

A theoretical study of imine-ene reaction influencing factors†

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Received 29th March 2011, Accepted 14th June 2011

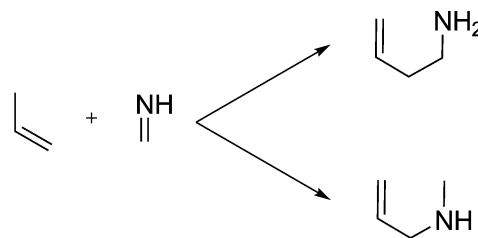
DOI: 10.1039/c1ob05493g

Potential energy surfaces of the imine-ene reaction between methanimine and propene have been calculated using restricted and unrestricted density functional theory at the B3LYP level. The results show that a concerted mechanism with an *exo* configuration for lone pair electrons transition structure is more favourable for the intermolecular bare imine-ene reaction. In addition, the C–C bond formation and the migration of the propene α -hydrogen occur simultaneously. The promoting effect of seventeen Lewis acids was also studied. When a Lewis acid is used as a promoter, the corresponding activation and reaction energies decline greatly compared to those of the bare imine-ene reaction. A good correlation ($R^2 > 0.9$) was found between the activation barriers and the polar character of the transition states. Lewis acids and electron-withdrawing substituents on methanimine were proven to facilitate the imine-ene reaction, whereas electron-donating groups, conjugated groups or a bulky group hinders the reaction. The steric factor is the most unfavourable. The reactivity indices defined by the conceptual density functional theory were also studied and there is a good correlation between the activation barrier and electrophilicity. Frontier molecular orbital theory gives a good explanation for the above results.

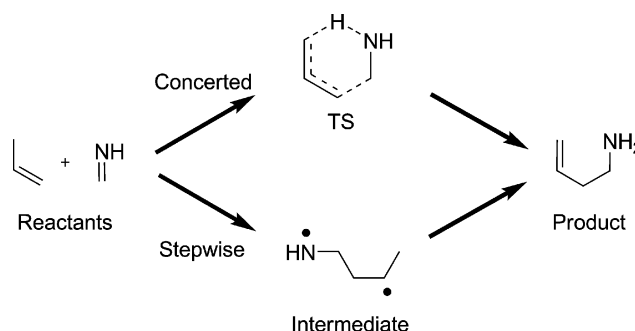
Introduction

The ene reaction, as a useful tool in organic synthesis, was discovered by Alder.¹ The scope, synthetic potential and application of ene reactions have been reviewed extensively.^{2–6} Recently, Arai and Ohkuma⁷ synthesized amino substituted chromans and Shimizu *et al.*⁸ provided a good methodology for the production of α -amino esters through ene reactions. An ene reaction, which uses a Schiff base as an enophile, is often called an imine-ene reaction or an imino-ene reaction. It provides an alternative pathway for C–C bond formation, and is potentially valuable for the synthesis of organic nitrogen compounds^{9–13} There are two possible routes for an imine-ene reaction, *i.e.*, a C–C bond formation and a C–N bond formation (Scheme 1). The C–C bond formation is energetically more favorable in intermolecular imine-ene reactions.^{13–15} However, a C–N bond formation occurs in some intramolecular reactions where molecular geometry, product stability and other factors play a role.^{16,17}

Similar to the Diels–Alder (D–A) reaction,^{18,19} there might be two possible paths for imine-ene reactions, a concerted and a two-step path (Scheme 2). Paderes and Jorgensen estimated the relationship between the frontier molecular orbital (FMO) gap and the reaction temperature, and found that the regioselectivity of the ene reaction can be predicted by the FMO coefficients and the topological geometry as the reactants approach each other.²⁰ Thomas and Houk analyzed the *exo/endo* stereoselectivity of an



Scheme 1 Two pathways of imine-ene reactions.



Scheme 2 Two possible mechanisms of the imine-ene reactions.

ene reaction by studying the electrostatic interaction between the π system of propene and the lone pair of nitrogen, and found that the stereoselectivity of the reaction depends on a stabilizing electrostatic interaction.¹⁵ Domingo *et al.* discovered good correlations between the D–A reaction rates, the activation energies, the polar character of the transition states (TSs) and the

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob05493g

electrophilicity of the reactants, and classified D–A reactions into three types: non-polar, polar and ionic reactions.^{19,21–23} Compared with D–A reactions and other types of ene reactions, there have been far fewer theoretical studies on imine-ene reactions. Therefore, a study of imine-ene reactions in the presence of different Lewis acid catalysts and with different substituents on the enophile is needed to determine the main factors responsible for the activation energy of the reactions.

In the present work, a comparison of potential energy surfaces for the concerted and stepwise pathways of the simplest intermolecular imine-ene reaction (methanimine and propene for C–C bond formation) was performed. The properties including the electronic characteristics of the reactants, the charge transfer (CT) of the reactions in the TSs and the frontier orbital energies of the reactants were analyzed and the relationships among them were investigated.

Theoretical calculations

The calculations were carried out with a Gaussian 03 program package²⁴ The geometries of the reactants, products and transition structures were optimized using the B3LYP^{25,26} functional. A restricted B3LYP was used for closed-shell concerted species, whereas an unrestricted B3LYP was used for the diradical stepwise species. Frequency calculations at the same level of theory were performed to identify all the stationary points as minima (zero imaginary frequency) or the TSs (one imaginary frequency). The 6-31G(d) basis set was used for C, N, O, B, F and Mg atoms, whereas the 6-31G(d,p) was used for the H atom. The calculated energy difference between 6-31G(d) and LanL2DZ on Al and Cl is small (See ESI Table S1†), therefore, the effective core potentials (ECPs) of Hay and Wadt with a double- ζ basis set (LanL2DZ)^{27–29} were used for Al, Cl and the other metal atoms in the following calculations. Polarization functions were added for Cl ($\zeta_d = 0.514^{30,31}$). This method has previously been proven to be suitable for this type of study.^{15,32,33} The intrinsic reaction coordinate (IRC)^{34,35} was performed on the TSs to confirm that such structures are indeed connecting the two minima. The CT between the two reagents in the TSs were analyzed with the Natural Bond Order (NBO) method, and the values are the charge on the propene.^{36,37} The solvent effect (water, CH₂Cl₂, or cyclohexane) was examined by performing single-point self-consistent reaction field (SCRf) calculations based on the polarizable continuum model (PCM)^{38,39} for all of the gas-phase-optimized species. And the atomic radii used for PCM calculations were specified using the UFF keyword. The dielectric constants were set as the default in Gaussian 03. A series of Lewis acids (LAs) were taken into account in monomeric form,⁴⁰ including AlCl₃, GaCl₃, YCl₃, BCl₃, SnCl₄, AlCH₃Cl₂, SnCl₂, BF₃, MgCl₂, ZnCl₂, Al(OCH₃)₃, TiCl₄, Al(CH₃)₂Cl, HCOOAg, HCOOCu, CuCl and Al(CH₃)₃ (structures are shown in ESI Chart S1†).

