

N-Heterocyclic Carbene-Catalysed Mukaiyama–Michael Reaction and Mukaiyama Aldol/Mukaiyama–Michael Three-Component Coupling Reaction*

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An *N*-heterocyclic carbene-catalysed Mukaiyama–Michael addition between several trimethylsilyl (TMS) enol ethers and chalcone derivatives has been discovered. In addition, a related reaction cascade involving dehydrative Mukaiyama aldol followed by a Mukaiyama–Michael addition process has been developed. The later reaction can also be achieved as a three-component coupling reaction. The enantioselective variant of these reactions has been examined with homochiral catalysts. Though these catalysts were active, they fail to achieve enantioinduction.

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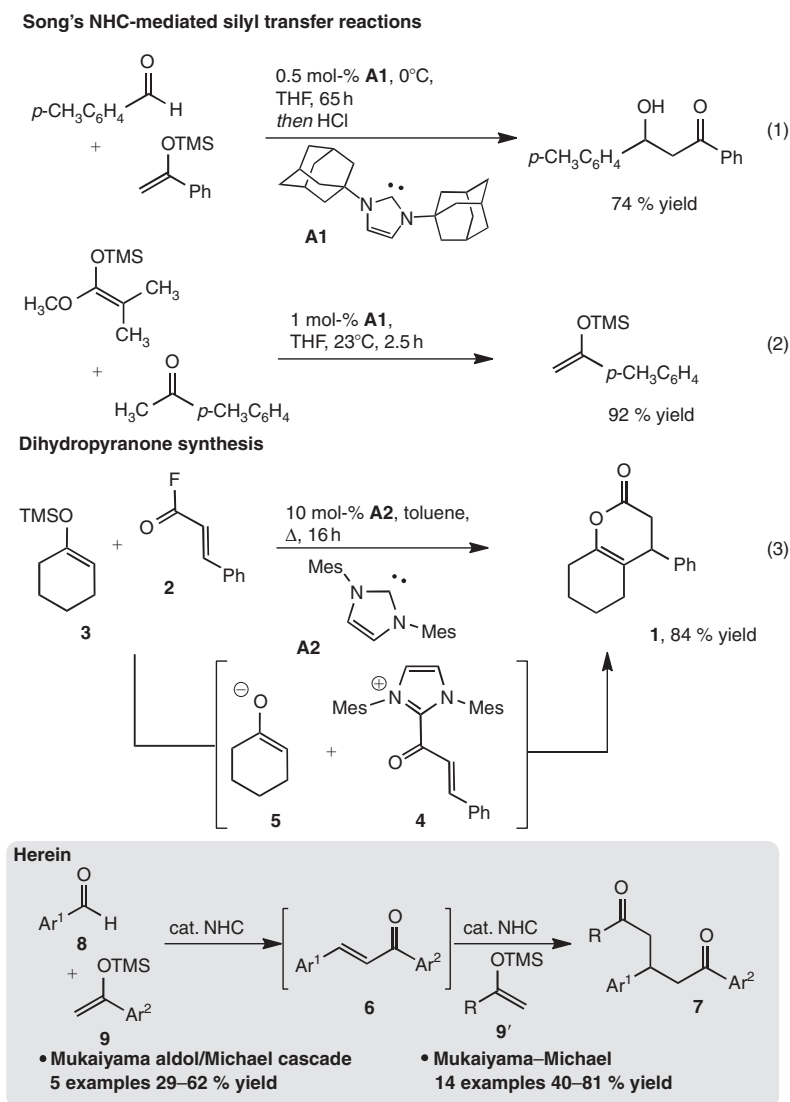
In the preceding decades, *N*-heterocyclic carbene (NHC) organocatalysis has evolved as a powerful approach to discover and develop reactions.^[1,2] While catalysis by NHC addition to the carbonyl is most common, several less developed modes of catalysis have been reported.^[1h] For example, studies led by Song et al. at Boehringer Ingelheim have demonstrated novel silyl transfer reactions^[3–6] such as the NHC-catalysed Mukaiyama aldol reaction (Eqn 1, Scheme 1)^[5] and a silyl enol ether synthesis (Eqn 2, Scheme 1).^[6] Building on these early observations, elegant studies, particularly regarding vinylogous Mukaiyama chemistry, have since been reported.^[7,8]

