Ene Reaction Using the Iminium Salt Generated by the Oxidation of Aminoketene Silyl Aetal

Makoto Shimizu,* Hiroyuki Itou, Takuya Iwao, and Yuki Umeda
Department of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu 514-8507

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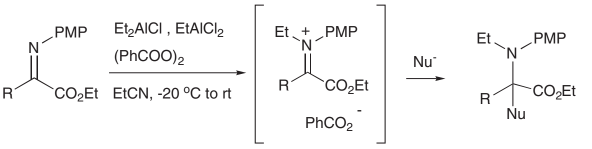
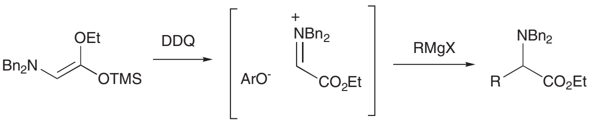
Ene reaction of various olefins proceeded with the iminium salt generated by the oxidation of aminoketene silyl acetal to give addition products in good yields.

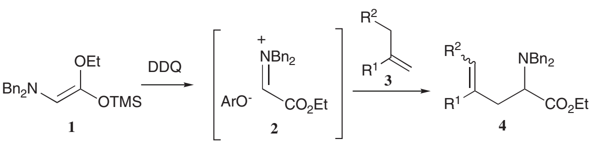
Whereas carbonyl ene reactions offer useful methodologies for C–C bond forming reactions in a stereocontrolled manner, their imino versions have not been widely exploited.[1] This is in part due to the lack of powerful activation methods for the imino moieties in ene reactions, since the imino ene reaction involves larger energies for activation than their carbonyl counterparts.[1a,2] We have been interested in activation methods for imino moieties by transforming into iminium species. Intriguing reactivity of the iminium salts generated by the oxidation of aluminum enolate derivatives has enabled the use of α-imino esters as acceptors of two nucleophiles (eq 1).[3] Generation of iminium species by the oxidation of the intermediary enolates was extended to the use of aminoketene silyl acetal, readily isolable enolate derivatives as starting materials, and this methodology offers a simple approach to a variety of α-amino esters in a short sequence (eq 2).[4] When these iminium salts are used as enophiles, this methodology offers a rapid preparation of homoallylic amines. This paper describes a facile imino ene reaction using the iminium salt **2** generated by the oxidation of aminoketene silyl acetal **1** (eq 3).



(1)



(2)

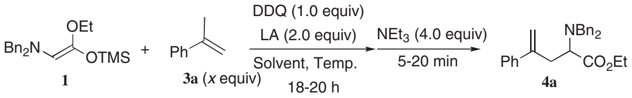


(3)

The initial examination was carried out to find optimum imino ene reaction conditions using 2-phenylpropene (**3a**) as nucleophile, and Table 1 summarizes the results.

In the absence of an added Lewis acid the reaction gave the adduct in low to moderate yields, whereas $TiCl_4$ was not an effective promoter (Entries 1–3). When the reaction was carried out in the presence of $BF_3 \cdot Et_2O$ in THF, CH_2Cl_2, or EtCN, moderate to good yields of the adducts were obtained (Entries 5, 6, and 8). The best result was realized using 1.2 or 2.0 equivalents of the olefin (Entries 9 and 11). When the reaction was carried out without NEt_3 treatment, a much decreased amount of the adduct was obtained (Entry 13). Diisopropylethylamine could be used with almost equal efficiency as base, whereas diisopropylamine and pyridine were not effective (Entries 14–16). Under the optimum conditions a variety of olefins were subjected to the imino ene reaction, and Table 2 summarizes the results.

Table 1. Imino ene reaction of 2-phenylpropene with an iminium salt under various conditions[a]



Entry	Olefin/equiv	Solvent	Lewis acid	Temp/°C	**4a**/%[b]
1	4.0	MeCN	none	−45–rt	10
2	4.0	DMF	none	−60–rt	45
3	4.0	EtCN	$TiCl_4$	−78–rt	8
4	4.0	MeCN	$BF_3 \cdot Et_2O$	−45–rt	26
5	4.0	THF	$BF_3 \cdot Et_2O$	−78–rt	50
6	4.0	CH_2Cl_2	$BF_3 \cdot Et_2O$	−78–rt	60
7	4.0	PhMe	$BF_3 \cdot Et_2O$	−78–rt	17
8	4.0	EtCN	$BF_3 \cdot Et_2O$	−78–rt	63
9	2.0	EtCN	$BF_3 \cdot Et_2O$	−78–rt	70
10	1.5	EtCN	$BF_3 \cdot Et_2O$	−78–rt	67
11	1.2	EtCN	$BF_3 \cdot Et_2O$	−78–rt	70
12	1.0	EtCN	$BF_3 \cdot Et_2O$	−78–rt	65
13	4.0	EtCN	$BF_3 \cdot Et_2O$[c]	−78–rt	36
14	4.0	EtCN	$BF_3 \cdot Et_2O$[d]	−78–rt	62
15	4.0	EtCN	$BF_3 \cdot Et_2O$[e]	−78–rt	36
16	4.0	EtCN	$BF_3 \cdot Et_2O$[f]	−78–rt	27

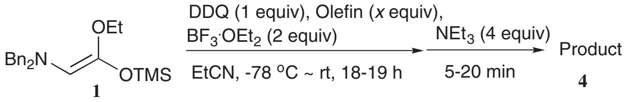
[a] Carried out according to the typical procedure (Ref. 5). [b] Isolated yield. [c] Without NEt_3 treatment. [d] *i*-Pr_2NEt was used in place of NEt_3. [e] *i*-Pr_2NH was used in place of NEt_3. [f] Pyridine was used in place of NEt_3.

