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Studies on the intramolecular Kulinkovich–de Meijere reaction of disubstituted alkenes bearing carboxylic amide groups

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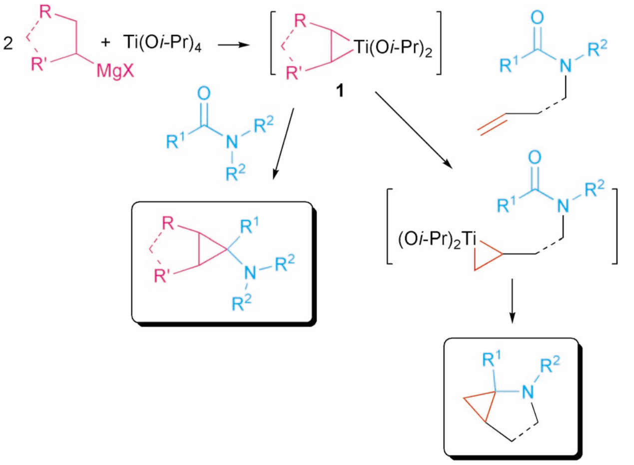
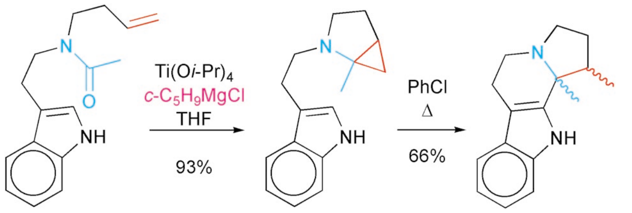
1,2-Disubstituted olefins bearing an acetamide group were found to undergo intramolecular Kulinkovich–de Meijere cyclopropanation in moderate yield but almost complete diastereoselectivity.

The de Meijere variation of the Kulinkovich reaction[1–4] is an efficient method for the synthesis of cyclopropyl amines from carboxylic amides.[5] It was initially performed by treating the amide with a stoichiometric amount of Ti(O*i*-Pr)$_4$ and more than two equivalents of a Grignard reagent. The commonly accepted mechanism operates *via* a dialkoxytitanacyclopropane intermediate **1**, arising from an initially formed dialkoxy(dialkyl)titanium complex.[2] Organotitanium species **1** have been demonstrated to undergo ligand exchange with alkenes.[6] This provides an easy access to more substituted products, and allows intramolecular reactions to be performed in an efficient and convenient way (Scheme 1).[7]



Scheme 1

We have recently developed a novel two-step sequence featuring an intramolecular Kulinkovich–de Meijere reaction and an intramolecular Friedel–Crafts type alkylation leading to nitrogen-containing polycyclic systems (Scheme 2).[8] In a view to applying this method to the total synthesis of alkaloids, we were interested in the possibility of using disubstituted olefins as starting materials.

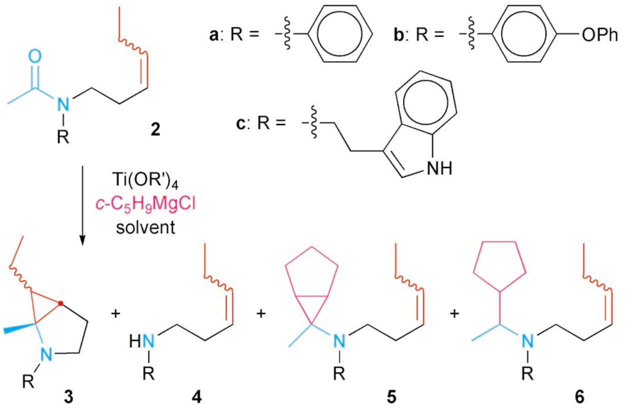


Scheme 2

To the best of our knowledge, apart from special cases like cycloalkenes[9] or conjugated dienes,[10,11] the only disubstituted alkenes having been reported to give cyclopropyl amines or alcohols after ligand exchange with dialkoxy(η^2-alkene)titanium complexes are (*Z*)-pent-2-ene and (*E*)-hex-3-ene, in modest yield and with poor diastereoselectivity.[12]

We reasoned that in the case of intramolecular reactions, better results were likely to be achieved, the amide group being able to coordinate to the titanium and direct the ligand exchange process. Indeed, the related intramolecular cyclopropanation of a *gem*-disubstituted alkene with a nitrile in good yield (Szymoniak's variation of the Kulinkovich reaction)[13] has just been described.[14] This prompts us to report the preliminary results of our own investigations.

