Olefin cross-metathesis with vinyl halides†

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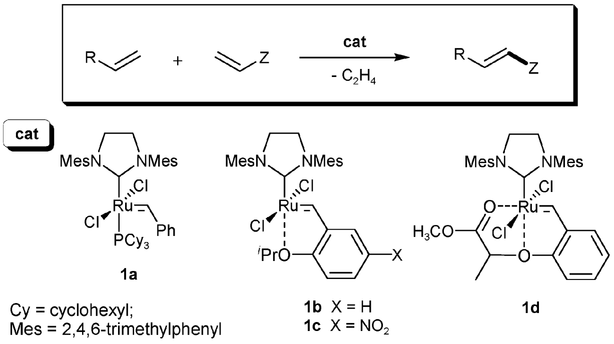
The first successful example of olefin cross-metathesis with chloroalkenes is reported.

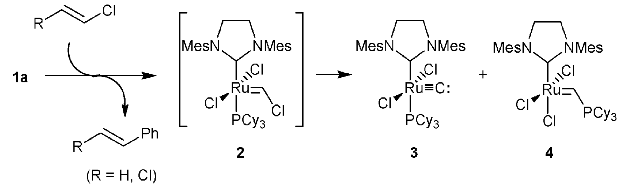
Functionalised olefins are important building blocks for organic synthesis. Catalytic olefin cross-metathesis (CM) is a convenient route to functionalise olefins from simple alkene precursors.[1] One of the most appealing facets of this transformation is that a carbon–carbon double bond of one or both cross-metathesis partners can be substituted by a heteroatom-containing group Z (Scheme 1).[1d]

With the advent of highly active catalysts[2] **1a–1c** the range of functionalised olefins that participate in CM now includes α,β-unsaturated carbonyl-containing olefins,[1a–c] acrylonitrile,[3] vinylphosphonates,[4] vinyl phosphine oxides,[5] perfluorinated alkane containing olefins,[6] vinyl sulfones,[7] vinyl-azulenes[8] and others.



Scheme 1 Cross-metathesis of functionalized olefins and selected Ru-precatalysts.

Therefore, CM complements other C–C coupling methods, such as Wittig, Horner–Wadsworth–Emmons or Heck reactions.[1] However, not all functional groups are compatible with Ru-based catalysts in CM reactions. In particular, phosphine-containing catalysts such as **1a** have been reported to fail to mediate CM of vinyl halides.[9] This is unfortunate, given that alkenyl halides are key building blocks in transition-metal-catalysed syntheses, particularly in various Pd-catalysed coupling reactions.[10,11] Johnson *et al.* studied the fate of complex **2**, the product of an initial metathesis cycle in CM of some alkenyl chlorides. The Authors observed that complex **2** is formed initially in CM, but undergoes rapid decomposition into catalytically inactive **3** and **4** (Scheme 2).[9a]

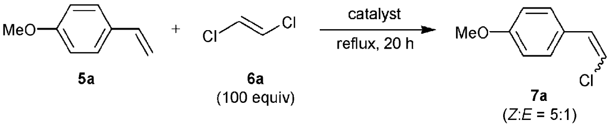


Scheme 2 The fate of chloromethylidene **2** according to Johnson *et al.*[9a]

In a separate experiment it was shown that **2**, generated at −70 °C, underwent PCy_3 shift to form **4** upon increasing the temperature to 0–20 °C. The Authors conclude that rapid decomposition of **2**, not the failure to form **2**, accounts for the failure of attempted CM reactions of vinyl chloride using catalysts such as **1a**[9a] and, therefore, that modified catalysts for olefin metathesis with vinyl halides *are needed*.[9b] Inspired by this excellent mechanistic study, we decided to investigate the same reaction using complexes **1b–d**.[12] We expected that the phosphine-free catalysts will promote the CM of alkenyl chlorides, instead of undergoing the PCy_3-involving decomposition pathway, described by Johnson *et al.*[9]

The CM reaction of 4-methoxystyrene **5a** with (*E*)-1,2-dichloroethylene (**6a**) used as a solvent (100 equiv. relative to **5a**) at reflux temperature was chosen as a model transformation.‡ As expected, use of 5 mol% of **1a**[2a] led to rather low conversion of **5a**; GC analysis revealed that CM product **7a** was formed in 15% yield, thus indicating only three turnovers (Table 1, entry 1). Importantly, we observed that the addition of CuCl, which is known to sequester PCy_3 into an

Table 1 Comparative screening of catalysts in CM of **5a**



Entry	Catalyst (mol%)	Yield (%)[a]	TON
1	**1a** (5)	15	3
2	**1a** (5)[b]	32	6
3	**1b** (5)	24	5
4	**1c** (5)	54	11
5	**1c** (1)	21	21
6	**1d** (5)	24	5

[a] Yields were determined by GC. [b] With 5% mol of CuCl.

