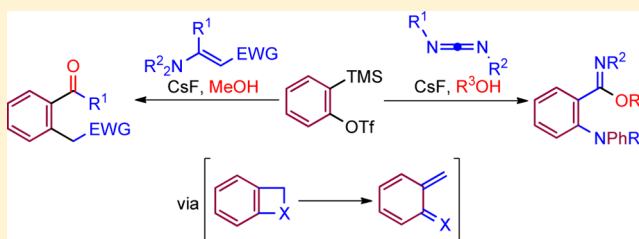


Arynes Double Bond Insertion/Nucleophilic Addition with Vinylogous Amides and Carbodiimides

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Supporting Information

ABSTRACT: Arynes are shown to insert into some C=X double bonds, leading to benzannulated four-membered rings. The strain of these rings allow for a ready, spontaneous opening to afford *o*-quinomethide analogues. Subsequent nucleophilic addition re-aromatizes the intermediates to achieve *ortho*-difunctionalization of arynes. In this report, we describe the aryne insertion into the C=C double bonds of vinylogous amides and the C=N double bonds of carbodiimides. The correlation and comparison with aryne single bond insertion chemistry will be discussed. Computational studies for the ring-opening step, as well as the nature of the *o*-quinomethide intermediates, will also be discussed.



INTRODUCTION

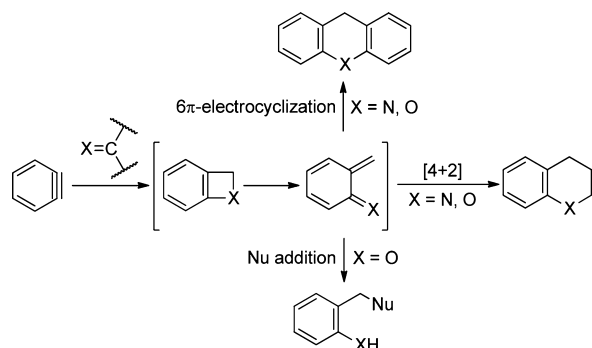
Arynes have been shown to insert into a number of single bonds.¹ However, the corresponding aryne insertion into double bonds is much less reported. This insertion involves first a [2 + 2] cycloaddition that affords a benzannulated four-membered ring intermediate, which may exhibit different levels of instability and under the same or different reaction conditions may undergo subsequent ring-opening processes to afford *o*-quinomethides (*o*QMs) or analogues thereof (Scheme 1). The two-step process furnishes a formal enyne metathesis outcome and generates another reactive intermediate, *o*QM, from an existing one, aryne.

Some double bonds that are known to undergo aryne insertion include the C=C bonds of enamides² and enolates,³

the C=O bonds of formamides⁴ and aldehydes,⁵ the C=N bonds of imines,⁶ and some miscellaneous double bonds.⁷ Depending on the exact structure, the generated *o*QMs (or the analogues) may undergo a number of different subsequent processes to afford stable final products, including 6π electrocyclization,^{5b,6b,7a} [4 + 2] cycloaddition or annulation,^{2,5a,6a} and nucleophilic addition (Scheme 1).^{4a-c} Very recently, a [4 + 1] annulations mode has also been disclosed.^{4d,8} Overall, either an *ortho*-difunctionalization of arynes or formation of another ring is achieved.

Despite this much discovery, to date, the aryne double bond insertion chemistry remains in its infancy and awaits further study. For example, the mechanistic details for the [2 + 2] cycloaddition as well as the ring opening have not been adequately studied, and the dependency on the electronic properties and the atomic compositions of the double bonds remains unknown. Moreover, the aryne insertion into the C=N bonds of imines and the C=C bonds of enolates was executed on diazotized anthranilic acid and is highly substrate-dependent and poorly yielding, thus necessitating further development. The insertion into the C=O bonds of formamides requires the use of the latter as solvents under highly diluted conditions and thus poses scope, economy, and workup issues. The insertion into the C=C bonds of enamides needs high temperature and is restricted to certain substitution patterns. For this reason, continuing study is necessary to further broaden the substrate scope and to find further utility of

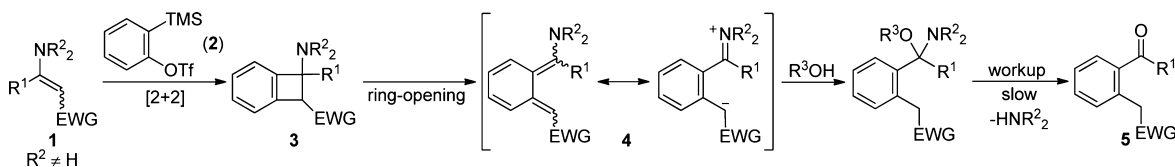
Scheme 1. Aryne Double Bond Insertion and Subsequent Events



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Scheme 2. Aryne Insertion into Vinylogous Amides/Nucleophilic Addition/Hydrolysis Sequence



this event. Herein, we wish to continue from our communication⁹ and report our additional results in the carbodiimide system. Chemistry-wise, we are focusing our attention on the nucleophilic addition interception of the *o*QM intermediates. We also wish to study some mechanistic details to enrich the understanding of these reactions.

RESULTS AND DISCUSSIONS

Insertion to C=C Double Bonds of Vinylogous Amides. At the outset of our program, we wished to study the C=C double bond insertion. Given the electrophilic nature of arynes, this insertion appeared reasonable only for electron-rich, nucleophilic C=C double bonds. As enamides have been previously shown to undergo C=C double bond insertion,² the analogous vinylogous amides appeared an ideal candidate and were thus chosen as the substrate for testing. The overall event is outlined in Scheme 2, which involves first a [2 + 2] cycloaddition followed by a ring opening to afford the *o*-quinodimethide (*o*QDM) intermediate **4**, which may also have an iminium inner salt resonance structure, followed by a nucleophilic attack by an alcohol to eventually afford **5** after hydrolytic workup. Putatively, the push–pull nature of the olefin moiety in vinylogous amides would make the C=C double bond more polarized and facilitate the initial aryne [2 + 2] cycloaddition, and the intermediate **4** was also believed to be much more stable and easily generated than the counterpart derived from regular enamides. Both would help to achieve milder reaction conditions.

As the amino group was lost in the overall reaction, it can be varied for achieving a better yield or scope. Thus this amino group was considered as part of the reaction “parameters” during the optimization of the reaction conditions (Table 1). Aliphatic alcohols were ideal nucleophiles in the reaction because they are poorly reactive with arynes.¹⁰ We used methanol for this purpose. As seen, the overall process worked best with a slight excess of methanol using CsF as the fluoride source in acetonitrile at room temperature (entry 3). Mild heating to 50 °C was tolerated with only a slight decrease in yield (not shown). As for the amino group, both dibenzylamino and diisopropylamino were capable of delivering high yields of the desired product (entries 3 and 6). The morpholino group afforded lower but acceptable result (entry 7), but pyrrolidinyl was not a group of choice (entry 8).

Using this set of conditions, we next examined a diverse range of substrates with different substitutions and functionalities (Table 2). However, we quickly realized that the dibenzylamino-substituted vinylogous amides (**1-Bn**) afforded poor results for α -substituted substrates. This prompted us to go back and re-examine the amino group. Luckily, the morpholino variants (**1-mor**) were found to show broader compatibility (entries 1 and 3) with these substituted substrates. Thus, further studies were executed on the corresponding **1-mor** substrates. The scope of vinylogous amides was reasonable. In terms of the α -substitution (R), hydrogen and aryl groups were generally compatible. Aliphatic groups such as

Table 1. Optimization of the Reaction of Vinylogous Amides^a

entry	NR ₂ (1a)	MeOH (equiv)	conditions	yield ^b (%)
1	NBn ₂ (1a-Bn)	0 ^c	MeCN, rt, 36 h	39
2	NBn ₂	0 ^c	THF, 70 °C, 36 h	28
3	NBn ₂	1.5	MeCN, rt, 24 h	83
4	NBn ₂	3	MeCN, rt, 36 h	52
5 ^d	NBn ₂	1.5	MeCN, rt, 20 h	<10
6	N ⁱ Pr ₂ (1a-Pr)	1.5	MeCN, rt, 24 h	82
7	morpholino (1a-mor)	1.5	MeCN, rt, 24 h	66
8	pyrrolidinyl (1a-pyr)	1.5	MeCN, rt, 24 h	23

^aReactions were carried out on 0.3 mmol of **1a** with 1.5 equiv of **2a** and 3 equiv of CsF in 4.5 mL of solvent. ^bIsolated yield. ^cThe reaction might be proceeding with adventitious moisture. ^dTBAF (3 equiv) was used in place of CsF.

a methyl worked but were less productive (entries 1 vs 2, 4 vs 5). Within the scope of substituted phenyl groups, either a strong electron-donating or a strong electron-withdrawing group was tolerated, although the desired products were delivered in lowered yields (entries 10 and 11; also compare with entry 2). A thiophenyl group was also well tolerated (entry 12). Regarding the electron-withdrawing group (EWG), ester (entries 1 and 2), ketone (entries 3–5), and cyano (entry 8) groups were all compatible. Again, for different ketone groups as the EWG, aromatic ketones appeared superior to aliphatic ones (entries 3 vs 4). The reactivity of amides as the EWG was reasonable for tertiary amides only (entry 7), and **1g-mor** with a secondary amide (with an NH bond) reacted only modestly (entry 6). Unfortunately, to date, we were unable to prepare substrates with R being a *tert*-butyl group or substrates bearing β -substitutions. The only one we could access was **1j-mor** (entry 9), which did not lead to any meaningful products.

Two special cases were worth highlighting. Substrate **1n-mor** with the vinylogous amide embedded into a ring did not lead to any C=C insertion event. Rather, it underwent a β -arylation¹¹ to afford product **6** in a low yield (entry 13). Here the [2 + 2] event did not seem to happen, and the nucleophile did not participate in the reaction. The vinylogous amide **1o-mor**, derived from acetylenedicarboxylate and with R being another EWG, underwent a formal C–C single bond insertion to afford **7** (Scheme 3). In this case, the [2 + 2] event can be viewed to occur to the undesired “C=C double bond” (the enolate double bond if one draws the polar resonance structure of **1o-mor**), and again the nucleophile did not participate in the reaction.

