Regiodivergent Kinetic Resolution of Terminal and Internal *rac*-Aziridines with Malonates under Dinuclear Schiff Base Catalysis

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Ⓢ *Supporting Information*

ABSTRACT: Regiodivergent parallel kinetic resolution of aziridines with malonates was achieved under dinuclear Schiff base catalysis. The regiodivergent reaction proceeded under catalyst-control irrespective of the substituents on the aziridines, and 2.5−10 mol % of a Y(OTf)$_3$/La(OiPr)$_3$/a dinucleating Schiff base = 1:1:1 mixture gave versatile γ-amino acid derivatives in 96 → >99.5% ee. Not only terminal but also internal racemic aziridines reacted smoothly under suitably combined Lewis acid/Brønsted base catalysis.
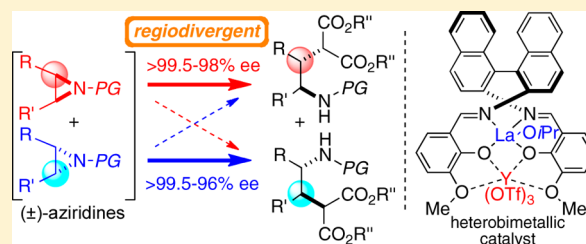
1. INTRODUCTION

Enantioselective aziridine ring-opening reactions are powerful tools for developing nitrogen-containing chiral building blocks useful for the synthesis of biologically active molecules.[1] Tremendous efforts, therefore, have been devoted to the development of these reactions over the past decade, leading to a variety of chiral metal- and organo-catalyzed desymmetrization reactions of *meso* aziridines with nitrogen,[2] halogen,[3] sulfur,[4] phosphorus,[5] carbon,[6] and other nucleophiles[7] (Scheme 1a).

More recently, Ooi[8a,b] and Morgan[8c] reported a couple of elegant methods for kinetic resolution of racemic aziridines via ring-opening reactions.[8] For efficient kinetic resolution of racemic aziridines, however, sufficiently large steric and/or electronic differences between two possible reacting sites are needed (Scheme 1b). Thus, high selectivity in kinetic resolution is achieved mostly with terminal racemic aziridines, and moderate selectivity is observed with internal racemic aziridines when two substituents are sterically and electronically similar but not identical (R ≈ R′).

Divergent parallel kinetic resolution[9−11] can be a good alternative for such racemic aziridines (Scheme 1c), where each enantiomer is transformed into a different enantiomerically enriched product at a similar reaction rate. Divergent kinetic resolution is, in principle, advantageous over conventional kinetic resolution for achieving high enantioselectivity (>98% ee) even using substrates with similar reacting sites. Regiodivergent parallel kinetic resolution of racemic aziridines, however, is rare. In 2009, RajanBabu, Parquette and co-workers for the first time realized regiodivergent ring-opening of terminal racemic aziridines with an azide nucleophile,[10] but this is currently the only successful example of parallel kinetic resolution of racemic aziridines. Thus, it is highly desirable to

Scheme 1. Classification of Enantioselective Aziridine Ring-Opening Reactions
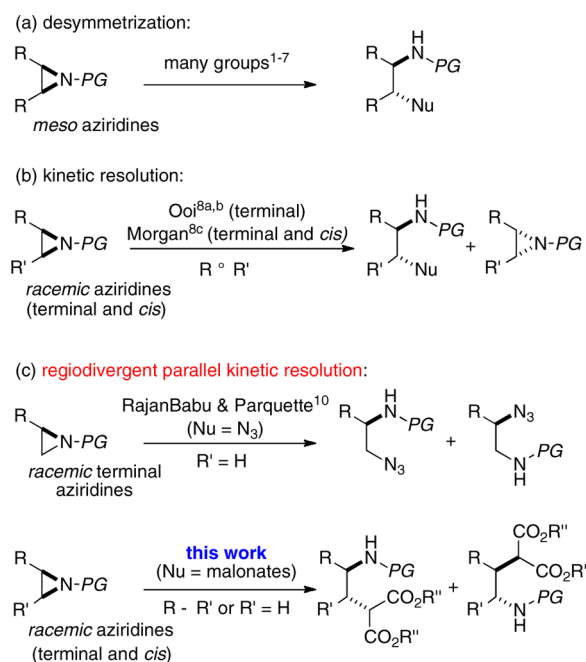
expand the scope of both aziridines and nucleophiles to broaden the synthetic utility of the process.