Four alkenes (*Z*)-**2a**, (*E*)-**2a**, (*Z*)-**2b** and (*Z*)-**2c** were prepared and put under study using a modification of a literature procedure.[15] Four types of products were isolated and identified: the expected cyclopropyl amines **3**, secondary amines **4**, cyclopropyl amines **5** and tertiary amines **6** (Scheme 3).[16]



Scheme 3

Amines **4** might be formed by direct attack of the starting amides by the Grignard reagent. We believe products **5** and **6** stem from a common intermediate **7** resulting from attack of the amide group by the *in situ*-generated dialkoxy(η^2-cyclopentene)titanium complex before the ligand exchange takes place (Scheme 4). To the best of our knowledge, only one report describing a process similar to the one that leads to the unexpected amines **6** can be found in the literature.[12] In our case, the mechanism proposed by the authors is inconsistent with our observation that replacing titanium(IV) *iso*-propoxide with titanium(IV) *tert*-butoxide or titanium(IV) cresylate completely suppresses the formation of **6**. Although further studies are needed, we tentatively propose the mechanism depicted in Scheme 4 that involves intramolecular hydride shift from one of the *iso*-propoxide ligands of titanium.

Various solvents were used: heptane, toluene, diethyl ether and tetrahydrofuran. Our best results are presented in Table 1.

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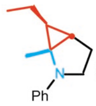
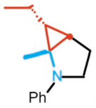
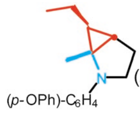
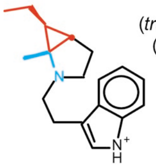
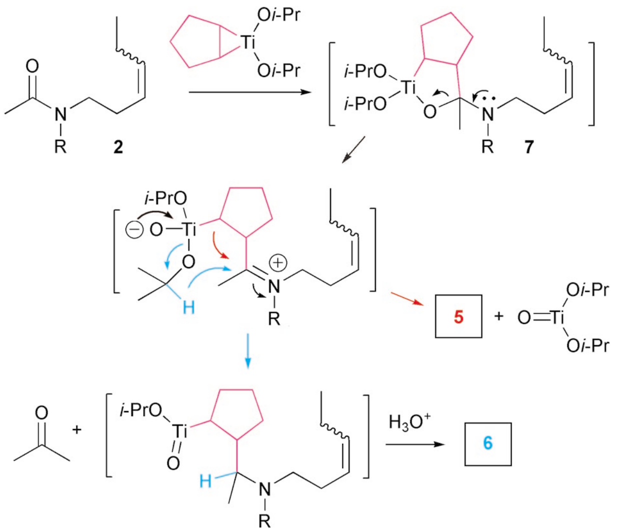
Table 1 Intramolecular Kulinkovich–de Meijere cyclopropanations from disubstituted alkenes[a]

Starting amide	Solvent	Cyclopropyl amine[b](yield)[c]	Other isolated products (yield)
(*Z*)-**2a**	Toluene	 (*trans*)-**3a** (40%)	Starting material (19%) Amine (*Z*)-**4a** (17%) Amines (*Z*)-**5a** and (*Z*)-**6a** (12%)
(*E*)-**2a**	Et_2O	 (*cis*)-**3a** (24%)[d]	Starting material (35%) Amine (*E*)-**4a** (12%) Amines (*E*)-**5a** and (*E*)-**6a** (12%)
(*Z*)-**2b**	Et_2O	 (*trans*)-**3b** (38%)	Starting material (19%) Amine (*Z*)-**4b** (7%) Amines (*Z*)-**5b** and (*Z*)-**6b** (19%)
(*Z*)-**2c**	THF	 (*trans*)-**3c** (20%)	Starting material (59%)

[a] In each case 1.5 equiv. of Ti(O*i*-Pr)$_4$ and 4.0 equiv. of *c*-C_5H_9MgCl were used. [b] (*cis*) and (*trans*) refer to the relative configurations of the amino and ethyl groups of the cyclopropanes **3**. [c] After purification by neutral alumina (activity 2) column chromatography. [d] The yield was 12% when the reaction was performed in toluene.