Our interest in NHC catalysis in many cases has focused on the coupling of acyl fluorides and silicon-masked nucleophiles.^[9,10] For example in 2009, we reported that IMes (A2) catalysed the synthesis of dihydropyranone (**1**) from acyl fluorides (i.e. **2**) and silyl enol ethers (i.e. **3**).^[9a] This reaction presumably proceeds via substitution at the acyl fluoride with concomitant desilylation to provide acyl azolium **4** and enolate **5**. In those studies, a plausible mechanistic alternative involving NHC addition to the silyl ether (i.e. **3**), analogous to the proposals of Song and others,^[3–8] could also be evoked. To allow clarification of mechanistic aspects of our earlier work, we envisaged a study focused on NHC-mediated silyl addition reactions. By gaining an appreciation of such chemistry, we hoped that we could clarify the differences between NHC-mediated silyl addition chemistry and our earlier work. Herein, we report the outcome of these studies with the discovery of an NHC-catalysed Mukaiyama–Michael addition (i.e. **6** + **9** → **7**; 14 examples) and a related dehydrative Mukaiyama aldol/Mukaiyama–Michael cascade (i.e. **8** + **9** → [**6**] + **9** → **7**;

5 examples reported).^[11] Both reactions have acceptable scope with the later allowing three-component coupling reactions to be achieved. Finally, while the transformations defined previously are viable using homochiral NHC catalysts they proceed without enantioselectivity using several catalysts. Completion of these studies and comparison with our earlier work involving acyl fluorides highlight that the conditions for these two types of NHC catalysis are distinct and unlikely to compete with each other.

Studies commenced by examining the reaction between trimethylsilyl (TMS) enol ether **9a** and chalcone (**6a**) in the presence of 10 mol-% NHC catalyst (**A1**), which was generated by deprotonation of the corresponding imidazolium salt.^[12] Though the reaction reached completion, a modest yield of Michael adduct **7a** was obtained (Table 1, entry 1); with oligomeric by-products also observed. Changing the solvent to benzene (Table 1, entry 2), toluene (Table 1, entry 3), or diethyl ether (Table 1, entry 4), while maintaining the same temperature (0°C), failed to improve the yield of **7a**. Similarly, alternate bases for NHC generation had little impact on the yield (Table 1, entries 5 and 6). At a lower temperature (i.e. –35°C), the reaction was sluggish and oligomerisation predominated, as determined by ¹H NMR spectroscopy analysis. This result is presumably due to the occurrence of base-induced anionic polymerisation (Table 1, entry 7). Using a higher temperature (i.e. 66°C), a slight increase in yield was observed (Table 1, entry 8). To retard oligomerisation, the reaction was performed at higher dilution (0.017 M cf. 0.1 M). Though the higher dilution used suppressed decomposition pathways, allowing the product to be formed in 65 % yield (based on recovered starting

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Scheme 1. Project background.

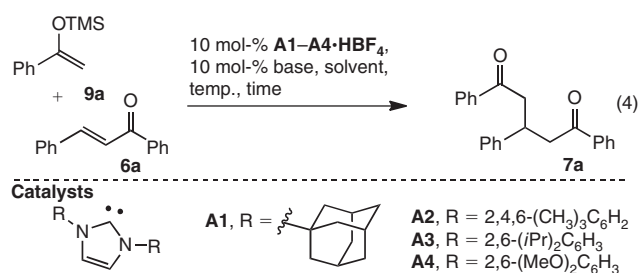
materials), the reaction failed to reach completion (Table 1, entry 9). A more useful modification involved performing the reaction at a higher stoichiometry of **9a** (1.3 cf. 1.2 equiv.), affording **7a** in 77 % isolated yield (Table 1, entry 10). This result could not be improved further upon using alternate imidazole-derived NHCs (**A3**–**A5**); a maximum yield of 10 % was obtained for adduct **7a** under identical conditions (Table 1, entries 11–13). Finally, performing the reaction at room temperature with NHC **A1** gave **7a** in 80 % yield, and when closely monitored, the reaction was found to reach completion after 3 h (Table 1, entry 14).

