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Alkanoylation of quinazoline by nucleophilic aromatic substitution: Combined experimental and computational study

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ABSTRACT

A combined experimental and computational study on the key intermediates of NHC-catalyzed acylation reaction, Breslow intermediates (BIs), has been conducted in order to achieve a direct nucleophilic alkanoylation of *N*-heterocycles. Various BI precursors are alternatively prepared and used in the reaction with 4-chloroquinazoline. The present study reveals that the intermediates having benzimidazole moiety serve as acylating agents for the introduction of straight-chain alkanoyl groups. Natural bond orbital analysis indicates that the reactivity of intermediates partly correlates to the occupancy of the $\pi_{C\text{-}C}$ bonds of the hydroxyl enamine moieties. The putative rate-determining step of the acylation reaction has been theoretically investigated. Several new 4-alkanoylquinazolines are synthesized using the BI precursors.

1. Introduction

Heterocycles are important class of frameworks in medicinal and agricultural chemistry.[1,2] Compounds containing heterocycles often exhibit bioactivities, as they can interact with biomolecules through ionic and hydrogen bonds, ion-dipole, dipole-dipole, hydrophobic, and Van der Waals interactions. Thus, heterocycles, especially nitrogen-containing ones, are frequently seen as cores for pharmacophores in medicines.

We have been investigating methodologies to construct heterocyclic compounds,[3] and to introduce functionalities to heteroarenes.[4] Earlier, we focused on *N*-heterocyclic carbene (NHC)-catalyzed nucleophilic substitution reaction,[4] through which aroyl groups originating from aromatic aldehydes are introduced to π-deficient heteroarenes in one step. In this reaction, the nucleophile is the acylanion equivalent, also known as the "Breslow intermediate (BI)", which is produced from NHC and aldehyde. This reaction allows to access synthetically versatile ketones through C–C bond formation. In fact, the product ketones have been successfully used as intermediates to synthesize natural products[5] and anticancer agents.[6]

It should be noted, however, that this catalytic reaction suffers from the use of aldehydes. When aliphatic aldehydes and 4-nitrobenzaldehyde were used, the corresponding acylated products were not obtained. Furthermore, although the keto product could be obtained depending on the substrates, in the case of 4-(*N*,*N*-dimethylamino)benzaldehyde, the yield is very low.[4d] To elucidate the cause of this limitation so as to expand substrate scope, the present study is conducted in the following steps: (1) firstly, various BI precursors[7] were synthesized (Scheme 1), (2) secondly, BIs were generated from these precursors by treatment with a base, and (3) finally, the intermediates were used as acylating agents in the nucleophilic aromatic substitution reaction of 4-chloroquinazoline. Computational studies were performed to support the experimental results. It should be mentioned that Taylor et al.[8] synthesized 4-alkanoylquinazolines in the early 1970s, and a few studies were made in the recent years to synthesize these quinazolines.[9] However, the product examples are very much limited and all of them should go through multistep routes either

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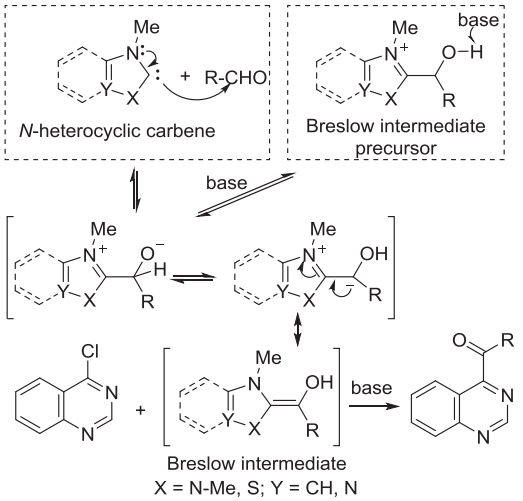

Scheme 1. Generation of Breslow Intermediate and Acylation of 4-Chloroquinazoline.

from 4-chloroquinazolines or from quinazolines without substituents at C4 position. Considering the synthetic versatilities of alkanoyl groups and the importance of quinazolines in medicinal chemistry,[10] finding a way to synthesize these biologically important compounds by directly introducing alkanoyl groups to quinazoline's π-deficient positions would be highly useful and it would allow us facile access to a variety of potentially bioactive derivatives.

2. Results and discussion

2.1. Synthesis of BI precursors

Synthesis of the BI precursors was commenced with the lithiation of azoles using ^{n}BuLi in THF (Table 1). The resulting lithioazoles derived from thiazole, benzimidazole, and triazole, were then reacted with aliphatic aldehydes to afford adducts, which were then treated with iodomethane to obtain the quaternized azoles **1**–**3**, the BI precursors for alkanoylation. The use of imidazolium-derived NHCs as catalysts in alkanoylation reaction is not favorable; since imidazoliums are less acidic than thiazoliums, benzimidazoliums, and triazoliums, and strong bases are needed to deprotonate to generate NHCs, causing undesired products such as aldols.

The reactions of 4-(*N*,*N*-dimethyamino)benzaldehyde and 2-nitrobenzaldehyde with lithioimidazole afforded the corresponding adducts quantitatively, whereas the reaction of 4-nitrobenzaldehyde with the same lithioazole produced the adduct only in low yield. Quaternization of the imidazole-based adducts with MeI yielded imidazolium **4**.

2.2. Acylation reactions of 4-chloroquinazolines using BI precursors

Next, the acylation reactions were investigated using BI precursor **1**–**3** bearing various azoles (Table 2). When triazole **1a** and thiazole **2a** with straight-chain alkyl groups originating from octanal were used in the reaction with 4-chloroquinazoline **5**, the desired acylated compounds **6a** were not obtained (entries 1–3). In contrast, the reaction of benzimidazole **3a**, and **3b** bearing straight-chain alkyl groups with **5** in THF, DMF, or NMP produces **6a**, and **6b**, respectively (entries 4–8). Either DBU or DBN was used as a base to produce BIs in situ from the precursors. *N*-methyl-2-pyrrolidone (NMP) suits better as a reaction medium than THF and DMF (entries 4–6). There is a tendency in which BIs with a longer straight-chain alkyl group afford the corresponding 4-alkanoylquinazolines in higher yields (Table 2, entries 4,8; Table 3, entries 1–3). In the cases of benzimidazole-based BIs with branched-alkyl chains, the desired acylated quinazolines were not obtained (Table 3, entries 4–7). The nucleophilic attack at the *ipso*-position of **5** may be less favorable than the dissociation to NHC and aldehydes due to the steric bulkiness around the carbon atom originating from the carbonyl group of the aldehydes.

The proposed reaction mechanism is shown in Scheme 2. Our previous study revealed that imidazolium-derived NHCs are the most effective catalysts for the reaction.[4] It has been previously shown that the BIs are the key intermediates for the catalytic aroylation reaction by generating them in situ from precursor **3** and **4** bearing aromatic substituents.[7] The precursors used in that earlier study[7] were prepared from aromatic aldehydes, which successfully served as acylating agents in the catalytic reaction. However, the reactions using the precursors originating from 2- or 4-nitrobenzaldehyde, and 4-dimethylaminobenzaldehyde have not been conducted. In general, NHC-catalyzed aroylation of haloheteroarenes with aromatic aldehydes having either strong electron-withdrawing or strong electron-donating groups does not provide the desired aroylated product, except that aroylation of **5** with 4-dimethylaminobenzaldehyde using 25 mol% of 1,3-dimethylimidazolium iodide produced **6m** in 31% yield.[4d] Thus, the reactions of **4k** and **4m** using DBN as a base in NMP were performed to obtain aroylated product **6k** and **6m** in 40% and 68% yield, respectively (Table 4, entries 1, 2). The product yield of the reaction of **4m** using NaH as a base in THF is dropped significantly to 14% (entry 3). In comparison, the reaction yield using **4n** derived from benzalehyde as a catalyst together with extra benzaldehyde in the same condition was 80% (entry 4).[7]

2.3. Computational study

2.3.1. Natural bond orbital analysis

The reactivity of BIs was studied using density functional theory (DFT). The B3LYP functional[11] with two different basis sets [6-311+G(d) and 6-311++G(2d,p)] was utilized for this purpose. All the calculations were performed by considering bulk solvent effect with DMF as the solvent using polarizable continuum model (PCM).[12] Gaussian09 package was used for all the theoretical calculations.[13] Orbital occupancies were calculated by using natural bond orbital (NBO) analysis.[14] The results of NBO analysis (Table 5) indicate that the reactivity of the intermediates **1aBI**, **2aBI**, **3bBI**, and **4nBI** correlates with the occupancy of the $\pi_{C\text{-}C}$ bond [$\pi_{C1\text{-}C2}$ (BD)] but not with that of the two lone pairs of the oxygen atom [O_3 (LP1), O_3 (LP2)] in the hydroxyenamine moieties (The related orbitals were given in Fig. S1 of the Supporting Information). The results roughly indicate that when the occupancy of the $\pi_{C\text{-}C}$ bond is smaller than those of the oxygen lone pairs, the acylation proceeds (**3bBI** and **4nBI**).

