



## Diastereoselective Ti-mediated preparation of bicyclic aminocyclopropanes from *N*-alkenyl amides

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### ABSTRACT

Intramolecular Ti-mediated alkene–amide couplings of a range of *N*-alk-3-enyl amides fitted with a substituent at the homoallylic position are described. CF<sub>3</sub>-substituted compounds are suitable substrates and bicyclic aminocyclopropanes bearing a CF<sub>3</sub> group can be prepared in this way. Good diastereoselectivities can be observed depending on the substitution pattern, and best results are obtained in diethyl ether rather than in THF.

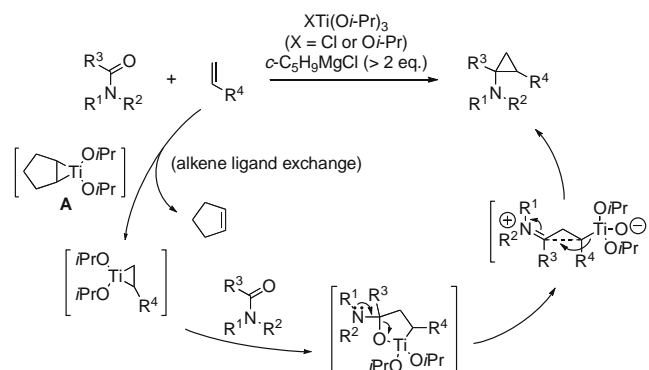
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### 1. Introduction

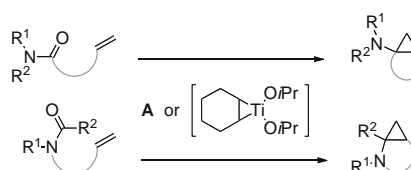
The titanium-mediated cyclopropanation of carboxylic amides (Kulinkovich-de Meijere reaction) has become the method of choice for the preparation of aminocyclopropanes.<sup>1,2</sup> The ligand exchange variation of this reaction, especially efficient when promoted by an intermediate titanacyclopentane (e.g., **A**) generated from Ti(O*i*-Pr)<sub>4</sub> [or ClTi(O*i*-Pr)<sub>3</sub>] and a cyclic Grignard reagent such as *cyclo*-pentylmagnesium chloride or *cyclo*-hexylmagnesium chloride, allows alkene–amide coupling (Scheme 1).<sup>3</sup>

This process has triggered the development of new applications. In particular, it has opened a practical possibility to perform intramolecular Kulinkovich-de Meijere reactions starting from carboxylic amides fitted with an alkene moiety (Scheme 2).<sup>3–10</sup> Various transformations of the resulting bicyclic aminocyclopropanes have been developed recently,<sup>6</sup> highlighting their potential as useful intermediates for the construction of polycyclic nitrogen-containing systems.<sup>10b–d</sup> In the context of this previous work, we became interested in the study of intramolecular Kulinkovich-de Meijere reactions of *N*-alk-3-enyl amides containing a chiral centre at the homoallylic position, α to the nitrogen atom. These raised an interesting stereoselectivity issue: to the best of our knowledge, the

diastereoselectivities of similar intramolecular Kulinkovich-de Meijere reactions have been little documented.<sup>8</sup>



Scheme 1. Kulinkovich-de Meijere alkene–amide coupling.



Scheme 2. Intramolecular Kulinkovich-de Meijere reactions.

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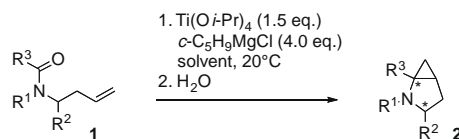
## 2. Results

Accordingly, a range of *N*-alk-3-enyl formamides and acetamides **1** fitted with a methyl, a trifluoromethyl or a phenyl group were prepared by Barbier-type reactions of allyl bromide with the corresponding imines in the presence of Mg turnings or Zn coarse powder, followed by

acylation.<sup>11</sup> For comparison purposes, non-chiral compounds **1b-H**, **1d-H** and **1e-H** were synthesised as well. The results of the transformations of these molecules under the conditions of Kulinkovich-de Meijere alkene–amide coupling are presented in Table 1.<sup>12</sup>

