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Chiral Brønsted Acid Catalyzed Kinetic Resolutions

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Abstract

The synthesis of enantioenriched small molecules is an ongoing goal of organic chemists. This focus review explores the use of kinetic resolutions catalyzed by chiral Brønsted acids. Methods include classic kinetic resolutions and dynamic kinetic resolutions. The small molecules obtained are potentially valuable intermediates in the synthesis of biologically important compounds.

Graphical abstract

Keywords

Brønsted acid; kinetic resolution; asymmetric; enantioselective; organocatalytic

1. Introduction

The development of methods for the asymmetric synthesis of organic compounds is an area of constant need in organic chemistry. Kinetic resolutions offer an attractive method for the

synthesis of highly enantioenriched molecules. The use of chiral Brønsted acids in asymmetric reactions has grown exponentially over the past 10 years. This review focuses on kinetic resolutions that are catalyzed by chiral Brønsted acids.

1.1. Chiral Brønsted Acids

Chiral Brønsted acids can be divided into two categories: 1) neutral hydrogen-bonding catalysts, or 2) stronger acids (Figure 1). This review will focus on stronger acids such as phosphoric acid based compounds. These small organic molecules typically serve to activate C=X bonds for nucleophilic attack by lowering the LUMO energy. In general, Brønsted acids are more stable to air or water than Lewis acids and thus more amenable to less rigorous conditions and larger scales. The available scaffolds are highly tunable for electronic and steric factors. Many informative reviews have examined different chiral Brønsted acid scaffolds, and this focused review seeks to not duplicate those examples.^[1]

1.2. Kinetic Resolutions

Kinetic resolutions (KR) are an important tool in the synthetic chemist's arsenal for the synthesis of enantioenriched molecules (Scheme 1).^[2] In a classical kinetic resolution (KR), a racemic substrate ((±)-SM) is allowed to react in the presence of a chiral reagent or catalyst. Activation of the SM by the chiral compound generates two diastereomeric transition states and effectively lowers the activation energy for the reaction for one of the enantiomers. If the difference in rates is great enough, the fast reacting enantiomer will go on to form enantioenriched product (P_S) and the slow reacting enantiomer can be recovered as unreacted starting material (SM_R). While two enantioenriched compounds can be isolated from the reaction with a possible 100% mass recovery, because there is only 50% of each enantiomer at the start, the maximum yield of either SM or P is 50%. Alternatively, if the starting material undergoes a rapid racemization ($k_{\text{inv}}/k_{\text{inv}}^{-1}$) it is possible to push the reaction to give one enantiomer of product with a theoretical yield of 100%. This variation on classical kinetic resolution is termed dynamic kinetic resolution (DKR).^[3]

Over the progress of a kinetic resolution reaction, the enantiopurity of recovered starting material increases and that of the product decreases. As such, in order to compare kinetic resolutions it is often useful to look at the difference between the rate of reaction of the fast reacting enantiomer over the slow reaction enantiomer ($k_{\text{rel}} = k_{\text{fast}}/k_{\text{slow}}$). If the reaction is first order in substrate, one can utilize the equations developed by Kagan and Fiaud which correlates conversion (c) and the ee of the recovered starting material (ee_{SM}) to k_{rel} or the selectivity factor, s (Figure 2).^[4]

2. Synthetic Uses

2.1. Brønsted Acid Catalyzed Kinetic Resolution of Alcohols

Alcohols are ideal substrates for kinetic resolutions. They are often readily obtained as racemates and can be easily modified via a plethora of reactions.

