**Tandem Buildup of Complexity of Aromatic Molecules Through Multiple Successive Electrophile Generation in One Pot, Controlled by Varying the Reaction Temperature**

| Journal:       | *Organic & Biomolecular Chemistry*                     |
|----------------|--------------------------------------------------------|
| Manuscript ID  | OB-ART-10-2015-002240.R1                              |
| Article Type:  | Paper                                                  |
| Date Submitted by the Author: | 16-Dec-2015                                           |
| Complete List of Authors: | Sumita, Akinari; The University of Tokyo, Graduate School of Pharmaceutical Sciences  
                          Otani, Yuko; The University of Tokyo, Graduate School of Pharmaceutical Sciences  
                          Ohwada, Tomohiko; The University of Tokyo, Graduate School of Pharmaceutical Sciences |
Tandem Buildup of Complexity of Aromatic Molecules Through Multiple
Successive Electrophile Generation in One Pot, Controlled by Varying the
Reaction Temperature

Akinari Sumita, a Yuko Otani, a Tomohiko Ohwada * a

Abstract

While some sequential electrophilic aromatic substitution reactions, known as tandem/domino/cascade reactions, have been reported for construction of aromatic single skeletons, one of the most interesting and challenging possibilities remains the one-pot build-up of complex aromatic molecule from multiple starting components, i.e., ultimately multi-component electrophilic aromatic substitution reactions. In this work, we show how tuning of the leaving group ability of phenolate derivatives from carbamates and esters provides a way to successively generate multiple unmasked electrophiles in a controlled manner in one pot, simply by varying the temperature. Here, we demonstrate autonomous formation of up to three bonds in one pot and formation of two bonds arising from a three-component electrophilic aromatic substitution reaction. This result provides a proof-of-concept of our strategy.
applicable for self-directed construction of complex aromatic structures from multiple simple molecules, which can be a potential avenue to realize multi-component electrophilic aromatic substitution reactions.

(146 words)
**Introduction**

Assembly of multiple functionalized aromatic structures into a single molecule is of interest both in drug design, as exemplified by the integration of multiple functionalized aromatic pharmacophores. For this purpose, the idea of sequentially connecting structurally simple aromatic compounds seems an attractive approach. Electrophilic aromatic substitution (S$_E$Ar) reactions can be used for individual functionalization of several different aromatic moieties in a single molecule (Chart 1). The conventional methodology would be convergent connection of several substituted aromatic compounds through electrophilic centers, as shown in Chart 1(a). However, this approach often requires workup/isolation processes to minimize side reactions or to remove excess reactants or by-products. For example, the reactivity of electrophiles is frequently insufficient to drive the reaction to completion, so an excess amount of aromatic compound(s) is often used to promote the intermolecular S$_E$Ar reaction (vide infra). On the other hand, one of the most interesting and challenging possibilities is one-pot build-up of a complex aromatic molecule from multiple starting components, i.e., ultimately **multi-component electrophilic aromatic substitution reactions** (Chart 1(b)). This strategy requires precise temporal control of bond formation via multiple sequential electrophilic aromatic substitution reactions in order to increase molecular complexity in a precisely defined manner. Several sequential electrophilic aromatic substitution reactions, known as tandem/domino/cascade reactions, have already been reported for construction of aromatic single skeletons such as indoles, indenes, dihydroindenes, indanones, fluorenes, carbazoles, di- and triphenylmethane, naphthoquinones, and other skeletons. However, most of these reactions are limited to only two kinds of reactions, i.e., involving formation of two bonds, often via intermolecular-intramolecular or intramolecular-intermolecular sequences (Chart
The main reason for this is that most of the reactions require the use of an excess amount of aromatic compound(s) to effectively promote the intermolecular S<sub>E</sub>Ar reaction, and thus the following S<sub>E</sub>Ar reaction is inevitably restricted to a *kinetically favorable intramolecular reaction* (Chart 1(c-1)), or vice versa (Chart 1(c-2)). Low reactivity of electrophiles is also a reason why many electrophilic reactions are unsuitable for multi-component electrophilic aromatic substitution reactions: specifically, the second S<sub>E</sub>Ar reaction can start before the first S<sub>E</sub>Ar reaction is completed, and therefore the chemoselectivity is impaired. Thus, current methodology in this field is commonly restricted to the formation of two bonds, of which one is intramolecular.

**Chart 1.** (a) Conventional step-by-step build-up of aromatic molecules through electrophilic substitution. (b) Hypothetical multi-component aromatic electrophilic reactions in one pot. (c-1/c-2) Previous examples of two-step tandem reactions.

One way to achieve multi-component electrophilic aromatic substitution reactions would be precise temporal control of the generation of highly reactive electrophiles, which can react rapidly with the target aromatic compound even when the target
aromatic compound is present only in a stoichiometric amount.

An approach to the generation of such electrophiles has been to transform masked (deactivated or latent) electrophiles into active (unmasked) electrophiles. For example, ureas and carbamates can be regarded as masked isocyanate cations that can be activated via N-C and O-C bond cleavage. There have been a few reports of application of masked isocyanate cations to $S_E\text{Ar}$ reactions. These $S_E\text{Ar}$ reactions of masked isocyanate cations have been used for intramolecular reactions, such as construction of dihydroisoquinolones or isoindoline-1-one, but they are not suitable for intermolecular $S_E\text{Ar}$ reactions due to the moderate yields, requirement of excess amounts of aromatic compounds, and the need for heating. These are obstacles for application to tandem/cascade/domino reactions. To our knowledge, there are few reports of sequential multiple unmasking reactions, mainly because the unmasking reaction rate is usually dependent on the substrate structure, not on the leaving group, resulting in severe limitations on suitable reactants. Thus, for the development of multi-component $S_E\text{Ar}$ reactions, new chemical species of leaving groups are required, which can control the unmasking reaction rates.

In this paper, we report successive reaction-temperature-controlled generation of multiple unmasked electrophiles, particularly isocyanate cations and related cations, leading to autonomous sequential electrophilic aromatic substitution reactions. To achieve this, we focused on control of the bond strength of leaving groups in carbamates as a strategy to obtain differential leaving ability in order to control the generation of multiple electrophiles. We demonstrated autonomous formation of up to three bonds in one pot and formation of two bonds arising from a three-component electrophilic aromatic substitution reaction. The present study provides a proof-of
-concept of our strategy applicable for self-directed construction of complex aromatic structures from multiple simple molecules, which can be a potential avenue to realize multi-component electrophilic aromatic substitution reactions, as illustrated in Chart 1(b).

**Results and discussion**

**Tuning of leaving groups in aromatic amidation and acylation**

We recently have shown that methyl salicylate is a good leaving group from carbamate (which is a stable functional group) under relatively strong acid-catalyzed conditions. The methyl ester group, located at the ortho position with respect to the phenolic oxygen atom, assists partial protonation of, or H-bonding to, the phenolic oxygen atom, which weakens the C-O (phenolic) bond, resulting in ready C-O bond cleavage to generate isocyanate cation at 20°C (20°C for 90 minutes: **1b**, Figure 1(a)).

We demonstrated previously that N-H and N-alkyl or N-aryl isocyanate cations show different reactivities: N-alkyl and N-aryl isocyanate cations are generated from the carbamates more slowly than N-H isocyanate cations. While multiple amidation can be achieved by using isocyanate cations with different reactivities, we found here that tuning of the leaving group ability to generate the isocyanate cations is a more effective strategy to achieve multiple amidations.