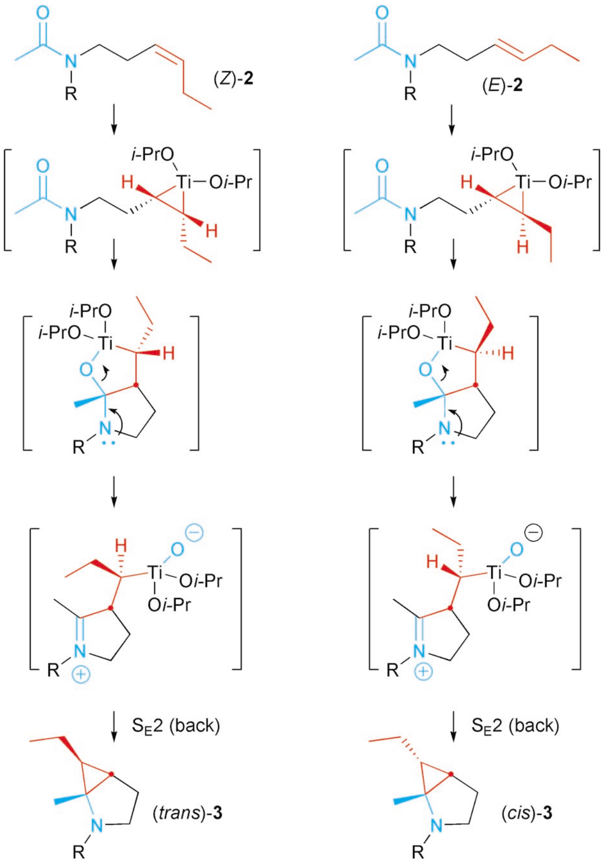


Scheme 4

Replacing cyclopentyl magnesium chloride with cyclohexyl magnesium chloride had no beneficial effect on these reactions.

The intramolecular cyclopropanations were moderately efficient but highly diastereoselective. In each case one of the two possible diastereoisomers was either produced in trace amounts or could not be detected at all by ^1H NMR analysis of the crude product. It is also noteworthy that (*E*)-**2a** performed less well than the corresponding (*Z*) alkene (*Z*)-**2a**.[17] Only poor conversion occured from the indole derivative (*Z*)-**2c** in all the solvents listed above. We have no satisfactory explanation for this fact at present (compare with the result shown in Scheme 2).

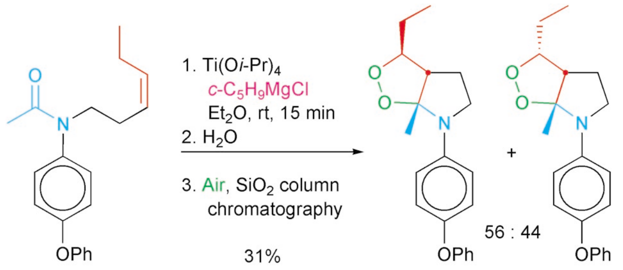
The determination of the relative configuration of (*trans*)-**3a** was based on two-dimensional ROESY NMR spectroscopy and on the value of the coupling constant between the two cyclopropyl vicinal protons (^3J = 5 Hz, in agreement with the *trans* relationship).[18] For (*cis*)-**2a**, which was a different compound as shown by NMR spectroscopy, the other possible stereochemistry was thus assigned. The stereochemistry of (*trans*)-**3b** was assigned on the basis of the coupling constant between the cyclopropyl protons (^3J = 5 Hz). Moreover, it displayed NMR signals very similar to those of (*trans*)-**3a** for the ring protons alpha to the nitrogen atom. The relative configuration of (*trans*)-**3c** was determined by two-dimensional NOESY NMR spectroscopy. The high diastereoselectivity of the cyclopropanation may be rationalised as depicted in Scheme 5. After ligand exchange with the originally formed di-*iso*-propyloxy(η^2-cyclopentene)titanium complex and cyclisation onto the amide, an oxatitanacyclopentane intermediate is formed. Subsequent carbon–oxygen bond cleavage and rotation around a carbon–carbon single bond generates a zwitterion where the titanium is placed in such a way as to reduce steric interactions with the five-membered ring. In this conformation,



Scheme 5

cyclopropane ring-closure may proceed with inversion of configuration by electrophilic substitution of the titanium with the amino-stabilised carbonium ion.

