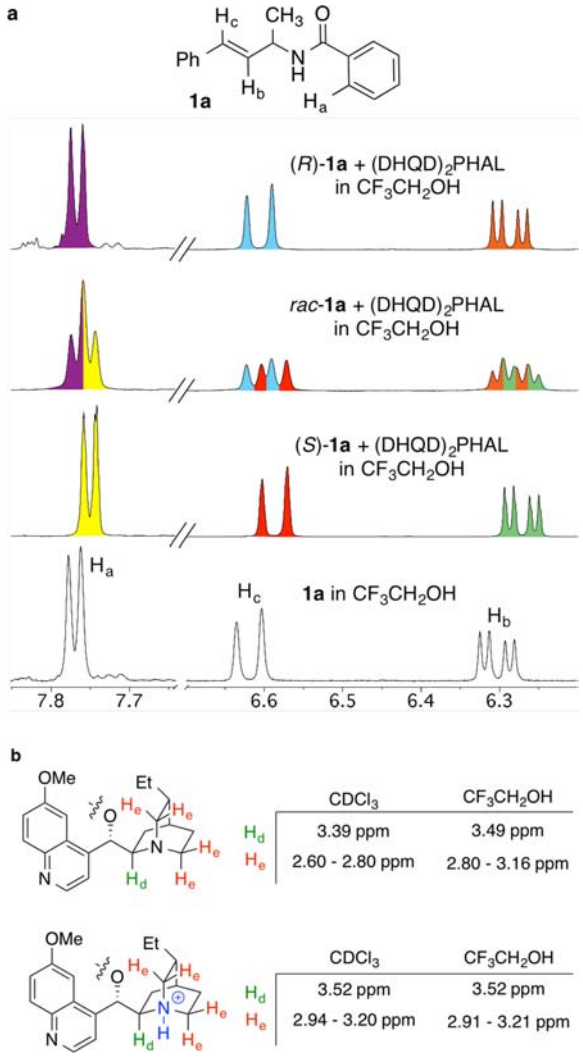


Figure 2. (a) Stoichiometric NMR studies of substrate-catalyst mixtures in CF_3CH_2OH at ambient temperature and 0.02 M concentration of substrate and catalyst: Both enantiomers bind to the chiral catalyst. (b) Diagnostic quinuclidine proton shifts of free and protonated catalyst in $CDCl_3$ and CF_3CH_2OH: Catalyst is likely protonated in CF_3CH_2OH even without acid additive.

Numerous characteristics of enzyme-type catalysis is evident—a remarkable selectivity for binding one enantiomer of the substrate, extensive preorganization of the substrate-catalyst-reagent triad leading to rapid reaction rates for the catalyzed process for the "matched" enantiomer and finally, exquisite levels of face selectivity in the delivery of the chlorenium ion on to the olefin functionality of the substrates. An in-depth analysis of the enthalpic and entropic drivers for this transformation is currently underway.