Indeed, we found that when the ester group is substituted at the para-position with respect to the phenolic oxygen atom (**1a**, Figure 1(a)), C-O (phenolic) bond cleavage occurs slowly even on heating (at 40°C, 26 hours). Therefore, change of the reaction temperature can be used to control the time of generation of even the same reactive electrophile, the isocyanate cation.
(a) Comparison between ortho- and para- ester in salicylates

\[
\begin{align*}
&\text{MeOOC}_\text{para} \quad \text{MeOOC}_\text{ortho} \\
&\text{MeOOC}_\text{Ph} \quad \text{MeOOC}_\text{Ph}
\end{align*}
\]

1a 2 3a 64% 1a 6% (recovery)

(b) Comparison between phenol containing one ester group and two ester groups

\[
\begin{align*}
&\text{MeOOC}_\text{para} \quad \text{MeOOC}_\text{ortho} \\
&\text{MeOOC}_\text{Ph} \quad \text{MeOOC}_\text{Ph}
\end{align*}
\]

1c 4 3b 85% 1c 9% (recovery)

1d 4 3b 84%

a) Isolation Yields b) NMR Yield.

**Figure 1. Control of amide formation based on different leaving abilities**

Because the substitution position of ester groups dramatically changes the C-O bond cleavage reaction rates of carbamates bearing methyl salicylates, we expected that adding another ester group into the leaving group (methyl salicylate) would increase the unmasking reaction rate. It turned out that dimethyl 4-hydroxyisophthalate (1d), containing two ester groups at the ortho- and para-positions with respect to the phenolic oxygen atom, is a better leaving group than methyl salicylate (1c). In the case of 1d, the leaving group is cleaved to form isocyanate cation even at 0°C, and the reaction is completed within 20 minutes (Figure 1(b)). Thus, at 0°C, the reaction of methyl salicylate (1c) can be differentiated from the reaction of diester 1d.

This concept is also applicable to differentiate between esters and carbamates, that is,
between generation of acyl cations and isocyanate cations. Because the C-O bond strength in esters 1e is weaker than that in carbamates 1c, the C-O bond in esters is cleaved faster than the C-O bond in carbamates: this enables temperature control of the generation of acyl cation (at 0°C) and isocyanate cation (at 20°C) (Figure 2). Thus, we can control the speed of unmasking to generate different reactive electrophiles simply by changing the temperature.

![Diagram of reaction between 1c carbamates and 1e esters](image)

**Figure 2. Comparison of amide formation rate and ketone formation rate**

**Activation of leaving group through protonation and hydrogen bonding**

We conducted kinetic studies to characterize the difference in leaving ability between the monoester leaving group (see 1b) and diester leaving group (see 1f). Figure 3 shows the dependence of the reaction profiles on the acidity of the medium. In the case of monoester leaving group (1b), as the acidity is increased, the reaction rate increases to a broad maximum, and then decreases in the strong acidity region. O,O-Diprotonation of salicyl carbamates (like TS-1b’, Figure 3a) can be observed by proton NMR spectroscopy in strong acid (\( \text{pH}_0 = 14 \)). Cleavage of C-O bond of the diprotonated species will be difficult because of the generation of one neutral species
(methyl salicylate) and one rather unstable dicationic species (O-protonated carbamate dication). Therefore, this means that the monocationic species (TS-1b, Figure 3a) rather than the diprotonated species (TS-1b’, Figure 3a) is involved in the bond dissociation transition state.\textsuperscript{13}

\[ \begin{align*}
\text{(a) the reaction of monoester 1b} & & \text{(b) the reaction of diester 1f} \\
\text{TS-1b’ (dicationic)} & & \text{TS-1f’ (another dication)}
\end{align*} \]

**Figure 3.** Acidity-dependence of the reaction profiles of different leaving groups (measured at 31°C for (a), and at -6°C for (b))

On the other hand, in the case of diester leaving group (1f), as the acidity increased, the reaction rate increases monotonically to a broad maximum from relatively weak acidic region (-$H_0 = 10$) to strong acidic region (-$H_0 = 14$) (Figure 3b). Because ortho-monoester-substituted carbamate (1b) is diprotonated under strong acidic region...
disubstituted carbamate (1f) also can be diprotonated under strong acidic region \((-H_0 = 14)\). When the carbonyl oxygen atom of the carbamate functional group of diester-substituted carbamate (1f) is protonated (TS-1f’, Figure 3), the C-O bond cleavage of this diprotonated species will be difficult because of the generation of one neutral species and one rather unstable gitonic (close) dicationic isocyanate cation species. Therefore, the C-O bond cleavage of the diprotonated species will take place through the alternative diprotonated state TS-1f rather than the dication state TS-1f’ (Figure 3).

**Computational support for leaving group activation**

These kinetic results are supported by the results of calculations (Figure 4). The calculated energy differences are shown in terms of $\Delta\Delta G$ at 25°C (298K), together with the $\Delta\Delta H$.

In the continuum environment of TfOH, there are several possible stable conformers of diester-substitued carbamate 1f in protonated states, because the diester carbamate functionalities have several basic sites. The ester carbonyl oxygen atom(s), the most basic sites, is mono-protonated or are di-protonated, such cationic species, 1f-SM$_0$-H$^+$ and 1f-SM$_0$-2H$^+$ are most stable (Figure 4). On the other hand, a proton can switch the protonation site to the less basic phenolic oxygen atom, and such isomeric conformers, 1f-SM-H$^+$ and 1f-SM-2H$^+$ are destabilized as compared with the most stable conformers (1f-SM$_0$-H$^+$, 1f-SM$_0$-2H$^+$). Destabilization is similar in magnitude in both cases of the monocation and the dication, and the energy gaps are attainable probably because of formation of intramolecular hydrogen bonding. Through the intervention of these equilibrating species, 1f-SM-H$^+$ and 1f-SM-2H$^+$, the transition states of C-O bond dissociation can be obtained (Figure 4): the
activation energy from the most stable conformer 1f-SM_0^-2H^+ through the dicationic state (1f-TS-2H^+) (\(\Delta\Delta G_{298K}\): 18.6 kcal/mol; \(\Delta\Delta H\): 19.1 kcal/mol) is lower than that from 1f-SM_0^-H^+ through the monocaticonic state (1f-TS-H^+) (\(\Delta\Delta G_{298K}\): 22.2 kcal/mol; \(\Delta\Delta H\): 22.2 kcal/mol). Other calculation levels (M06, M06-HF, B3LYP, B3PW91, MP2) also converged to similar results (Supporting Information, Figure SI-1, 2). Thus, the observed acidity-rate relationship (Figure 3) can be rationally explained. Moreover, the difference in energy between the dicationic pathway and monocaticonic pathway amounts to 3 kcal/mol, which means that the reaction pathway of C-O bond dissociation through the dicationic state should be dominant.

![Diagram of C-O bond cleavage step of 1f](image)

**Figure 4. Calculated energy diagram of C-O bond cleavage step of 1f**

(CPCM-M06-2X/6-311++G(d,p)//CPCM-B3LYP/6-31+G(d))

The reaction rate of ester (1e) could not be measured due to the very rapid
unmasking rate; however, the calculation results support a marked difference in reaction rates between the relevant carbamate and ester (Figure 5). From the calculation result, the activation energy of C-O bond cleavage of the monoester-substituted carbamate 1b from the most stable conformer (SM$_0$-1b) through the equilibrating minor monocationic species (SM-1b), $\Delta \Delta G_{298K}$: 23.0 kcal/mol; $\Delta \Delta H$: 24.5 kcal/mol, is higher than that of C-O bond cleavage of the ester from the more stable monocationic species (SM-1e), $\Delta \Delta G_{298K}$: 13.1 kcal/mol; $\Delta \Delta H$: 13.7 kcal/mol. This may be partially because the carbamate is more stable than the ester due to Y-type conjugation,$^{11i, 15}$ and thus more energy is needed to break the stable C-O bond of the carbamate. In the case of ester, it is worthwhile to note that when the intramolecular hydrogen bonding is formed to the phenolic oxygen atom, the conformer SM-1e is the more stable than the isomeric SM$_0$-1e (Figure 5). Therefore, an ester compound bearing methyl salicylester group can be easily cleavage its O-C bond. These calculations are consistent with the experimental results: the reaction of ester (1e) is dramatically faster than that of monoester-substituted carbamate 1b, and 1e is distinctly faster than diester-substituted carbamate 1f. Other calculation levels (M06, MP2) also support this conclusion (Supporting Information, Figure SI-3, 4) and the observed relationship (Figure 2).
Temperature control of multiple electrophile generation, enabling two-step buildup of complexity of aromatic molecules

Based on the above findings, we considered that temperature control of unmasking of electrophiles could be applied to build-up aromatic molecular complexity in one-pot reactions (Figures 6-8 and Tables 1-3). First, we explored formation of two bonds.