Fig. 1 shows the schematic structures of various BIs, and occupancy values and the energies of π_{C1-C2} (BD) bond orbitals. Among the BIs derived from aromatic aldehydes, there is no significant difference in the electronic state between experimentally the "more reactive" intermediate **4nBI** and the "less reactive" ones **4kBI**, **4lBI**, and **4mBI**. The π_{C1-C2} bond occupancy values of BIs derived from aliphatic aldehydes (**3bBI** and **3hBI)** are higher than those derived from aromatic aldehydes (**4nBI**, **4kBI**, **4lBI**, and **4mBI**). As expected, **4lBI** and **4kBI** have the least π_{C1-C2} bond occupancies. The results of NBO analysis on the nucleophiles, however, did not fully explain the differences in the reactivity of the BIs with various substituents. The occupancy and the orbital energy values of **3bBI** and **3hBI** are comparable, whereas only **3bBI** served

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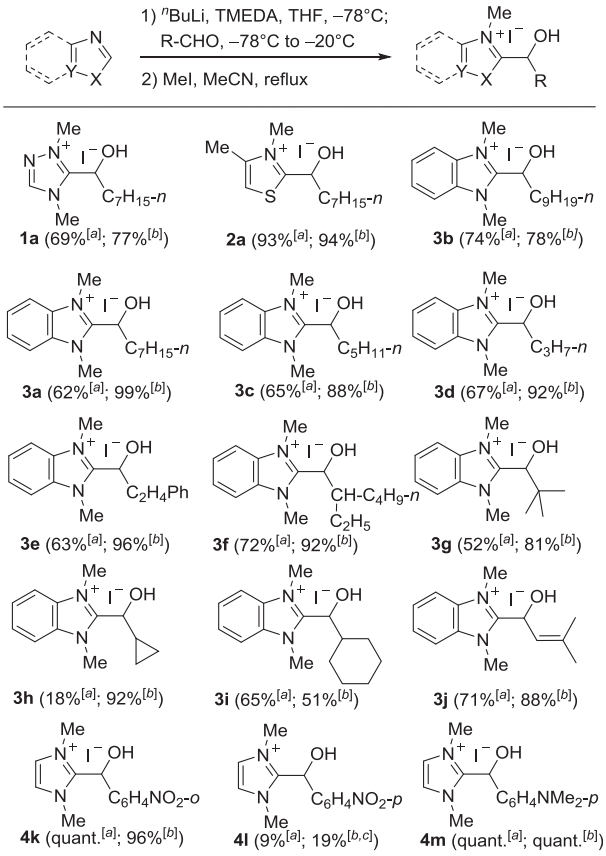
Table 1
Synthesis of the Breslow intermediate precursors.



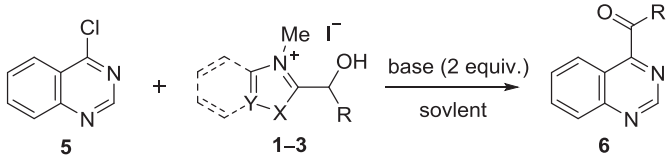
[a] Yield of the first step, lithiation.
[b] Yield of the second step, quaternization.
[c] Toluene was used as a solvent.

as an acylating agent to afford **6b**. It indicates that NBO results alone cannot explain the reactivity of these compounds.

2.3.2. Rate-determining step

Next, the transition state of the putative rate-determining step was investigated. Fig. 2 shows the related transition state structures of the reaction between BIs **4nBI**, **3bBI**, and **3hBI** and quinazoline **4**. The calculated activation energy (E_a), free energy of activation ($\Delta^{\ddagger}G^{o}$), and free energy of reactions (ΔG) were also given in Fig. 2. The results show that the E_a and $\Delta^{\ddagger}G^{o}$ values are ranging from 11 to 17 and 29–34 kcal/mol, respectively, and all the reactions are exothermic (ΔG of around 22–26 kcal/mol). The study also shows that though there is no difference in calculated E_a and $\Delta^{\ddagger}G^{o}$ values of the reactions involving **3bBI** and **3hBI**, acylation of the former

Table 2
Reaction using BI precursor **1**–**3** bearing a straight-chain alkyl group.



Entry	Azolium salt	R	Solvent	Base	Temp. (°C)	Time (h)	Product	Yield (%)
1	**1a**	-C_7H_{15}-*n*	NMP	DBU	80	1.5	**6a**	–
2	**2a**	-C_7H_{15}-*n*	THF	TEA	40	12	**6a**	–
3	**2a**	-C_7H_{15}-*n*	DMF	DBU	80	6.5	**6a**	–
4	**3a**	-C_7H_{15}-*n*	NMP	DBN	80	1.5	**6a**	63
5	**3b**	-C_9H_{19}-*n*	THF	DBU	reflux	2.5	**6b**	18
6	**3b**	-C_9H_{19}-*n*	DMF	DBU	80	1.5	**6b**	46
7	**3b**	-C_9H_{19}-*n*	NMP	DBU	80	1.5	**6b**	68
8	**3b**	-C_9H_{19}-*n*	NMP	DBN	80	1.5	**6b**	70

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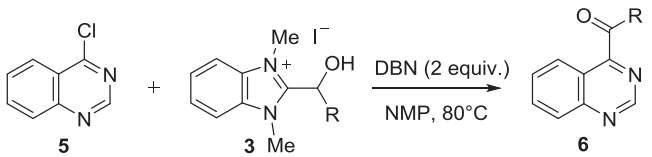
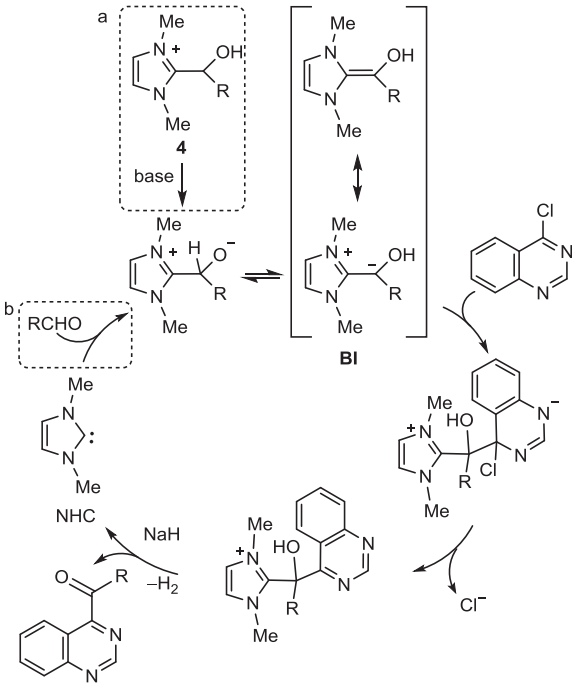
Table 3
Reaction using BI precursor **3** bearing a straight-chain or a branched-chain alkyl group.



Entry	3	R	Time (h)	Product	Yield (%)
1	**3c**	-C_5H_{11}-*n*	1.5	**6c**	43
2	**3d**	-C_3H_7-*n*	2	**6d**	34
3[a]	**3e**	-C_2H_4Ph	3	**6e**	11
4	**3f**	-CH(Et)C_4H_9	2	**6f**	–
5	**3g**	-CMe_3	2	**6g**	–
6	**3h**	cyclopropyl	2	**6h**	–
7	**3i**	cyclohexyl	2	**6i**	–
8	**3j**	-CH=CMe_2	2	**6j**	13

[a] DBU was used as a base.



Scheme 2. Proposed reaction mechanism. (a) In situ generation of BI from **4**. (b) For catalytic version.

alone proceeds (Table 2, entry 8; Table 3, entry 6). In fact, the E_a and $\Delta^{\ddagger}G^{o}$ values obtained for the reaction involving **4nBI**, which proceeds experimentally,[7] is around 5 kcal/mol larger than those obtained for the reaction involving **3bBI**. The calculated reaction free energies also are not decisive. A close look reveals that all these calculated values differ within 4–5 kcal/mol among these reactions. By considering the fact that this putative step is one among a few reaction steps in the whole acylation process, the calculated values indicate the importance of studying the remaining reactions of the acylation process to have a clear picture.