The general scope of the NHC-catalysed Mukaiyama–Michael addition was initially examined by exploring changes to the TMS enol ether **9** (Table 2). Electron-poor acetophenone-derived enol ethers (i.e. **9b**) and mildly electron-rich variants (i.e. **9c**) gave the expected products **7ab** and **7ac** in 79 % and 72 % yields, respectively. The TMS enol ether of *p*-methoxyacetophenone (**9d**) reacted very slowly, thereby requiring heating to give a modest yield of **7ad** (40 %). Acetonaphthone enol ether **9e** gave the expected product **7ae** in 75 % isolated yield, whereas furan-containing **7af** formed in

51 % yield when the reaction was heated. TMS enol ethers bearing an α -substituent (i.e. **9g** and **h**) reacted in acceptable yield to form a 1 : 1 diastereomeric mixture of **7ag** and a 2 : 1 mixture of **7ah** favouring the *syn* adduct. Electron-poor β -aryl groups about the chalcone were poorly accommodated, with **7ba** (*p*-NO₂) and **7ca** (*p*-Br) formed in 26 % and 39 % yield respectively. The former was prepared as a 2 : 1 isolable mixture with cyclohexanol **10** (see below). In comparison, β -tolyl-containing product **7da** was formed in 81 % yield. Introduction of a tolyl group as the acyl substituent also gave positive results i.e. **7ea** was produced in 63 % yield. However, this yield was reduced when a *p*-BrC₆H₄ group (i.e. **7fa**) was used instead. Finally, a 2-naphthyl group was incorporated into this position in acceptable yield (i.e. **7ga**).

The poor yield of Michael adduct **7ba** from nitrochalcone **6b** (Table 2 and Eqn 6) arises due to a competing proton transfer from the initially formed Michael adduct to give enolate **11** that can then unite with a second equivalent of chalcone **6b**, via Michael addition and aldol cyclisation, to yield Kostanecki and Rossbach-type cyclohexanol **10**.^[13] This pathway may account for the modest yield observed with both chalcone **6b** and **6c**.

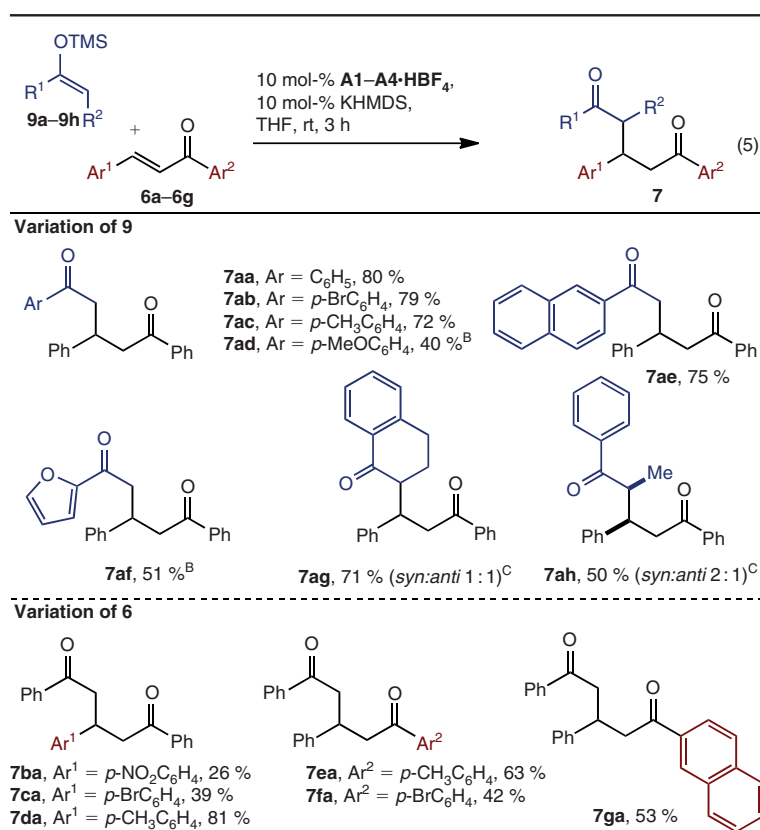
Table 1. Selected reaction optimisation



Entry	Catalyst	Solvent ^A	Base	Reaction temperature [°C]	Time [h]	Yield ^B [%]
1	A1	THF	KHMDS	0	5	47
2	A1	C ₆ H ₆	KHMDS	0	9	34
3	A1	CH ₃ C ₆ H ₅	KHMDS	0	6	38
4	A1	Et ₂ O	KHMDS	0	8	39
5	A1	THF	NaHMDS	0	5	46
6	A1	THF	KO ^t Bu	0	5	50
7	A1	THF	KHMDS	−35	13	24
8	A1	THF	KHMDS	66	1	50
9	A1	THF ^C	KHMDS	66	14	65 ^D
10 ^E	A1	THF	KHMDS	66	14	77
11 ^E	A3	THF	KHMDS	66	14	10
12 ^E	A4	THF	KHMDS	66	14	9
13 ^E	A5	THF	KHMDS	66	14	10
14 ^E	A1	THF	KHMDS	rt ^F	3	80

