Asymmetric Syntheses of Aziridine-2-carboxylates via Reductive Kinetic Resolution of 2*H*-Azirines

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Abstract

Enantioenriched aziridine-2-carboxylates are valuable organic compounds thanks to their versatility as chiral building blocks. Several syntheses of bioactive molecules employ aziridine-2-carboxylates as a crucial synthetic intermediate, e.g. the total synthesis of dynobacin A. However, traditional strategies only access N-protected aziridines, which are poorly stable and can undergo unwanted side reactions as ring-opening. Herein, we present the first copper hydride kinetic resolution of racemic 2H-azirines for the asymmetric preparation of N-H aziridine-2-carboxylates and the corresponding enantioenriched 2H-azirines. This is relevant as N-H aziridine-2-carboxylates are a generally bench stable and easily diversifiable building block. After an extensive catalyst screening and reaction optimization, the N-H aziridines were obtained with excellent diastereoselectivity (>20:1) and high enantioselectivity (up to 94%). Additionally, we conducted a Hammett study and we observed a linear free energy relationship between the ΔΔG‡ of the diastereomeric transition states and the σ_p- values.

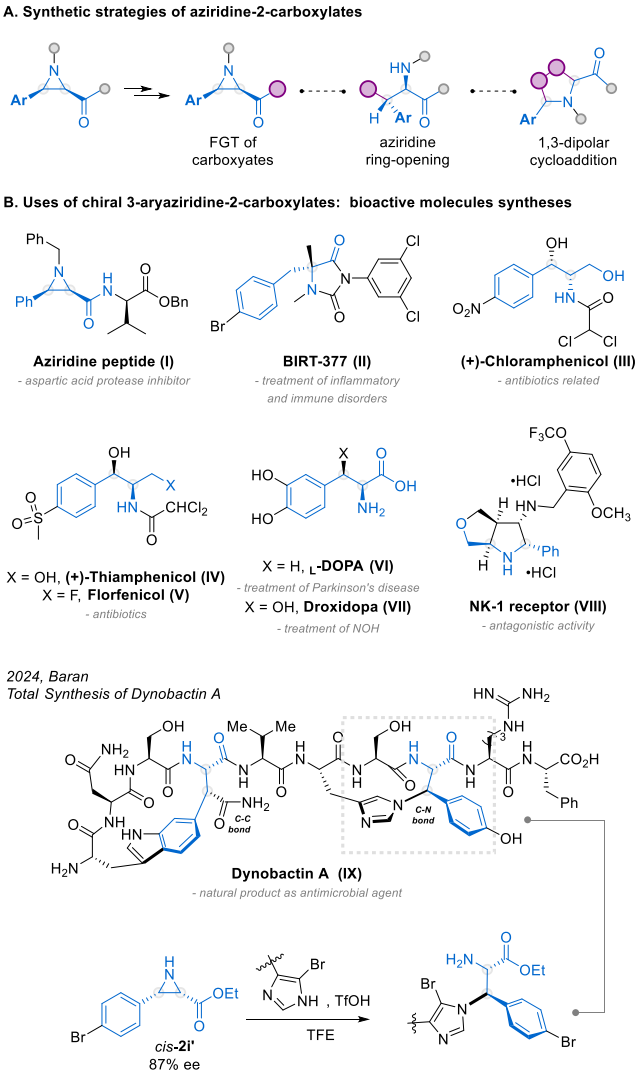
Introduction

Aziridine-2-carboxylates are often employed as chiral building blocks via the permutation of the aziridine by ring opening, 1,3-dipolar cycloaddition, and functional group transformation of carboxylate (Scheme 1A).[1] In fact, the merits of this moiety are well demonstrated by extensive syntheses of bioactive molecules with defined stereochemistry (Scheme 1B). For example, aziridine peptide (I), an aspartic acid protease inhibitor, was prepared by amidation of the corresponding

racemic carboxylate followed by separation with a chiral column.[2] Recognized for the treatment of inflammatory and immune disorders, BIRT-377 (II) hydantoin skeleton could be reached by the reaction between a 3,5-dichlorophenylisocyanate and α-amino ester which originated from the reductive ring opening of the corresponding chiral 3-arylaziridine-2-carboxylate.[3] Antibiotics like (+)-chloramphenicol (III),[4] (+)-thiamphenicol (IV)5 and florfenicol (V),[5] pro-drugs like L-DOPA (VI)[6] and droxidopa (VII),[7] featuring two stereocenters were prepared by the regio- and stereoselective nucleophilic ring-openings and elaborations of the carboxylate and amino group. Moreover, the aziridine moiety could serve as the 1,3-dipole precursor in Pad-wa's intramolecular 1,3-dipolar cycloaddition to afford the neurokinin (NK)-1 receptor (VIII).[1d] Recently, Baran and coworkers reported the first total synthesis of the potent antimicrobial agent dynobactin A (IX). The synthetic route highlights the utility of free N-H aziridines (eg. **cis-2i'**, 87% ee) as the key building blocks in stereo- and regioselective C-C (western fragment) or N-C (eastern fragment) ring opening events.[8]

