

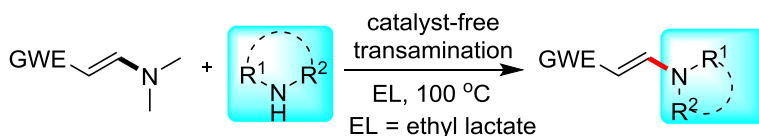
Synthesis of enaminones containing diverse *N,N*-disubstitution via simple transamination: a study with sustainable catalyst-free operation

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Abstract A systematic investigation on the synthesis of β -enaminones containing diverse *N,N*-disubstitution via the transamination of *N,N*-dimethyl amino functionalized β -enaminones and secondary amines has been conducted by employing biomass available green solvent ethyl lactate as reaction medium. A class of β -enaminones containing different *N,N*-disubstitutions have been smoothly synthesized under the sustainable conditions without using any catalyst.

Graphical Abstract



Keywords Enaminone · *N,N*-disubstitution · Catalyst-free · Transamination · Bio-based medium

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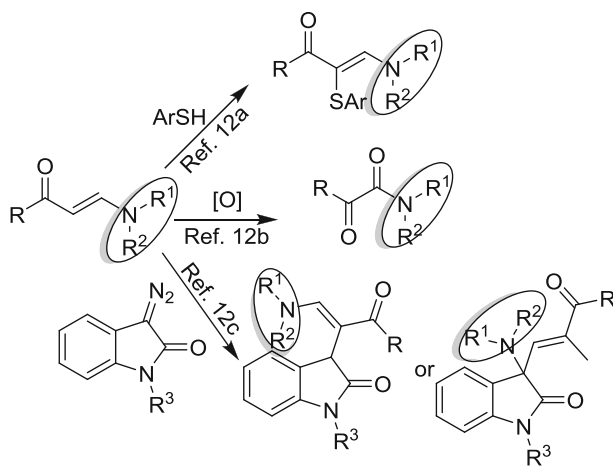
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Introduction

β -Enaminones are important synthons with a long history of application in organic synthesis [1–4]. Their unique advantages lie not only in the multiple reactive sites in the structures, but also in the presence of versatile forms as well as satisfactory shelf stability. In addition to the broad application in organic synthesis as synthons, the enaminone structure has also been observed in many biologically active organic molecules [5–7]. Unsurprisingly, the synthesis of functional enaminones has been an issue of everlasting interest. Typically, enaminones can be accessed by the condensation of 1,3-dicarbonyl compounds with amines [8–10], the addition of amine to alkynones [11–13], the Eschemmoser reaction [14, 15], the C–H amination of enones [16–18], the reactions of imidoylbenzotriazoles with ketones or related enolates [19], the cascade C–H amination and elimination of ketones [20], various multicomponent reactions [21–26] and some other methods [27–33]. Interestingly, regardless of the availability of enriched methods toward enaminone synthesis, most of them are mainly applicable for the synthesis of *NH* or *NH*₂ functionalized enaminones. Practical methods for the *N,N*-disubstituted tertiary enaminones, on the other hand, are rather scarce.

Presently, the most frequently employed tertiary enaminones are the *N,N*-dimethyl substituted ones which are usually prepared via the condensation of methyl ketones and DMF–DMA [34]. This method is simple and practical, but not suitable for the synthesis of tertiary enaminones with other *N,N*-disubstituted amino groups. Due to the limited known methods for the synthesis of tertiary enaminones with diversity in the amino group, the potential of the amino group in enaminone-based organic synthesis has been seriously hampered. Instead, most known syntheses employing tertiary enaminones end with the elimination of the amino group. Recently, some tertiary enaminone-based syntheses wherein the amino group participates in the product construction have been developed [35–37], which outline the significance of the amino group in enaminones for the generation of molecular diversity (Scheme 1). Therefore, preparation of tertiary



Scheme 1 Synthesis involving the construction of the amino group in tertiary enaminones

enaminones bearing diverse *N,N*-disubstitution turns out to be an important issue in the chemistry of enaminones. As occasional examples, the transamination reactions between a tertiary enaminone (usually *N,N*-dimethyl enaminones) with a different secondary amine has been employed for the preparation of tertiary enaminones bearing different amino groups [21, 38, 39]. However, no work has hitherto systematically investigated the scope and limitation of such a synthetic approach.

