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Synthesis of Chiral Tetrasubstituted Azetidines from Donor–Acceptor Azetines via Asymmetric Copper(I)-Catalyzed Imido-Ylide [3+1]-Cycloaddition with Metallo-Enolcarbenes

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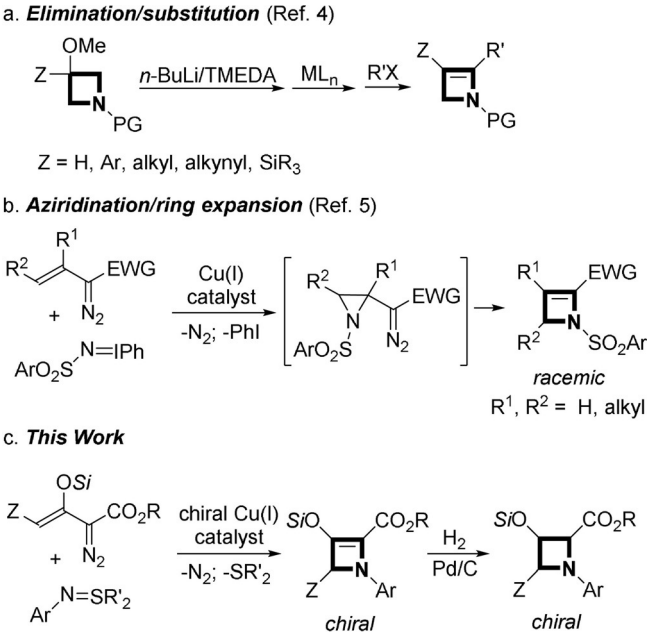
Dedicated to Professor James M. Takacs on the occasion of his 65th birthday

Abstract: *The all-cis stereoisomers of tetrasubstituted azetidine-2-carboxylic acids and derivatives that possess three chiral centers have been prepared in high yield and stereocontrol from silyl-protected Z-γ-substituted enoldiazoacetates and imido-sulfur ylides by asymmetric [3+1]-cycloaddition using chiral sabox copper(I) catalysis followed by Pd/C catalytic hydrogenation. Hydrogenation of the chiral p-methoxybenzyl azetine-2-carboxylates occurs with both hydrogen addition to the C=C bond and hydrogenolysis of the ester.*

Four-membered ring heterocyclic compounds are of increasing importance and interest, not only because of the biological activities of β-lactams[1] but, also, due to expanding interest in unsaturated four-membered ring azetines and their applications.[2] These relatively high energy compounds have not been widely explored because of limited synthetic methods for their formation and because their well-recognized ability to undergo four-electron electrocyclic ring-opening to 1-aza-1,3-butadienes.[3] Available methods for 2-azetine synthesis include those from already-formed four-membered ring heterocycles (3-methoxyazetidine derivatives and 3-azetidinones),[4] vinyldiazo compounds via aziridination/ring expansion reactions,[5] as well as from benzyne via [2+2]-cycloaddition[6] or allenyl imides with imines[7] (Scheme 1 a,b). However, none of the available methods are suitable for the synthesis of chiral 2-azetines.

Chiral azetidine-2-carboxylic acid, the first known example of naturally occurring azetidines,[8] and their derivatives (potential products from reduction of 2-azetine-carboxylates) are structural units of several natural products[9] and the thrombin inhibitor *melagatran*[10] (Figure 1). Various methods have been used for their preparation,[11] but all of them are multistep syntheses from chiral reactants that provide access only to mono- or disubstituted azetidine-2-carboxylic acids and their derivatives. Herein, we report a robust methodology



Scheme 1. Synthetic methods for construction of azetine ring.