Traditional strategies for the asymmetric synthesis of aziridine-2-carboxylates include intramolecular substitution of chiral β-amino ester,[10] asymmetric aziridination of imine with chiral ruthenium[9] or borate catalysts,[3, 10] and asymmetric aziridination of alkene with copper catalysts as chiral induction (Scheme 2A).[11] However, most of the reported procedures deliver N-electron-withdrawing groups aziridines, such as N-sulfinate,[12] N-sulfonate,[11,13] N-phosphonate,[14] and N-carbamate.[15] These activated substrates can be poorly stable and undergo unwanted ring-opening.[8] On the other hand, chiral N-H aziridines are more applicable building blocks as they are generally bench stable under most circumstances for a long period of time. Moreover, their ring-opening reactivity can be tuned in one step by N-functionalization. A seemingly straightforward preparation of chiral aziridine-2-carboxylates is the asymmetric nucleophilic additions of 2H-azirines.[16] Recently, kinetic resolution (KR) of racemic 2,3-disubstituted 2H-azirines has emerged as a mild and useful tool to enantioselectively access N-H aziridines and 2H-azirines (Scheme 2B).[16a, b, i]

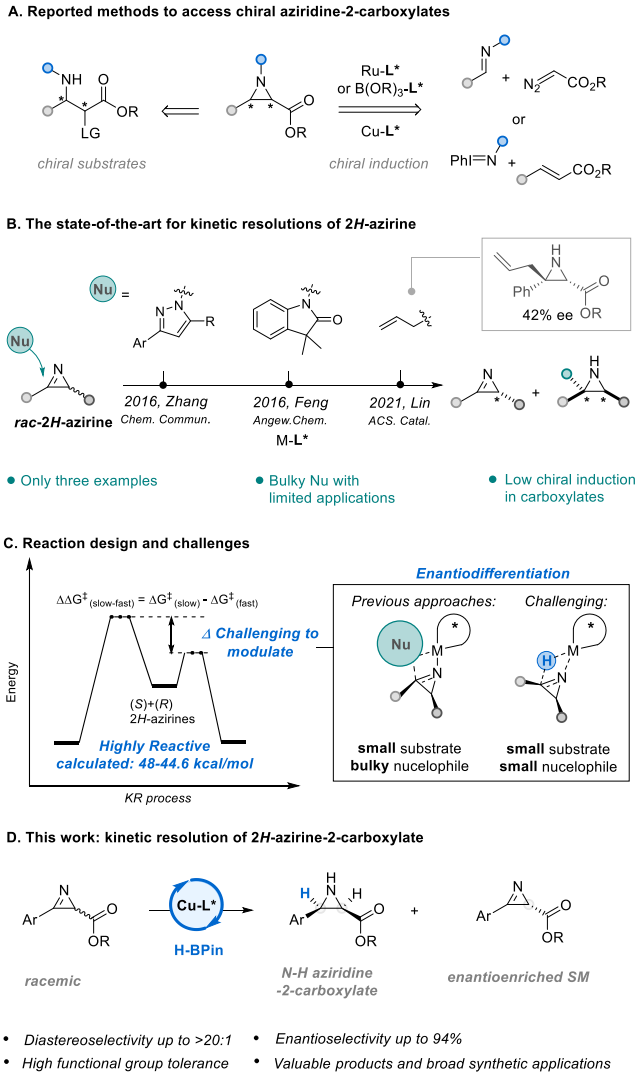
While highly enabling, only three examples of 2H-azirines KR are reported. Although excellent ees (up to 99%) were achieved by the groups of Zhang and Feng, the incorporation of exotic nucleophiles severely limits their protocols' application. Recently, Lin and coworkers were able to prepare a more desirable 3-ally-aziridine-2-carboxylate, but with low chiral induction (42% ee).[16i]



Scheme 1. A) Chiral aziridine-2-carboxylates can be leveraged as building blocks via S_N2 ring-opening, ester group interconversion and as chiral 1,3-dipoles; B) Reported bioactive molecules that derive from aziridine-2-carboxylates.

Inspired by these reports and propelled by our ongoing research in enantioselective copper hydride chemistry,[17] we speculated that the combination of copper hydrides and commercially available chiral ligands could be leveraged to differentiate the enantiomers of a racemic 2H-azirine-2-carboxylate to access a more widely applicable chiral N-H-aziridine-2-carboxylate (Scheme 2C). We note that copper-catalyzed kinetic resolutions have been applied to substrates whose reactivity is relatively low and therefore the enantiodiscrimination is facilitated.[18] The 2H-azirine-2-carboxylates are highly reactive,[19] with a calculated total ring strain of 48-44.6 kcal/mol.[20] Moreover, hydrides are small nucleophiles in comparison to the previous examples, making the enantiodiscrimination very

challenging. Herein, we describe the realization of this goal, which represents the first highly enantioselective reduction of 2H-azirines by Cu–H kinetic resolution process (Scheme 2D).