In the context of our longstanding and extensive efforts in exploring enaminone-based organic synthesis, especially the synthesis employing tertiary enaminones [4, 40], we have been encouraged to make efforts to develop applicable synthetic approaches for the synthesis of tertiary enaminones with diversity in the tertiary amino group. Here, we wish to report the results of our systematic research in the transamination-based synthesis of tertiary enaminones by employing the bio-based green solvent ethyl lactate (EL) as medium [41].

Experimental

General procedure for the synthesis of β -enaminones 3

To a round-bottom flask (25 mL) were added enaminones **1** (0.2 mmol), secondary amines **2** (0.8 mmol) and ethyl lactate (2 mL). Then, the mixture was heated to 100 °C, and stirred at the same temperature for 12 h under air atmosphere (TLC). After cooling to room temperature, 5 mL of water was added, and the resulting mixture was extracted with ethyl acetate. The organic phases were collected and washed with small amounts of water six times. After drying with anhydrous Na₂SO₄, the solid was filtered and the solvent was removed under reduced pressure. The resulting residue was subjected to flash silica gel column chromatography to provide pure products with the elution of mixed petroleum ether/ethyl acetate (*v/v* = 1:1).

Compound **3a** [32]: Yellow solid; m.p. 89–94 °C (lit. 90.6–91.1 °C); ¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, *J* = 7.2 Hz, 2 H), 7.74 (d, *J* = 12.6 Hz, 1 H), 7.47–7.40 (m, 3 H), 5.88 (d, *J* = 12.6 Hz, 1 H), 3.76 (t, *J* = 4.8 Hz, 4 H), 3.40 (t, *J* = 4.8 Hz, 4 H); ¹³C NMR (100 MHz, CDCl₃): 189.2, 152.8, 140.2, 131.2, 128.2, 127.5, 92.5, 66.3.

Compound **3c**: Yellow liquid; ¹H NMR (400 MHz, CDCl₃): δ 7.73 (d, *J* = 12.4 Hz, 1 H), 7.44 (d, *J* = 6.8 Hz, 2 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 5.85 (d, *J* = 12.6 Hz, 1 H), 3.86 (s, 3 H), 3.76 (t, *J* = 4.8 Hz, 4 H), 3.39 (t, *J* = 4.4 Hz, 4 H); ¹³C NMR (100 MHz, CDCl₃): 188.9, 159.7, 152.8, 141.7, 129.1, 119.9, 117.5, 112.3, 92.6, 66.2, 55.4; ESI–HRMS Calcd for C₁₄H₁₈NO₃ [M + H]⁺ 248.1281, found 248.1282.

Compound **3d** [42]: Yellow liquid; ¹H NMR (400 MHz, CDCl₃): δ 7.33–7.16 (m, 5 H), 5.50 (d, *J* = 13.0 Hz, 1 H), 3.73 (t, *J* = 4.8 Hz, 4 H), 3.32 (t, *J* = 4.8 Hz, 4 H), 2.40 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): 195.1, 153.4, 141.7, 135.5, 130.8, 129.0, 127.1, 125.3, 98.1, 66.3, 19.9.

Compound **3e** [32]: Yellow solid; m.p. 111–115 °C (lit. 107.1–107.2 °C); ¹H NMR (400 MHz, CDCl₃): δ 7.83 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 12.5 Hz, 1 H),

7.38 (d, $J = 8.4$ Hz, 2 H), 5.82 (d, $J = 12.5$ Hz, 1 H), 3.76 (t, $J = 4.8$ Hz, 4 H), 3.40 (s, 4 H); ^{13}C NMR (100 MHz, CDCl_3): 195.4, 187.6, 153.0, 138.5, 137.3, 128.9, 128.4, 91.9, 66.3.