The scope of arynes included both the symmetrical **2d** and the unsymmetrical **2b/2c**. For the latter, the regioselectivity was in accordance with the traditional electronic rationale,^{1b} i.e.,

Table 2. Scope of the Reaction of Vinylogous Amides with Arynes^a

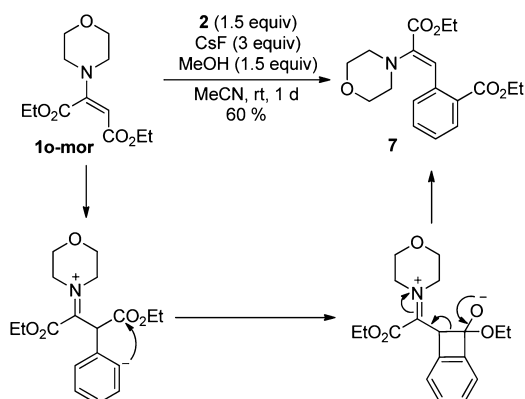
entry	1	2	product	yield ^b /%	entry	1	2	product	yield ^b /%
1		2a		31 (CM ^c)	9		2a		CM ^c
2		2a		81 ^d	10		2a		55
3		2a		23 ^e (trace)	11		2a		50
4		2a		49 ^d	12		2a		83
5		2a		71	13		2a		22 ^f
6		2a		20	14		2b		69

Table 2. continued

entry	1	2	product	yield ^b /%	entry	1	2	product	yield ^b / %
7		2a		57	15	1a-mor	2c		50
8		2a		45	16	1a-mor	2d		60

^aReactions were performed with 0.3 mmol of **1** in 4.5 mL of MeCN. Reactions may not be individually optimized. ^bIsolated yield. Yields in parentheses were obtained from the corresponding **1-Bn** substrates (dibenzylamino group in place of morpholino group). ^cComplex mixture. ^dReaction took 12 h. ^eReaction took 6 h. ^fReaction took 36 h.

Scheme 3. Formation of **7** from **1o-mor** and the Proposed Mechanism^a



^aThe Z-geometry is assigned by NOE (see the Supporting Information).

the nucleophilic site of the vinylogous amides attacking the *distal* position of the methoxy-substituted arynes (entries 14 and 15). The yields were satisfactory and comparable to that for **5aa**.

Insertion to C=N Double Bonds of Carbodiimides.

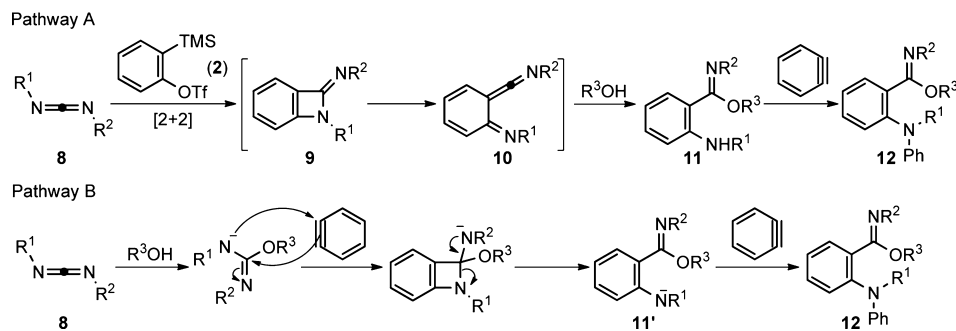
Having achieved the C=C bond insertion of vinylogous amide, we next turned our attention to the C=N bond insertion. Although arynes are known to insert into the C=N bonds of some imines,⁶ such a reaction does not work well as indicated both in our own experiences and from Yoshida's report.¹² We reasoned that the carbon atom of the imine might be insufficiently electrophilic for the aryl anion to cyclize back to achieve the initial [2 + 2] cycloaddition, despite that the imine nitrogen is sufficiently nucleophilic to arynes. Thus, a proper substrate with increased electrophilicity was sought. Carbodiimides possess C=N double bonds with much more electrophilic carbon atoms and appeared an ideal candidate in such a scenario. Putatively, the aryne insertion of C=N double bonds of carbodiimides would feature the aza-o-quinomethide

(aoQM) intermediate **10**, which can be easily quenched by alcohols or water to afford the amide/imide products **11**. Depending on the stoichiometry and the reaction conditions, **11** might react with a second equivalent of aryne to afford **12** as the final product (Scheme 4, pathway A). That said, one should keep in mind that carbodiimides may first react with the alcohol (not arynes) to afford carbamimidate intermediates (Scheme 4, pathway B, first step). However, we envisioned that even if this was happening, this carbamimidate would still afford the same product **11** or **12** following the mechanism described in pathway B. Computational studies support pathway A as the preferred mechanism (see the Supporting Information).

Again, we commenced at optimizing the reaction conditions (Table 3). Here we used water as the nucleophile and expected an amide functionality at the end of the reaction. The reaction required elevated temperature and afforded good yields only at 80 °C in acetonitrile (entry 4). Stopping at the stage of **11** proved difficult, and a continuing arylation was taking place. Of note is that this continuing N-arylation took place only at the amine nitrogen, but not the amide nitrogen.

Different nucleophiles and carbodiimides were then examined (Table 4). Under the standard conditions, MeOH, EtOH, and ^tPrOH were all successfully employed as the nucleophile. Different from the amide products derived from the reaction using water, these reactions using alcohols afforded the corresponding imidates (entries 2–4). The less nucleophilic ^tBuOH proved incompatible as a nucleophile (entry 5), and formation of **12ba-H** was observed likely due to the involvement of adventitious moisture. Use of ethylene glycol as the nucleophile led to a hydrolysis of the imidate moiety to afford the ester functionality (entry 6).¹³ Other than alcohols, N-hydroxylamines such as N-hydroxylphthalimide proved not effective (entry 7). For nitrogen nucleophiles, hydantoin and succinimide (entry 8) were both reactive. Yet unfortunately we were unable to purify the former product.¹⁴ Interestingly, use of both ethylene glycol and succinimide as the nucleophile led to two products **11** and **12**, where the subsequent N-phenylation was somewhat suppressed.¹⁵

Scheme 4. Three-Component Reaction of Aryne, Carbodiimides, and a Nucleophile

Table 3. Optimization of the Reaction of Carbodiimides^a

entry	H ₂ O (equiv)	conditions	yield ^b (%)
1	1.2	THF, 70 °C, 24 h	35
2	1.2	MeCN, rt, 24 h	37
3	1.2	MeCN, 50 °C, 10 h	55
4	1.2	MeCN, 80 °C, 5 h	77
5	1.2	MeCN, 90 °C, 5 h	63
6	3	MeCN, 80 °C, 5 h	25
7 ^c	1.2	THF, rt, 12 h	40

^aReactions were carried out on 0.15 mmol of **8a**, 0.2 mmol of **2a**, and 0.25 mmol of CsF in 2 mL of solvent. Compound **2a** was the limiting agent. One equivalent of H₂O = 0.1 mmol. ^bIsolated yield. ^cReaction was performed with 18-crown-6 (2 equiv).

In terms of carbodiimides, the commercially available dicyclohexyl and diisopropyl ones worked well under our conditions. More sterically hindered di-*tert*-butylcarbodiimide afforded a lower yield (entry 9). Carbodiimides with two small primary alkyl groups, such as methyl or ethyl, are highly unstable and were not examined.¹⁶ Those with aromatic groups exhibited very low reactivity at 80 °C and led to complex mixtures upon further heating.¹⁴ Although we did not anticipate a good regioselectivity in the C=N bond insertion step for unbiased unsymmetrical carbodiimides, substrate **8d** bearing a tertiary and a primary alkyl groups afforded a complete regioselectivity with the C=N insertion taking place on the less hindered site (entry 10). *N*-Alkyl-*N'*-arylcarbodiimides tested were either unstable or did not afford the desired products (not shown). A few arynes were also examined. The biased 3-methoxybenzyne derived from **2b** resulted in a complete regioselectivity (entry 11). This time, the less biased 4-methoxybenzyne derived from **2c** afforded a mixture of all four possible regioisomers (entry 12). The reaction with **2d** was uneventful despite a modest yield (entry 13).

Before we conclude this section, it should be additionally noted that Hsieh and co-workers have previously reported that isocyanates, which are isoelectronic to carbodiimides, react with arynes in a completely different mechanism and outcome.¹⁷ The nitrogen atom of isocyanate is sufficiently nucleophilic to arynes, but the [2 + 2] cycloaddition did not occur (vide infra, cf. Scheme 5a). Since our reaction conditions are slightly different from Hsieh's (no lutidine, different stoichiometry, and use of MeOH in place of water), we attempted to employ


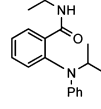
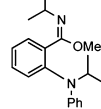
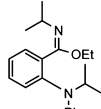
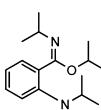
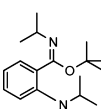
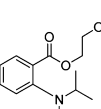
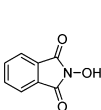
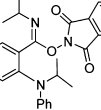
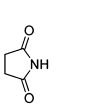
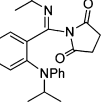
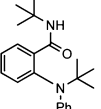
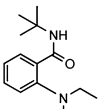
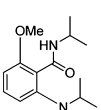
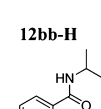
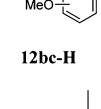
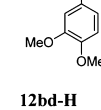
4-chlorophenylisocyanate **13** (entry 14) under our reaction conditions to see if it could lead to a successful [2 + 2] cycloaddition. To our disappointment, product **14** was isolated in 38% yield coming from Hsieh's chemistry, and no product **11** or **12** was obtained. Such results showcase another example that isoelectronic replacement of atoms in substrates for arynes chemistry can result in significantly altered mechanism and final product.