The global electrophilicity index,⁴¹ ω , which was proposed by Parr *et al.* to classify the global electrophilicity of reactants is given by the following equation:

$$\omega = (\mu^2/2\eta)$$

The electronic chemical potential μ and the chemical hardness η are calculated from the HOMO and LUMO energies (*i.e.*, ε_H and

ε_L) as $\mu = (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx \varepsilon_L - \varepsilon_H$, respectively.⁴² The empirical (relative) nucleophilicity index, N , which has been introduced by Domingo^{22,43} is based on the HOMO energies and is defined as: $N = E_{\text{HOMO}}(\text{Nu}) - E_{\text{HOMO}}(\text{diMe})$, where $E_{\text{HOMO}}(\text{diMe})$ is the HOMO energy of *N,N*-dimethylmethaniminium. This was used as the reference because it has the lowest HOMO energy among all the selected imine enophiles.

Results and discussions

Study of the simplest reaction between propene and methanimine

For the imine-ene reaction between methanimine and propene, there are two different mechanisms (a) a one-step mechanism containing TS_c, and (b) a two-step mechanism with an intermediate INT (Scheme 2). The energy profiles of the two mechanisms are shown in Fig. 1. The stationary geometries of the TSs and intermediates are shown in Chart 1.

For the two-step process, the first step is the formation of the C1–C11 bond. The N4–C1–C11–C9 dihedral angle is *ca.* 170 degrees, which means that the C1 and C11 carbons are far away from each other, which does not allow the σ bond to form in one step. Compared with the distances between the reactants (1.33 Å for C9–C11 and 1.27 Å for C1–N4), the variation of these bond lengths indicates that the π bond between C9–C11 breaks preferentially, and the C1–C11 σ bond forms later. This result suggests that the first step of the stepwise process is concerted but asynchronous. The migration of H5 requires a rotation of the C1–C11 bond and it has been ignored because the rotation step does not have an appreciable barrier. The C1–C11 length in Stepwise-TS1 is 2.26 Å, which is about 0.4 Å longer than the C–C bond formed in the TS *via* a diradical intermediate (1.8–1.9 Å), *e.g.* the corresponding calculated distances in D–A reactions are 1.877 and 1.921 Å, respectively.⁴⁴ It is worth noting that the solvent has little effect on the mechanism (see ESI Table S2†). The bond difference and little solvent effect reveal that the two-step path maybe a radical process involving a early transition state. So vacuum values were considered in the following discussion.

In the one-step mechanism, the hydrogen on the nitrogen can be *exo* or *endo* with respect to the central carbon of propene (Chart 1). (*Exo/endo* indicates the orientation of the lone pair with respect to the central carbon of the ene). The energy of the TS with an *exo* configuration is 2.5 kcal mol^{–1} lower than that with the *endo* configuration which is consistent with Houk's report that there is a 2.9 kcal mol^{–1} difference at the RHF/6-31G* level between the two TS configurations.¹⁵ This is the difference for the D–A reaction between methanimine and butadiene.⁴⁵ This difference may be due to two factors: (a) The *exo* TS is somewhat chair-like and the *endo* one is twist-boat-like (Chart 1); the former is obviously more favorable in energy. (b) The nitrogen lone pair in the *exo* TS is ideally located to interact with the central ene carbon with a good staggering conformation to form the C1–C11 bond.¹⁵ A dihedral angle of *ca.* 40 degrees is suitable for concerted C1–C11 bond formation and H5 migration, because it allows the C1 and N4 of the enophile to simultaneously approach the C11 and H5 of the ene, respectively. In the first step of the stepwise path, one σ -bond (C1–C11) forms and two π -bond (C1=N4 and C9=C11) cleave, it is unfavorable in energy. The calculated barrier

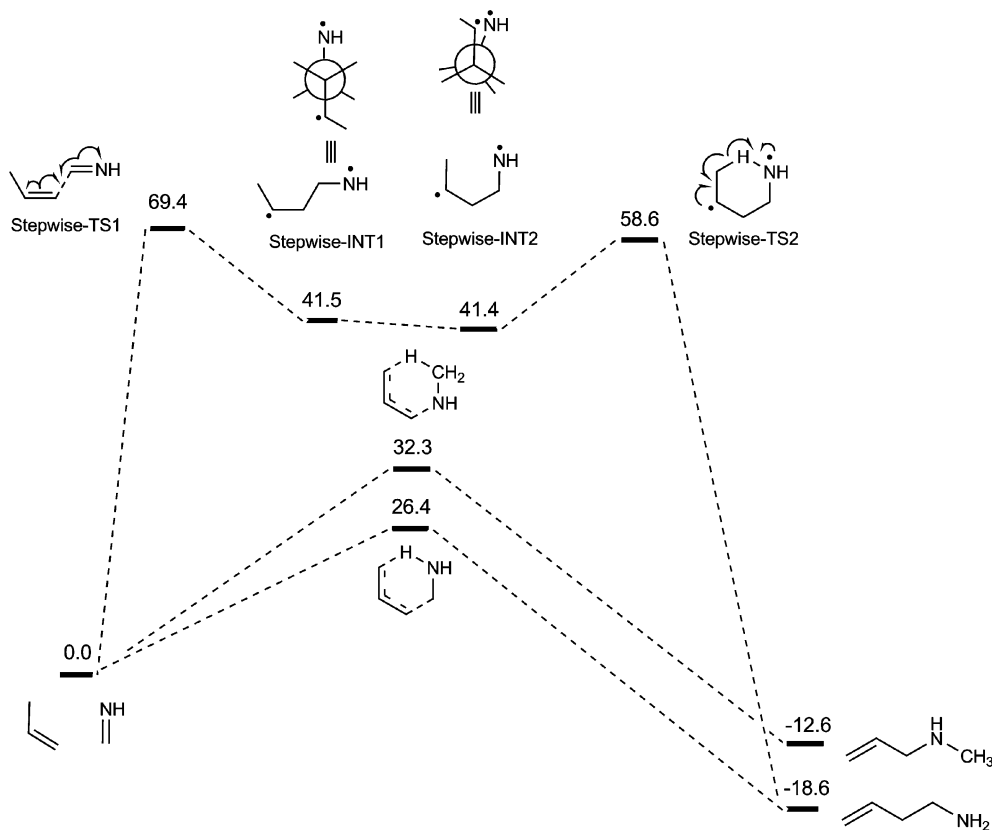


Fig. 1 The energy profiles of the three mechanisms. Electronic energies are given in kcal mol⁻¹.

of the C1–C11 bond formation is 69.4 kcal mol⁻¹. The energy of the formed intermediate is 41.5 kcal mol⁻¹ higher than the sum of the energy of the reactants. The staggered intermediate (Stepwise-INT1) is 0.1 kcal mol⁻¹ higher than the eclipsed one (Stepwise-INT2) as observed from the C9–C11 bond axis, and this small energy difference shows that the staggered intermediate can easily convert to the eclipsed one. The barrier from the eclipsed intermediate (Stepwise-INT2) to the second TS (Stepwise-TS2) is 17.2 kcal mol⁻¹. Therefore, the C1–C11 bond forming step is the rate-determining step of the stepwise mechanism. Meanwhile in the concerted path, two σ -bond (C1–C 11 and N4–H5) and one π -bond (C6=C9) forms, and one σ -bond (C6–H5) and two π -bonds (C9=C11 and C1=N4) cleave simultaneously. In contrast to the barrier of the two-step pathway, the activation energy (26.4 kcal mol⁻¹) of the concerted pathway with an *exo* configuration TS structure is much lower, which indicates that the concerted pathway is preferred. Formation of the product amine is exothermic by –18.6 kcal mol⁻¹.