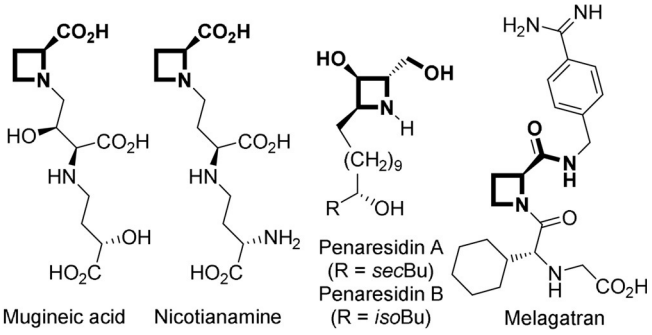


Figure 1. Natural products and a pharmaceutical containing the structural unit of chiral azetidine-2-carboxylates or their reduced forms.

for the highly enantioselective synthesis of 2-azetine-carboxylates catalyzed by copper(I) with chiral sabox ligand and their stereoselective hydrogenation to form a single stereoisomer of tetrasubstituted azetidine-2-carboxylate derivatives (Scheme 1 c).

In previous research from our laboratory we reported that copper(I)-catalyzed [3+1]-cycloaddition of silyl group pro-

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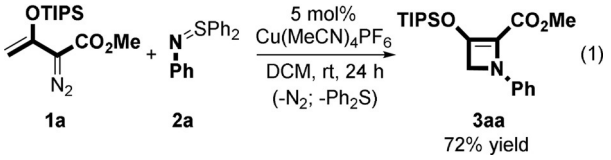
tected enoldiazoacetates with α-acyl sulfur ylides was effective in forming 2-silyloxy-1-cyclobutene carboxylates.[12] This transformation was the first example in which the dipolar intermediate underwent nucleophilic displacement of a leaving group (R_2S) to achieve product formation in a metal carbene [3 + *n*]-cycloaddition reaction.[13]

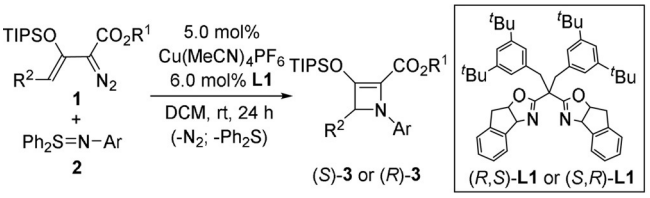
The high yields and enantioselectivities achieved in these reactions prompted us to investigate whether [3+1]-cycloaddition could also occur with "nitrene" donor species. However, *N*-acyl-imido sulfur ylides,[14] used in place of the *N*-acylsulfur ylides, with the same catalysts and under the same conditions, were unreactive even at elevated temperatures due to a lack of reactivity of the imido ylide. Aryl-, sulfonyl-, and acyl-azides were, similarly, unable to undergo cycloaddition with metal carbenes formed from enoldiazoacetates and, instead, formed imine products.[15] However, use of *N*-arylimido sulfur ylides (*S*,*S*-disubstituted *N*-arylsulfilimines)[16] allowed cycloaddition to proceed smoothly at room temperature. Only copper(I) catalysis was effective for this transformation, and $Cu(MeCN)_4PF_6$ gave the highest product yield [Eq. (1)]. Dichloromethane was the preferred solvent, and diphenylsulfur ylides gave higher product yields than their dimethyl or methylphenyl analogues. Reactions were performed at room temperature to avoid electroreversion of the azetine.[3] Moreover, [3+1]-cycloaddition occurred with the triisopropylsilyl (TIPS)- but not with the *tert*-butyldimethylsilyl (TBS)-protected enoldiazoacetate.



