A simple amine protection strategy for olefin metathesis reactions†

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Acyclic diamines are valuable feedstocks for polyamide synthesis. Ruthenium-alkylidene catalysed cross metathesis of amino alkenes is problematic and acyl derivatisation can result in less efficient syntheses, poor catalyst turnover and isomerisation. Temporary amine masking *via* stable and soluble ammonium salts delivers cyclic and acyclic aminoalkenes in high yield and purity.

Advances in homogeneous catalysts have led to their widespread use in organic synthesis.[1] The recent rise in popularity of olefin metathesis can be directly attributed to the commercial availability of the catalysts **1–3**, the ease in which they can be handled, and the broad variety of olefins and functional groups that these catalysts accommodate (Fig. 1).[2] These catalyst systems however, are susceptible to poisoning by substrates containing moieties that act as strong donor ligands. Amines, for example, can result in inhibition of the catalytic cycle by competitively binding to the ruthenium metal centre.[3] This phenomenon may be avoided by masking the problematic functional group with a protecting group, reducing the donating capabilities of the relevant heteroatom. Unfortunately, protection can lead to competing olefin isomerization[4] and unproductive catalytic cycles due to deleterious protecting group chelation.[5] Hence, finding alternate methods to mask strong donors such as amines remains a challenge and an important endeavour.

Towards this end, *in situ* deactivation of the amino group, *via* Brønsted[6] or Lewis acid addition,[7] has been used to affect ring closing metathesis (RCM) of dienes containing secondary and tertiary amines. Our investigations, however, sought to enable cross metathesis (CM) of unprotected amine-containing substrates, with a particular emphasis on primary amines as they have previously proven to be particularly difficult metathesis substrates.[8] Our attempts to homodimerise salt-masked

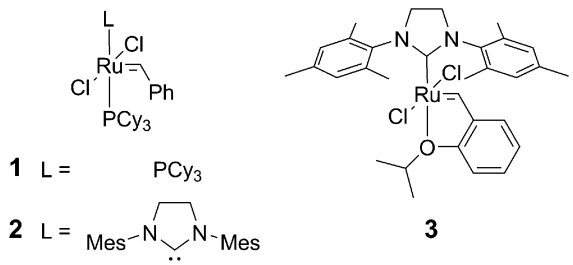

Fig. 1 Olefin metathesis catalysts.

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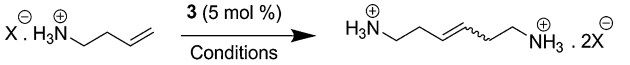
† Electronic supplementary information (ESI) available: Spectral data for compounds **4a–m** and **5a–m**. See DOI: 10.1039/c0cc03716h

Table 1 CM of 3-butenyl ammonium salts



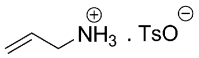
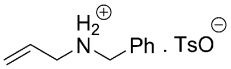
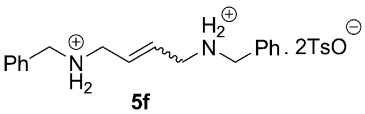
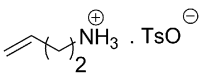
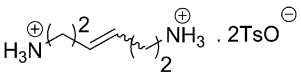
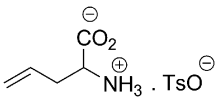
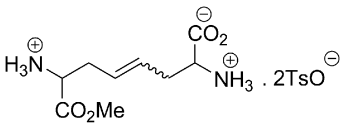
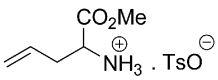
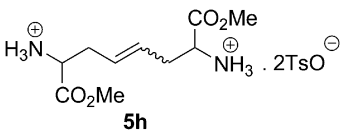
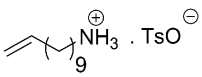
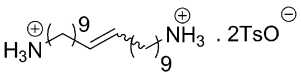
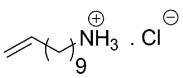
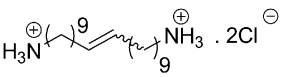
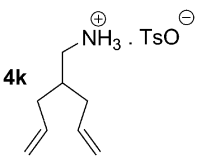
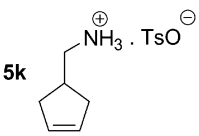
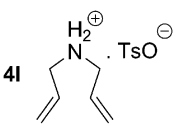
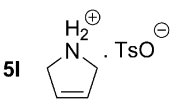
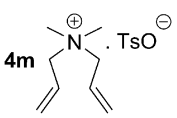
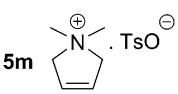
4a-d **5a-d**