The IRC pathway using mass-weighted internal coordinates for the concerted reaction with a step size of 0.1 amu^{1/2} bohr was calculated, which is a rational method to study the reaction path.⁴⁶ The energy change during the concerted reaction procedure is shown in Fig. 2. The energy change of the path from the transition state to the product decline a little more quickly than that of the energy from the TS to the reactant (the slopes are –0.019 and 0.012, respectively), and the reaction energy shows that the product has a lower potential energy than the sum of the reactants. This indicates that the reaction tends to the products ($s > 0$).

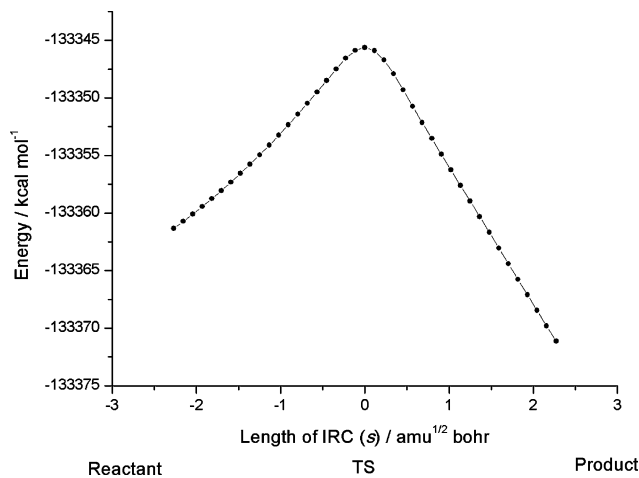


Fig. 2 Energy profile as a function of the IRC length for the reaction.

Influence of Lewis acids and substituents

A one-step mechanism for the imine-ene reaction has been demonstrated in the above section. It is well known that imine-ene reactions can be facilitated by Lewis acids,^{14,47–50} such as aluminum,^{14,51,52} boron,¹⁴ titanium^{11,52} and other transition metal salts,^{12,48,52,53} which are commonly used as catalysts or promoters. In addition, experimental results have also shown that a substituent on methanimine, especially a tosylimino group, plays an important role.^{11,48,50} In general, like the D–A reaction, ene reactions are facilitated by electron-donating group (EDG) on the ene and electron-withdrawing group (EWG) on the enophile.

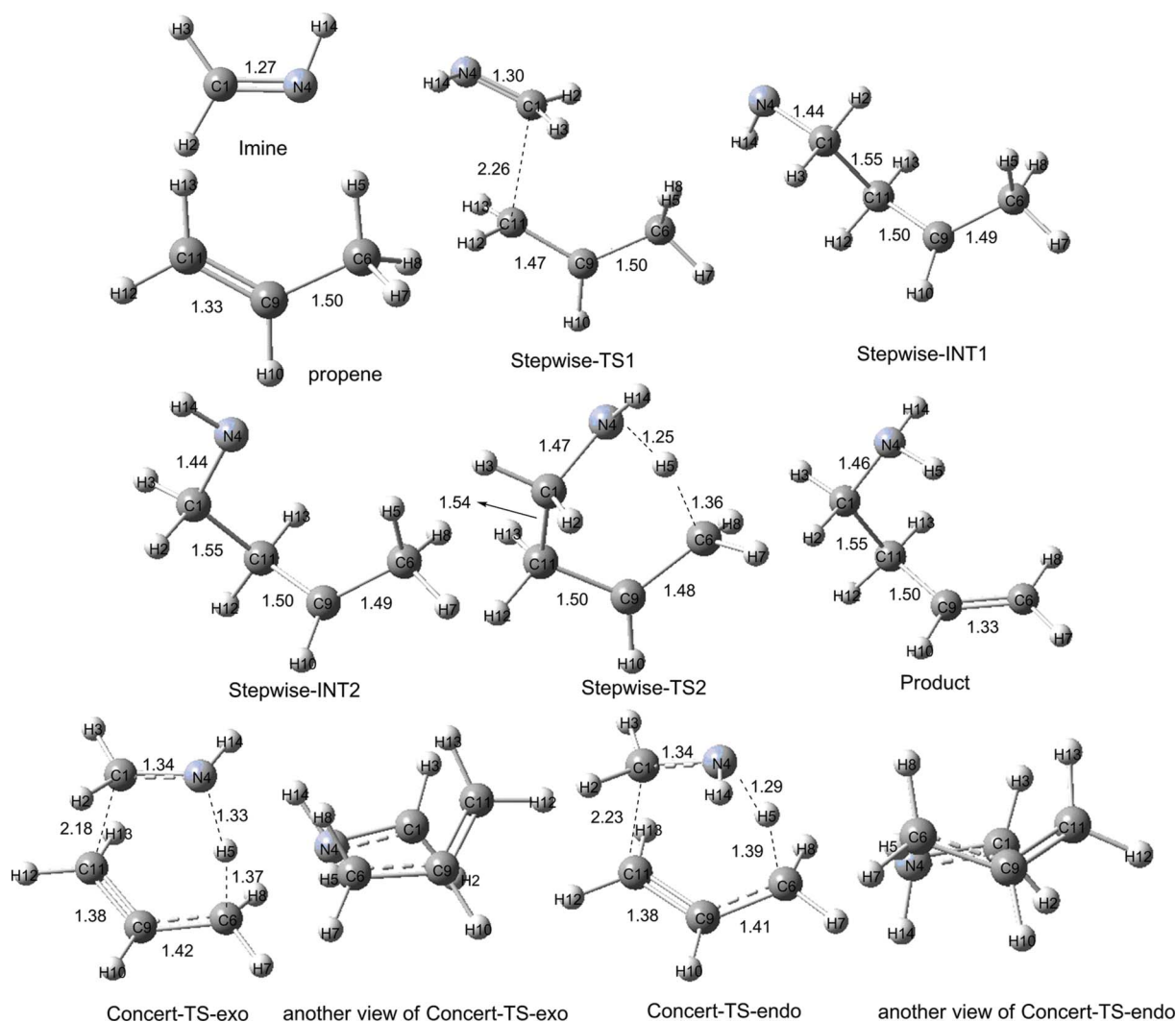


Chart 1 Stationary-point geometries with bond distances in Å for the two mechanisms of the imine-ene reaction between methanimine and propene.

