

代表性论文 6

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有机催化吡内酯的羟胺化反应——动力学拆分氧杂吡啶和不对称合成恶唑林酮:

氧杂吡啶具有丰富的反应活性,除作为氧化剂外,作为氧氮杂三元环化合物可参与环化反应,但反应历程多样,对反应中氧杂吡啶立体选择性的认识不明确,手性氧杂吡啶的动力学拆分研究还不系统深入。我们设计了消旋氧杂吡啶和吡内酯之间的不对称羟胺化反应,利用双胍的 HBAr^{F}_4 盐催化剂 BGs-PiDPh_2 , 高对映和非对映选择性的得到相应的恶唑林酮产物,并回收得到了光学纯的氧杂吡啶,为光学纯氧杂吡啶的合成提供了新途径。通过控制实验阐明了氧杂吡啶发生羟胺化反应时的立体构型保持的问题。通过控制实验和催化剂单晶衍射分析,发现了双胍单盐在溶液中存在双胍-双胍单盐-双胍双盐的动态平衡现象,为进一步提高催化剂效率提供了指导。

Organocatalytic Oxyamination of Azlactones: Kinetic Resolution of Oxaziridines and Asymmetric Synthesis of Oxazolin-4-ones

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Supporting Information

ABSTRACT: The first example of oxyamination of azlactones with oxaziridines was realized using a chiral bisguanidinium salt. Efficient catalytic asymmetric oxyamination and kinetic resolution of oxaziridines occurred simultaneously. Various chiral oxazolin-4-one derivatives with potential biological activity were obtained (up to 92% ee). Meanwhile, a series of optically pure oxaziridines were recovered with up to 99% ee and successfully used in the asymmetric oxyamination of 3-methyl-1*H*-indole and styrene. The triple stereodifferentiation process was also studied via control experiments.

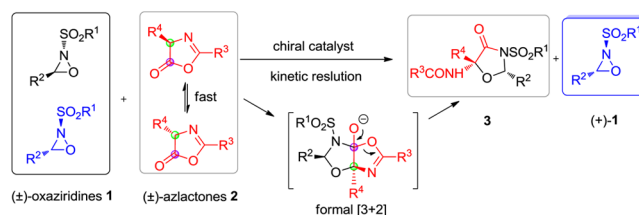
Kinetic resolution (KR)¹ of racemic compounds is one of the most powerful tools to obtain enantiopure molecules in both academia and industry, complementing approaches such as asymmetric synthesis and classic resolution. With racemates and a chiral agent (reagent, catalyst, solvent, etc.), a substantial difference in matched and mismatched reactions provides the underpinnings for KR. Catalytic nonenzymatic KR^{1b–f} and some modified versions such as parallel KR² and dynamic KR (DKR)³ have been actively investigated. The major types of functional compounds that have been resolved via KR processes mostly involve alcohols, epoxides, amines, alkenes, carbonyl derivatives, sulfur compounds, and ferrocenes.

N-sulfonyl oxaziridines, as a class of aprotic and neutral oxidizing reagents, are versatile reagents in organic synthesis.^{4,5} In particular, optically active oxaziridines have been used in a variety of oxidation reactions.⁴ Nevertheless, the catalytic enantioselective synthesis⁶ of *N*-sulfonyl oxaziridines was first described only recently, by Jørgensen^{6a} and Yamamoto^{6b} in 2011. In addition, the phenomenon of KR was observed in asymmetric reactions of racemic oxaziridines,^{5c,d} which provides another route to chiral oxaziridines. Ye's group reported a catalytic formal [3 + 2] cycloaddition of ketenes and oxaziridines in which a special oxaziridine was recovered via KR.^{5d} Therefore, it was intriguing to explore useful reactions to achieve two objectives: asymmetric catalytic reaction and KR of oxaziridines.

Azlactones contain multiple reactive sites and thus exhibit diverse and interesting reactivity in organic synthesis.⁷ Racemic azlactones can react with a variety of electrophiles as a result of the acidity of the α -hydrogen. On the other hand, the electrophilic nature of the carbonyl group allows for nucleophilic attack to give the corresponding ring-opened compounds. One representative example is the successful

catalytic DKR of α -substituted azlactones by alcoholysis to synthesize α -amino acids.⁸ To explore the ambiphilic nature of this type of substrate, we envisioned that α -substituted azlactones could be subjected to oxaziridine-mediated oxyamination^{5a–c} (Scheme 1). The *N*-sulfonyl oxaziridine electro-