Compound **3g**: Yellow solid; m.p. 127–132 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.70 (d, $J = 12.6$ Hz, 1 H), 7.47 (d, $J = 8.1$ Hz, 1 H), 7.42 (s, 1 H), 6.82 (d, $J = 8.1$ Hz, 1 H), 6.00 (s, 2 H), 5.81 (d, $J = 12.6$ Hz, 1 H), 3.74 (t, $J = 4.6$ Hz, 4 H), 3.37 (t, $J = 4.6$ Hz, 4 H); ^{13}C NMR (100 MHz, CDCl_3): 187.3, 152.5, 150.2, 147.8, 134.8, 122.7, 107.9, 107.6, 101.5, 92.0, 66.2, 49.6; ESI–HRMS Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 262.1074, found 262.1073.

Compound **3h**: Yellow solid; m.p. 115–119 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.96–7.92 (m, 1 H), 7.76–7.65 (m, 2 H), 7.48–7.41 (m, 1 H), 5.79–5.72 (m, 1 H), 3.76–3.71 (m, 4 H), 3.40 (s, 4 H); ^{13}C NMR (100 MHz, CDCl_3): 185.9, 153.3, 140.0, 135.1, 132.5, 130.2, 129.5, 126.7, 91.4, 66.2; ESI–HRMS Calcd for $\text{C}_{13}\text{H}_{14}\text{Cl}_2\text{NO}_2$ $[\text{M} + \text{H}]^+$ 286.0396, found 286.0393.

Compound **3i**: Yellow solid; m.p. 187–192 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.95 (d, $J = 8.1$ Hz, 2 H), 7.80 (d, $J = 12.4$ Hz, 1 H), 7.72–7.70 (m, 2 H), 5.82 (d, $J = 12.5$ Hz, 1 H), 3.79–3.77 (m, 4 H), 3.45 (s, 4 H); ^{13}C NMR (100 MHz, CDCl_3): 186.9, 153.6, 144.0, 132.1, 127.9, 118.5, 114.2, 91.8, 66.2; ESI–HRMS Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 243.1128, found 243.1129.

Compound **3j**: Yellow solid; m.p. 150–154 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.68 (t, $J = 2.0$ Hz, 1 H), 8.33–8.30 (m, 1 H), 8.24 (d, $J = 7.8$ Hz, 1 H), 7.84 (d, $J = 12.4$ Hz, 1 H), 7.61 (t, $J = 8.0$ Hz, 1 H), 5.88 (d, $J = 12.4$ Hz, 1 H), 3.80 (t, $J = 4.8$ Hz, 4 H), 3.48 (s, 4 H); ^{13}C NMR (100 MHz, CDCl_3): 185.9, 153.7, 148.2, 141.7, 133.4, 129.3, 125.5, 122.3, 91.3, 66.2; ESI–HRMS Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 263.1026, found 263.1030.

Compound **3k** [42]: Yellow solid; m.p. 119–125 °C (lit. 114.1–114.7 °C); ^1H NMR (400 MHz, CDCl_3): δ 8.39 (s, 1 H), 8.02–7.77 (m, 5 H), 7.55–7.48 (m, (t, $J = 4.8$ Hz, 4 H)); ^{13}C NMR (100 MHz, CDCl_3): 188.9, 152.8, 137.5, 134.9, 132.8, 129.2, 128.0, 127.9, 127.7, 127.4, 126.3, 124.5, 92.6, 66.3.

Compound **3m**: Yellow solid; m.p. 132–137 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, $J = 12.8$ Hz, 1 H), 7.50 (s, 1 H), 7.09 (d, $J = 3.4$ Hz, 1 H), 6.50–6.49 (m, 1 H), 5.84 (d, $J = 12.8$ Hz, 1 H), 3.76 (t, $J = 4.8$ Hz, 4 H), 3.41 (t, $J = 4.8$ Hz, 4 H); ^{13}C NMR (100 MHz, CDCl_3): 177.9, 154.6, 152.0, 144.4, 113.8, 111.9, 91.8, 66.2; ESI–HRMS Calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 208.0968, found 208.0973.