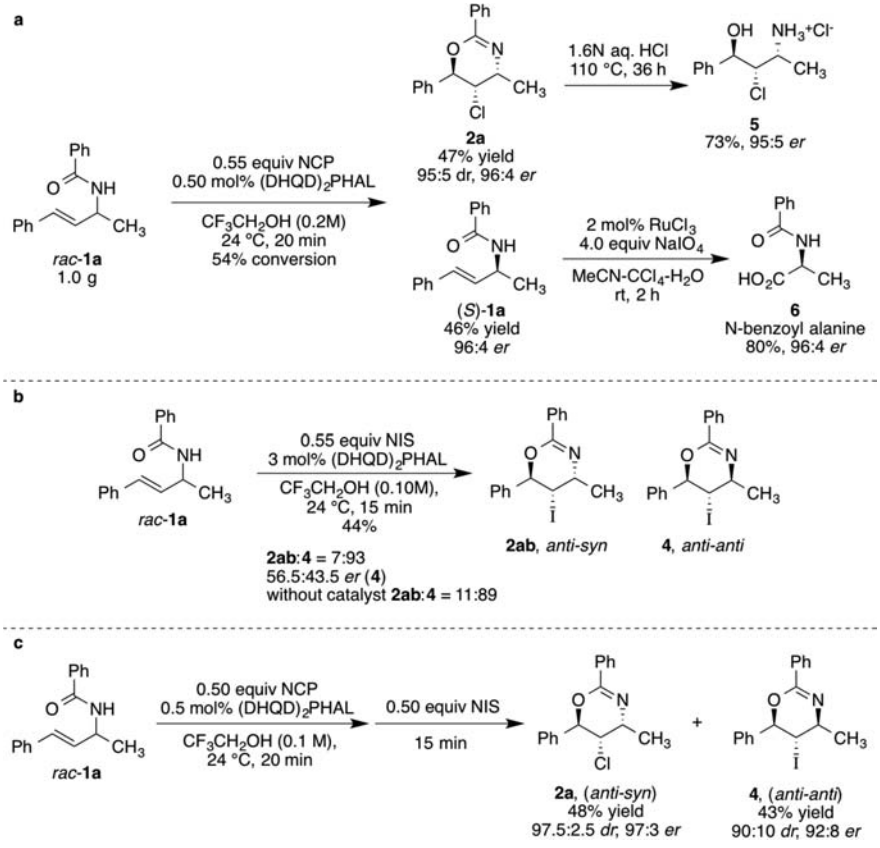
Features and Utility of the Resolution. A number of aspects of this kinetic resolution warrant emphasis. Kinetic resolutions are seldom used for the synthesis of the enantioenriched products (as opposed to the unreacted substrate in enantioenriched form). This is because K_{rel} values (selectivity factors) of ~50 are required to obtain products with >95:5 *er*s and in yields approaching 50%. For example, for a K_{rel} value of 10, the theoretical maximum *er* for the products even at conversions as low as 10% is only ~90:10. At 65% conversion for the same reaction, the unreacted substrate can be recovered in 97:3 *er* and 35% yield. The resolution presented here can lead to the formation of diastereomeric mixture of products. The excellent diastereo- and enantioselectivity for the cyclized products and recovered substrates at <1 mol % catalyst loading suggests that high selectivity factors are in operation in addition to exquisite face selectivity in the chlorenium delivery. In order to quantify the efficiency of the resolution, K_{rel} values were calculated for four of these reactions on the basis of the yields and *er*s of the cyclized products.[18] The resolution of substrate **1a** proceeded with a K_{rel} value of 113. Likewise, K_{rel} values of 89, 90, and 56 were calculated for substrates **1b**, **1l**, and **1k**, respectively. It must also be emphasized that conversions used in the calculations were based on *isolated yields* of the products on 2.0 mmol (~0.5 g) scale reactions, and therefore, the values obtained for K_{rel} represent the lower limits. As such, this kinetic resolution has the potential to *simultaneously* access the products and the substrates in highly enantioenriched form and at yields approaching 50% on a preparative scale.

Most of the reactions were rapid (~10 min) and run in open reaction vessels at up to 200 mM concentrations. The resolution is conveniently scaled to gram quantities with no detrimental effect on the *dr*s and *er*s (Scheme 2). The catalyst was found to be stable to the reaction conditions and was isolated using routine silica gel chromatography. The catalyst could be recycled up to three times with negligible loss in activity (catalyst recovery and recycling studies are detailed in the SI). Routine hydrolytic and oxidative transformations of the products and the unreacted substrates are shown in Scheme 2a. Acid hydrolysis of **2a** gave amino alcohol **5**. The oxidative cleavage of the recovered olefin (*S*)-**1a** gave protected alanine **6**. Taken together with the recyclability of the catalyst and solvent, this reaction paves the way for efficient, multigram scale synthesis of densely functionalized chiral building blocks.

Attempts to uncover analogous kinetic resolution phenomena in iodocyclization reactions of the racemic compounds led to intriguing results. While the resolution was inefficient, the cyclization exhibited a complementary diastereoselectivity to the chlorocyclization reaction and favored the formation of the anti-anti diastereomer in a 93:7 ratio (Scheme 2b).[19] The iodocyclized products **2ab** and **4** exhibited low enantioenrichment. Notably, unlike the chlorocyclization reaction, the noncatalyzed and catalyzed reactions exhibited similar levels of diastereoselectivity for the iodocyclization (see SI). The transformation was rapid; no significant rate acceleration or change in product distribution was observed even at up to 3 mol % catalyst loadings. Taken together with the complementary diastereoselectivity and negligible reagent control at ambient temperatures, a tandem one-pot kinetic resolution/diastereoselective iodocyclization cascade was conceptualized (Scheme 2c) that would allow for a 100% conversion of the racemic substrate into densely functionalized sterotriads. ***rac-1a*** was resolved via a chlorocyclization reaction under optimized reaction conditions; this was followed by the addition of 0.50 equiv of NIS in to the reaction vessel to initiate the diastereoselective iodocyclization of the enantioenriched substrate. This tandem protocol gave chlorocyclized product **2a** in 97.5:2.5 *dr* with the major anti-syn diastereomer being formed in 97:3 *er* and the iodocyclized product **4** in a 90:10 *dr* with the major anti-anti diastereomer being formed in a 92:8 *er* (Scheme 2c). Products **2a** and **4** were readily separable by column chromatography and were isolated in 48% and 43% yields, respectively.