This type of substitution favors an asynchronous concerted mechanism.¹⁹

Based on the above realities, the effect of seventeen Lewis acids and substitution on methanimine was studied, and discussed below.

Influence of Lewis acids

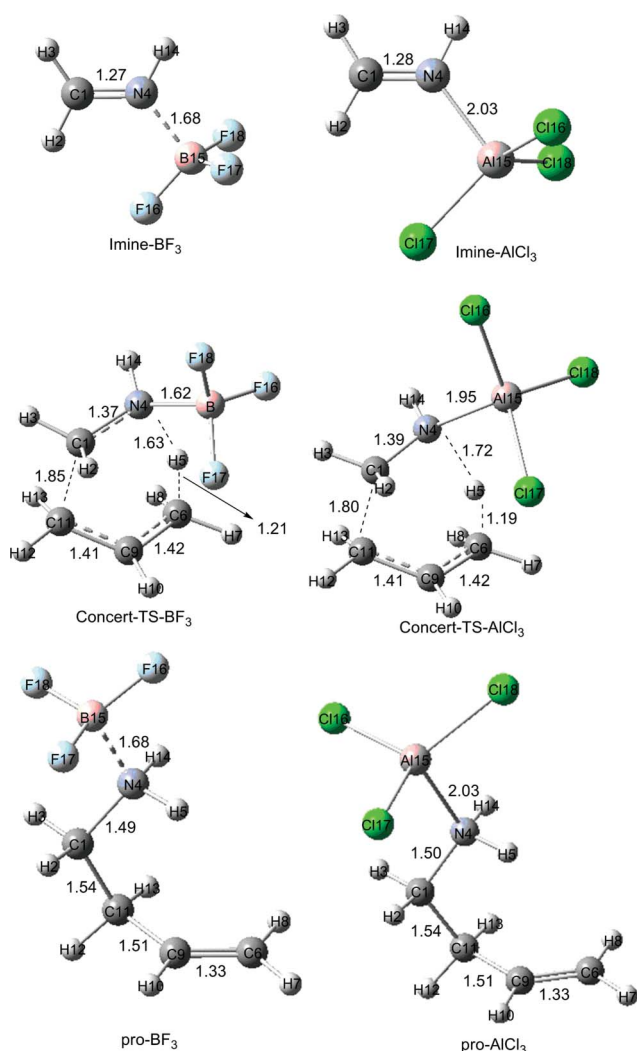
To investigate the influence of Lewis acids, 17 widely used Lewis acids were selected (Chart S1 in ESI†). The binding energies (ΔE_b , ΔG_b) of methanimine with various Lewis acids, the activation energies (ΔE_a^* , ΔG_a^*), the reaction energies (ΔE_{rxn} , ΔG_{rxn}), and the corresponding frontier molecular orbitals (FMOs) energy gaps are summarized in Table 1. The formation of a complex between the Lewis acid and the imine is the first step of the reaction. In the complexation step, each ΔE_b is negative, in other words, the coordination process is exothermic for all the selected Lewis acids (Table 1), whereas some of the coordination processes between formaldehyde and these same Lewis acids are endothermic.⁵⁴ The ΔE_b generally relates to the order of acidity of the Lewis acids (e.g. in the series of aluminum with different ligands, the

acidity decreases in the order $\text{AlCl}_3 > \text{AlCH}_3\text{Cl}_2 > \text{Al}(\text{CH}_3)_2\text{Cl} > \text{Al}(\text{CH}_3)_3$, and the respective energy changes are -39.3 , -31.5 , -26.1 and -21.9 kcal mol⁻¹; for boron salts, BCl_3 is -24.9 kcal mol⁻¹ and BF_3 is -20.9 kcal mol⁻¹). The activation energy of the concerted process is 20.7 kcal mol⁻¹. The energy difference between the *endo* and *exo* configurations (Chart 2) can be reasonably ignored since the difference is less than 0.2 kcal mol⁻¹ (20.55 kcal mol⁻¹ for *endo* and 20.73 kcal mol⁻¹ for *exo*). The *exo* configuration was chosen for all subsequent TSs in order to keep the location of the hydrogen atoms consistent with the TS of a bare imine-ene reaction.

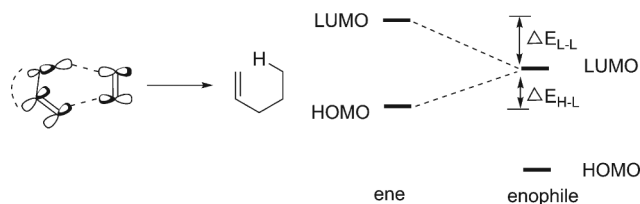
The evolution of the IRC for the concerted reaction promoted by BF_3 shows that the H migration starts a little later (at about $s = 0$) than in the reaction without a Lewis acid (at about $s = -0.5$) (See ESI Fig. S1 and S2†). The presence of a Lewis acid causes the bond formation and H migration to not occur simultaneously. All the activation barriers of the Lewis acid promoted reactions are lower than that of the bare reaction (Table 1). It is noteworthy that the length of the C1–N4 double bond in the TS geometries increases with the acidity of the Lewis acid (1.34 Å for the bare, 1.37 Å for BF_3 , and 1.39 Å for AlCl_3).⁵⁵ This indicates that the Lewis acids

Table 1 Relative energies (kcal mol⁻¹), CT (e) of the reactions and enophile reactivity indices with various Lewis acids