2.1.1 Etherification or Acetalization of Alcohols—The first type of kinetic resolution of alcohols covered, involve KR through formation of an ether or acetal.

ori, Müller, and List developed a highly enantioselective kinetic resolution of homoaldol acetals via an intramolecular transacetalization. (Scheme 2).^[5] Racemic homoaldol acetals ($\pm$)-**6** were prepared from Grignard addition to the corresponding aldehyde or ketone. Brønsted acid **8**, or (*S*)-STRIP, with a 1,1' spirobiindane backbone was shown to most efficiently catalyze the cyclization of one enantiomer of ($\pm$)-**6** to acetal **7-cis**. Fortuitously, any cyclization of the other enantiomer leads to the opposite diastereomer of the cyclic acetal, **7-trans**. This partial parallel kinetic resolution leads to high yields of enantiomerically enriched acetal **7-cis** and good recovery of starting alcohol **6** in high enantiopurity. The methodology works well for both secondary (12 examples) and tertiary (6 examples) alcohols. Selectivity factors that would be required to achieve similar results in classical kinetic resolutions would be >90 for most examples.

To highlight their methodology, the authors used the reaction to prepare both enantiomers of the natural product boivinianin A, (**9**) (Scheme 3).^[6] Jones oxidation of both cyclic acetal **7a** and homoaldol acetal **6a** led to (+)- and (–)-**9** with no loss in enantiopurity. The methodology could be used on preparative scale (1.0 mmol) and catalyst load could be lowered to 0.1 mol% with minimal procedural changes and loss of enantiopurity.

Enantioenriched 1,2,4-trioxanes **12** were prepared via a Brønsted acid catalyzed cascade reaction (Scheme 4).^[7] Acetalization of *p*-peroxyquinols **10** with aldehydes **11** led to racemic peroxyhemiacetals ($\pm$)-**13** which underwent an oxa-Michael reaction to yield trioxanes **12** in excellent yield and enantioselectivity. Brønsted acid **8**, is utilized along with a thiourea cocatalyst **14**. The authors propose that the reaction proceeds via a dynamic kinetic resolution of the intermediate ($\pm$)-**13**. Trioxane products showed modest anticancer activity against a number of cancer cell lines.

A new class of Brønsted acids based on a C_2 -symmetric imidodiphosphoric acid motif was developed for the asymmetric cyclization of hydroxyenol acetals (Scheme 5).^[8] This new catalyst **17a** provides a more confined space such that racemic alcohol ($\pm$)-**15** at 50% conversion provided spirocycle **11** in 35% isolated yield and 95% ee (>50:1 dr) and recovered alcohol (*R*)-**10** in 43% isolated yield and 94% ee (this corresponds to a selectivity factor of 115).

Recently, List and colleagues reported another kinetic resolution utilizing chiral imidodiphosphoric acids **17b** and **17c** (Scheme 6).^[9] Here, diols ($\pm$)-**18** with a tertiary stereocenter underwent an asymmetric acetalization with aldehyde **19** to yield acetals **20** with good diastereoselectivity and recovered enantioenriched alcohols **18**. Selectivities factors were best (up to 389) when R^1 = aryl, n = 1, and aldehydes with bulk at the β -carbon where used. An oxocarbenium intermediate where the tertiary alcohol and the aldehyde form hydrogen bonds to the chiral imidodiphosphate anion and the aldehyde alkyl chain and larger alcohol substituent take pseudoequatorial positions in a 5 membered ring transition state (complex **I**) is evoked to explain the *cis* relationship of the acetal products.

A novel kinetic resolution of alcohols via an S_N2 -type alkylation mechanism was recently reported (Scheme 7).^[10] Here, (*S*)-TRIP (**23**) was shown to catalyze the intramolecular cyclization of alcohols containing a secondary benzylic ether such as ($\pm$)-**21**. Of the 12

examples given, the reaction was most selective when tertiary homobenzylic alcohols were used (benzene ring intact and $R^2 = H$, $s = 142$). Substrates without the aromatic tether were also competent in the reaction, although sometimes required higher temperatures (up to 120 °C).

An S_N2 -type mechanism is supported by both experimental and computational evidence (Scheme 8). When enantioenriched ether **21a** is cyclized using an achiral acid catalyst inversion of the stereocenter is observed. Computational studies suggest that the Brønsted acid acts as a bifunctional activator and the mechanism exhibits classical S_N2 behaviour.

