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Ti-mediated intramolecular cyclopropanation of *N*-alkenyl thioamides: scope and mechanistic study

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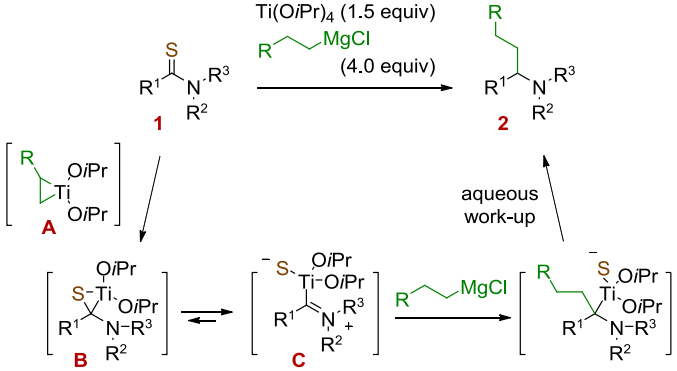
ABSTRACT

Although thioamides generally undergo a reductive alkylation process when they are treated with a Grignard reagent in the presence of $Ti(OiPr)_4$, substrates fitted with a but-3-enyl substitution at the nitrogen atom are shown to be converted into bicyclic aminocyclopropanes. These reactions are compared with the similar cyclisations of the corresponding carboxylic amide substrates. A mechanistic study is provided. Coincidently, new reagent systems are identified for the mediation of the same transformation.

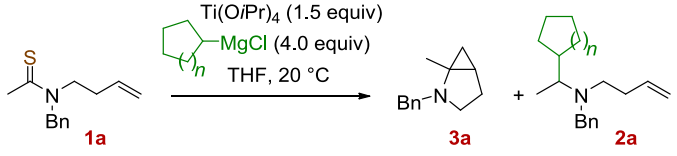
1. Introduction

Since the seminal report by Kulinkovich et al. on the synthesis of cyclopropanols,[1] methods that rely on the combined use of Grignard reagents and titanium(IV) alkoxide derivatives have emerged as a whole family of valuable reactions.[2–5] In this context, we have recently investigated the behaviour of thioamides **1** and found that they generally undergo a reductive alkylation process to afford tertiary amines **2** (Scheme 1).[6] This is in sharp contrast with the behaviour of the corresponding carboxylic amides under the same conditions. Indeed, these compounds undergo the Kulinkovich-de Meijere aminocyclopropanation.[3] To explain our results, a ligand exchange process can be proposed, taking place from the initially generated titanacyclopropane **A** to afford the thiatitanacyclopropane species **B**. The latter would presumably be in equilibrium with the metallated iminium zwitterion **C**. Alkylation of **C** by the Grignard reagent employed would then operate and the observed amine **2** would be obtained after hydrolysis.[6]

A particular case was represented by the *N*-but-3-enyl substituted thioamide **1a**. Indeed, the major product, starting from this substrate, was the bicyclic aminocyclopropane **3a**, either using cyclopentylmagnesium chloride or cyclohexylmagnesium chloride as the Grignard reagent (Scheme 2).[6]



Scheme 1. Titanium-mediated reductive alkylation of thioamides with Grignard reagents.[6]



n = 1	64%	17%
n = 2	56%	28%

Scheme 2. Reaction of thioamide **1a**.[6]

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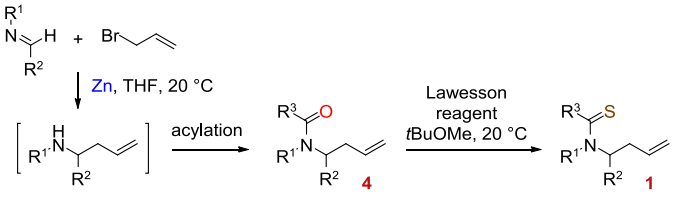
Interestingly, the cyclopropane **3a** is also the 'normal' expected[3] product starting from the corresponding carboxylic amide **4a**, where the sulfur atom of **1a** is replaced with an oxygen atom.[7] Since the production of **3a** from **1a** is rather peculiar in the light of the results obtained with the other thioamides studied so far, we decided to investigate the generality and mechanism of this intramolecular cyclopropanation of *N*-alk-3-enyl thioamides. In addition, we wished to evaluate whether this process could be of some advantage compared to the reactions of the corresponding carboxylic amides.