**Double aromatic amidations**

Figure 6 shows a representative example of build-up of two kinds of aromatic amide molecules. Mixing of 4 and 5 in the presence of TfOH produced compound 7 in 86% yield (Figure 6(a), in which the reaction temperature was changed from 0°C to 20°C).

First, the corresponding isocyanate cation (4-cation) was generated from carbamate bearing ortho, para-disubstituted phenol at 0°C, and then the electron-rich aromatic ring (magenta) of 5 reacted with the resulting isocyanate cation (blue) to form a C-C
bond in the aromatic amide structure 6 (red bond) (Figure 6(b)). Under cooling (0°C), the carbamate containing para-monosubstituted phenol did not uncage to form the isocyanate cation (4-cation). When the reaction mixture was warmed to room temperature (20°C), the second isocyanate cation (6-cation, red) was generated from the carbamate containing para-monosubstituted phenol (6), and the second aromatic compound (orange) reacted with the isocyanate cation (6-cation) to form a C-C bond in the aromatic amide structure, affording 7 in an intramolecular manner in this example (red bond) (Figure 6(b)). The yield shown is that over the two steps; thus, the average yield of each reaction is larger than 93%.

Figure 6. Formation of two amide bonds through temperature-controlled multiple electrophile generation: (a) overall reaction (b) individual steps
Table 1. Two-step buildup of complexity of aromatic molecules by dual amidation

| Entry | Substrates | Reaction Temperature 1 | Intermediate | Reaction Temperature 2 and 3rd substrate | Final Product |
|-------|------------|------------------------|--------------|------------------------------------------|---------------|
| 1     | 4 + 5      | 0°C                    | 6            | 20°C                                     | 7: 86%        |
| 2     | 8 + 5      | 0°C                    | 9            | 20°C                                     | 10: 36%       |
| 3     | 11 + 5     | 0°C                    | 12           | 20°C                                     | 13: 55%       |
| 4     | 14 + 15    | 0°C                    | 16           | 17                                       | 18: 67%       |
| 5     | 4 + 19     | 0°C                    | 20           | 21                                       | 22: 62%       |
| 6     | 14 + 23    | 0°C                    | 24           | 25                                       | 25: 48%       |

The generality of this sequential dual amidation reaction was examined and the results are shown in Table 1, which supports the feasibility of multiple intermolecular or intramolecular amidation reactions. Because the reaction temperature (20°C) is not so high, ethyl carbamate ($^{12}$), ester groups ($^{14}$ and $^{16}$), and a methoxy group ($^{15}$)
can be tolerated; the former substituents can generate electrophile species, and the latter substituent can be demethylated. Examples of successive double intermolecular reactions were also obtained (entries 4 and 5, Table 1). After the first S_{E}Ar reaction was completed (the formation of 16 or 20), one aromatic molecule (17 or 21) was added and the reaction mixture was warmed to 20°C to produce a double amidation product (18 and 22), respectively. Importantly, a three-component reaction to make two amide bonds can be realized (Entry 6, Table 1): when TfOH was added into a mixture of three components (14, 23, 26) at 0°C and then at 20°C, the product 25 was obtained, though in moderate yield (overall yield for the two step reaction is 48%). One of the (equivalent) aromatic rings of the substrate 23 can react with the first electrophile (generated at 0°C from 14), leading to the intermediate 24 smoothly, because we used a stoichiometric amounts of the aromatic substrate (23) and the electrophile (14), to minimize side reactions. Then, the intermediate 24 reacted with the second electrophile, generating from 26 at 20°C, to give the compound 25. This result demonstrates that the strategy of tuning of the leaving group ability of masked electrophiles, e. g., the phenolate derivatives, should be valid for real multi-component electrophilic aromatic substitution reactions. The average yield of each reaction ranged from 60% to 93% (Table 1).

**Sequential aromatic acylation-amidation**

Figure 7 shows a representative example of one-pot build-up of aromatic ketone and aromatic amide molecules. Mixing of 27 and 5 in the presence of TfOH produced compound 29 in 79% yield, by means of a change of the reaction temperature from 0°C to 20°C (Figure 7(a)). First, the corresponding acyl cation (27-cation) was generated from the carbamate bearing ortho-substituted phenol at 0°C, and then the
electron-rich aromatic ring (magenta) of 5 reacted with the resulting acyl cation (blue) to form a C-C bond in the aromatic ketone structure 28 (red bond)(Figure 7(b)). At 0°C, the carbamate containing para-monosubstituted phenol did not decompose to isocyanate cation. However, on warming the reaction mixture to room temperature (20°C), the second isocyanate cation (28-cation, red) was generated from the carbamate containing para-monosubstituted phenol (28), and the second aromatic compound (orange) reacted with the resulting isocyanate cation (28-cation) in an intramolecular manner to form an aromatic amide bond (red bond in product 29) (Figure 7(b)). Again the yield shown is the two-step yield, and the average yield of each reaction was larger than 89%.

Figure 7. Ketone and amide bond formations through temperature control of multiple electrophile generation: (a) overall reaction (b) individual steps
The generality of this sequential acylation-amidation reaction was examined and the results are shown in Table 2, which supports the feasibility of multiple intermolecular or intramolecular acylation-amidation reactions. Substrates bearing a trifluoromethyl group (27) or an ester group (30) can produce electrophile species, but because of the low temperature (0°C to 20 °C), acylation-amidation reactions are accomplished without interference from these functional groups. After the first S_{E}Ar reaction was completed (the formation of 36 or 39), the aromatic substrate (37 or 40) was added, and therefore three kinds of starting materials are combined sequentially into a single aromatic molecule (38 or 41) in one pot. The average yield of each reaction ranged
from 77% to 89%.

**Formation of three bonds in a one-pot reaction**

Finally, we demonstrate the formation of three inter- and intramolecular bonds constituting ketone/amide functionalities in one pot (Figure 8). The first electrophiles (blue) are generated from ester (27) containing ortho-mono-substituted phenol (methyl salicylate) (Figure 8(a)) or carbamate (4) (Figure 8(b)) containing ortho, para-disubstituted phenol at 0°C, followed by generation of the second electrophiles (red) from carbamate (36 or 20) containing ortho-monosubstituted phenol at 20°C for around 30 min. The third electrophiles (green) are generated very slowly (in around half a day) from carbamates (42 or 44) containing para-monosubstituted phenol at 20°C. As described above, these combined reactions enable temporally controlled generation of highly reactive electrophiles (blue, red, and green), which react rapidly with one equivalent of the target aromatic compounds (pink, orange, and brown).
(a) ketone-amide-amide formation

(b) amide-amide-amide formation

Figure 8. Temperature control of multiple electrophile generation, enabling three-step buildup of complexity of aromatic molecules

((a) ketone □ amide □ amide; (b) amide □ amide □ amide).
The desired compounds were obtained in relatively good yields (43: 56%; 45: 53%) (these yields are three-step yields, so the average yield in reaction (a) is 82% and that in reaction (b) is 81%, respectively). Thus, we can control the unmasking reaction rates and the time of generation of highly reactive electrophiles.