Scheme 5a illustrates the contrasted mechanisms for isocyanates and carbodiimides. As the direct [2 + 2] cycloaddition is forbidden in both cases by the Woodward–Hoffmann rule, the real reactions should take a stepwise mechanism by bonding N(isocyanate/carbodiimide)–C(benzyne) first leading to species **15** and then closing the C–C bond afterward. A brief intrinsic reaction coordinate calculation (IRC, electronic energies) has shown that species **15** are not stationary points and lie on a fairly flat plateau (see the Supporting Information for details). The energetic profile for the transition from **8** to **15A**/**15B** comes with a big difference: it takes 10.5 kcal/mol (Gibbs free energies, B3LYP/6-31++(d,p) level, using dimethylcarbodiimide as the substrate, solvation effect considered) to convert **8** to **15A**, but 20.6 kcal/mol (Gibbs free energies, B3LYP/6-31++(d,p) level, using methyl isocyanate as the substrate, solvation effect considered) to convert **13** to **15B**. This difference is in agreement with a decrease in the negative charges on the X atoms during the [2 + 2] cycloaddition step (see the Supporting Information for details), which might partially account for the latter reaction coming with a higher energy barrier (as it is energy-costing for an oxygen atom to suffer from substantial decrease in negative charge). It is also probably why, in Hsieh's chemistry, lutidine has to be employed so as to generate a much more nucleophilic anionic species to attack arynes.

Another difference lies in the reactivity of species **15**, which remains not well understood to us. For **15A** derived from carbodiimides (X = NR), the aryl anion prefers to cyclize to the central *sp*-carbon and leads to **9**, thus finishing the [2 + 2] event, whereas for **15B** derived from isocyanates, water (or methanol) reacts with it leading to a quick protonation of the aryl anion and the spontaneous formation of carbamate **14**. Although a clear explanation is still lacking, calculation shows that **15B** from isocyanate features a more negatively charged (Mulliken) aryl anion that could be more easily protonated (or quenched by other electrophiles). However, certainly other unclear factors are also in play to account for this difference in reactivity.

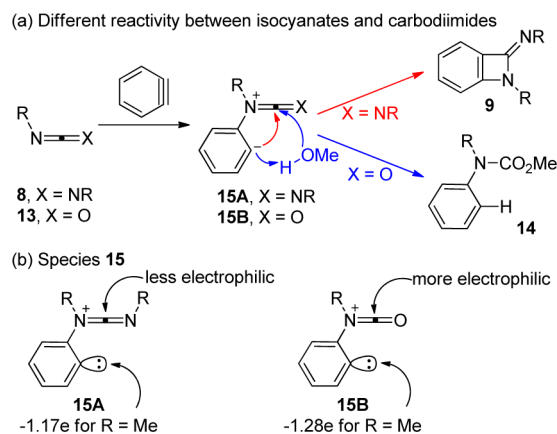
Ring-Opening Step and the Nature of the QM Intermediate. As mentioned before (cf. Scheme 1), the arynes insertion of C=X bonds is the net result of two steps, an

Table 4. Scope of the Reaction of Carbodiimides with Arynes^a

$ \begin{array}{c} \text{R}^1 \\ \text{N}=\text{C}=\text{N} \\ \text{R}^2 \end{array} \xrightarrow[\text{MeCN, 80 } ^\circ\text{C, 5 h}]{\begin{array}{c} \text{2 (2 equiv)} \\ \text{CsF (2.5 equiv)} \\ \text{HNu (1.2 equiv)} \end{array}} \begin{array}{c} \text{R}^1 \\ \text{N} \\ \text{Nu} \\ \text{R}^2 \\ \text{Ph} \end{array} $						
entry	8	2	HNu	product	yield ^b /%	
1		2a	H ₂ O		71	8
	8b			12ba-H		2a
2	8b	2a	MeOH		81 ^c	9
				12ba-Me		8c
3	8b	2a	EtOH		69 ^c	10
				12ba-Et		8d
4	8b	2a	ⁱ PrOH		64 ^c	11
				12ba-Pr		8b
5	8b	2a	^t BuOH		- (56)	12
				12ba-Bu		8b
6	8b	2a	ethylene glycol		57 ^d	13
				12ba-G		8b
7	8b	2a			- (29)	14
				12ba-Phth		8b
8	8b	2a			37 ^c	
				12ba-Su		
9	8c	2a	H ₂ O		35	
				12ca-H		
10	8d	2a	H ₂ O		41	
				12da-H		
11	8b	2b	H ₂ O		46	
				12bb-H		
12	8b	2c	H ₂ O		76 ^f	
				12bc-H		
13	8b	2d	H ₂ O		43	
				12bd-H		
14	13	2a	MeOH		38	
				14		

^aReactions were performed with 0.3 mmol of **8** in 4 mL of MeCN. Aryne was the limiting agent. One equivalent = 0.2 mmol. ^bIsolated yield. Yields in parentheses refer to the corresponding amide products obtained by moisture intrusion. ^cUsing 2.4 equiv of alcohol. ^dThe corresponding **11ba-G** product (without the N-phenylation) was also isolated in ~18% yield. ^eThe corresponding **11ba-Su** product (without the N-phenylation) was also isolated in ~12% yield. ^fContaining four inseparable regioisomers; see the Experimental Section for details.

Scheme 5. Difference between Carbodiimides and Isocyanates



initial [2 + 2] cycloaddition and a subsequent ring opening. The latter step may have two distinctly different mechanistic concerns. As reported by Oppolzer,¹⁸ the ring opening of benzannulated four-membered rings was found to be highly dependent upon the exocyclic substituents on the four-membered ring: the more electron-rich the exocyclic atoms are, the easier the rings would open. This is in high agreement with the possibility that the π -electrons of the exocyclic substitution are involved in the ring-opening process, as described in Scheme 6, pathway C. In this mechanism, both the ring-opening process from 3 to 4 (for vinylogous amides) and that from 9 to 10 (for carbodiimides) can be considered as a lone-pair-assisted, strain-driven ring opening that leads to inner-salt-typed intermediates 4-IS and 10-IS, where the aromaticity of the benzene rings remains intact. A second possibility is the classical retro-4 π electrocyclization process, which to some extent breaks the aromaticity of the benzene rings and leads to classical *o*-quinomethide intermediates 4-QM and 10-QM (Scheme 6, path D). Although we believed that these two pathways should be considered as two extremes and the real events should be hybrids of the two, we were still interested to look into these mechanistic details, in hope of shedding light on future reaction design and development.

We first studied the ring-opening process from 3 to 4 at the B3LYP/6-31++(d,p) level, using a simplified system of methyl 3-(dimethylamino)acrylate. According to Figure 1, it can be seen that structure 3 features a benzene ring with a significant level of bond length averaging, except that the right side of the benzene ring is slightly compressed. The harmonic oscillator model of aromaticity (HOMA) index¹⁹ for this benzene ring is 0.965, close to unity for an ideal benzene. Since 4-IS and 4-QM

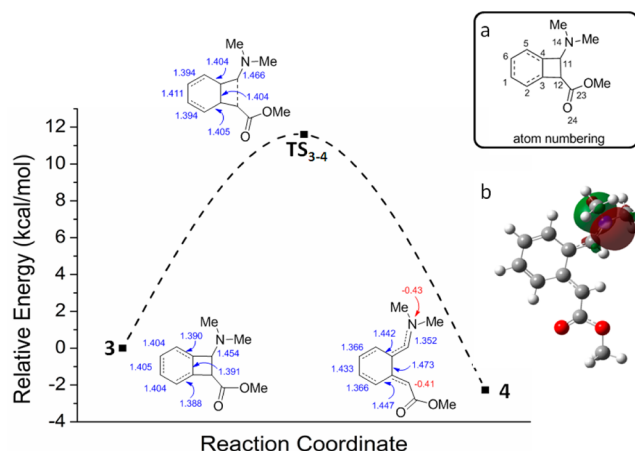
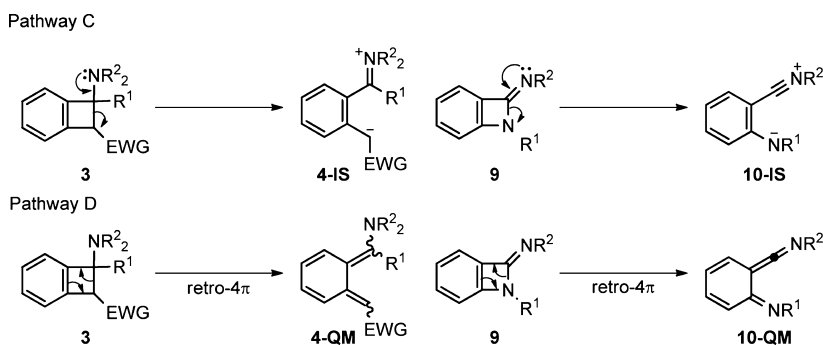


Figure 1. Ring-opening mechanism of vinylogous amides in acetonitrile (bond lengths are in Å, and NBO charges are in red; Gibbs free energies are reported here). Insets: (a) atom numbering, (b) the lone pair NBO orbital on nitrogen in 4.

are two resonance structures representing the same chemical entity, the ring opening from 3 to 4 should experience a single transition state $TS_{3,4}$ (not one for 4-IS and another for 4-QM), which can be located along the reaction coordinate (Figure 1; intrinsic reaction coordinate analysis can be found in the Supporting Information). From 3 to 4, the three shorter bonds on the right side of the benzene ring (C2–C3, C3–C4, and C4–C5) were considerably lengthened, and the C11–C12 bond was broken. At the same time, the C1–C2 and C5–C6 bonds were significantly shortened. For structure 4, the C1–C2 and C5–C6 bonds have more double bond character and the other four on the benzene ring have more single bond character. In particular, the C3–C4 bond is the longest and closest to a single bond, arguing against an aromatized structure in 4-IS. The HOMA index for the benzene ring in 4 is only 0.284, suggesting a big loss of aromaticity, another piece of clear evidence that 4 has a significant quinomethide (4-QM) character. Moreover, the natural bond orbital (NBO) charges of N14 and C12 in structure 4 are –0.43 and –0.41, respectively. This further disfavors the inner salt (IS) structure, which should have positive charge on N14. Further NBO calculation for structure 4 reveals a lone pair on N14 (Figure 1b), contrary to the 4-IS structure. All of these results support 4 as mainly an *o*QM, and the ring opening of 3 is featured mainly with a retro-4 π electrocyclic process. That said, the C5–C4–C11–N14 dihedral angle in $TS_{3,4}$ was 50°, suggesting not to rule out a weak interaction of the N14 lone pair with the C11–C12 σ^* orbital in the transition state (the ideal dihedral angle for path C should be 90°).