Chiral phosphoric acid **23** has recently been shown to catalyze the asymmetric cyclization of *trans*-(±)-**24** via a kinetic resolution (Scheme 9).^[11] On a 100 mg scale, 32% yield of recovered *trans*-(+)-**24** was obtained in 97% optical purity. Cyclization of *trans*-(+)-**24** with trifluoroacetic acid followed by deprotection of silyl ethers gave the natural product (+)-sacidumlignan D (**26**) in 87% yield.

Terada and co-workers developed a kinetic resolution of amino alcohols via an intermolecular acetalization utilizing Brønsted acid **30** (Scheme 10).^[12] Utilizing acid (±)-**27** and enol ether **28** in ethyl acetate at 0.2M, the authors were able to form the thermodynamically more stable acetal **29** essentially irreversibly leading to recovery of enantioenriched starting material. For secondary alcohols, s values were enhanced by increasing the sterics on R^1 (for $R^1 = iPr$, $s = 11$ and for $R^1 = C(CH_3)_2OTBS$, $s = 460$). Tertiary alcohol **27a** was seen to show a decrease in s value ($s = 11$) and of the two diastereomers **27b** and **27c**, the *syn* was found to be more selective than the *trans* ($s = 17$ versus $s = 2.4$). The authors postulate a hydrogen bond between the N-H and the oxygen atom of the hydroxyl group, a hypothesis which is supported by the control experiment with **27d** where when the H is replaced with a methyl and the selectivity factor drops to 1.5.

2.1.2. Esterification of Alcohols—Esterification of alcohols to yield enantioenriched products is the second type of KR examined.

The kinetic resolution of secondary alcohols through acetylation was recently described by Mandai, Suga and coworkers (Scheme 11).^[13] The procedure utilized a combination of (*S*)-TRIP (**23**), DABCO, and acetyl chloride. The authors highlight the methodology with 8 examples, including alcohols containing aromatic, vinyl and propargyl groups with selectivity factors ranging from 11–105. While the mechanism was not formally probed for this heterogeneous reaction, a dicationic intermediate (**33** or **34**) with a chiral phosphate counter ion is suggested to be the active intermediate.

The kinetic resolution of *cis*-2-substituted cyclic alcohols (±)-**35** was accomplished through acylation with isobutyric anhydride, **36** (Scheme 12).^[14] The electronically tuned TRIP-based phosphoric acid (*R*)-**38** containing 6,6' nitro groups with stronger acidity was found to be most effective in the reaction. *cis*-2-Arylcyclohexanols (±)-**35a** were good substrates for the resolution, with selectivity factors between 116–215. Small ringed cyclopentanols (±)-**35b** lost some selectivity ($s = 55$) as did moving to *trans*-substituted alcohols (±)-**35f** ($s = 39$) or uncyclic substrates (±)-**35g** ($s = 23$).

The authors provide mechanistic support for a dual activation mode of the phosphoric acid via activation of the anhydride through protonation coupled with enhancement of the nucleophilicity of the alcohol through coordination with the basic P=O. Formation of a mixed anhydride with the phosphoric acid was ruled out via NMR and the calculated lowest energy transition state corresponded to the proposed dual activation model (Figure 3).

We recently reported an asymmetric synthesis of α -substituted γ -hydroxy esters ($\pm$)-**39** through a Brønsted acid catalyzed kinetic resolution with TRIP (**23**) (Scheme 13).^[15] This intramolecular transesterification was effective for substrates with small substituents at the α -position (such as $R^1 = \text{CH}_3$ and $R^2 = \text{H}$, $s = 20$) and when forming an all-carbon quaternary stereocenter ($R^1 = \text{CH}_3$ and $R^2 = \text{Ph}$, $s = 16.7$).

Alcohol (–)-**39a**, which could be prepared on a synthetically useful scale using this methodology (102 mg in 34% yield and 93% ee), was shown to be a versatile synthetic intermediate and readily underwent a variety of transformations (Scheme 14). The small building block products were prepared in good yields with minimal to no loss of enantiopurity.