3. Conclusions

In summary, we have demonstrated the difference in reactivity of various BIs in acylation of **5** through experimentally examining the reactions using alternatively synthesized BI precursors and through performing DFT calculations. The BIs bearing a benzimidazole and a straight-chain alkyl group react with **5** to afford 4-alkanoylquinazolines **6**, which had not been synthesized before. This is the first evidence to obtain alkanoylquinazolines from easily accessible starting material **5** in one step. NBO analysis shows that the occupancy values of the $\pi_{C\text{-}C}$ bonds of the BIs and the reactivity toward the acylation are partly correlated. However, the bulkiness of the nucleophiles impedes the reaction when the intermediates with branched alkyl groups are used. In the case of benzaldehydes bearing either strong electron-withdrawing groups or strong electron-donating groups, the reaction using the precursors afforded the products. Thus, the generation of the intermediates in catalytic condition should be considered as unfavorable. Further investigation is going on to find a suitable catalyst and an appropriate reaction condition to successfully perform the catalytic version of the alkanoylation reaction.

4. Experimental section

4.1. General information

Chemicals were purchased and used without further purification unless otherwise specified. All non-aqueous reactions were conducted under an atmosphere of argon. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F245 plates (Merck). Column chromatograpy was performed using spherical silica gel (63–219 μm) (Kanto Chemicals). Melting points were uncorrected. NMR measurements were recorded with 300, 400 or 500 MHz spectrometers for ^{1}H NMR and with 76, 100, or 126 MHz spectrometer for ^{13}C NMR. Chemical shifts (δ) of ^{1}H NMR are expressed in parts per million. Multiplicities are indicated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and coupling constants (*J*) are reported in hertz units. Mass spectra were recorded using a TOF (ESI) analyzer or a magnetic sector (EI and FAB) analyzer.

4.2. 1-(4-Methyl-4H-1,2,4-triazol-3-yl)octan-1-ol

To a solution of 4-methyl-1,2,4-triazole (681 mg, 7.78 mmol), TMEDA (0.40 ml) in dry THF (10 ml) and at −60 °C, 2.69 M *n*-BuLi solution (2.9 ml, 7.80 mmol) was added drop wise. After stirring at −60 °C for 30 min, 10 ml of dry THF solution of octanol (1.30 mL, 8.33 mmol) was added and the mixture was stirred for additional 4 h at −60 °C to −30 °C. Then H_2O was added and the mixture was extracted three times with ethyl acetate. The organic layer was washed with saturated brine and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1–5% methanol/chloroform) as a colorless solid (1.13 g, 69%): Mp. 63–65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.6 Hz), 1.30–1.26 (9H, m), 1.46 (1H, q, J = 5.2 Hz), 1.93–1.84 (2H, m), 3.50 (1H, br s), 3.93 (3H, s), 4.82 (1H, q, J = 6.3 Hz), 7.76 (1H, s); ^{1}H NMR (300 MHz, DMSO) δ 0.88 (3H, t, J = 6.9 Hz), 1.26–1.49 (14H, m), 1.87–1.93 (2H, m), 2.70 (1H, d, J = 7.5 Hz) 3.92 (3H, s), 4.84 (1H, q, J = 6.9 Hz), 7.79 (1H, s); ^{13}C NMR (126 MHz) δ 14.1, 22.7, 25.2, 29.5, 31.9, 33.7, 35.4, 39.8, 64,2, 143.6, 155.0; HRMS (ESI) *m/z* calcd for $C_{11}H_{21}N_3NaO$ $(M + Na)^+$ 234.1582, found. 234.1573.

4.3. 1-(4-Methylthiazol-2-yl)octan-1-ol

To a solution of 4-methylthiazole (1.40 mL, 15.3 mmol), TMEDA (0.70 ml) in dry THF (10 ml) at −78 °C, 1.66 M *n*-BuLi solution (10 mL, 10 mmol) was added drop wise. After stirring at −78 °C for 30 min, 10 ml of dry THF solution of octanol (2.40 mL, 15.3 mmol)

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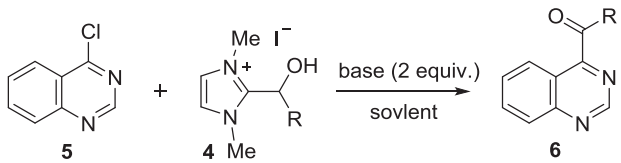
Table 4
Reaction using BI precursor **4** bearing an aromatic group.

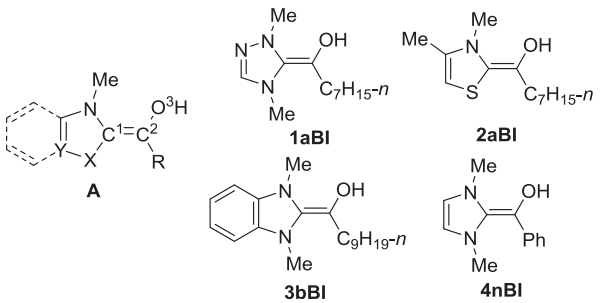


Entry	4	R	Solvent	Base	Temp. (°C)	Time (h)	Product	Yield (%)
1	**4k**	-$C_6H_4NO_2$-*o*	NMP	DBN	80	1.5	**6k**	40
2	**4m**	-$C_6H_4NMe_2$-*p*	NMP	DBN	80	1.5	**6m**	68
3	**4m**	-$C_6H_4NMe_2$-*p*	THF	NaH	reflux	0.5	**6m**	14
4[a]	**4n**[7]	-Ph	THF	NaH	reflux	1	**6n**	80

[a] 10 mol% of **4n** was used as a catalyst with benzaldehyde.[7]

was added and the mixture was stirred for additional 4 h at −60 °C to −30 °C. The rest of the procedure is the same as described above. 10% methanol/chloroform was used as an eluent in silica gel chromatography: Yellow oil (3.25 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.9 Hz), 1.51–1.24 (10H, m), 1.86–1.79 (1H, m), 1.90–1.96 (1H, m), 2.42 (3H, s), 2.86 (1H, d, J = 4.6 Hz), 4.95–4.91 (1H, m), 6.81 (1H, d, J = 1.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 17.0, 22.6, 25.2, 29.1, 29.3, 31.8, 38.4, 72.0, 113.2, 152.3, 174.3; HRMS (EI^+) *m/z* calcd for $C_{12}H_{21}NOS$ M^+ 227.1334, found. 227.1326.

Table 5
Occupancies [at B3LYP/6-311++G(2d,p)] of Breslow intermediates.



Nu	acylation	Occupancy		
		$\pi_{C1\text{-}C2}$ (BD)[a]	O^3 (LP1)[b]	O^3 (LP2)[b]
1aBI	Not detected	1.95	1.98	1.94
2aBI	Not detected	1.96	1.98	1.91
3bBI	Proceeded	1.94	1.98	1.94
4nBI	Proceeded	1.82	1.98	1.95

[a] π bond of the enamine-carbons (C^1=C^2 in **A**).
[b] lone pair of the oxygen atom (O^3 in **A**).

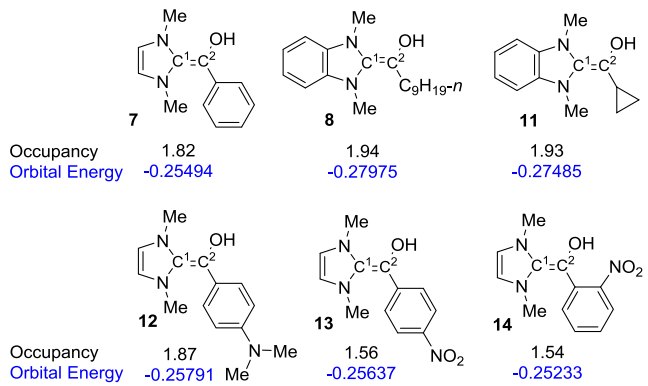


Fig. 1. Occupancies of the $\pi_{C1\text{-}C2}$ bonds and orbital energies (in hartree) of Breslow Intermediates. All the values obtained at B3LYP/6-311++G(2d,p) level.

