Unsymmetrical maleates from stereoselective decomposition of diazoesters using Grubbs' 2nd-generation Ru carbene catalyst

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Abstract

A range of unsymmetrical *cis*-2-ene-1,4-diesters has been synthesized from two different α-diazoacetates using Grubbs' 2nd-generation catalyst (0.5 mol%, RT, 12–16 h). Formation of the enediesters occurred with high stereoselectivity (≥95% *cis*).
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1. Introduction

α-Diazo carbonyl compounds undergo a number of synthetically useful transition metal-catalysed transformations, for example a plethora of inter/intramolecular cyclopropanation and C–H insertion reactions have been reported [1]. The formation of olefins by the dimerisation of diazo compounds has mostly been regarded as an unwanted side reaction, although the dimerisation reaction has been shown to be synthetically useful [2]. Metal complexes of Rh, Ru, Cu and Os have been used to generate olefins with high *cis*-stereoselectivity from diazo compounds [2,3]. We recently reported that the most commonly used catalyst for olefin metathesis, the carbene-based Grubbs' catalyst **1**, also catalyses the coupling of α-diazocarbonyl compounds, under mild conditions to give *cis*-olefins (Scheme 1) [4]. This stereoselectivity contrasts with that observed when using catalyst **1** for the synthesis of *trans*-α,β-unsaturated carbonyl compounds by olefin metathesis [5].

Intrigued by the ability of catalyst **1** to homocouple diazoacetates, we were interested in determining the scope of the reaction between two different diazoacetates and catalyst **1** to generate unsymmetrical *cis*-enediesters (maleates). Unsymmetrical maleates have found use in synthetic lubricating oils [6], modifying poly(vinyl chloride) to induce freeze resistance [7], exhibit sex pheromone activity (comparable to that of dis-
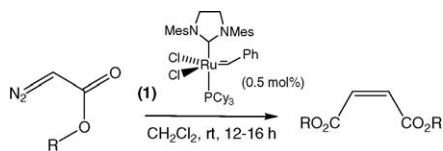
parlure) [8] and chiral (non-racemic) unsymmetrical maleates can deliver high asymmetric induction in Diels–Alder reactions to give unsymmetrical *cis*-cyclohex-4-ene-1,2-dicarboxylates [9].

The formation of unsymmetrical *cis*-enediones by coupling of two different α-diazoketones has been described using $(PPh_3)_2ClRu(\eta^5\text{-}C_5H_5)$ [10], but to the best of our knowledge synthesis of unsymmetrical maleates by reaction between two different diazoacetates has not been reported [11]. Here we communicate the ability of Grubbs' 2nd-generation catalyst **1** to achieve the latter.
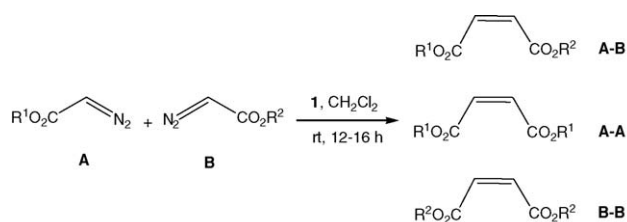
2. Results and discussion

Reactions between different diazoacetates (in 1:1 molar ratio) were carried out using catalyst **1** (0.5 mol%) in CH_2Cl_2 at RT, for 12–16 h (Scheme 2, Table 1). In each case after this time none of the starting diazoacetates were detected, and the only products observed were the symmetrical (**A–A/B–B**) and unsymmetrical (**A–B**) maleates arising from homo and heterocoupling, respectively. This allowed us to calculate yields on the basis of ^{1}H NMR and GC–MS analyses. In several cases, unsymmetrical maleates could be cleanly isolated by column chromatography from the mixture, thus providing a preparative entry to this class of unsaturated diesters. Alternative methods for the synthesis of such mixed systems typically involve a two stage procedure comprising alcohol-induced ring opening of maleic anhydride, followed by esterification of the half acid esters [9a]. In the present chemistry, with a 1:1 mixture of two diazoac-

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Scheme 1.

