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Intramolecular Kulinkovich–de Meijere reactions of various disubstituted alkenes bearing amide groups

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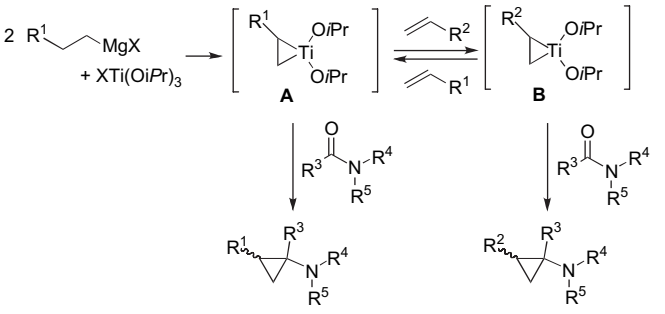
ABSTRACT

A range of amides fitted with (*E*) or (*Z*) disubstituted alkene groups were prepared and evaluated in intramolecular Kulinkovich–de Meijere reactions. The corresponding aminocyclopropanes were obtained with high diastereoselectivity. Good yields could be achieved with substrates bearing suitable substitutions at the olefin moieties.

1. Introduction

The reaction of tertiary carboxylic amides with titanium alkoxides of the form $XTi(O^iPr)_3$ (X=Me, Cl, O^iPr) and excess amounts of Grignard reagents (normally more than 2 equiv when X≠Me) is a powerful method for the preparation of aminocyclopropanes (Kulinkovich–de Meijere reaction).[1–4] In the presence of alkenes, the putative intermediate titanacyclopropane species **A** initially formed can undergo ligand exchange to give complex **B**, which leads to cyclopropane products resulting from alkene–amide coupling (Scheme 1).[5,6] This process is essentially limited to monosubstituted alkenes, even using cyclic Grignard reagents such as *cyclo*-pentylmagnesium chloride or *cyclo*-hexylmagnesium chloride, which have been shown to generally drive the equilibrium towards the formation of complex **B**.[7] Good yields have nonetheless been obtained from disubstituted alkenes in the special cases where they were part of conjugated polyene systems or geometrically constrained rings.[8–10]

A few years ago, we reported a study dealing with intramolecular Kulinkovich–de Meijere reactions starting from a few (*Z*) and (*E*) *N*-hex-3-enyl acetamides.[11] Although these reactions were poorly efficient because of competitive intermolecular reactions, they were found to be totally diastereoselective. A mechanistic hypothesis was formulated to account for the stereochemistry of the desired products, supported by a study published afterwards by Casey et al.[12]



Scheme 1. Kulinkovich–de Meijere reactions, without or with alkene ligand exchange.

In order to improve these intramolecular reactions, we decided to investigate the effect of an additional functional group on the substrate. Indeed, a suitable group might coordinate to the titanium intermediate complex **C** and direct the ligand exchange elementary step (Scheme 2). Our strategy for a rapid access to various substrates was to prepare them by cross-metathesis from the parent compound *N*-but-3-enyl-*N*-phenylacetamide **1a**.

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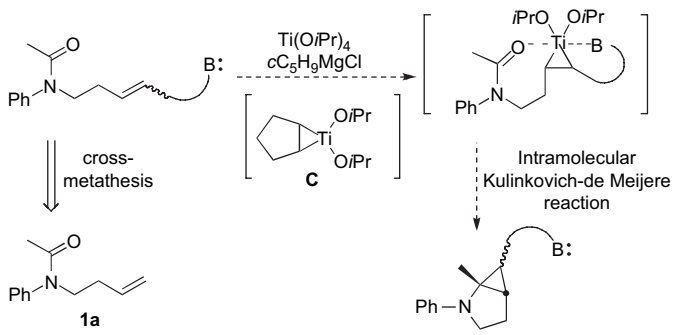


Scheme 2. Intramolecular Kulinkovich–de Meijere reaction with substrate-directed ligand exchange.

