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Enantiocontrol over Acyclic Quaternary Stereocenters by Acylative Organocatalyzed Kinetic Resolution

Xueyang Liu,^[a] Jean-Marc Pons,^[a] Valérie Monnier,^[b] Laurence Charles,^[c] Adrien Quintard,^{*[a]} and Cyril Bressy^{*[a]}

In the present paper, we described the efficient enantioselective kinetic resolution (KR) of racemic diastereocontrolled secondary alcohols bearing a quaternary stereocenter using a commercially available chiral isothiourea organocatalyst. This method-

ology is a general KR leading to the enantiocontrol of acyclic quaternary stereocenter with high levels of stereoselectivity (s up to 185) on a large scope. The hydroxyl function can easily serve as a traceless group by oxidation or reduction process.

Introduction

Although organic synthesis dedicated to the elaboration of a broad range of structural motifs has evolved to maturity, preparing enantiopure molecules possessing an acyclic all-carbon stereocenter still represents a daunting challenge.^[1,2] The prevalence of this motif in numerous natural products and drugs requires the continuous identification of selective approaches for its elaboration. The four different carbon substituents around the carbon atom minimize the reactivity through a strong steric congestion while complexifying all recognition processes necessary to obtain a single enantiomer. Classically, (all-carbon) quaternary stereocenters are prepared through enantioselective methods creating the new carbon-carbon bond (Figure 1a).^[1] However, defining the incoming reagent approach during the transition state requires the appropriate discrimination between likely close carbon substituents, a fine balance between reactivity and selectivity often resulting in the narrowing of the scope. Alternatively, desymmetrization by discriminating two enantiotopic positions of a prochiral substrate bearing a pre-existing quaternary center avoids the issues associated with the difficult creation of the quaternary center during the enantioselective step (Figure 1a).^[3] The resulting scope is complementary but limited to compounds bearing two closely related substituents arising from the desymmetrization.

Surprisingly, an alternative approach based on a kinetic resolution (KR) of racemic molecules^[4] possessing a pre-installed

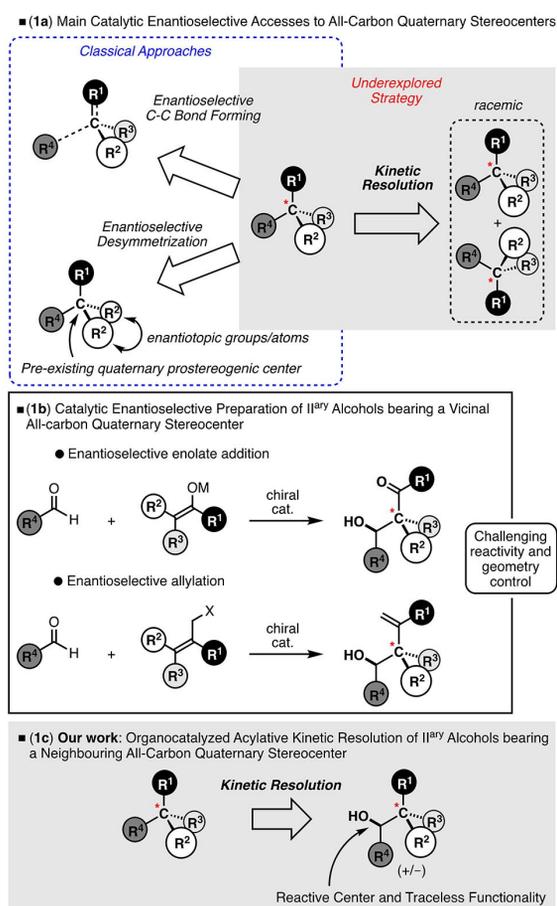


Figure 1. Different approaches towards enantioenriched quaternary stereocenters.

quaternary center is underexplored (highlighted in grey, Figure 1a). Since racemic quaternary centers are by far easier to prepare, this could avoid the reactivity issues associated with the enantioselective carbon-carbon bond formation. However, aside from some enzymatic processes,^[5] to the best of our

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knowledge, only few isolated catalytic methods have been developed until now with limited success and generality.^[6] These catalytic KR concerned cyclization processes or transformation of cyclic substrates and in sharp contrast, the challenging acyclic series have been neglected. The limited number and the lack of generality of KR studies lead us to investigate this synthetic challenge focusing on the reactivity in the acyclic series.