We next explored the kinetic resolution of hydroxy esters with multiple stereocenters using the same conditions optimized for the simpler substrates (see Scheme 15 for examples).^[16] With the exception of ($\pm$)-**45**, most linear substrates were not competent in the reaction-only yielding selectivity factors <3 (**46–49**). Cyclic substrates, on the other hand, generally performed well under the reaction conditions (**49–51**, selectivity factors between 10–16). Computational studies were shown to favour a dicoordination pathway for the reaction (complex **II**). In this model, the acidic H of the phosphoric acid complexes to the carbonyl oxygen of the ester and the Lewis basic oxygen of the phosphoric acid activates the hydroxyl group.

2.2. Brønsted Acid Catalyzed Kinetic Resolution of Axially Chiral Compounds

Axially chiral biaryls are important structures in biologically active natural products and ligand scaffolds.^[17] However, the synthesis of these compounds is often challenging. Kinetic resolutions are a useful strategy that complement other methods.^[18]

The enantioselective synthesis of multisubstituted biaryls was recently reported by Akiyama and co-workers utilizing a combined desymmetrization/kinetic resolution strategy (Scheme 16).^[19] Monobromination of C_s -symmetric biphenols **52** with *N*-bromophthalimide (NBP) in the presence of chiral phosphoric acid (*R*)-**55** lead to the desymmetrized major isomer of **53**. Conveniently, the minor isomer of **53**, underwent a second bromination to compound **54** at a faster rate thus enhancing the enantiopurity of **53**. This combined desymmetrization/kinetic resolution process was effective for a variety of substrates with multiple substitution patterns on the lower aromatic moiety (76–91% yield and 91–99% ee).

In order to explore the mechanism of the reaction, the authors prepared several carefully designed substrates (Figure 4). The methoxymethyl group was shown to be important when substitution of an ethyl group in **56** led to a complete loss of selectivity (0% ee). Also important were the hydroxy groups, the dimethoxy analog **57** was formed in low yield

(14%) and with minimal selectivity (17% ee). From these results and DFT calculations, a hydrogen bond network between the acid proton of the Brønsted acid and the carbonyl of the NBP and the phosphoryl oxygen of the catalyst and the phenols was proposed.

Additionally, Akiyama and co-workers developed a ^1H NMR tool to predict suitable catalysts for the reaction (Scheme 14).^[20] In the absence of chiral catalyst, hydrogens H_a and H_b of **58** are enantiotopic and are a single peak in the ^1H spectrum ($\delta[\text{H}_a - \text{H}_b] = 0$). However, when a phosphoric acid is added, a hydrogen bond network is established as in **59** and H_a and H_b can be differentiated ($\delta[\text{H}_a - \text{H}_b] \neq 0$). It was predicted that the greater the difference between H_a and H_b with the respective catalyst, the higher the enantioselectivity of the reaction would be. The authors found excellent correlation between predicted relative enantioselectivities and experimental values for a number of chiral phosphoric acid catalysts.

The enantioselective synthesis of axially chiral BINAM derivatives **60** and **62** was recently realized via kinetic resolution (Scheme 18).^[21] This kinetic resolution utilized aryl aldehyde **61** and Brønsted acid (*R*)-**64** to catalyze imine formation followed by Hantzsch ester **63** mediated transfer hydrogenation to give enantioenriched product **62** and recovered starting material **60**. When bulky nitrogen protecting groups were used (R^1) generally good selectivity factors were obtained (8 examples $s > 50$). Substitution at the 6 and 6' position such as halogens or TMS was well tolerated. Removal of the protecting groups on **60** and **62** was accomplished in good yield and free amine (*R*)-BINAM and (*S*)-BINAM were readily obtained.

