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A UNIQUELY ACCESSIBLE ROUTE TO THE DIASTEREOSELECTIVE SYNTHESIS OF AZETINE DERIVATIVES

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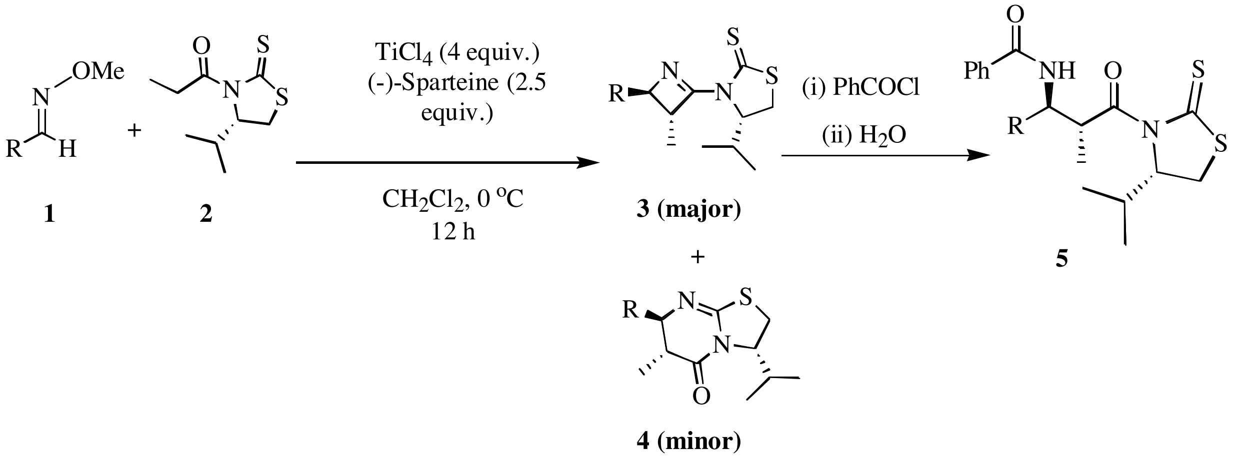
Abstract – In the diastereoselective additions of chlorotitanium enolate of *N*-propionylthiazolidine-2-thione (**2**) to nitriles *via* the corresponding *N*-metalloaldimines (Al, B, Zr as metals), thiazolidine-2-thioneazetines (**3**) are preferentially formed over the dihydropyrimidinones (**4**), with the ratios of compounds (**3/4**) ranging from 5:1 to 17:1 (for R = phenyl, 1-naphthyl and 2-thienyl).

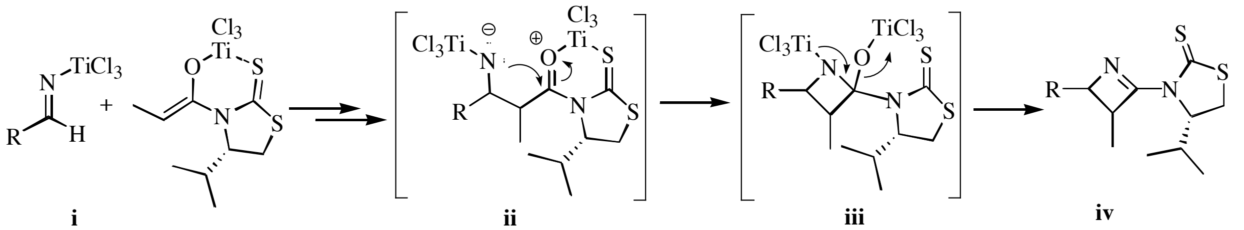
Recently, our research group reported the thiazolidine-2-thione directed diastereoselective additions of the chlorotitanium enolate to *O*-methylaldoxime ethers,[1] which led to the preferential formation of a four membered azetine derivative over the six membered dihydropyrimidinone (Scheme 1). These products were formed as single diastereomers and the reaction was shown to be applicable with enolizable as well



