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Asymmetric Synthesis of Hydroquinolines with α,α-Disubstitution via Organocatalyzed Kinetic Resolution

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Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry

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Abstract: The first kinetic resolution of hydroquinoline derivatives with α,α-disubstitution has been achieved through asymmetric remote aminations with azodicarboxylates enabled by chiral phosphoric acid catalysis. Mechanistic studies suggest a monomeric catalyst pathway proceeding via rate- and enantio-determining electrophilic attack promoted by a network of attractive non-covalent interactions between the substrate and catalyst. Facile subsequent removal and transformations of the newly introduced hydrazine moiety enable these protocols to serve as powerful tools for asymmetric synthesis of N-heterocycles with α,α-disubstitution.

N-containing heterocycles are the most important class of structural motifs in the pharmaceutical and agrochemical industries. In particular, the tetrahydroquinolines (THQs) and their derivatives are found in numerous biologically active natural products and small molecules.[1] Consequently, the asymmetric catalytic synthesis of THQs has drawn considerable research interest, and gained tremendous progress in recent years, particularly through the strategy of asymmetric hydrogenations[2], asymmetric additions[3] and asymmetric Povarov reactions[4]. However, asymmetric synthesis of THQs with α,α-disubstitution through these methods was either inaccessible or extremely challenging and presented with limited scope[5].

Kinetic resolution (KR) of amines is another powerful and practical method to produce N-containing heterocycles[6]. Since the pioneer work of kinetic resolution of amines by Fu and co-workers[7], a series of elegant asymmetric N-acylations protocols have been developed for the KR of (cyclic) amines, which were developed by Birman[8], Seidel[9], Miller[10], Bode[11] and Spivey[12] groups, respectively (Figure 1, a). Additionally, the asymmetric dehydrogenation reactions were also well applied in the KR of N-containing heterocycles, though the products of these reactions were generated without chiral information. The Akiyama group developed a delicate method for KR of cyclic secondary amines through asymmetric dehydrogenation with imines enabled by chiral phosphoric acid (CPA) catalysis[13] (Figure 1, b). Recently, the Liu group disclosed KR of α-substituted 1,2-dihydroquinolines (DHQs) and 5,6-dihydrophenanthridines through chiral iron complex catalyzed asymmetric dehydrogenation, in which air was used as the oxidant[14]. However, to the best of our knowledge, the scope of all the aforementioned methods have been limited to KR of cyclic amines with α-mono-substitution, and KR of cyclic amines with α,α-disubstitution through these methods is formidable.

Recently, our group has disclosed the asymmetric construction of axially chiral aniline derivatives through CPA catalyzed asymmetric aminations of anilines with azodicarboxylates[15]. Herein, we report the first highly efficient KR of hydroquinolines (including THQs, DHQs and 5,6-dihydrophenanthridines) bearing α,α-disubstitution through asymmetric remote amination reactions, in which the introduced hydrazine moiety could be facilely removed to return the chiral hydroquinolines (Figure 1, c).

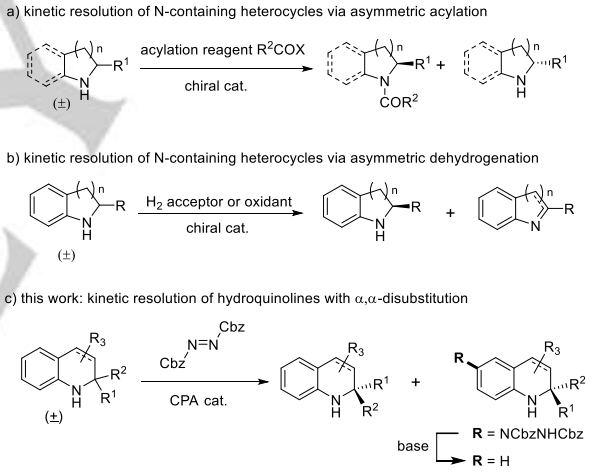
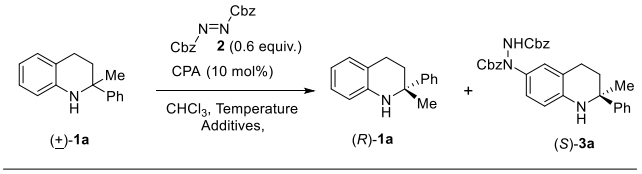


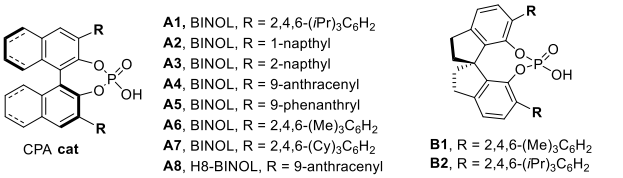
Figure 1. Kinetic resolution of N-containing heterocycles with α-stereocenters.