To produce azetines that possess a chiral center, γ-substituents on the enoldiazoacetate were introduced. Because [3+1]-cycloaddition with *N*-arylsulfilimines occurred with the *Z*- but not the *E*-enoldiazoacetate isomer, a new methodology for the nearly exclusive synthesis of the Z-geometrical isomer was developed.[17] A series of TIPS-protected γ-substituted *Z*- enoldiazoacetates ($Z:E > 20:1$) was prepared, and we identified the optimal chiral sabox ligand **L1** that provided highest yield and % *ee* of azetine in the reaction of γ-methyl-substituted enoldiazoacetate **1b** with *N*-(*p*-chlorophenyl)imido diphenyl sulfur ylide **2b**.[18] Competing reactions that included 1,4-hydrogen transfer from the intermediate metallo-vinylcarbene to produce conjugated diene products were minor. Although azetine **3bb** was obtained in good yield (82%), enantioselectivity was only moderate (75% *ee*). To improve enantiocontrol of the cycloaddition we varied substituents at the γ-position of enoldiazoacetates and studied the effects of the carboxylate ester group and substituents in the aromatic ring of *N*-arylimido sulfur ylides **2** (Table 1).

Analysis of substituent effects revealed the influence of the three variable substitution patterns on reactivity and enantioselectivity for [3+1]-cycloaddition as a function of either or both electronic and steric factors. Increasing the size of the aliphatic chain at the γ-position of enoldiazoacetate **1** led to an improvement in yield and enantiocontrol of the reaction [82% yield, 75% *ee* (Me, **3bb**) to 92% yield, 90% *ee* (Et, **3cb**); entries 1 and 4 in Table 1]. However, introduction of octyl, benzyl and isopropyl substituents resulted in reduced reactivity (70–78% yield after 3 days, entries 16–18), but with excellent enantioselectivity (90–95% *ee*). These results suggest a significant steric effect by the γ-substituent on enantiocontrol for cycloaddition, and the Et substituent at the γ-position was chosen for further studies (diazo com-

Table 1: Substrate scope of donor–acceptor azetines obtained via Cu^I-catalyzed [3+1]-cycloaddition of enoldiazoacetates **1** and *N*-arylimido sulfur ylides **2**.