dx.doi.org/10.1021/ja407241d | J. Am. Chem. Soc. 2013, 135, 14806−14813

Scheme 2. Synthetic Utility of the Kinetic Resolution[a]



[a](a) Gram-scale reaction and transformation of cyclized products and recovered substrate. (b) Diastereoselectivity of analogous iodocyclization reaction under catalyzed and non-catalyzed conditions. (c) Development of a one-pot kinetic resolution-diastereoselective iodocyclization reaction.

CONCLUSIONS

In summary, the first example of a highly diastereoselective kinetic resolution in a chlorofunctionalization reaction of olefins has been developed. Two distinct and highly stereoselective events mediated by the *same* catalyst are crucial to the success of this reaction. The catalyst not only ensures rate acceleration for one of the two enantiomers of a chiral substrate, but also serves to impart exceptional stereoselectivity in the alkene chlorination and cyclization events, resulting in stereotriad products with excellent relative and absolute stereocontrol starting from easily accessed racemic starting materials. Low catalyst loadings, ambient reaction temperatures, open reaction vessels, short reaction times, and recyclability of the catalyst are some of the features of this chemistry. The K_{rel} values for many substrates are sufficiently high to permit the use of the resolution protocol for the simultaneous synthesis of products and substrates in highly enantioenriched form. NMR studies have uncovered a substrate-catalyst hydrogen-bonding interaction as a potentially key molecular recognition event in enabling the resolution; these studies have also hinted at the transformation of a chiral Lewis base catalyst into a hydrogen-bonding catalyst in CF_3CH_2OH, thereby opening the doors to hitherto unknown modes of activation for this class of catalyst. The results serve as a starting point for detailed mechanistic studies. Efforts to further improve the scope and utility of this transformation and its application in natural products' syntheses are currently being pursued.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, optimization, and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

babak@chemistry.msu.edu

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was funded by NSF Grant CHE-0957462. The authors thank the MSU mass spectrometry facility for HR-MS analyses. Ms. Yanmen Yang and Dr. Daniel Holmes are acknowledged for experimental assistance and NMR assistance respectively. A.J. thanks the College of Natural Sciences at MSU for the Tracy Hammer graduate student award. A.J. was a Harold Hart Endowed Fellow in the Chemical Sciences at MSU during the commencement of this project (June–September 2012).

REFERENCES

(1) (a) Gao, J.; Ma, S.; Major, D. T.; Nam, K.; Pu, J.; Truhlar, D. G. *Chem. Rev.* **2006**, *106*, 3188. (b) Warshel, A.; Sharma, P. K.; Kato, M.; Xiang, Y.; Liu, H.; Olsson, M. H. M. *Chem. Rev.* **2006**, *106*, 3210.

(2) For a review of enzymatic and biomimetic polyene cascades leading to terpene skeletons, see: (a) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730. For application of cascade reactions in natural product synthesis, see: (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(3) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20678.

(4) (a) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613. (b) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407.

(5) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.

(6) (a) Castellanos, A.; Fletcher, S. P. *Chem.—Eur. J.* **2011**, *17*, 5766. (b) Chen, G.; Ma, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8306. (c) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938. (d) Hennecke, U. *Chem. Asian J.* **2012**, *7*, 456. (e) Murai, K.; Fujioka, H. *Heterocycles* **2013**, *87*, 763.

(7) (a) Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2593. (b) Garzan, A.; Jaganathan, A.; Salehi Marzijarani, N.; Yousefi, R.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. *Chem.—Eur. J.* **2013**, *19*, 9015. (c) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298.