2.3. Brønsted Acid Catalyzed Kinetic Resolution of Azlactones

Enantioenriched aryl glycine derivatives such as **67** were prepared through a Brønsted acid catalyzed dynamic kinetic resolution of azlactones such as ($\pm$)-**65** (Scheme 19).^[22] Here the authors take advantage of the rapid racemization of azlactones via enol **69** under acidic conditions. In the presence of chiral phosphoric acid (*R*)-**68**, one enantiomer of ($\pm$)-**65** reacts more quickly with alcohol **66** to afford ring opened product **67** in excellent yield and enantiopurity. Modest substitution of the azlactone was tolerated and β -substituted primary alcohol **66** was found to be the most effective.

During this same period, the Birman group also reported a DKR of azlactones (Scheme 20).^[23] In this follow up to an earlier report^[24] they demonstrate that a strong chiral Brønsted acid such as (*S*)-**73** could activate azlactones ($\pm$)-**70** for alcoholysis to product **71** through a reversible protonation step (see intermediate **72**). The use of a 3,5-dimethoxyphenyl group at the C2-position and a bulky alcohol such as 1-naphthylmethanol led to enhanced selectivity in the process. When R is an aryl group, good yields and enantioselectivities were observed (82–90% yield and 85–92% ee). However, when R is an alkyl group such as methyl or isopropyl enantioselectivity drastically decreased (ee = 59%).

2.4. Miscellaneous Brønsted Acid Catalyzed Kinetic Resolutions

An asymmetric reductive amination of aldehydes via a dynamic kinetic resolution was reported by List and co-workers (Scheme 21).^[25] The novel reaction transforms racemic aldehydes with an α -substituent such as ($\pm$)-**74** in the presence of Brønsted acid catalyst

(*R*)-**23** and Hantzsch ester **77** into enantioenriched β -branched amines such as **76**. The authors provide 16 examples. Yields and enantioselectivities are best when R^1 is an aromatic group and when the electron-rich PMP amine is used. Mechanistically, the reaction is postulated to involve the formation of an imine which can be racemized via tautomerization (key for the dynamic kinetic resolution). One of the imines is activated faster by phosphoric acid (*R*)-**23** and then can be reduced in the presence of ester **77** to give the desired amine **76**.

The asymmetric synthesis of 1,3-disubstituted indoles via a novel stereoablative dynamic kinetic resolution was recently reported (Scheme 22).^[26] Phosphoramidate **85** catalyzed the Friedel–Crafts addition of indoles **79** to imines **80** to yield intermediate isoindolines **82** which can undergo rapid isomerization. Enantiomer **82a** goes on to form 1,3-disubstituted indole products **81** via an aza-Michael reaction, while enantiomer **82b** undergoes dissociation of the tosylamide to form the undesired bisindoles **84**.

A novel Brønsted acid catalyzed kinetic resolution was recently reported that combined a Michael addition with an aldol reaction (Scheme 23).^[27] In the first step, β -keto esters ($\pm$)-**86** underwent an asymmetric Michael addition via phosphoric acid catalyst (*R*)-**90** to yield 1,4-adducts **88** in moderate enantiopurity. Treatment of **88** with a second chiral phosphoric acid (*R*)-**23** generates Robinson annulation products **89** with increased enantioselectivity due to a kinetic resolution.

The authors detail extensive theoretical studies which confirm a dicoordination model for the aldol reaction and are able to correlate how the substituent at the 3 and 3' position of the catalyst influences the selectivity of the reaction (Figure 5).

A highly efficient and selective oxidative kinetic resolution of racemic 2-substituted indoline derivatives such as ($\pm$)-**91** was achieved through hydrogen transfer to an imine catalyzed by Brønsted acid (*R*)-**23** (Scheme 24).^[28] This reaction was optimized for indolines with both aryl substituents and alkyl substituents at the 2-position (although longer reaction times were required for the alkyl groups). The optimum imine for hydrogen transfer was ketamine **92**, which is prepared from acetophenone and 3,4,5-trimethoxyaniline. As control experiments, both enantiomers of the simplest indoline were subjected to standard reaction conditions. The (*R*)-enantiomer of **91** after 19 hours afforded 38% of recovered (*R*)-**91** and 58% of oxidized product **95** while the (*S*)-enantiomer only saw <2% conversion to product (no racemization was seen with either enantiomer).