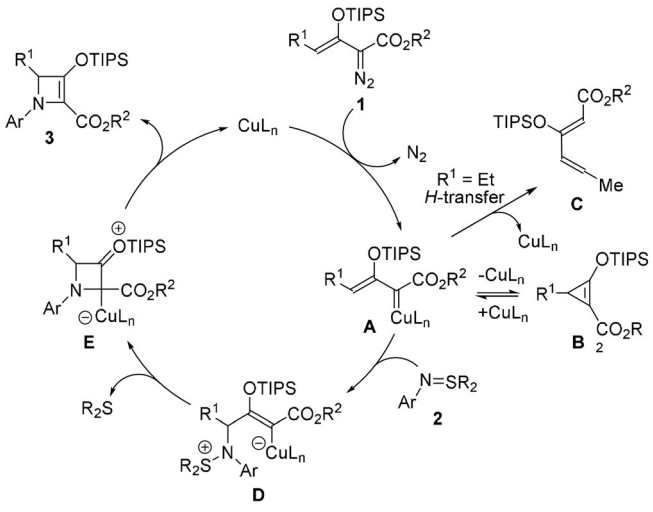


Entry[a]	R^1	R^2	Ar	3	Yield [%][b]	*ee* [%][c]
1	Me	Me	4-Cl-C_6H_4	**3bb**	82	75
2	Me	Me	3-F-C_6H_4	**3bc**	83	90
3	Me	Et	C_6H_5	**3ca**	86	85
4	Me	Et	4-Cl-C_6H_4	**3cb**	92	90
5	Me	Et	3-Cl-C_6H_4	**3cd**	89	91
6	Me	Et	3,5-diCl-C_6H_3	**3ce**	80	82
7	Me	Et	4-Br-C_6H_4	**3cf**	88	89
8	Me	Et	4-F-C_6H_4	**3cg**	84	88
9	Me	Et	3-F-C_6H_4	**3cc**	87	92
10	Me	Et	2-F-C_6H_4	**3ch**	86	88
11	Me	Et	4-CF_3-C_6H_4	**3ci**	87	91
12	Me	Et	3-OMe-C_6H_4	**3cj**	80	77
13	Me	Et	3-Me-C_6H_4	**3ck**	85	74
14	Me	Et	4-Me-C_6H_4	**3cl**	76	70
15	Me	Et	4-Et-C_6H_4	**3cm**	78	80
16[d]	Me	octyl	3-F-C_6H_4	**3dc**	78	95
17[d]	Me	Bn	4-Cl-C_6H_4	**3hb**	73	90
18[d]	Me	*i*-Pr	4-Cl-C_6H_4	**3ib**	70	92
19	PMB	Me	3-F-C_6H_4	**3ec**	92	90
20[d]	PMB	Et	C_6H_5	**3fa**	83	88
21	PMB	Et	3-F-C_6H_4	**3fc**	94	99
22	PMB	Et	4-Cl-C_6H_4	**3fb**	95	99
23	Bn	Et	4-Cl-C_6H_4	**3jb**	87	92
24	^{p}CF_3-Bn	Et	4-Cl-C_6H_4	**3kb**	73	87
25	PMB	Et	2,4-diF-C_6H_3	**3fn**	83	87
26[d]	PMB	Et	3-Me-C_6H_4	**3fk**	82	86
27[d]	PMB	Et	4-CN-C_6H_4	**3fo**	75	96
28[d]	PMB	Et	4-CO_2Et-C_6H_4	**3fp**	68	82
29[d]	PMB	Et	4-NO_2-C_6H_4	**3fq**	66	93
30	PMB	Et	4-F-C_6H_4	**3fg**	88	99
31	PMB	Et	2-F-C_6H_4	**3fh**	76	90
32[d]	PMB	Et	4-Et-C_6H_4	**3fm**	76	84
33[d]	PMB	octyl	3-F-C_6H_4	**3gc**[e]	87	99

[a] Reactions were carried out on a 0.20 mmol scale of *N*-arylsulfilimine **2** and 0.24 mmol of *Z*-enoldiazoacetate **1** with 5 mol% of $Cu(MeCN)_4PF_6$ and 6 mol% of (*S*,*R*)-**L1** or (*R*,*S*)-**L1** in 4.0 mL of DCM at room temperature. [b] Isolated yields after flash-chromatography are reported (average of two runs). [c] Enantiomeric excess was determined using a Daicel Chiralpak AD-H or a Chiralcel OD-H chiral column. [d] Reaction time was 72 h. [e] For additional examples of the synthesis of azetines **3**, see: Table S2, Supporting Information.

pound **1c**). Only modest variations in yields and enantioselectivities were observed for the Cu^I-catalyzed reaction of **1c** with a series of sulfilimines **2**. The introduction of halogen and CF_3 substituents to the aromatic ring of **2** at the *ortho* or *para* positions (entries 4, 7, 8, 10, 11) had virtually no influence on product yields (82–92%) or their *ee* values (86–91%) compared to the results obtained with unsubstituted sulfilimine **2a** (**3ca**, 86% yield, 85% *ee*). However, with *para*-alkyl substituents (entries 14 and 15) diminished enantiocontrol (70–80% *ee*) and yields (76–78%) of the [3+1]-cycloaddition products were obtained. Moreover, changing the position of the substituent on the aromatic ring (*para*-, *meta*-, *ortho*-) of **2** (entries 5, 9, 12, 13) did not provide much difference in %*ee* or yield of **3**, which suggests minor electronic or steric influence by arylsulfilimine substituents. Optimization of the carboxylate group revealed that 4-methoxybenzyl (PMB) enoldiazo esters **1e–g** exhibit exceptionally high enantiocontrol (entries 21, 22, 30, 33) compared to their methyl ester analogues, although reaction times were extended to 3 days to achieve full conversions. Employment of benzyl or 4-CF_3-benzyl enoldiazo esters led to decreases in % *ee* compared to the PMB ester (entries 23, 24). Sulfilimines **2** that possess strong EWGs (nitro, cyano, CO_2Et) produced the corresponding azetines **3** in lower yields (66–75%, entries 27–29) but with excellent enantioselectivities (up to 96% *ee*).