The absence of efficient KR of acyclic quaternary stereocenters lies in the difficulty to effectively discriminate between different carbon substituents. As a result, discovering a general strategy enabling the enantioselective preparation of quaternary stereocenter through kinetic resolution is highly desirable. For this purpose, we propose a new approach for the kinetic resolution of acyclic racemic substrates bearing all-carbon quaternary centers based on the selective recognition at the contiguous position.

Among quaternary stereocenters, those bearing a vicinal secondary alcohol are ubiquitous in many different natural products. Enantioselective synthesis of this acyclic fragment can be based on different classical methods.^[7] For example, one can envision aldolization through condensation of ketones on aldehydes (Figure 1b).^[8] However, the difficulty to selectively generate an enolate of appropriate geometry considerably limits the efficiency of this approach.^[9] The most common alternative relies on enantioselective allylation (Figure 1b).^[10] Nonetheless, as for aldolization, both steric requirement and geometry control considerably limit the potential of these transformations. In sharp contrast, a broad range of highly diastereoselective methods exists in order to efficiently prepare racemic quaternary stereocenters possessing a vicinal secondary alcohol, as popularized notably by the groups of Denmark, Knochel, Marek or Krische.^[11] Most notably, these transformations enable to generate even quaternary stereocenter bearing sterically closely related substituents (e.g., Me, Et and *n*-Pr on the same carbon).^[11c] As a result, developing an efficient KR of these substrates could provide a general approach to a broad range of otherwise impossible to access enantioenriched key frameworks. Herein, we report the results at developing an efficient KR of such alcohols (Figure 1c). The system is based on selective organocatalytic acylation of the secondary alcohol,^[12] where the selective recognition between the hindered quaternary center and the alcohol substituent on the other side (R⁴), is responsible for the excellent overall selectivity. This study demonstrates all the power of KR to complement known enantioselective approaches for the control of all-carbon quaternary stereocenters. While we were completing our study, the group of Xu and Fang reported a closely related approach for the synthesis of challenging tertiary alcohols and quaternary stereocenters.^[13] Our complementary study enables to further increase the scope of these indirect Kinetic Resolutions.

Results and Discussion.

To confirm the possibility of a good kinetic resolution on such scaffolds, we first focused on the reactivity of alcohol **1a**

prepared using Knochel's method (Table 1). For this purpose, different chiral isothioureas were screened using propionic anhydride as the acylating reagent and *i*-PrNEt₂ as organic base.^[14] Using these conditions, tetramisole (TM, **Cat1**) or benzotetramizole^[15] (BTM, **Cat2**), only provided less than 15% conversion to the ester **2a**, highlighting the challenge of performing the acylation in such an overcrowded environment (entries 1–2). However, despite this low reactivity, an *s* value of 26–27 was obtained, demonstrating an excellent enantiomeric recognition by these chiral catalysts. Moving to homobenzotetramizole^[16] (HBTM, **Cat3**) considerably improved the reactivity albeit at the expense of the selectivity (32% conv, *s* = 11, entry 3). In sharp contrast, using Hyper-BTM^[17] (**Cat4**) considerably improved the selectivity while keeping a high reactivity (conv = 39%, *s* = 42, entry 4). While using sterically demanding isobutyric anhydride suppressed the reactivity (entry 5), acetic anhydride slightly improved both conversion and selectivity (conv = 40%, *s* = 56, entry 6). Among the different solvents tested (entries 7–10), we found that the best balance between reactivity and selectivity was found in *t*-AmOH providing an excellent 50% conversion with a *s* value of 56 (entry 11). The improvement observed might be due to a better

