A General, Polymer-Supported Acid Catalyzed Hetero-Michael Addition

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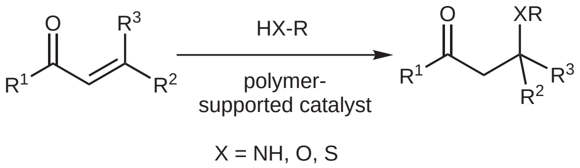
Abstract: Hetero-Michael additions of nitrogen, oxygen and sulfur nucleophiles to α,β-unsaturated ketones were efficiently catalyzed by Nafion® SAC-13 perfluorinated resinsulfonic acid.

Key words: hetero-Michael additions, heterogeneous catalysis, enones, polymer-support, Nafion®

Polymer-supported catalysts have attracted much attention in organic synthesis owing to easy workup procedures and minimization of cost and waste generation due to reuse and recycling of the catalysts. Therefore it is not surprising that applications are covering an ever-increasing part of the spectrum of organic transformations.[1]

In our ongoing research towards synthetically facile and environmentally friendly routes for the construction of β-heteroatom substituted carbonyl compounds we realized that no general procedures using polymer-supported catalysts exist in this field. Although numerous methods for Mannich and aldol reactions using resin-bound catalysts have been reported, they often involve strong bases for stoichiometric preparation of pre-activated enolates,[2] metal salts which are not always easy to remove,[3] or they suffer from side reactions such as elimination of water from the reaction products.[4] The alternative strategy to create the desired functionalities is the Michael addition of heteroatom nucleophiles to α,β-unsaturated carbonyl compounds (Scheme 1). This methodology has been routinely applied to additions of thiols where polymer-supported base catalysts have been found to be effective.[5] Surprisingly, although heterogeneous catalysts play a key role in industrial olefin hydroalkoxylations and hydroaminations, only very few examples of solid catalysts have been reported for the closely related oxa- and aza-Michael reactions.[6]



Scheme 1 Polymer-supported hetero-Michael addition

Encouraged by the recent discovery that bis(trifluoromethanesulfon)imide is superior to transition metal catalysts in the hetero-Michael addition of weakly basic nucleophiles such as carbamates and alcohols,[7] we examined the use of polymer-supported acids in the addition of benzyl carbamate ($CbzNH_2$) to α,β-unsaturated ketones. Whilst Dowex®-50W cation-exchange resins were not effective, we were pleased to discover high catalytic activity with polystyrene-based Amberlyst®-15 and with solid perfluorinated resinsulfonic acids (Nafion®-H), which are the strongest class of polymer-supported acids commercially available.[8] Nafion® SAC-13, a silica nanocomposite with greatly increased surface area and higher reactivity compared to conventional Nafion®-H beads (Nafion® NR-50) was chosen as a standard catalyst.[9] Due to increasing environmental concerns associated with the use of chlorinated media, CH_3CN was selected as a solvent, although similar reaction rates were observed in CH_2Cl_2 and $CHCl_3$.

The results of the aza-Michael addition of benzyl carbamate to a series of α,β-unsaturated ketones are summarized in Table 1.[10] Good yields were obtained with vinyl ketones (entries 1,2) and disubstituted enones (entries 3–5). Increased steric hindrance led to lower yields (entries 6, 7) and enones bearing additional α-substituents could not be converted. Aniline, representing a class of more nucleophilic nitrogen species, could also be used and the addition product with methyl vinyl ketone was isolated in excellent yield (entry 8).

Oxygen nucleophiles, which are very difficult to use in hetero-Michael additions,[11] were found to be considerably less reactive than carbamates under the same conditions. Only moderate yields were obtained after prolonged reaction times with benzyl alcohol and methanol as nucleophiles (entries 9, 10).

In contrast, additions of benzyl mercaptan proceeded rapidly in the presence of Nafion® SAC-13. Terminal, disubstituted and trisubstituted enones could be used and good yields of the corresponding benzyl sulfides were obtained (entries 11–13).

It should be noted that the amount of Nafion® SAC-13 used in these reactions corresponds to a catalyst loading of just 0.7% based on the number of acid functionalities present in the polymer.[12] Substrates other than ketones were less reactive under these conditions and only sluggish conversion was observed with acetacrylimide (entry 14). However, in order to compare catalyst efficiency to procedures involving homogeneous transition metal salts

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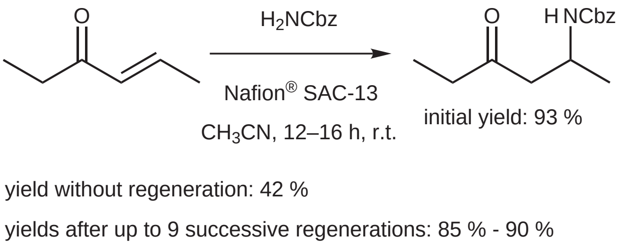
Table 1 Nafion® SAC-13 Catalyzed Hetero-Michael Addition of Nitrogen, Oxygen and Sulfur Nucleophiles to α,β-Unsaturated Ketones