In most cases, including with the CF<sub>3</sub>-substituted substrates, the cyclisations proceeded efficiently, and the aminocyclopropane

**Table 1**  
Intramolecular Kulinkovich-de Meijere reactions of *N*-alkenyl amides **1**



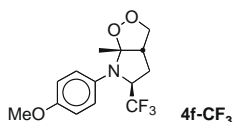
| Entry | <i>N</i> -Alkenyl amide <b>1</b> | Solvent           | Aminocyclopropane <b>2</b> <sup>a</sup> (yield) | dr <sup>b</sup> | Other product (yield)           |
|-------|----------------------------------|-------------------|---|-----------------|---------------------------------|
| 1     |                                  | THF               | <b>2a-Ph</b> (80%) <sup>c</sup>                 | 54:46           |                                 |
| 2     |                                  | THF               | <b>2b-H</b> (42%)                               | –               | <b>3b-H</b> (32%)               |
| 3     |                                  | Et <sub>2</sub> O | <b>2b-H</b> (37%)                               | –               | <b>3b-H</b> (32%)               |
| 4     |                                  | THF               | <b>2c-Ph</b> (30%) <sup>c</sup>                 | 52:48           | <b>3c-Ph</b> (15%) <sup>c</sup> |
| 5     |                                  | Et <sub>2</sub> O | <b>2c-Ph</b> (49%)                              | 62:38           | <b>3c-Ph</b> (15%) <sup>c</sup> |
| 6     |                                  | THF               | <b>2d-H</b> (75%)                               | –               |                                 |
| 7     |                                  | THF               | <b>2d-Me</b> (55%)                              | 58:42           |                                 |
| 8     |                                  | THF               | <b>2d-CF<sub>3</sub></b> (67%)                  | 60:40           |                                 |
| 9     |                                  | THF               | <b>2d-Ph</b> (54%)                              | 74:26           |                                 |
| 10    |                                  | Et <sub>2</sub> O | <b>2d-Ph</b> (71%)                              | 82:18           |                                 |
| 11    |                                  | THF               | <b>2e-H</b> (≈100%)                             | –               |                                 |
| 12    |                                  | Et <sub>2</sub> O | <b>2f-Me</b> (71%) <sup>c</sup>                 | 89:11           |                                 |
| 13    |                                  | THF               | <b>2f-CF<sub>3</sub></b> (40%)                  | 75:25           |                                 |
| 14    |                                  | Et <sub>2</sub> O | <b>2f-CF<sub>3</sub></b> (57%)                  | 89:11           |                                 |
| 15    |                                  | THF               | <b>2f-Ph</b> (77%)                              | 88:12           |                                 |
| 16    |                                  | Et <sub>2</sub> O | <b>2f-Ph</b> (80%) <sup>c</sup>                 | 90:10           |                                 |

<sup>a</sup> Only the major diastereoisomer is shown, when relevant. Unless otherwise stated, yields are given for the isolated products.

<sup>b</sup> The diastereoisomeric ratios of compounds **2** were measured in the crude products by NMR spectroscopy (see Supplementary data).

<sup>c</sup> Yield estimated by <sup>1</sup>H NMR spectroscopy of the crude product (see Supplementary data).

products **2** were obtained in fair yields, even though they showed a tendency to undergo partial decomposition during purification. For instance, when the crude product of the experiment displayed in entry 13 was purified by flash column chromatography on silica gel, the oxidation product **4f-CF<sub>3</sub>** was isolated in significant amounts.<sup>12</sup> The mechanism leading to this type of peroxide has been the subject of previous studies.<sup>10a,d</sup>



