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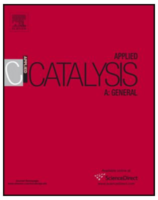

Synthesis of α,β-unsaturated aldehydes and nitriles via cross-metathesis reactions using Grubbs' catalysts

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ABSTRACT

A series of α,β-unsaturated aldehydes and nitriles of significant interest in the fragrance industry have been prepared using Grubbs' catalysts in cross-metathesis reactions of electron-deficient olefins (i.e., acrolein, crotonaldehyde, methacrolein, and acrylonitrile) with various 1-alkenes, including 1-decene, 1-octene, 1-hexene and 2-allyloxy-6-methylheptane. The latter is of particular interest, as it has not previously being used as a substrate in cross-metathesis reactions and allows access to valuable intermediates for the synthesis of new fragrances. Most reactions gave good selectivity of the desired CM product (≥90%). Detailed optimisation and mechanistic studies have been performed on the cross-metathesis of acrolein with 1-decene. Recycling of the catalyst has been attempted using ionic liquids.

1. Introduction

α,β-Unsaturated aldehydes and nitriles are of significant interest in the fragrance and flavour industries, either by themselves or as key intermediates in the preparation of other synthetic scents [1]. They are also important intermediates in numerous organic processes, such as Diels Alder reactions [2], Michael additions [3] or aldol condensations [4], to name a few. Wittig-type reactions are commonly used to prepare α,β-unsaturated aldehydes and nitriles [5], but a variety of other methods have also been reported, including, for example, catalytic oxidation of allylic alcohols [6], Ru-catalysed isomerisation of propargylic alcohols [7], or synthesis via Grignard reagents [8]. In addition, cross-metathesis (CM) reactions have been applied to prepare α,β-unsaturated aldehydes and nitriles, but this route is still relatively unexplored, in particular with substrates containing electron deficient double bonds such as acrolein and related α-carbonyl compounds [9]. It should be noted that synthetic routes involving cross-metathesis have been shown to be advantageous over more conventional methods. For example, they allow direct access to chiral pharmaceutical intermediates without the need for a chiral resolution step [9c].

It has been established that α,β-unsaturated aldehydes and nitriles do not react with Grubbs' first generation catalyst (**1**, Chart 1) [10], but are able to react in cross-metathesis reactions using ruthenium catalysts with NHC ligands (e.g., **2**–**3** in Chart 1). This is attributed to the greater electron donating ability of the NHC ligand compared to tricyclohexylphosphine (PCy_3) [10a]. Thus, good yields of CM products using NHC-Ru catalysts have been reported, for example, in reactions involving acrolein, methacrolein, acrylic acid, crotonaldehyde or acrylates [9b–e, 9g, 11]. Cross-metathesis reactions using acrylonitrile as substrate are more common and include processes using Schrock's molybdenum catalyst [12], as well as a variety of NHC-ruthenium catalysts [9g,13]. As in the case of acrolein, acrylonitrile shows poor reactivity with catalyst **1** [10c,13e]. Some of these reactions have been reported to work in neat conditions [11].

Selective formation of the cross-metathesis product can be achieved by combining an olefin that shows slow or no self-metathesis (classified as Type II/III olefins) with an olefin able of fast self-metathesis or Type I (e.g., 1-alkenes; see Scheme 1) [14]. In these reactions, the Type I homo-dimer may form initially [Scheme 1(b)], but undergoes secondary metathesis with the Type II/III olefin to produce the desired CM product [Scheme 1(c)]. Although the classification of a particular olefin depends on the catalyst, acrolein and related compounds, including acrylonitrile, are generally classified as Type II or Type III olefins [14].

Ruthenium-catalysed cross-coupling reactions with terminal olefins almost always occur with a high degree of *E*-selectivity [15],

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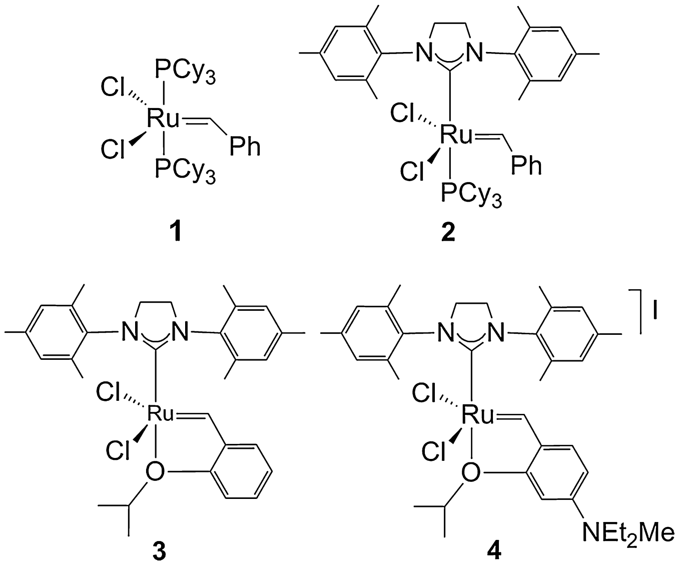
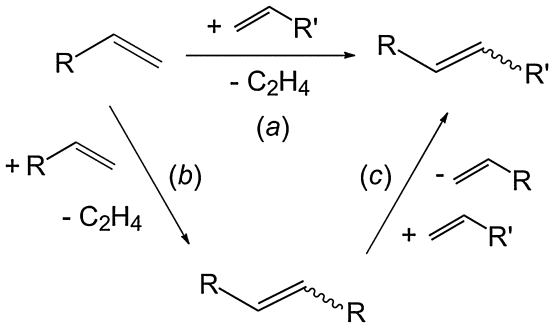


Chart 1. Grubbs' first (**1**) and second (**2**) generation catalysts, and Hoveyda-Grubbs' catalysts (**3**, **4**).

although strategies to favour *Z*-selectivity have been developed [16]. Acrylonitrile, however, generally produces cross-metathesis products where the *Z* isomer is predominant, and it has been proposed that this *Z*-stereoselectivity must be kinetically controlled and most likely related to the small size and/or electron-withdrawing properties of the cyano group [12,13b,13e,17]. A few examples in which cross-metathesis reactions of acrylonitrile have produced the *E*-isomer as the major component have also been reported [18].