As a part of our ongoing studies on dinuclear Schiff base catalysis,[12,13] we previously reported desymmetrization of *meso* aziridines with malonates using a heterodinuclear rare earth

metals/Schiff base **1** complex (Figure 1). Suitable selection of a Brønsted basic rare earth metal alkoxide and a Lewis acidic rare
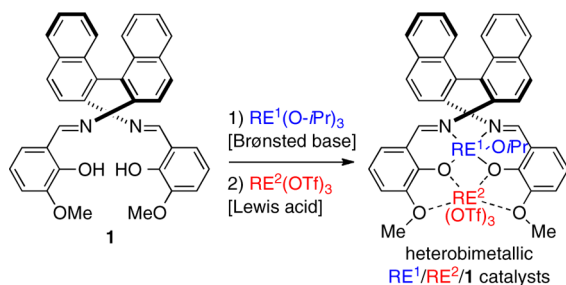

Figure 1. Dinucleating Schiff base **1** and postulated structures of heterobimetallic rare earth (RE) catalysts bearing acid/base moieties.

earth metal triflate was important to achieve good reactivity and enantioselectivity, and a La(OiPr)$_3$/Yb(OTf)$_3$/Schiff base **1** was the optimum one, giving ring-opened products in 97 → >99.5% ee (Scheme 1a, PG = 3,5-dinitrobenzoyl; Nu = malonate).[14] On the basis of high enantio-discriminating ability of the heterodinuclear rare earth metals/Schiff base **1** complex for *meso* aziridines, we hypothesized that the same catalyst would be applicable even for racemic aziridines bearing two sterically and electronically similar but not identical substituents (Scheme 1c, bottom). In this article, we describe trials to expand the utility of our dinuclear Schiff base catalysis to regiodivergent parallel kinetic resolution of racemic aziridines.
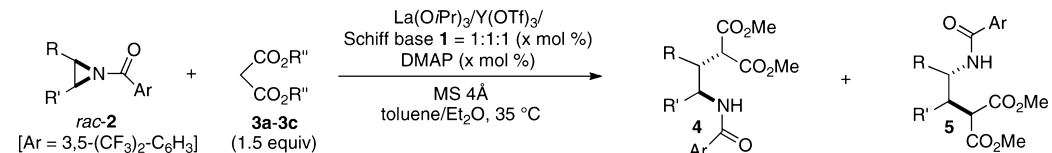
2. RESULTS AND DISCUSSION

Optimization studies of regiodivergent parallel kinetic resolution of racemic aziridines are summarized in Table 1. Because a racemic terminal aziridine bearing a 3,5-dinitrobenzoyl protecting group was unstable, racemic aziridine **2a** bearing a 4-nitrobenzoyl group and malonate **3a** were initially selected as model substrates. We first applied the reaction conditions, previously optimized for *meso* aziridines, for **2a** and **3a** (Table 1, entries 1−3). Although the enantioselectivity was promising in the presence of Et$_3$N additive (entries 2−3, 95−98% ee), the reactivity was poor, giving products **4aa** and **5aa** in <10% yield. Thus, we fully optimized the reaction conditions toward a regiodivergent ring-opening of racemic aziridines. Among the various solvents screened, toluene/Et$_2$O = 1:2 mixture was the best (entry 4, **4aa**: 14% yield, 99% ee, **5aa**: 11% yield, 98% ee). *N*-Acyl protecting groups affected the reactivity (entries 4−6) and aziridine **2c** bearing a 3,5-ditrifluoromethyl-benzoyl group showed the best reactivity (entry 6). An amine additive was also important to obtain the desired ring-opening adducts, while suppressing undesired Lewis acid-promoted rearrangement into oxazolines.[15] Among amine additives, DMAP was the best, and the yield of **4ca** and **5ca** improved to 30% and 29%, respectively (entry 10). Rare earth metal effects are summarized in entries 10−18. Among Brønsted basic rare earth metal alkoxides screened (entries 10−14), the most Brønsted basic La(OiPr)$_3$ gave the highest yield. The yield of products was also well correlated with the Lewis acidity of rare earth metal triflates [Y(OTf)$_3$ > Yb(OTf)$_3$ > Gd(OTf)$_3$ > Sm(OTf)$_3$ > La(OTf)$_3$]