Entry	Counterion X	Conditions	Product	Yield
1	Free amine	CH_2Cl_2, Δ	—	0[a]
2	**4a**, Cl	80 °C in HCl satd toluene	**5a**	38[a]
3	**4b**, OTf[b]	CH_2Cl_2, Δ	**5b**	8[a]
4	**4b**, OTf[c]	CH_2Cl_2, Δ	**5b**	83[d]
5	**4c**, BF_4[c]	CH_2Cl_2, Δ	**5c**	91[a]
6	**4d**, OTs[c]	CH_2Cl_2, Δ	**5d**	92[d], 95[d,e]

Conditions: catalyst = **3**, substrate concentration = ~0.1 mol L^{-1}, 24 h, under N_2. [a] % Conversion determined by ^1H NMR spectroscopy in D_2O. [b] Salt metathesis preformed *in situ* with AgOTf. [c] Preformed ammonium salt. [d] Isolated yield. [e] Microwave heating used, 2 h, 100 °C, 100 W.

amines in organic media therefore began by investigating 3-butenyl ammonium salts **4a–d** (Table 1). While cross metathesis of unadultered 3-butenylamine was unsuccessful (entry 1, 0%), metathesis of **4a** in HCl-saturated toluene gave reasonable conversion (38%) to the target homodimer **5a** (Table 1, entry 2). The observed incomplete reaction was attributed to poor substrate solubility in toluene. We therefore sought to rectify this problem by solubilising the ammonium chloride salt of 3-butenylamine *in situ* by the addition of AgOTf. The resultant triflate salt **4b** was immediately treated with Hoveyda Grubbs' catalyst (**3**, 5 mol%). Unfortunately, only poor conversion to the desired product **5b** was obtained (Table 1, entry 3, 8%). The low cross metathesis conversion was attributed to the deleterious coordination of the AgCl by-product to the butenyl olefin resulting in a non-reactive olefinic substrate. In light of this result it was deemed important to preform the ammonium salts and completely remove the AgCl prior to olefin cross metathesis (entries 4–6). The ammonium salts **4b–d**, prepared by a standard silver chloride salt elimination reaction, were subjected to cross metathesis to generate their respective homodimers **5b–d** (entries 4–6). Solubility tests revealed that the tosylate adduct **4d** readily dissolved in dichloromethane at room temperature, whereas the triflate **4b** and tetrafluoroborate **4c** salts displayed only partial solubility at ambient temperature but became soluble upon heating. The results of the cross metathesis of the AgCl-free olefinic ammonium salts **4b–d** are displayed in Table 1 (entries 4–6) and show high conversions (83–95%) for all three salts. The tosylate analogue marginally out performed the other two salts screened. The homodimer products **5b–d** were readily separated from the reaction mixture by selective precipitation. Conveniently, the crude products were simply

Table 2 CM and RCM of olefinic ammonium salts (**4e–m**)

Entry	Substrate	Product[e]	Yield[a] Conv.	Yield[a] MW
1	 **4e**	 **5e**	40	74
2	 **4f**	 **5f**	23[c]	46
3	 **4d**	 **5d**	92	95
4	 **4g**	 **5g**	0	0
5	 **4h**	 **5h**	92	90
6			94[b]	—
7	 **4i**	 **5i**	92[d]	88[d]
8	 **4j**	 **5j**	81	82
9	 **4k**	 **5k**	>95[c]	>95[c]
10	 **4l**	 **5l**	>95[c]	>95[c]
11	 **4m**	 **5m**	9[c]	>95[c]

Conventional conditions: catalyst = **3**, substrate concentration = ~0.1 mol L^{-1}, catalyst loading 5 mol%, 24 h, 40 °C, under N_2. Microwave conditions: substrate concentration = ~0.1 mol L^{-1}, 2 h, 100 °C 100 W, under N_2. [a] Isolated yield. [b] Salt formation performed *in situ*. [c] Conversion determined by ^{1}H NMR spectroscopy in d_4-MeOH. [d] Olefin isomerisation products observed by ESI-MS. [e] Stereochemical assessment of acyclic products was examined by NMR spectroscopy and GC analysis of derivative diacetates.

washed with solvent to remove catalyst and ruthenium residues. Homodimerisation of the tosylate adduct **4d** could be further improved to >95% by the use of microwave heating. Importantly, no olefin isomerisation was observed in any of these reactions. This was a significant result as exposure of carbamate protected 3-butenylamine (Fmoc or Boc) to ruthenium-alkylidene catalyst **2** results in significant isomerisation of the starting amine and poor conversion (<30%) to the

target homodimer. Given the success of this approach in providing a temporary and expedient mask of amines during CM we decided to extend this methodology to additional amine-containing substrates (Table 2). To remove the likelihood of AgCl contamination we applied an alternative method to preparing the starting olefinic ammonium salts by direct proton exchange of an olefinic amine with anhydrous *p*-toluenesulfonic acid. The tosylate salts **4d–m** were found to possess excellent solubility in dichloromethane and their low hygroscopic nature facilitated easy handling.