Although the third electrophilic reaction was intramolecular and the third component (5) was added after the first S$_E$Ar reaction between the first and second components was completed, three components were combined into a single aromatic molecule in one pot with high regioselective formation of three bonds.

This reaction design is, therefore, a potential avenue to realize ultimate multi-component electrophilic aromatic substitution reactions (as shown in Chart 1(b)).

**Conclusion**

Tuning of the leaving group ability of phenolate derivatives from carbamates (1a-1d) and ester (1e) enables temporal control of the generation of multiple electrophiles (unmasking) simply by appropriate selection of the reaction temperature, so that autonomous sequential electrophilic aromatic substitution reactions can proceed in one pot. This chemistry thus allows individual functionalization of several different aromatic moieties in one molecule by means of multiple electrophilic aromatic substitution reactions, affording complex aromatic assemblies in one pot. While the number of bonds that can be formed is unlimited in theory, in the present work, we demonstrated autonomous formation of up to three bonds in one pot, and we realized one example of three-component reaction to make two amide bonds. In order to use this system for practical reactions applicable to synthesis of libraries of compounds, it will be necessary to reduce the amount of acid and to design sophisticated leaving
group systems. Nevertheless, in this work, we have demonstrated the conceptual validity of one-pot build-up of complex aromatic molecule from multiple starting components, ultimately leading to multi-component electrophilic aromatic substitution reactions (Chart 1(b)).
Acknowledgments: This work was supported by University of Tokyo. The computations were performed at the Research Center for Computational Science, Okazaki, Japan. We thank the computational facility for generous allotments of computer time.

Experimental Procedure

General Procedures

Melting points were determined with a Yanaco micro melting point apparatus without correction. $^1$H- (400 MHz) and $^{13}$C- (100 MHz) NMR spectra were recorded on a Bruker Avance400. Chemical shifts were calibrated with tetramethylsilane as an internal standard or with the solvent peak, and are shown in ppm (ppm) values, and coupling constants are shown in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, dq = double quartet, h = hextet, m = multiplet, and brs = broad singlet. Electron spray ionization time-of-flight mass spectra (ESI-TOF MS) were recorded on a Bruker micrOTOF-05 to give high-resolution mass spectra (HRMS). All reagents were commercially available and used without further purification, unless otherwise noted. Flash column chromatography was carried out on silica gel (silica gel (40–63µm)). The combustion analyses were carried out in the microanalytical laboratory of this department.

Preparation of Substrates

Preparation of dimethyl 4-((diphenylcarbamoyl)oxy)isophthalate (4)

To a solution of dimethyl 4-hydroxyisophthalate (698.2 mg, 3.32 mmol) in $i$Pr$_2$NEt
(0.65 mL), diphenylcarbamic chloride (717.8 mg, 3.10 mmol) was added at rt. The whole mixture was stirred for 13 hours at rt. After the reaction completed, added 2M aqueous solution of HCl (40 mL). Then extracted with CH₂Cl₂ (40 mL x 3). The organic phase was washed with brine (40 mL), dried over Na₂SO₄, and the solvent was evaporated under reduced pressure to give a residue, which was flash column-chromatographed on silica-gel (eluent: EtOAc/n-Hexane = 1/2) to afford dimethyl 4-((diphenylcarbamoyl)oxy)isophthalate (4) (1223.8 mg, 3.02 mmol, 97%) as a colorless solid. Mp. 158.9-159.7°C (colorless needles, recrystallized from CH₂Cl₂/n-Hexane).

**¹H-NMR (CDCl₃, 400 MHz) δ (ppm):** 8.649 (1H, d, J = 2.0 Hz), 8.173 (1H, dd, J = 8.4, 2.0 Hz), 7.448-7.352 (8H, m), 7.265-7.197 (3H, m), 3.933 (3H, s), 3.920 (3H, s).

**¹³C-NMR (CDCl₃, 100 MHz) δ (ppm):** 166.10, 164.86, 154.82, 152.75, 142.75, 135.13, 133.67, 129.60, 128.27, 127.23 (br), 124.67, 124.56, 52.98, 52.92.

HRMS (ESI-TOF, [M+Na]⁺): Calcd. for C₂₃H₁₉NNaO₆⁺: 428.1105. Found: 428.1105. Anal. Calcd. for C₂₃H₁₉NO₆: C, 68.14; H, 4.72; N, 3.46. Found: C, 67.79; H, 4.90; N, 3.32.

**Preparation of methyl 4-(((2-(2,5-dimethylphenyl)-2-phenylethyl)-carbamoyl)oxy)benzoate (5)**

To a solution of para-xylene (5 mL) in TfOH (10 mL), 2-amino-1-phenylethanol (1011.2 mg, 7.37 mmol) was added at 0°C. The whole was warmed up from 0°C to 20°C, and stirred for 2 hours. After the reaction completed, the whole was poured into ice-water and added 2M aqueous solution of NaOH (50 mL). This reaction mixture was extracted with CH₂Cl₂ (30 mL x 4). The organic phase was washed with brine (30 mL), dried over Na₂SO₄, and the solvent was evaporated under reduced pressure to give a yellow crude (1784.3 mg). Then this crude was added to the solution of dimethyl 4,4'-(carbonylbis(oxy))dibenzoate (2109.0 mg, 6.39 mmol) in THF (20 mL)
at rt. The whole was stirred for 4 hours at rt. After the reaction completed, added 2M aqueous solution of NaOH (40 mL), then extracted with CH₂Cl₂ (30 mL x 4). The organic phase was washed with brine (30 mL), dried over Na₂SO₄, and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica-gel (eluent: EtOAc/n-Hexane=2/3) to afford methyl 4-(((2-(2,5-dimethylphenyl)-2-phenylethyl)carbamoyl)oxy)benzoate (5) (222.0 mg, 4.99 mmol, 68% in two steps) as a colorless amorphous material.

¹H-NMR (CDCl₃, 400 MHz) δ (ppm): 8.011 (2H, d, J = 8.4 Hz), 7.297 (2H, t, J = 7.6 Hz), 7.230-7.194 (3H, m), 7.135 (2H, td, J = 8.8, 2.0 Hz), 7.080-7.047 (2H, m), 6.990-6.971 (1H, m), 5.190-4.866 (1H, m), 4.419 (1H, t, J = 8.0 Hz), 3.878 (5H, m), 2.333 (3H, s), 2.229 (3H, s.) ¹³C-NMR (CDCl₃, 100 MHz) δ (ppm): 166.92, 155.23, 154.20, 141.77, 139.50, 136.17, 134.34, 131.55, 131.45, 129.23, 128.79, 128.08, 127.54, 127.31, 121.77, 52.60, 47.24, 46.00, 21.78, 19.80. HRMS (ESI-TOF, [M+Na]⁺): Calcd. for C₂₅H₂₅NNaO₄⁺: 426.1676. Found: 426.1652. Anal. Calcd. for C₂₅H₂₅NO₄+0.2H₂O: C, 73.76; H, 6.29; N, 3.44. Found: C, 73.46; H, 6.02; N, 3.25.