A proposed mechanism for [3+1]-cycloaddition of enoldiazoacetates with imido-sulfur ylides, consistent with our previous report on carbonyl-sulfur ylides[12] (Scheme 2) includes a Cu^I-catalyzed generation of *Z*-metallo-enolcarbene **A** that, depending on reaction conditions, can form the corresponding stable donor–acceptor cyclopropene **B**, which serves as a resting state for *Z*-metallo-enolcarbene **A**,[13] or undergo an irreversible proto-decupration to produce diene **C**. The major reaction pathway proceeds by nucleophilic addition of imido-sulfur ylide **2** onto the electrophilic vinylogous carbon of *Z*-metallo-enolcarbene **A** to generate vinylcopper-carbene intermediate **D**. Displacement of the diphenyl sulfide, a good leaving group, forms cyclic intermediate **E**, which upon dissociation of the copper catalyst produces donor–acceptor azetine **3**. The facility of *N*-arylimidosulfur ylides for this cycloaddition compared to *N*-acylimidosulfur ylides does not appear to be due to enhanced electron donation from the aryl group because of the limited influence by substituents on product yields and selectivities but, instead, on the inherently low nucleophilicity of the imido nitrogen of acylimidosulfur ylides.



Scheme 2. Proposed mechanism for copper(I)-catalyzed [3+1]-cycloaddition of silyl-protected γ-substituted *Z*-enoldiazoacetates with *N*-arylsulfilimines and possible competing reactions.

Removal of the silyl-protective group of these chiral azetine structures produces a β-ketoester that is inherently unstable to nucleophilic ring opening.[19] We anticipated that classic (Pd/C)-catalyzed *cis*-hydrogenation of the double bond of the highly reactive, strained donor–acceptor azetines **3** would retain the four-membered ring, but also lead to strain release and provide easy access to chiral tetrasubstituted 2-azetidine-carboxylates that possess three chiral centers. Indeed, we observed very efficient hydrogenation of methyl azetine-2-carboxylates **3** to azetidine-2-carboxylates **4** at room temperature under 1 atm. of H_2 using only 2 wt.% of palladium metal (Table 2).

What is particularly striking, *cis*-hydrogenation occurs from the site opposite to substituent R at the 4-position of azetidine ring with exceptional diastereocontrol (dr > 20:1). A noticeable decrease in diastereocontrol is only observed with fluorinated azetidines **4ch** (dr = 7:1) and **4ci** (dr = 10:1), however all azetidine-2-carboxylates **4** are obtained in excellent yields (> 90%) and with complete retention of enantiopurity (confirmed by comparison of HPLC traces for racemic and chiral **3ca** and **4ca**). As anticipated, methyl azetidine-2-carboxylate without a substituent at the 4-posi-

Table 2: Substrate scope of azetidine-2-carboxylates **4** obtained via palladium-catalyzed hydrogenation of donor–acceptor azetines **3**.

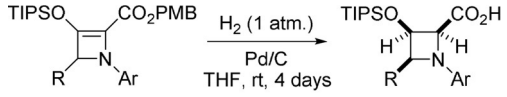
(*S*)-**3** or (*R*)-**3** → (2*S*,3*R*,4*S*)-**4** or (2*R*,3*S*,4*R*)-**4**

Entry[a]	R	Ar	4	Yield [%][b]	dr[c]	*ee* [%][d]
1	H	C_6H_5	**4aa**	93	N/A	racemic
2	Me	3-F-C_6H_4	**4bc**	96	> 20:1	90
3	Et	C_6H_5	**4ca**	95	> 20:1	85
4	Et	4-Cl-C_6H_4	**4cb**	92	> 20:1	90
5	Et	3-Cl-C_6H_4	**4cd**	90	> 20:1	91
6	Et	4-F-C_6H_4	**4cg**	92	> 20:1	88
7	Et	3-F-C_6H_4	**4cc**	96	> 20:1	92
8	Et	2-F-C_6H_4	**4ch**	97	7:1	88
9	Et	4-CF_3-C_6H_4	**4ci**	96	10:1	91
10	Et	3-OMe-C_6H_4	**4cj**	94	> 20:1	77
11	Et	3-Me-C_6H_4	**4ck**	95	> 20:1	74
12	Et	4-Me-C_6H_4	**4cl**	97	> 20:1	70
13	Et	4-Et-C_6H_4	**4cm**	93	> 20:1	80
14	octyl	3-F-C_6H_4	**4dc**	95	> 20:1	95