Our study commenced with racemic 2-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline (**1a**) as a model substrate and dibenzyl azodicarboxylate (**2**) as the amination reagent enabled by CPA catalysis (Table 1). In the presence of TRIP catalyst (**A1**, 10 mol%) in $CHCl_3$ at room temperature, the reaction between racemic **1a** (1.0 equiv.) and azodicarboxylate **2** (0.6 equiv.) proceeded smoothly to generate the 6-aminated product **3a** with 63% ee and recovered **1a** with 71% ee, (corresponding to a selectivity factor[16] of 9.1, entry 1). Next, a range of BINOL-derived CPA catalysts were examined (entries 2-7), which indicated the 3,3'-di-(9-anthracenyl)-substituted CPA **A4** could give a better *s*-factor of 13 (entry 4). Encouragingly, switching the chiral scaffold of CPA **A4** to H8-BINOL-type (**A8**) provided a significantly improved *s*-factor of 22 (entry 8). The SPINOL-derived CPA catalyst **B1** and **B2** were also evaluated, which couldn't improve the stereoselectivities (entries 9 and 10). Due to the fast reaction rate enabled by catalyst **A8** at ambient temperature (reaction completed within 1 h), decreasing the reaction temperature was also studied (entries 11-12), which

proved exceptionally beneficial for the KR performance of this reaction. Finally, −40 °C was determined to be the optimal temperature, at which the amination product **3a** was obtained with 91% ee and **1a** was recovered with 95% ee, giving an *s*-factor of 79 (entry 12, for more reaction condition optimizations see Table S1 in SI).

Table 1. Optimizations of reaction conditions.[a]



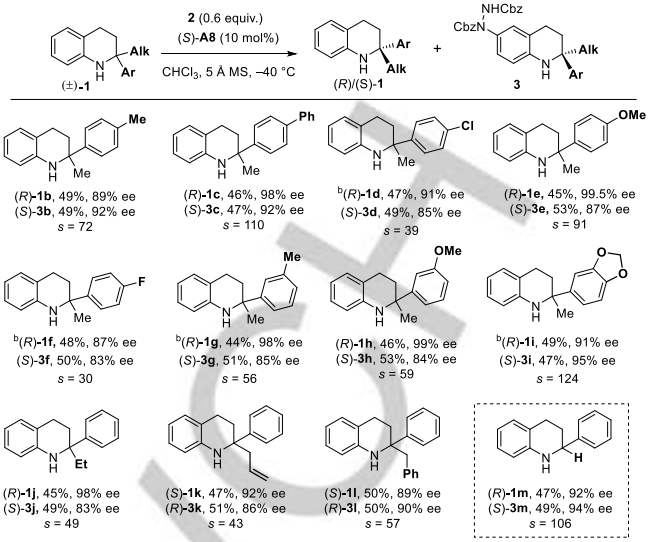


Entry	Cat	Time (h)	T (^{o}C)	ee_s[b] (%)	ee_p[b] (%)	C[c] (%)	*s*[d]
1	**A1**	12	20	71	63	53	9.1
2	**A2**	12	20	34	56	38	5.0
3	**A3**	12	20	12	23	33	1.8
4	**A4**	12	20	81	68	54	13
5	**A5**	12	20	63	61	51	7.7
6	**A6**	12	20	74	55	57	7.4
7	**A7**	12	20	59	53	53	5.8
8	**A8**	1	20	77	81	49	22
9	**B1**	12	20	63	76	45	14
10	**B2**	12	20	9	25	27	1.8
11[e]	**A8**	3	−20	86	90	49	53
12[e]	**A8**	12	−40	95	91	51	79

[a] Reactions were run with **1a** (0.1 mmol), **2** (0.06 mmol) with CPA catalyst (0.01 mmol, 10 mol%) in $CHCl_3$ (2 mL) at designated temperatures. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Conversion (C) = $ee_s/(ee_s+ee_p)$. [d] $s = \ln[(1-C)(1-ee_s)]/\ln[(1-C)(1+ee_s)]$. [e] With 5 Å molecular sieves (50 mg).