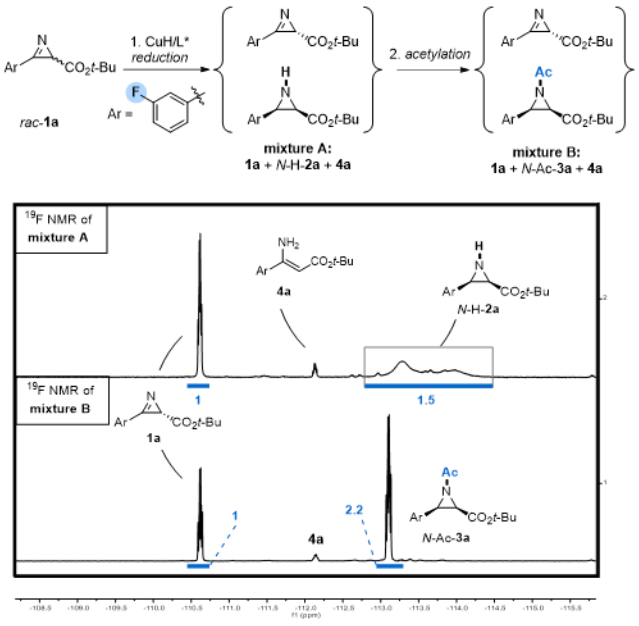


Scheme 2. A) Reported strategies for the construction of chiral aziridine-2-carboxylates; B) Reported KR of 2*H*-azirines with the corresponding used nuclophiles; C) representation of the challenges of developing a reductive KR of 2*H*-azirines with hydride as the nucleophile; D) Current work highlights.

Results and Discussion

To streamline our initial study of the kinetic resolution system, we designed an experimental setup that could precisely evaluate the crude mixtures without chromato-graphic isolation. We employed fluorinated racemic tert-butyl 3-(3-fluorophenyl)-2H-azirine-2-carboxylate (**1a**), which was selected as the model because of the merits of ^{19}F NMR spectral analysis on crude reaction mixtures (Scheme

3). The free “N-H” brings about a negative effect of quadrupolar coupling to both ^{1}H and ^{19}F NMR analysis, and depending on the acid content of the deuterated solvent different shifts can be observed (mixture A). To address this, we executed an additional acetylation step on the crude after the CuH-catalyzed reduction, which enabled distinct and informative crude ^{19}F NMR spectra for the kinetic resolution (mixture B). Indeed, the ratio in the acetylated product and free N-H do not match, there-fore highlighting the necessity of protection for precise measurement. It is worth mentioning that we also observed a variable amount of side product **4a**, which stems from a hydride ring opening at the C-2 position.

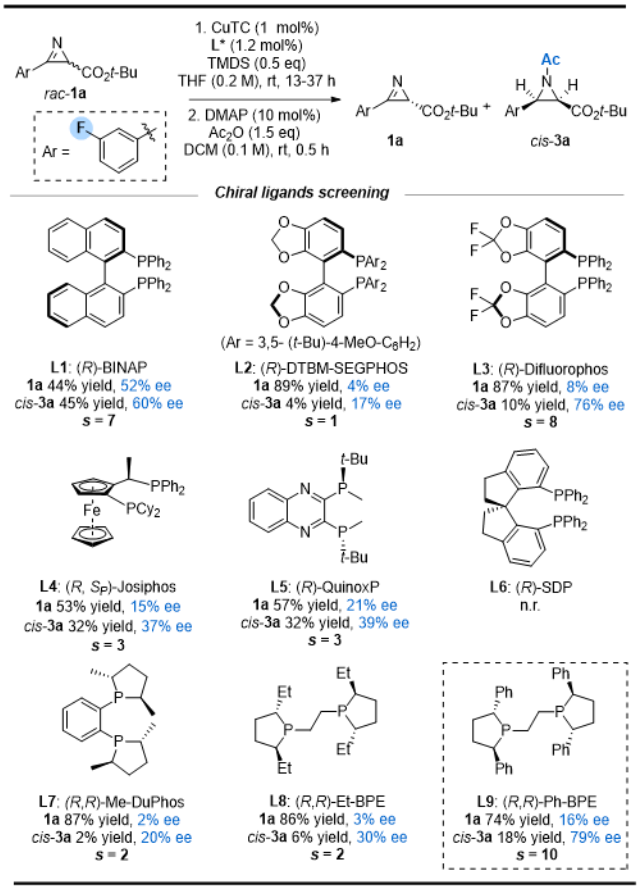


Scheme 3. Reaction optimization workflow for the reductive KR by ^{19}F NMR and acetylation to obtain precise measurements of the **1a/2a** ratio.