Scheme 1. Asymmetric Oxyamination of Azlactones and KR of Oxaziridines as a Consequence of Triple Diastereoselection



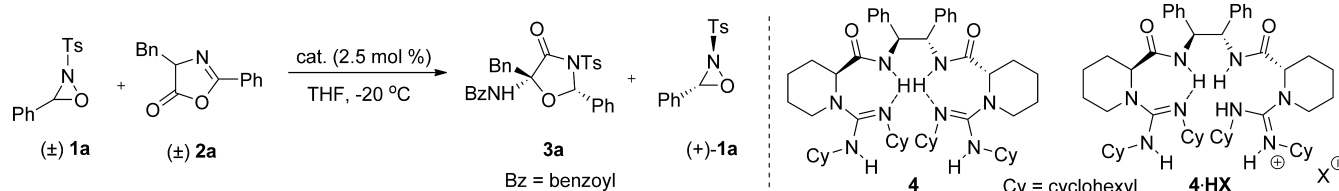
phile would attach to the azlactone at first. Ring closure of the sulfonamide onto the carbonyl group would then result in ring opening of the azlactone⁹ to generate an oxazolin-4-one. Oxazolin-4-ones are biologically useful intermediates.¹⁰

In the realization of the asymmetric version of the above reaction, a further interesting issue arose: the rare occurrence of triple diastereoselection.¹¹ In this case, three chiral components (racemic oxaziridine, racemic azlactone, and chiral catalyst) participate in the reaction, and one new stereogenic unit is generated in the product. Since each component can exert some control on stereochemical events, the permutations of matched/mismatched reactions and chiral-catalyst-induced KR are more complex. Herein we disclose our preliminary results on the catalytic asymmetric oxyamination of azlactones and KR of oxaziridines. This method not only provides an effective alternative route to a series of optically active oxaziridines (up to 99% ee) but also affords various oxazolin-4-ones with good results (up to 98:2 dr and 92% ee).

In our preliminary study, we chose racemic *N*-sulfonyl oxaziridine (±)-1a and 0.5 equiv of phenylalanine-derived azlactone 2a as the model substrates. Chiral guanidines¹² were chosen as the organocatalysts in view of their good performance in our previous study.¹³ The initial results were far from encouraging, as the oxyamination reaction proceeded smoothly with a 2.5 mol % loading of chiral bisguanidine 4 to give racemic oxazolin-4-one derivative 3a in 45% yield with 64:36 dr

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Table 1. Optimization of the Reaction Conditions^a

entry	cat.	T (°C)	t (h)	3a			1a		S
				yield (%) ^b	cis:trans ^c	ee (%) ^c	yield (%) ^b	ee (%) ^c	
1	4	−20	24	45	64:36	0/0	51	0	—
2	4·HCl	−20	24	40	66:34	0/0	54	0	—
3	4·HBF ₄	−20	24	41	75:25	20/11	55	8	2
4 ^d	4·HBAr ^F ₄	−20	24	48	86:14	55/37	50	40	5
5	4·HBAr ^F ₄	−45	48	41	90:10	63/53	49	50	7
6	4·HBAr ^F ₄	−78	48	33	94.5:5.5	81	65	40	14
7 ^e	4·HBAr ^F ₄	−78	48	47	95:5	87	49	76	32
8 ^{e,f}	4·HBAr ^F ₄	−78	46	52	95:5	84	43	95	43
9 ^{e,f}	ent-4·HBAr ^F ₄	−78	46	52	95:5	−84	41	−96	45

^aUnless otherwise noted, the reaction was carried out with catalyst **4** or **4·HX** (5×10^{-3} mmol, 2.5 mol %), **1a** (0.20 mmol), and **2a** (0.10 mmol) in THF (1.5 mL). ^bIsolated yields according to the amount of **1a**. ^cDetermined by chiral HPLC analysis. ^dHBAr^F₄ = HB[3,5-(CF₃)₂C₆H₃]₄. ^eA 1:2 (v/v) THF/*t*-BuOMe mixed solvent (1.5 mL) and 4 Å MS (10 mg) were used. ^f**2a** (0.125 mmol) was used.

