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Dissecting Alkynes: Full Cleavage of Polarized C≡C Moiety via Sequential Bis-Michael Addition/Retro-Mannich Cascade

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Supporting Information

ABSTRACT: The reaction of diaryl ketoalkynes with 1,2-diamino ethane leads to the full scission of the triple bond with the formation of acetophenone and imidazoline fragments. In this transformation, one of the alkyne carbons undergoes formal reduction with the formation of three C−H bonds, whereas the other carbon undergoes formal oxidation via the formation of three C−N bonds (one π and two σ). Computational analysis confirmed that the key fragmentation step proceeds via a six-membered TS in a concerted manner. Both amines are involved in the fragmentation: the N−H moiety of one amine transfers a proton to the developing negative charge at the enolate oxygen, while the other amine provides direct stereoelectronic assistance to the C−C bond cleavage via a hyperconjugative $n_N \rightarrow \sigma^*_{C-C}$ interaction.

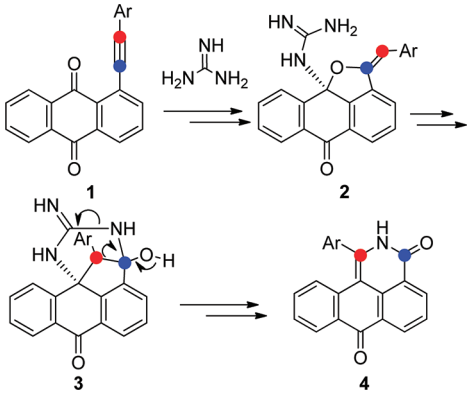
INTRODUCTION

The alkyne moiety plays an important role in organic chemistry, lending itself to a variety of cascade transformations.[1] Expanding earlier studies on the development of new organic reactions where multiple C−H and C−C bonds[2] are formed at the expense of the two alkyne π-systems,[3,4] we have shown that it is possible to break all three bonds of the alkyne moiety, thus accomplishing its full disassembly via the formation of six new bonds (Scheme 1).[5]

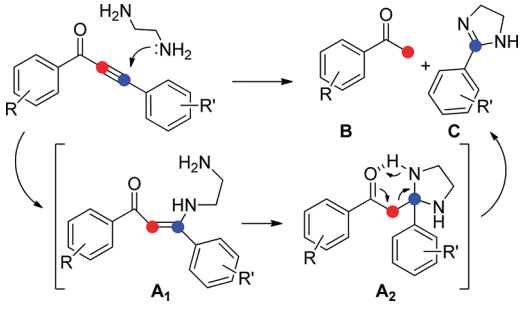
Since the strategic use of fragmentation steps occupies an important niche in the arsenal of synthetic transformations[6] and bioanalytical tools,[7,8] we would like to disclose another example of full alkyne disassembly via the formation of six new bonds at the two alkyne carbons.[9] In this process one carbon undergoes three formal reduction steps with the formation of three C−H bonds, whereas the second alkyne carbon undergoes formal oxidation via the formation of three carbon−nitrogen bonds. This process can be considered as a cleavage of the alkyne moiety via disproportionation (Scheme 2).

This work is conceptually related to the literature examples of efficient Grob fragmentations in 1,4-disubstituted push−pull systems. Communication of suitable donors (anionic centers, heteroatom lone pairs, radical centers,[10e] carbon−metal[4] σ-bonds) with a variety of acceptors (cationic,[4] radical,[10e] and radical-cationic[8,11] centers; $\pi^*_{C=O}$, $\pi^*_{C=N}$,[18] $\pi^*_{C=C}$,[12] and σ^*_{C-X} orbitals[6a]) via a bridge σ-bond weakens this bond, enabling a number of efficient fragmentation patterns (Figure 1). Due to the high donor ability of nitrogen lone pairs[13] and high acceptor ability of carbonyl π^*-orbitals, we envisioned that the through-bond interactions[10] between a nitrogen and a β-carbonyl group would also render such a fragmentation possible. Because the reactant for the fragmentation should be readily available from

Scheme 1. Alkyne Disassembly with the Formation of C═C, C═O, and two C−N Bonds at the Expense of the Alkyne Moiety