After an initial screening, CuTC was elected as the Cu source as it provided the most reliable Cu–H formation (see section 4.1 in the supporting information for details). Moreover, we found that at low catalyst loading oxygen exclusion was necessary to ensure the stability of the Cu–H, although degassing of freshly dried THF was unnecessary. In the presence of CuTC (1 mol%), (R)-BINAP (**L1**) (1.2 mol%), and TMDS (0.5 equiv) in THF (0.2 M with respect to **1a**) at room temperature for 18 hours, the kinetic resolution of racemic-**1a** and acetylation successfully afforded the desired aziridine cis-**3a** featuring two stereocenters with >20:1 dr, 60% ee and recovered 1a with 52% ee (Table 1, **L1**). As previously reported, high diastereoselectivity results from the delivery of hydride from the less hindered side.[16a, d, i] Then we proceeded to an extensive ligand (see section 4.2 in the supporting

information for details) of which we treat here the more salient examples. Biaryl ligand (R)-DTBM-SEGPHOS (**L2**), which has been frequently employed in chiral copper-catalyzed reductions of ketones[21] and imines,[22] was then examined. Disappointingly, low conversion (4% yield of cis-**3a**) and enantioselectivity (17% ee of cis-**3a**) were detected, indicating the difficulty of chiral induction in 2H-azirines. The use of electron-deficient biaryl ligand (R)-difluorophos (**L3**) was promising, resulting in the 76% ee of cis-3a albeit with low conversion (13%). Other diphos-phine ligands (**L4**-**L7**) bearing varied chiral backbones were also evaluated, either to yield aziridines with both low yield and enantioselectivities or no reaction. To our delight, when (R,R)-Ph-BPE (**L9**) was tested, the N-protected aziridine **3a** gave a promising 79% ee , while the higher electron-donating and less rigid (R,R)-Et-BPE (**L8**) only led to 30% ee of cis-**3a**.

Table 1. Selected examples of the chiral ligands screening[a]



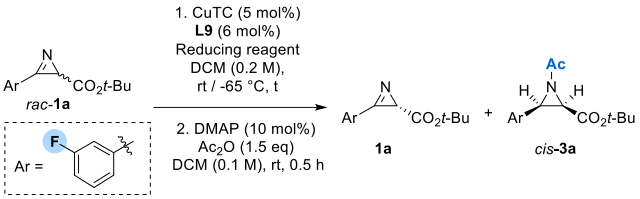
[a] Conditions: rac-**1a** (0.2 mmol), CuTC (1 mol%), L* (1.2 mol%), TMDS (0.5 eq) in dry THF (1.0 mL) at rt. Acetylation conditions: DMAP (10 mol%), Ac_2O (1.5 eq), and Et_3N (2.5 eq) in DCM (2.0 mL) at rt for 0.5 hour. [b] Yield was determined by ^{19}F NMR of the crude mixture using trifluorotoluene as the

internal standard. [c] Ee was determined by HPLC analysis. [d] Selectivity factors s, s = ln[(1-C)(1-eesub)]/ln[(1-C)(1+eesub)], C = (eesub)/(eesub+eepro). The dr values of **3a** were all over 20:1 as detected by ^{19}F NMR spectroscopy. CuTC, CuI thiophene-2-carboxylate; TMDS, 1,1,3,3-Tetramethyldisiloxane.

With the optimal ligand **L9** at hand, dramatic improvement in enantioselectivity (91% ee of cis-**3a** Table 2, entry 2) could be realized by switching the solvent from THF to dichloromethane (see the complete solvents screening section 4.3 in supporting information for details), as well as reducing the temperature to -60 °C. Due to the low temperature, more reactive hydride donors as $PhSiH_3$ were necessary to ensure the turnover within an acceptable amount of time.[23]

As we previously discussed, 2H-azirines are very reactive electrophiles, and although temperature decreases both the rate constants for R and S, the rates are still very similar and conversion control needs to be enforced also by the reductant stoichiometry. Striking this balance is challenging, as 40% conversion of rac-**1a** led to the remaining **1a** in only 53% ee (Table 2, entry 2). Considering the synthetic utilities of both chiral 2H-azirines **1** and aziridines **2**, we prolonged the reaction time to 20 hours to reach an equimolar ratio between **1a** to cis-**3a** but over-reduction occurred (36% ee for cis-**3a**, 99% ee for **1a** Table 2, entry 3). As $PhSiH_3$ can in principle donate three hydrides, other hydride sources were screened. Thus, single hydride $(EtO)_3SiH$ and dimethylmethoxy silane (DMMS) were tested, but they were too inert under cryogenic environment (Table 2, entry 4-5). Pinacolborane (HBPin) was an ideal alternative (Table 2, entry 6-8), with an experimental 0.65 equivalents to achieve the most effective kinetic resolution regarding the yields and enantioselectivities of both **1a** and cis-**3a** (Table 2, entry 7). Notably, throughout the optimization at low temperature, the generation of ring-opening product **4a** was suppressed. While we ultimately moved forward with HBPin as the optimal reductant, we found that -65 °C is the ideal temperature for this kinetic resolution (see the full survey of temperature in section 4.5 of supporting information), where the cis-N-H-**2a** was isolated in 51% yield with 88% ee and **1a** was recovered in 49% yield with 83% ee (s = 41) (Table 2, entry 9).