With the optimal kinetic resolution conditions in hand, we set out to explore the scope of this reaction under the catalysis of (*S*)-**A8** catalyst (Table 2). A range of substituted phenyl groups at the 2-position of THQs were initially examined, which indicated that various *para*- and *meta*-substituted phenyl groups could be well tolerated, regardless of the electronic nature of the substituents (**1b**-**1i**). Next, a series of alkyl groups other than the Me group at the 2-position of THQs were investigated under the standard conditions, which were amenable variants, including the Et (**1j**), allyl (**1k**) and benzyl (**1l**) groups. In addition, the optimal KR reaction conditions were also attempted on α-mono-substituted THQ (**1m**), which also provided excellent KR performances, generating both recovered SM and product with high enantioselectivities.

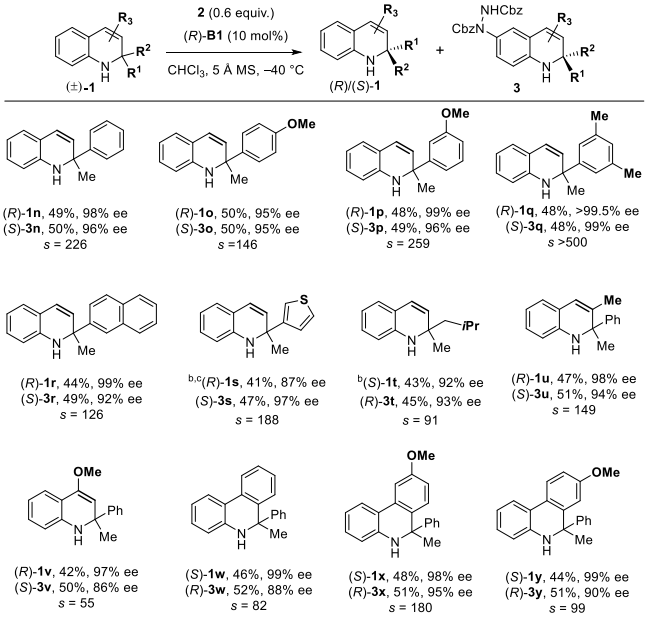
Table 2. Scope for kinetic resolution of THQs with α,α-disubstitution.[a]



[a] Reactions were run with **1** (0.2 mmol), **2** (0.12 mmol) with CPA (*S*)-**A8** (0.02 mmol, 10 mol%) in $CHCl_3$ (4 mL) at –40 °C in the presence of 5 Å molecular sieves (100 mg) for 16 ~ 36 h. Yields were isolated yields. Ee values were determined by HPLC analysis on a chiral stationary phase. $s = \ln[(1-C)(1-ee_s)]/\ln[(1-C)(1+ee_s)]$. Conversion (C) = $ee_s/(ee_s+ee_p)$. [b] At −50 °C.

With the excellent KR performances of this method on THQs with α,α-disubstitution, we turned our attention to DHQs, which possessed a C=C bond for further derivatizations and would be a valuable building block for the synthesis of THQ derivatives (Table 3). However, applying the previous optimal conditions on DHQ **1n** only provided moderate selectivities. Satisfyingly, after brief screening of the CPA catalysts (see Table S2 in SI), we found the KR of DHQ **1n** in the presence of SPINOL-derived CPA catalyst (*R*)-**B1** provided the 6-aminated product **3n** in 50% yield with 96% ee and recovered (*S*)-**1n** in 49% yield with 98% ee, with an *s*-factor of 226. A variety of aryl groups instead of the phenyl group were screened under these optimal conditions, which showed that substituted phenyl groups (**1o**-**1q**), 2-naphthyl group (**1r**) as well as the thienyl group (**1s**) could be well tolerated. Notably, an α,α-dialkyl substituted DHQ could be kinetically resolved as well, giving an *s*-factor of 91 (**1t**). Substitutions at the 3- and 4-position of DHQ substrates were also examined, which were well compatible with the standard conditions (**1u** and **1v**). Finally, the KR of 6,6-disubstituted 5,6-dihydrophenanthridines was also studied. Satisfyingly, applying the optimal reaction conditions for DHQs on these substrates provided both the amination products and recovered SMs with high enantioselectivities (**1w-1y**).