**Preparation of dimethyl 4-(((4-(ethoxycarbonyl)cyclohexyl)methyl)-carbamoyl)oxy)-isophthalate (14)**

To a solution of SOCl₂ (0.5 mL, 6.9 mmol) in EtOH (20 mL), added 4-(aminomethyl)cyclohexane-1-carboxylic acid (847.2 mg, 5.39 mmol) at 0°C, the whole was stirred for 30 minutes at rt, then for 1 hour at reflux. After the reaction completed, poured into ice-water and quenched with 2M aqueous solution of NaOH (50 mL). Then, EtOAc (100 mL) was added and the mixture was washed with 2M aqueous solution of NaOH (50 mL x 2). The organic phase was washed with brine (30 mL), dried over Na₂SO₄, and the solvent was evaporated under reduced pressure to give a crude (947.6 mg). To a solution of tetramethyl
4,4′-(carbonylbis(oxy))diisophthalate (1362.0 mg, 3.05 mmol) in THF (8.0 mL), crude (947.6 mg) in THF (2.0 mL) was added at 0°C. The whole mixture was stirred for 10 minutes at 0°C. The reaction mixture was purified by column-chromatography on silica gel (eluent : EtOAc / n-Hexane = 2 / 3) to afford dimethyl 4-(((4-(ethoxycarbonylcyclohexyl)methyl)carbamoyl)oxy)isophthalate (14) (947.6 mg, 2.25 mmol, 42% in two steps) as a colorless solid. Mp. 122.3-123.2°C (colorless needles, recrystallized from CH₂Cl₂/n-Hexane). ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) (presence of two amide conformers): 8.646-8.607 (1H, m), 8.186 (1H, dd, J = 8.6, 2.0 Hz), 7.236 (1H, d, J = 8.4 Hz), 5.413 (0.89H, t, J = 13.2 Hz), 5.085 (0.11H, brs),4.121 (2H, q, J = 6.8 Hz), 3.930 (3H, s), 3.883 (3H, s), 3.238 (0.24H, t, J = 6.4 Hz), 3.129 (1.84H, t, J = 6.4 Hz), 2.238 (1H, tt, J = 12.1, 3.6 Hz), 2.051-2.017 (2H, m), 1.929-1.850 (2H, m), 1.605-1.390 (3H, m), 1.250 (3H, t, J = 7.2 Hz), 1.015 (2H, qd, J = 13.2, 3.2 Hz). ¹³C-NMR (CDCl₃, 100 MHz) δ (ppm): 176.33, 166.10, 165.05, 154.57, 154.35, 134.99, 133.49, 127.97, 124.78, 124.65, 60.69, 52.87, 52.81, 47.81, 43.72, 38.00, 30.06, 28.88, 14.70. HRMS (ESI-TOF, [M+Na]⁺): Calcd. for C₂₁H₂₅N₃NaO₈⁺: 444.16129. Found: 444.1619. Anal. Calcd. for C₂₁H₂₅N₃O₈: C, 59.85; H, 6.46; N, 3.32. Found: C, 59.73; H, 6.35; N, 3.29.

**Preparation of methyl 2-((diphenylcarbamoyl)oxy)benzoate (26)**

To a solution of triphosgene (300.3 mg, 1.01 mmol) in CH₂Cl₂ (3.0 mL) was added a solution of diphenylamine (364.4 mg, 2.15 mmol) in CH₂Cl₂ (4.0 mL) and dry pyridine (1.0 mL) at 0°C. The resulting mixture was stirred at 0°C for 15 min and at rt for an additional 17.5 hr. The reaction was quenched with 2M aqueous solution of HCl (20 mL). The reaction mixture was extracted with CH₂Cl₂ (20 mL x 5). The organic phase was washed with brine (20 mL), dried over Na₂SO₄, and the solvent was evaporated to give the crude isocyanate (498.9 mg). To a solution of methyl
2-hydroxybenzoate (518.3 mg, 3.41 mmol), pyridine (3.0 mL) and \( \text{iPr}_2\text{NEt} \) (0.5 mL, 2.87 mmol), a solution of the above crude isocyanate (498.9 mg) in \( \text{CH}_2\text{Cl}_2 \) (4.0 mL) was added at rt. The whole was stirred for 3 hr at rt. The crude reaction mixture was purified by column-chromatography on silica gel (eluent: EtOAc / n-Hexane = 1 / 2) to afford methyl 2-((diphenylcarbamoyl)oxy)benzoate (26) (636.2 mg, 1.83 mmol, 85%) as a colorless solid. Mp. 82.6-84.9°C (colorless needles, recrystallized from \( \text{CH}_2\text{Cl}_2/n\)-Hexane).

\( ^1\text{H}-\text{NMR} \) (CDCl\(_3\), 400 MHz) \( \delta \) (ppm): 7.976 (1H, d, \( J = 7.6 \) Hz), 7.519-7.340 (9H, m), 7.277-7.118 (4H, m), 3.907 (3H, s).

\( ^{13}\text{C}-\text{NMR} \) (CDCl\(_3\), 100 MHz) \( \delta \) (ppm): 165.51, 153.24, 151.24, 142.89, 134.05, 131.97, 129.43, 127.51, 126.92, 126.16, 124.22, 124.19, 52.64. HRMS (ESI-TOF, [M+Na]\(^+\)):
Calcd. for \( \text{C}_{21}\text{H}_{17}\text{NNaO}_4^+ \) : 370.10498. Found: 370.10432. Anal. Calcd. for \( \text{C}_{21}\text{H}_{17}\text{NO}_4 \): C, 72.61; H, 4.93; N, 4.03. Found: C, 72.77; H, 4.82; N, 4.12.

**Preparation of methyl 2-((4-(trifluoromethyl)benzoyl)oxy)benzoate (27)**

To a solution of methyl salicyalate (15657.5 mg, 10.3 mmol) in \( \text{CH}_2\text{Cl}_2 \) (20 mL) and \( \text{iPr}_2\text{NEt} \) (9.0 mL), 4-(trifluoromethyl)benzoyl chloride (1823.9 mg, 8.74 mmol) in \( \text{CH}_2\text{Cl}_2 \) (10 mL) was added at 0°C. The whole mixture was stirred for 40 minutes at 0°C. The reaction mixture was purified by column-chromatography on silica gel (eluent: EtOAc/n-Hexane = 1 / 4) to afford methyl 2-((4-(trifluoromethyl)benzoyl)oxy)benzoate (27) (1142.8 mg, 3.52 mmol, 40%) as a colorless solid. Mp. 68.7-69.2°C (colorless plates, recrystallized from \( \text{CH}_2\text{Cl}_2/n\)-Hexane).

\( ^1\text{H}-\text{NMR} \) (CDCl\(_3\), 400 MHz) \( \delta \) (ppm): 8.339 (2H, d, \( J = 8.0 \) Hz), 8.091 (1H, dd, \( J = 7.8, 1.6 \) Hz), 7.788 (2H, d, \( J = 8.0 \) Hz), 7.627 (1H, td, \( J = 7.6, 2.0 \) Hz), 7.383 (1H, td, \( J = 7.8, 1.2 \) Hz), 7.252-7.230 (1H, m), 3.750 (3H, s).

\( ^{13}\text{C}-\text{NMR} \) (CDCl\(_3\), 100 MHz) \( \delta \) (ppm): 165.33, 164.83, 151.14, 135.55 (q, \( J = 32 \) Hz), 134.60, 133.39, 132.60, 131.25, 126.98, 126.22 (q, \( J = 3 \) Hz), 124.39, 124.18 (q, \( J = 271 \) Hz), 123.73, 52.81. HRMS
Preparation of methyl 2-(((4-methoxyphenethyl)carbamoyl)oxy)benzoate (15)

To a solution of dimethyl 2,2'-carbonyldibenzoate (1660.9 mg, 5.03 mmol) in THF (10.0 mL), a solution of 2-(4-methoxyphenyl)ethan-1-amine (776.1 mg, 5.13 mmol) in THF (5.0 mL) was added at rt. The whole was stirred for 1 hour at rt. The reaction mixture was directly purified by column-chromatography on silica gel (eluent: EtOAc/n-Hexane=1/1) to afford methyl 2-(((4-methoxyphenethyl)carbamoyl)oxy)benzoate (15) (1630.2 mg, 4.95 mmol, 90%) as a colorless solid. Mp. 61.2-61.5°C (colorless cube, recrystallized from CH2Cl2/n-Hexane).