The silver-free olefinic ammonium salts were subjected to both the conventional and microwave reaction conditions used for **4d**, with the results shown in Table 2. In most cases pure target homodimer **5** was obtained by precipitation from solution using cold dichloromethane, acetone or hexane, and washing the filtered product with the same solvent. The tosylate salt of propenylamine **4e** underwent smooth homodimerisation under microwave conditions (entry 1). Notably, Miller *et al.* showed that homodimerisation of *N*-acyl derivatives of propenylamine are unsuccessful: in all cases, a complex mixture of isomerised starting material/product resulted and the target homodimer could not be isolated.[9] Gratifyingly, the *N*-benzyl derivative of propenylamine **4f**, a secondary amine, also underwent cross metathesis without isomerization (entry 2), although the use of microwave heating was required to achieve a respectable yield.

The tosylate salt of butenylamine underwent near quantitative homodimerisation without isomerization (entry 3). Poor solubility of the zwitteric allylglycine **4g** in DCM prevented homodimerisation (entry 4), however the tosylate salt of the methyl ester derivative **4h** underwent smooth cross metathesis to generate the target dimer **5h** as a mixture of geometric isomers and in excellent yield (entry 5). Conveniently, we also found that the tosylate salts of these substrates could be generated *in situ* prior to addition of the metathesis catalyst by direct proton exchange without affecting yield. This is exemplified by homodimerisation of **4h** in 94% yield under conventional heating conditions (entry 6).

An interesting relationship between alkyl chain length of the ammonium salts and the yield of homodimer was also observed (entries 7 and 8). Short chain homodimers, such as those derived from **4d** and **4e**, 3-butenyl and allylamine, respectively, immediately precipitate from solution reducing the chance of concomitant isomerization. As the alkyl chain length is increased however, to undecenylamine for example, the dimerised product can remain soluble for an extended period of time potentiating the chance for secondary reaction (Table 2, entry 7). The mass spectrum of the bis-tosylate product **5i** showed molecular ion peaks separated by m/z 14 a.m.u. suggesting that isomerization processes were operating. By switching the counterion from tosylate **4i** to chloride **4j** however, the solubility of the dichloride homodimer product **5j** was decreased to promote early precipitation and eliminate undesired olefin isomerisation (Table 2, entry 8). Hence, the point at which the dimerisation product precipitates can be tuned *via* modification of the counterion, making product purification straightforward. Significantly, this feature also appears to minimise, and in some cases prevent, *trans–cis* isomerisation of the acyclic homodimers.

Lastly, to show the general applicability of the approach, we examined three ring closing metathesis reactions involving primary, secondary and quaternary amines (entries 9–11). Under conventional and microwave heating conditions, the tosylate salts of **4k** and **4l** underwent near quantitative (>95%) conversion to the expected aminocyclopentene analogues (entries 9 and 10). Quaternary amine **4m**, however, resisted RCM when heated at reflux in DCM in the presence of Hoveyda Grubbs' catalyst **3**. This result is consistent with a report by Grubbs and Hong where only low RCM conversion (<5%) of the analogous chloride salt derivative was observed using a specialised water soluble metathesis catalyst.[9] Significantly, under microwave irradiation, the amine salt **4m** underwent smooth RCM to provide the target pyrrolidine analogue in excellent yield (>95%, entry 11).

In conclusion, we have developed a method to directly and temporarily mask primary amines as stable and soluble ammonium salt derivatives to enable olefin metathesis to proceed in good to excellent yields without olefin isomerization. The bis-ammonium tosylate products **5e–l** can be readily used in subsequent chemical transformations by 'deprotecting' the ammonium salt pair with a base, such as triethylamine or potassium carbonate. This approach therefore provides an efficient strategy for the metathesis of substrates containing amine functionality. It is also applicable to the synthesis of a broad range of diamines and could therefore find widespread use in polyamide and pharmaceutical production.

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Notes and references

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