Scheme 2. Proposed Pathway for the Complete Disproportionation of Alkyne Moiety



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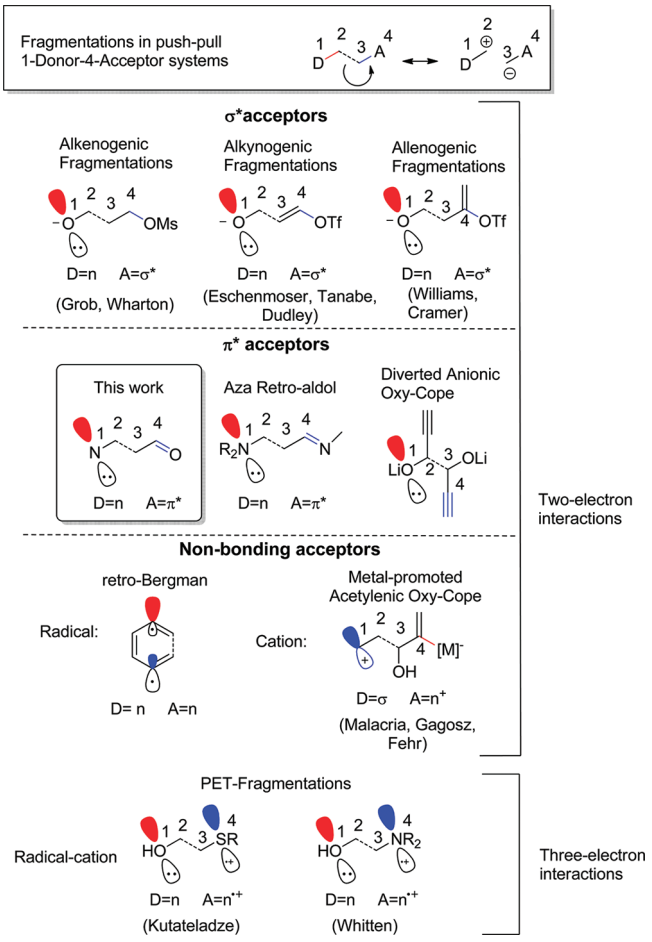


Figure 1. Selected examples of fragmentation patterns in push−pull 1,4-donor−acceptor systems. Donors are shown in red, and acceptors are shown in blue.

double Michael addition to acetylenic ketones, we have chosen these ketones as our model fragmentation substrates.

RESULTS AND DISCUSSION

The keto acetylenes have been prepared via two approaches: (1) addition of Li-acetylides to an aromatic aldehyde followed by MnO_2 oxidation of the intermediate benzylic alcohol (Scheme 3a) and (2) one-step reaction involving Pd-catalyzed coupling of benzoyl chlorides and terminal alkynes[14] (Scheme 3b).

If the starting benzoyl chloride is readily available, the latter synthetic strategy is very efficient and convenient, providing ketoalkynes in 90−97% yields (Table 1).

Initial experiments found that the first (intermolecular) Michael addition proceeds smoothly at room temperature in THF as solvent. Interestingly, the second (intramolecular) Michael addition proceeds much more slowly despite corresponding to a 5-*exo-trig* closure favored according to the Baldwin rules.[16] Even after 18 h of reflux in THF (65 °C), the initial Michael adduct remained unchanged. This lack of reactivity can be attributed to the deactivating effect of the donor amino moiety on the Michael acceptor π-system. Since intramolecular addition is slow, an *inter*molecular reaction of the NH_2 group in the initial adduct with a second ketoalkyne is observed. The formation of bis-adducts can be minimized by decreasing concentrations of the reagents.

Scheme 3. Two Approaches to the Preparation of Ketoalkynes: (a) from Aldehydes, (b) from Benzoyl Chlorides

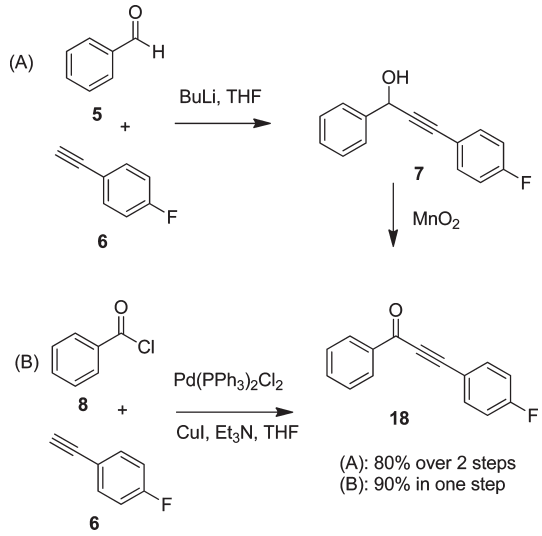
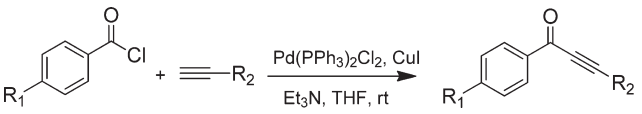


Table 1. Structures and Isolated Yields of Ketoalkynes



entry	R_1	R_2	Product[15]	Yield (%)[a]
1	H, **8**	Ph, **13**	**16**	96
2	H, **8**	*p*-MePh, **14**	**17**	97
3	H, **8**	*p*-FPh, **6**	**18**	90
4	CH_3, **9**	Ph, **14**	**19**	97
5	F, **10**	Ph, **14**	**20**	96
6	Cl, **11**	Ph, **14**	**21**	95
7	 , **12**	Ph, **14**	**22**	95
8	F, **10**	*n*-C_4H_9, **15**	**23**	97

[a] Isolated yield.