2D NOESY NMR experiments were performed on the major diastereoisomers of aminocyclopropanes **2f-Me** and **2f-CF<sub>3</sub>**, evidencing trans relative configurations (Fig. 1).<sup>13</sup> Moreover, the signal of the proton borne by the tertiary centre at the  $\alpha$ -position relative to the nitrogen atom has a chemical shift of 3.23 ppm in the case of *trans*-**2f-Me** and of 3.94 ppm in the case of *trans*-**2f-CF<sub>3</sub>**, while they lie around one ppm higher in the cases of the minor (*cis*)<sup>13</sup> diastereoisomers, with values of 4.33 and 4.79 ppm, respectively. This is also consistent with the proposed stereochemical assignment: in *trans*-**2f-Me** and *trans*-**2f-CF<sub>3</sub>**, a shielding effect might be exercised by the cyclopropane ring on this proton.

The relative configurations of the major diastereoisomers of all the other aminocyclopropane products **2** were also assigned as trans by analogy with those of compounds **2f-Me** and **2f-CF<sub>3</sub>**.<sup>13</sup> This is in full agreement with the chemical shifts of the protons  $\alpha$  to the R<sup>2</sup> substituents that were found to be lower than those of the minor diastereoisomers in every case (see Supplementary data).

With respect to the influence of the substituents of the starting alkenyl amides, all other parameters being equal, the diastereoselectivities of the reactions tended to be higher with *N*-aryl substrates than with *N*-benzyl substrates (entry 13 vs entry 8, and entry 15 vs entry 9; however, see entry 4 vs entry 1), and increased with the nature of the R<sup>2</sup> substituent at the homoallylic position in the order Me < CF<sub>3</sub> < Ph (entries 7–9, 13 vs 15, and to a minor extent 12, 14 and 16). Substituent R<sup>3</sup> has a dramatic effect on the reaction: the diastereoselectivities of the cyclisations of formamides **1a-Ph** and **1c-Ph** are much lower than those of the corresponding acetamides **1d-Ph** and **1f-Ph** (entry 1 vs entry 9, entry

4 vs entry 15, and entry 5 vs entry 16). Moreover, significant amounts of unexpected compounds **3b-H** and **3c-Ph** are produced from formamides **1b-H** and **1c-Ph**,<sup>14</sup> while the acetamide analogues **1e-H** and **1f-Ph** cyclise without complication (entry 2 vs entry 11, and entry 4 vs entry 15). However, and interestingly, by-products **3b-H** and **3c-Ph** are no longer observed when the transformations of **1b-H** and **1c-Ph** are carried out in diethyl ether rather than in THF (entries 3 and 5).

The influence of the solvent is further evidenced by the diastereoselectivities of the cyclisations of the chiral substrates. Indeed, these are consistently and notably higher in diethyl ether than in THF (entries 4–5, 9–10, 13–14 and 15–16).

Other reactions mediated by XTi(Oi-Pr)<sub>3</sub> and Grignard reagents can be found in the literature that are significantly influenced by the nature of the solvent used.<sup>15–18</sup> Notably, examples of Kulinkovich reactions<sup>17</sup> and transformations of cyanoesters<sup>18</sup> have been reported to be more diastereoselective in THF than in diethyl ether, thereby exhibiting an opposite behaviour to the presently described cyclisations.

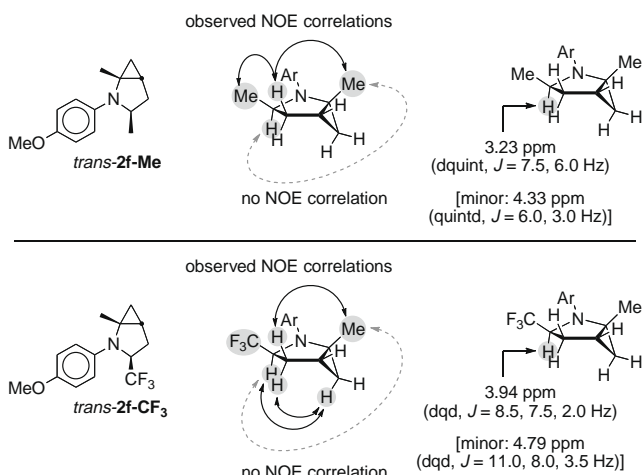
Among the new bicyclic aminocyclopropanes synthesised, the trifluoromethyl-substituted products are especially interesting. The impact of the presence of the CF<sub>3</sub> substituent on their reactivity is evidenced by the fact that compound *trans*-**2f-CF<sub>3</sub>** is essentially unaffected under conditions previously described for the acetylation of structurally related substrates (Scheme 3).<sup>10b</sup> Nonetheless, the isolation of peroxide **4f-CF<sub>3</sub>** shows that the CF<sub>3</sub> group does not preclude aerobic oxidation.<sup>19</sup>