	Binding energy		Activation energy		Reaction energy		ΔE_{H-L} [ΔE_{L-L}] (a.u.)	CT (e)	μ (a.u.)	η (a.u.)	ω (eV)	N (eV)
	ΔE_b	ΔG_b	ΔE_a^\ddagger	ΔG_a^\ddagger	ΔE_{rxn}	ΔG_{rxn}						
AlCl ₃ ^a	-39.3	-25.8	16.5	30.0	-23.7	-7.8	0.135 [0.142]	0.444	-0.206	0.182	3.17	3.05
GaCl ₃	-35.7	-22.4	16.6	30.1	-24.2	-8.2	0.139 [0.138]	0.439	-0.204	0.186	3.04	3.05
YCl ₃	-38.8	-26.2	17.7	31.2	-22.3	-6.5	0.137 [0.140]	0.419	-0.206	0.186	3.10	2.99
BCl ₃	-24.6	-9.9	17.6	31.5	-23.9	-7.7	0.142 [0.135]	0.449	-0.191	0.166	2.99	3.67
SnCl ₄	-18.3	-5.7	18.0	32.2	-24.4	-8.2	0.148 [0.129]	0.422	-0.203	0.202	2.77	2.86
AlCH ₃ Cl ₂	-31.5	-17.7	18.0	32.2	-23.8	-7.6	0.148 [0.129]	0.408	-0.191	0.177	2.79	3.54
SnCl ₂	-23.5	-10.8	19.0	33.2	-23.1	-7.2	0.166 [0.111]	0.404	-0.165	0.162	2.29	4.43
BF ₃	-20.9	-7.0	20.7	34.0	-24.0	-8.1	0.162 [0.115]	0.393	-0.211	0.246	2.46	2.04
MgCl ₂	-36.9	-24.6	20.7	34.0	-20.6	-5.0	0.153 [0.124]	0.360	-0.187	0.179	2.64	3.62
ZnCl ₂	-28.4	-17.8	20.8	34.2	-21.3	-5.7	0.155 [0.122]	0.365	-0.188	0.185	2.58	3.51
Al(OCH ₃) ₃	-30.0	-17.2	20.0	34.6	-22.8	-7.6	0.175 [0.102]	0.393	-0.154	0.158	2.04	4.79
TiCl ₄	-15.8	-7.5	21.7	35.4	-22.7	-6.6	0.109 [0.168]	0.395	-0.225	0.168	4.10	2.72
Al(CH ₃) ₂ Cl	-26.1	-11.7	22.6	35.4	-22.7	-7.0	0.162 [0.115]	0.349	-0.167	0.157	2.40	4.46
HCOOAg	-32.7	-20.9	23.3	35.8	-22.1	-6.1	0.151 [0.126]	0.328	-0.154	0.109	2.94	5.47
HCOOCu	-46.0	-34.3	23.6	36.6	-20.8	-4.9	0.151 [0.126]	0.332	-0.156	0.114	2.90	5.33
CuCl	-42.7	-31.2	24.2	36.9	-20.7	-5.0	0.160 [0.117]	0.322	-0.161	0.141	2.48	4.84
Al(CH ₃) ₃	-21.9	-7.0	24.3	37.6	-21.4	-5.8	0.177 [0.100]	0.327	-0.151	0.155	1.99	4.92
no LA	—	—	26.4	38.2	-18.6	-3.4	0.240 [0.037]	0.147	-0.139	0.257	1.02	3.86

^a The monomer forms were selected for all LAs.**Chart 2** Stationary-point geometries with bond distances in Å for the imine-ene reaction with BF₃ and AlCl₃.

weaken the π bond between C1 and N4, and facilitate electron separation. The results also reveal that the Lewis acid acts as an EWG in the reaction, which lowers the enophile LUMO energy to promote the reaction. The order of the activation energies should be predicted by the order of the enophile LUMO energies. However, the LUMO energy of the TiCl₄ complex is the lowest, but the corresponding activation energy is much higher (Table 1). To interpret this, all of the frontier orbital interactions of the ene reaction were considered. The ene HOMO electrons transfer to the enophile LUMO followed by the enophile LUMO electrons transferring back to the LUMO of the C–H bond.⁵⁶ Therefore, the barrier is not only determined by ΔE_{H-L} but also by the larger of the two orbital energy gaps, ΔE_{H-L} or ΔE_{L-L} , (Scheme 3). The LUMO and HOMO energies of propene are 0.027 a.u. and -0.250 a.u., respectively, and the corresponding ΔE_{H-L} and ΔE_{L-L} are listed in Table 1. The larger gap in the bare imine-ene reaction is 0.240 a.u., and when the reaction is promoted by a Lewis acid, the gap decreases by 0.140 to 0.180 a.u. TiCl₄ effectively lowers the LUMO of the enophile to decrease the ΔE_{H-L} , whereas the ΔE_{L-L} becomes larger. This explains well why the activation energy of the reaction promoted by TiCl₄ is not the lowest even though its enophile LUMO energy is the lowest.

**Scheme 3** The FMO analysis of the ene reaction.

The charge transfers (CT, also referred to as the polar character) in the TS structures are listed in Table 1. The relationship between the polar character of the reactions and the corresponding barriers was studied. Fig. 3 shows that there is a good linear correlation ($R^2 = 0.91$) between the CT and the corresponding barrier. The Lewis acid promoted imine-ene reactions are all

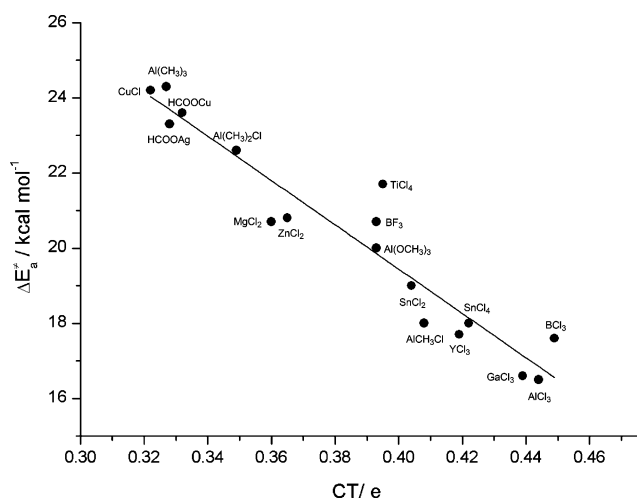


Fig. 3 Plot of the activation barriers (ΔE_a^\ddagger) vs. the charge transfer (CT) of the reactions promoted by various Lewis acids. $R^2 = 0.91$.

polar reactions with $0.300 \text{ e} < \text{CT} < 0.500 \text{ e}$ (the CT of *N,N*-dimethylmethaniminium is 0.551 e). In addition, the polar character reveals that the imine-ene reactions have asymmetric electron movement, which means that the TS has a zwitterionic character. The good correlation may indicate the existence of a relationship between the rate of the imine-ene reaction and the polar character of the TS, similar to the D–A reaction.¹⁹ The

reactivity indices are presented in Table 1. Compared to the bare imine-ene reaction, in the presence of BF_3 , the electrophilicity increases (ω from 1.02 to 2.46 eV), and the nucleophilicity decreases (N from 3.86 to 2.04), which explains the promotional effect of the selected Lewis acids.