The cascade proceeds beyond the first step only when the reaction temperature was increased to 101 °C (refluxing dioxane). Interestingly, only the final retro-Mannich fragmentation products **B** and **C** were found. The intermediate cyclic products of the second (intramolecular) Michael addition were not observed. This observation suggests that the σ_{C-C} bond cleavage in the cyclized intermediate is faster than 5-*exo-trig* closure at the π-bond, in an apparent contradiction to the conventional wisdom that σ-bonds are stronger than π-bonds.

In the case of fragmentation products with a relatively low molecular weight, a more convenient procedure, which facilitated further analysis and isolation, involves running the reaction in a pressure tube in THF. In several cases, the cascade proceeded to full conversion only at 125 °C and longer reaction times (entries 1−7, Table 2). In the case of reactive substrates, however, increase

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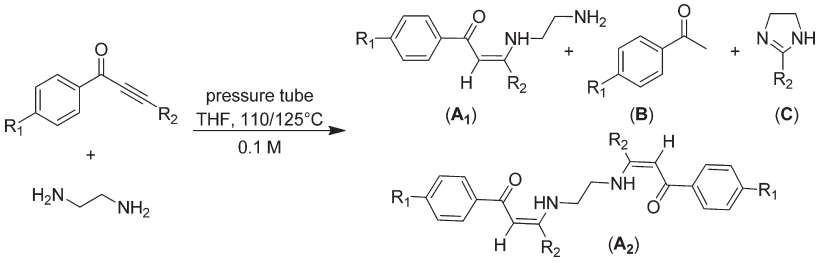
Table 2. Reactions of Ketoacetylenes with 1,2-Diaminoethane at Elevated Temperatures[a]



entry	R_1	R_2	Reaction conditions	Yield B(%)	Yield C(%)	Yield A_1(%)	Yield A_2(%)
1	H	Ph	110°C, 3h	**16b** (59)	**16c** (70)	**16a**$_1$ (12)	**16a**$_2$ (6)
2	H	*p*-MePh	110°C, 3h	**16b** (27)	**17c** (65)	**17a**$_1$ (18)	**17a**$_2$ (1)
3	H	*p*-FPh	110°C, 3h	**16b** (46)	**18c** (90)	**18a**$_1$ (5)	**18a**$_2$ (2)
4	CH_3	Ph	110°C,12h	**19b** (27)	**16c** (54)	**19a**$_1$ (44)	**19a**$_2$(<1)
			125°C,24h	**19b** (48)	**16c** (62)	-	-
5	F	Ph	110°C,12h	**20b** (45)	**16c** (58)	**20a**$_1$ (35)	**20a**$_2$ <1)
			125°C,24h	**20b** (52)	**16c** (96)	-	-
6	Cl	Ph	110°C,12h	**21b** (37)	**16c**, (55)	**21a**$_1$ (42)	**21a**$_2$ <1)
			125°C,24h	**21b** (56)	**16c**, (77)	-	-
7		Ph	110°C,12h	**22b** (50)	**16c** (86)	**22a**$_1$ (13)	**22a**$_2$ (<1)
			125°C,24h	**22b** (35)	**16c** (79)	-	-
8	F	*n*-C_4H_9	125°C,14h	**20b** (34)	**23c** (69)	**23a**$_1$ (9)	**23a**$_2$ (3)

[a] Yields were determined by ^{1}H NMR with benzyl phenyl ether as standard.

in the conversion at higher temperature does not lead to a proportional increase in the product yields (entry 7).