Scheme 6. Two Mechanism Extremes for the Ring-Opening Step



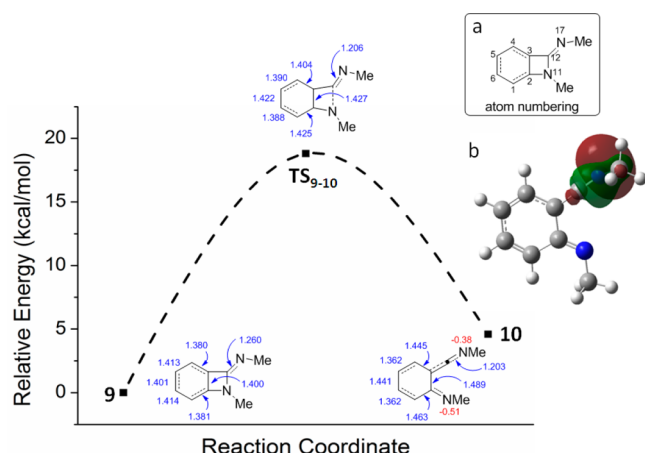


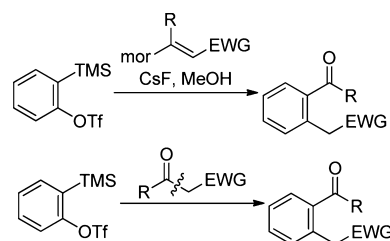
Figure 2. Ring-opening mechanism of **9** in acetonitrile (bond length are in Å, and NBO charges are in red; Gibbs free energies are reported here). Insets: (a) atom numbering, (b) the lone pair NBO orbital on nitrogen in **10**.

Next, the same step from **9** to **10** was calculated, again using a simplified system of dimethylcarbodiimide. As shown in Figure 2, structure **9** also features a benzene ring with a significant level of bond length averaging, but less than the extent for **3**. Here, the C1–C2, C3–C4, and C5–C6 bonds are shorter than the other three. The HOMA aromaticity index for this benzene ring is 0.926, less than that for **3** but again close to unity for an ideal benzene. From **9** to **10**, it is very clear that the C2–C3 bond is considerably lengthened with the separation of C12–N11. Once again, the resultant structure **10** features more double bond character for C4–C5 and C1–C6 and more single bond character for the other four bonds, in particular C2–C3. These results are again consistent to the classical view of an aza-quinomethide (**10-QM**) structure but not the inner salt (**10-IS**). The HOMA aromaticity index for the benzene ring of **10** is 0.007, indicative of a complete loss of aromaticity. The NBO charges of the two nitrogen atoms in **10** are -0.38 and -0.51 , respectively, arguing against a positively charged N17 atom in the structure of **10-IS**. Further calculation for **10** also reveals a lone pair at N17 (Figure 2b), further suggesting the QM structure. All of these pieces of evidence, plus a less aromatized structure of **10** compared to that of **4**, are in agreement of **10** as mainly an aoQM. In turn, they also support the process from **9** to **10** being a retro- 4π electrocyclic event. Here the dihedral angle of C4–C3–C12–N17 in TS_{9-10} is small (21° , the ideal dihedral angle for path C should be 0°), again suggesting not to rule out the interaction of N17 lone pair and the C12–N11 σ^* orbital in path C. However, considering that they are not in parallel, their interaction should not be very strong even if they are coplanar.

The energy profiles illustrated in Figures 1 and 2 can be correlated to the Bell–Evans–Polanyi principle: for two similar processes, the higher the activation energy, the less exothermic the reaction is. Thus, the shift from a slight exothermic reaction from **3** to **4** to a slight endothermic reaction from **9** to **10** is well correlated to the much higher activation energy of the latter process, which can be partly linked to the extent of the aromaticity loss according to our calculation.

Correlation to Aryne Single Bond Insertion. Although the two reactions described in this report feature a different mechanism, synthetic chemists would easily wish to compare these reactions to the previously reported arylene insertion into

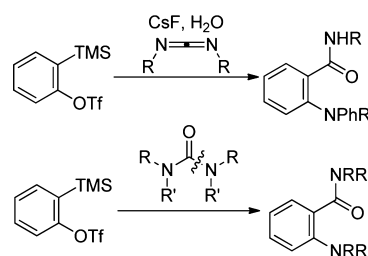
Scheme 7. Comparison of Aryne Insertion Chemistry with Vinylogous Amides and 1,3-Dicarbonyl Compounds



single bonds. For example, the reaction with vinylogous amides appears similar to, at least in the perspective of product formation, the arylene C–C single bond insertion reaction with active methylene compounds (Scheme 7).²⁰ Indeed, compounds **5ba**, **5ca**, **5da**, **5fa**, and **5ia** (cf. Table 2) can all be prepared from the corresponding 1,3-diketones, 3-ketoesters, or 3-ketonitriles according to literature reports. Since some vinylogous amides, including **1b-mor**, **1d-mor**, and **1e-mor** used here, can be prepared from these dicarbonyl compounds, detouring via the intermediacy of vinylogous amides might not seem chemically sound from a synthetic point of view. However, in a more broad perspective, one should keep in mind that arylene C–C single bond insertion does not come up with a substrate scope broad enough to cover every type of active methylene compound. For instance, to date, arynes have not been known to insert into the C–C single bonds of 3-ketoamides,²¹ and therefore compounds **5ga** and **5ha** are inaccessible through such chemistry. The scope of 1,3-diketones has not yet been able to cover unsymmetrical substrates, and therefore formation of compound **5ea** with high regioselectivity would imaginably be an issue. For both 1,3-diketones or 3-ketoesters, the known arylene insertion does not yet cover aldehydic substrates, and therefore formation of compound **5aa** would also be questionable. On the other hand, the difficulty in preparing β -substituted vinylogous amides and the different reactivity of cyclic vinylogous amides (such as **1n-mor**) make the C–C single bond insertion of active methylene compounds more attractive for those particular products. For these reasons, the arylene C=C double bond insertion developed by us and the arylene C–C single bond insertion developed by Stoltz and Yoshida are complementary. Even more so, the vinylogous amides can be prepared more easily from a Michael addition of morpholine to alkynes equipped with EWGs, making a wider scope of substrates accessible.

Similarly, the reaction with carbodiimides would be compared with, at least in the perspective of product formation, the arylene C–N single bond insertion with ureas (Scheme 8).²² Again, as the carbodiimides are prepared from the corresponding ureas, going through the carbodiimides would also appear as a detour. However, careful comparison with the literature

Scheme 8. Comparison of Aryne Insertion Chemistry with Carbodiimides and Ureas



conditions and scopes reveals that these two events are even less alike. For one thing, the urea insertion reaction has to be carried out using the urea as a solvent, thus posing economy and purification problems. The substrate scope of the urea insertion²³ was also limited to those ureas bearing no free NH bonds, primary alkyl groups as R, and only methyls as R', and the sole unsymmetrical urea reported in literature afforded very low yield. Thus at least in these aspects, the carbodiimide chemistry does not have these drawbacks. Interestingly, the urea chemistry and the carbodiimide chemistry offer complementary scopes of substrates: the former is best for substrates bearing small, primary R/R' groups, while the latter is best for those with branched R groups. In addition, the urea insertion could only afford amide products, and access to imidates or amidines remains out of the question. It is yet unfortunate that some carbodiimides are difficult to access and the arylcarbodiimides do not react well.

CONCLUSIONS

In summary, arynes were found to insert into the C=C double bonds of vinylogous amides and the C=N double bonds of carbodiimides. These insertion reactions furnish unstable *o*-quinomethide-typed intermediates, which are confirmed favorable over inner-salt structures by computational studies. These *o*QMs were demonstrated to be intercepted by various nucleophiles to achieve a net *ortho*-difunctionalization of arynes.

EXPERIMENTAL SECTION

The solvents THF and MeCN were distilled from Na/benzophenone and CaH₂, respectively. The silica gel for column chromatography was supplied as 300–400 mesh, and basic alumina for column chromatography (preactivated) was supplied as 200–300 mesh. Powdered CsF was used as received and stored in a desiccator. Anhydrous alcohols were dried over 4 Å molecular sieves before use. All aryne reactions were carried out in oven-dried glassware and were magnetically stirred. A closed system was used, but no efforts were made to exclude air.

All melting points are uncorrected. The ¹H and ¹³C NMR spectra are referenced to the residual solvent signals (7.26 ppm for ¹H and 77.0 ppm for ¹³C in CDCl₃, or 2.05 ppm for ¹H and 29.8 ppm for ¹³C in acetone-*d*₆). The HRMS spectra are recorded using a Fourier-transformed ion cyclotron resonance analyzer.

All compounds in Table 2, with the exception of **1b-Bn**, **1d-Bn**, **1d-mor**, **1g-mor**, **1j-mor**, **5da**, and **5ga**, have been reported in our previous communication⁹ and are adequately characterized. Aryne precursors, carbodiimides, and isocyanate **13** are commercially available and were used as received. The remainder are listed here.