2. Results and discussion

2.1. Syntheses of the substrates

For the purpose of this study, several homoallylamines were prepared by zinc-mediated Barbier-type imine allylation[8] and directly acylated, without purification, to afford the carboxylic amides **4b**–**h**. The amide **4i**, bearing the chiral centre on another substituent of the nitrogen atom, was synthesised following another route.[9] The amides **4b**–**i** were then converted into the corresponding thioamides **1b**–**i** using the Lawesson reagent. The results are summarised in Table 1.

Table 1
Syntheses of the *N*-but-3-enylamide and *N*-but-3-enylthioamide substrates



Entry	Substituents	Amide **4** (yield)	Thioamide **1** (yield)
1	R^1=Bn R^2=4-(OMe)C_6H_4 R^3=Me	**4b** (84%)[a]	**1b** (41%)
2	R^1=Ph R^2=Ph R^3=Me	**4c** (75%)[a]	**1c** (80%)
3	R^1=4-(OMe)C_6H_4 R^2=Ph R^3=Me	**4d** (90%)[b]	**1d** (69%)
4	R^1=4-(OMe)C_6H_4 R^2=Ph R^3=*n*Pr	**4e** (n.d.)[c]	**1e** (41%)[d]
5	R^1=4-(OMe)C_6H_4 R^2=CF_3 R^3=Me	**4f** (80%)[10]	**1f** (59%)
6	R^1=4-(Cl)C_6H_4 R^2=4-(OMe)C_6H_4 R^3=Me	**4g** (53%)[a]	**1g** (58%)
7	R^1=4-(Cl)C_6H_4 R^2=4-(OMe)C_6H_4 R^3=H	**4h** (86%)[e]	**1h** (78%)
8	R^1=CH(Me)Ph R^2=H R^3=Me	**4i** (prepared by another route)[9]	**1i** (56%)

[a] Conditions: Ac_2O, pyridine, 20 °C.
[b] Conditions: Ac_2O, DMAP (cat.), pyridine, 20 °C.
[c] Conditions: *n*PrCOCl, Et_3N, $CHCl_3$ 20 °C. The yield was not determined because this amide was only partially purified and engaged as such in the next step.
[d] Yield for the whole sequence from the imine.
[e] Conditions: HCO_2H/Ac_2O, HCO_2Na, CH_2Cl_2, 20 °C. The yield given is for the formylation step only.

2.2. Titanium-mediated cyclisations

The new thioamide substrates **1b**–**i** were submitted to the titanium-mediated cyclisation procedure. The effects of the nature of the solvent and of the rate of the Grignard reagent addition were put under scrutiny. The results are presented in Table 2, along with the outcomes of experiments performed, for comparison purposes, from the carboxylic amides **4b**–**i**.

The thioamides **1b**–**i** evaluated were all successfully converted into the corresponding bicyclic aminocyclopropanes **3b**–**i**. Relatively little influence of the addition time of the Grignard reagent was observed, although a slow addition (30–60 min) gave somewhat better results than a typical dropwise addition (2–3 min) in the syntheses of aminocyclopropanes **3c**, **3d** and **3g** (entries 3, 4 and 7). ^{t}BuOMe generally proved to be the best solvent with respect to the yields and the diastereoselectivities. These were markedly better than in THF in almost all cases (entries 3–6, 8–9). A similar observation had been made in an earlier study carried out with related carboxylic amide substrates, where higher diastereoselectivities were generally obtained in Et_2O rather than in THF.[10] The case of the synthesis of **3b** (entry 2) can be considered as an exception. Indeed, either starting from **1b** or from **4b**, the reaction mixtures appeared heterogeneous in Et_2O and in ^{t}BuOMe and fairly large variations in the yields and diastereoselectivities were observed when the experiments were repeated, which suggests a problem of solubility.

Overall, comparative analysis of the results gathered starting from the carboxylic amide substrates **4b**–**i** indicates that they produce the desired cyclopropanes **3** more cleanly, often in higher yields (entries 1, 4, 6, 8 and 9). The diastereoselectivities of these reactions are also consistently more sharply in favour of the β diastereoisomers,[11] under otherwise identical conditions (entries 2–4 and 6–8). This stereochemical assignment is supported by NMR analysis of the isolated products and is unambiguously illustrated by the crystallographic structure of the major diastereoisomer of cyclopropane **3g** (Fig. 1).[13] Most interestingly, there are a few instances where the diastereoselectivities of intramolecular cyclopropanations of thioamides **1** are reversed compared to the those of the same transformations carried out from the corresponding amides **4**: this is the case for the syntheses of **3c** and **3d** in THF (entries 3 and 4), of **3h** in ^{t}BuOMe (entry 8) and of **3i** in THF (entry 9). In the latter case, where the chiral centre of the substrates is not included in the chain linking the olefin and the (thio)amide moieties, this difference is especially significant with a 3 to 1 selectivity obtained starting from **1i** versus an almost non-selective reaction starting from **4i**.