Compound **3n**: Yellow solid; m.p. 147–152 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.09 (d, $J = 10.9$ Hz, 1 H), 6.73 (d, $J = 10.9$ Hz, 1 H), 3.78 (t, $J = 4.8$ Hz, 4 H), 3.36 (s, 4 H); ^{13}C NMR (100 MHz, CDCl_3): 149.6, 113.1, 66.1, 53.2; ESI–HRMS Calcd for $\text{C}_6\text{H}_{11}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 159.0764, found 159.0766.

Compound **3o**: Yellow liquid; ^1H NMR (400 MHz, CDCl_3): δ 6.86 (d, $J = 13.8$ Hz, 1 H), 3.94 (d, $J = 13.8$ Hz, 1 H), 3.72 (t, $J = 4.8$ Hz, 4 H), 3.16 (t, $J = 4.8$ Hz, 4 H); ^{13}C NMR (100 MHz, CDCl_3): 153.6, 121.4, 65.9, 62.8, 48.1; ESI–HRMS Calcd for $\text{C}_7\text{H}_{11}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 139.0866, found 139.0863.

Compound **3q** [32]: Yellow liquid; ^1H NMR (400 MHz, CDCl_3): δ 7.90–7.82 (m, 3 H), 7.45–7.39 (m, 3 H), 5.77 (d, $J = 12.5$ Hz, 1 H), 3.33 (s, 4 H), 1.24 (t, $J = 7.0$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3): 188.8, 152.5, 140.8, 130.8, 128.1, 127.5, 91.8, 50.7, 42.9, 14.9, 11.6.

Compound **3s** [20]: Yellow solid; m.p. 122–127 °C (lit. 105.2–105.3 °C); ^1H NMR (400 MHz, CDCl_3): δ 8.17 (d, $J = 12.6$ Hz, 1 H), 7.85 (d, $J = 7.1$ Hz, 2 H), 7.45–7.20 (m, 13 H), 6.01 (d, $J = 12.6$ Hz, 1 H), 4.41 (d, $J = 24.1$ Hz, 4 H); ^{13}C NMR (100 MHz, CDCl_3): 189.3, 154.2, 140.4, 131.1, 129.0, 128.2, 127.6, 93.2, 59.4, 50.9.

Compound **3t**: Yellow solid; m.p. 102–105 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.23 (d, $J = 12.7$ Hz, 1 H), 7.94 (d, $J = 6.8$ Hz, 2 H), 7.50–7.35 (m, 5 H), 7.21–7.15 (m, 3 H), 6.10 (d, $J = 12.7$ Hz, 1 H), 3.38 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): 189.4, 150.0, 146.4, 140.1, 131.4, 129.5, 128.3, 127.7, 125.0, 120.5, 96.9, 37.4; ESI–HRMS Calcd for $\text{C}_{16}\text{H}_{16}\text{NO}$ $[\text{M} + \text{H}]^+$ 238.1226, found 238.1230.

Results and discussion

To begin the investigation, the reaction of *N,N*-dimethyl enaminone **1a** and morpholine **2a** was selected to probe practical reaction conditions. The entries conducted at 100 °C in different media, including water, EtOH, DMF, MeCN, PEG-400 and EL (ethyl lactate), all provided the target enaminone product **3a** without employing any catalyst, and EL was found to be the best medium (Table 1, entries 1–7). On the other hand, no product was observed using lactic acid (LA) as medium, suggesting that an acidic condition was not favored in this transamination process (Table 1, entry 8). Considering the satisfactory yield acquired under the catalyst-free condition, no further efforts by employing catalysts were made. Instead, the impact of reaction temperature to the reaction was examined. It was found that a slightly lower yield of the product was given in the entries with either higher or lower temperature (Table 1, entries 9–10). A higher temperature might lead to the occurrence of more side transformations such as decomposition, oxidation or cyclotrimerization, etc., while a lower temperature was negative for an endothermic reaction.