Scheme 2.

Table 1
Unsymmetrical maleates formed using Grubbs' 2nd-generation catalyst

Entry	R^1	R^2	A–B (%) $(Z:E)$[a]
1	Et	Bn	63 (98:2)
2	Et	i-Pr	53[b] (98:2)
3	Et	Cy	67[c] (99:1)
4	Et	t-Bu	55[d] (>99:1)
5	Et	2-Adamantyl	46[e] (>99:1)
6	Cy	Bn	52[f] (>99:1)
7	Cy	i-Pr	52 (>99:1)
8	Cy	2-Adamantyl	48 (>99:1)
9	t-Bu	Bn	50[g] (97:3)
10	t-Bu	i-Pr	50 (>99:1)
11	t-Bu	Cy	50 (>99:1)
12	t-Bu	2-Adamantyl	50 (96:4)

[a] ^{1}H NMR and GC–MS of crude.
[b] 42% isolated.
[c] 57% isolated.
[d] 42% isolated.
[e] 44% isolated.
[f] 50% isolated.
[g] 45% isolated.

etates, symmetrical and unsymmetrical maleates are formed in a ratio close to the statistical (**A–A:B–B:A–B**, 1:1:2). Unsymmetrical maleates are formed highly stereoselectively, with only traces of *trans*-enediesters (fumarates) detected ($\leq$5%, typically $\leq$1%).

Following previous suggestions in the literature using other transition metal catalysts [3b,c,4] a tentative catalytic cycle rationalising the diazoacetate to maleate coupling is outlined in Scheme 3. The reaction is proposed to proceed via ester carbene **3**, generated from the reaction of coordinatively unsaturated intermediate **2** [12] and a diazoacetate, which subsequently undergoes reaction with the same ($R^1 = R^2$) or different ($R^1 \neq R^2$) diazoacetate ($3 \rightarrow 4 \rightarrow 5$). Dissociation of maleate from **5** completes the catalytic cycle. The origin of the stereo selectivity for maleate over fumarate in the metal-catalysed coupling of diazoacetates has been suggested to arise from highly diastereoselective attack by diazoacetate on a (Cu-based) ester carbene, resulting in a less sterically crowded confor-

mation, followed by anti-elimination of the metal and N_2 [13].

During the reaction between diazoacetates possessing significantly sterically different alkyl groups (Table 1, entries 1–5), unsymmetrical maleates are, in general, formed in higher than statistical yields [14]. This suggests that in these cases the Ru carbene **2** displays no preference for either diazoacetate in the initial formation of ester carbene **3**. However, once intermediate **3** is formed, the less hindered diazoacetate is subsequently incorporated preferentially. As expected, the reactions between cyclohexyl diazoacetate and benzyl/i-propyl/adamantyl diazoacetates (entries 6–8), yield homodimers and unsymmetrical maleates in a 1:1:2 ratio. Similar results are observed for coupling of *t*-butyl diazoacetate with other bulky diazoacetates (entries 9–12). The anomalous $Z:E$ ratio for the heterocoupling of *t*-butyl
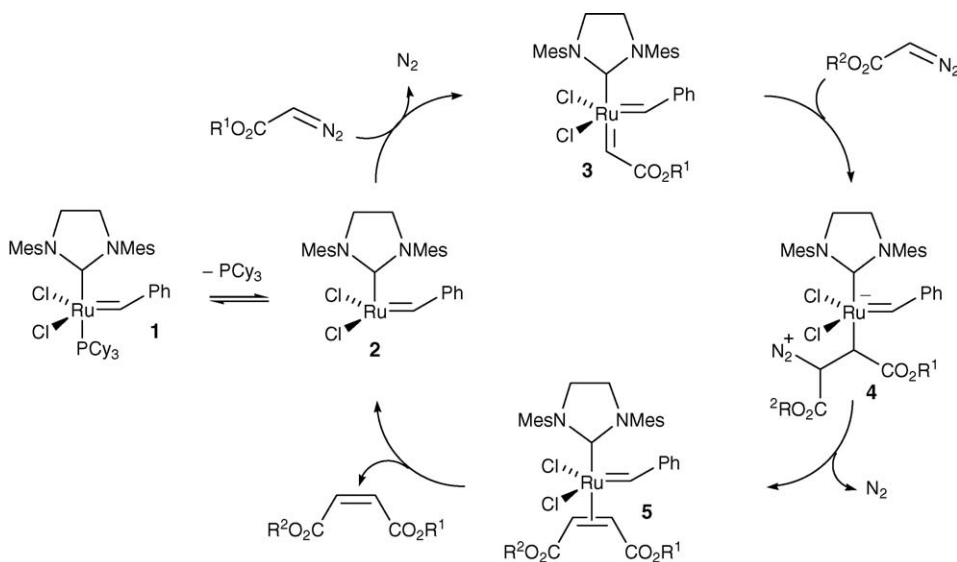
Scheme 3.