1H-NMR (CDCl3, 400 MHz) δ (ppm) (presence of two amide conformers): 7.954 (1H, dd, J = 8.0, 1.2 Hz), 7.519 (1H, td, J = 7.8, 1.6 Hz), 7.268 (1H, t, J = 7.2 Hz), 7.192-7.128 (3H, m), 5.196 (0.93H, brs), 4.828 (0.14H, brs), 3.845 (3H, s), 3.792 (3H, s), 3.495 (2H, q, 6.8 Hz), 2.839 (3H, t, J = 7.2 Hz) 13C-NMR (CDCl3, 100 MHz) δ (ppm): 165.89, 158.94, 154.94, 151.21, 134.06, 132.01, 131.22, 130.35, 126.11, 124.67, 124.55, 114.70, 55.84, 52.64, 43.32, 35.68. HRMS (ESI-TOF, [M+Na]+): Calcd. for C19H18NNaO5+: 352.1152. Found: 352.1165. Anal. Calcd. for C19H18NO5: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.32; H, 5.79; N, 4.11.

Multiple Successive Electrophile Substitution Reactions in One Pot

Dual amidation in one pot (7) (Table 1, Entry 1)

To TfOH (2.0 mL), methyl 4-(((2-(2,5-dimethylphenyl)-2-phenylethyl)carbamoyl)oxy)benzoate 5 (222.5 mg, 0.50 mmol) in CH2Cl2 (0.5 mL) was added at 0°C. Then, dimethyl 4-((diphenylcarbamoyl)oxy)isophthalate 4 (202.9 mg, 0.50 mmol) in CH2Cl2 (1.0 mL) was added at 0°C. The whole was warmed up from 0°C to 20°C, and stirred for 12 hours. After the reaction completed, the whole was poured
into ice-water. Added 2M aqueous solution of NaOH (50 mL), and this reaction mixture was extracted with CH$_2$Cl$_2$ (40 mL x 3). The organic phase was washed with brine (40 mL), dried over Na$_2$SO$_4$, and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica-gel (eluent: Acetone/n-hexane = 4 / 3) to afford 2,5-dimethyl-4-(1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N-diphenyl-benzamide (7) (191.7 mg, 0.43 mmol, 86%) as a colorless solid. Mp. 240.7-241.3°C (colorless plates, recrystallized from CH$_2$Cl$_2$/n-Hexane). $^1$H-NMR (CDCl$_3$, 400 MHz) δ (ppm): 8.133 (1H, dd, $J = 9.2$, 3.6 Hz), 7.394-6.969 (16H, m), 6.831-6.796 (2H, m), 6.760 (1H, s), 5.617 (1H, t, $J = 6.0$ Hz), 4.550 (1H, t, $J = 7.2$ Hz), 3.634 (2H, dd, $J = 7.8$, 2.8 Hz), 3.485 (2H, q, $J = 6.4$ Hz), 2.749 (2H, t, $J = 6.8$ Hz), 2.413 (3H, s), 2.342 (3H, s), 2.220 (3H, s). $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ (ppm): 171.33, 166.81, 143.51, 141.94, 139.49, 136.06, 133.96, 133.79, 132.91, 130.88, 130.66, 129.63, 129.45, 128.58, 127.89, 127.74, 127.49, 127.03, 46.13, 40.50, 19.81, 19.58. HRMS (ESI-TOF, [M+Na]$^+$): Calcd. for C$_{30}$H$_{26}$N$_2$O$_2$Na$: 469.1886. Found: 469.1876. Anal. Calcd. for C$_{30}$H$_{26}$N$_2$O$_2$: C, 80.05; H, 5.91; N, 6.22. Found: C, 80.13; H, 6.17; N, 6.07.

**Three-component dual amidation reactions (25) (Table 1, Entry 6)**

To a solution of 1,2-bis(3,4-dimethylphenyl)ethane 14 (120.3 mg, 0.51 mmol), dimethyl 4-(((4-ethoxycarbonyl)cyclohexyl)methyl)carbamoyloxy)isophthalate 23 (210.8 mg, 0.50 mmol) and methyl 2-((diphenylcarbamoyl)oxy)benzoate 26 (175.9 mg, 0.51 mmol) in CH$_2$Cl$_2$ (1.0 mL), TfOH (2.0 mL) was added at 0°C. The whole was stirred for 15 minutes. Then, the whole was warmed up from 0°C to 20°C, and stirred for 1 hour. After the reaction completed, the whole was poured into ice-water and added 2M aqueous solution of NaOH (30 mL). This reaction mixture was extracted with CH$_2$Cl$_2$ (40 mL x 3). The organic phase was washed with brine (40 mL x 3).
mL), dried over Na$_2$SO$_4$, and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica-gel (eluent: EtOAc / n-Hexane = 1 / 2) to afford ethyl 4-((2-(2-(diphenylcarbamoyl)-4,5-dimethylphenethyl)-4,5-dimethylbenzamido)methyl)cyclohexane-1-carboxylate 25 (155.3 mg, 0.24 mmol, 48 %) as a colorless oil. $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ (ppm) (presence of two amide conformers): 7.181-6.792 (14H, m), 6.101-6.032 (1H, m), 4.028 (2H, q, $J = 7.2$ Hz), 3.103 (2H, t, $J = 6.4$ Hz), 2.994-2.865 (5H, m), 2.157-2.122 (6H, m), 2.053 (3H, s), 1.954 (3H, m), 1.873-1.692 (5H, m), 1.411-1.337 (1H, m), 1.267 (2H, qd, $J = 13.2$, 3.2 Hz), 1.162 (3H, t, $J = 7.2$ Hz), 0.856 (2H, qd, $J = 12.8$, 3.6 Hz). $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ (ppm): 175.96, 175.88, 171.14, 171.10, 170.84, 170.34, 143.44, 143.34, 138.38, 138.03, 137.86, 137.80, 137.47, 137.25, 136.92, 135.70, 134.68, 134.33, 134.25, 133.55, 133.52, 133.33, 133.25, 132.55, 131.52, 131.06, 130.88, 130.13, 129.35, 129.05, 128.92, 128.53, 127.42, 126.90, 126.75, 126.31, 126.28, 60.39, 60.13, 53.45, 45.66, 45.45, 43.32, 43.28, 37.36, 37.18, 35.24, 34.99, 34.93, 34.78, 29.97, 29.86, 28.49, 28.44, 21.04, 19.90, 19.64, 19.57, 19.19, 19.03, 16.51, 14.25. HRMS (ESI-TOF, [M+Na]$^+$): Calcd. for C$_{40}$H$_{37}$N$_3$NaO$_3$: 630.2727. Found: 630.2731. Anal. Calcd. for C$_{40}$H$_{37}$N$_3$O$_3$+0.6 CH$_2$Cl$_2$: C, 74.03; H, 5.85; N, 6.38. Found: C, 74.06; H, 6.07; N, 6.18.

**Sequential aromatic acylation-amidation reaction 29 (Table 2, Entry 1)**

To a mixture of TfOH (2.0 mL), methyl 4-(((2-(2,5-dimethylphenyl)-2-phenylethyl)carbamoyl)oxy)benzoate 5 (441.8 mg, 1.1 mmol) in CH$_2$Cl$_2$ (2.0 mL) was slowly added at 0°C. Then, methyl 2-((4-(trifluoromethyl)benzoyl)oxy)benzoate 27 (359.4 mg, 1.11 mmol) was added at 0°C. The whole was warmed up from 0°C to 20°C, and stirred for 15 hours. After the reaction completed, the whole was poured into ice-water. This reaction mixture was extracted with CH$_2$Cl$_2$ (30 mL x 4).
organic phase was washed with brine (40 mL), dried over Na₂SO₄, and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica-gel (eluent: EtOAc/n-Hexane = 1/1) to afford 4-(2,5-dimethyl-4-(4-(trifluoromethyl)benzoyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (29) (367.5 mg, 0.87 mmol, 79%) as a colorless solid. Mp. 237.2-237.9°C (colorless needles, recrystallized from EtOAc).