Table 1. Optimization Studies of Regiodivergent Resolution of Aziridine with Malonate

entry	RE^1 source	RE^2 source	solvent	additives	PG:Ar	2	temp (°C)	time (h)	% yield[a] of 4	% ee[b] of 4	% yield[a] of 5	% ee[b] of 5
1	La(OiPr)$_3$	Yb(OTf)$_3$	THF	none	4-NO$_2$-C$_6$H$_4$	2a	25	45	trace	ND	trace	ND
2	La(OiPr)$_3$	Yb(OTf)$_3$	THF	Et$_3$N	4-NO$_2$-C$_6$H$_4$	2a	25	45	5	97	5	ND
3	La(OiPr)$_3$	Yb(OTf)$_3$	toluene	Et$_3$N	4-NO$_2$-C$_6$H$_4$	2a	25	45	9	95	7	98
4	La(OiPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	Et$_3$N	4-NO$_2$-C$_6$H$_4$	2a	25	45	14	99	11	98
5	La(OiPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	Et$_3$N	4-CF$_3$-C$_6$H$_4$	2b	25	45	trace	ND	trace	ND
6	La(OiPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	Et$_3$N	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	45	22	99	20	98
7	La(OiPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	iPr$_2$NEt	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	45	trace	ND	trace	ND
8	La(OiPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	TMEDA	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	45	trace	ND	trace	ND
9	La(OiPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	pyridine	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	45	19	99	19	97
10	La(OiPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	DMAP	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	45	30	99	29	97
11	Nd(OiPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	DMAP	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	48	12	98	11	97
12	Sm(OiPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	DMAP	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	48	trace	ND	trace	ND
13	Gd(OPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	DMAP	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	48	trace	ND	trace	ND
14	Er(OiPr)$_3$	Yb(OTf)$_3$	toluene/Et$_2$O	DMAP	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	48	trace	ND	trace	ND
15	La(OiPr)$_3$	La(OTf)$_3$	toluene/Et$_2$O	DMAP	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	48	5	ND	trace	ND
16	La(OiPr)$_3$	Sm(OTf)$_3$	toluene/Et$_2$O	DMAP	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	48	12	99	14	99
17	La(OiPr)$_3$	Gd(OTf)$_3$	toluene/Et$_2$O	DMAP	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	48	20	99	22	99
18	La(OiPr)$_3$	Y(OTf)$_3$	toluene/Et$_2$O	DMAP	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	48	33	>99.5	36	>99.5
19	La(OiPr)$_3$	Y(OTf)$_3$	toluene/Et$_2$O	DMAP + MS 4 Å	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	25	48	40	>99.5	47	>99.5
20	La(OiPr)$_3$	Y(OTf)$_3$	toluene/Et$_2$O	DMAP + MS 4 Å	3,5-(CF$_3$)$_2$-C$_6$H$_3$	2c	35	38	45[c]	>99.5[d]	49[c]	>99.5[d]

[a]Determined by ^{1}H NMR analysis of the crude mixture. [b]Determined by chiral HPLC analysis. [c]Isolated yield after purification by column chromatography. [d](S)-Schiff base **1** was used, giving *ent*-**4ca** and *ent*-**5ca** in major.