### 3. Mechanistic rationale

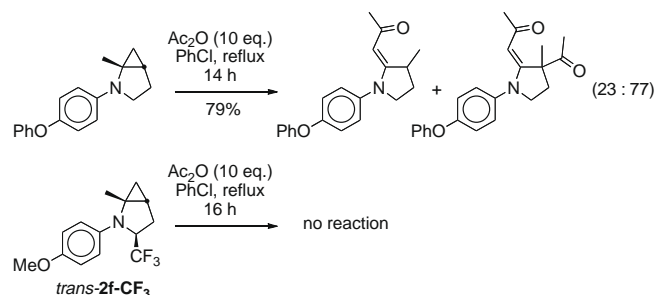
The origin of the diastereoselectivities of the presently described reactions can be analysed as follows. After ligand exchange of complex **A** with substrate **1**, two diastereoisomeric titanacyclopropanes *trans*-**B** and *cis*-**B** can be formed, where the titanium centre is coordinated by the carbonyl oxygen atom (Scheme 4). As far as we are aware of, the mechanism of this transformation—irreversible in this case—has not been clearly elucidated, and it is therefore uneasy to predict which diastereoisomer would be favoured. Nonetheless, it appears reasonable to suppose that diastereochemical differentiation does not operate significantly at this stage, and there is probably little energy difference between *trans*- and *cis*-**B**.

The next elementary step of the cyclisation process, the insertion of the carbonyl group into a C–Ti bond, is thought to proceed diastereospecifically following an S<sub>E</sub>i mechanism, giving the intermediates *trans*- and *cis*-**C** via transition states *trans*-**TS** and *cis*-**TS**, eventually yielding the corresponding aminocyclopropane diastereoisomers **2**, again diastereospecifically.

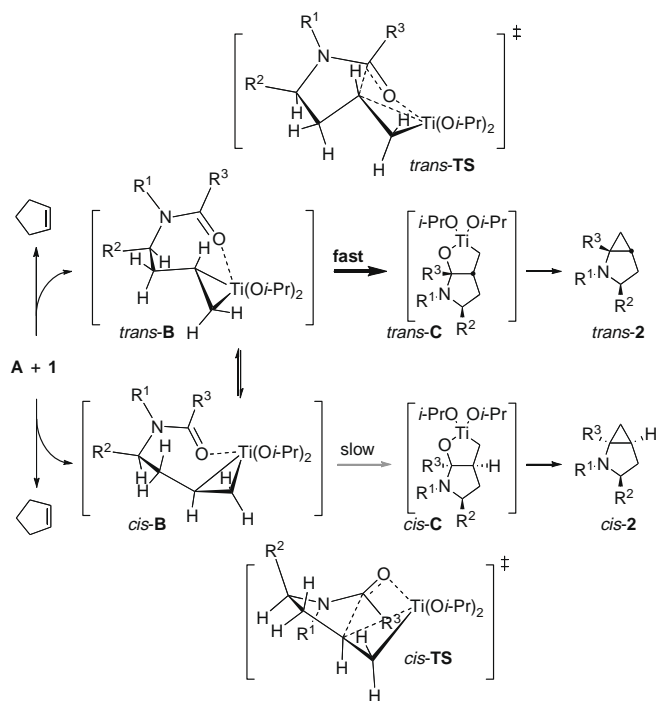
In *cis*-**TS**, the R<sup>2</sup> group adopts an *endo* position relative to the developing oxatitanacyclopentane ring, while it is *exo* and *pseudo-equatorial* in *trans*-**TS**.<sup>20</sup> *cis*-**TS** is therefore probably lying at a higher energy than *trans*-**TS**, and *trans*-**B** is expected to cyclise



**Figure 1.** Evidence for the relative configurations of the major diastereoisomers of **2f-Me** and **2f-CF<sub>3</sub>**.