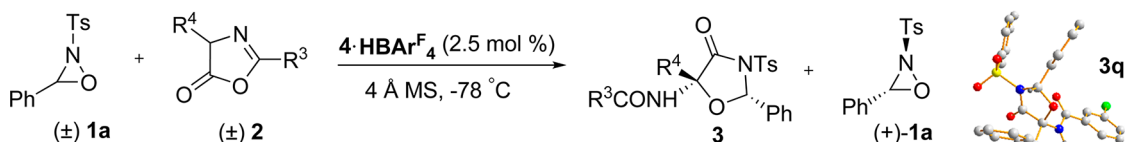
Table 2. Substrate Scope of Oxaziridines **1** for Asymmetric Oxyamination of Azlactone **2a**^a

entry	R ¹	R ²	t (h)	3			1		S
				yield (%) ^b	cis:trans ^c	ee (%) ^c	yield (%) ^b	ee (%) ^c	
1	4-MeC ₆ H ₄	C ₆ H ₅	46	52 (3a)	95:5	84	43 (1a)	95	43
2	C ₆ H ₅	C ₆ H ₅	46	47 (3b)	94:6	80	39 (1b)	93	31
3	4-ClC ₆ H ₄	C ₆ H ₅	48	54 (3c)	94:6	80	41 (1c)	90	28
4 ^{d,e}	4-O ₂ NC ₆ H ₄	C ₆ H ₅	80	67 (3d)	85:15	43 (99) ^f	29 (1d)	98	10
5	4- <i>i</i> PrC ₆ H ₄	C ₆ H ₅	48	48 (3e)	94:6	81	44 (1e)	93	32
6	4-MeC ₆ H ₄	2-MeC ₆ H ₄	48	53 (3f)	>95:5	83	46 (1f)	87	31
7	4-MeC ₆ H ₄	3-MeC ₆ H ₄	48	51 (3g)	97:3	86	45 (1g)	91	42
8	4-MeC ₆ H ₄	4-MeC ₆ H ₄	48	54 (3h)	97:3	85	41 (1h)	91	39
9	4-MeC ₆ H ₄	3-MeOC ₆ H ₄	48	58 (3i)	97:3	80	30 (1i)	97	37
10	4-MeC ₆ H ₄	3-FC ₆ H ₄	48	54 (3j)	95:5	80	39 (1j)	98	41
11	4-MeC ₆ H ₄	3-furyl	120	43 (3k)	95:5	85	36 (1k)	85	34
12	4-MeC ₆ H ₄	3-thienyl	96	49 (3l)	95:5	83	45 (1l)	98	49
13 ^d	4-MeC ₆ H ₄	1-naphthyl	96	43 (3m)	95:5	82	33 (1m)	85	32
14	4-MeC ₆ H ₄	Bn	120	48 (3n)	90:10	71	40 (1n)	82	15
15	4-MeC ₆ H ₄	Et	120	49 (3o)	95:5	88	39 (1o)	82	40
16 ^g	4-MeC ₆ H ₄	C ₆ H ₅	48	57 (3a)	94:6	81	36 (1a)	99	49

^aUnless otherwise noted, the reaction was carried out with **4·HBAr^F₄** (2.5 mol %), **1** (0.20 mmol), and **2a** (0.125 mmol) in 1:2 (v/v) THF/*t*-BuOMe (1.5 mL) at −78 °C. ^bIsolated yields. ^cDetermined by chiral HPLC analysis. ^dTHF (1.5 mL) was used as the solvent without 4 Å MS. ^e**2a** (0.14 mmol) was used. ^fAfter recrystallization (21% yield). ^g**1a** (6.0 mmol) and **2a** (3.75 mmol) were used.

(Table 1, entry 1). On the basis of our previous finding that the identity of the counteranion affects the outcome in reactions promoted by chiral bisguanidinium salts,^{13,14} we examined a series of counteranions, such as Cl[−], BF₄[−], and BAr^F₄[−] [Ar^F = 3,5-bis(trifluoromethyl)phenyl].¹⁵ To our delight, a distinct increase in diastereo- and enantioselectivity was observed. The chiral catalyst **4·HBAr^F₄** was promising (55% ee, 86:14 dr for **3a**), and oxaziridine **1a** was recovered in 50% yield with 40% ee (entries 2–4). Attempts to improve the reaction parameters

next focused on the effect of temperature, solvent, and additives.¹⁶ Lowering the reaction temperature to −78 °C led to a significant improvement in both the diastereo- and enantioselectivity of the product **3a**, but at the expense of the reactivity (entries 5 and 6). It should be noted that the unreacted azlactone was recovered as a racemate. Delightfully, using a 1:2 (v/v) THF/*t*-BuOMe mixed solvent and adding 4 Å molecular sieves (MS) resulted in a better *S* factor of 32 related to the higher yield (entry 7). We next studied the influence of