2.3. Mechanistic aspects

A straightforward explanation for the formation of the bicyclic aminocyclopropane products **3** is intramolecular 1,2-insertion of the alkene group into the putative thiatitanacyclopropane complex **B** (Scheme 3, hypothesis a). This would lead to a thiatitanacyclopentane intermediate **D**. This complex is analogous to the intermediate involved in the cyclisation of the carboxylic amides **4**, the only difference being the sulfur atom in place of an oxygen atom. The next elementary steps can thus be put forward following this analogy: cleavage of the carbon–sulfur bond and cyclopropane ring-closure according to an S_E2(back) mechanism after adoption of a W-shaped conformation.[14]

Another consideration worth taking into account is the close structural similarity between the metallated iminium species **C**, likely to be in equilibrium with **B**, and the corresponding zincated iminium **E**, the proposed key-organometallic intermediate involved in the conversion of α-*N*-homoallylamino nitriles **5** into bicyclic aminocyclopropanes **3**, as described by the group of Chemla (Scheme 4).[15] In that work, careful mechanistic studies have provided evidence that a carbenoid insertion pathway and/or a process involving an aza-Cope rearrangement can operate, depending on

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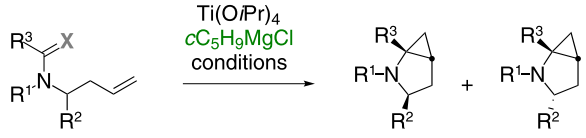
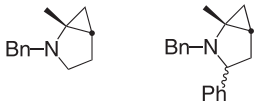
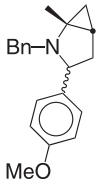
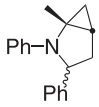
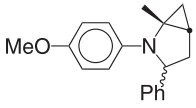
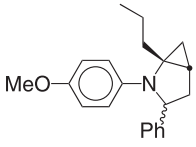
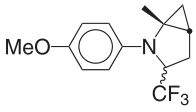
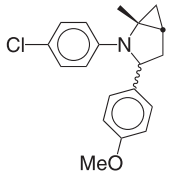
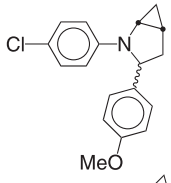
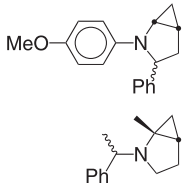
Table 2
Titanium-mediated cyclisations of *N*-but-3-enylthioamide derivatives **1a**–**i**, compared with the reactions of the corresponding amides **4a**–**i.** The best results are displayed in bold



1 (X = S)
4 (X = O)

3-β **3**-α

Entry	Product **3**	Substrate	Solvent	Conditions[a]	Yield[b]	β/α ratio[11]
1		**1a**	**THF**	**A**[c]	**64%**[6]	—
			^{t}BuOMe	**A**[c]	**62%**	—
		4a	**THF**	**A**[c]	**75%**[7]	—
2		**1b**	**THF**	**A**	**66%**	**88:12**
			Et_2O	A	54%	70:30
			^{t}BuOMe	A	51%	71:29
				B	46% (35%)	65:35
		4b	Et_2O	A	29%	84:16
			^{t}BuOMe	**A**	**54% (49%)**	**80:20**
3		**1c**	THF	A	40%	48:52
			Et_2O	A	43%	72:28
			^{t}BuOMe	A	53%	76:24[d]
				B	**69%** (**55%**)	**77:23**[e]
				C	**70%**	**77:23**
		4c	THF	A	68%	86:14
			Et_2O	**A**	**60%**	**98:02**
			^{t}BuOMe	A	51%	98:02
4		**1d**	THF	A	44%	45:55
			^{t}BuOMe	A	50% (46%)	84:16
				B	**55%**	**85:15**
		4d	**THF**	**A**[c]	**84% (77%)**	**88:12**[10]
5		**1e**	THF	A	35%	46:54
			^{t}BuOMe	**A**	**60%** (**50%**)	**85:15**
6		**1f**	THF	A	32%	59:41
			^{t}BuOMe	**A**	**44%** (**37%**)	**73:27**
		4f	**THF**	**A**[c]	**>95% (40%)**	**75:25**[10]
7		**1g**	**^{t}BuOMe**	A	60%	77:23
				B	**77%** (**68%**)	**73:27**
		4g	**^{t}BuOMe**	**A**	**67%**	**96:04**
				B	60%	95:05
8		**1h**	THF	A	<5%	n.d.
			^{t}BuOMe	**A**	**28%**	**23:77**
				B	30%	33:67
				D	22%	41:59
		4h	**^{t}BuOMe**	**A**	**42%** (**37%**)	**64:36**
9		**1i**	THF	A	33%	33:67[f]
			^{t}BuOMe	**A**	**40%** (**32%**)	**25:75**[f]
		4i	**THF**	**A**[c]	(**63%**)	**54:46**[12 f]