[a] Reactions were carried out on a 0.25 mmol scale of azetine-2-carboxylate **3** in 4.0 mL of THF at room temperature with Pd on activated charcoal (2 wt. % of Pd metal) under H_2 (1 atm) for 24 h. [b] Isolated yields after flash-chromatography are reported. [c] Determined from the ^1H NMR spectra of purified compounds. [d] Enantiomeric excesses were determined using a Daicel Chiralpak AD-H and Chiralcel OD-H chiral columns.

tion (**4aa**, R = H) is obtained as a racemic mixture of *cis*-hydrogenation products, and this is also confirmed by chiral HPLC analysis. Hydrogenation of PMB azetine-2-carboxylates **3** performed under the same reaction conditions as their methyl analogs led to mixtures of PMB azetidine-2-carboxylates **4** and azetidine-2-carboxylic acids **5**—products of hydrogenolysis of the PMB group (Table 3) obtained in 24 h. The reaction time (4 days) that provided complete conversion to azetidine-2-carboxylic acids **5** as the sole product in very high yields (87–95%) was determined, and exceptional diastereoselectivities with dr >20:1 (Table 3) were obtained. The structure and absolute configuration of azetidine-2-carboxylic acid **5ec** obtained using sabox ligand (*R*,*S*)-**L1**, was established by X-ray diffraction crystallographic analysis as 2*S*,3*R*,4*S*- (Figure 2 represents the monomeric structure of dimeric **5ec**).[20]

Table 3: Substrate scope of azetidine-2-carboxylic acids **5** obtained via palladium-catalyzed hydrogenation of donor–acceptor azetines **3**.



(*S*)-**3** or (*R*)-**3** (2*S*,3*R*,4*S*)-**5** or (2*R*,3*S*,4*R*)-**5**

Entry[a]	R	Ar	5	Yield [%][b]	dr[c]	*ee* [%][d]
1	Et	4-Me-C_6H_4	**5 fl**	88	>20:1	80
2	Et	C_6H_5	**5 fa**	94	>20:1	88
3	Et	4-CN-C_6H_4	**5 fo**	93	>20:1	96
4[e]	Et	4-CF_3-C_6H_4	**4 fi**	86	>20:1	97
5	Et	3-Me-C_6H_4	**5 fk**	93	>20:1	86
6	Et	3-OMe-C_6H_4	**5 fj**	90	>20:1	88
7	Et	4-Et-C_6H_4	**5 fm**	87	>20:1	84
8	Et	2,4-diF-C_6H_3	**5 fn**	89	>20:1	87
9	Et	4-F-C_6H_4	**5 fg**	95	>20:1	99
10	Et	3-F-C_6H_4	**5 fc**	92	>20:1	99
11	Et	2-F-C_6H_4	**5 fh**	92	>20:1	90
12	Me	3-F-C_6H_4	**5 ec**	95	>20:1	90
13	octyl	3-F-C_6H_4	**5 gc**	95	>20:1	99

[a] Reactions were carried out on a 0.25 mmol scale of azetine-2-carboxylate **3** in 4.0 mL of THF at room temperature with Pd on activated charcoal (2 wt.% of Pd metal) under H_2 (1 atm) for 4 days. [b] Isolated yields after flash-chromatography are reported. [c] Determined from the ^{1}H NMR spectra of purified compounds. [d] Enantiomeric excess is reported based on the *ee* values of corresponding azetines **3** and confirmed by HPLC analyses. [e] PMB-ester was isolated.