Preparation of Vinylogous Amides (1b-Bn, 1d-Bn, 1d-mor, 1g-mor, 1j-mor, and 1o-mor). Ethyl 3-(Dibenzylamino)but-2-enoate (**1b-Bn**). To a mixture of 22 mg of Zn(OAc)₂·2H₂O (0.1 mmol, 5 mol %) and 260 mg of ethyl acetoacetate (2 mmol) was added 0.58 mL of dibenzylamine (3 mmol, 1.5 equiv) under N₂. The mixture (neat) was stirred at 50 °C for 12 h. The product was recrystallized from petroleum ether. It was collected via suction filtration to afford 457 mg of **1b-Bn** (74%) as a white solid; mp 110–111 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.35 (apparent t, *J* = 7.3 Hz, 4 H), 7.29 (apparent d, *J* = 7.2 Hz, 2 H), 7.14 (apparent d, *J* = 7.1 Hz, 4 H), 4.86 (s, 1 H), 4.52 (s, 4 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 2.61 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

4-(Dibenzylamino)pent-3-en-2-one (1d-Bn). The above procedure was applied to 110 mg of Zn(OAc)₂·2H₂O (0.5 mmol, 5 mol %), 1.03 mL of acetoacetone (10 mmol), and 2.9 mL of dibenzylamine (15 mmol) for 48 h. The product was purified by silica gel column chromatography eluting with 4:1 petroleum ether/EtOAc (with 1.5 vol % Et₃N) to afford 1.12 g of **1d-Bn** (40%) as a light yellow solid (the small quantity of contaminating dibenzylamine can be removed by washing with cold petroleum ether); mp 166–167 °C. ¹H NMR

(400 MHz, CDCl₃): δ 7.37 (apparent t, *J* = 8.2 Hz, 4 H), 7.31–7.28 (m, 2 H), 7.14 (apparent d, *J* = 7.1 Hz, 4 H), 5.33 (s, 1 H), 4.54 (s, 4 H), 2.66 (s, 3 H), 2.02 (s, 3 H).

4-Morpholinopent-3-en-2-one (1d-mor). The above procedure was applied to 55 mg of Zn(OAc)₂·2H₂O (0.25 mmol, 5 mol %), 500 mg of acetoacetone (5 mmol), and 435 μL of morpholine (5 mmol) to afford 540 mg of **1d-mor** (64%) as a white solid (crystallized from petroleum ether at –10 °C); mp 44–45 °C (lit.²⁴ 45–47 °C). ¹H NMR (400 MHz, CDCl₃): δ 5.23 (s, 1 H), 3.72 (apparent t, *J* = 5.0 Hz, 4 H), 3.30 (apparent t, *J* = 5.0 Hz, 4 H), 2.47 (s, 3 H), 2.09 (s, 3H).

N-(p-Tolyl)-3-morpholinobut-2-enamide (1g-mor). To a solution containing 9.5 mg of TsOH·H₂O (0.05 mmol, 5 mol %) and 191 mg of N-(p-tolyl)-3-oxobutanamide²⁵ (1 mmol) in 5 mL of benzene was added 131 μL of morpholine (1.5 mmol). The mixture was stirred at 80 °C for 12 h. The product was recrystallized from benzene to afford 148 mg of **1g-mor** (57%) as a white solid; mp 181–182 °C. ¹H NMR (400 MHz, acetone-*d*₆): δ 8.59 (s, 1 H), 7.54 (d, *J* = 8.2 Hz, 2 H), 7.03 (d, *J* = 8.1 Hz, 2 H), 5.04 (s, 1 H), 3.66 (apparent t, *J* = 4.6 Hz, 4 H), 3.13 (apparent t, *J* = 4.6 Hz, 4 H), 2.45 (s, 3 H), 2.24 (s, 3 H). ¹³C NMR (100 MHz, acetone-*d*₆): δ 167.3, 159.5, 139.3, 131.8, 129.7, 119.5, 93.8, 66.9, 47.4, 20.7, 15.1. HRMS (ESI): calcd for C₁₅H₂₁N₂O₂⁺ [M + H]⁺ 261.1598, found 261.1595.

2-(Morpholinomethylene)malononitrile (1j-mor). To a solution of 610 mg of ethoxymethylenemalononitrile²⁶ (5 mmol) in 5 mL of DCM at 0 °C was added a solution of morpholine (457 μL, 5.25 mmol in 2.8 mL of THF) dropwise over 15 min. The mixture was then allowed to warm to room temperature and stirred for 1 h. The volatiles were evaporated, and the product was crystallized from EtOAc to afford 594 mg of **1j-mor** (73%) as a white solid; mp 148–149 °C (lit.²⁷ 148–149 °C). ¹H NMR (400 MHz, CDCl₃): δ 7.02 (s, 1 H), 3.96 (br, 2 H), 3.81–3.78 (m, 4 H), 3.49 (br, 2 H).

Diethyl 2-Morpholinomaleate (1o-mor). To a solution of 209 mg of morpholine (2.4 mmol) in 7 mL of H₂O was added 340 mg of diethyl acetylenedicarboxylate (2 mmol). The reaction mixture was stirred vigorously at room temperature for 2 h. The product was extracted with ethyl acetate, and the combined extracts were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (3:1 petroleum ether/EtOAc) to afford 461 mg of **1o-mor** (90%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 4.79 (s, 1 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 3.74 (apparent t, *J* = 4.9 Hz, 4 H), 3.14 (apparent t, *J* = 4.9 Hz, 4 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H). The 4.79 ppm signal corresponds to the *E*-isomer.²⁸

Reaction of Arynes with Vinylogous Amides (5da, 5ga, and 7). **1-(2-Acetylphenyl)acetone (5da).** To an oven-dried 10 mL round-bottom flask equipped with a stirrer were added 134 mg of aryne precursor **2a** and 51 mg of **1d-mor**. Dry MeCN (4.5 mL) was added, followed by 0.45 mmol of MeOH (18 μL, reagent grade). CsF (137 mg, 0.9 mmol) was added last, and the mixture was stirred at room temperature for 6 h. Upon completion, the reaction mixture was poured into brine and extracted three times with EtOAc. The combined extracts were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (7:1 petroleum ether/EtOAc) to afford 12 mg of **5da** (23%) as a slightly yellow glass (containing a trace of petroleum ether residue, not affecting yield). ¹H NMR (400 MHz, CDCl₃): δ 7.85 (d, *J* = 7.7 Hz, 1 H), 7.48 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.39 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.18 (d, *J* = 7.5 Hz, 1 H), 4.03 (s, 2 H), 2.58 (s, 3 H), 2.29 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ 205.7, 201.0, 136.5, 135.1, 132.9, 132.2, 130.2, 127.3, 49.4, 30.0, 28.6. HRMS (ESI): calcd for C₁₁H₁₃O₂⁺ [M + H]⁺ 177.0910, found 177.0907.

N-(p-Tolyl)-2-(2-acetylphenyl)acetamide (5ga). The above procedure was applied to 78 mg of **1g-mor** to afford 16 mg of **5ga** (20%) as a white solid; mp 138–139 °C. ¹H NMR (400 MHz, CDCl₃): δ 9.61 (brs, 1 H), 8.17 (dd, *J* = 7.8, 1.1 Hz, 1 H), 7.97 (d, *J* = 7.0 Hz, 1 H), 7.88 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.79–7.73 (m, 3 H), 7.44 (d, *J* = 8.3 Hz, 2 H), 4.18 (s, 2 H), 3.08 (s, 3 H), 2.65 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ 203.9, 168.7, 137.1, 135.9, 135.3, 133.2, 132.7, 132.4, 129.9, 129.3, 127.2, 119.4, 43.1, 29.4, 20.8. HRMS (ESI): calcd for C₁₇H₁₇NNaO₂⁺ [M + Na]⁺ 290.1152, found 290.1152.

Ethyl 2-(3-Ethoxy-2-morpholino-3-oxoprop-1-en-1-yl)benzoate (7). The above procedure was applied to 77 mg of **10-mor** to afford 60 mg of **7** (60%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.40–7.36 (m, 1 H), 7.18 (dd, J = 8.0, 1.6 Hz, 1 H), 7.13–7.09 (m, 2 H), 6.75 (s, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 4.08 (q, J = 7.1 Hz, 2 H), 3.71 (br, 4 H), 2.88 (br, 4 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.11 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, CDCl_3): δ 167.7, 165.7, 150.9, 145.6, 131.5, 130.8, 130.1, 126.8, 123.7, 119.4, 67.1, 61.4, 60.7, 52.2, 14.2, 13.8. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_5^+ [\text{M} + \text{H}]^+$ 334.1649, found 334.1647. A weak NOE correlation was observed: 7.1 to 2.88.

Reaction of Arynes with Carbodiimides (12). Representative procedure (outlined for **12aa-H**, *N*-cyclohexyl-2-(cyclohexyl(phenyl)amino)benzamide in the conditions shown in entry 5, Table 3). To an oven-dried 8 mL vial equipped with a stirrer were added 59.6 mg of **2a** (0.2 mmol) and 30.9 mg of DCC (0.15 mmol). Dry MeCN (2 mL) was added, followed by 2.2 μL of H_2O (0.12 mmol). CsF (38 mg, 0.25 mmol) was added last, and the mixture was stirred at 80 $^\circ\text{C}$ for 5 h. Upon completion, the reaction mixture was poured into brine and extracted three times with EtOAc. The combined extracts were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by silica gel column chromatography (9:1 petroleum ether/EtOAc) to afford 28.8 mg of **12aa-H** (77%) as a slightly yellow solid; mp 83–84 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 8.18 (d, J = 6.8 Hz, 1 H), 7.59 (br, J = 6.8 Hz, 1 H), 7.50–7.41 (m, 2 H), 7.19 (t, J = 7.9 Hz, 2 H), 7.09 (d, J = 7.5 Hz, 1 H), 6.77 (t, J = 7.2 Hz, 1 H), 6.58 (d, J = 8.2 Hz, 2 H), 3.91–3.76 (m, 2 H), 2.08–2.02 (m, 2 H), 1.80–1.60 (m, 5 H), 1.46–1.24 (m, 7 H), 1.13–0.86 (m, 6 H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.3, 147.8, 141.2, 135.7, 132.3, 131.9, 131.2, 129.5, 127.6, 118.2, 114.4, 57.6, 47.6, 32.3, 30.6, 25.9, 25.7, 25.4, 24.0. HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}^+ [\text{M} + \text{H}]^+$ 377.2587, found 377.2578.