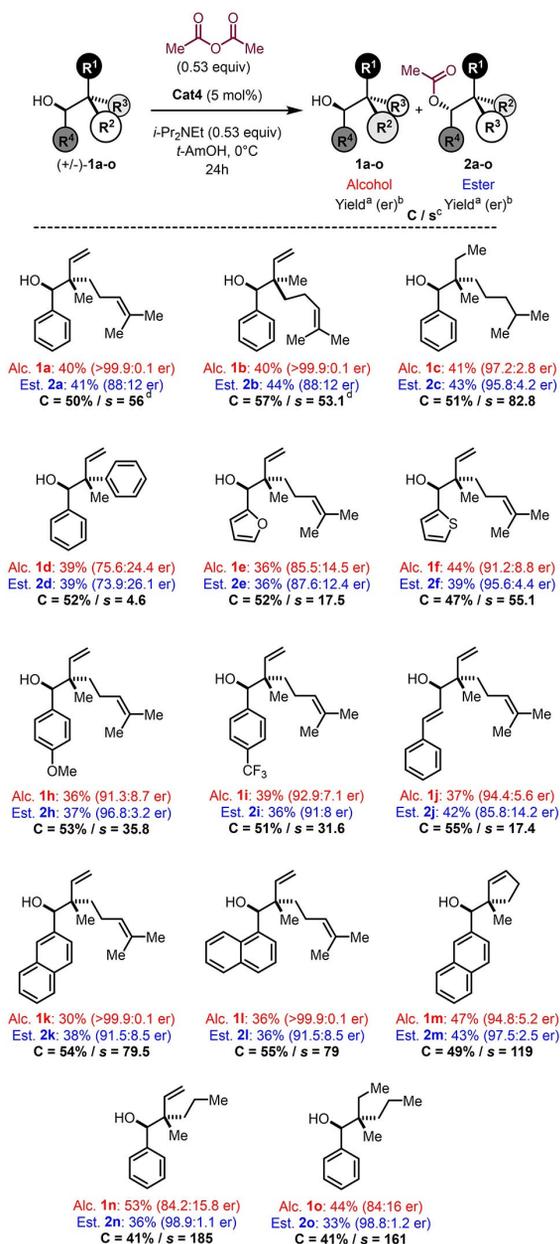
Table 1. Optimization of the KR.^[a]

Entry	Cat [x mol %]	Solvent	T [°C], time [h]	R	C ^[a]	<i>s</i> ^[b]
1	Cat1 (10)	CH ₂ Cl ₂	0 °C, 3 h	Et	15%	27 ^[c]
2	Cat2 (10)	CH ₂ Cl ₂	0 °C, 3 h	Et	11%	26 ^[c]
3	Cat3 (10)	CH ₂ Cl ₂	0 °C, 3 h	Et	32%	11
4	Cat4 (5)	CH ₂ Cl ₂	0 °C, 3 h	Et	39%	42
5	Cat4 (5)	CH ₂ Cl ₂	0 °C, 3 h	<i>i</i> -Pr	< 5%	nd
6	Cat4 (5)	CH ₂ Cl ₂	0 °C, 3 h	Me	40%	56
7	Cat4 (5)	EtOAc	0 °C, 3 h	Me	40%	84
8	Cat4 (5)	THF	0 °C, 3 h	Me	38%	160
9	Cat4 (5)	<i>t</i> -AmOH	0 °C, 3 h	Me	20%	230
10	Cat4 (5)	<i>t</i> -AmOH	0 °C, 24 h	Me	45%	85
11 ^[d]	Cat4 (5)	<i>t</i>-AmOH	0 °C, 24 h	Me	50%	56

[a] Reactions run by using 0.53 equiv. of anhydride. [b] Determined using Kagan's equations: $C = ee_{\text{substrate}} / (ee_{\text{substrate}} + ee_{\text{product}})$ and $s = (\ln(1 - C(1 + ee_{\text{product}}))) / (\ln(1 - C(1 - ee_{\text{product}})))$. [c] Opposite enantiomer obtained. [d] Use of 0.6 equiv. of anhydride.

solubilization of the different reaction components as well as potential hydrogen bonding interactions in the transition state.^[18]

With these optimized conditions in hand, the kinetic resolution was performed on a broad range of different substrates (Scheme 1). Alcohol **1b**, diastereomer of **1a**, was prepared and evaluated in the KR process affording a similar *s* value. This result highlights that the stereochemistry of the bulky quaternary center has a limited impact on the selectivity



Scheme 1. Scope of the Kinetic Resolution. ^a Isolated yields; ^b Determined by HPLC on chiral stationary phase; ^c Calculated with Kagan's equations (Ref [4a]); ^d Using 0.6 equiv. of anhydride and 0.6 equiv. of *i*-Pr₂NEt.