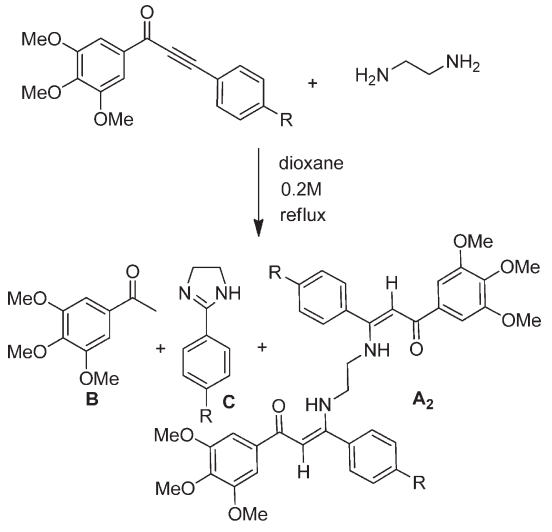
The role of π-system polarization is illustrated by the contrasting effects of *p*-F substituents at the keto and the acetylene ends. Whereas fluorine introduction at the alkyne termini accelerated the overall cascade (~90% completion at 110 °C after 3 h), the same substitution at the carbonyl end decreased the reactivity (~55% of the cyclic product even after 12 h at the same temperature). We have also investigated the reactivity of an aliphatic ketoalkyne (Table 2, entry 8). A lower reaction yield was observed but the fragmentation still proceeded.

We have further investigated the effect of donor groups and alkyne polarization on the efficiency of this cascade using ketoalkynes deactivated by multiple donor substituents at the keto end. Considerably longer times are needed to reach comparable conversions when a donor substituent is added at the alkyne terminus as well (Table 3).

The nature of the intermediates isolated from these reaction mixtures supports the proposed sequence of reactions in the fragmentation cascade. Michael addition to the ketoalkyne quickly provides the vinyl amine A (Scheme 4). The subsequent intramolecular Michael addition via a 5-*exo*-*trig* closure requires higher temperatures and is likely to be the rate-limiting step in the overall cascade. The accelerating effect of the *p*-NO_2 substituent agrees with this notion. The final fragmentation step can be considered as a retro-Mannich reaction which furnishes the enol of acetophenone and an oxidized form of imine formally equivalent to a protected benzoic acid.[17]

A similar transformation has been reported recently by Nenajdenko et al.,[18] who found that treatment of styrenes bearing acceptors with ethylene diamine gave a mixture of fluorinated imidazolidines **30** and nonfluorinated imidazolines **32** and **33** (Scheme 5). Formation of imidazolidines **30** occurred via addition of ethylene diamine at the β-styrene carbon, whereas

Table 3. Reaction of Trimethoxy Substituted Substrates with 1,2-Diaminoethane in Refluxing Dioxane



entry	R	reaction time (h)	yield B (%)	yield C (%)	yield A_2 (%)
1	**24**, -OCH_3	16	**24b** (47)	**24c** (23)	**24a**$_2$ (12)
2	**25**, -Ph	14	**24b** (43)	**25c** (18)	**25a**$_2$ (6)
3	**26**, -H	9	**24b** (45)	**16c** (42)	**26a**$_2$ (6)
4	**27**, -NO_2	0.5	**24b** (35)	**27c** (34)	**27a**$_2$ (13)

compound **31** was formed by the double addition of ethylene diamine to the halostyrene (or acetylene formed *in situ* from the styrene) followed by a fragmentation similar to the one reported in this work. The CF_3 group of the reactant was converted into C2 of the second imidazoline. Again, one of the alkyne

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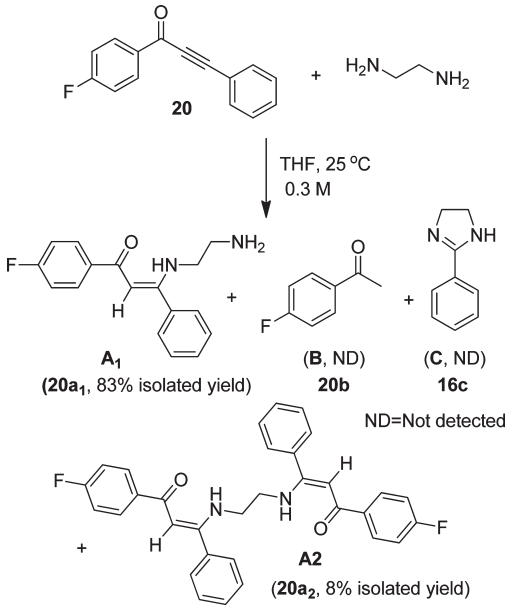
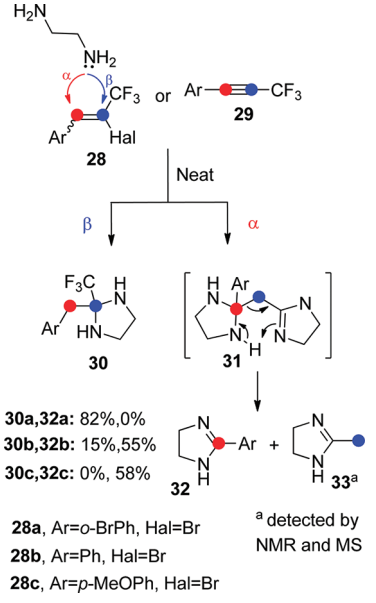
Scheme 4. Reaction at Room Temperature with THF as Solvent