Table 2. Selected examples of the further optimization.[a]

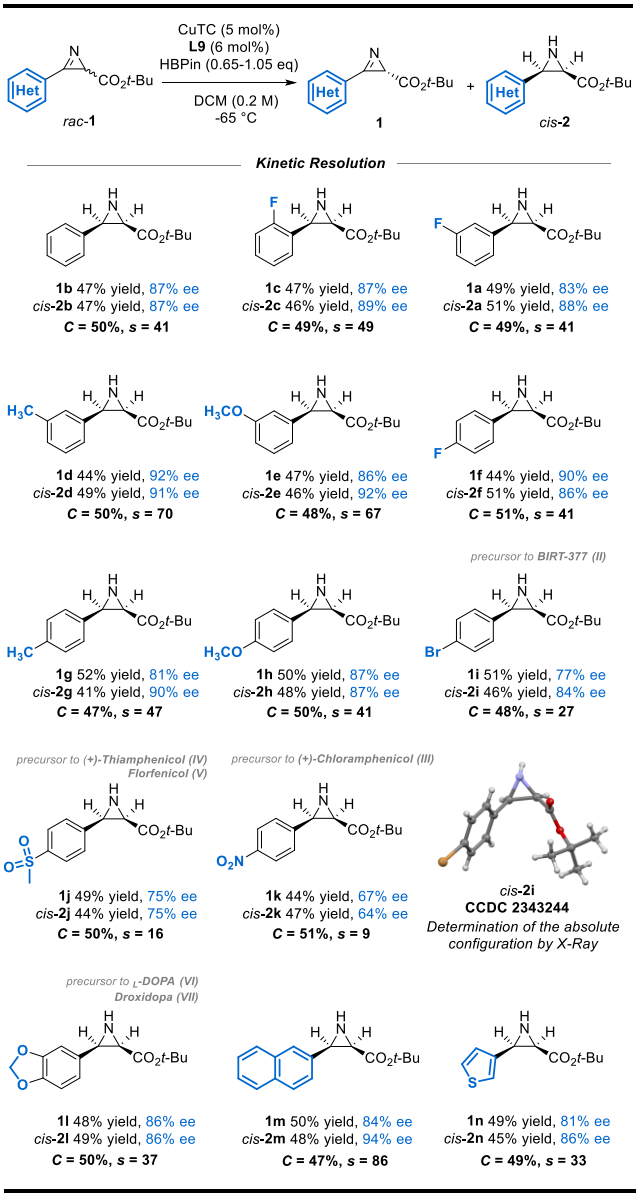


Entry	Reducing reagent (eq)	t/h	**1a**[b,c] Yield (%)	**1a**[b,c] ee (%)	*cis*-**3a**[b,c] Yield (%)	*cis*-**3a**[b,c] ee (%)	*C* (%)	*s*[d]
1[e]	TMDS (0.5)	13	74	16	18	79	17	10
2	$PhSiH_3$ (0.5)	17	60	53	40	91	37	36
3	$PhSiH_3$ (0.5)	20	25	99	75	36	73	9
4[f]	$(EtO)_3SiH$ (0.5)	72	-	-	n.r.	-	0	-
5	DMMS (0.5)	-	-	-	trace	-	0	-
6	HBPin (0.5)	24	66	38	30	92	29	35
7	HBPin (0.65)	24	51	70	48	88	44	33
8	HBPin (0.7)	24	40	97	55	79	55	35
9[g]	**HBPin (0.65)**	**36**	**49**	**83**	**51**	**88**	**49**	**41**

[a] Conditions: rac-**1a** (0.2 mmol), CuTC (5 mol%), **L9** (6 mol%), reducing reagent in dry DCM (1.0 mL) at -60 °C. Acetylation conditions: DMAP (10 mol%), Ac_2O (1.5 eq), and Et_3N (2.5 eq) in DCM (2.0 mL) at rt for 0.5 hour. [b] Yield was determined by ^{19}F NMR of the crude mixture using trifluorotoluene as the internal standard. [c] Ee was determined by HPLC analysis. [d] Selectivity factors s, s = ln[(1-C)(1-eesub)]/ln[(1-C)(1+eesub)], C = (ee-sub)/(eesub+eepro). The dr values of **3a** were all over 20:1 as detect-ed by ^{19}F NMR spectroscopy. [e] CuTC (1 mol%), **L1** (1.2 mol%), dry THF (1.0 mL) at rt instead. [f] No reaction. [g] 0.3 mmol scale, -65 °C, no acetylation step, isolated yields of **1a** and cis-N-H-**2a**.