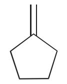
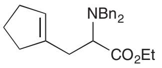
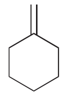
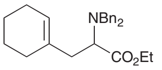
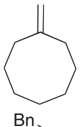
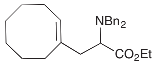
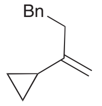
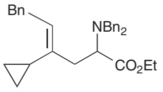
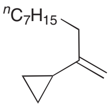
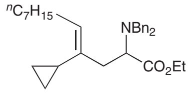
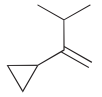
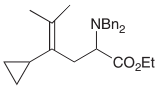
As shown in Table 2, methylidenecyclopentane and its cyclohexane and cyclooctane analogues gave the adduct in good yields, in which methylidenecyclohexane needed 4 equivalents of the olefin for completion of the addition (Entries 1–3).

Cyclopropyl derivatives also served as good enes to give the adducts in moderate to good yields (Entries 4–6). We also attempted to use tri- and tetra-substituted olefins such as 2-methyl-2-butene and 2,3-dimethyl-2-butene as enes. However, no adduct arising from the ene reaction was observed.

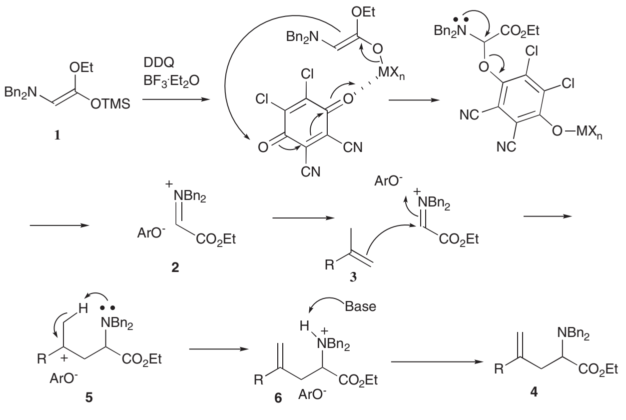
A possible reaction mechanism is depicted in Scheme 1. First, oxidation of the amino ketene silyl acetal **1** with DDQ gives the iminium salt **2**, which in turn is attacked by olefin to give the initial adduct **5**. This adduct is further deprotonated by the dibenzylamino moiety to give the second iminium salt **6**. This species is finally neutralized with the added base to give

Table 2. Imino ene reaction of the iminium salt with various olefins[a]



Entry	Olefin	x/equiv	Product **4**	Yield/%[b]
1		1.2		55
2		4.0		62
3		1.2		82
4		3.0		94[c]
5		3.0		43[c]
6		3.0		49

[a]Carried out according to the typical procedure (Ref. 5). [b]Isolated yield. [c]Z:E = >99:1.



Scheme 1.

the ene adduct **4**. Since the added base promoted the reaction and that the high stereoselectivity was observed presumably by an intramolecular deprotonation, an involvement of a stepwise mechanism was proposed.

In conclusion, we have found that a facile imino ene reaction proceeds with the iminium salt generated by the oxidation of amino ketene silyl acetal. Since a variety of α-amino esters were produced in good yields, the present methodology offers a useful addition to the existing imino ene reactions.

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References and Notes

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5 A typical procedure for the preparation of ethyl 2-dibenzylamino-4-phenylpent-4-enoate (**4a**) is as follows: Under an argon atmosphere, A solution of 2-phenylpropene (**3a**) (21.2 mg, 0.18 mmol) in EtCN (2.0 mL) and of $BF_3{\cdot}Et_2O$ (34.3 mg, 0.300 mmol) in EtCN (1.0 mL) were added successively to a mixture of dibenzylaminoketene ethyl trimethylsilyl acetal (**1**) (0.30 mL, 0.150 mmol, 0.5 M in CH_2Cl_2) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (35.1 mg, 0.15 mmol) in EtCN (0.5 ml) at −78 °C. The reaction mixture was allowed to warm to ambient temperature with stirring for 19 h. Et_3N (0.08 mL, 0.600 mmol) was added to the mixture, and the whole was stirred for an additional 20 min. The reaction was quenched with sat aq $NaHCO_3$, and the whole mixture was extracted with ethyl acetate (10 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (eluent: EtOAc/toluene = 1/50, and then CH_2Cl_2) to give ethyl 2-dibenzylamino-4-phenylpent-4-enoate (**4a**) (70%, 41.9 mg) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (t, $J = 7.0$ Hz, 3H), 2.89 (dd, $J = 7.2$, 14.6 Hz, 1H), 3.09 (dd, $J = 7.8$, 14.6 Hz, 1H), 3.50 (d, $J = 13.7$ Hz, 2H), 3.53 (dd, $J = 7.2$, 7.8 Hz, 1H), 3.94 (d, $J = 13.7$ Hz, 2H), 4.16 (dq, $J = 7.0$, 10.6 Hz, 1H), 4.26 (dq, $J = 7.0$, 10.6 Hz, 1H), 5.05 (d, $J = 1.0$ Hz, 1H), 5.32 (d, $J = 1.0$ Hz, 1H), 7.12–7.29 (m, 15H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 14.6, 35.9, 54.5, 59.5, 60.1, 115.2, 125.9, 126.8, 127.3, 128.1, 128.2, 128.7, 139.4, 140.0, 144.3, 172.3. IR (neat): 3852, 3125, 2359, 2341, 1727, 1557, 1494, 1454, 1172, 1027, 777, 744, 697, 668 cm^{-1}; HRMS (EI) m/z: M^+ calcd for $C_{27}H_{29}NO_2$, 399.2198; found 399.2200.

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