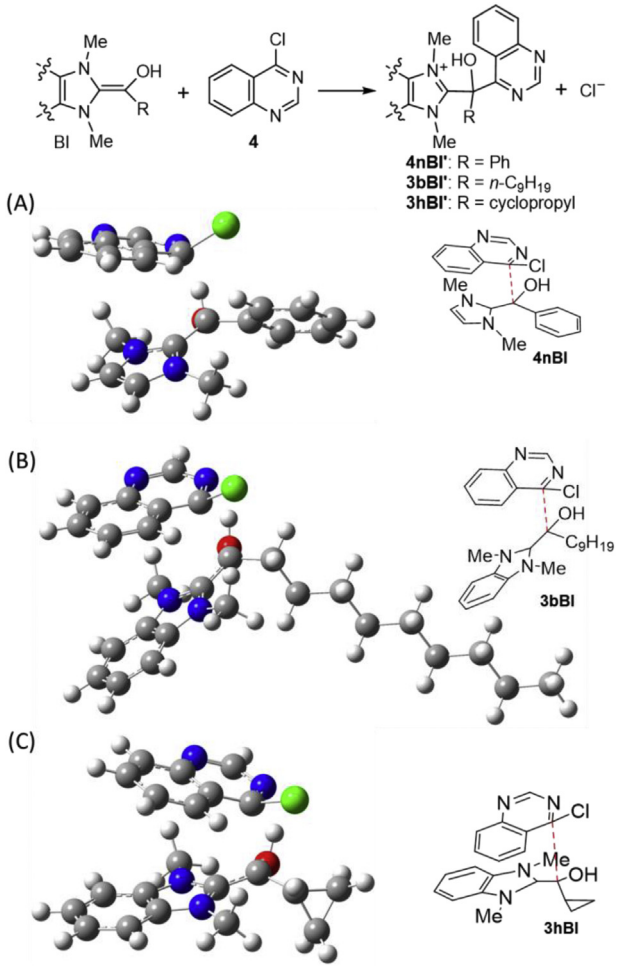


Fig. 2. Transition state structures of the reaction between BIs **4nBI**, **3bBI**, **3hBI,** and quinazoline **4**. Activation energy (E_a), free energy of activation ($\Delta^{\ddagger}G^{o}$), and the free energy of reaction (ΔG) in kcal/mol at 353 K, R and ν (of the newly forming bond) in Å and in cm^{-1}, respectively: (A) E_a = 16.83; $\Delta^{\ddagger}G^{o}$ = 33.71; ΔG = 26.03; R = 2.339; ν = 209.3i; (B) E_a = 11.16; $\Delta^{\ddagger}G^{o}$ = 28.62; ΔG = 21.90; R = 2.260; ν = 239.9i; (C) E_a = 11.47; $\Delta^{\ddagger}G^{o}$ = 29.48; ΔG = 25.44; R = 2.282; ν = 241.7i. All the values were obained at B3LYP/6-311+G(d) level.

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4.4. General procedure for the preparation of benzimidazole-aldehyde adducts

To a dry THF solution (10 ml) of *N*-methylbenzimidazole (1.33 g, 10 mmol) and TMEDA (0.3 eq), 1.6 M *n*-butyllithium solution (6.4 mL, 10 mmol) was added dropwise at −78 °C and the reaction mixture was stirred for 30 min. Then, to the mixture, a dry THF solution (10 mL) of aldehydes (10 mmol) was added dropwise at −78 °C and was stirred allowing the reaction mixture to warm to −20 °C for 4 h unless otherwise noted. After reaction, water was added to the reaction mixture and it was stirred for 10 min at room temperature. The mixture was extracted three times with ethyl acetate and washed with saturated brine. After concentrating under reduced pressure, the residue was purified by silica gel column chromatography (10% ethyl acetate/*n*-hexane) to give a desired product.

4.4.1. 1-(1-Methyl-1H-benzo[d]imidazol-2-yl)decan-1-ol

Colorless solid (2.13 g, 74%): Mp. 81–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.6 Hz), 1.14–1.38 (14H, m), 1.89–1.99 (2H, m), 3.77 (3H, s), 4.87 (1H, dd, J = 3.0 Hz, 13.8 Hz), 7.21–7.26 (3H, m), 7.69–7.72 (1H, m); ^{13}C NMR (126 MHz) δ 14.1, 22.6, 25.6, 29.3, 29.4, 29.5, 30.0, 31.9, 36.0, 67.7, 109.1, 119.1, 122.0, 122.6, 135.8, 141.3, 156.2; HRMS (EI$^+$) *m/z* calcd for $C_{18}H_{29}N_2O$ $(M + H)^+$ 289.2280, found. 289.2272.

4.4.2. 1-(1-Methyl-1H-benzo[d]imidazol-2-yl)octan-1-ol

From *N*-methylbenzimidazole (1.38 g, 10.4 mmol), the title compound was obtained as a colorless solid (1.62 g, 62%): Mp. 75–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 6.9 Hz), 1.25–1.56 (10H, m), 1.90–2.02 (2H, m), 3.30 (1H, br s), 3.80 (3H, t, J = 6.0 Hz), 4.94 (1H, dd, J = 7.7, 5.4 Hz), 7.21–7.31 (4H, m), 7.70–7.74 (1H, m); ^{13}C NMR (126 MHz) δ 14.1, 22.6, 25.6, 29.2, 29.4, 29.6, 30.1, 31.8, 36.1, 67.6, 109.1, 119.2, 122.0, 122.6, 136.0, 141.3, 156.1; HRMS (FAB$^+$) *m/z* calcd for $C_{16}H_{25}N_2O$ $(M + H)^+$ 261.1961. Found. 261.1975.

4.4.3. 1-(1-Methyl-1H-benzo[d]imidazol-2-yl)hexan-1-ol

After the lithiation, hexanal was added, and the mixture was stirred at −78 °C to −20 °C for 3 h: Colorless solid (2.41 g, 65%): Mp. 90–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90–0.83 (3H, m), 1.42–1.25 (5H, m), 1.56–1.47 (1H, m), 1.99–1.91 (2H, m), 3.80–3.60 (3H, m), 4.16 (1H, s), 4.91 (1H, t, J = 6.9 Hz), 7.25–7.20 (3H, m), 7.67–7.71 (1H, m); ^{13}C NMR (126 MHz) δ 14.0, 22.5, 25.3, 30.1, 31.6, 36.0, 67.6, 109.1, 119.2, 122.0, 122.6, 136.0, 141.4, 156.1; HRMS (FAB$^+$) *m/z* calcd for $C_{14}H_{21}N_2O$ $(M + H)^+$ 233.1654, found. 233.1670.

4.4.4. 1-(1-Methyl-1H-benzo[d]imidazol-2-yl)butan-1-ol

After the lithiation, butanal was added, and the mixture was stirred at −78 °C to −20 °C for 17 h: Colorless solid (1.40 g, 67%): Mp. 104-104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 20 Hz), 1.35–1.60 (2H, m), 1.89–1.98 (2H, m), 3.74 (3H, s), 4.93 (1H, dd, J = 8, 10.4 Hz), 7.17–7.26 (3H, m), 7.65–7.69 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 18.9, 30.0, 38.0, 67.4, 109.1, 119.1, 122.0, 122.5, 135.9, 141.3, 156.1; HRMS (EI$^+$) *m/z* calcd for $C_{12}H_{16}N_2O$ M^+ 204.1263. Found. 204.1261.

4.4.5. 1-(1-Methyl-1H-benzo[d]imidazol-2-yl)-3-phenylpropan-1-ol

From *N*-methylbenzimidazole (1,32 g, 9.9 mmol), the title compound was obtained as a colorless solid (1.66 g, 63%): Mp. 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20–2.35 (2H, m), 2.73–2.90 (2H, m), 1.89–1.98 (2H, m), 3.63 (3H, s), 4.89 (1H, dd, J = 7.6, 10 Hz), 7.14–7.33 (9H, m), 7.66–7.71 (1H, m); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.15–2.29 (2H, m), 2.61–2.69 (1H, m), 2.73–2.81 (1H, m), 2.81 (3H, s), 4.80–4.84 (1H, m), 5.68 (1H, d, J = 3.9 Hz), 7.13–7.28 (7H, m), 7.49 (1H, d, J = 8 Hz), 7.57 (1H, d, J = 8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.9, 31.6, 37.6, 66.4, 109.2, 119.3, 122.2, 122.7, 126.0, 128.4, 128.5, 136.1, 141.2, 155.7; HRMS (FAB$^+$) *m/z* calcd for $C_{17}H_{19}N_2O$ $(M + H)^+$ 267.1497. Found. 267.1495.

4.4.6. 2-Ethyl-1-(1-methyl-1H-benzo[d]imidazol-2-yl)hexan-1-ol

After the lithiation, 2-ethylhexanal was added, and the mixture was stirred at −78 °C to −20 °C for 5 h: From *N*-methylbenzimidazole (664 mg, 5.0 mmol), the title compound was obtained as a colorless solid (936 mg, 72%): Mp. 95–96 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.71 (3H, t, J = 7 Hz), 0.85 (3H, t, J = 6.5 Hz), 1.44–1.53 (1H, m), 1.68–1.67 (1H, m), 1.95–1.98 (1H, bs), 3.82 (3H, s), 4.66–4.69 (1H, m), 5.53 (1H, d, J = 5.5 Hz), 7.14 (1H, t, J = 7.5 Hz), 7.19 (1H, t, J = 7.5 Hz), 7.48 (1H, d, J = 7.5 Hz), 7.55 (1H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.1, 11.5, 14.3, 14.4, 21.3, 21.8, 22.7, 23.1, 27.7, 27.9, 28.2, 28.7, 33.1, 43.0, 43.5, 67.3, 67.4, 113.7, 127.1, 127.7, 128.1, 130.0, 132.1, 153.5; HRMS (EI$^+$) *m/z* calcd for $C_{16}H_{24}N_2O$ M^+ 260.1889. Found. 260.1873.