Influence of N-Substituents on imine

In addition to Lewis acids, functional groups on the nitrogen or carbon atom of the imine can influence the reaction. To study the effect of the substituent on the imine nitrogen, a series of calculations with different groups were performed. These groups included EDGs (CH_3 and CH_3O), EWGs (CF_3 , CH_3CO and *p*- $\text{CF}_3\text{-C}_6\text{H}_4\text{SO}_2$), conjugated groups (C_6H_5 , $\text{CH}_2=\text{CH}$) and a bulky group (*t*-Bu). The corresponding imine structures are given in ESI Chart S2† and the ΔG_a^\ddagger , ΔE_a^\ddagger , ΔG_{rxn} , ΔE_{rxn} and FMO energy gaps are given in Table 2. The energies of methanimine (substituent is hydrogen) were selected as the standard to compare with the other energies of the substituted methanimine. When the substituent is an electron-withdrawing group (CF_3 , CH_3CO or *p*- $\text{CF}_3\text{-C}_6\text{H}_4\text{SO}_2$), the activation energy of the reaction is lower than that of the bare reaction, and the total reaction is exothermic during the reaction, *i.e.* the EWGs on the imine not only speed up the reaction dynamics, but also facilitate the reaction thermodynamically. When the substituent is an EDG, the reaction barrier becomes higher and so does the reaction energy. This means that the reaction is generally hindered by EDGs on the imine. For the

Table 2 Relative Energies (kcal mol^{-1}) and CT (e) for the reactions and enophile reactivity indices with various functional groups on N atom

		<i>t</i> -Bu	CH_3O	CH_3	C_6H_5	$\text{CH}_2=\text{CH}$	H	CF_3	CH_3CO	<i>p</i> - $\text{CF}_3\text{-C}_6\text{H}_4\text{SO}_2$	diMe
no LA	ΔE_a^\ddagger	32.4	31.3	30.1	28.8	29.0	26.4	23.6	22.0	18.4	8.5
	ΔG_a^\ddagger	44.6	43.9	41.7	41.2	41.2	38.2	36.4	34.8	31.6	21.9
	ΔE_{rxn}	-11.9	-8.3	-13.6	-18.0	-16.7	-18.6	-21.6	-29.5	-23.2	-23.5
	ΔG_{rxn}	3.4	6.9	1.7	-2.5	-1.6	-3.4	-6.1	-14.2	-7.6	-6.8
	$\Delta E_{\text{H-L}}$	0.251	0.247	0.248	0.214	0.211	0.240	0.197	0.198	0.168	0.035
	$[\Delta E_{\text{L-L}}]$ (a.u.)	[0.026]	[0.030]	[0.029]	[0.063]	[0.066]	[0.037]	[0.080]	[0.079]	[0.109]	[0.216]
	CT	0.147	0.173	0.149	0.209	0.214	0.147	0.282	0.283	0.384	0.551
	μ (a.u.)	-0.120	-0.126	-0.127	-0.132	-0.144	-0.138	-0.178	-0.152	-0.197	-0.339
	η (a.u.)	0.242	0.246	0.249	0.191	0.210	0.257	0.250	0.199	0.229	0.140
	ω (eV)	0.81	0.88	0.88	1.24	1.34	1.01	1.72	1.58	2.31	11.17
	N (eV)	4.57	4.35	4.30	4.95	4.35	3.86	2.88	4.30	2.67	0
	BF_3	ΔE_a^\ddagger	27.3	25.5	25.4	23.4	22.8	20.7	13.9	13.1	8.7
ΔG_a^\ddagger		41.1	39.2	38.3	37.3	36.5	34.0	27.9	27.5	23.5	—
ΔE_{rxn}		-14.4	-14.6	-18.5	-16.7	-16.1	-24.0	-22.2	-19.5	-20.5	—
ΔG_{rxn}		1.7	1.2	-2.2	-0.8	-0.3	-8.1	-6.0	-4.3	-4.2	—
$\Delta E_{\text{H-L}}$		0.184	0.186	0.177	0.165	0.159	0.162	0.144	0.132	0.136	—
$[\Delta E_{\text{L-L}}]$ (a.u.)		[0.093]	[0.091]	[0.100]	[0.112]	[0.118]	[0.115]	[0.133]	[0.145]	[0.141]	—
CT		0.391	0.343	0.378	0.439	0.434	0.393	0.511	0.535	0.526	—
μ (a.u.)		-0.195	-0.180	-0.203	-0.177	-0.191	-0.211	-0.229	-0.215	-0.231	—
η (a.u.)		0.257	0.231	0.260	0.183	0.199	0.246	0.246	0.194	0.234	—
ω (eV)		2.01	1.91	2.16	2.33	2.49	2.46	2.90	3.24	3.10	—
N (eV)		2.34	3.10	2.07	3.84	3.24	2.04	1.55	2.64	1.66	—
AlCl_3		ΔE_a^\ddagger	24.9	21.0	21.4	20.6	18.8	16.5	8.8	9.6	4.9
	ΔG_a^\ddagger	39.5	35.1	35.2	35.2	32.7	30.0	23.4	24.1	19.4	—
	ΔE_{rxn}	-13.1	-13.9	-17.8	-16.8	-17.0	-23.7	-20.9	-19.3	-18.5	—
	ΔG_{rxn}	3.6	2.5	-1.3	-1.0	-1.2	-7.8	-4.5	-3.7	-1.8	—
	$\Delta E_{\text{H-L}}$	0.160	0.160	0.151	0.144	0.137	0.135	0.118	0.113	0.113	—
	$[\Delta E_{\text{L-L}}]$ (a.u.)	[0.117]	[0.117]	[0.126]	[0.133]	[0.140]	[0.142]	[0.159]	[0.164]	[0.164]	—
	CT	0.442	0.402	0.427	0.462	0.472	0.444	0.567	0.570	0.631	—
	μ (a.u.)	-0.191	-0.196	-0.198	-0.193	-0.205	-0.206	-0.218	-0.221	-0.223	—
	η (a.u.)	0.202	0.211	0.197	0.174	0.183	0.182	0.171	0.168	0.170	—
	ω (eV)	2.46	2.48	2.71	2.91	3.12	3.17	3.78	3.96	3.98	—
	N (eV)	3.18	2.94	3.07	3.51	3.07	3.05	2.88	2.83	2.77	—

reaction between propene and the iminium cation, the barrier is much lower than the others.

The data in Table 2 shows that generally there is a proportional relationship between the activation energy and the larger orbital gap of ΔE_{H-L} or ΔE_{L-L} , which is in accord with the conclusion for Lewis acids. However, the phenyl group is an exception. Here the reaction barrier between *N*-phenylmethanimine and propene is 28.8 kcal mol⁻¹, which is 2.4 kcal mol⁻¹ higher than that of the standard. However, the larger gap is ΔE_{H-L} with a value of 0.214 a.u., and the activation energy should be lower than that of the standard. This exception may be explained by the fact that excess energy is needed to break the π - π conjugation between the phenyl group and the C=N moiety. To test this conjecture, a vinyl group was selected as a substituent and the result supports this conclusion. A *t*-Bu group was selected as a bulky substituent to investigate the steric effect on the imine-ene reaction. Here the larger gap was 0.251 a.u. and the activation energy of the reaction is even higher than that of the methoxyl substituent (Table 2). The results show that a bulky group is the most unfavorable factor for imine-ene reactions. When a Lewis acid is present, the energies of all parts of the reaction decrease proportionally and the relationship mentioned above is maintained.