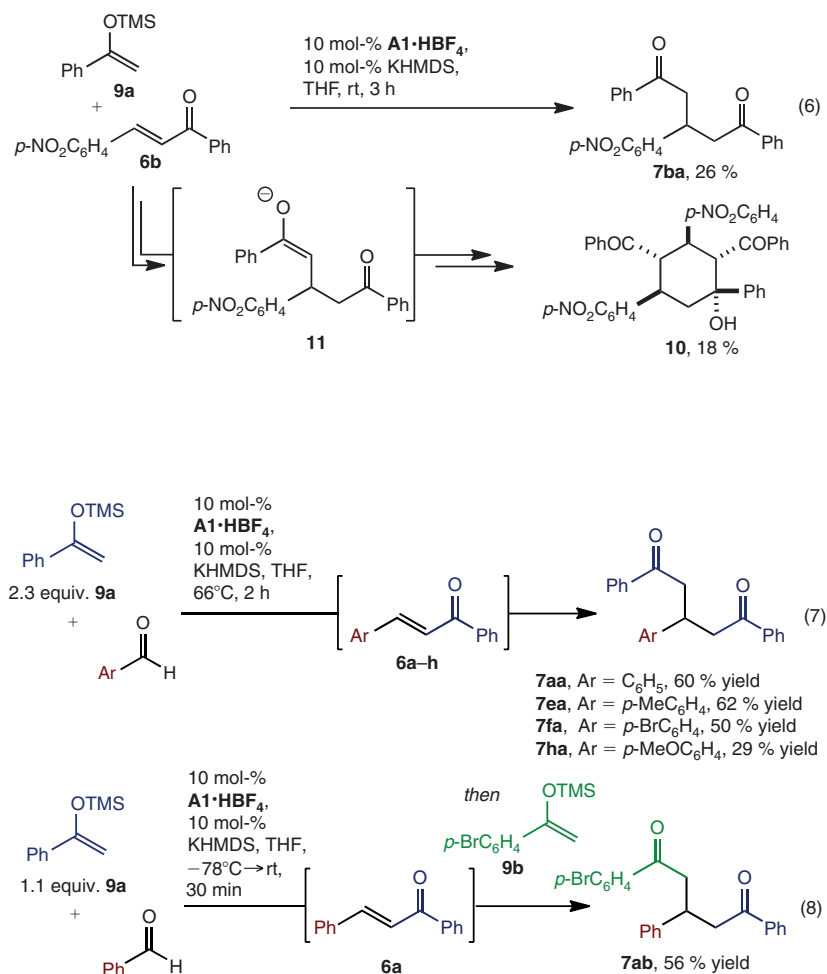
^AAll reactions were performed at 0.1 M with respect to **6a** except as noted. ^BIsolated yield following column chromatography. ^C0.017 M.

^DBased on recovered starting material (45 % isolated). ^EThe amount of **9a** used was 1.3 equiv. ^Frt, Room temperature.

Table 2. Scope for Mukaiyama–Michael addition^A

^AIsolated yield following column chromatography. ^BHeating at 66°C was used.

^CDiastereomeric ratio determined by ¹H NMR analysis.