diazoacetate and adamantyl diazoacetate (entry 12) can be ratio-nalised as an intermediate selectivity between that observed in the homodimerisations of *t*-butyl diazoacetate (*Z*:*E* 99:1) [4] and adamantyl diazoacetate (*Z*:*E* 95:5).

3. Conclusions

In summary, commercially available Grubbs' 2nd-generation ruthenium carbene is shown to act as an efficient catalyst for highly stereoselective heterocoupling of a range of diazoacetates to give unsymmetrical *cis*-enediesters. This demonstrates the versatility of the Grubbs' 2nd-generation catalyst for the syn-thesis of olefins with both *cis* and *trans* geometries from diazo coupling and cross-metathesis, respectively.

4. Experiments

Reactions were performed in flame-dried glassware under an atmosphere of argon. Ethyl diazoacetate (EDA), *t*-butyl diazoac-etate and Grubbs 2nd-generation catalyst were purchased from Sigma–Aldrich and used without purification. Dichloromethane was degassed and dried over alumina under argon [15]. Diazoac-etates were synthesised from the corresponding alcohols and glyoxylic acid chloride tosyl hydrazone following the literature procedure [16]. NMR spectra were recorded in $CDCl_3$. Data are expressed as chemical shifts in parts per million (ppm) relative to residual chloroform (^1H δ 7.26), $CDCl_3$ (^{13}C δ 77.4) as the internal standard on the δ scale. The multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; t, triplet. Coupling constants *J* are given in Hz.

4.1. Typical procedure for unsymmetrical cis-enediester formation

Grubbs' 2nd-generation catalyst (1.5 mg, 1.7 μmol) was added to a solution of *t*-butyl diazoacetate (47 μL, 0.34 mmol) and benzyl diazoacetate (60 mg, 0.34 mmol) in CH_2Cl_2 (5.0 mL) and the mixture was stirred at RT for 14 h. The mixture was analysed by ^1H NMR and GC–MS and then concentrated under reduced pressure and purified by flash chromatography (5% Et_2O in petroleum ether) to afford *cis*-enediester (40 mg, 45%) as a yellow liquid. $R_f = 0.69$ (30% Et_2O in petrol); ν_{max} (neat)/cm^{-1} 2980 s, 1727 s, 1641 m, 1498 m, 1456 s, 1397 s, 1213 s, 1149 s; δ_H (400 MHz, $CDCl_3$) 7.40–7.30 (m, 5H, CH aromatic), 6.20 and 6.17 (2× d, 2H, J 12, 2× =CH), 5.23 (s, 2H, OCH_2), 1.49 (s, 9H, CMe_3); δ_C (100 MHz, $CDCl_3$) 165.1 and 164.3 (2× CO), 135.3 (C aromatic quat.), 132.0 (=CH), 128.6, 128.5, 128.4 (3× CH aromatic), 127.8 (=CH), 82.3 (CMe_3), 66.8 (OCH_2), 27.9 (*C*Me$_3$); *m/z* (ES) 224 (100%), 226 (25), 263 (15), 280 (15); found *M* + H 263.1280, $C_{15}H_{19}O_4$ requires 263.1278.

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