Table 3. Scope for kinetic resolution of DHQs and 5,6-dihydrophenanthridines with α,α-disubstitution.[a]



[a] The same conditions as in Table 2 expect CPA (*R*)-**B1** (10 mol%) was used instead. [b] CPA (*R*)-**B2** (10 mol%) was used as catalyst. [c] At −20 °C.

To shed light on the mechanism of these highly selective KR reactions, some control experiments were performed (Figure 2). Kinetic resolution of the α,α-disubstituted *N*-Me-THQ **4a** under the standard conditions afforded the amination product with 61% ee and recovered (*R*)-**4a** with 60% ee, with an *s*-factor of 7.6, which suggested the potential hydrogen-bonding between the N-H moiety of THQ and the P=O functional group of the catalyst is important for the stereoselectivity (Figure 2, a). However, on the other hand, moderate stereoselectivity was still achieved without the N-H group in the THQ substrate, which implied the likely presence of other non-covalent interactions (NCIs) between the substrate and catalyst[17]. To investigate this hypothesis, catalytic hydrogenation of CPA (*S*)-**A8** facilely provided the (*S*)-**A8'** catalyst, which should have similar steric environments with the (*S*)-**A8** catalyst, while possessing substantially reduced capacity to engage in attractive aromatic NCIs (Figure 2, b). Indeed, KR of racemic **1a** using this catalyst under the standard conditions only provided the product **3a** with 59% ee and the recovered (*R*)-**1a** with 70% ee, corresponding to an *s*-factor of 10, in sharp contrast to the excellent *s*-factor obtained under CPA **A8** catalysis. Moreover, (*S*)-**A8'** promoted the reaction with a slower rate compared to **A8** (see Figure S1 in SI), suggesting that the polyaromatic nature of the *ortho*-substitutions of the CPA **A8** is critically important not only for the excellent stereoselectivity but also the high reactivity observed in this reaction. To obtain additional insight into the basis of kinetic resolution, Eyring analysis in the 20 °C to −40 °C temperature range of catalyst (*S*)-**A8** was studied. An excellent linear relationship between ln(*s*) and 1/T was observed, from which the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ of this reaction could be calculated (Figure 3, a). These results implied that the high *s*-factor of this reaction was controlled by enthalpy, with relatively small entropic compensations. On the other hand, a linear relationship between ln(s) and 1/T was only found in the temperature range of 20 °C to −20 °C for the (*S*)-**A8'** catalyzed reaction, with a significantly smaller $\Delta\Delta H^{\ddagger}$ value and comparable $\Delta\Delta S^{\ddagger}$ value (Figure 3, b). This change is consistent with attractive NCIs (e.g. π-π or CH-π) being critical to the mechanism of enantioinduction for catalyst **A8**.[18]

In order to gain a clearer picture of the enantiodetermining transition state, the relationship between differential kinetic enantiomeric enhancement (DKEE)[19] and the ee of catalyst **A8** in the KR reaction of THQ **1h** was studied, and an approximately linear relationship was observed, which suggested the absence of multiple chiral components in the asymmetric transition state (Figure 3, c)[19-20]. The order of catalyst in the KR reaction of THQ **1h** was also studied, and a linear relationship was found between the initial reaction rate and the concentration of the catalyst, suggesting a first-order dependence on CPA catalyst, further consistent with the absence of non-linear effect (Figure 3, d). The intermolecular competitive kinetic isotope effect (KIE) experiment between (*R*)-**1a**$_D$ and (*R*)-**1a** was performed under the catalysis of (*R*)-**A8** (the matched substrate–catalyst pair), giving a KIE value of 1.0 (see Figure S2 in SI), which suggested the C-H cleavage step is probably not involved in the rate-determining step.