[a] Conditions: A: cyclopentylmagnesium chloride (4.0 equiv) was added within 2–3 min, at 0 °C, to a solution of the substrate **1** or **4** (1.0 equiv) and $Ti(O^iPr)_4$ (1.5 equiv) in the specified solvent; B: same as A, except the Grignard reagent was added during ≈30 min; C: same as A, except the Grignard reagent was added during ≈60 min; D: same as B, except the Grignard reagent was added at −30 °C.
[b] Yield estimated by NMR. Yields in parentheses are those of the isolated products.
[c] The addition of the Grignard reagent was performed at 20 °C.
[d] Using $cC_6H_{11}MgCl$ instead of cC_5H_9MgCl under otherwise identical conditions, the yield dropped to 30% (*dr* 73:27).
[e] Using 0.5 equiv of $Ti(O^iPr)_4$ and 3.0 equiv of cC_5H_9MgCl, the yield dropped to 17% (*dr* 70:30).
[f] The relative configurations of the chiral centres of the two diastereoisomers were not determined and the β/α naming does not apply in this case.

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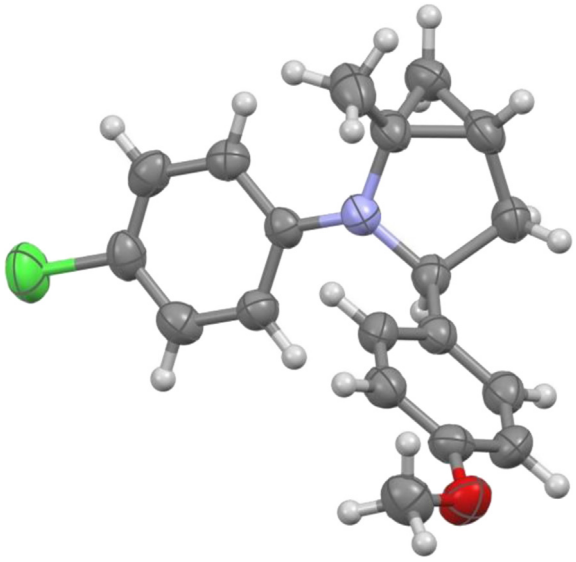
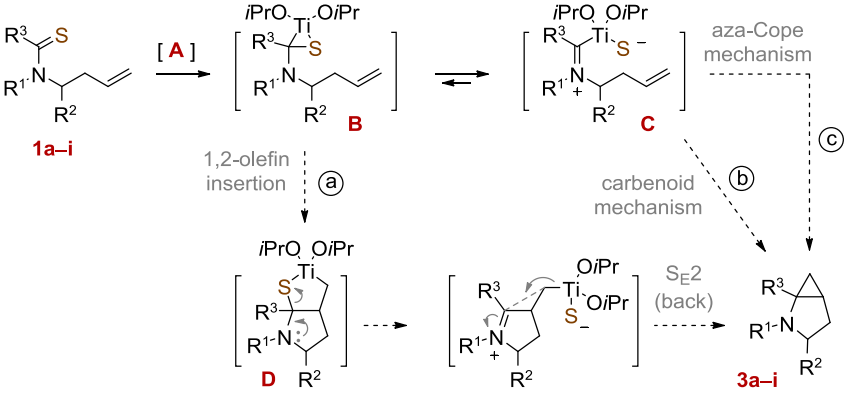


