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A convenient imino aldol reaction in ethyl alcohol catalyzed by a cation-exchange resin

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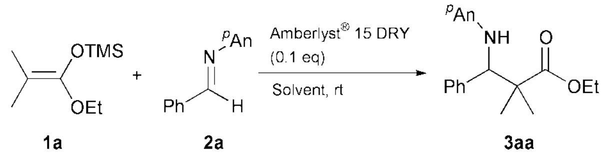
Imino aldol reaction of ketene silyl acetals with imines proceeds smoothly to give β-amino esters in good yields under the influence of a cation-exchange resin in ethanol, and the work-up of the reaction consists only of a simple filtration followed by concentration of the crude mixture and purification.

Cation-exchange resins have been found to be excellent activators for imino aldol reaction of ketene silyl acetals with imines in dichloromethane or in some cases in isopropyl alcohol.[1] Although a variety of activators for such transformations have been reported,[2] polymer supported catalysts such as ion-exchange resins have not received much attention for promotion of imino aldol reaction until recently.[3] Use of ion-exchange resins offers several advantages in organic synthesis,[4] *e.g.* simplification of reaction procedures, easy separation of products without discharging harmful waste water, repeated use, and so on. In our previous report, a cation-exchange resin, in particular Amberlyst® 15 DRY, having a large surface area (45 m^2 g^{-1}), was found to be one of the most useful resins that promoted aldol type reaction, where the addition reactions proceeded with high chemoselectivity in the presence of two kinds of imines and/or nucleophiles. From an environmental point of view, however, this reaction needs modifications, because it is carried out in dichloromethane as a solvent and an equimolar amount of a cation-exchange resin is needed in most cases. Recent papers describing imino aldol reaction carried out in water or organic solvent–water as a convenient system[5] prompted us to report our approach which reduces harmful wastes such as waste water containing metal ions and organic wastes. We wish to report herein a convenient imino aldol reaction using a cation-exchange resin as a recyclable catalyst in ethanol as a solvent.

First, reaction of the imine **2a** and the ketene silyl acetal **1a** was chosen as a model for comparison of solvents, and the results are shown in Table 1. Among the alcohols examined the use of ethyl alcohol proved to be the most effective, whereas in methyl alcohol the ketene silyl acetal **1a** hydrolized to some extent and in *tert*-butyl alcohol the desired reaction proceeded very slowly.

Table 1 Effects of solvent[a]



Entry	Solvent	Time/h	Yield (%)[b]
1	EtOH	10.5	99
2	*i*-PrOH	11.0	81
3[c]	*t*-BuOH	11.5	30
4	MeOH	12.5	66

[a] The reaction was carried out according to the typical experimental procedure. [p]An = *p*-anisyl (*p*-methoxyphenyl). [b] Isolated yield. [c] Amberlyst® 15 DRY (0.2 eq.) was used.

Examples of the Amberlyst® 15 DRY catalyzed imino aldol reactions of ketene silyl acetals with imines in ethyl alcohol are shown in Table 2.† In the reactions of ketene silyl acetal **1a** with the imines derived from aromatic amines, the addition reaction proceeded smoothly to afford β-amino esters **3** in moderate to high yields. However, the imine derived from benzyl amine did not give the addition product in good yield (entry 7). A moderate diasteroselectivity was observed in the reaction of the ketene silyl acetal **1b** derived from propionate (entry 8). Ketene silyl thioacetals also worked well to give the corresponding adducts in good yields (entries 9 and 10).

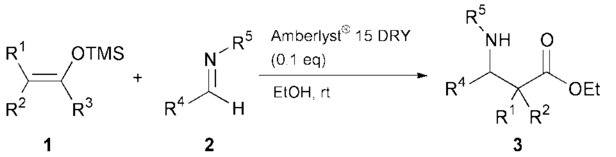
The present reaction conditions were also effective for the addition of ketene silyl acetal **1a** to the imine equivalent **2h** derived from formaldehyde,[6] and the β-amino ester was obtained in 66% yield. As shown in Scheme 1, the *in situ* preparation of a relatively unstable imine could be used for the present addition, and the adduct was formed in good yield.

Furthermore, Amberlyst® 15 DRY was recovered by simple filtration after the reaction, and could be reused at least four times without loss of activity.‡ The results are shown in Table 3.

Regarding the chemoselectivity, the ketene silyl acetal **1a** reacted with the anisyl imine **2a** preferentially even in the presence of benzaldehyde to give β-amino ester **3aa** in 83% yield, and none of the adduct **4** arising from benzaldehyde was detected.[7]

Competition reactions between two kinds of imines were examined next. Amberlyst® 15 DRY selectively promoted the

Table 2 Imino aldol reaction promoted by Amberlyst® 15 DRY in EtOH[a]



1b: R^1 = H, R^2 = Me, R^3 = OEt
1c: R^1 = H, R^2 = Me, R^3 = SEt
1d: R^1 = R^2 =H, R^3 = SEt

2b: R^4 = (*E*)-PhCH=CH, R^5 = *p*-An
2c: R^4 = PhCO, R^5 = *p*-An
2d: R^4 = 2-Furyl, R^5 = *p*-An
2e: R^4 = 2-Thienyl, R^5 = *p*-An
2f: R^4 = Ph, R^5 = *p*-ClPh
2g: R^4 = Ph, R^5 = Bn

Entry	1	2	Time/h	Yield (%)[b]
1	**1a**	**2a**	10.5	99
2	**1a**	**2b**	24.5	73
3	**1a**	**2c**	18.0	81
4	**1a**	**2d**	23.5	69
5	**1a**	**2e**	9.0	57
6	**1a**	**2f**	4.0	94
7	**1a**	**2g**	24.0	27
8	**1b**	**2a**	16.5	60[c]
9	**1c**	**2a**	9.0	96[d]
10	**1d**	**2a**	20.5	86

[a] The reaction was carried out according to the typical experimental procedure. [b] Isolated yield. [c] *syn*:*anti* = 39:61. [d] *syn*:*anti* = 48:52.