Table 2. Substrate Scope of Regiodivergent Resolution of Aziridines with Malonates

| entry	R	R′	2	cat. (× mol %)	R″	3	time (h)	4	% yield[a] of 4	% ee[b] of 4	5	% yield[a] of 5	% ee[b] of 5
1	cyclo-hex	H	2c	10	Me	3a	38	4ca	45	>99.5[c]	5ca	49	>99.5[c]
2	cyclo-hex	H	2c	10	Et	3b	39	4cb	46	99	5cb	46	>99.5
3	cyclo-hex	H	2c	10	Bn	3c	64	4cc	29	99	5cc	40	99
4	cyclo-pent	H	2d	10	Me	3a	48	4da	36	>99.5	5da	48	96
5	iPr	H	2e	10	Me	3a	48	4ea	36	98	5ea	49	>99.5
6	nBu	H	2f	10	Me	3a	26	4fa	49	>99.5	5fa	46	>99.5
7	cyclo-hex-CH$_2$−	H	2g	10	Me	3a	26	4ga	45	99	5ga	46	>99.5
8	iBu	H	2h	10	Me	3a	37	4ha	49	99	5ha	49	>99.5
9	iBu	H	2h	2.5	Me	3a	72	4ha	36	99	5ha	44	>99.5
10	Et	Me	2i	10	Me	3a	26	4ia	43	>99.5	5ia	44	96
11	nPr	Me	2j	10	Me	3a	35	4ja	42	99	5ja	49	>99.5
12	nPr	Et	2k	10	Me	3a	48	4ka	47	99	5ka	47	98

[a]Isolated yield after purification by column chromatography. [b]Determined by chiral HPLC analysis. [c](S)-Schiff base 1 was used, giving ent-4ca and ent-5ca in major.

(entries 10, 15−18),[16] and the best yield was achieved with a combination of La(OiPr)$_3$ and Y(OTf)$_3$ (entry 18, 4ca: 33% yield, 5ca: 36% yield). Finally, the addition of molecular sieves 4 Å further improved the yield, and ring-opening adducts were obtained in 94% isolated yield (4aa: 45%, 5aa: 49%) with >99.5% ee each at 35 °C (entry 20).

The substrate scope of aziridines and malonates as well as a trial to reduce catalyst loading are summarized in Table 2. The present regiodivergent reaction was rather sensitive to the steric hindrance of nucleophiles. While the reaction proceeded smoothly with dimethyl malonate (3a, entry 1) and diethyl malonate (3b, entry 2), the reactivity of the bulkier dibenzyl malonate (3c) decreased. The reaction pathway to produce 4, in which an enolate should attack the sterically more hindered site under catalyst-control, was significantly affected by a subtle change in nucleophiles. In entry 3 using malonate 3c, product 4cc was obtained in only 29% yield (99% ee), while product 5cc was obtained in 40% yield (99% ee). The results with other terminal racemic aziridines are summarized in entries 4−8. Both branched- and linear-alkyl substituted aziridines 2d−2h gave products 4 and 5 in good yield (4: 36−49%, 5: 46−49%) and excellent enantioselectivity (96 → >99.5% ee). Catalyst loading was successfully reduced to 2.5 mol %, and products 4ha and 5ha were obtained in 36% and 44%, respectively (entry 9). Internal cis-aziridines 2i−2k bearing sterically and electronically similar substituents were also applicable without problems, and products 4 and 5 were obtained in good yield (42−49%) and high enantioselectivity (entries 10−12, 96 → >99.5% ee). On the other hand, trans-aziridines did not produce any desired products under the present heterodinuclear Schiff base catalysis.

The products in the present reaction are useful precursors for γ-amino acids. Decarboxylation of 4ha gave 6ha in 81% yield. Protection of 6ha with Boc-group, followed by treatment with NaOMe at rt gave Boc-protected γ-amino ester 7ha in 87% yield (2 steps, Scheme 2). The absolute stereochemistry of product 4ha was determined to be (R) by comparing the optical rotation of 7ha with reported data.[17] The absolute stereochemistry of products 4ka and 5ka was also unequivocally determined by X-ray crystallographic analysis (Figure 2).