Table 3. Substrate Scope of Azlactones **2** for Asymmetric Oxyamination with Oxaziridine **1a**^a


entry	R ³	R ⁴	t (h)	3			1a		S
				yield (%) ^b	cis:trans ^c	ee (%) ^c	yield (%) ^b	ee (%) ^c	
1 ^d	2-ClC ₆ H ₄	Bn	48	49 (3p)	98:2	81	41	98	43
2 ^d	3-ClC ₆ H ₄	Bn	48	55 (3q)	97:3	82	41	93	34
3 ^d	4-MeC ₆ H ₄	Bn	60	53 (3r)	95:5	80	40	90	28
4 ^d	3,5-Me ₂ C ₆ H ₃	Bn	60	49 (3s)	97:3	88	39	92	52
5 ^d	4-O ₂ NC ₆ H ₄	Bn	48	53 (3t)	95:5	72	38	99	31
6	C ₆ H ₅	4-HOC ₆ H ₄ CH ₂	96	36 (3u)	95:5	92	60	55	42
7	C ₆ H ₅	3-indolylmethyl	118	54 (3v)	98:2	88	45	82	40

^{a-c}See Table 2, footnotes a–c. ^dDMAP (0.5 mg, 2 mol %) was added.

the ratio of oxaziridine (±)-**1a** and azlactone **2a**. Remarkably, the use of 0.625 equiv of **2a** was the best choice, giving rise to an *S* factor of 43 (52% yield with 84% ee for **3a**; 43% yield with 95% ee for the recovered **1a**) after 46 h (entry 8).¹⁶ The use of *ent*-**4-HBARF**₄ furnished **3a** and recovered **1a** with comparable results but the opposite configuration (entry 9).

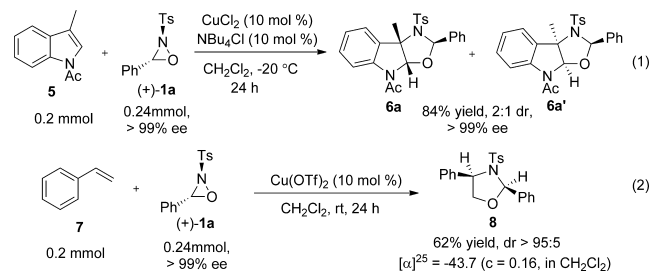
With the optimized reaction conditions established, the scope of oxaziridines **1** in the KR via asymmetric oxyamination of azlactone **2a** was studied (Table 2). Comparatively, *N*-tosyl-substituted oxazolin-4-one **1d** gave the corresponding product with lower stereoselectivities than other substituents (entries 1–5), although the starting substrate was recovered with a high ee of 98% but in low yield. A broad range of *N*-tosyl-substituted oxaziridines with different aryl substituents on the C atom proceeded smoothly, affording the desired oxazolin-4-one derivatives **3f–m** with high diastereo- and enantioselectivities (43–58% yield, 95:5–97:3 dr, and 80–86% ee), while the unreacted oxaziridines **1f–m** were recovered in 30–46% yield with 85–98% ee (entries 6–13). Remarkably, chiral oxaziridines **1k** and **1l** were obtained for the first time with 85% and 98% ee, respectively (entries 11 and 12). Oxaziridines **1n** and **1o** with aliphatic substituents also underwent the asymmetric oxyamination and KR processes with *S* factors of 15 and 40, respectively, although a longer reaction time was required (entries 14 and 15). To evaluate further the synthetic potential of the catalytic system, the reaction was conducted on a gram scale, and **3a** and recovered **1a** were obtained with similar results (entry 16).¹⁶ Enantiomerically pure product **3a** (>99% ee) was obtained via recrystallization.¹⁶

Having investigated the scope of oxaziridines, we tried to expand the oxyamination to other azlactones. A representative selection of azlactones with different aromatic substituents at the C2 position were used in the reaction. The bisguanidinium salt **4-HBARF**₄ promoted the stereoselective formation of the oxyaminated products (72–88% ee) when 4-dimethylamino-pyridine (DMAP) was added to increase the conversion of the reaction, and the unreacted oxaziridine **1a** was recovered in 38–41% yield with 90–99% ee (Table 3, entries 1–5). Moreover, azlactones bearing free OH and NH groups derived from tyrosine and tryptophan also participated successfully in the asymmetric oxyamination reactions, giving *S* factors of 42 and 40, respectively (entries 6 and 7). In some cases, small amounts of byproducts were detected.¹⁶ The stereochemistry of product **3q** was established to be (2*S*,5*S*) by X-ray crystal

structure analysis.¹⁷ The absolute configuration of the recovered oxaziridine **1a** was determined to be the (*R,R*) by comparison of the optical rotation with that reported in the literature.^{6a} The results also convincingly demonstrated that (*S,S*)-**1** is more favorable in the oxyamination process using **4-HBARF**₄ as the catalyst.