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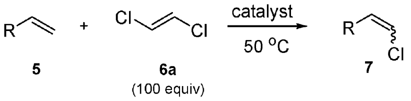
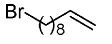
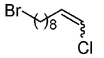
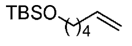
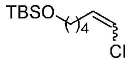
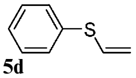
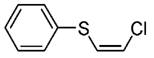
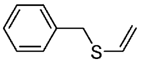
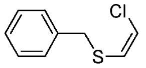
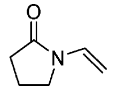
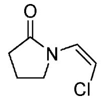
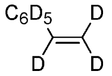
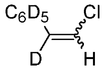
† Electronic supplementary information (ESI) available: Experimental details for the preparation of the reported compounds and copies of NMR spectra. See DOI: 10.1039/b801687a

Table 2 CM between **6a** and alkenes **5**



Entry	Substrate	Catalyst (mol%)	Time/h	Product	Yield (%)[a]
1	 **5b**	**1c** (5%)	20	 **7b** ($Z:E$ = 1.4 : 1)	41
2	**5b**	**1c** (10%)[b]	20	**7b** ($Z:E$ = 1.4 : 1)	87
3	 **5c**	**1c** (15%)[c]	20	 **7c** ($Z:E$ = 1.5 : 1)	76
4	**5a**	**1d** (15%)[c]	6	**7a** ($Z:E$ = 5 : 1)	91
5	 **5d**	**1d** (10%)[d]	20	 **7d** (only Z isomer)	85
6	 **5e**	**1c** (5%)	24	 **7e** (only Z isomer)	35 (66)
7	 **5f**	**1c** (10%)[e]	20	 **7f** (only Z isomer)	32 (34)[f]
8	 **5g**	**1c** (10%)[e]	20	 **7g** ($Z:E$ = 2.6 : 1)	(52)

[a] Isolated yields of analytically pure products. In parenthesis are yields determined by GC or ^{1}H NMR. [b] Catalyst added in 4 equal portions over 4 h. [c] Catalyst added in 3 equal portions over 3 h. [d] Catalyst added in 6 equal portions over 6 h. [e] Catalyst added in 5 equal portions over 5 h. [f] Substrate **5f** was consumed completely during the reaction.

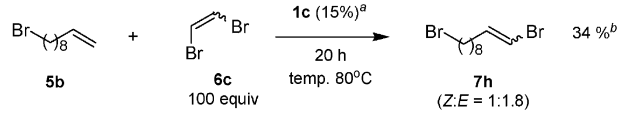
insoluble ill-defined complex,[3b] positively influenced the reaction, leading to formation of **7a** in 32% yield (entry 2). The phosphine-free Hoveyda–Grubbs complex[2b] **1b** exhibited a similar level of reactivity (entry 3) without any additive. To our delight, complex **1c**,[12a] the boosted version of Hoveyda's catalysts, led to formation of **7a** in remarkable 54% yield (TON = 11, entry 4) when used in 5 mol%. An even higher turnover number, TON = 21, was achieved when the same catalyst was used in 1 mol% (entry 5). The newly developed complex **1d**, although quite reactive in other CM reactions,[12b] in this particular case was only moderately active (entry 6).

The CM product, **7a**, was formed, irrespective of the catalyst used, as a mixture of (Z) and (E) isomers in the ratio 5 : 1. Recent computational studies on the CM reaction pathways of **1a** with ethylene, (E)-1,2-difluoroethylene and (E)-1,2-dichloroethylene demonstrated that the metathesis of halogenated olefins is a kinetically controlled process.[13] This theoretical result is in good agreement with the observed preference to form thermodynamically less stable product (Z)-**7a** (Table 1). Interestingly, application of (Z)-1,2-dichloroethylene (**6b**)[14] led to a distinctly different outcome—the reaction of **5a** with **6b** catalysed by 5 mol% of **1c** gave **7a** in much lower stereoselectivity ($Z:E$ = 1.08 : 1) and yield (32%).