Having identified the conditions for the catalytic system, we sought to study how the variation of the electronic and local steric profile of the aryl group would influence the kinetic resolution process (Table 3). Racemic 2H-azirines (**1a-1b**, **1d-1k**) representing classic “Hammett” type with mono-substituent at the meta- or para- position were examined. We found that the presence and the position of fluorine atom, with respect to a bare phenyl (**1b**) exerted a small influence on the reaction outcome (**1a, 1f**), leading to the same selectivity factor (s = 41).

Table 3: Scope with (hetero) aryl group[a,b]

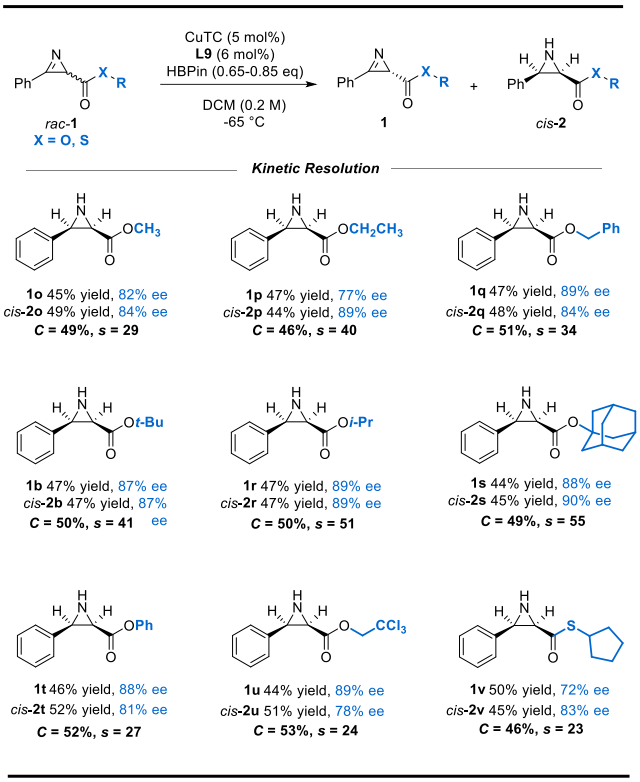


[a] Unless noted, conditions: rac-**1a** (0.3 mmol), CuTC (5 mol%), L* (6 mol%), HBPin (0.65 eq) in DCM (1.0 mL), -65 °C, Ar, 36-45 h. [b] Isolated yield; Ee was determined using HPLC analysis on a chiral stationary phase; Selectivity factors s, s = ln[(1-C)(1-eesub)]/ln[(1-C)(1+eesub)], C = (eesub)/(eesub+eepro); The dr values of **2** were all over 20:1 as detected by ^{1}H NMR spectroscopy.

While in the case of ortho-fluorinated **1c**, the reduction led to cis-**2c** with marginally increased ee in 89% and a higher s factor in 48. This discrepancy might be attributed to the steric profile of the o-

fluorine atom. In sharp comparison, enantioselectivities could be dramatically improved when 2H-azirines (meta-: **1d-1e**, para-: **1g-1h**) were equipped with electron-donating groups (EDG). Notably, meta Me- and MeO- substituted azirines generated reduced products **2d** and **2e** with excellent yields (46-49%) and good ee values (91-92%). Moreover, the reisolated **1d** and **1e** were recovered in equally excellent yields (44-47%) and enantioselectivities (86%-92%). Reactions proceed efficiently with moderate to high electronic deficiency (p-Br, p-SO_2Me, p-N_2O) in 44-47% yields of free aziridines (**2i-2k**). The fruitful transformations of these medicinally relevant substrates highlight the utility of this methodology in bioactive compound syntheses (Scheme 1B). The absolute configuration of the cis-N-H aziridine (**2i**) was confirmed by X-ray crystallography. By analogy, the *R,R* stereochemistry was therefore assigned for the remaining products. A particular sensitivity to the electronic effects of para-substituted 2H-azirine (**1g-1k**) was thus noticed: while the para-EDGs contributed to the enantiodiferentiating process, the electron-withdrawing group (EWGs) on para-position could lead to the opposite tendency evidently with the more electron-withdrawing effects (N_2O>SO_2Me>Br), the more decrease in enantioselectivities (N_2O<SO_2Me<Br). The electronics-enantioselectivity relationship was further investigated by the Hammett plot study (Scheme 4). Challenging substrate **1l** with a sensitive acetal prosperously leads to the cis-aziridine **2l** in 86% ee which is of great value respecting the preparation of prodrugs L-DOPA (VI) and droxidopa (VII) (Scheme 2B). In addition, naphthyl- and thiophenyl- groups were also well-tolerated, providing the corresponding cis-**2i** with excellent chiral induction (94% ee, s = 86), as well as cis-**2j** with slightly diminished enantioselectivity (81% ee, s = 33).