1H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 8.002-7.888 (6H, m), 7.458 (2H, td, J = 24.5, 7.2 Hz), 7.276 (1H, s), 6.973 (1H, d, J = 7.2 Hz), 6.779 (1H, s), 4.619 (1H, t, J = 6.0 Hz), 3.699-3.524 (2H, m), 2.394(3H, s), 2.102 (3H, s). 13C-NMR (DMSO-d₆, 100 MHz) δ (ppm): 196.52, 164.35, 142.46, 141.00, 140.68, 135.64, 134.06, 133.65, 132.53 (q, J = 32 Hz), 132.20, 131.02, 130.81, 130.32, 129.86, 127.46, 127.27, 127.23, 125.79 (q, J = 4 Hz), 123.76 (q, J = 271 Hz), 44.44, 39.16, 19.43, 18.68.

HRMS (ESI-TOF, [M+Na]+): Calcd. for C₂₅H₂₀F₃NNaO₂+: 446.1338. Found: 446.1334. Anal. Calcd. for C₂₅H₂₀F₃NO₂+0.8 H₂O: C, 68.58; H, 4.97; N, 3.20. Found: C, 68.74; H, 5.04; N, 3.09.

Formation of three bonds in a one-pot reaction 43 (Figure 8, Reaction (a))

To TfOH (2.0 mL), methyl 2-(((4-methoxyphenethyl)carbamoyl)oxy)benzoate 15 (166.1 mg, 0.50 mmol) was added at 0°C. Then, methyl 2-((4-(trifluoromethyl)benzoyl)oxy)benzoate 27 (164.0 mg, 0.51 mmol) was added at 0°C. The whole was stirred for 15 minutes. Then, methyl 4-(((2-(2,5-dimethylphenyl)-2-phenylethyl)carbamoyl)oxy)benzoate 5 (230.3 mg, 0.52 mmol) in CH₂Cl₂ (2.0 mL) was added at 0°C. The whole was warmed up from 0°C to 20°C, and stirred for 15 hours. After the reaction completed, the whole was poured into ice-water and added 2M aqueous solution of NaOH (30 mL). This reaction mixture was extracted with CH₂Cl₂ (40 mL x 3). The organic phase was
washed with brine (40 mL), dried over Na$_2$SO$_4$, and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica-gel (eluent: EtOAc) to afford N-(4-methoxy-3-(4-(trifluoromethyl)benzoyl)phenethyl)-2,5-dimethyl-4-(1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)benzamide 43 (172.7 mg, 0.29 mmol, 56%) as amorphous material. $^1$H-NMR (CDCl$_3$, 400 MHz) δ (ppm):
8.143-8.120 (1H, m), 7.869 (2H, d, $J = 8.0$ Hz), 7.673 (2H, d, $J = 8.4$ Hz), 7.424-7.373 (3H, m), 7.301 (1H, d, $J = 2.4$ Hz), 7.183 (1H, s), 6.961 (1H, d, $J = 8.4$ Hz), 6.818-6.796 (1H, m), 6.747 (1H, s), 6.608 (1H, brs), 5.956 (1H, t, $J = 6.0$ Hz), 4.546 (1H, t, $J = 7.6$ Hz), 3.725-3.630 (7H, m), 2.934 (2H, t, $J = 7.6$ Hz), 2.327 (3H, s), 2.232 (3H, s). $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ (ppm): 195.93, 170.41, 166.80, 156.86, 141.69, 141.30, 140.66, 135.88, 134.54 (q, $J = 28$ Hz), 134.37, 134.31, 133.62, 133.15, 131.79, 131.52, 131.02, 130.70, 130.35, 129.73, 128.72, 128.56, 127.97, 127.84, 125.79 (q, $J = 3$ Hz), 124.24 (q, $J = 271$ Hz), 112.43, 56.20, 46.31, 41.38, 40.56, 35.25, 19.94, 19.67. HRMS (ESI-TOF, [M+Na]$^+$): Calcd. for C$_{35}$H$_{31}$F$_3$N$_2$NaO$_4$ $^+$: 623.2128. Found: 623.2128. Anal. Calcd. for C$_{35}$H$_{31}$F$_3$N$_2$O$_4$+0.5 CH$_2$Cl$_2$: C, 66.30; H, 5.02; N, 4.36. Found: C, 66.05; H, 5.33; N, 4.35.

**Computational Methods**

We carried out computational studies by using the Gaussian 09 suites of programs.$^{[19]}$ The geometries of the reactants (SM), transition states (TS), and products (PM) for dissociation step were fully optimized using the CPCM(Complete Polarizable Continuum Model)-B3LYP/6-31+G(d) level.$^{[20]}$ Harmonic vibrational frequency computations characterized the optimized structures. Intrinsic reaction coordinate (IRC) computations$^{[21]}$ of the transition structures verified the reactants, intermediates, and products on the potential energy surface (PES). Bulk solvation effects (self-consistent reaction field, SCRF) were simulated by the CPCM method$^{[22]}$ in
trifluoromethanesulfonic acid as a solvent (\(\varepsilon = 77.4^{[23]}\) \(\text{r}_{\text{solv}} = 2.5985274^{[23]}\)
density = 1.696,\(^{[24]}\) \(\varepsilon_{\text{inf}} = 1.882384\) (the value of acetic acid was employed)).

Single point energies were calculated with CPCM-M06-2X/6-311++G(d,p) (and some other calculation levels) on the basis of the optimized structures.\(^{[25]}\) The zero-point vibrational energy corrections were done without scaling.
Notes and References

1. P. J. Hajduk, J. Greer, Nat. Rev. Drug. Discov., 2007, 6, 211-219.
2. S. L. Schreiber, Science, 2000, 287, 1964-1969.
3. Y. Takayama, T. Yamada, S. Tatekabe, K. Nagasawa, Chem. Commun., 2013, 49, 6519.
4. (a) H. Kheira, P. Li, J. Xu, J. Mol. Catal. A: Chem., 2014, 391, 168-174. (b) X. Zhang, W. T. Teo, P. W. H. Chan, Org. Lett., 2009, 11, 4990-4993. (c) M. Shi, L. Wu, J. Lu, Tetrahedron, 2008, 64, 3315-3321. (d) J. A. Kozak, B. O. Patrick, G. R. Dake, J. Org. Chem., 2010, 75, 8585-8590.
5. (a) Y. Zhang, L. Chen, T. Lu, Adv. Synth. Catal., 2011, 353, 1055-1060. (b) R. O. lakovenko, A. N. Kazakova, V. M. Muzalevskiy, A. Y. Lvanov, I. A. Boyarskaya, A. Chicca, V. Petrucci, J. Gertsch, M. Krasavin, G. L. Starova, A. A. Zolotarev, M. S. Avdontceva, V. G. Nenajdenko, A. V. Vasilyev, Org. Biomol. Chem., 2015, 13, 8827-8842.
6. (a) B. R. Park, S. H. Kim, Y. M. Kim, J. N. Kim, Tetrahedron lett., 2011, 52, 1700-1704. (b) B. V. Ramulu, G. Satyanarayana, RSC Adv., 2015, 5, 70972-70976. (c) R. Rendy, Y. Zhang, A. McElrea, A. Gomez, D. A. Klumpp, J. Org. Chem., 2004, 69, 2340-2347.
7. (a) F. Sun, M. Zeng, Q. Gu, S. You, Chem. Eur. J., 2009, 15, 8709-8712. (b) Q. Li, W. Xu, J. Hu, X. Chen, F. Zhang, H. Zheng, RSC Adv., 2014, 4, 27722-27725. (c) S. Wang, L. Han, M. Zeng, F. Sun, W. Zhang, S. You, Org. Biomol. Chem., 2012, 10, 3202-3209.
8. (a) A. Suárez, P. García-García, M. A. Fernández-Rodríguez, R. Sanz, Adv. Synth. Catal., 2014, 356, 374-382. (b) R. Sureshbabu, V. Saravanam, V. Dhayalan, A. K. Mohanakrishnan, Eur. J. Org. Chem., 2011, 922-935. (c) L. Bianchi, M. Maccagno, M. Pani, G. Petrillo, C. Scapolla, C. Tavani, Tetrahedron, 2015, 71, 7421-7435. (d) A. Kulkarni, P. Quang, B. Török, Synthesis, 2009, 23, 4010-4014.
9. (a) J. Liu, T. He, L. Wang, Tetrahedron, 2011, 67, 3420-3426. (b) M. Shiri, M. A. Zolfigol, R. Ayazi-Nasrabadi, Tetrahedron, 2010, 51, 264-268. (c) J. Xu, J. Xia, Y. Lan, Synth. Commun., 2005, 35, 2347-2353. (d) S. Saito, T. Ohwada, K. Shudo, J. Am. Chem. Soc., 1995, 117, 11081-11084. (e) G. A. Olah, G. Rasul, C. York, G. K. S. Prakash, J. Am. Chem. Soc., 1995, 117, 1121-11214. (f) P. Thirupathi, S. S. Kim, J. Org. Chem., 2009, 74, 7755-7761. (g) C. Huo, C. Sun, C. Wang, X. Jia, W. Chang, ACS Sustainable Chem. Eng., 2013, 1, 549-553. (h) C. Huo, C. Wang, C. Sun, X. Jia,
X. Wang, W. Chang, M. Wu, *Adv. Synth. Catal.*, 2013, **355**, 1911-1916.