Interestingly, aerobic oxidation occurred more or less extensively when aminocyclopropanes **3** were flash-chromatographed on silica gel. This autocatalytic process has been described recently.[19] Less substituted but otherwise very similar compounds previously prepared by us from mono-substituted alkenes have proven much less sensitive.[8] The enhanced reactivities of cyclopropanes **3** are probably due to a lowering of their ionisation potentials by the extra ethyl group. The phenoxy substitution of **3b** would be expected to lower it further. Indeed, oxidation of **3b** was especially facile: after running silica gel thin-layer chromatographies of this compound, only peroxides (*trans*)-**8b** and (*cis*)-**8b** could be detected.[20] Accordingly, when the crude product of the reaction from (*Z*)-**2b** was purified by silica gel column chromatography, no expected cyclopropyl amine **3b** was obtained at all, but diastereoisomers **8b** were isolated in 31% yield (Scheme 6). Diastereoselectivity was poor, which is consistent with a literature precedent.[19] Replacing silica gel with neutral alumina (activity 2) suppressed the formation of these peroxides and enabled the purification of cyclopropyl amines **3**.



(*Z*)-**2b** (***trans***)-**8b** (***cis***)-**8b**

Scheme 6

In summary, we have studied the intramolecular Kulinkovich–de Meijere cyclopropanation of some disubstituted alkenes bearing amide groups. These reactions proved to be moderately efficient but highly diastereoselective: single diastereoisomers were obtained from diastereoisomerically pure alkenes. We believe the modesty of the yields arises from the poor efficiency of the ligand exchange step. Our next studies will be devoted to the resolution of this problem.

Acknowledgements

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16 Experimental procedure for the preparation of (*trans*)-**3a**: titanium(IV) *iso*-propoxide (750 µmol, 221 µL) was added at room temperature to a solution of (*Z*)-**2a** (500 µmol, 109 mg) in toluene (20 mL). Cyclopentylmagnesium chloride (2.00 mmol, 2.14 M in Et_2O, 935 µL) was then added dropwise. The mixture turned yellow, and then black. After 15 minutes of stirring at room temperature, water (100 mL) was added carefully, followed by diethyl ether (100 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated. ^{1}H NMR analysis of the crude product revealed that it contained only traces of the diastereoisomer (*cis*)-**3a**. Purification by flash column chromatography led to the isolation of a 33/67 mixture of (*Z*)-**5a** and (*Z*)-**6a** (17 mg, 8% and 4% respectively), starting material (*Z*)-**2a** (20 mg, 19%), and a 70/30 mixture of (*trans*)-**3a** and (*Z*)-**4a** (56 mg, 40% and 17% respectively). (*trans*)-**3a** could be purified further by flash column chromatography. (*trans*)-**3a**: colourless liquid (Found: C, 83.27; H, 9.63. $C_{14}H_{19}N$ requires C, 83.53; H, 9.51%); ν_{max}(film)/cm^{-1} 2959, 2931, 2870, 1601, 1500, 1482, 751, 695; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.78 (1H, td, *J* 7 and 5 Hz, cyclopropane CH), 0.97 (1H, t, *J* 5 Hz, cyclopropane CH), 1.06 (3H, t, *J* 7 Hz, CH_3), 1.45 (2H, m, CH_2CH_3), 1.48 (3H, s, CH_3), 1.95 (1H, ddd, *J* 12, 9 and 3 Hz, CH_2), 2.29 (1H, dtd, *J* 12, 9 and 5 Hz, CH_2), 2.87 (1H, q, *J* 9 Hz, NCH_2), 3.93 (1H, td, *J* 9 and 3 Hz, NCH_2), 6.75 (1H, t, *J* 7 Hz, ArH), 6.79 (2H, d, *J* 8 Hz, ArH), 7.22 (2H, dd, *J* 8 and 7 Hz, ArH); δ_C (75.4 MHz; $CDCl_3$; Me_4Si) 14.1, 15.1, 23.4, 26.8, 31.1, 32.3, 46.9, 53.4, 116.3, 117.6, 128.8, 149.9; *m*/*z* (EI) 172, 173, 186, 201 (MH^+).

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20 (*trans*)-**8b** and (*cis*)-**8b** could not be separated. Their structures have been assigned on the basis of mass, infra-red, 1D and 2D NMR spectroscopies. Their relative stereochemistries were determined according to the coupling constants found between the ring-junction proton and the CH proton alpha to the ethyl group: $^3J = 2.5$ Hz in (*trans*)-**8b** and $^3J = 5$ Hz in (*cis*)-**8b**.