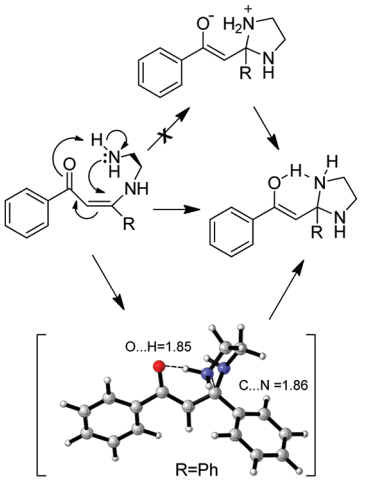
Scheme 5. Fragmentations of Acceptor Styrenes Reported by Nenajdenko et al.[18 a]



[a] Note that C═N moiety serves as the electrophilic component in the retro-aldol step instead of C═O moiety in our system.

carbons is reduced, and the other is oxidized from the formal point of view.

Computational Studies. To gain further insight into the reaction in the previous section, we performed computational studies of the key intramolecular steps of the reaction cascade. All the reactant, product, and transition-state geometries involved in the fragmentation reaction and intramolecular Michael addition were optimized at the B3LYP/6-31+G(d,p) level of theory[18,20]



R	Phase	E_a	$\Delta H^{\neq}$	$\Delta G^{\neq}$	ΔG_r
phenyl	Gas phase	26.2	25.0	28.3	16.5
	SCRF (THF)*	22.8	22.9	23.2	14.8
methyl	Gas phase	27.6	26.5	29.3	17.0
	SCRF (THF)*	24.5	24.1	25.6	16.8

E_a=activation energy, $\Delta H^{\neq}$=activation enthalpy, $\Delta G^{\neq}$=activation free energy, ΔG_r= Gibbs free energy for the reaction. *Single point calculation at the gas phase B3LYP/6-31+G(d,p)geometry, SCRF: Self-consistent reaction field.

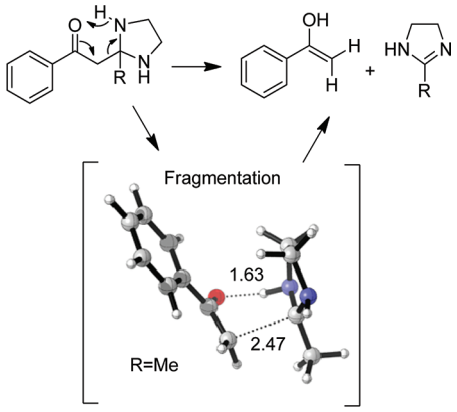
Figure 2. Calculated activation energies, enthalphies and free energies, reaction free energies, and transition state geometries (incipient bond lengths are given in Å) for intramolecular Michael additions via 5-*exo-trig* ring closure.

and single point calculations at the SCRF-B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p) level with THF solvent using Gaussian 03 programs.[21]

The calculated barriers for the 5-*exo-trig* ring closure via intramolecular Michael addition at the α,β-unsaturated carbonyl compound were calculated to be substantial (>26−30 kcal/mol), with the barrier height correlating with the donor ability of the vinyl substituent R. An interesting feature of this process is that the 5-*exo* ring closure is coupled with intramolecular proton transfer from the nucleophilic nitrogen to the incipient enolate oxygen via a six-membered resonance-assisted hydrogen bond (RAHB). The cyclizations are endergonic, slightly less so in THF than in the gas phase. The data are summarized in Figure 2.

The calculated barrier for the σ_{C-C} bond fragmentation is predicted to be slightly lower than that for the 5-*exo-trig* closure. This final step proceeds through a six-membered TS in a concerted fashion[22] where the C−C, N−H and C═O bond cleavage are coupled with the N═C, C═C and O−H bond formation. This process is slightly exergonic for the formation of conjugated enol (R = Ph) and essentially thermoneutral for R = Me (Figure 3). Enol−ketone tautomerization should make the overall process thermodynamically favorable for both substituents. Moreover, inclusion of solvation effects (Self-Consistent Reaction Field calculations in THF) slightly decreased the barriers due to the higher polarity of transition states in comparison to that of starting materials and made both cyclizations exergonic.[23]

The TS geometries are shown in Figure 4. These geometries illustrate the contrasting roles of two amino groups for the



R	Phase	E_a	$\Delta H^{\neq}$	$\Delta G^{\neq}$	ΔG_r
phenyl	Gas phase	25.2	22.7	22.3	-1.8
	SCRF (THF)*	21.4	17.6	21.8	-8.6
methyl	Gas phase	25.2	22.7	22.5	0.6
	SCRF (THF)*	22.2	18.5	21.2	-6.4

E_a=activation energy, $\Delta H^{\neq}$=activation enthalpy, $\Delta G^{\neq}$=activation free energy, ΔG_r= Gibbs free energy for the reaction. * Single point calculation at the gas phase B3LYP/6-31+G(d,p) geometry, SCRF: Self-consistent reaction field.