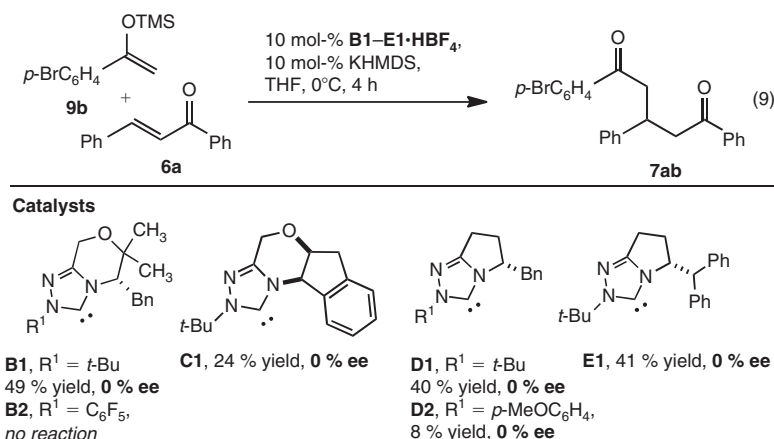


As the reaction conditions developed herein should be compatible with the related aldol reaction, a cascade dehydrative aldol/Mukaiyama–Michael sequence was trialled. Specifically, the reaction between 2.3 equiv. of TMS enol ether **9a** and either benzaldehyde, *p*-methylbenzaldehyde, *p*-bromobenzaldehyde, or *p*-methoxybenzaldehyde gave the expected chalcone-derived Michael adducts **7aa**, **7ea**, **7fa**, and **7ha** in 60 %, 62 %, 50 %, and 29 % yields, respectively (Eqn 7). A related three-component coupling reaction using different silyl enol ethers was more challenging to develop. Using various TMS enol ethers and aldehydes, non-selective coupling occurred, presumably due to the similar rates of the dehydrative aldol reaction to the Mukaiyama–Michael addition. To achieve selective coupling, a one-pot, two-step sequence was developed in which benzaldehyde was reacted initially with 1.1 equiv. of TMS enol **9a**, then TMS enol ether **9b**, to afford the dehydrative aldol/Mukaiyama–Michael adduct **7ab** in 56 % isolated yield (Eqn 8).

To expand the utility of the Mukaiyama–Michael transformation, an enantioselective variant was examined. The use of *t*-butyl *N*-substituted NHCs^[9f] seemed an appropriate starting place for optimisation due to the marked improvement in reaction outcome with sterically demanding NHCs (i.e. Table 1, entries 11–13 cf. 14). Gratifyingly, we found that by using morpholinone-containing **B1**, the reaction proceeded in acceptable yield, however no enantioselectivity was observed (Eqn 9,

Scheme 2). Using the more common *N*-C₆F₅-substituted NHC (i.e. **B2**), the reaction failed. When the *t*-butyl *N*-substituent was examined on the indanol (**C1**) and pyrrolidone (**D1** and **E1**) scaffolds, the reaction was viable but once more no enantioselectivity was observed. Moreover, using an electron-rich aryl *N*-substituent **D2** did not improve the outcome. The lack of enantioselectivity either is related to poor control of the chiral space, potentially due to a distal positioning of the catalyst, or a mechanism in which the nucleophilic catalyst dissociates the silyl group rather than providing a hypervalent silicate.^[14] Furthermore, a general base-induced retro-Michael/Michael sequence may result in racemisation. To investigate whether a dissociative pathway was operative and could be suppressed, thereby allowing enantioinduction via either the hypervalent silicate or an ion-paired silyl azolium enolate, the reaction was performed in non-coordinating solvents. Unfortunately, in all cases no product formed.

The NHC-catalysed Mukaiyama–Michael addition is a viable transformation, albeit one sensitive to the electronics of both the silyl enol ether and the Michael acceptor. The conditions for this reaction are similar to those developed by Song et al. for the related Mukaiyama aldol reaction, thereby allowing a dehydrative Mukaiyama aldol/Mukaiyama–Michael cascade to develop. This can be executed as a three-component coupling reaction. The observation of rapid dehydration in these studies, when none is observed in the studies of Song et al.,^[5] is



Scheme 2. Studies on enantioselectivity.

striking, with the only differences in reaction conditions relating to the method of NHC generation (preformed or via in situ deprotonation). This highlights the non-innocent effects of the salt by-products formed upon NHC generation – something we, and others, have documented.^[15] Studies on the enantioselective variant of this reaction could not expand the utility of the reaction.

A few observations can be made about the competition between NHC-mediated desilylation and NHC-mediated defluorination–desilylation as we have previously reported.^[9] First, the former reaction appears to only proceed in a useful fashion at room temperature or above, whereas our previously reported chemistry is viable at low temperatures in several cases.^[9] Second, while the former chemistry shows high sensitivity to the nature of the *N*-substituent (i.e. Table 1, entries 11–13 cf. 14), the latter chemistry can be achieved with various types of NHC. Thus, the two pathways for silyl enol ether reactivity are likely to be easily selected for, based on catalyst selection and other reaction conditions.

Supplementary material

Common procedures, experimental details and NMR spectra are available for **A1**·HBF₄, **7ab**, **7ca**, and **10** on the Journal's website.

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