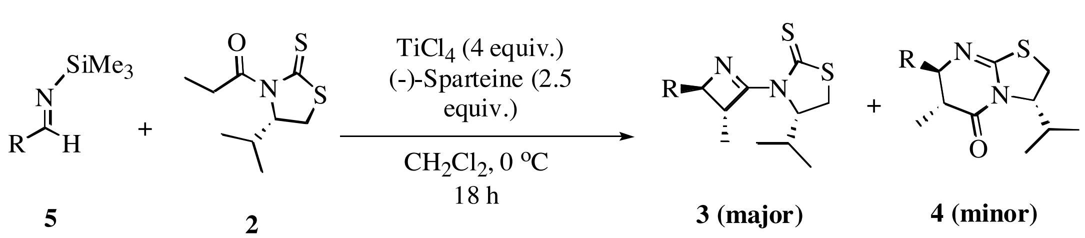
Scheme 1

as non-enolizable oxime ethers. The azetine ring could be opened to afford diastereoisomerically pure α,β-disubstituted β-aminocarbonyl derivatives.[2] Herein, we report an alternative synthetic approach to the above azetine derivatives starting from the more accessible nitriles.

Based on subsequent studies, we propose here that the formation of azetine derivatives could be rationalized by the generation of a highly reactive *N*-chlorotitanium aldimine species, *via* the reductive cleavage of the nitrogen-oxygen bond (species (**i**), Scheme 2). Species (**i**) was expected to undergo addition by the enolate, followed by subsequent cyclization and elimination of bis(trichlorotitanium) oxide to form the four membered thiazolidinyl azetine ring.[1] In principle, intermediates of this type could also be formed by a transmetallation reaction of an *N*-trialkylsilylimine with titanium tetrachloride. Indeed, allowing **2**[3a] to react with *N*-TMS benzaldimine[3b] in the presence of four equivalents of $TiCl_4$ and 2.5 equivalents of (-)-sparteine at 0 °C resulted in an optimum product yield of 85% (Scheme 3). Using these conditions, we then subjected other non-enolizable *N*-TMS imines, which proceeded in comparable yields (see Table 1).[4] Unfortunately, in our hands enolizable *N*-TMS aldimines proved to be quite prone to oligomerization[5] and thus could never be subjected to the reaction conditions.



Scheme 2

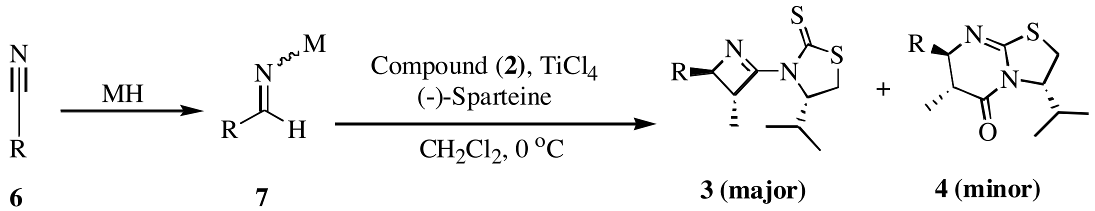


Scheme 3

Table 1. Addition of chlorotitanium enolate to *N*-TMS aldimines

R	Yield (%)	Ratio (3/4)
Phenyl	85	8:1
1-Naphthyl	75	6:1
2-Thienyl	58	15:1

Our apparent ability to intersect the putative *N*-chlorotitanium imine intermediates from either oxime ethers or *N*-silylimines suggested the possibility that other *N*-metalloimines could also be induced to undergo transmetallation with titanium tetrachloride to produce these azetine derivatives (**3**) (Scheme 4). We therefore decided to examine the use of nitriles, which could be hydrometallated *in situ* to form the corresponding *N*-metalloaldimines, followed by transmetallation to form species (**i**)[6] and subsequent reaction with the chlorotitanium enolate of **2** (Scheme 4).[7] If successful, these reactions would obviate the need for imine derivatives by providing a one-pot procedure, starting from the more accessible nitriles.