***N*-Isopropyl-2-(isopropyl(phenyl)amino)benzamide (12ba-H).** The above procedure was applied to 119 mg of **2a**, 38 mg of **8b**, 4.3 μL of H_2O , and 76 mg of CsF to afford 42 mg of **12ba-H** (71%) as a slightly yellow glass (containing a trace of petroleum ether residue). ^1H NMR (400 MHz, CDCl_3): δ 8.21 (dd, J = 7.6, 1.9 Hz, 1 H), 7.68 (br, J = 6.5 Hz, 1 H), 7.47 (td, J = 7.5, 1.9 Hz, 1 H), 7.42 (td, J = 7.5, 1.4 Hz, 1 H), 7.20 (dd, J = 8.6, 7.4 Hz, 2 H), 7.09 (dd, J = 7.6, 1.2 Hz, 1 H), 6.78 (t, J = 7.3 Hz, 1 H), 6.62 (d, J = 8.1 Hz, 2 H), 4.27 (sept, J = 6.5 Hz, 1 H), 4.09 (oct, J = 6.5 Hz, 1 H), 1.16 (d, J = 6.5 Hz, 6 H), 0.95 (d, J = 6.5 Hz, 6 H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.2, 147.9, 141.3, 135.3, 131.93, 131.92, 131.2, 129.4, 127.6, 118.5, 114.9, 48.8, 41.2, 22.3, 20.3. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}^+ [\text{M} + \text{H}]^+$ 297.1961, found 297.1964.

Methyl *N*-Isopropyl-2-(isopropyl(phenyl)amino)benzimidate (12ba-Me). The above procedure was applied to 119 mg of **2a**, 38 mg of **8b**, 15 mg (2.4 equiv) of MeOH, and 76 mg of CsF to afford 52 mg of **12ba-Me** (contaminated by a small quantity of petroleum ether residue, NMR ratio product:PE (as dodecane) 100:6, corresponding to ~50 mg of pure **12ba-Me**, 81%) as yellow oil after chromatography on basic alumina. ^1H NMR (400 MHz, acetone- d_6): δ 7.49 (td, J = 7.8, 1.7 Hz, 1 H), 7.32 (td, J = 7.4, 1.0 Hz, 1 H), 7.29–7.26 (m, 2 H), 7.09 (dd, J = 8.5, 7.4 Hz, 2 H), 6.69 (t, J = 7.3 Hz, 1 H), 6.64 (d, J = 8.0 Hz, 2 H), 4.22 (sept, J = 6.6 Hz, 1 H), 3.50 (s, 3 H), 3.25 (sept, J = 6.6 Hz, 1 H), 1.21 (d, J = 6.6 Hz, 6 H), 0.84–0.81 (br, 6 H) (this compound may have two rotamers or *E/Z* isomers; some signals can be attributed to the minor rotamer/isomer: 7.21 (td, J = 8.8, 1.5 Hz), 6.94 (dd, J = 7.5, 1.3 Hz), 6.73 (d, J = 8.5 Hz), 3.70 (s), 3.71–3.68 (m), 3.31 (sept, J = 6.3 Hz), 1.17 (d, J = 6.3 Hz), 1.02 (d, J = 6.2 Hz)). ^{13}C NMR (100 MHz, acetone- d_6): δ 158.8, 149.1, 145.1, 135.1, 131.6, 130.7, 130.6, 129.2, 126.2, 119.0, 118.3, 52.5, 51.7, 50.0, 25.1, 21.4. HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}^+ [\text{M} + \text{H}]^+$ 311.2118, found 311.2114.

Ethyl *N*-Isopropyl-2-(isopropyl(phenyl)amino)benzimidate (12ba-Et). The above procedure was applied to 119 mg of **2a**, 38 mg of **8b**, 22 mg of EtOH (2.4 equiv), and 76 mg of CsF to afford 47 mg of **12ba-Et** (contaminated by a small quantity of petroleum ether residue, NMR ratio product:PE (as dodecane) 100:7, corresponding to ~45 mg of pure **12ba-Et**, 69%) as a yellow oil after chromatography on basic alumina. ^1H NMR (400 MHz, acetone- d_6): δ 7.49 (td, J = 7.6, 1.9 Hz, 1 H), 7.33 (td, J = 7.3, 1.1 Hz, 1 H), 7.30–7.27 (m, 2 H),

7.08 (dd, J = 8.7, 7.3 Hz, 2 H), 6.67 (t, J = 7.3 Hz, 1 H), 6.62 (dd, J = 7.3, 0.9 Hz, 2 H), 4.26 (sept, J = 6.6 Hz, 1 H), 3.94 (q, J = 7.1 Hz, 2 H), 3.25 (sept, J = 6.1 Hz, 1 H), 1.22 (d, J = 6.6 Hz, 6 H), 1.05 (t, J = 7.1 Hz, 3 H), 0.87–0.83 (br, 6 H) (this compound may have two rotamers or *E/Z* isomers; some signals can be attributed to the minor rotamer/isomer: 7.21 (td, J = 7.8, 1.6 Hz), 6.95 (dd, J = 7.4, 1.6 Hz), 6.73 (d, J = 8.2 Hz), 4.19 (q, J = 7.1 Hz), 3.68 (sept, J = 6.3 Hz), 3.33 (sept, J = 6.2 Hz), 1.17 (d, J = 6.3 Hz), 1.02 (d, J = 6.2 Hz)). ^{13}C NMR (100 MHz, acetone- d_6): δ 158.3, 149.1, 144.7, 135.4, 131.8, 130.65, 130.56, 129.1, 126.3, 118.7, 118.5, 61.0, 51.3, 50.0, 25.2, 21.3, 14.4. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}^+ [\text{M} + \text{H}]^+$ 325.2274, found 325.2276.

Isopropyl *N*-Isopropyl-2-(isopropyl(phenyl)amino)benzimidate (12ba-Pr). The above procedure was applied to 119 mg of **2a**, 38 mg of **8b**, 29 mg of *i*-PrOH (2.4 equiv), and 76 mg of CsF to afford 45 mg of **12ba-Pr** (contaminated by a small quantity of petroleum ether residue, NMR ratio product:PE (as dodecane) 100:8, corresponding to ~43 mg of pure **12ba-Pr**, 64%) as a yellow oil after chromatography on basic alumina. ^1H NMR (400 MHz, acetone- d_6): δ 7.50 (td, J = 7.7, 1.8 Hz, 1 H), 7.36 (td, J = 7.4, 1.1 Hz, 1 H), 7.30 (dd, J = 7.6, 1.7 Hz, 1 H), 7.27 (dd, J = 7.9, 0.8 Hz, 1 H), 7.07 (dd, J = 8.7, 7.3 Hz, 2 H), 6.64 (t, J = 7.3 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 2 H), 4.98 (sept, J = 6.2 Hz, 1 H), 4.30 (sept, J = 6.6 Hz, 1 H), 3.25 (sept, J = 6.1 Hz, 1 H), 1.22 (d, J = 6.6 Hz, 6 H), 1.07 (d, J = 6.2 Hz, 2 H), 0.87–0.83 (br, 6 H) (this compound may have two rotamers or *E/Z* isomers; some signals can be attributed to the minor rotamer/isomer: 7.20 (td, J = 7.8, 1.6 Hz), 6.93 (dd, J = 7.4, 1.6 Hz), 6.74–6.70 (m), 5.22 (sept, J = 6.8 Hz), 3.68 (sept, J = 6.1 Hz), 3.32 (sept, J = 6.2 Hz), 1.26 (d, J = 6.2 Hz), 1.17 (d, J = 6.3 Hz), 1.01 (d, J = 6.2 Hz)). ^{13}C NMR (100 MHz, acetone- d_6): δ 157.4, 149.3, 144.1, 136.1, 132.4, 130.6 (2C), 129.1, 126.6, 118.2, 117.7, 67.0, 50.9, 50.0, 25.1, 21.9, 21.2. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{31}\text{N}_3\text{O}^+ [\text{M} + \text{H}]^+$ 339.2431, found 339.2428.

2-Hydroxyethyl 2-(isopropyl(phenyl)amino)benzoate (12ba-G). The above procedure was applied to 119 mg of **2a**, 38 mg of **8b**, 15 mg of ethylene glycol, and 76 mg of CsF to afford 34 mg of **12ba-G** (57% based on aryne, high-running spot, a yellow oil, containing a trace of petroleum ether residue) and 12 mg of **11ba-G** (18% based on carbodiimide, low-running spot)¹⁵ eluting with 10:7.5:1 petroleum ether/ CH_2Cl_2 /EtOAc. **12ba-G:** ^1H NMR (400 MHz, CDCl_3): δ 7.92 (dd, J = 7.7, 1.6 Hz, 1 H), 7.60 (td, J = 7.7, 1.6 Hz, 1 H), 7.44 (td, J = 7.6, 1.0 Hz, 1 H), 7.22–7.15 (m, 3 H), 6.70 (t, J = 7.2 Hz, 1 H), 6.52 (d, J = 8.1 Hz, 2 H), 4.31 (sept, J = 6.5 Hz, 1 H), 4.16–4.14 (m, 2 H), 3.46–3.44 (m, 2 H), 1.13 (d, J = 6.5 Hz, 6 H), OH not observed. ^{13}C NMR (100 MHz, CDCl_3): δ 167.8, 148.4, 141.8, 133.9, 133.1, 133.0, 131.4, 129.0, 127.2, 116.6, 113.2, 67.0, 60.9, 48.5, 21.0. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_3^+ [\text{M} + \text{H}]^+$ 300.1594, found 300.1592.