(8) (a) Chen, J.; Zhou, L.; Yeung, Y.-Y. *Org. Biomol. Chem.* **2012**, *10*, 3808. (b) Chen, Z.-M.; Zhang, Q.-W.; Chen, Z.-H.; Li, H.; Tu, Y.-Q.; Zhang, F.-M.; Tian, J.-M. *J. Am. Chem. Soc.* **2011**, *133*, 8818. (c) Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256. (d) Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068. (e) Fang, C.; Paull, D. H.; Hethcox, J. C.; Shugrue, C. R.; Martin, S. F. *Org. Lett.* **2012**, *14*, 6290. (f) Haas, J.; Bissmire, S.; Wirth, T. *Chem.—Eur. J.* **2005**, *11*, 5777. (g) Hennecke, U.; Muller, C. H.; Frohlich, R. *Org. Lett.* **2011**, *13*, 860. (h) Huang, D.; Wang, H.; Xue, F.; Guan, H.; Li, L.; Peng, X.; Shi, Y. *Org. Lett.* **2011**, *13*, 6350. (i) Jiang, X.; Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 7771. (j) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748. (k) Kwon, H. Y.; Park, C. M.; Lee, S. B.; Youn, J.-H.; Kang, S. H. *Chem.—Eur. J.* **2008**, *14*, 1023. (l) Li, H.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, Q.-W.; Chen, Z.-M.; Chen, Z.-H.; Li, J. *Chem. Sci.* **2011**, *2*, 1839. (m) Lozano, O.; Blessley, G.; del Campo, T. M.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 8105. (n) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174. (o) Murai, K.; Nakamura, A.; Matsushita, T.; Shimura, M.; Fujioka, H. *Chem.—Eur. J.* **2012**, *18*, 8448. (p) Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134. (q) Paull, D. H.; Fang, C.; Donald, J. R.; Pansick, A. D.; Martin, S. F. *J. Am. Chem. Soc.* **2012**, *134*, 11128. (r) Phipps, R. J.; Hiramatsu, K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 8376. (s) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (t) Tan, C. K.; Le, C.; Yeung, Y.-Y. *Chem. Commun.* **2012**, *48*, 5793. (u) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 2738. (v) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (w) Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 12928. (x) Wilking, M.; Muck-Lichtenfeld, C.; Daniliuc, C. G.; Hennecke, U. *J. Am. Chem. Soc.* **2013**, *135*, 8133. (y) Zhang, W.; Liu, N.; Schienebeck, C. M.; Decloux, K.; Zheng, S.; Werness, J. B.; Tang, W. *Chem.—Eur. J.* **2012**, *18*, 7296. (z) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (aa) Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 9164. (ab) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474.

(9) (a) Ohta, B. K.; Hough, R. E.; Schubert, J. W. *Org. Lett.* **2007**, *9*, 2317. (b) Olah, G. A.; Bollinger, M. *J. Am. Chem. Soc.* **1968**, *90*, 947. (c) Olah, G. A.; Bollinger, M.; Brinich, J. *J. Am. Chem. Soc.* **1968**, *90*, 6988. (d) Olah, G. A.; Peterson, P. E. *J. Am. Chem. Soc.* **1968**, *90*, 4675. (e) Olah, G. A.; Westerman, P. W.; Melby, E. G.; Mo, Y. K. *J. Am. Chem. Soc.* **1974**, *96*, 3565. (f) Solling, T. I.; Radom, L. *Int. J. Mass Spectrom.* **1999**, *185*, 263.

(10) Unpublished mechanistic studies of the analogous chlorolactonization reaction have uncovered strong evidence for the intermediacy of β-chlorocarbenium ions as intermediates in this chemistry.

(11) (a) Corey, E. J.; Noe, M. C.; Guzman-Perez, A. *J. Am. Chem. Soc.* **1995**, *117*, 10817. (b) Yun, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 767. (c) Brimble, M. A.; Johnston, A. D. *Tetrahedron-Asymmetry* **1997**, *8*, 1661. (d) Xing, X.; Zhao, Y.; Xu, C.; Zhao, X.; Wang, D. Z. *Tetrahedron* **2012**, *68*, 7288.

(12) Ikeuchi, K.; Ido, S.; Yoshimura, S.; Asakawa, T.; Inai, M.; Hamashima, Y.; Kan, T. *Org. Lett.* **2012**, *14*, 6016.

(13) (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155.

(14) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20655.

(15) The absolute stereochemistry of **2a** and **3a** was determined by single crystal X-ray diffraction (CCDC 948806–948807 are the corresponding Cambridge Structural Database deposition numbers for the crystal structures of **2a** and **3a**).

(16) No-D ^{1}H NMR were run in CF_3CH_2OH using gradient shimming and solvent suppression; see SI for details.

(17) For a leading reference of chiral Lewis base assisted Bronsted acid catalysis, see: Sakakura, A.; Sakuma, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 3130.

(18) A straightforward calculation of selectivity factors is precluded by the formation of a diastereomeric mixture of products; although such calculations have been used previously for analogous kinetic resolutions, they may lead to significant errors if contributions of the minor diastereomer are ignored or when diastereoselectivities are not very high. See SI for a brief discussion and calculation of K_{rel} values for selected transformations.

(19) The bromocyclization reaction with NBS had a 57:43 diastereoselectivity marginally favoring the anti-syn diastereomer.