In order to improve recyclability of Grubbs' catalysts, ionic liquids (ILs) have been used as reaction media or for the immobilisation of the catalyst onto silica (e.g., using the 'supported ionic liquid phase' or SILP concept) [19]. For example, Grubbs' second generation catalyst **2** has shown enhanced activity in CM reactions in ionic liquids, compared to dichloromethane [20], and Hoveyda-Grubbs' type catalysts immobilised onto silica gave excellent yields in RCM metathesis reactions [19a]. In both cases, the catalysts could be easily recycled up to four times. In addition to conventional Grubbs' catalysts, ionic analogues have been developed (e.g., complex **4** in Chart 1) with the aim of increasing the catalyst's retention time in the ionic liquid, thus improving its recyclability and reducing leaching into the organic phase [21].

In this paper, a series of α,β-unsaturated aldehydes and nitriles of significant interest in the fragrance industry have been prepared using Grubbs' catalysts in cross-metathesis reactions of electron-deficient olefins (i.e., acrolein, crotonaldehyde, methacrolein, and acrylonitrile) with various 1-alkenes. Detailed kinetic and mechanistic studies have been performed on the cross-metathesis of acrolein with 1-decene and attempts to recycle the catalyst by using ILs are also reported. Of particular interest are the reactions using 2-allyloxy-6-methylheptane, as this substrate has not previously being used in cross-metathesis. The product from its reaction with acrolein, 6,10-dimethyl-5-oxoundec-2-enal, is of use in the synthesis of a novel fragrance material [22].



Scheme 1. Reactions involved in the cross-metathesis of olefins of Type I ($RC{=}CH_2$) and Type II/III ($R'C{=}CH_2$).

2. Experimental

2.1. Catalyst preparation

Catalysts **1**–**3** were obtained from Aldrich and used as received. Ionic catalyst **4** was synthesised following a literature procedure [21e]. The ionic liquids were prepared as described elsewhere [23]. Catalysts and ionic liquids were handled and stored in a glovebox.

2.1.1. Preparation of supported catalyst 3

Buffered silica was first prepared by stirring 5 g of the corresponding Davicat silica 1 or 2 (see Table 4) in distilled water (100 mL) with a BHD buffer capsule (pH 7) for 2 h at 25 °C. The silica was then filtered, washed with distilled water (3 mL × 20 mL) and dried in an oven (85 °C) on a watch-glass overnight. Catalyst **3** (6.7 mg, 0.01 mmol) was weighed into a Schlenk flask, under nitrogen. To this was added dichloromethane (5 mL), $[C_4mim][NTf_2]$ (0.1 mL) and pre-dried silica (0.2 g, either untreated or buffered). This mixture was stirred for 10–15 min and the dichloromethane then removed under vacuum. Further drying under vacuum (4–5 h) produced the supported catalyst as a green powder.

2.2. Catalyst characterisation

Catalyst **4** was characterised by NMR spectroscopy. Its ^1H and ^{13}C NMR spectra were in good agreement with literature data [24]. NMR spectra were performed on either a Bruker Avance DRX (300 MHz) or DPX (500 MHz) spectrometer.

ICP analyses were performed at the ASEP unit in Queen's University Belfast. Samples to determine the amount of catalyst dissolved in various solvents were prepared by adding 9 mg (0.014 mmol) of catalyst **3** and 10 mL of solvent (dichloromethane, 1,2-dichloroethane, ethyl acetate, methanol, tetrahydrofuran, 2-propanol or pentane) into a Schlenk flask, under nitrogen. The mixtures were stirred for 10 min and then passed through a sintered glass funnel. Any undissolved catalyst remaining on the funnel was washed with dichloromethane (5 mL) into a crucible. The dichloromethane was allowed to evaporate and the remaining residue in the crucible was submitted for ICP-MS analysis. A sample was also analysed containing the same amount of catalyst (9 mg, 0.014 mmol) and 10 mL of dichloromethane but no filtration was undertaken, giving a value of 250 ppm of Ru. Compared with this standard the % of undissolved Ru in each solvent was calculated: dichloromethane (2%), 1,2-dichloroethane (8%), ethyl acetate (14%), methanol (17%), tetrahydrofuran (49%), 2-propanol (50%) and pentane (88%).

2.3. Catalytic tests

2.3.1. General

The reagents 1-decene, 1-octene, 1-hexene, 2-allyloxy-6-methylheptane, acrolein, methacrolein, crotonaldehyde, acrylonitrile and decane (all obtained from Aldrich), and solvents (dichloromethane, 1,2-dichloroethane, ethyl acetate, 2-propanol and pentane) were dried over activated molecular sieves (85 °C) and degassed with nitrogen for 1–2 h prior to use. Methanol and tetrahydrofuran were collected from a MBRAUN manual solvent