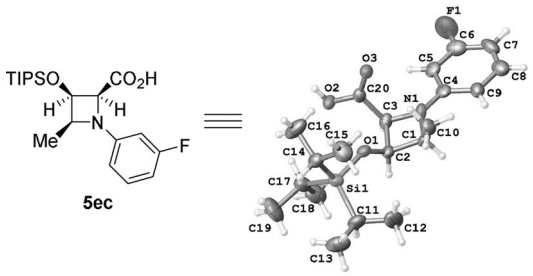
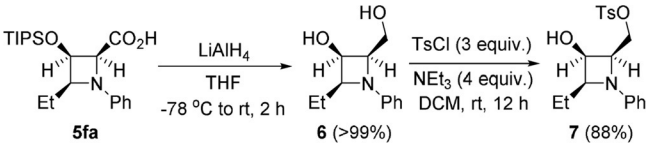


Figure 2. ORTEP diagram of the X-ray crystal structure of (2*S*,3*R*,4*S*)-1-(3-fluorophenyl)-4-methyl-3-[(triisopropylsilyl)oxy]azetidine-2-carboxylic acid **5ec** obtained using (*R*,*S*)-**L1**.

Cleavage of the PMB group in hydrogenation of 4-CF_3 substituted azetine-2-carboxylate **3 fi** was not observed even after 4 days, and PMB azetidine-2-carboxylate **4 fi** was isolated in high yield (86%, entry 4). With the exception of **3 fi**, variation of the carboxylate ester group in **3** provided formation of either methyl azetidine-2-carboxylates **4** (Table 2) or azetidine-2-carboxylic acids **5** (Table 3), and both were formed in excellent yields and with exceptional stereocontrol.

Diol or polyol products from reduction of azetine-2-carboxylates or -carboxylic acids form derivatives that are a common structural unit in penaresidins A and B (Figure 1) and other naturally occurring or synthetic azetidine iminosugars—a class of compounds with potent glycosidase inhibitory activities also suitable for incorporation into peptides.[11d,21] Chiral azetidine-carboxylates **4** or -carboxylic acids **5** appear to be suitable substrates for the synthesis of azetidine iminosugar derivatives. We have successfully demonstrated reduction/TIPS removal of azetidine **5 fa** using lithium aluminum hydride to produce chiral azetidine-diol **6** in near quantitative yield (Scheme 3). Further functionalization of **6** with excess of *p*-toluenesulfonyl chloride and triethylamine afforded monotosyl-protected product **7** at the primary hydroxyl group exclusively in 88% isolated yield at room temperature.



Scheme 3. Functionalization of chiral azetidine-2-carboxylic acids. Synthesis of chiral azetidine iminosugar derivatives.

In summary, we have established a new methodology for the highly enantioselective synthesis of tetrasubstituted azetines via asymmetric [3+1]-cycloaddition of γ-substituted enoldiazo-acetates with imido-sulfur ylides using chiral copper(I)-sabox catalysis. This reaction is remarkably versatile with TIPS-protected enoldiazo compounds and *N*-arylsulfilimines, affording a broad spectrum of 2-azetine derivatives in high yields and with good to excellent enantiocontrol. The azetine-2-carboxylates provide convenient access to tetrasubstituted azetidine-2-carboxylates and their carboxylic acids that possess three chiral centers, with exceptional diastereocontrol and retention of enantiopurity from the original 2-azetine using Pd-catalyzed hydrogenation. The reduction of azetidine-2-carboxylic acids results in the formation of chiral primary-secondary diols—azetidine iminosugar derivatives suitable for further functionalization. Other enantioselective transformations of strained and highly reactive 2-azetines and applications of [3+1]-cycloaddition methodology are currently in progress in our laboratory.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: azetidines · azetines · copper catalysis · cycloaddition · hydrogenation

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