10. (a) H. Ishida, H. Nukaya, K. Tsuji, H. Zenda, T. Kosuge, *Chem. Pharm. Bull.*, 1992, **40**, 308-313. (b) H. Naeimi, S. S. Brojerdi, *Polycyclic Aromat. Compd.*, 2014, **34**, 504-517. (c) A. P. Krapcho, Z. Getahun, K. J. Avery Jr, *Synth. Commun.*, 1990, **24**, 2139-2146. (d) G. A. Guerrero-Vásquez, C. K. Z. Andrade, J. M. G. Molinillo, F. A. Macías, *Eur. J. Org. Chem.*, 2013, 6175-6180. (e) R. Huot, P. Brassard, *Can. J. Chem.*, 1974, **52**, 838-842.

11. (a) L. Bianchi, M. Maccagno, M. Pani, G. Petrillo, C. Scapolla, C. Tavani, *Tetrahedron*, 2015, **71**, 7421-7435. (b) G. Gangadhararao, A. Uruvakilli, K. C. K. Swamy, *Org. Lett.*, 2014, **16**, 6060-6063. (c) L. Hao, Y. Pan, T. Wang, M. Lin, L. Chen, Z. Zhan, *Adv. Synth. Catal.*, 2010, **352**, 3215-3222. (d) S. Sarkar, K. Bera, U. Jana, *Tetrahedron Lett.*, 2014, **55**, 6188-6192. (e) X. Xie, X. Du, Y. Chen, Y. Liu, *J. Org. Chem.*, 2011, **76**, 9175-9181. (f) A. C. Silvanus, S. J. Heffernan, D. J. Liptrot, G. Kociok-Köhn, B. I. Andrews, D. R. Carbery, *Org. Lett.*, 2009, **11**, 1175-1178. (g) H. Li, R. Guillot, V. Gandon, *J. Org. Chem.*, 2010, **75**, 8435-8449. (h) K. Fuchibe, H. Jyono, M. Fujiwara, T. Kudo, M. Yokota, J. Ichikawa, *Chem. Eur. J.*, 2011, **17**, 12175-12185.

12. Up to the present, masked (blocked) electrophiles have mainly been limited to masked (blocked) isocyanates. For a review of masked (blocked) isocyanates, see: E. Delebecq, J. Pascault, B. Boutevin, F. Ganachaud, *Chem. Rev.*, 2013, **113**, 80-118. Recent studies on application masked isocyanates to synthetic organic chemistry: (a) M. Hutchby, C. E. Houlden, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.*, 2009, **48**, 8721-8724. (b) C. Clavette, J. V. Rocan, A. M. Beauchemin, *Angew. Chem. Int. Ed.*, 2013, **52**, 12705-12708. (c) H. Ying, Y. Zhang, J. Cheng, *Nat. Commun.*, 2014, **5**, 3218. (d) Y. Wei, J. Liu, S. Lin, H. Ding, F. Liang, B. Zhao, *Org. Lett.*, 2010, **12**, 4220-4223. (f) C. Spyropoulos, C. G. Kokotos, *J. Org. Chem.*, 2014, **79**, 4477-4483. (g) S. Adachi, M. Onozuka, Y. Yoshida, M. Ide, Y. Saikawa, M. Nakata, *Org. Lett.*, 2014, **16**, 358-361. (h) E. K. Raja, S. O. N. Lill, D. A. Klumpp, *Chem. Commun.*, 2012, **48**, 8141-8143. (i) H. Kurouchi, K. Kawamoto, H. Sugimoto, S. Nakamura, Y. Otani, T. Ohwada, *J. Org. Chem.* 2012, **77**, 9313–9328.

13. (a) A. Sumita, H. Kurouchi, Y. Otani, T. Ohwada, *Chem. Asian J.* 2014, **9**, 2995–3004. (b) H. Kurouchi, A. Sumita, Y. Otani, T. Ohwada, *Chem. Eur. J.* 2014, **20**, 35.
14. In recent years, several reports have shown that isocyanates are useful chemical species to form aromatic amides. (a) G. Schäfer, C. Matthey, J. W. Bode, Angew. Chem. Int. Ed., 2012, 57, 9173-9175. (b) G. Schäfer, J. W. Bode, Org. Lett., 2014, 16, 1526-1529. And reference 12(h).
15. P. Gund, J. Chem. Educ., 1972, 49, 10-103.
16. J. P. Hwang, G. K. S. Prakash, G. A. Olah, Tetrahedron, 2000, 56, 7199-7203.
17. M. Kozelj, A. Petric, Synlett. 2007, 11, 1699–1702.
18. A. Kethe, A. F. Tracy, D. A. Klumpp, Org. Biomol. Chem. 2011, 9, 4545.
19. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmolyov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, (2009) Gaussian 09, Gaussian, Inc., Wallingford CT.
20. A. D. Becke, J. Chem. Phys., 1993, 98, 5648.
21. K. Fukui, Acc. Chem. Res., 1981, 14, 363–368.
22. (a) V. Barone, M. Cossi, J. Phys. Chem. A, 1998, 102, 1995-2001. (b) M. Cossi, N. Rega, G. Scalmani, V. Barone, J. Comp. Chem., 2003, 24, 669-681.
23. A. L. Lira, M. Zolotukhin, L. Fomina, S. Fomine, J. Phys. Chem. A, 2007, 111, 13606–13610.
24. R. Corkum, J. Milne, Can. J. Chem., 1978, 56, 1832-1835.
25. Y. Zhao, D. G. Truhlar, Theor. Chem. Acc., 2008, 120, 215-241.
Tandem Buildup of Complexity of Aromatic Molecules Through Multiple Successive Electrophile Generation in One Pot, Controlled by Varying the Reaction Temperature
Akinari Sumita, Yuko Otani, Tomohiko Ohwada *

The unmasking reaction rates and the time of generation of highly reactive electrophiles can be controlled. This reaction system demonstrates the conceptual validity of one-pot build-up of complex aromatic molecule from multiple starting components.