Entry	R^1	R^2	R^3	RXH	Time/h	Yield (%)
1	Me	H	H	Cbz-NH$_2$	12	83
2	Et	H	H	Cbz-NH$_2$	12	65
3	Et	Me	H	Cbz-NH$_2$	12	93
4	Me	Me	H	Cbz-NH$_2$	12	78
5	Ph	Et	H	Cbz-NH$_2$	24	99
6	Me	*i*-Pr	H	Cbz-NH$_2$	12	48
7	Me	Me	Me	Cbz-NH$_2$	12	62
8	Me	H	H	Ph-NH$_2$	12	98
9	Me	H	H	Bn-OH	72	67
10[a]	Ph	Et	H	MeOH	72	33
11	Et	H	H	Bn-SH	1	81
12	Et	Me	H	Bn-SH	1	98
13	Me	Me	Me	Bn-SH	3	95
14	AcNH	H	H	Cbz-NH$_2$	72	30
15[b]	AcNH	H	H	Cbz-NH$_2$	12	81

[a] MeOH as solvent.
[b] 205 mg (10 mol%) Nafion® SAC-13 were used (see text).

or acids,[7,13] catalyst loadings of 10% (based on acid groups present) were examined and unprecedented levels of activity were observed (entry 15), exceeding those attained with homogeneous catalysts.[14]

Apart from reactivity, reusability is also a crucial issue with polymer-supported catalysts. Investigations carried out on the addition of benzyl carbamate to 4-hexen-3-one revealed a sharp drop in activity when the resin was reused directly (Scheme 2). However, the catalyst could be regenerated easily with aqueous acid and only a minor loss of reactivity was observed when the reaction was carried out ten times with the same catalyst.[15,16]



yield without regeneration: 42 %

yields after up to 9 successive regenerations: 85 % - 90 %

Scheme 2 Regeneration of Nafion SAC-13

These examples demonstrate that the convenient synthesis of benzyloxycarbonyl or benzyl protected amino, oxy and thio functionalities can be achieved by the use of a single solid catalyst. Byproducts arising from acid-mediated breakdown reactions of the reactants or products were not observed in the presence of polymer-supported acids, once more underlining the great potential of this method.

In summary, the first general method for hetero-Michael reactions of nitrogen, oxygen and sulfur nucleophiles using a highly active polymer-supported acid catalyst, Nafion® SAC-13, has been developed. Efficient catalyst regeneration and simple workup are advantages of this procedure. Further studies will focus on the development of resin-bound Brønsted superacids[17] in order to exceed current levels of catalyst activity and on the extension of the reaction scope.

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(10) Experimental procedure: Enone (0.25 mmol) and nucleophile (0.375 mmol, 1.5 equiv.) were dissolved in CH_3CN (0.5 mL) and stirred over Nafion® SAC-13 (15 mg, 60 g·mol^{-1}) at room temperature. The reaction was monitored by TLC and the product was isolated by preparative TLC after filtering off the catalyst.

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(14) Only sluggish conversion was observed with acetacrylimide and benzyl carbamate: 34% yield (48 h) with $Pd(CH_3CN)_4(BF_4)_2$; 84% yield (72 h) with Tf_2NH (see ref.[7]).

(15) Catalyst regeneration: Spent Nafion® SAC-13 was stirred over 6 N HCl (0.5 mL) overnight. After filtration, the catalyst was dried in vacuo for 20 h and reused.

(16) Analytical data for 5-(benzyloxycarbonylamino)hexan-3-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.3 Hz, 3 H), 1.19 (d, *J* = 6.7 Hz, 3 H), 2.38 (q, *J* = 7.3 Hz, 2 H), 2.53 (dd, *J* = 5.9 Hz, 15.7 Hz, 1 H), 1.65 (dd, *J* = 4.8 Hz, 15.7 Hz, 1 H), 4.00–4.10 (m, 1 H), 5.05 (s, 2 H), 5.33 (br, 1 H), 7.22–7.38 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.9, 20.9 (CH_3), 36.9 (CH_2), 44.3 (CH), 48.2, 66.9 (CH_2), 128.4, 128.7, 129.9 (Ar-C), 137.0 (*ipso*-Ar-C), 156.0, 210.5 (C=O). IR (neat, film): cm^{-1} 3323, 3061, 2975, 1706, 1680, 1534, 1254. HRMS [+ESI]: calc. 272.1263, found: 272.1250 ($[C_{14}H_{19}NO_3Na]^+$). Mp: 55–57 °C.

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