The CT values for the TSs of the N-substituted reactions are listed in Table 2. The CT values reflect the reaction's polar character. The EDGs (*t*-Bu, methyl and methoxyl) in methanimine do not substantially affect the polar character of the reaction, and neither do the conjugated groups (phenyl, CT = 0.209 and vinyl, CT = 0.214). An obvious change in the polar character was found for the reactions with EWGs substituents. Furthermore, the enophile with a cationic charge has the largest CT and the lowest barrier. When a cationic reactant is involved, the reaction is referred to as ionic reaction. A good linear correlation ($R^2 = 0.92$ compared with $R^2 = 0.89$ for the D-A reaction¹⁹) between the CT in the TSs and the corresponding reaction barriers is depicted in Fig. 4(a). The plot can be divided into three regions, non-polar reactions are on the top left, polar ones are in the middle (CTs less than 0.5) and the ionic reaction (the imine cation) is located in the lower right region. Finally, there is a good correlation ($R^2 = 0.90$) between the CT in the TSs and the corresponding reaction barriers for both Lewis acids and N-substituents (Fig. 4(b)).

The conceptual DFT descriptors including global electrophilicity (ω),^{41,57} electronic chemical potential (μ), chemical hardness (η) and nucleophilicity (N)^{22,43} are powerful tools for predicting reactivity and establishing polar character.⁵⁸ The reactivity indices are listed in Table 2. The indices for propene are $\mu = -0.112$ a.u., $\eta = 0.277$ a.u., $\omega = 0.61$ eV and $N = 4.33$ eV. The μ value of propene is higher than those of imines which range from -0.120 a.u. to -0.339 a.u. This higher potential indicates that the CT of the reactions will occur from the ene to the enophile.

The electrophilicity data indicate that propene is a moderate electrophile and a good nucleophile, which is in agreement with its high nucleophilicity ($N = 4.33$ eV). Methanimine has a low electrophilicity ($\omega = 1.02$ eV), and the $\Delta\omega$ of the reaction has a low value of 0.41 eV. This low polar character is in good agreement with the high barrier (26.5 kcal mol⁻¹) of the bare imine-ene reaction. Moreover, EDGs decrease the electrophilicity of the imine, and conjugated groups slightly increase the electrophilicity, e.g. the reaction between propene and *N*-phenylmethanimine has a low $\Delta\omega$ value (0.58 eV) and, consequently, a high activation barrier.

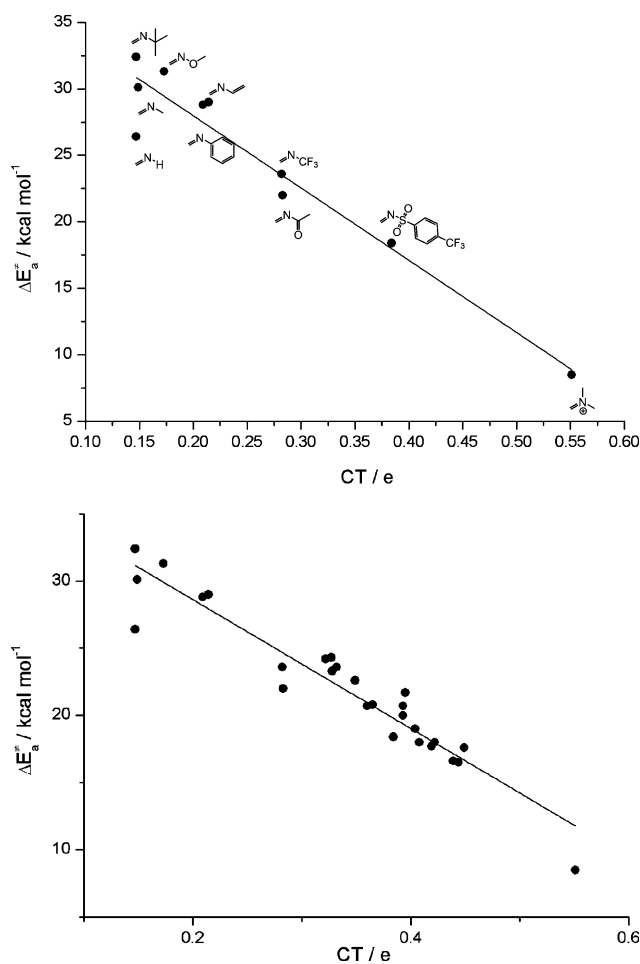


Fig. 4 (a) Plot of the activation barriers (ΔE_a^\ddagger) vs. the charge transfer (CT) of the reactions between propene and the N-substituted imine series. $R^2 = 0.92$. (b) Plot of the activation barriers (ΔE_a^\ddagger) vs. the charge transfer (CT) of the reactions with various Lewis acids and N-substituted imine series. $R^2 = 0.90$.

The electrophilicity of N-substituted imines with EWGs range from 1.57 eV to 2.29 eV, and the corresponding barriers range from 23.6 to 18.4 kcal mol⁻¹. A representation of the activation

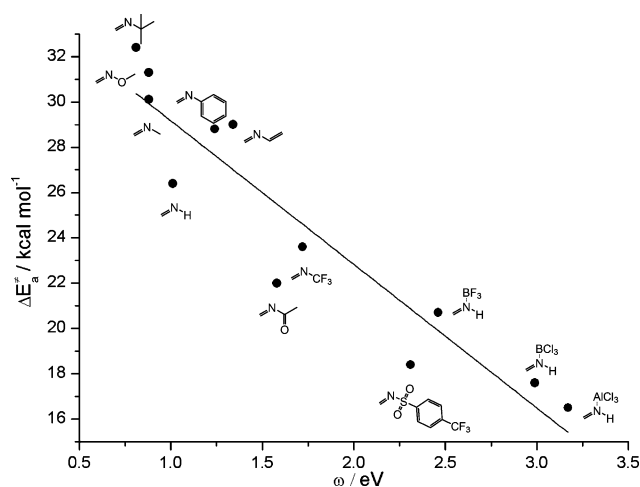


Fig. 5 Plot of the activation barriers (ΔE_a^\ddagger) vs. the electrophilicity ω of the N-substituted imine series. $R^2 = 0.87$.