**Scheme 3.** The low reactivity of **2f-CF<sub>3</sub>** towards acylation.



Scheme 4. Origin of the diastereoselectivity.

faster than *cis-B*. This being stated, the preferential formation of *trans-2* can be readily understood by invoking the possibility of rapid interconversion between *cis-B* and *trans-B*. This process could operate by internal rearrangement or by ligand exchange with residual substrate **1**. This explanation is analogous to that formulated by Cha et al. to explain the diastereoselectivities of Kulinkovich reactions of homoallyl alcohols.<sup>21</sup> Moreover, it can readily account for the lower diastereoselectivities observed with formamides. Indeed, the rates of formation of *cis-C* and *trans-C* should increase importantly in the case of these compounds, with rates of interconversion between *cis-B* and *trans-B* comparable to those met with acetamides, and diastereoselectivity would hence be eroded.

With respect to the solvent effect we observed, providing an accurate explanation seems difficult at this stage, since it could be caused by a number of factors.

#### 4. Summary and conclusion

In summary, the *N*-alk-3-enyl amides investigated, that bear a methyl, a trifluoromethyl or a phenyl group at the homoallylic position, undergo intramolecular Kulinkovich-de Meijere cyclopropanation in moderate to good yields with up to 90:10 diastereoselectivity. The influence of the solvent is noteworthy, with the cyclisation reactions being consistently more diastereoselective in diethyl ether than in THF. The syntheses of other CF<sub>3</sub>-containing bicyclic aminocyclopropanes, their oxidations to endoperoxides and the *in vitro* activities of the latter against *Plasmodium falciparum* are under progress and will be reported in due course.

#### Acknowledgements

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#### Supplementary data

Method used for the evaluation of the yields and diastereoselectivities of the cyclopropanation reactions by analysis of the NMR spectra of the crude products. Analytical data for compounds **2a-Ph**, **2c-Ph**, **3c-Ph**, **2d-Me**, **2d-CF<sub>3</sub>**, **2d-Ph**, **2f-Me** and **2f-Ph**. Basic molecular modelling of titanacyclopropane intermediates *trans*- and *cis-B*. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.031.