Figure 3. Calculated activation barriers, reaction energies, and transition state geometries for fragmentation reaction.

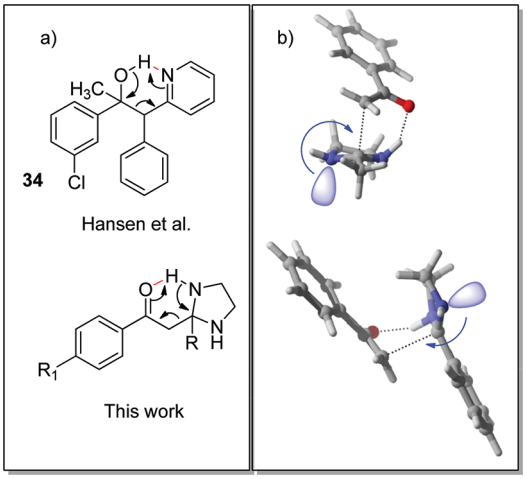
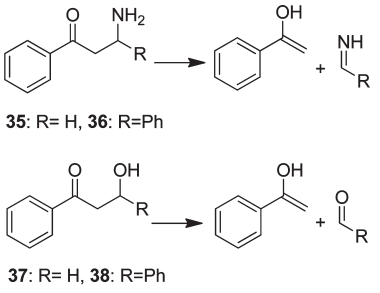


Figure 4. (a) Two patterns for H-bond assisted retro-aldol fragmentation: O−H···N assistance identified by Hansen et al.[24] and N−H···O assistance reported in this work. (b) Stereoelectronic alignment of the second amine lone pair with the breaking C−C bond in the transition state of Ph- and Me-substituted substrates.

fragmentation. Both roles are, however, essential. The first amine provides an N−H moiety for proton transfer to the developing negative charge at the enolate oxygen. The effect of N−H···O is interesting considering that its formal reverse, an O−H···N interaction, has been suggested to play an important role in amine-catalyzed retro-aldol reactions.[24] The second amine provides direct stereoelectronic assistance to the C−C bond cleavage via a hyperconjugative $n_N \rightarrow \sigma^*_{C-C}$ interaction. Hyperconjugative donor ability of the second nitrogen lone pair is enhancing by rehybridization[13,25] from $sp^{4.3}$ (80.9% s-character) to $sp^{8.9}$ (89.8%) for Me and from $sp^{4.1}$ (80.3%) to $sp^{10.5}$ (91.3%) for Ph in the reactants and transition states.

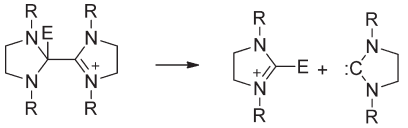


Compound	E_a	$\Delta H^{\neq}$	$\Delta G^{\neq}$	ΔG_r
35	41.2	36.5	37.0	22.9
36	36.6	32.2	32.9	14.4
37	35.5	31.9	32.6	20.5
38	30.3	26.2	26.9	8.8

E_a=activation energy, $\Delta H^{\neq}$=thermal enthalpy, $\Delta G^{\neq}$=thermal free energy, ΔG_r=Reaction free energy. *Calculation at the gas phase B3LYP/6-31+G(d,p) geometry

Figure 5. Calculated activation barriers and reaction energies for classical retro-Mannich[27] and retro-aldol reaction.

The important role of the second nitrogen is not surprising; the presence of two heteroatoms is known to enable the fragmentation even when orbitals are misaligned, e.g., in carbenogenic fragmentations.[26]



Carbenogenic fragmentations
(Wanzlick, Lemal)

To further understand the importance of the above $n_N \rightarrow \sigma^*_{C-C}$ stereoelectronic assistance, we have also calculated retro-aldol barriers for the simpler retro-Mannich[27] reaction of β-amino and retro-aldol reaction of β-hydroxy 1-phenylpropan-1-ones (Figure 5). In the absence of other substituents at the breaking bond, the retro-aldol barriers are very high, especially for the fragmentations of amines.

The presence of a Ph group at the breaking C−C bond decreased activation barriers for the classic retro-aldol and its amino version by ∼4−5 kcal/mol. In our substrates, the effect of Ph group is much smaller. We attribute this difference to the effect of the second amino group described above, which provides so much stabilization to the TS that the additional conjugating moiety (the Ph group) does not make a big difference.