Table 1 Optimization on reaction conditions

CN(C)C=C(c1ccccc1)C(=O)c2ccccc2 + C1CCNCC1 $\xrightarrow{\text{Solvent, T}}$ CN1CCNCC1C=C(c1ccccc1)C(=O)c2ccccc2

Entry	Solvent	T (°C)	Yield (%) ^a
1	H ₂ O	100	43
2 ^b	EtOH	Reflux	78
3	DMF	100	77
4	Toluene	100	75
5 ^b	MeCN	Reflux	76
6	PEG-400	100	75
7	EL	100	81
8	LA	100	0
9	EL	120	78
10	EL	80	71

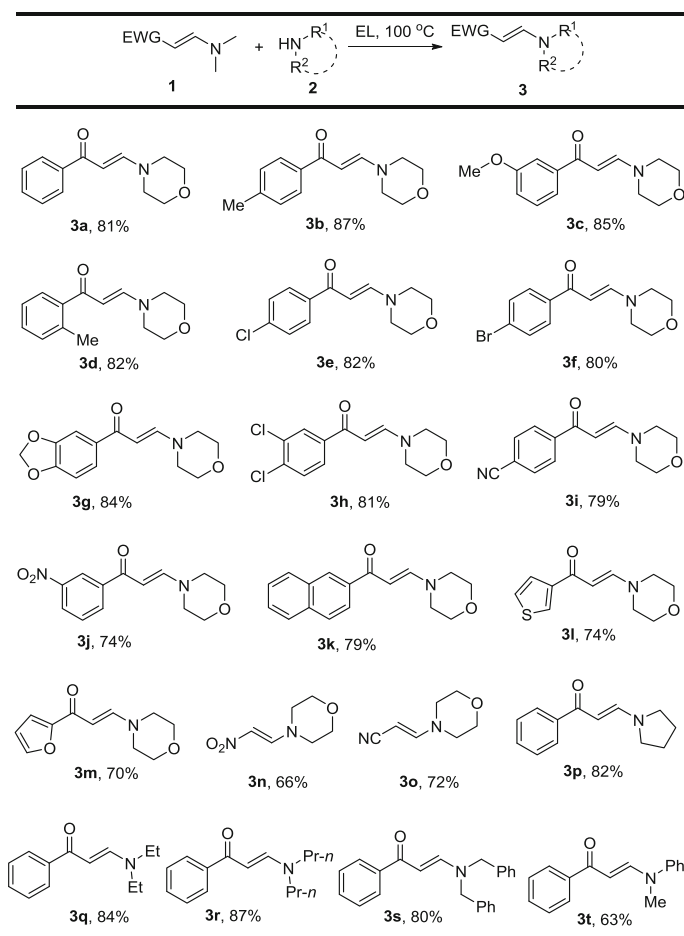
General conditions are: **1a** (0.2 mmol), **2a** (0.8 mmol) in solvent (2 mL) stirred for 12 h

^a Yield of isolated products base on **1a**

^b The outside heating temperature was 100 °C

After the brief optimization on reaction conditions, the scope of this catalyst-free transamination in the synthesis of different *N,N*-disubstituted enaminones was then carried out. As presented in Table 2, the transamination between *N,N*-dimethyl enaminones (and analogous enamines) **1** and secondary amine **2** both exhibited fine tolerance toward the synthesis of product **3**. According to the results in hand, the *N,N*-dimethyl enaminones functionalized by conventional benzene substructure took part in the transformation to provide target products with generally excellent yield (**3a–3h**), but the strong electron-withdrawing group (cyano and nitro) in the phenyl ring of the enaminone **1** led to the formation of corresponding products with slightly lower yield (**3j–3k**). The smooth employment of naphthyl and heteroaryl functionalized enaminones further demonstrated the broad application scope of this