4.4.7. 2,2-Dimethyl-1-(1-methyl-1H-benzo[d]imidazol-2-yl) propan-1-ol

After the lithiation, pivaladehyde was added, and the mixture was stirred at −78 °C to −20 °C for 4.5, and then at room temperature for 1.5 h: From *N*-methylbenzimidazole (663 mg, 5.0 mmol), the title compound was obtained as a colorless solid (565 mg, 52%): Mp. 229–230 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.01 (9H, s), 3.36 (3H, s), 3.87 (1H, s), 4.62 (1H, s), 7.19 (1H, sextet d, J = 1.2, 7.2 Hz), 7.19 (1H, dd, J = 1.2, 6.9 Hz), 7.58 (1H, dd, J = 1.2, 6.9 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 26.2, 30.8, 36.2, 73.8, 109.9, 118.7, 121.3, 121.6, 135.7, 141.7, 154.8; HRMS (FAB$^+$) *m/z* calcd for $C_{13}H_{19}N_2O$ $(M + H)^+$ 219.1492. Found. 219.1501.

4.4.8. Cyclopropyl(1-methyl-1H-benzo[d]imidazol-2-yl)methanol[15]

After the lithiation, cyclopropane carboaldehyde was added, and the mixture was stirred at −78 °C to −20 °C for 6 h; Colorless solid (365 mg, 18%): Mp. 179–180 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 0.37–0.39 (1H, m), 0.56–0.62 (2H, m), 0.71–0.76 (1H, m), 1.56 (1H, dd, J = 3.0, 5.2 Hz), 3.96 (3H, s), 4.42 (1H, d, J = 8.7 Hz), 7.21–7.33 (2H, m), 7.49 (1H, dd, J = 1.2, 7.5 Hz), 7.62 (1H, dd, J = 1.2, 7.5 Hz); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.66–0.39 (4H, m), 1.49–1.42 (1H, m), 3.77 (3H, s), 4.33 (1H, dd, J = 8.0, 1.7 Hz), 4.98 (1H, s), 7.26–7.18 (3H, m), 7.68–7.66 (1H, m); ^{13}C NMR (126 MHz, DMSO-d_6) δ 3.1, 4.8, 16.6, 30.88, 73.5, 110.83, 119.6, 123.4, 124.1, 137.4, 142.4, 156.3; HRMS (FAB$^+$) *m/z* calcd for $C_{12}H_{15}N_2O$ $(M + H)^+$ 203.1184. Found. 203.1206.

4.4.9. Cyclohexyl(1-methyl-1H-benzo[d]imidazol-2-yl)methanol

After the lithiation, cyclopropane carboaldehyde was added, and the mixture was stirred at −78 °C to −20 °C for 4.5 h: From *N*-methylbenzimidazole (672 mg, 5.05 mmol), the title compound was obtained as a colorless solid (800 mg, 65%): Mp. 135–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99–1.15 (5H, m), 1.35 (1H, d, J = 12.3 Hz), 1.64 (2H, t, J = 2.4 Hz), 1.73–1.94 (1H, m), 2.01–2.05 (1H, d, J = 10.5 Hz), 3.75 (3H, s), 4.54 (1H, bs), 4.61–4.65 (1H, m), 7.18–7.25 (3H, m), 7.62–7.69 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.8, 25.9, 28.8, 29.3, 30.3, 43.4, 72.3, 109.1, 119.2, 122.0, 122.5, 135.9, 141.5, 155.8; HRMS (FAB$^+$) *m/z* calcd for $C_{15}H_{21}N_2O$ $(M + H)^+$ 245.1648. Found. 245.1655.

4.4.10. 3-Methyl-1-(1-methyl-1H-benzo[d]imidazol-2-yl)but-2-en-1-ol

After the lithiation, cyclopropane carboaldehyde was added, and the mixture was stirred at −78 °C to −20 °C for 7 h: From *N*-methylbenzimidazole (403 mg, 3.03 mmol), the title compound

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was obtained as a yellow solid (464 mg, 71%): Mp. 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (3H, d, J = 2 Hz), 1.84 (3H, d, J = 2 Hz), 3.71 (3H, s), 5.54–5.58 (1H, m), 5.67 (1H, d, J = 11.6 Hz), 7.17–7.27 (4H, m), 7.65–7.70 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.4, 25.9, 30.0, 64.7, 109.1, 119.4, 122.0, 122.6, 123.4, 136.3, 138.1, 141.5, 155.7; HRMS (EI$^+$) m/z calcd for $C_{13}H_{16}N_2O$ M^+ 216.1263. Found. 216.1257.

4.4.11. Synthesis of (1-methyl-1H-imidazol-2-yl)(2-nitrophenyl) methanol

The procedure is the same as the general procedure of benzimidazole-aldehyde adducts as a yellow solid. From 1-methylimidazole (410 mg, 5.0 mmol), the title compound was obtained in quantitive yield (1.17 g) Mp. 187–188 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.75 (3H, s), 6.42 (2H, bs), 6.59 (1H, s), 7.07 (1H, s), 7.56 (1H, t, J = 7.5 Hz), 7.80 (1H, t, J = 7.5 Hz), 7.99 (2H, d, J = 8.1 Hz); ^{1}H NMR (300 MHz, CD_3OD) δ 3.84 (6H, s), 6.57 (1H. s), 6.70 (1H, d, J = 1.5 Hz), 7.04 (1H, d, J = 1.5 Hz), 7.54 (1H, td, J = 7.5, 1.5 Hz), 7.78 (1H, td, J = 7.5, 1.5 Hz), 8.03–8.08 (2H, m); ^{13}C NMR (126 MHz) δ 33.2, 65.0, 123.1, 125.7, 127.0, 129.6, 129.7, 134.7, 138.5, 148.8, 149.3; HRMS (FAB+) m/z calcd for $C_{11}H_{12}N_3O_3$ $(M + H)^+$ 234.0877. Found. 234.0891.

4.5. Synthesis of (1-methyl-1H-imidazol-2-yl)(4-nitrophenyl) methanol

To a solution of 1-methylimidazole (0.79 ml, 10 mmol) in dry THF (10 ml), TMEDA (1.35 ml, 30 mmol) was added under argon atmosphere. Then, at 0 °C, 1.65 M n-BuLi solution (7 ml, 10 mmol) was added drop wise. After stirring at r.t. for 30 min, a solution of 4-nitrobenzaldehyde (1.50 g, 10 mmol) in dry THF (15 ml) was added at −40 °C and the mixture was stirred for additional 2.5 h at r.t. Then H_2O was added and the organic layer was extracted three times with ethyl acetate and washed with saturated brine. After drying over sodium sulfate, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% hexane/ethylacetate) and (10% methanol/chloroform) to give the product (0.21 g, 9%) as a yellow solid: Mp. 175–176 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 3.47 (3H, s), 6.01 (1H, s), 6.85(1H, s), 6.99(1H, s), 7.55 (2H, d, J = 9.6 Hz) 8.21 (2H, d, J = 9.6 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.66, 67.29, 122.52, 123.10, 126.22, 127.49, 146.51, 147.62, 149.99; HRMS (FAB+) m/z calcd for $C_{11}H_{11}N_3O_3$ $(M + H)^+$ 234.0879. Found. 234.0866.