On the basis of these experimental results, we proposed that electrophilic addition to generate the dearomatized intermediate (**INT A**) is the rate- and enantio-determining step (Figure 2, c). Taken together, the mechanistic studies suggest a model in which activation of both the THQ **1a** and azodicarboxylate **2** by a single CPA catalyst through dual hydrogen-bonding facilitates the addition of C-6 of THQ **1a** with azodicarboxylate **2** to give the dearomatized addition product **INT A**, in which the (*S*)-configurated **1a** reacted preferentially. Though steric effects cannot be ruled out as contributors to the mechanism of enantioinduction, our results suggest that attractive NCIs between substrates and the CPA catalyst are critical to realize the kinetic resolution.[21] Facile aromatization of **INT A** ultimately affords the 6-aminated THQ (*S*)-**3a**.

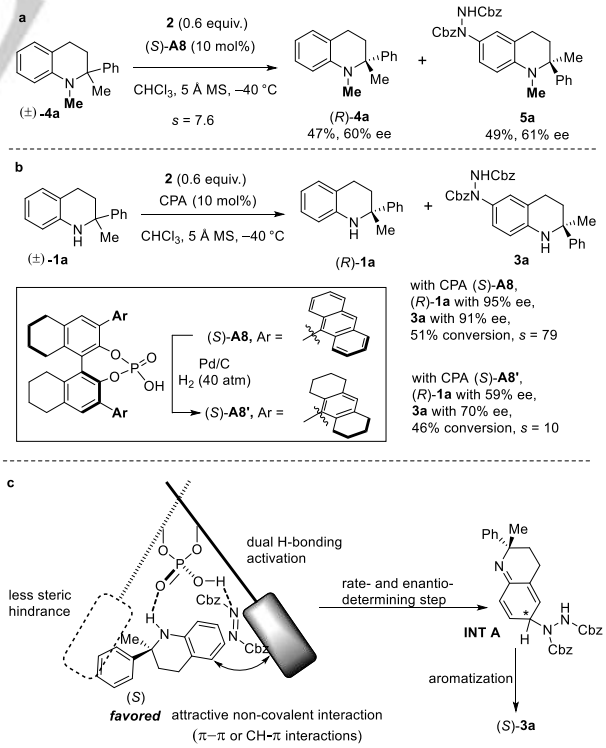


Figure 2. Control experiments and proposed reaction mechanism.

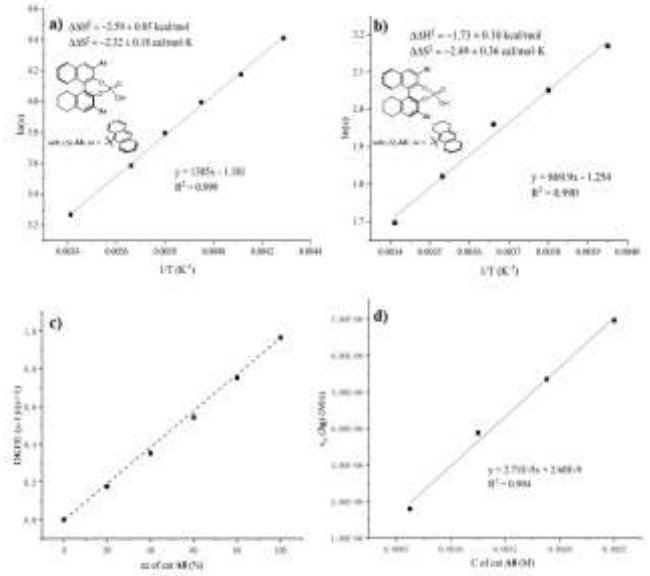
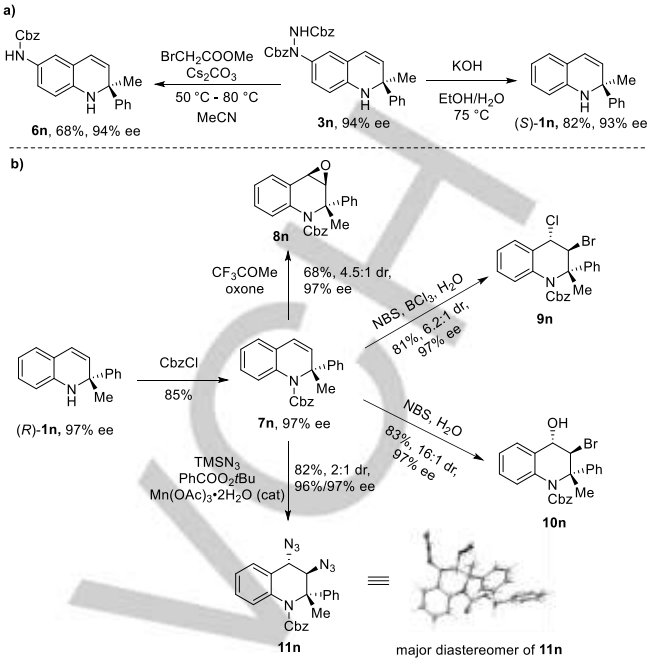