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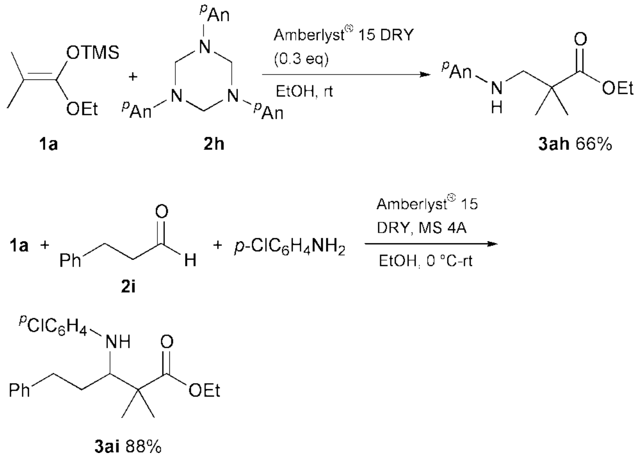
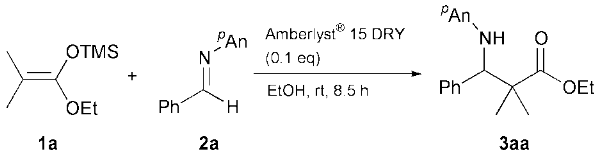
addition to anisyl imine in the presence of the tosyl **2j** or ethoxycarbonyl imine **2k** with an electron-withdrawing *N*-substituent. One of the reasons for the chemoselectivity may be due to the difference in the ability of the imino nitrogen to be protonated by the catalyst. A better chemoselectivity between the imines **2a** and **2k** was observed in the present case than that in the previous report, showing that the present reaction conditions are much milder than the previous ones.



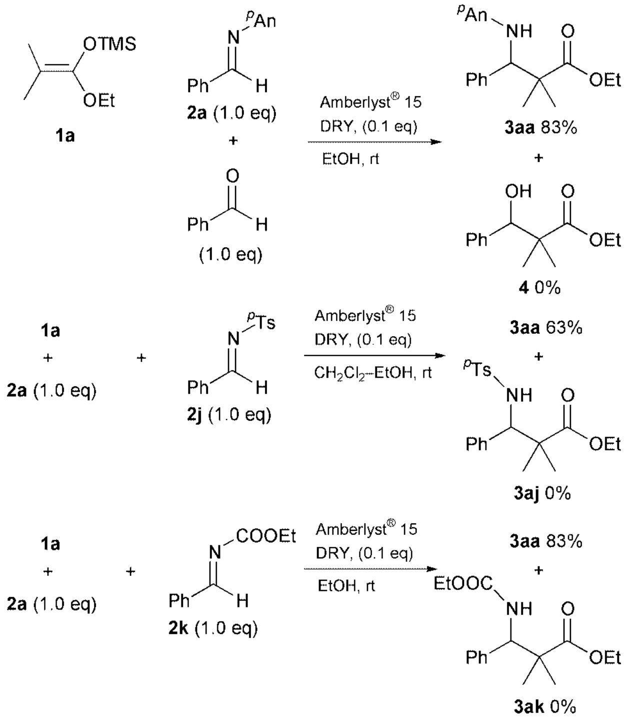
Scheme 1

Table 3 Reuse of Amberlyst® 15 DRY[a]



	Run			
	1st	2nd	3rd	4th
3aa (%)[b]	98	93	97	94

[a] The reaction was carried out according to the typical experimental procedure. [b] Isolated yield.



Scheme 2

In conclusion, we have developed a convenient imino aldol reaction catalyzed by a cation-exchange resin. The present reaction has the following several advantages. (1) The cation-exchange resin was recovered by simple filtration without discharging harmful waste water from the reaction medium and it was used repeatedly without loss of activity. (2) The reaction could be carried out in ethyl alcohol, which is a relatively safe organic solvent. (3) High chemoselectivity was observed.

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Notes and references

† A typical experimental procedure is as follows: to a suspension of Amberlyst® 15 DRY (4.3 mg, 0.02 mmol of the sulfonic acid portion, washed with EtOH and dried *in vacuo* at 100 °C) and aldimine **2a** (42.3 mg, 0.2 mmol) in EtOH (1.0 ml) was added a solution of ketene silyl acetal **1a** (45.2 mg, 0.24 mmol) in EtOH (1.0 ml) at room temperature under an argon atmosphere. After being stirred at room temperature for 10.5 h, the suspension was filtered through a Celite pad. The filtrate was concentrated *in vacuo* to afford a crude oil. Purification on preparative silica gel TLC (*n*-hexane–AcOEt = 10:1, as an eluent) gave the adduct **3aa** (64.7 mg, 99%) as a colorless oil.

‡ The sulfonic acid groups on the recovered resin are involved in the salt formation with amine moieties,[8] and therefore, such salts may be also responsible for the present imino aldol reaction. We are currently investigating such salt formation in more detail.

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