1-((2-(isopropyl(phenyl)amino)phenyl)(isopropylimino)methyl)pyrrolidine-2,5-dione (12ba-Su), and 1-((2-(isopropylamino)phenyl)(isopropylimino)methyl)pyrrolidine-2,5-dione (11ba-Su). The above procedure was applied to 119 mg of **2a**, 38 mg of **8b**, 24 mg of succinimide, and 76 mg of CsF to afford 28 mg of **12ba-Su** (37% based on aryne, high-running spot, a light yellow solid; mp 170 $^\circ\text{C}$) and 11 mg of **11ba-Su** (12% based on carbodiimide, low-running spot, a yellow solid; mp 136–137 $^\circ\text{C}$). **12ba-Su:** ^1H NMR (400 MHz, CDCl_3): δ 7.82 (dd, J = 7.2, 2.1 Hz, 1 H), 7.52–7.45 (m, 2 H), 7.15–7.06 (m, 3 H), 6.70 (t, J = 7.2 Hz, 1 H), 6.40 (d, J = 6.5 Hz, 2 H), 4.26 (sept, J = 6.5 Hz, 1 H), 3.47 (sept, J = 6.1 Hz, 1 H), 2.32–2.24 (m, 2 H), 1.81–1.38 (m, 2 H), 1.26–1.21 (br, 6 H), 1.11–1.04 (br, 6 H) (this compound may have two rotamers or *E/Z* isomers; some signals can be attributed to the minor rotamer/isomer: 7.62–7.54 (m), 7.21 (d, J = 7.8 Hz), 6.33 (d, J = 8.1 Hz), 4.34 (sept, J = 6.5 Hz), 3.86 (sept, J = 6.1 Hz)). ^{13}C NMR (100 MHz, CDCl_3): δ 174.7 (br), 148.0, 145.7, 140.5, 138.7, 133.2, 132.0, 131.5, 129.1, 128.2, 116.8, 113.7, 52.7, 48.4, 26.5, 23.0 (br), 19.6 (br). HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}_2^+ [\text{M} + \text{H}]^+$ 378.2176, found 378.2177. **11ba-Su:** ^1H NMR (400 MHz, CDCl_3): δ 9.47 (br, 1 H), 7.16 (t, J = 7.5 Hz, 1 H), 6.86 (d, J = 7.9 Hz, 1 H), 6.68 (br, 1 H), 6.44 (br, 1 H), 3.65 (sept, J = 6.3 Hz, 1 H), 3.39 (sept, J = 6.1 Hz, 1 H), 2.94–2.82 (m, 4 H), 1.22 (d, J = 6.3 Hz, 6 H), 1.17 (d, J = 6.2 Hz, 6 H). ^{13}C NMR (150 MHz, CDCl_3): δ 174.9, 149.2 (br), 145.0, 132.1, 129.0, 113.7 (br), 112.0 (br), 111.6 (br), 52.5, 43.6 (br), 28.6, 24.4, 22.8. HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{24}\text{N}_3\text{O}_2^+ [\text{M} + \text{H}]^+$ 302.1863, found 302.1857.

N-(tert-Butyl)-2-(tert-butyl(phenyl)amino)benzamide (12ca-H). The above procedure was applied to 119 mg of **2a**, 46 mg of **8c**, 4.3 μL of H_2O , and 76 mg of CsF to afford 23 mg of **12ca-H** (35%) as a yellow oil (containing a trace of petroleum ether residue). ^1H NMR (400 MHz, CDCl_3): δ 8.23 (brs, 1 H), 8.18 (dd, $J = 7.4, 2.1$ Hz, 1 H), 7.44–7.31 (m, 2 H), 7.16 (dd, $J = 8.7, 7.4$ Hz, 2 H), 7.07 (dd, $J = 7.5, 1.4$ Hz, 1 H), 6.89 (d, $J = 8.2$ Hz, 2 H), 6.80 (t, $J = 7.3$ Hz, 1 H), 1.45 (s, 9 H), 1.30 (s, 9 H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.4, 147.7, 144.8, 136.0, 131.9, 131.4, 130.5, 128.6, 127.0, 119.6, 119.1, 57.2, 51.0, 29.1, 28.6. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{NaO}^+ [\text{M} + \text{Na}]^+$ 347.2094, found 347.2093.

N-(tert-Butyl)-2-(ethyl(phenyl)amino)benzamide (12da-H). The above procedure was applied to 119 mg of **2a**, 38 mg of **8d**, 4.3 μL of H_2O , and 76 mg of CsF to afford 24 mg of **12da-H** (41%) as a slightly yellow glass (containing a trace of petroleum ether residue). ^1H NMR (400 MHz, CDCl_3): δ 8.12 (dd, $J = 7.8, 1.6$ Hz, 1 H), 7.65 (brs, 1 H), 7.45 (td, $J = 7.8, 1.5$ Hz, 1 H), 7.37 (t, $J = 7.5$ Hz, 1 H), 7.20 (dd, $J = 8.6, 7.4$ Hz, 2 H), 7.12 (dd, $J = 7.8, 0.8$ Hz, 1 H), 6.80 (t, $J = 7.3$ Hz, 1 H), 6.67 (d, $J = 8.0$ Hz, 2 H), 3.66 (q, $J = 7.1$ Hz, 2 H), 1.23–1.19 (m, 12 H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.2, 148.1, 144.1, 134.4, 132.0, 131.2, 129.8, 129.4, 127.0, 118.8, 114.5, 50.8, 46.7, 28.5, 12.3. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}^+ [\text{M} + \text{H}]^+$ 297.1961, found 297.1961.

N-Isopropyl-2-(isopropyl(3-methoxyphenyl)amino)-6-methoxybenzamide (12bb-H). The above procedure was applied to 131 mg of aryne precursor **2b**, 38 mg of **8b**, 4.3 μL of H_2O , and 76 mg of CsF to afford 33 mg of **12bb-H** (46%) as a white solid; mp 90–91 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 7.37 (t, $J = 8.1$ Hz, 1 H), 7.04 (t, $J = 8.1$ Hz, 1 H), 6.92 (d, $J = 8.4$ Hz, 1 H), 6.75 (d, $J = 7.8$ Hz, 1 H), 6.23 (d, $J = 7.2$ Hz, 1 H), 6.05–6.02 (m, 2 H), 5.43 (d, $J = 7.5$ Hz, 1 H), 4.21 (sept, $J = 6.4$ Hz, 1 H), 3.99 (oct, $J = 6.8$ Hz, 1 H), 3.86 (s, 3 H), 3.72 (s, 3 H), 1.19 (d, $J = 6.5$ Hz, 6 H), 0.80 (d, $J = 6.5$ Hz, 6 H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.3, 160.9, 158.0, 150.3 (br), 140.7, 130.6, 130.0, 129.0, 123.9, 110.3, 106.5 (br), 100.8 (br), 100.0 (br), 55.9, 55.1, 48.8 (br), 41.1, 22.0, 20.9. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}]^+$ 357.2173, found 357.2168.

N-Isopropyl-2-(isopropyl(3/4-methoxyphenyl)amino)-4/5-methoxybenzamide (12bc-H, 4 regioisomers). The above procedure was applied to 131 mg of aryne precursor **2c**, 38 mg of **8b**, 4.3 μL of H_2O , and 76 mg of CsF to afford 56 mg of **12bc-H**. This mixture can be separated into two fractions. The high-running fraction (33 mg) contains two regioisomers (NMR ratio 1:0.75, 46.5% combined yield, with a trace of petroleum ether residue). ^1H NMR (400 MHz, CDCl_3): δ 8.81 (d, $J = 5.9$ Hz, 1 H, major), 7.81 (br, 1 H, major), 7.69 (dd, $J = 2.3, 0.9$ Hz, 1 H, minor), 7.56 (d, $J = 6.5$ Hz, 1 H, minor), 7.09 (t, $J = 8.2$ Hz, 1 H, minor), 6.99–6.98 (m, 2 H, minor), 6.96–6.95 (m, 2 H, major), 6.77 (d, $J = 9.0$ Hz, 2 H, major), 6.68 (d, $J = 8.9$ Hz, 2 H, major), 6.32 (dd, $J = 8.1, 1.9$ Hz, 1 H, minor), 6.19 (dd, $J = 8.3, 2.1$ Hz, 1 H, minor), 6.16 (t, $J = 2.3$ Hz, 1 H, minor), 4.24–4.03 (m, 2 H, major + 2 H, minor), 3.86 (s, 3 H, minor), 3.85 (s, 3 H, major), 3.73 (s, 3 H, major), 3.71 (s, 3 H, minor), 1.13 (d, $J = 6.3$ Hz, 6 H, major), 1.12 (d, $J = 6.4$ Hz, 6 H, minor), 1.05 (d, $J = 6.5$ Hz, 6 H, major), 0.95 (d, $J = 6.5$ Hz, 6 H, minor). ^{13}C NMR (150 MHz, CDCl_3): δ 165.1, 164.7, 160.8, 158.6, 158.0, 153.1, 149.6, 142.1, 136.4, 136.3, 134.6, 133.1, 133.0, 132.1, 130.2, 119.0, 118.7, 117.8, 114.6, 114.4, 114.0, 107.6, 102.7, 101.2, 55.53, 55.50 (2C), 55.1, 49.6, 48.8, 41.23, 41.19, 22.5, 22.3, 20.5, 20.3. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}]^+$ 357.2173, found 357.2174. The low-running fraction (23 mg, contaminated by a small quantity of petroleum ether residue, NMR ratio product:PE (as dodecane) 100:19, corresponding to ~ 21 mg of pure product) contains the other two regioisomers (NMR ratio 1:0.9, 29.5% combined yield); ^1H NMR (400 MHz, CDCl_3): δ 8.87 (br, 1 H, major), 8.28–8.26 (br, 1 H, major), 8.20 (d, $J = 8.8$ Hz, 1 H, minor), 7.67–7.70 (br, 1 H, minor), 7.11 (t, $J = 8.2$ Hz, 1 H, minor), 6.95 (dd, $J = 8.8, 2.5$ Hz, 1 H, minor), 6.88 (d, $J = 8.8$ Hz, 1 H, major), 6.76–6.81 (br, 4 H, major), 6.57 (d, $J = 2.5$ Hz, 1 H, minor), 6.55 (br, 1 H, major), 6.36 (dd, $J = 8.0, 2.0$ Hz, 1 H, minor), 6.25–6.21 (m, 2 H, minor), 4.25–4.05 (m, 2 H, major + 2 H, minor), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 1.18–1.16 (m, 6 H, major isomer + 6 H, minor isomer), 1.08 (d, $J = 6.1$ Hz, 6 H, a signal for its rotamer