4.6. Synthesis of (4-N,N-dimethylamino)phenyl)(1-methyl-1H-imidazol-2-yl)methanol

To a solution of 1-methylimidazole (0.80 ml, 10 mmol) in dry THF (10 ml), TMEDA (0.45 ml, 3.0 mmol) was added under argon atmosphere. Then, at 0 °C, 1.65 M n-BuLi solution (7 ml, 10 mmol) was added drop wise. After stirring at r.t. for 30 min, a solution of p-dimethylaminobenzaldehyde (1.45 g, 10 mmol) in dry THF (15 ml) was added at −20 °C and the mixture was stirred for additional 4.5 h at r.t. Then H_2O was added at 0 °C and the organic layer was extracted three times with ethyl acetate and washed with saturated brine. After drying over sodium sulfate, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% ethyl acetate/hexane) to give 13b (1.44 g, 62%) as a yellow solid: Mp. 157–159 °C; (lit.[2] 141–142 °C). ^{1}H NMR (300 MHz, CD_3OD) δ 2.89 (6H, s), 3.49 (3H, s), 5.88 (1H, s), 6.73 (2H, d, J = 6.9 Hz), 6.85 (1H, d, J = 1.4 Hz), 6.95 (1H, d, J = 1.4 Hz), 7.14–7.12 (2H, d, J = 6.9 Hz); ^{13}C NMR (76 MHz, CD_3OD) δ 32.3, 39.7, 68.9, 112.6, 122.2, 125.3, 126.6, 128.8, 149.2, 150.4; HRMS (FAB$^+$) m/z calcd for $C_{13}H_{18}N_3O$ $(M + H)^+$ 232.1450, found. 232.1447.

4.7. General procedure for the synthesis of azolium salts **1**–**4**

To an acetonitrile solution (8–15 ml) of 2-hydroxymethylazoles (1–10 mmol), iodomethane (1.5–5 equiv.) was added and the mixture was stirred at reflux for 1–13 h at 90 °C. After concentrating under reduced pressure, the residue was purified by silica gel column chromatography (chloroform) or recrystallization from acetonitrile/ethyl acetate.

4.7.1. 5-(1-Hydroxyoctyl)-1,4-dimethyl-4H-1,2,4-triazol-1-ium iodide (**1a**)

From the corresponding triazole (1.01 g, 4.8 mmol), the title compound was obtained as a slightly yellow solid (1.36 g, 77%): Mp. 62–64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.9 Hz), 1.37–1.24 (9H, m), 1.60–1.55 (1H, m), 1.69–1.76 (1H, m), 1.95–2.02 (1H,m), 4.10 (3H, s), 4.18 (3H, s), 5.22 (1H, d, J = 4.0 Hz), 5.37–5.33 (1H, m), 8.76 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0, 22.5, 25.2, 28.9,29.0, 31.6, 33.7, 35.3, 39.7, 64.6, 143.6, 154.9; HRMS (ESI) m/z calcd for $C_{12}H_{24}N_3O$ M^+ 226.1919, found. 226.1928.

4.7.2. 3,4-Dimethyl-2-(1-hydroxyoctyl)thiazolium iodide (**2a**)

From the corresponding thiazole (2.22 g, 9.79 mmol), the title compound was obtained as a slightly yellow solid (3.39 g, 94%): Mp. 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.93 (5H, m), 1.23–1.40 (10H, m), 2.59 (3H, s), 4.06 (3H, s), 5.50 (2H, s), 7.65 (1H, d, J = 1.2 Hz); ^{13}C NMR (76 MHz, CD_3OD) δ 14.5, 14.7, 24.0, 26.4, 30.6, 30.7, 33.2, 37.4, 38.6, 70.3, 119.5, 149.6, 183.2; Anal. Calcd for $C_{13}H_{24}INOS$: C, 42.28; H, 6.55; N, 3.79, found: C, 42.26; H, 6.73; N, 3.68.

4.7.3. 2-(1-Hydroxyoctyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide (**3a**)

From the corresponding benzimidazole (786 mg, 3.02 mmol), the title compound was obtained as a colorless solid (1.20 g, 99%): Mp. 123–124 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (3H, t, J = 6.5 Hz), 1.26–1.64 (9H, m), 1.74–2.02 (1H, m), 2.04–2.12 (2H, m), 4.13 (6H, s), 5.35–5.45 (1H, m), 6.44 (1H, br s), 7.65–7.72 (2H, m), 7.90–8.06 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0, 22.5, 25.4, 29.0, 31.6, 33.6, 34.3, 65.1, 112.5, 127.0, 131.7, 154.10; HRMS (FAB$^+$) m/z calcd for $C_{17}H_{27}N_2O$ M^+ 275.2123, found. 275.2148.

4.7.4. 2-(1-Hydroxydecyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide (**3b**)

From the corresponding benzimidazole (2.13 g, 7.39 mmol), the title compound was obtained as a colorless solid (2.47 g, 78%): Mp. 131–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 6.5 Hz), 1.14–1.39 (13H. m), 1.50–1.82 (2H, m), 1.96–2.10 (1H, m), 4.15 (6H, s), 5.41–5.62 (2H, m), 7.55–7.69 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0, 22.5, 25.3, 29.1, 29.3, 31.7, 33.3, 33.3, 34.2, 65.0, 112.5, 127.0, 131.6, 153.9; Anal. Calcd for $C_{19}H_{31}IN_2O$: C, 53.03; H, 7.26; N, 6.51, found: C, 53.24; H, 7.20; N, 6.49. IR (ATR, cm^{-1}) 3291.9 (OH).

4.7.5. 2-(1-Hydroxyhexyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide (**3c**)

From the corresponding benzimidazole (1.98 g, 8.5 mmol), the title compound was obtained as a colorless solid (2.79 g, 88%): Mp. 167–169 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 7.2 Hz), 1.23–1.60 (6H, m), 1.80–2.00 (2H, m), 4.11 (3H, s), 5.36–5.42 (1H, m), 6.43–6.44 (1H, m), 7.64–7.70 (2H, m), 7.95–8.02 (2H, m); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.5, 22.5, 25.0, 31.4, 33.0, 34.3, 65.0, 113.7, 127.0, 132.1, 153.5; HRMS (FAB$^+$) m/z calcd for $C_{15}H_{23}N_2O$ M^+ 247.1805, found. 247.1824.

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*4.7.6. 2-(1-Hydroxybutyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide (**3d**)*

From the corresponding benzimidazole (1.17 g, 5.73 mmol), the title compound was obtained as a colorless solid (1.87 g, 92%); Mp. 185–186 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.94 (3H, t, J = 7.2 Hz), 1.35–1.63 (2H, m), 1.79–2.00 (2H, m), 4.09 (6H, s), 5.40–5.47 (1H, m) 6.60 (1H, br s), 7.71–7.72 (2H, m), 8.00–8.06 (2H, m); ^{13}C NMR (126 MHz, DMSO-d_6) δ 2.1, 4.0, 14.7, 32.5, 66.9, 113.2, 126.6, 131.5, 152.6; HRMS (FAB$^+$) *m/z* calcd for $C_{13}H_{19}N_2O$ M$^+$ 219.1492, found. 219.1511.

*4.7.7. 2-(1-Hydroxy-3-phenylpropyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide (**3e**)*

From the corresponding benzimidazole (815 mg, 3.1 mmol), the title compound was obtained as a colorless solid (1.20 g, 96%) Mp. 185–187 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20–2.30 (2H, m), 2.68–2.78 (1H, m), 2.86–2.97 (1H. m), 2.90–2.93 (1H, m), 4.09 (6H, s), 5.43 (1H, s), 6.61 (1H, s), 7.08–7.16 (1H, m), 7.19–7.27 (4H, m), 7.64–7.70 (2H, m), 7.95–8.02 (2H, m); ^{13}C NMR (126 MHz, CD_3OD) δ 32.0, 32.9, 36.9, 65.5, 113.8, 127.4, 128.0, 129.4, 129.6, 133.4, 141.3, 154.0; HRMS (FAB$^+$) *m/z* calcd for $C_{18}H_{21}N_2O$ M$^+$ 281.1654, found. 281.1636.

*4.7.8. 2-(2-Ethyl-1-hydroxyhexyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide (**3f**)*

From the corresponding benzimidazole (1.45 g, 5.58 mmol), the title compound was obtained as a colorless solid (2.13 g, 92%): Mp. 166–168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10–1.33 (7H, m), 1.55–2.22 (7H, m), 2.21–2.30 (1H, m), 1.99 (1H, bs), 4.15 (6H, s), 5.21–5.26 (1H, m), 6.49 (1H, d, J = 4.5 Hz), 7.71 (2H, quint, J = 3.0 Hz), 8.02–8.07 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.5, 13.8, 21.3, 22.7, 28.0, 28.9, 33.5, 43.4, 67.2, 112.1, 127.1, 131.7, 154.6; HRMS (FAB$^+$) *m/z* calcd for $C_{17}H_{27}N_2O$ M$^+$ 275.2123, found. 275.2099.