Table 3 Relative energies of the reactions with various functional groups on the C atom (kcal mol⁻¹) and Charge Transfer (CT) (in e) is the charge transfer at the corresponding TSS

		<i>t</i> -Bu	CH ₃ O	CH ₃	C ₆ H ₅	H	CF ₃	CH ₃ OOC	<i>p</i> -CF ₃ -C ₆ H ₄ SO ₂
<i>E</i> -configuration	ΔE_a^\ddagger	33.4	31.5	30.5	30.7	26.4	24.0	24.3	19.7
	ΔG_a^\ddagger	45.9	44.4	42.4	42.2	38.2	36.8	36.4	32.9
	ΔE_{rxn}	-7.9	-6.6	-12.3	-7.6	-18.6	-20.8	-16.0	-25.1
	ΔG_{rxn}	8.6	9.5	3.3	7.5	-3.4	-4.8	-1.2	-8.9
	$\Delta E_{\text{H-L}}$	0.254	0.270	0.254	0.206	0.240	0.206	0.186	0.177
	[$\Delta E_{\text{L-L}}$] (a.u.)	[0.023]	[0.007]	[0.023]	[0.071]	[0.037]	[0.071]	[0.091]	[0.100]
	CT	0.132	0.105	0.123	0.154	0.147	0.222	0.219	0.300
	μ (a.u.)	-0.126	-0.121	-0.127	-0.144	-0.139	-0.171	-0.168	-0.188
	η (a.u.)	0.259	0.281	0.262	0.199	0.257	0.253	0.208	0.229
	ω (eV)	0.83	0.70	0.84	1.41	1.02	1.56	1.85	2.09
	<i>N</i> (eV)	4.19	4.03	4.11	4.52	3.86	3.05	3.73	2.91
<i>Z</i> -configuration	ΔE_a^\ddagger	33.6	35.5	30.2	30.2	26.4	25.8	24.8	23.3
	ΔG_a^\ddagger	45.4	47.4	42.2	41.8	38.2	38.3	36.5	36.1
	ΔE_{rxn}	-10.2	-4.4	-13.6	-8.7	-18.6	-19.8	-14.8	-21.8
	ΔG_{rxn}	5.4	10.8	2.0	6.6	-3.4	-4.2	0.2	-5.8
	$\Delta E_{\text{H-L}}$	0.256	0.271	0.255	0.201	0.240	0.204	0.182	0.165
	[$\Delta E_{\text{L-L}}$] (a.u.)	[0.021]	[0.006]	[0.022]	[0.076]	[0.037]	[0.073]	[0.095]	[0.112]
	CT	0.108	0.082	0.127	0.150	0.147	0.220	0.216	0.291
	μ (a.u.)	-0.122	-0.122	-0.126	-0.150	-0.139	-0.171	-0.168	-0.193
	η (a.u.)	0.256	0.286	0.262	0.202	0.257	0.250	0.199	0.215
	ω (eV)	0.79	0.71	0.82	1.52	1.02	1.59	1.92	2.35
	<i>N</i> (eV)	4.33	3.92	4.13	4.30	3.86	3.07	3.86	2.97

barrier (ΔE^\ddagger) with respect to the electrophilicity of the imines is shown in Fig. 5, and a correlation ($R^2 = 0.87$) between the two parameters exists. By examining the nucleophilicity, it can be seen that *N*-phenylmethanimine is the strongest nucleophile whereas *N*-4-(trifluoromethyl)benzenesulfonylmethanimine is the poorest nucleophile but the best electrophile. For the selected functionalized molecules, there is in general a clear inverse relationship between the electrophilicity ω and the nucleophilicity *N*.

In all cases, EDGs on the imine appreciably increase the barrier of the reaction, conjugated groups have almost no effect and EWGs lower it effectively to promote the interaction of the reactants by electron transfer. The general substituent sequence from the most to least favorable is *p*-CF₃-C₆H₄SO₂ (strong -C and -I) > CF₃ (-I) > H > C₆H₅ (+C) > CH₃ (+I) > CH₃O (strong +C and -I) > *t*-Bu (Steric and +I).

Influence of C-substituents on imine

The effect of a substituent on the imine carbon was also investigated. The substituents included electron-donating groups (CH₃ and CH₃O), electron-withdrawing groups (CF₃, CH₃CO and *p*-CF₃-C₆H₄SO₂), a conjugated group (C₆H₅) and a bulky group (*t*-Bu). The corresponding imine structures and the energies are given in ESI Chart S3† and Table 3, respectively. The imines can be either *Z*- or *E*-configurations and there is a small difference between the activation energies of these configurations. The CT in the TSS and the corresponding barriers have relative linear correlations ($R^2 = 0.83$ for *E*-configuration and $R^2 = 0.80$ for *Z*-configuration, see Chart S4 in ESI†). Like the *N*-substituted reactions, EWGs on the carbon increase the electrophilicity of the imine. The conjugated group exhibited a low electrophilic activation and the EDGs have a decreasing effect. The reaction barriers of the EWGs (*p*-F₃C-C₆H₄SO₂, CH₃OOC and CF₃) on the imine carbon are lower than that of the standard, whereas the barriers of the electron-donating

substituents (CH₃ and CH₃O) are higher. The conjugated (C₆H₅) and bulky (*t*-Bu) groups are still unfavorable for the imine-ene reaction (entry 1 and 5). The steric effect is more unfavorable than the conjugation effect, which is different from carbonyl-ene reactions where the conjugation effect is more unfavorable.⁵⁴ The reaction barrier with a substituent on the imine carbon is slightly higher than that with the same group on the imine nitrogen. This may be explained by the difference in electronegativity between nitrogen and carbon. The electronegativity of N is larger than that of C, and the electron density is higher on N. Therefore an EWG group on N weakens the C=N π bond, which lowers the LUMO energy more effectively than for C.

In general, the following can be concluded from the comparison of the selected Lewis acids and substituents. 1. An EWG on nitrogen is more favorable in energy than one on carbon. 2. In view of lowering the activation energy, a Lewis acid makes a greater contribution than a substituent does. In other words, an appropriate Lewis acid is more effective and convenient in lowering the reaction temperature, which is in complete agreement with experimental results.^{11,12,48,52} 3. Good correlations exist between the activation energies and the corresponding CT, as well as between the activation barrier and electrophilicity. 4. The steric effect has a larger influence than the electronic effect.

Conclusions

The potential energy surfaces of the imine-ene reaction between methanimine and propene were calculated using restricted and unrestricted density functional theory at the B3LYP level. The results show that a one-step concerted mechanism with an *exo* configuration transition structure is more favorable for the intermolecular bare imine-reaction, and that bond formation and hydrogen migration occur simultaneously. The promotion effect of seventeen Lewis acids was studied and the results show that the

polarity of the TSs controls the activation energies of the corresponding reaction. An increase of the electron-deficient character of the enophile (the electrophilicity) results in an enhancement of the CT, accompanied by a lowering of the activation barrier. The reactivity indices of eight substituted methanimines including electrophilicity, ω and nucleophilicity, N were analyzed, and the results indicate that the ω and the activation barrier have a good linear relationship. Lewis acids and electron-withdrawing substituents on methanimine facilitate the ene-reaction. Frontier molecular orbital theory gives a good explanation for these results. Finally, electron-donating, conjugated and bulky groups are all unfavorable factors, with the bulky effect being the most unfavorable factor for the imine-ene reaction.

Acknowledgements

We acknowledge the suggestions of Dr Hai-tao Zhao and Teng Wang and the financial support of the Key Program of the National Natural Science Foundation of China (No 20834002).

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