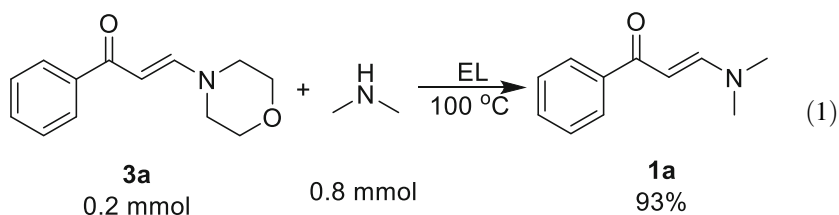
Table 2 Synthesis of various β -enaminones via transamination



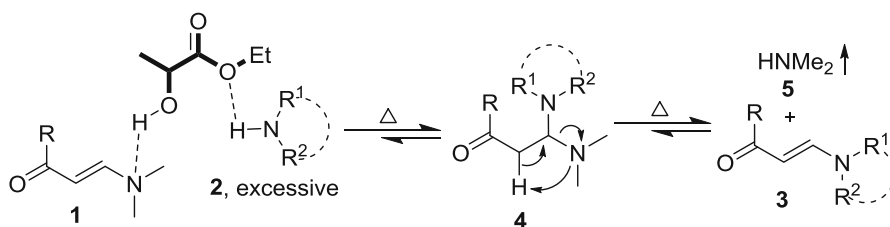
Yield of isolated product based on enamine **1** was reported

transamination-based synthesis of tertiary enaminones (**3k**, **3m**). More notably, like the reactions of enaminones, other analogous electron deficient enamines, such as *N,N*-dimethyl nitro and cyano enamines also underwent the transamination with morpholine to give new enaminone products (**3n–3o**). Finally, as expected, the application of different secondary amines, including both alkyl and aryl functionalized secondary amines were found effective for related synthesis (**3p–3t**). It should be noted that the secondary amine containing *N*-aryl substructure gave lower yield of the corresponding enaminone product (**3t**) probably because of the undermined amino nucleophilicity resulting from the presence of the aryl via *p*- π conjugation. Among these synthesized products, **3a**, **3b**, **3d**, **3e**, **3f**, **3k**, **3l**, **3p**, **3q**, **3r**, and **3s** are known in the literature, and all other compounds are newly synthesized in this work (see Supplementary information for full characterization data of all products).

Subsequently, to examine the reversibility of such transamination, the reaction of product **1a** with aqueous dimethyl amine (40 wt% commercial reagent) was conducted under the standard reaction condition. As shown in Eq. 1, it was found that the reverse transamination took place smoothly to provide **1a** with excellent yield, demonstrating that the present approach was flexible and versatile in preparing different *N,N*-disubstituted enaminones without encountering much restriction of the substrate.



According to the reaction conditions and outcomes, a plausible mechanism for this transamination reaction is proposed. As outlined in Scheme 2, the hydrogen bond interactions of EL with both the dimethyl enaminone and secondary amine assist the substrates to keep close to each other, which facilitates the addition of the secondary amine **2** to the C=C double bond in the enaminone **1** to provide intermediate **4**. Subsequently, the elimination of dimethyl amine on **4** leads to the production of enaminone **3**. Besides the employment of excessive substrate **2**, the practical synthesis of products **3** can also be ascribed to the formation of the low



Scheme 2 The proposed reaction mechanism

boiling point dimethyl amine **5** which evaporates from the reaction system to promote the reaction to move in the expected direction under the heating condition.

Conclusions

We have presented here a systematic approach for the synthesis of diverse *N,N*-disubstituted β -enaminones and analogous nitro- and cyano-enamines. This catalyst-free approach employs bio-based ethyl lactate as the green medium, and exhibits satisfactory application scope in the synthesis of various *N,N*-disubstituted enaminones by employing both different *N,N*-dimethyl enaminones and secondary amines. This simple and environmentally benign protocol provides a reliable route for the synthesis of these useful *N,N*-disubstituted tertiary enaminones.

Supporting information

Full experimental details, ^1H and ^{13}C NMR spectra. This material can be found via the Supporting information.

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