*4.7.9. 2-(1-Hydroxy-2,2-dimethylpropyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide (**3g**)*

From the corresponding benzimidazole (837 mg, 3.84 mmol), the title compound was obtained as a colorless solid (1.12 g, 81%): Mp. 184–186 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07 (9H, s), 1.19–1.44 (13H, m), 4.11 (3H, s), 4.27 (3H, s), 5.24 (1H, d, J = 5.1 Hz), 6.58–6.61 (1H, m), 7.69–7.74 (2H, m), 7.97–8.01 (1H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.5, 33.9, 34.9, 72.8, 113.6, 113.9, 127.0, 127.1, 132.0, 132.9, 152.6; HRMS (FAB$^+$) *m/z* calcd for $C_{14}H_{21}N_2O$ M$^+$ 233.1654, found. 233.1661.

*4.7.10. 2-(Cyclopropyl(hydroxy)methyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide (**3h**)*

From the corresponding benzimidazole (379 g, 1.87 mmol), the title compound was obtained as a colorless solid (617 mg, 92%): Mp. 189–191 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (3H, t, J = 7.2 Hz), 1.19–1.44 (13H. m), 1.58–2.18 (3H, m), 4.20 (6H, s), 5.57 (1H, d, J = 4.2 Hz), 5.64 (1H, dt, J = 4.2 Hz, 9.9 Hz), 7.64 (4H, m); ^{13}C NMR (100 MHz, DMSO-d_6): δ 2.6, 4.5, 15.2, 33.1, 67.5, 113.8, 127.1, 132.0, 153.1; HRMS (FAB$^+$) *m/z* calcd for $C_{13}H_{17}N_2O$ M$^+$ 217.1341, found. 217.1350.

*4.7.11. 2-(Cyclohexyl(hydroxy)methyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide (**3i**)*

From the corresponding benzimidazole (245 mg, 1.0 mmol), the title compound was obtained as a colorless solid (197 mg, 51%): Mp. 189–190 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10–1.30 (6H, m), 1.57–1.64 (2H, m), 1.72–1.78 (1H, m), 1.90–2.07 (2H, m), 4.12 (6H, s), 5.1 (1H, dd, J = 8.3 Hz, 4.5 Hz), 6.44 (1H, d, J = 4.5 Hz), 7.64–7.70 (2H, m), 7.96–8.03 (2H, m); ^{13}C NMR (126 MHz, DMSO-d_6) δ 25.1, 25.1, 25.6, 27.7, 28.4, 32.6, 41.8, 68.7, 113.2, 126.5, 131.5, 152.5; HRMS (FAB$^+$) *m/z* calcd for $C_{16}H_{23}N_2O$ M$^+$ 259.1810, found. 259.1822.

*4.7.12. 2-(1-Hydroxy-3-methylbut-2-enyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide (**3j**)*

From the corresponding benzimidazole (350 mg, 1.62 mmol), the title compound was obtained as a yellow solid (510 mg, 88%): Mp. 200–202 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (3H, s), 1.95 (3H, s), 4.22 (6H, s), 5.44–5.48 (1H, m), 5.72 (1H, d, J = 4 Hz), 6.40 (1H, dd, J = 9 Hz, 4 Hz), 7.60–7.68 (4H, m); ^{13}C NMR (126 MHz, CD_3CD) δ 18.7, 26.0, 33.1, 64.0, 113.8, 120.2, 128.1, 133.4, 143.6, 153.6; HRMS (FAB$^+$) *m/z* calcd for $C_{14}H_{19}N_2O$ M$^+$ 231.1497, found. 231.1507.

*4.7.13. 2-(Hydroxy(2-nitrophenyl)methyl)-1,3-dimethyl-1H-imidazol-3-ium iodide (**4k**)*

From the corresponding imidazole (731 mg, 3.15 mmol), the title compound was obtained as a yellow solid (1.13 g, 96%): Mp. 175–177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.67 (6H, s), 6.85 (1H. s), 7.54 (1H, bs), 7.70 (2H, bs), 7.74 (1H, dt, J = 1.2, 7.5 Hz), 7.94 (1H, dt, J = 1.2, 7.5 Hz), 8.08 (2H, d, J = 7.8 Hz), 8.21 (1H, d, J = 7.8 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.7, 61.3, 123.2, 125.6, 129.1, 130.3, 132.2, 134.6, 144.2, 146.6; HRMS (FAB$^+$) *m/z* calcd for $C_{12}H_{14}N_3O_3$ M$^+$ 248.1030, found. 248.1051.

*4.7.14. 2-((4-(Dimethylamino)phenyl)(hydroxy)methyl)-1,3-dimethyl-1H-imidazol-3-ium iodide (**4m**)*

From the corresponding imidazole (685 mg, 2.95 mmol), the title compound was obtained quanititively as a yellow solid (1.1 g): Mp. 184–186 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.93 (6H, s), 3.87 (6H. s), 6.32 (1H, s), 6.77 (2H, d, J = 9.0 Hz), 7.15 (2H, d, J = 9.0 Hz), 7.51 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.1, 40.3, 65.3, 112.5, 122.5, 122.6, 126.7, 148.3, 150.8; HRMS (FAB$^+$) *m/z* calcd for $C_{14}H_{20}N_3O$ M$^+$ 246.1606, found. 246.1613.

*4.8. Synthesis of 2-(hydroxy(4-nitrophenyl)methyl)-1,3-dimethyl-1H-imidazol-3-ium iodide (**4l**)*

To a solution of 13a (18 mg, 0.078 mmol) in toluene (2 ml) in a sealed tube, iodomethane was added. The mixture was stirred at 115 °C for 9 h, and then cooled. The mixture was filtrated to obtain 15a (6 mg, 19%) as a yellow solid: Mp. 172–174 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 3.89 (6H,s), 6.62 (1H, s), 7.60 (2H, s), 7.65 (2H, d, J = 11.4 Hz), 8.31 (2H, d, J = 11.4 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.7, 63.2, 123.8, 123.9, 127.1, 144.3, 144.6, 147.4; HRMS (FAB$^+$) *m/z* calcd for $C_{12}H_{14}N_2O$ M$^+$ 248.1030, found.1021.

*4.9. General procedure for the synthesis of 4-acylquinazoline **6***

Under argon atmosphere, to a dry THF, DMF, or NMP solution (10 ml) of 4-chloroquinazoline (164 mg, 1 mmol) and azolium salts (1 mmol), a base (2 mmol) was added and stirred. The organic layer was extracted three times with ethyl acetate and then washed with saturated brine for one time. Then, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% ethyl acetate/*n*-hexane).

*4.9.1. 1-(Quinazolin-4-yl)octan-1-one (**6a**)*

Yellow oil (179 mg, 70%; entry 8, Table 2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.7 Hz), 1.30–1.39 (8H, m), 1.73–1.82 (2H, td, J = 7.4 14.7 Hz), 3.28 (2H, t, J = 7.4 Hz), 7.69–7.74 (1H, m), 7.92–7.98 (1H, m), 8.11 (1H, d, J = 8.6 Hz), 8.66 (1H, ddd, J = 8.6, 0.7, 0.3 Hz), 9.41 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 22.6, 23.8, 29.1, 29.2, 31.7, 40.2, 120.9, 126.3, 128.8, 129.3, 134.2, 152.0, 154.0, 159.9, 204.1; HRMS (FAB$^+$) *m/z* calcd for $C_{16}H_{21}N_2O$ (M + H)$^+$ 257.1648, found: 257.1666.

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*4.9.2. 1-(Quinazoline-4-yl)decan-1-one (**6b**)*

Yellow oil (157 mg, 63%; entry 7, Table 2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 6.0 Hz), 1.13–1.42 (m, 13H), 7.64 (1H, t, J = 15 Hz), 7.88 (1H, t, J = 15 Hz), 8.04 (1H, d, J = 9.0 Hz), 8.61 (1H, d, J = 9.0 Hz), 9.35 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 23.7, 27.1, 29.2, 29.4, 29.7, 31.8, 40.1, 120.1, 126.3, 128.8, 129.2, 134.1, 152.0, 154.0, 159.8, 204.1; HRMS (EI^+) m/z calcd for $C_{18}H_{24}N_2O$ M^+ 284.1889, found: 284.1880.

*4.9.3. 1-(Quinazolin-4-yl)hexan-1-one (**6c**)*

Yellow oil (98 mg, 43%; entry 9, Table 2): ^{1}H NMR (300 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.7 Hz), 1.30–1.39 (4H, m), 1.73–1.82 (2H, td, J = 7.4 14.7 Hz), 3.28 (2H, t, J = 7.4 Hz), 7.69–7.74 (1H, m), 7.92–7.98 (1H, m), 8.11 (1H, d, J = 8.6 Hz), 8.66 (1H, ddd, J = 8.6, 0.7, 0.3 Hz), 9.41 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.5, 23.4, 31.4, 40.1, 120.9, 126.3, 128.8, 129.3, 134.2, 151.9, 154.0, 159.9, 204.1; HRMS (FAB^+) m/z calcd for $C_{14}H_{17}N_2O$ $(M + H)^+$ 229.1341, found: 229.1334.