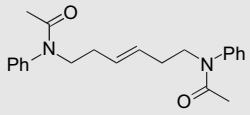
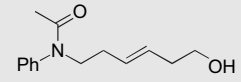
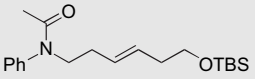
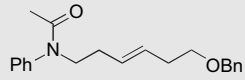
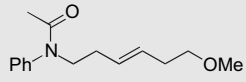
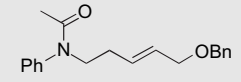
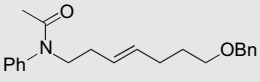
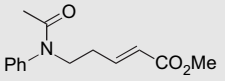
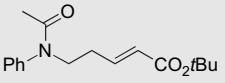
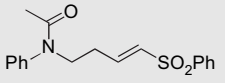
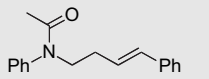
2. Results and discussion

Using Grubbs second generation catalyst, the cross-coupling metathesis of **1a** with various alkenes turned out to be of poor efficiency and feeble reproducibility due to double-bond migration and/or competition with homo-coupling processes. The use of a catalytic amount of 2,6-dichloro-1,4-benzoquinone (DQ), which inhibits double-bond migration,[13] gave satisfactory and reliable results in the preparation of **1b** as well as the cross-metathesis of **1a** with excess amounts of allyl alcohol, 3-buten-1-ol or 4-penten-1-ol, readily granting access to compounds **1c**–**h** (Table 1, entries 1–7).[14] We recently reported that a catalytic amount of a boron-based Lewis acid such as chlorocatecholborane could enhance the efficiency of cross-metathesis reactions involving nitrogen-containing alkenes.[15] Compounds **1i**–**l** were prepared in moderate to excellent yields using this method, with high diastereoselectivity in favour of the *E* isomers (Table 1, entries 8–11).

For comparison purposes, *n*-butyl derivatives (*E*)-**1m** and (*Z*)-**1m** were prepared in pure diastereoisomeric form following independent routes (Scheme 3). A range of pure (*Z*) alkenyl amides were also synthesised from alcohol (*Z*)-**1c**, obtained by standard cleavage of the *para*-methoxybenzyl (PMB) protected compound (*Z*)-**1n**.[16] This (*Z*) homoallylether, as well as the analogous benzyl derivative (*Z*)-**1e**, was prepared as a single diastereoisomer using the chemistry of Sato, namely via the intermediary of titanacyclopropene complexes generated from the corresponding alkynes (Scheme 4).[17,18]

With alkenyl amides **1b**–**q** in hand, they were submitted to the intramolecular Kulinkovich–de Meijere reaction conditions. The results are presented in Table 2, as well as that obtained from the reference compound **1a** (entry 1).[5,19] In agreement with our

Table 1
Preparation of alkenyl amides **1b**–**l** by cross-metathesis using Grubbs second generation catalyst

Entry	Starting alkene(s)	Method[a]	Product		Yield % (*E*/*Z* ratio)
1	**1a**	A		**1b**	60 (85:15)
2	**1a** (1.0 equiv) and 3-buten-1-ol (4.0 equiv)	A		**1c**	71 (75:25)[b]
3	**1a** (1.0 equiv) and 3-buten-1-ol (4.0 equiv)	A		**1d**	66 (85:15)[c]
4	**1a** (1.0 equiv) and 3-buten-1-ol (4.0 equiv)	A		**1e**	59 (85:15)[c]
5	**1a** (1.0 equiv) and 3-buten-1-ol (4.0 equiv)	A		**1f**	60 (85:15)[c]
6	**1a** (1.0 equiv) and allyl alcohol (4.0 equiv)	A		**1g**	33 (89:11)[c]
7	**1a** (1.0 equiv) and 4-penten-1-ol (4.0 equiv)	A		**1h**	45 (80:20)[c]
8	**1a** (1.0 equiv) and methyl acrylate (1.0 equiv)	B		**1i**	91 (>98:2)
9	**1a** (1.0 equiv) and *tert*-butyl acrylate (1.0 equiv)	B		**1j**	72 (>98:2)
10	**1a** (1.0 equiv) and phenylvinylsulfone (1.0 equiv)	B		**1k**	44 (>98:2)
11	**1a** (1.0 equiv) and styrene (1.0 equiv)	B		**1l**	44 (>98:2)

[a] Method A: the cross-metathesis reaction was performed in the presence of a catalytic amount of DQ. Method B: reaction was performed in the presence of a catalytic amount of chlorocatecholborane (see Section 4 for details).
[b] Combined yield for the cross-metathesis reaction, protection of the alcohol function as a *tert*-butyldimethylsilyl ether **1d**, purification and deprotection under acidic conditions (see Ref. 14).
[c] Combined yield for the cross-metathesis reaction and protection of the alcohol function either as a *tert*-butyldimethylsilyl, a benzyl or a methyl ether (see Ref. 14).