In related work, enantioenriched 2-substituted cyclic secondary amines **96** were prepared in up to 55% yield and >99% ee via a Brønsted acid catalyzed kinetic resolution via transfer hydrogenation (Scheme 25).^[29] Asymmetric hydrogen transfer to ketimines **97** led to recovery of enantioenriched amines **96** and oxidized products **98**. The reaction was highly efficient, especially when R^1 was an aryl group or linear alkyl group. Amines **96a** and **96b**, which were prepared in 50% and 53% yield respectively, underwent methylation to yield natural products, (*R*)-angustureine (**100a**) and (*R*)-galipinine (**100b**) without loss in optical purity.

Enantioenriched tetrahydroquinolines **103** with 4 contiguous stereocenters were prepared through a dynamic kinetic resolution via a transfer hydrogenation of quinolones (Scheme 26).^[30] A combination of Hantzsch ester **102** and chiral phosphoric acid **107** were found to produce tetrahydroquinolines **103** in the highest yield and optical purity. Modest substitution on the phenyl ring and various aliphatic substituents at the 4-position were tolerated in the reaction. The authors postulate a reaction pathway where 1,4 hydride transfer is followed by rapid isomerization of the resultant iminium ion, and finally a highly diastereoselective 1,2-hydride addition to intermediate **105** yields the resultant tetrahydroquinoline **103**.

Gong and co-workers recently reported the synthesis of 2,3-allenoates **108** and 3-methylenepyrrolidine derivatives **111** via kinetic resolution (Scheme 27).^[31] In the presence of bisphosphoric acid **112**, racemic 2,3-allenoates ($\pm$)-**108** and azomethine ylides derived from aromatic aldehydes **110** and diethyl 2-aminomalonate (**109**) underwent an asymmetric 1,3-dipolar cycloaddition reaction. Variation of the allenoate structure and aldehyde led to the formation of 16 different enantioenriched sets of compounds with excellent stereocontrol.

A novel kinetic resolution via allenylboration reaction was devised by Roush and co-workers (Scheme 28).^[32] Previous studies had shown that the axial chirality of 3-substituted allenylboron species such as (*M*)-**113** is transferred to the resulting homopropargyl alcohol **ent-115** upon reaction with an aldehyde and that chiral phosphoric acid **23** can influence the preferred transition state leading to diastereoselectivity.^[33] Here, the authors utilize the corresponding finding that there is a matched/mismatched pairing between each enantiomer of the allene and the catalyst which influences the rate of reaction. In this kinetic resolution the matched allene reacts faster in the proposed **TS-1** to give anti-product **115** while the unmatched allene reacts more slowly to give the syn-product **116**. By using an excess of allenylboronate ($\pm$)-**113**, good yields and enantiopurity of the anti-homopropargyl alcohol **115** are obtained. Both aliphatic and aryl aldehydes are competent in the reaction and some minor modification of boronate was explored.

Beauchemin and co-workers recently reported an enantioselective kinetic resolution of azomethine imines catalyzed by a chiral Brønsted acid (Scheme 29).^[34] Here, readily prepared ketone and aldehyde derived azomethine imines ($\pm$)-**117**^[35] are asymmetrically reduced using phosphoric acid (*R*)-**23** and Hantzsch ester **119** to yield enantiomerically enriched product **118** and recovered imine **117**. The authors report 13 examples with selectivity factors that range from 13–43.

Azomethine imine ($\pm$)-**1171** was resolved on a 1 mmol scale and after recrystallization pyrazolidinone (–)-**1171** was obtained in 98% ee (Scheme 30). This product could then undergo reductive ring opening to yield enantioenriched β -amino amide (–)-**1201** in good yield. A model pre-transition state complex was proposed to account for the selectivity of the reduction. The model incorporated activation of both the azomethine imine and Hantzsch ester with the chiral phosphoric acid and places the large group of the imine (phenyl) away from the ester in the favoured complex.