Scheme 2. Transformation into γ-Amino Acid[a]
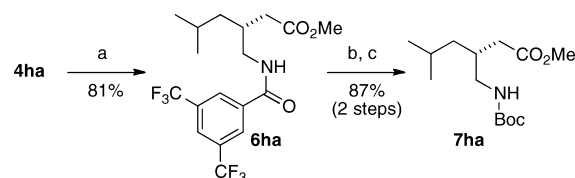
[a]Reagents and reaction conditions: (a) LiCl, H$_2$O, DMSO, 130 °C, 3.5 h, 85% yield; (b) Boc$_2$O, Et$_3$N, cat. DMAP, THF, rt, 2.5 h; (c) NaOMe, MeOH, rt, 17 h, 87% yield (2 steps).
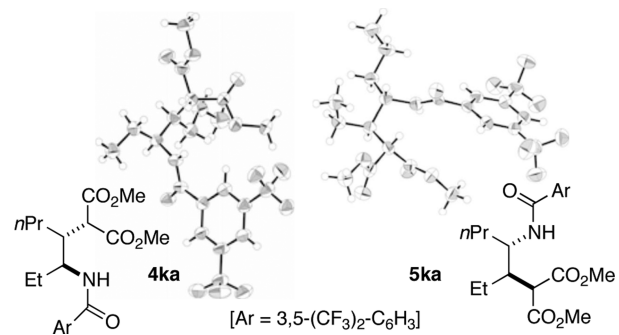

Figure 2. ORTEP drawings of 4ka and 5ka.

The exceptionally high enantioselectivity observed in the present regiodivergent ring-opening reaction represents the power of dinuclear Schiff base catalysis. The chiral catalyst strictly distinguished enantiomers of starting aziridines, and (2R,3S)-2i−2k selectively gave 4 while (2S,3R)-2i−2k gave 5 under chiral catalyst-control irrespective of the substituents on the aziridines (Figure 3). The results in Table 1, entries 10−18 implied that both Lewis acidity and Brønsted basicity of the catalyst are important. In the precedent regiodivergent ring-opening of aziridine, RajanBabu and Parquette utilized a dimeric Y/Schiff base 1 = 1:1 complex, and cooperative mechanism of two Y-metal centers was proposed.[10,18] By analogy, the Lewis acid/Brønsted base intramolecular cooperative mechanism would also be key in the present reaction to
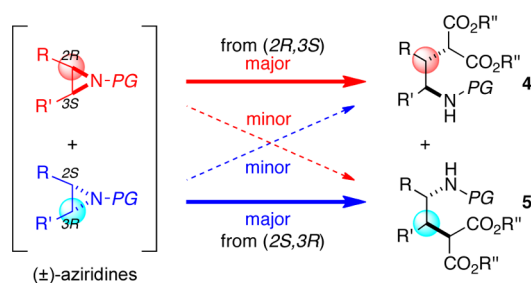
Figure 3. Reaction pathway of the regiodivergent ring-opening reaction under dinuclear Schiff base catalysis.

producing ring-opening adducts efficiently via proper activation of both aziridine and malonate.

3. CONCLUSION

In summary, we demonstrated the utility of dinuclear Schiff base catalysis for regiodivergent parallel kinetic resolution of aziridines with malonates. Both terminal and internal racemic aziridines reacted smoothly under suitably combined Lewis acid/Brønsted base catalysis, giving versatile γ-amino acid derivatives in 96 → 99.5% ee. Further studies are ongoing to broaden the scope of the regiodivergent reaction,[19] such as for *trans*-aziridines and other nucleophiles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimetal details, including procedures, syntheses and characterization of new products, ^{1}H and ^{13}C NMR charts, and cif. 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.

■ ACKNOWLEDGMENTS

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(19) Functional group compatibility of the present system also remained problematic. For example, aziridines bearing an ether functional group resulted in poor reactivity.