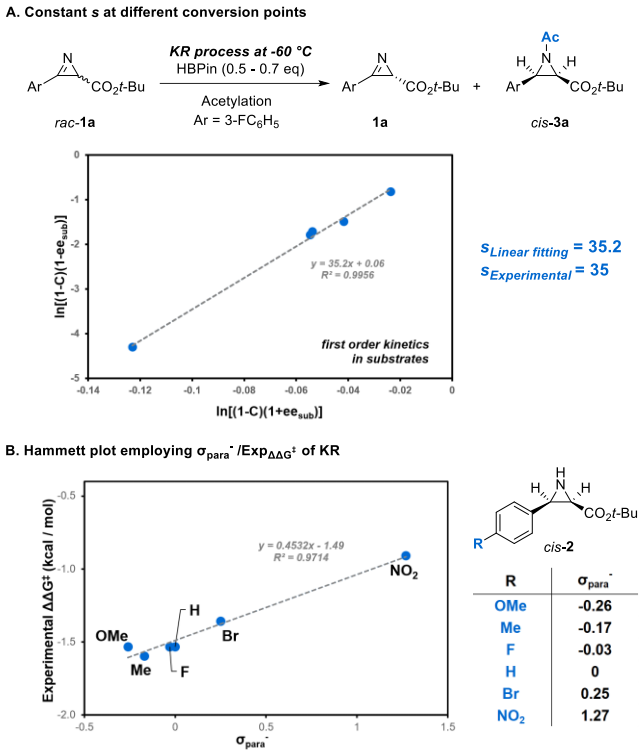
Table 4: Scope of esters[a,b]



[a] Unless noted, conditions: rac-**1a** (0.3 mmol), CuTC (5 mol%), L* (6 mol%), HBPin (0.65 eq) in DCM (1.0 mL), -65 °C, Ar, 36-45 h. [b] Isolated yield; Ee was determined using HPLC analysis on a chiral stationary phase; Selectivity factors s, s = ln[(1-C)(1-eesub)]/ln[(1-C)(1+eesub)], C = (eesub)/(eesub+eepro); The dr values of **2** were all over 20:1 as detected by ^{1}H NMR spectroscopy

Furthermore, 3-phenyl-2H-azirine-2-carboxylates (**1b, 1o-v**) with varied carboxylates were screened under the optimal KR conditions. All of the alkylated carboxylates aziridine, including methyl (**2o**), ethyl (**2p**), benzyl (**2q**), t-butyl (**2b**), i-propyl (**2r**), 2,2,2-trichloroethyl (**2u**) were satisfyingly produced in 44-51% yields and 84%-89% ee. Even the azirine (**1s**) with highly sterically hindered adamantyl carboxylic ester group could be successfully reduced, to afford the cis-**2s** in 90% ee and s factor in 55. Moreover, the carboxylate containing phenyl group cis-**2t** was converted smoothly, with remaining azirine **1t** obtained in 88% ee. Finally, we extended our substrate scope to thiol-esters, affording the S-containing aziridine cis-**2v** in ideal yield and moderate enantioselectivity without poisoning the copper catalyst.

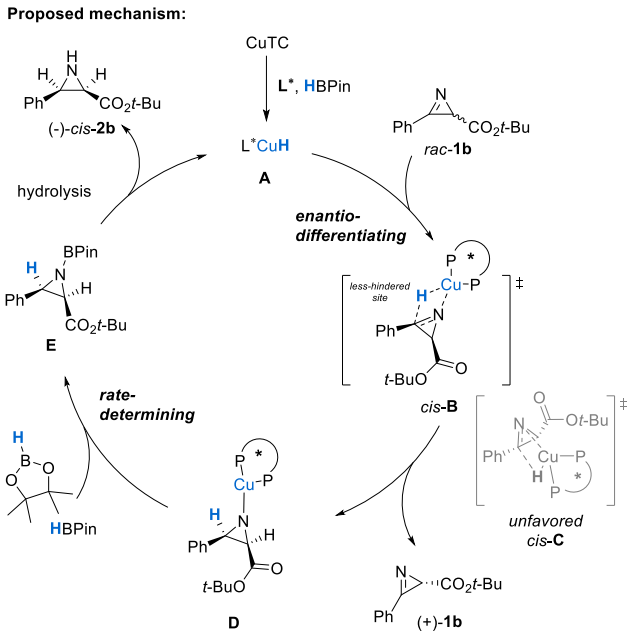
To gain insight into the reaction mechanism and obtain predictive ability in case of desirable new substates, we used the data in Table 3 for a Hammett plot study. First, we tested if s was constant and independent of the reaction conversion, which would also imply a first order in substrate for the selectivity determining step (Scheme 4A). [24] By linear fitting, we observed a first order kinetic profile for the KR of rac-**1a** at -60 °C with an R^2 = 0.996 and a fitted s = k_{rel} = 35.2.