3. Summary

In summary, by combining two important topics in asymmetric synthesis, kinetic resolutions and chiral Brønsted acids, selective methods for the preparation of enantioenriched small molecules can be achieved. These kinetic resolutions are most powerful when mass recovery of enantioenriched material is high (through either the isolation of two enantioenriched species or a racemization of starting material). The stability and robustness of the chiral Brønsted acids lends to the practicality of these resolutions.

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Biography

Kimberly S. Petersen received her B.S. in chemistry from the University of Wisconsin, Madison. She then earned her Ph.D. at Johns Hopkins University under the supervision of Professor Gary Posner followed by postdoctoral research at the California Institute of Technology with Professor Brian Stoltz. In 2011, she began her independent career at the University of North Carolina at Greensboro.

Hydrogen Bonding Compounds

Stronger Brønsted Acids

Figure 1.
Types of Brønsted acids.

selectivity factor

$$k_{\text{rel}} = s = k_{\text{fast}}/k_{\text{slow}} = e^{\Delta\Delta G^\ddagger/RT} = \frac{\ln[(1-c)(1-ee_{\text{SM}})]}{\ln[(1-c)(1+ee_{\text{SM}})]}$$
$$\Delta\Delta G^\ddagger = \Delta G^\ddagger_{\text{fast}} - \Delta G^\ddagger_{\text{slow}}$$

Figure 2.
Useful terms.

Figure 3.
Calculated transition-state model.

Figure 4.
Mechanistic investigations.

Figure 5.
Dicoordination transition state.

Scheme 1.
Kinetic resolution.

Scheme 2.
Kinetic resolution of homoaldol acetals via transacetalization.

Scheme 3.
Natural product synthesis.

Scheme 4.

Synthesis of trioxanes via a dynamic kinetic resolution of intermediate peroxyhemiacetals.

Scheme 5.
Kinetic resolution of hydroxyenol ether.

18 examples
s factors 1.6–389
up to 191:1 dr

Scheme 6.
Kinetic resolution of diols.

Scheme 7.
 S_N2 type kinetic resolution of alcohols.

experimental *computational*

Scheme 8.
Mechanistic evidence.

Scheme 9.

Kinetic resolution of diol and synthesis of (+)-sacidumlignan D.

Scheme 10.
Kinetic resolution via intermolecular acetalization.

Scheme 11.
Kinetic resolution of secondary alcohols via acetylation.

Examples

Scheme 12.
Kinetic resolution of *cis*-secondary alcohols via acylation.

Scheme 13. Kinetic resolution of α -substituted γ -hydroxy esters.

Scheme 14.
Synthetic transformations of hydroxy ester.

Scheme 15.

Examples of the kinetic resolution of hydroxy esters with multiple stereocenters.

Scheme 16.

Enantioselective synthesis of biaryls via a desymmetrization/kinetic resolution strategy

Scheme 17.
Use of 1H NMR to predict best catalyst

Scheme 18.
Kinetic resolution of axially chiral BINAM derivatives.

Scheme 19.
Dynamic kinetic resolution of azlactones.

Scheme 20.
Birman's dynamic kinetic resolution of azlactones.

Scheme 21.

Dynamic kinetic resolution yielding β -branched amines.

Scheme 22.
Stereoaablative dynamic kinetic resolution.

Scheme 23.
Enantioselective Robinson-type annulation reactions via kinetic resolution.

Scheme 24.
Kinetic resolution of 2-substituted indolines.

Scheme 25.

Kinetic resolution of 2-substituted cyclic secondary amines.

Scheme 26.
Dynamic kinetic resolution of quinolines.

Scheme 27.
Kinetic resolution of 2,3-allenoates.

Favored transition state with **(M)-113** leading to *anti*- products (diastereoselective control)

Scheme 28.
Kinetic resolution/allenylboration reaction.

Scheme 29.
Kinetic resolution of azomethine imines.

Scheme 30.
Synthesis of β -amino amide and pre-transition state complexes.