Scheme 4

Our initial attempts at probing the viability of this process involved the hydroalumination of nitriles.[8] Generation of aluminoaldimine (**7**) (M = Al) from aromatic nitriles (**6**) and diisobutylaluminum hydride (DIBAL), followed by reaction with the $TiCl_4$ and subsequent addition of the chlorotitanium enolate, resulted in the formation of a product mixture of **3** and **4** (Table 2) in yields ranging from 23% to 57%.[9] Despite considerable efforts on our part, however, the efficiency of these reactions could not be improved significantly. Nevertheless, the success of this transformation served as a proof of principle and encouraged us to explore alternative hydrometallation processes that could undergo efficient transmetallation with titanium tetrachloride. We next examined the possibility of employing hydroboration and hydrozirconation.

In our hands we found 9-borabicyclononane (9-BBN) to be a more convenient and effective hydroborating agent than either diborane or dichloroborane / dimethyl sulfide.[10] Although the yields of compound (**4**) were generally better using 9-BBN in place of DIBAL, the **3**:**4** ratio proved to be somewhat variable, with two cases (R = 1-naphthyl or 2-phenylethyl) exhibiting only moderate to poor selectivity. We attribute this lower selectivity to a more sluggish isomerization of **4** to **3** under the experimental conditions.[1] Alternatively, use of the Schwartz reagent, Cp_2ClZrH, which involves the initial formation of the corresponding *N*-zirconoaldimine, resulted in generally better yields and moderate to good selectivities. In addition, the initial hydrometallation reactions proceeded more rapidly using the Schwartz reagent instead of 9-BBN (two vs. four hours). Most importantly, however, the hydrozirconation / transmetallation process did prove applicable to enolizable nitriles, producing moderate yields of the desired azetine with little, if any, six membered ring by-product.

Table 2. Hydrometallation of nitriles and reaction with chlorotitanium enolates

Metal Hydride	**R**	**Yield (%)**	**Ratio (3/4)**
DIBAL	Phenyl	55	6:1
	1-Naphthyl	57	12:1
	2-Thienyl	23	15:1
	2-Phenylethyl	15	> 95:5
	Cyclohexyl	5	> 95:5
9-BBN	Phenyl	65	16:1
	1-Naphthyl	58	7:1
	2-Thienyl	56	16:1
	2-Phenylethyl	14	3:1
	Cyclohexyl	0	-
Cp_2ClZrH	Phenyl	75	17:1
	1-Naphthyl	51	8:1
	2-Thienyl	58	5:1
	2-Phenylethyl	46	>95:5
	Cyclohexyl	22	>95:5

In summary, the diastereoselective additions of chlorotitanium enolates of *N*-propionylthiazolidine-2-thione to various metalloaldimines, derived from hydrometallation of the corresponding nitriles, resulted in the formation of azetine and tetrahydropyrimidinone derivatives. Of the three hydrometallations studied, the overall yields and selectivities associated with the hydrozirconation processes, in general, proved to be the best approach. Additional studies that attempt to identify the factors that control the preferential formation of the four membered ring product over its six membered ring counterpart will be the subject of future reports.