Having optimised conditions,[15] we attempted to test the practicability and scope of this reaction (Table 2).§

Utilizing 5 mol% of **1c**, introduced in one portion, it was possible to obtain product **7b** in 41% isolated yield (entry 1). Much better results were obtained by adding 10 mol% of the catalyst in four equal portions over four hours (entry 2). This result suggests that the propagating species formed from **1c** are still relatively short-lived, therefore the portion-wise addition of the (pre)catalyst is optimal. Catalyst **1d**, used in a similar regime also led to a very good result (entry 4). Unexpectedly,[15] vinyl sulfides (**5d**, **5e**) were found to be good CM partners, leading to formation of the corresponding products with excellent stereoselectivities (entries 5, 6). Nitrogen-substituted alkene **5f** was also found to produce the expected (Z)-alkenyl chloride **7f** (entry 7), although in lower yield (Scheme 3).[16]

Reaction of **1a** with vinyl bromide, studied by Johnson *et al.*, was complicated by halogen exchange among Ru complexes; nevertheless, no productive CM was observed.[9a] Similarly, Weinreb and Chao reported a failure in RCM of a diene containing a bromo-substituted double bond (the same reaction



Scheme 3 CM between **5b** and 1,2-dibromoethylene (**6c**).[17] (a) Catalyst added in 5 equal portions over 5 h. (b) Isolated yields of analytically pure product.

with a chloro-substituted diene was high-yielding).[11d] Interestingly, in the reaction between 1,2-dibromoethylene (**6c**) and **5b** the expected dibromide **7h** was formed, albeit in low yield (34%). Calculations done recently by Fomine *et al.* show that the Gibbs free activation energy of the CM reaction of halogen substituted alkenes is strongly dependent on the volume of halogen substituents and therefore the steric factor makes the most important contribution to the outcome of such CM reactions.[13]

To summarize, we have shown that CM of alkenes with (*E*)-1,2-dichloroethylene promoted by phosphine-free catalysts like **1c** leads to formation of the expected chloroalkenes in acceptable yields while the analogous reaction with 1,2-dibromoethylene is more challenging. Fortunately, following the development of active palladium catalysts, even vinyl chlorides have become valuable substrates for Pd-couplings.[10b] Although not all mechanistic details of this transformation are fully explained, ongoing work is directed toward further applications of CM as a mild and selective method for the synthesis of chlorinated molecules.

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Notes and references

‡ Comparative CM experiments with diene **5a** (refer to Scheme 1): to a stirred solution of diene **5a** (0.2 mmol, 26.8 mg) and durene (used as an internal standard, 0.1 mmol) in (*E*)-1,2-dichloroethene (100 equiv., 1.6 mL) placed under argon in a Schlenk tube a catalyst (0.001–0.005 mmol) was added in a single portion at room temperature and the reaction mixture was refluxed for 20 h. Reaction mixtures were immediately analysed by GC, using an HP 6890 chromatograph with an HP 5 column. The responses of the FID detector were calibrated using **5a**–durene and **7a**–durene standard solutions. Each CM experiment was repeated at least twice.

§ Representative procedure of CM reaction: to a solution of alkene (0.60 mmol) in (*E*)-1,2-dichloroethene (100 equiv., 4.6 mL) was added a Ru-catalyst as a solid by portions (one portion per hour) or in one portion (0.03–0.09 mmol, 5.0–15.0 mol%). The resulting mixture was refluxed for 6–24 h. The solvent was removed under reduced pressure. The crude product was purified by flash or preparative thin layer chromatography (*c*-hexane–EtOAc).

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13 For a computational study on metathesis of halogenated olefins, see: S. Fomine, J. V. Ortega and M. A. Tlenkopatchev, *J. Mol. Catal. A: Chem.*, 2007, **263**, 121.

14 (*Z*)-1,2-Dichloroethylene used by us contained 15% of the (*E*)-isomer.

15 After screening of various conditions it was found that running CM in neat **6a** is optimal. For example, CM of **5a** with 10 equiv. of **6a** catalyzed by **1c** in refluxing dichloromethane lead to 10–20% lower conversions (compare with Table 1, entry 4). It should be noted that using **6a** as a solvent is justified from the economic point of view, as it can be fully recovered by distillation after reaction and reused.

16 For a study on the reactivity of Ru=CHER complexes (E = S, N, O), see: J. Louie and R. H. Grubbs, *Organometallics*, 2002, **21**, 2153, and the references cited herein.

17 1,2-Dibromoethylene was used as commercially available mixture of isomers, $Z : E = 1.8 : 1$.