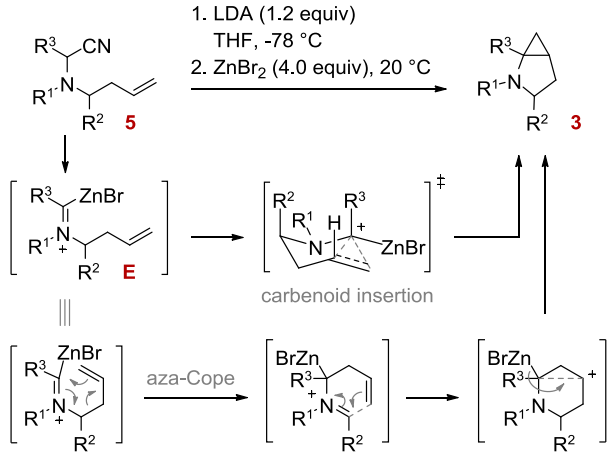
Fig. 1. Single-crystal X-ray diffraction structure of the major β diastereoisomer of **3g**. Ellipsoids are displayed at the 75% probability level.

In the documented syntheses of nitrogen-substituted cyclopropanes by the reaction of a carbenoid species with an olefin, the insertion of the carbenoid usually tends to proceed in a concerted fashion, which results in retention of stereochemistry when disubstituted alkene substrates are engaged.[16] Therefore, we prepared the (*E*)- and (*Z*)-*N*-alkenylthioamides **1j** and **1k** and submitted them to the reaction conditions. In both cases, the major products were the secondary amines resulting from loss of the thiocarbonyl group and the reductive alkylation products **2j** and **2k**. The cyclopropanes **3j** and **3k** were produced in poor yields but with exclusive inversion of configuration (Scheme 5). This result disqualifies the carbenoid pathway (hypothesis b). Indeed, even assuming that the carbenoid insertion could have proceeded in a stepwise manner,[17] inversion should not have been observed both from (*E*) and (*Z*) alkenes. In contrast, this is consistent with hypothesis a, with the inversion resulting from the S_E2(back) process operating in the final ring-closure.

In order to investigate a possible aza-Cope pathway (hypothesis c), the substrates **1l** and **1m** were next evaluated (Scheme 6). The results show that with increasing spacer length between the thioamide and the alkene functions, the yields decrease rapidly: 56–64%, 7% and 0% from **1a**, **1l** and **1m**, respectively. From compounds **1l** and **1m**, the structures of the corresponding metallated iminiums **Cl** and **Cm** are not suitable for an aza-Cope rearrangement to take place and yet, the aminocyclopropane **3l** is produced, notwithstanding the low yield. This rules out the possibility that pathway c may operate alone and further supports hypothesis a: intramolecular insertion of an alkene into the titanacycle **B** is expected to be the easiest when a five-membered ring is formed, then a six-membered ring and last, a seven-membered ring.



Scheme 3. Hypotheses for the formation of **3a**–**i** from **1a**–**i**.



Scheme 4. Chemla's zinc-mediated cyclopropanation of α-*N*-homoallylamino nitriles.[15]

the substitution pattern. The formation of aminocyclopropanes **3a**–**i** from the putative titanium-substituted iminium complex **C** could hence be envisaged to proceed by analogous pathways (Scheme 3, hypotheses b and c).

In conclusion, the mechanism of the intramolecular thioamide aminocyclopropanations most likely operates via the thiatitanacyclopentane intermediate **D**, according to pathway a displayed in Scheme 3.[18]

2.4. Additional results

A few test experiments were conducted with other reagent systems. Although none of them performed better than $Ti(O^iPr)_4$ associated with a Grignard reagent, these investigations revealed that $FeCl_3$, $ZnBr_2$, CuCN and CuCN·2LiCl can all, combined with cC_5H_9MgCl, mediate to some extent the formation of aminocyclopropanes **3**, however only from the thioamide substrates **1** and not from the corresponding amides **4**. In spite of the low yields attained so far, it is interesting to note that these transformations proceed with reversed diastereoselectivity, as illustrated by the example displayed in Scheme 7, to be compared with the results obtained from the same substrate **1g** with the usual reagent system