ACKNOWLEDGEMENTS

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4. Procedural details for synthesis of azetine derivatives have been provided in supporting information of Reference 1. Spectroscopic Data: (i) Compound (**3**) (R = Phenyl): Pale yellow crystalline solid. mp 116-118 °C (recrystallized from hexanes). R_f = 0.3 (Hexanes/EtOAc: 2/1). Stereochemistry established by X-Ray crystallography. Single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.99 (dd, 1H, J = 4.8 Hz, J = 7.9 Hz), 4.44 (d, 1H, J = 1.4 Hz), 3.96 (dd, 1H, J = 1.7 Hz, J = 7.2 Hz), 3.69 (dd, 1H, J = 8.6 Hz, J = 11.3 Hz), 3.19 (d, 1H, J = 0.7 Hz, J = 11.7 Hz), 2.82 (m, 1H), 1.58 (d, 3H, J = 7.3 Hz), 1.13 (d, 3H, J = 6.9 Hz), 1.08 (d, 3H, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.46, 173.50, 140.51, 128.64, 127.66, 126.38, 71.03, 69.86, 52.09, 30.68, 19.67, 16.90, 16.31. IR (neat) υ_{max} 2964, 1637, 1575, 1494, 1455, 1382, 1297, 1173, 856, 725. FABMS m/z 311.2841 ($[M+Li]^+$, $C_{16}H_{20}N_2LiS_2$ requires 311.1228). HRFABMS m/z 311.1241 ($[M+Li]^+$, $C_{16}H_{20}N_2LiS_2$ requires 311.1228). HRFABMS m/z 305.1153 ($[M+H]^+$, $C_{16}H_{21}N_2S_2$ requires 305.1146). (ii) Compound (**4**) (R = Phenyl): White crystalline solid. mp 110-112 °C (recrystallized from hexanes). R_f = 0.3 (Hexanes/EtOAc: 2/1). Absolute stereochemistry established by X-Ray crystallographic analyses. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.63 (td, 1H, J = 0.9 Hz, J = 7.9 Hz), 4.25 (d, 1H, J = 13.6 Hz), 3.39 (dd, 1H, J = 7.6 Hz, J = 11.4 Hz), 3.03 (dd, 1H, J = 0.9 Hz, J = 11.4 Hz), 2.44 (m, 1H), 2.23 (m, 1H), 1.05 (d, 3H, J = 7.0 Hz), 1.03 (d, 3H, J = 7.0 Hz), 1.01 (d, 3H, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.43, 158.63, 141.83, 28.73, 127.69, 67.14, 63.08, 40.54, 31.15, 29.05, 19.29, 18.42. IR (neat) υ_{max} 2930, 1698, 1633, 1455, 1351, 1324, 1266, 1200, 1123, 914, 760, 678 cm^{-1}. FABMS m/z 295.4897 ($[M+Li]^+$, $C_{16}H_{20}N_2OLiS$ requires 295.1456). HRFABMS m/z 289.1375 ($[M+H]^+$, $C_{16}H_{21}N_2OS$ requires 289.1375). *No fragments are seen in the FABMS spectrum of this compound.* Anal. Calcd for $C_{16}H_{20}N_2OS$: C, 66.63; H, 6.99; N, 9.71; O, 5.55; S, 11.12. Found: C, 67.37; H, 7.16; N, 9.19; O, 5.43; S, 10.77.
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9. Under argon, the nitrile (1.72 mmol) and the metal hydride (2.87 mmol of Cp_2ZrHCl or 1.95 mmol of DIBAL) were dissolved in a 50 mL flask in dry dichloromethane (2 mL) and stirred for 2 h (for Cp_2ZrHCl) or 4 h (for DIBAL) at room temperature. Titanium tetrachloride (3.45 mmol) was added and the reaction mixture stirred for 1 h at room temperature. During this time, titanium enolate of

compound (**2**) was generated by dissolving **2** in dry dichloromethane (5 mL) at 0 ºC under argon, then dropwise addition of titanium tetrachloride (1.15 mmol), stirring for 5 min and the addition of (-)-sparteine (2.87 mmol). The brown solution was stirred for 40 min at 0 ºC and then added to the first reaction mixture *via* a cannula. The reaction was stirred for 18 h at room temperature. The work up was the same as for the oxime ethers.

10. In a 25 mL ovendried flask under argon, nitrile (1.72 mmol) and $(9\text{-BBN})_2$ (1.72 mmol) were dissolved in dry toluene (3 mL) and refluxed for 4 h. The toluene was removed under vacuum and replaced with dry dichloromethane (2 mL). During this time, titanium enolate of compound (**2**) was generated by dissolving **2** in dry dichloromethane (5 mL) at 0 ºC under argon, then dropwise addition of titanium tetrachloride (1.15 mmol), stirring for 5 min and the addition of (-)-sparteine (2.87 mmol). The brown solution was stirred for 40 min at 0 ºC and to it was added the boronaldimine solution *via* a cannula. The reaction was stirred for 12 h at room temperature. The work up was the same as for the oxime ethers.