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- For instance, compound **1f-CF<sub>3</sub>** was obtained by acetylating 4-methoxy-*N*-(1,1,1-trifluoropent-4-en-2-yl)aniline, whose preparation has been described previously: Legros, J.; Meyer, F.; Colibœuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégue, J.-P. *J. Org. Chem.* **2003**, *68*, 6444–6446. *N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoropent-4-en-2-yl)acetamide (**1f-CF<sub>3</sub>**): To a solution of imine (*E*)-*N*-(2,2,2-trifluoroethylidene)-4-methoxyaniline (1.00 equiv, 5.51 mmol, 1.12 g) in THF (10 mL) were added allyl bromide (1.30 equiv, 7.15 mmol, 865 mg) and Zn coarse powder (1.30 equiv, 7.15 mmol, 467 mg) followed by two drops of Me<sub>3</sub>SiCl. The mixture was refluxed for 30 min, and then the solution was hydrolysed with a saturated aqueous solution of NH<sub>4</sub>Cl (20 mL) and extracted with Et<sub>2</sub>O (3 × 20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and the solvents were removed. To the crude product were then added Ac<sub>2</sub>O (6 mL) and a crystal of iodine, and the mixture was heated at reflux for 2 h. Then, the product was concentrated and finally purified by column chromatography on silica gel (Et<sub>2</sub>O/petroleum ether 20%) to afford pure **1f-CF<sub>3</sub>** (1.26 g, 4.39 mmol, 80%). **1f-CF<sub>3</sub>**: Bright yellow oil. IR (neat): 2960, 2935, 1672, 1510, 1371, 1291, 1250, 1216, 1169, 1147, 1107, 1030, 920, 837 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.80 (s, 3H), 2.15–2.49 (m, 2H), 3.85 (s, 3H), 5.19 (dq, *J* = 17.0, 1.5 Hz, 1H), 5.21 (dq, *J* = 10.5, 1.5 Hz, 1H), 5.68 (dq, *J* = 11.0, 8.0, 4.0 Hz, 1H), 5.81 (dddd, *J* = 17.0, 10.5, 7.0, 5.0 Hz, 1H), 6.79–7.24 (m, 4H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 22.9, 29.8, 53.6 (q, *J* = 29.5 Hz), 55.3, 114.3, 114.7, 118.1, 125.0 (q, *J* = 284 Hz), 130.4, 131.0, 132.7, 131.2, 159.8, 172.4. MS (ES<sup>+</sup>) *m/z* 288 (MH<sup>+</sup>), 310 (MNa<sup>+</sup>). HRMS (ES<sup>+</sup>) *m/z* calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub> (MH<sup>+</sup>) 288.1211, found 288.1221.
- The following procedure is representative for the intramolecular cyclopropanations of *N*-alkenyl amides **1**. *2*-(4-Methoxyphenyl)-1-methyl-3-(trifluoromethyl)-2-azabicyclo[3.1.0]hexane (**2f-CF<sub>3</sub>**): Titanium(IV) isopropoxide (1.50 equiv, 3.50 mmol, 1.04 mL) was added to a solution of *N*-alkenyl amide **1f-CF<sub>3</sub>** (1.00 equiv, 2.33 mmol, 670 mg) in freshly distilled THF (23.0 mL), followed by the addition of cyclopentylmagnesium chloride (≈2.32 M in Et<sub>2</sub>O, 4.00 equiv, 9.32 mmol, 4.02 mL) dropwise at 20 °C. After 30 min of stirring, water (1.00 mL) was added to the dark solution, which was exposed to air, and stirring was continued until decolouration. The mixture was then filtered through a 1-cm layer of Celite on a fritted-disc funnel that was then rinsed with Et<sub>2</sub>O (2 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a brown oil (684 mg). The crude product was analysed by NMR spectroscopy, showing the near exclusive presence of aminocyclopropane **2f-CF<sub>3</sub>** with a 75:25 diastereoisomeric ratio. Purification by flash column chromatography on silica gel (ethyl acetate/heptane, gradient from 0% to 10%) afforded analytically pure, diastereoisomer *trans-2f-CF<sub>3</sub>* (254 mg, 936 μmol, 40%), and (3*aS*,5*S*,6*aR*)-6-(4-methoxyphenyl)-6*a*-methyl-5-(trifluoromethyl)hexahydro-[1,2]dioxolo[3,4-*b*]pyrrole **4f-CF<sub>3</sub>** as a single diastereoisomer (84.0 mg, 277 μmol, 12%).

13. The cis or trans relative configurations of products **2** are defined by the relative configurations, on the pyrrolidine ring, of the fused cyclopropane and the substituent R<sup>2</sup> attached to the tertiary carbon at the  $\alpha$ -position relative to the nitrogen atom.
14. The mechanism of formation of compound **3b-H** has been discussed previously in the [Supplementary data](#) provided with Ref. 10d. Aminocyclopropane **3c-Ph** is assumed to be produced according to a similar pathway.
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19. This is an interesting property because endoperoxides prepared by the oxidation of similar bicyclic aminocyclopropanes have been found to exhibit antimalarial activity. See Ref. 10d.
20. With the help of plastic molecular models or by performing molecular mechanics calculations (see [Supplementary data](#)).
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