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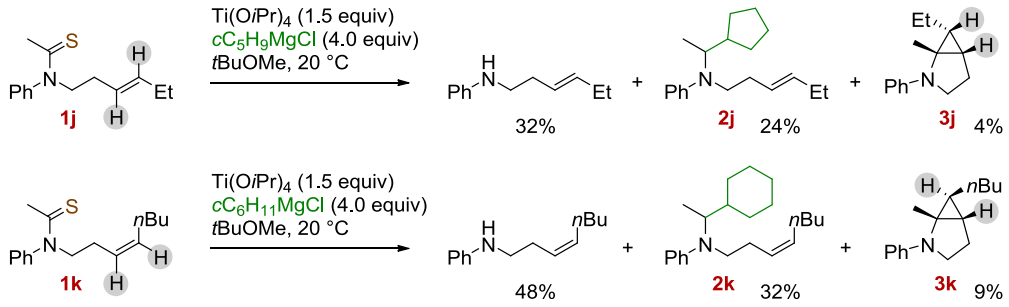
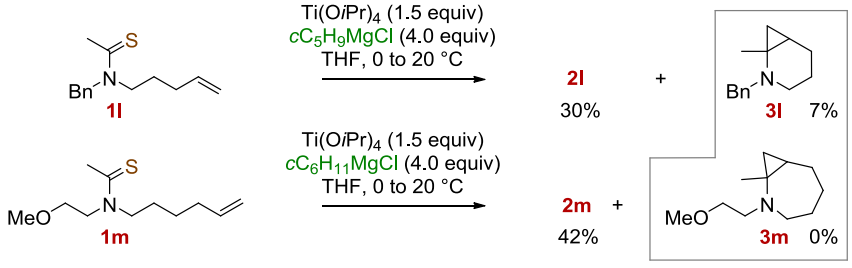
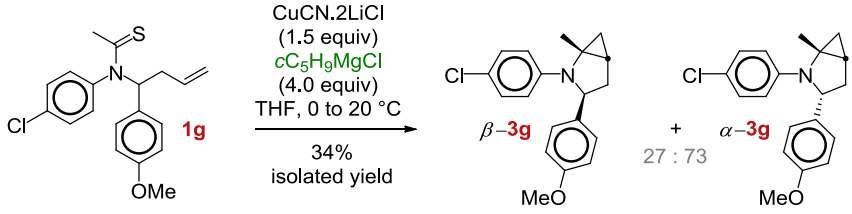


Scheme 5. Reactions of (*E*)- and (*Z*)-disubstituted alkene substrates **1j** and **1k**.



Scheme 6. Reactions of extended-chain substrates **1l** and **1m**.



Scheme 7. Intramolecular cyclopropanation of **1g** mediated by CuCN·2LiCl and cC_5H_9MgCl.

(Table 2, entry 7). This difference suggests that entirely different mechanisms operate, perhaps involving radical intermediates.

3. Conclusions

Our results demonstrate that 2-azabicyclo[3.1.0]hexane derivatives can be accessed from *N*-(but-3-enyl)thioamide substrates by an intramolecular titanium-mediated reaction. From a mechanistic viewpoint, all the experiments support a process operating similarly to the well-known intramolecular Kulinkovich-de Meijere reaction of *N*-(but-3-enyl)carboxylic amides. The latter substrates tend to give superior results to those obtained with their thioamide counterparts, with a few exceptions. Moreover, it is worthy of note that the intramolecular aminocyclopropanations of *N*-(but-3-enyl) thioamides can be mediated by other reagent systems, such as CuCN·2LiCl/cC_5H_9MgCl, so far with inferior yields but, interestingly, with reversed diastereoselectivity.

4. Experimental

4.1. General information

Titanium(IV) isopropoxide (VERTEC® TIPT) was purchased from Alfa Aesar, distilled under reduced pressure and stored under nitrogen for several months. Cyclopentylmagnesium chloride was purchased from Sigma–Aldrich or Acros and titrated once a month according to a method described earlier.[19] Zinc was activated by washing successively with 1 M HCl aqueous solution, H_2O, EtOH and dried thoroughly. Other commercial reagents were used as received, without purification. Tetrahydrofuran, diethyl ether, dichloromethane and methanol were purified using a MB SPS-800 solvent purification system (MBRAUN). *tert*-Butyl methyl ether and cyclopentyl methyl ether were purchased from Acros or Alfa Aesar and used as received. All the reactions were carried out under a stream of nitrogen or argon, unless specified otherwise. The temperatures mentioned are the temperatures of the cold baths used. Concentration under reduced pressure was carried out using rotary evaporators at 40 °C.