To highlight the utility of the recovered enantiomeric pure oxaziridine, we carried out the oxyaminations^{5a,b} of 3-methyl-1*H*-indole **5** and styrene **7** using chiral oxaziridine (+)-**1a** (Scheme 2). The oxyamination of **5** proceeded smoothly in the

Scheme 2. Application of Chiral Oxaziridine (+)-**1a**



presence of CuCl₂ and NBu₄Cl, affording the corresponding product **6** in 84% yield with 2:1 dr and >99% ee. Only one isomer of **8** was obtained in the asymmetric oxyamination of **7**.

To identify the “matched/mismatched” effect of the oxaziridine clearly, we investigated the reaction of azlactone **2a** and (*R,R*)-oxaziridine **1a** with both enantiomeric forms of the bisguanidinium salt catalyst. The comparative experiments gave very impressive stereodifferentiation.¹⁶ The matched reaction of **1a** with **2a** catalyzed by *ent*-**4-HBARF**₄ gave the optically pure product (2*R*,5*R*)-**3a** (>99% ee, >99:1 dr) in nearly quantitative yield. In contrast, the mismatched reaction with **4-HBARF**₄ as the catalyst afforded **3a** in poor yield (36%) and diastereoselectivity [(2*R*,5*R*)-**3a**:(2*R*,5*S*)-**3a** = 67:33] along with consistently excellent ee. Moreover, the reaction catalyzed by DMAP gave **3a** in moderate yield (41.5%) with 85:15 dr. Unfortunately, it seemed that the mismatched reaction gave different diastereo- and enantiomeric mixtures of the product isomers than the matched reaction. The diastereo- and enantioselectivity observed in the products are a combination of the KR and the diastereomer differentiation induced by the chiral catalyst and oxaziridine. No perceptible DKR was

observed in these cases, which precludes the major intermediacy of an epoxide as proposed in Ye's work.^{5d}

To elucidate the stereodifferentiation of the catalytic system, the structure of the bisguanidinium salt was pursued. Disappointingly, a series of attempts to get the crystal structure of bisguanidinium hemisalt **4·HX** failed. Instead, crystals of **4·2HBF₄**¹⁷ were obtained from solutions of either **4·2HBF₄** or **4·HBF₄**. It occurred to us that an equilibrium among **4**, **4·HX**, and **4·2HX** might exist. Therefore, comparison experiments were performed to confirm this presumption. A 1:1 mixture of **4** and **4·2HBAr^F₄** gave an outcome comparable to that for **4·HBAr^F₄**. However, catalyst **4** resulted in a racemic product, and its salt **4·2HBAr^F₄** gave no reaction at all. This observation provided a direct method to utilize bisguanidinium hemisalt catalyst **4·HBAr^F₄**. On the basis of the above results, we considered the possibility that the chiral bisguanidinium hemisalt serves as a bifunctional catalyst. The guanidine section of the catalyst might activate the azlactone. On the other hand, the guanidinium section in the catalyst could preferentially recognize and activate the (S,S)-oxaziridine. The spatial arrangement of **4·2HBF₄** seemed to make a great deal of difference in comparison with bisguanidine **4**.^{13a} The intramolecular hydrogen bonds between the amide and guanidine moieties disappear after protonation of the guanidine. The flexibility of the diamine backbone and the surrounding counterion appear to create a chiral environment suitable for the asymmetric reaction.

In conclusion, we have developed an efficient asymmetric oxyamination of azlactones catalyzed by a chiral bisguanidinium hemisalt that allows the generation of a variety of optically active oxazolin-4-one derivatives with potential biological activity. Furthermore, the reaction displays remarkable triple stereodifferentiation and kinetic resolution. Chiral nonracemic oxaziridines were readily recovered with good *S* factors. Efficient asymmetric oxyaminations of 3-methylindole and styrene were accomplished using the recovered chiral oxaziridine. Further exploration of the use of this catalyst in other reactions is underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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(16) See the Supporting Information for details.

(17) CCDC 931982 (*cis*-**3q**) and CCDC 936308 (**4·2HBF₄**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.