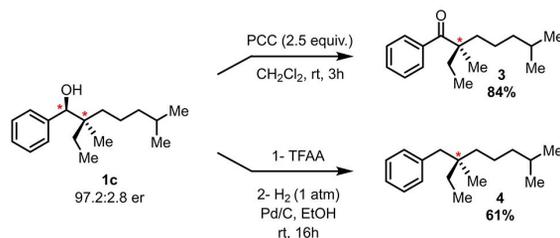
of the acylative KR. The *s* value was improved with alcohol **1c** bearing no unsaturation on the side chains. This increase in selectivity for **1c** is due to the absence of competing secondary interactions with the π -systems present on the quaternary stereocenter side chains in **1a**. Accordingly, introducing a phenyl group as substituent on the quaternary stereocenter led to poor selectivity probably due to a difficulty to discriminate both sides of the secondary alcohol able to create π -interactions with the catalyst. Then we explored, with compounds **1e-l**, the influence of the aromatic moiety which is crucial in the recognition phenomena by the catalyst. The influence of heteroaromatic substituents was evaluated with 2-furyl and 2-thienyl groups.

Lower selectivity was obtained with furane derivative **1e** (*s* value of 17.5) than with thiophene derivative **1f** which led to a *s* value similar to one obtained with the phenyl group. Electron-donating and electron-withdrawing functionalities on a phenyl group gave comparable results with a *s* value around 35 using alcohols **1h** or **1i**. Styrenyl substituent, known to have a limited recognition with isothiourea, was incorporated on allylic alcohol **1j** and led to a moderated *s* value of 17.5. Extended polyaromatic such as naphthalenyl groups (**1k** & **1l**) provided an excellent recognition leading to high *s* value close to 80. Alcohol **1m** bearing a quaternary stereocenter incorporated in a cyclic framework was examined and provided an excellent *s* value of 119. Finally, with challenging substrates bearing closely related quaternary stereocenter substituents such as alcohols **1n** (*n*-Pr vs Me vs vinyl) and **1o** (*n*-Pr vs Me vs Et), the highest *s* values were obtained reaching up to 185.

With a broad scope of enantioenriched complex scaffolds in hand, we explored the possibility of derivatizing the alcohol function in a traceless synthesis of quaternary stereocenters (Scheme 2). Oxidation of secondary alcohol **1c** afforded ketone **3** in 84% yield bearing only the all-carbon quaternary stereocenter as stereogenic element. Most interestingly, reduction of the benzylic hydroxyl group was also performed under standard conditions^[19] leading, in 61% yield, to the corresponding arene **4**, bearing a saturated sidechain.

Conclusion

In conclusion, we successfully developed an alternative and general method for the generation of compounds bearing all-



Scheme 2. Post-functionalizations of alcohol **1c**.

carbon quaternary stereocenters with high levels of enantiocontrols. This methodology is based on an organocatalyzed kinetic resolution of sterically hindered adjacent secondary alcohols. The proximity of the bulky quaternary center reduces the reactivity of the hydroxyl function, but excellent results were obtained using a small anhydride such as acetic anhydride in combination with the commercially available chiral isothiourea Hyper-BTM. High levels of enantioselectivity with *s* value up to over 185 were reached on a broad scope of acyclic substrates. Additionally, the traceless alcohol group was transformed by oxidation or reduction in challenging molecules possessing only an all-carbon quaternary stereocenter as controlled stereogenic element. We think that this general methodology can, in numerous cases, solve the challenge of the enantiocontrolled access to acyclic molecules bearing an all-carbon quaternary stereocenter.

Experimental section

Kinetic resolution general procedure

To a solution of the racemic alcohol **1a** (60 mg, 0.25 mmol, 1 equiv.) in anhydrous solvent (1 ml), isothiourea (1 mol%) was added and the mixture was placed under argon atmosphere at room temperature. DIPEA (0.53 equiv.) was added dropwise, and the mixture was stirred at room temperature for 10 min. The solution was placed at 0 °C, acetic anhydride (12.3 mg, 0.13 mmol, 0.53 equiv.) was added dropwise and the mixture was stirred at this temperature for 24 h. The reaction was quenched with MeOH (1 mL) and stirred for an additional 10 minutes. After rising to room temperature, a solution of saturated NaHCO₃ (2.5 mL) was added. The reaction mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried with MgSO₄, filtered, and concentrated in vacuo to give the crude reaction mixture. Flash chromatographic purification (PE/EtOAc 100/0 to 90/10) gave the desired isolated alcohols and esters, and these products were then analyzed by chiral HPLC.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alcohols · Isothiourea · Kinetic resolution · Organocatalysis · Quaternary stereocenters

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