■ CONCLUSION

In summary, we have reported an experimental and computational study describing a cascade transformation that breaks all three C−C bonds in a polarized alkyne moiety. Facile intermolecular Michael addition is followed by the relatively slow intramolecular steps. The slowest step corresponds to the 5-*exo-trig* closure at the carbonyl-substituted alkene. This process is facilitated by the coupling of the intramolecular Michael addition with a concerted proton transfer along a resonance-assisted H-bond path, which avoids the formation of an unfavorable

zwitterionic intermediate. The final retro-Mannich[27] fragmentation is also fully concerted.

EXPERIMENTAL SECTION

General Information. All NMR spectra were collected at 400, 500, and 600 MHz for ^{1}H NMR and 100, 125, and 150 MHz for ^{13}C NMR using $CDCl_3$ as solvent.

General Procedure for the Synthesis of Ketoalkyne Compounds. A stirred mixture of $Pd(PPh_3)_2Cl_2$ (19 mg, 0.028 mmol) and (11 mg, 0.056 mmol) of CuI in THF (5 mL) was purged with nitrogen for 30 min. Then 0.2 mL (1.42 mmol) of triethylamine, 1.42 mmol of acid chloride, and acetylene (1.7 mmol) were added successively. The reaction mixture was then stirred for 3 h at room temperature. Solvents were evaporated, and the residue was chromatographed on silica gel (ethyl acetate/hexane) to give the pure product.

General Procedure for the Alkyne Fragmentation. To a solution of ketoalkyne compound (0.25 mmol) in 2.5 mL of THF in a sealed tube was added neat ethylenediamine (0.25 mmol) via a syringe. Depending on the condition the temperature was raised to 110 or 125 °C and stirred for around 12−20 h. Solvent was carefully removed under reduced pressure, and the yield of the product was determined from crude reaction mixture by using ^{1}H NMR experiment with benzyl phenyl ether as internal standard.

Acetophenone (16b)[28]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98−7.95 (m, 2H), 7.58−7.55 (m, 1H), 7.48−7.44 (m, 2H), 2.61 (s, 3H).

2-Phenyl-4,5-dihydro-1*H*-imidazole (16c)[29]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.8 Hz, 2H), 7.40−7.47 (m, 3H), 6.92 (bs, 1H), 3.60 (s, 4H).

(*Z*)-3-((2-Aminoethyl)amino)-1,3-diphenylprop-2-en-1-one (16a$_1$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (bs, 1H), 7.89 (d, J = 6.6 Hz, 2H), 7.48−7.36 (m, 8H), 5.79 (s, 1H), 3.28 (dt, J = 6.1, 5.7 Hz, 2H), 2.86 (bs, 2H), 1.48 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 166.7, 139.9, 135.3, 130.4, 129.2, 128.3, 127.9, 127.4, 126.7, 93.4, 47.4, 42.2; HRMS (CI) calcd for $C_{17}H_{19}N_2O$ $[M + H]^+$ 267.1497, found 267.1493.

3,3′-(Ethane-1,2-diylbis(azanediyl))bis(1,3-diphenylprop-2-en-1-one) (16a$_2$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.26 (bs, 1H), 7.87 (d, J = 6.7 Hz, 2H), 7.48−7.36 (m, 6H), 7.30 (d, J = 6.7 Hz, 2H), 5.75 (s, 1H), 3.35 (t, J = 3.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.7, 166.6, 140.0, 135.1, 130.8, 129.5, 128.7, 128.2, 127.6, 127.1, 94.5, 45.1; HRMS (CI) calcd for $C_{32}H_{29}N_2O_2$ $[M + H]^+$ 473.2229, found 473.2231.

2-(*p*-Tolyl)-4,5-dihydro-1*H*-imidazole (17c)[28]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 5.03 (bs, 1H), 3.78 (s, 4H), 2.39 (s, 3H).

(*Z*)-3-((2-Aminoethyl)amino)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one (17a$_1$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (s, 1H), 7.89 (d, J = 7.0 Hz, 2H), 7.46−7.36 (m, 3H), 7.32 (d, J = 7.1 Hz, 2H), 7.28−7.21 (m, 2H), 5.78 (s, 1H), 3.29 (dt, J = 5.1, 5.0 Hz, 2H), 2.85 (bs, 2H), 2.41 (s, 3H), 1.45 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 167.3, 140.4, 139.7, 132.8, 130.7, 129.3, 128.2, 127.8, 127.1, 93.7, 47.8, 42.6, 21.4; HRMS (CI) calcd for $C_{18}H_{21}N_2O$ $[M + H]^+$ 281.1659, found 281.1654.