Figure 3. Mechanistic studies. **a)** Eyring analysis of KR of racemic **1a** catalyzed by (*S*)-**A8** catalyst. **b)** Eyring analysis of KR of racemic **1a** catalyzed by (*S*)-**A8'** catalyst. The differential activation parameters were calculated using the following relationship: $\ln(s) = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R$ [where R = 1.986 cal/(mol•K)]. **c)** Plot of the DKEE versus the ee of CPA (*S*)-**A8** in KR of racemic **1h**. DKEE = (*s*-1)/(*s*+1). **d)** Catalyst order determination for the KR reaction of substrate **1h** catalyzed by CPA (*S*)-**A8**.

To demonstrate the practicality of these reactions, large-scale KR experiment was performed. Encouragingly, the kinetic resolution of DHQ **1n** with reduced catalyst loading (0.5 mol% of CPA (*R*)-**B1**) still provided comparable KR performances, giving *s*-factor of 136 (see Figure S3 in SI).

A series of derivatizations of the chiral products were conducted to prove the utilities of these methods. Cleavage of the N-N bond of the 6-hydrazine group in **3n** with the treatment of bromoacetate and Cs_2CO_3 afforded the 6-*N*-Cbz substituted DHQ **6n**[22] (Scheme 1, a). Critically, treatment of **3n** with KOH solution at 75 °C led to the facile deamination reaction, providing (*S*)-**1n** in 82% yield with retained enantiomeric excess. This finding enables the hydrazine moiety to serve a temporary role facilitating separation of the reactant enantiomers, thus allowing the protocol above to serve as a catalytic resolution of both enantiomers formally without modification.

To highlight the versatile reactivities of the C=C bond in DHQ (*R*)-**1n**, a range of transformations were studied (Scheme 1, b). After protecting of the (*R*)-**1n** with the Cbz group, epoxidation[23], dihalogenation, hydroxylbromination and diazidation[24] of the olefin motif of **7n** provided a wide array of 3,4-difuntionalized THQ derivatives with high efficiencies and without erosion of optical purities.



Scheme 1. Derivatizations of chiral products.

In conclusion, we have disclosed the first highly efficient kinetic resolution of hydroquinoline derivatives with α,α-disubstitution through chiral phosphoric acid catalyzed remote aminations with azodicarboxylates. A range of THQs, DHQs and 5,6-dihydrophenanthridines possessing various α,α-disubstitution could be kinetically resolved with excellent yields and selectivities. Mechanistic studies elucidated the reaction mechanisms and highlighted the role of attractive non-covalent interactions between the substrate and catalyst in the stereodetermining step. Fruitful transformations of the products, notably including removal of the hydrazine moiety to return enantioenriched starting material, demonstrated the values of these methods in preparing of N-containing heterocycles with α,α-disubstitution.

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Keywords: asymmetric organocatalysis • α,α-disubstitution • hydroquinolines • kinetic resolution • remote amination

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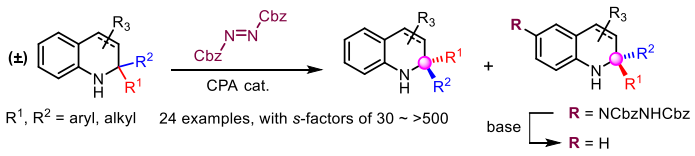
Entry for the Table of Contents



The first kinetic resolution of hydroquinoline derivatives with α,α-disubstitution was realized via organocatalyzed catalyzed asymmetric remote aminations with azodicarboxylates, which represents a powerful protocol for asymmetric synthesis of N-heterocycles with α-quaternary stereocenters. Mechanistic studies elucidate the reaction mechanisms and highlighted the role of attractive non-covalent interactions between the substrate and catalyst.