Flash column chromatography was performed on Merck silica gel 60 (40–63 μm). NMR spectra were recorded with AM 400 and AVANCE 400 Bruker spectrometers (^1H at 400 MHz, ^{13}C at 100.6 MHz). Infrared spectra were recorded with a Perkin–Elmer 2000 FT-IR spectrometer. Melting points were determined using a Büchi 535 apparatus. Low-resolution mass spectra were recorded on a Hewlett–Packard Quad GC–MS engine spectrometer via direct injection. High-resolution mass spectrometry was performed on a JEOL GC-mate II spectrometer.

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4.2. X-ray crystal structure of compound β-3g[13]

A colourless crystal of β-**3g** was coated in Paratone®-N oil and mounted on a loop. Data were collected at 150.0(1) K with a Bruker Kappa APEX II diffractometer using an Mo-*Kα* (λ=0.71070 Å) X-ray source and a graphite monochromator. All data were measured using *φ*- and *ω*-scans. The crystal structures were solved using SIR 97[20] and refined using SHELXL 2013.[21]

4.3. Typical procedure for the syntheses of the carboxylic amide substrates 4: preparation of 4b

To a solution of *p*-anisaldehyde (1.00 equiv, 20.0 mmol, 2.43 mL) in CH_2Cl_2 (50 mL) was added benzylamine (1.00 equiv, 20.0 mmol, 2.18 mL) and *p*TSA (1.00% equiv, 200 μmol, 38.0 mg). The mixture was stirred at 20 °C for 3 h, then filtered through a pad of silica gel (rinsing: CH_2Cl_2). The volatile components were removed under reduced pressure and THF (50 mL) was added. Allyl bromide (3.00 equiv, 60.0 mmol, 5.20 mL) and zinc powder (3.00 equiv, 60.0 mmol, 3.90 g) were added and the mixture was stirred at 20 °C overnight. 1 M HCl aqueous solution (0.10 L) was added. The phases were separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude *N*-benzyl-*N*-[1-(4-methoxyphenyl)but-3-en-1-yl]ammonium chloride. This salt was dissolved in pyridine (20 mL). Acetic anhydride (2.00 equiv, 40.0 mmol, 3.78 mL) was added and the mixture was stirred at 20 °C for 24 h, after, which time more acetic anhydride was added (1.00 equiv, 20.0 mmol, 1.89 mL). After three additional days of stirring, 1 M NaOH aqueous solution (40 mL) was added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed successively with water (2×10 mL), 1 M HCl aqueous solution (10 mL) and water (10 mL), then dried over $MgSO_4$. The volatile components were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether, gradient from 20 to 50%) to afford pure *N*-benzyl-*N*-[1-(4-methoxyphenyl)but-3-en-1-yl]acetamide **4b** as a yellow oil (5.18 g, 16.7 mmol, 84% over three steps).

4.4. General procedure for the transformations of the amides 4 into the thioamides 1

Lawesson reagent (0.500 equiv) was added at 20 °C to a solution of the amide substrate **4** (1.00 equiv) in ^{t}BuOMe (1.0–4.0 mL per mmol of **4**). The mixture was stirred at 20 °C. When the reaction was finished (as indicated by TLC), the mixture was filtered through a pad of silica gel (rinsing: Et_2O) and the volatile components were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/petroleum ether).

4.5. General procedure for the titanium-mediated intramolecular cyclopropanation reactions of the substrates 1 or 4

To a solution of **1** or **4** (1.00 equiv) in the specified solvent (20 mL per mmol of substrate) was added $Ti(O^iPr)_4$ (1.50 equiv). The reaction mixture was cooled to 0 °C, then the Grignard reagent (≈2.0 M solution in Et_2O, 4.00 equiv) was added dropwise over the indicated time (using a syringe pump for addition times of 30 min or more). During the addition, the temperature of the reaction mixture was maintained at 0 °C. A yellow colour was initially observed that gradually darkened to become black. After 1 h of stirring at room temperature, 25% aqueous NH_3 solution (0.50 mL per mmol of substrate) was added and the flask was exposed to air. The formation of a white precipitate was observed. After 0.5 h, the mixture was filtered through a short pad of Na_2SO_4 and Celite (rinsing: Et_2O). The solution was concentrated under reduced pressure. The resulting crude product was analysed by NMR spectroscopy before purification.

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Supplementary data

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