comes at 1.04), 0.97 (d, $J = 6.5$ Hz, 6 H, a signal for its rotamer comes at 0.99). ^{13}C NMR (150 MHz, CDCl_3): δ 164.8, 164.8–164.7 (br), 162.2 (2C), 160.7, 153.5 (br), 149.0, 146.3, 142.6, 141.7–141.4 (br), 132.8, 132.7 (br), 130.1, 127.4, 119.1 (br), 117.0, 116.0 (br), 114.6 (2C), 112.9, 112.0–111.8 (br), 108.2, 103.1, 101.9, 55.5, 55.4 (2C), 55.1, 50.1 (br), 49.0, 41.0 (2C), 22.7, 22.4, 20.6, 20.3. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}]^+$ 357.2173, found 357.2170. There are many “extra” signals in the ^{13}C NMR spectrum for the low-running fraction (see the Supporting Information). However, LC analysis (see the Supporting Information) shows that both fractions are quite clean. This, together with the broadening of the signals, suggests that these “extra” signals are most likely rotamers or *E/Z* isomers.

2-((3,4-Dimethoxyphenyl)(isopropyl)amino)-N-isopropyl-4,5-dimethoxybenzamide (12bd-H). The above procedure was applied to 143 mg of aryne precursor **2d**, 38 mg of **8b**, 4.3 mg μL of H_2O , and 76 mg of CsF to afford 37 mg of **12bd-H** as a yellow glass (contaminated by a small quantity of petroleum ether residue, NMR ratio product:PE (as dodecane) 100:9, corresponding to ~ 36 mg of pure **12bd-H**, 43%). ^1H NMR (400 MHz, CDCl_3): δ 8.70 (d, $J = 7.5$ Hz, 1 H), 7.82 (s, 1 H), 6.75 (d, $J = 8.8$ Hz, 1 H), 6.47 (s, 1 H), 6.33 (dd, $J = 8.8, 2.7$ Hz, 1 H), 6.27 (d, $J = 2.6$ Hz, 1 H), 4.19–4.08 (m, 2 H), 3.94 (s, 3 H), 3.80 (s, 2 H), 3.77 (s, 3 H), 3.69 (s, 3 H), 1.15 (d, $J = 6.6$ Hz, 6 H), 1.04 (d, $J = 6.6$ Hz, 6 H). ^{13}C NMR (100 MHz, CDCl_3): δ 164.5, 151.4, 149.8, 147.6, 142.9, 142.3, 136.6, 126.4, 112.9, 112.5, 112.4, 107.8, 102.3, 56.3, 55.97, 55.92, 55.8, 49.6, 41.1, 22.6, 20.5. HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{33}\text{N}_2\text{O}_5^+ [\text{M} + \text{H}]^+$ 417.2384, found 417.2375.

Methyl (4-Chlorophenyl)(phenyl)carbamate (14). The above procedure was applied to 119 mg of **2a**, 46 mg of **13**, 8 mg of MeOH, and 80 mg of CsF to afford 25 mg of **14** (contaminated by a small quantity of petroleum ether residue, NMR ratio product:PE (as dodecane) 100:8, corresponding to 24 mg of pure **14**, 38% based on MeOH) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.38–7.34 (m, 2 H), 7.31–7.17 (m, 7 H), 3.76 (s, 3 H). ^{13}C NMR (100 MHz, CDCl_3): δ 155.0, 142.1, 141.2, 131.6, 129.1, 129.0, 127.9, 127.0, 126.5, 53.2. HRMS (ESI): calcd for $\text{C}_{14}\text{H}_{13}^{35}\text{ClNO}_2^+ [\text{M} + \text{H}]^+$ 262.0629, found 262.0629.

■ ASSOCIATED CONTENT

Supporting Information

Computational details, full ^1H and ^{13}C NMR spectra of products and starting materials that are new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) For recent reviews, see: (a) Yoshida, H.; Takaki, K. *Synlett* **2012**, 23, 1725. (b) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, 83, 199.
- (2) (a) Feltenberger, J. B.; Hayashi, R.; Tang, Y.; Babiash, E. S. C.; Hsung, R. P. *Org. Lett.* **2009**, 11, 3666. (b) Ma, Z.-X.; Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2012**, 14, 2742. (c) Blackburn, T.; Ramtohul, Y. K. *Synlett* **2008**, 1159.
- (3) (a) For an overview of early work, see: Caubère, P. Complex bases and complex reducing agents: New tools in organic synthesis. *Top. Curr. Chem.* **1978**, 73, 49–103. (b) For a review of recent advances where ketene acetals or silyl ketene acetals are used, see: Flores-Gaspar, A.; Martin, R. *Synthesis* **2013**, 45, 563.
- (4) (a) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, 50, 6638. (b) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, 12, 1956. (c) Yoshioka, E.; Miyabe, H. *Tetrahedron* **2012**, 68, 179. (d) Yoshioka, E.; Tanaka, H.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2013**, 15, 3938.
- (5) (a) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, 6, 4049. (b) Zhang, T.; Huang, X.; Wu, L. *Eur. J. Org. Chem.* **2012**, 3507.
- (6) (a) Nakayama, J.; Midorikawa, H.; Yoshida, M. *Bull. Chem. Soc. Jpn.* **1975**, 48, 1063. (b) Aly, A. A.; Mohamed, N. K.; Hassan, A. A.; Mourad, A.-F. E. *Tetrahedron* **1999**, 55, 1111.
- (7) (a) Insertion into P=N double bonds: Alajarin, M.; Lopez-Leonardo, C.; Raja, R.; Orenes, R.-A. *Org. Lett.* **2011**, 13, 5668. (b) A formal insertion into C=S double bonds: Biswas, K.; Greaney, M. F. *Org. Lett.* **2011**, 13, 4946.
- (8) For related [4 + 1] processes involving oQMs generated by other means, see: (a) Chen, M.-W.; Cao, L.-L.; Ye, Z.-S.; Jiang, G.-F.; Zhou, Y. G. *Chem. Commun.* **2013**, 49, 1660. (b) Yang, Q.-Q.; Wang, Q.; An, J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem.—Eur. J.* **2013**, 19, 8401. (c) Osyanin, V. A.; Osipov, D. V.; Klimochkin, Y. N. *J. Org. Chem.* **2013**, 78, 5505.
- (9) Li, R.; Wang, X.; Wei, Z.; Wu, C.; Shi, F. *Org. Lett.* **2013**, 15, 4366.
- (10) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, 71, 3198.
- (11) This β -arylation is known for related substrates; see ref 2c and Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, 9, 1029.
- (12) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, 128, 11040.
- (13) The hydrolysis of the imidate may be caused by either the intrusion of moisture or the formation of an orthoamide-like intermediate.
- (14) We were able to detect the desired products by HRMS in the reaction mixture.
- (15) Data for byproduct **11ba-G** (2-hydroxyethyl 2-(isopropylamino) benzoate): off-white solid; mp 64–65 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.94 (dd, J = 8.0, 1.3 Hz, 1 H), 7.37 (ddd, J = 8.4, 7.1, 1.3 Hz, 1 H), 6.78 (d, J = 8.5 Hz, 1 H), 6.61 (t, J = 7.5 Hz, 1 H), 4.42–4.39 (m, 2 H), 3.95–3.93 (m, 2 H), 3.73 (sept, J = 6.3 Hz, 1 H), 1.28 (d, J = 6.3 Hz, 6 H), OH shows a very broad signal from 1.5 to 2.3 ppm. HRMS (ESI): calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_3$ $^+ [\text{M} + \text{H}]^+$ 224.1281, found 224.1277. We were unable to record a satisfactory ^{13}C NMR spectrum even after long scan.
- (16) Palomo, C.; Mestres, R. *Synthesis* **1981**, 373.
- (17) Lee, Y.-H.; Chen, Y.-C.; Hsieh, J.-C. *Eur. J. Org. Chem.* **2012**, 247.
- (18) Oppolzer, W. *Synthesis* **1978**, 793.
- (19) Kruszewski, J.; Krygowski, T. M. *Tetrahedron Lett.* **1972**, 36, 3839.
- (20) (a) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292. (b) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, 127, 5340. (c) Zahid, M.; Ibad, M. F.; Abilov, Z. A.; Langer, P. *J. Fluorine Chem.* **2013**, 146, 80. (d) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2005**, 46, 6729.
- (21) The reaction affords 2-arylation: Mohanan, K.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2012**, 14, 4686.
- (22) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, 41, 3247.
- (23) The aryne C–N single bond insertion may be accompanied by other events. For example, we have found that a five-membered cyclic carbamate undergoes epoxide extrusion during the C–N insertion process: Fang, Y.; Rogness, D. C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2012**, 77, 6262.
- (24) Zhang, Z.-H.; Yin, L.; Wang, Y.-M. *Adv. Synth. Catal.* **2006**, 348, 184.
- (25) Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, 56, 1713.
- (26) Ding, R.; He, Y.; Xu, J.; Liu, H.; Wang, X.; Feng, M.; Qi, C.; Zhang, J.; Peng, C. *Med. Chem. Res.* **2012**, 21, 523.
- (27) Sundaramoorthi, R.; Keenan, T. P. *Synth. Commun.* **2007**, 37, 417.
- (28) Zhou, Y.; Angelici, R. J.; Woo, L. K. *Catal. Lett.* **2010**, 137, 8.