Scheme 4. a) Experimental conversion and enantioselectivity of sm rac-**1a** from the reaction of Scheme 3 shows first order kinetics and gives a linear fitting k_{rel} = 35.2 with an R^2 = 0.996. b) Correlation between experimental enantioselectivities and the σpara- parameter for R.

Following, the s parameter was expressed as ΔΔG‡ (ΔΔG‡ = −RT ln(s)) and plotted against several σ standard parameters. The best correlation was found with found with σpara- (Scheme 4B, y = 0.4532x+1.49, R^2 = 0.971, see the SI for correlations with other parameters).[25] There-fore, through conjugation effects seem to impact s more than field / inductive ones, with strong electron with-drawing groups lowering the selectivity. The positive sign, and small magnitude of the slope value ρ is diagnostic of electrons flowing in the system at the TS with little developing charge at the reaction centre and an increase in rate with electron with-drawing groups, which is in reasonable given the

proposed reaction mechanism profile (Scheme 5).[26] During the irreversible enantiodifferentiating step, the chiral copper hydride complex A, formed from precatalyst CuTC-**L9**-HBPin, will associate with the two substrates forming two diastereomeric transition structures (cis-B and cis-C). A more reactive, electron-poor aziridine (e.g. p-NO_2 **1k**) should proceed via an early reactant-like transition state (TS) with a less tight association to the catalyst and concomitantly a similarity of the diastereomeric ΔG‡. Vice versa, an electron-rich substrate will react forming a more product-like TS, therefore with increased ΔΔG‡. Moreover, the results of **L8** in Table 1 suggest that given a similar type of ligand the enantio-differentiation is dependent on the specific nonbonded interactions between the catalyst complex A and the substrate (**L8** Et fragment on the phosphine, s = 2 vs **L9** Ph fragment, s = 10).

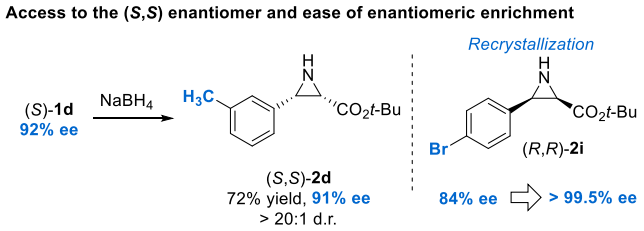


Scheme 5. Proposed reaction mechanism for the KR of 2H-azirines.

Following, the formed species D needs to undergo a sigma bond metathesis to regenerate A and trap the reduced product as a Bpin adduct E. Upon quenching, this will provide the aziridine-2-carboxylates product. During the course of our study, the identity of the reductant did not seem to impact the ee[27] which taken together with the previous observations for related copper hydride reduc-tions suggests that the reductant is not partaking in the enantio-differentiating step.[27] On the other hand, we observed an increase in conversion upon increase of the HBpin reductant over the

same 24 hours timespan (see Table 2, Entry 6-8). In line with previous findings,[23, 28] this could entail that the rate determining step is the slow sigma bond metathesis to regenerate species A.

An advantage of our KR is that it also corresponds to an asymmetric preparation of chiral 2H-azirines carboxylates, which cannot be easily accessed in high enantiopurity.[29] With the material at hand, we explored the viability of a dynamic kinetic resolution process. Unfortunately, the subjection of enantioenriched substrate **1a** to the common bases compatible with copper hydride chemistry at room temperature revealed that no deprotonation and therefore racemization could occur (See Section 8 in Supporting Information). Another advantage was the possibility to access both the enantiomers of a given substrate by simple reduction with $NaBH_4$ (Scheme 6).[29c] Additionally, we note that it is possible to achieve excellent ee by subjecting the enantioenriched 2H-azirine-2-carboxylates to one recrystallization as exemplified by substrate cis-2i which was enriched from 84% ee to >99.5%.



Scheme 6. KR permits the synthesis of both the enantiomers of a given substrate, exemplified by the preparation of (S,S)-**2d** and excellent ees (> 99.9%)can be reached with one pass of recrystallization, as demonstrated with substrate **2i**.

Conclusions

To conclude, we disclose the first Cu–H catalyzed kinetic resolution of 2H-azirines. Several 3-aryl-2H-azirine-2-carboxylates with functional group complexity could be prepared in high diastereo- and enantioselectively. These chiral N-H aziridines are valuable synthetic intermediates and enjoy broad synthetic applications. In addition, we found the linear free-energy relationships between ΔΔG and σpara- which accounts for the decreased enantioselectivities p-NO_2 substrate and gives more insights into the mechanism. Finally, we demonstrate the advantage of the KR by accessing both the enantiomers of 2H-azirine-2-carboxylates and show how to obtain excellent ees with one recrystallization.

Associated content

Supplemental figures, experimental procedures, and characterization of substrates are available within this article Supplementary Information.

CCDC 2343244 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Competing interests

The authors declare no competing interests.

Additional Information

Supplementary Information

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