*4.9.4. 1-(Quinazolin-4-yl)butan-1-one (**6d**)*[16]

Yellow oil (68 mg, 34%; entry 10, Table 2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (3H, t, J = 7.5 Hz), 1.82 (2H, q, J = 7.5 Hz), 3.28 (2H, t, J = 7.5 Hz), 7.72 (1H, t, J = 7.5 Hz), 7.96 (1H, t, J = 7.5 Hz), 8.11 (1H, d, J = 8.6 Hz), 8.67 (1H, d, J = 8.6 Hz), 9.42 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 17.2, 42.0120.6, 126.3, 128.8, 129.3, 134.2, 152.0, 154.0, 159.8, 204. HRMS (FAB^+) m/z 201 M^+.

*4.9.5. 3-Phenyl-1-(quinazolin-4-yl)propan-1-one (**6e**)*

Yellow oil (29 mg, 11%; entry 11, Table 2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 (2H, t, J = 7.5 Hz), 3.69 (2H, t, J = 7.5 Hz), 7.13–7.31 (5H, m), 7.70 (1H, t, J = 7.8 Hz), 7.94 (1H, t, J = 7.8 Hz), 8.14 (1H, d, J = 4.3 Hz), 8.66 (1H, dt, J = 0.6, 4.3 Hz), 9.39 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.8, 41.6, 121.0, 126.3, 126.5, 128.55, 128.6, 128.9, 129.5, 134.3, 140.8, 152.2, 154.1, 159.2, 203.1; HRMS (FAB+) m/z calcd for $C_{17}H_{15}N_2O$ $(M + H)^+$ 263.1184, found. 263.1176.

*4.9.6. 3-Methyl-1-(quinazolin-4-yl)but-2-en-1-one (**6j**)*

Yellow oil (26 mg, 12%; entry 16, Table 2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (3H, s), 2.39 (3H, s), 7.08 (1H, s), 7.69 (1H, t, J = 7.5 Hz), 7.94 (1H, t, J = 7.5 Hz), 8.10 (1H, d, J = 8.7 Hz), 8.63 (1H, d, J = 8.7 Hz), 9.39 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.7, 28.6, 121.8, 126.6, 128.8, 128.9, 134.2, 151.8, 153.9, 162.2, 162.4, 191.3; HRMS (FAB^+) m/z calcd for $C_{13}H_{13}N_2O$ $(M + H)^+$ 213.1028, found. 213.1034.

*4.9.7. (2-Nitrophenyl)(quinazolin-4-yl)methanone (**6k**)*

Colorless solid (112 mg, 40%; entry 17, Table 2): Mp. 230–231 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.87 (4H, m), 7.69 (1H, dt, J = 1.5, 6.7 Hz), 8.13 (1H, d, J = 8.7 Hz), 8.20 (1H, d, J = 8.1 Hz), 9.06 (1H, dd, J = 0.6, 8.7 Hz), 9.20 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.6, 123.9, 126.5, 128.8, 129.9, 130.3, 131.4, 134.5, 135.9, 147.1, 152.1, 153.5, 158.1, 194.0; HRMS (FAB^+) m/z calcd for $C_{15}H_{10}N_3O_3$ $(M + H)^+$ 280.0722, found. 280.0720.

*4.9.8. (4-(Dimethylamino)phenyl)(quinazolin-4-yl)methanone (**6m**)*[6,17]

Using 4-chloroquinazoline (161 mg, 0.98 mmol), the title compound was obtained as a yellow solid (184 mg, 68%): Mp. 157–159 °C; 1H NMR (300 MHz, CDCl3) δ 3.08 (6H, s), 6.65 (2H, d, J = 9.3 Hz), 7.60 (1H, dt, J = 0.9, 6.9 Hz), 7.81 (2H, d, J = 9.3 Hz), 7.93 (1H, dt, J = 1.5, 6.9 Hz), 8.02 (1H, dd, J = 0.9, 1.5 Hz), 8.05 (1H, dd, J = 0.9, 1.5 Hz), 8.12 (1H, d, J = 8.4 Hz), 9.39 (1H, s); 13C NMR (126 MHz, CDCl3) δ 40.0, 110.8, 122.3, 122.9, 126.3, 128.3, 128.8, 132.9, 150.9, 154.0, 154.3, 166.0, 190.5.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.11.071.

References

1. (a) Patel AB, Raval R. *Importance of Heterocycles in Medicinal Chemistry*. LAP Lambert Academic Publishing; 2015;
   (b) Li JJ. *Heterocyclic Chemistry in Drug Discovery*. Wiley; 2013.
2. (a) Saini MS, Kumar A, Dwivedi J, Singh R. *Int J Pharm Sci Res*. 2013;4:66–77;
   (b) Dua R, Shrivastava S, Sonwane SK, Srivastava SK. *Adv Biol Res*. 2011;5:120–144;
   (c) Taylor DC. *Heterocycles*. 1999;50:5.
3. (a) Suzuki Y, Murofushi M, Manabe K. *Tetrahedron*. 2013;69:470–473;
   (b) Suzuki Y, Toyota T, Miyashita A, Sato M. *Chem Pharm Bull*. 2006;54:1653–1658.
4. (a) Miyashita A, Matsuda H, Suzuki Y, Iwamoto K, Higashino T. *Chem Pharm Bull*. 1994;42:2017–2022;
   (b) Miyashita A, Suzuki Y, Iwamoto K, Higashino T. *Chem Pharm Bull*. 1998;46:390–399;
   (c) Miyashita A, Suzuki Y, Iwamoto K, Oishi E, Higashino T. *Heterocycles*. 1998;49:405–413;
   (4d) Miyashita A, Matsuda H, Higashino T. *Chem Pharm Bull*. 1992;40:43–48.
5. Suzuki Y, Fukuta Y, Ota S, Kamiya M, Sato M. *J Org Chem*. 2011;76:3960–3967.
6. Kuroiwa K, Ishii H, Mastuno K, Asai A, Suzuki Y. *ACS Med Chem Lett*. 2015;6:287–291.
7. Miyashita A, Kurachi A, Matsuoka Y, et al. *Heterocycles*. 1997;44:417–426.
8. Taylor EC, Chittenden ML, Martin SF. *Heterocycles*. 1973;1:59–65.
9. (a) Giovannini R, Cui Y, Doods H, Ferrara M, Just S, Kuelzer R, Lingard I, Mazzaferro R, Rudolf K. PCT Int. Apple., 2014184275. 20 Nov 2014; (b) Soussi MA, Provot O, Bernadat G, et al. *ChemMedChem*. 2015;10:1392–1402;
   (c) Anderson C, Moreno J, Hadida S. *Synlett*. 2014;25:677–680;
   (d) Fan L, Wang T, Tian Y, et al. *Chem Commun*. 2016;52:5375–5378.
10. (a) Selvam TP, Kumar PV. *Res Pharm*. 2015;1:1–21;
    (b) Ravez S, Castillo-Aguilera O, Depreux P, Goossens L. *Expert Opin Ther Pat*. 2015;25:789–804;
    (c) Asif M. *Int J Mater Chem*. 2014;2014:395637;
    (d) Wang D, Gao F. *Chem Cent J*. 2013;7:95.
11. (a) Becke A. *J Chem Phys*. 1993;98:5648–5652;
    (b) Lee C, Yang W, Parr RG. *Phys Rev B*. 1998;37:785–789.
12. (a) Cossi M, Scalmani G, Rega N, Barone V. *J Chem Phys*. 2002;117:43–54;
    (b) Tomasi J, Mennucci B, Cammi R. *Chem Rev*. 2005;105:2999–3093.
13. Frisch MJ, Trucks GW, Schlegel HB, et al. *Gaussian 09, Revision D.03*. Wallingford, CT: Gaussian, Inc.; 2010.
14. (a) Reed AE, Curtiss LA, Weinhold F. *Chem Rev*. 1988;88:899–926;
    (b) Reed AE, Weinstock RB, Weinhold F. *J Chem Phys*. 1985;83:735–746;
    (c) Reed AE, Weinhold F. *J Chem Phys*. 1985;83:1736–1749;
    (d) Reed AE, Weinhold F. *J Chem Phys*. 1983;78:4066–4073.
15. Banno Y, Hara R, Tokunoh R. PTC Int. Appl., 2009110520. 11 Sep 2009.
16. Yan Y, Zhang Y, Feng C, Zha Z, Wang Z. *Angew Chem Int Ed*. 2012;51:8077–8081.
17. Miyashita A, Matsuda H, Iijima C, Higashino T. *Chem Pharm Bull*. 1992;40:43–48.