(2*Z*,2′*Z*)-3,3′-(Ethane-1,2-diylbis(azanediyl))bis(1-phenyl-3-(*p*-tolyl)prop-2-en-1-one) (17a$_2$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 7.85 (d, J = 7.4 Hz, 2H), 7.46−7.34 (m, 5H), 7.19 (d, J = 9.0 Hz, 2H), 5.74 (s, 1H), 3.36 (d, J = 3.4 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 166.9, 140.2, 135.1, 139.7, 132.3, 130.8, 129.4, 128.2, 127.6, 127.1, 94.3, 45.1, 21.4; HRMS (CI) calcd for $C_{34}H_{33}N_2O_2$ $[M + H]^+$ 501.2542, found 501.2548.

2-(4-Fluorophenyl)-4,5-dihydro-1*H*-imidazole (18c)[18]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.83 (m, 2H), 7.06 (t, J = 8.6 Hz, 2H), 5.59 (bs, 1H), 3.78 (s, 4H).

(*Z*)-3-((2-Aminoethyl)amino)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (18a$_1$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (s, 1H), 7.89 (d, J = 7.1 Hz, 2H), 7.47−7.36 (m, 5H), 7.14 (t, J = 8.1 Hz, 2H), 5.76 (s, 1H), 3.27 (dt, J = 5.8, 5.8 Hz, 2H), 2.86 (bs, 2H), 1.41 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 165.9, 163.4 (d, J = 255.7 Hz), 140.1, 130.8, 129.9, 129.8, 128.2, 127.1, 115.6 (d, J = 22.0 Hz), 93.9, 47.8, 42.5; HRMS (CI) calcd for $C_{17}H_{18}FN_2O$ $[M + H]^+$ 285.1403, found 285.1402.

(2*Z*,2′*Z*)-3,3′-(Ethane-1,2-diylbis(azanediyl))bis(3-(4-fluorophenyl)-1-phenylprop-2-en-1-one) (18a$_2$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.2 (s, 1H), 7.86 (d, J = 7.3 Hz, 2H), 7.48−7.37 (m, 3H), 7.31−7.24 (m, 2H), 7.1 (t, J = 7.3 Hz, 2H), 5.73 (s, 1H), 3.33 (d, J = 3.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 165.6, 163.3 (J = 250 Hz), 139.8, 131.1, 129.8, 129.7, 128.3, 127.1, 115.8, 94.6, 45.1; HRMS (CI) calcd for $C_{32}H_{27}F_2N_2O_2$ $[M + H]^+$ 509.2041, found 509.2035.

1-(*p*-Tolyl)ethanone (19b)[28]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 2.58 (s, 3H), 2.41 (s, 3H).

(*Z*)-3-((2-Aminoethyl)amino)-3-phenyl-1-(*p*-tolyl)prop-2-en-1-one (19a$_1$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (s, 1H), 7.80 (d, J = 7.9 Hz, 2H), 7.48−7.38 (m, 5H), 7.19 (d, J = 7.9 Hz, 2H), 5.78 (s, 1H), 3.27 (dt, J = 6.2, 6.0 Hz, 2H), 2.84 (t, J = 6.0 Hz, 2H), 2.37 (s, 3H), 1.45 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 166.7, 141.1, 137.6, 135.8, 129.4, 128.9, 128.6, 127.1, 93.6, 47.8, 42.6, 21.4; HRMS (CI) calcd for $C_{18}H_{21}N_2O$ $[M + H]^+$ 281.1654, found 281.1665.

(2*Z*,2′*Z*)-3,3′-(Ethane-1,2-diylbis(azanediyl))bis(3-phenyl-1-(*p*-tolyl)prop-2-en-1-one) (19a$_2$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (s, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.49−7.36 (m, 3H), 7.31−7.24 (m, 2H), 7.19 (d, J = 7.8 Hz, 2H), 5.73 (s, 1H), 3.34 (t, J = 3.2 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 166.7, 141.3, 137.3, 135.5, 129.5, 128.9, 127.8, 127.7, 127.2, 94.2, 45.1, 21.5; HRMS (CI) calcd for $C_{34}H_{33}N_2O_2$ $[M + H]^+$ 501.2542, found 501.2536.

1-(4-Fluorophenyl)ethanone (20b)[18]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.97 (m, 2H), 7.16−7.11 (m, 2H), 2.60 (s, 3H).

(*Z*)-3-((2-Aminoethyl)amino)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one (20a$_1$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.46 (s, 1H), 7.90 (dd, J = 8.7, 5.6 Hz, 2H), 7.48−7.39 (m, 5H), 7.06 (dd, J = 8.6, 8.6 Hz, 2H), 5.73 (s, 1H), 3.28 (dt, J = 6.2, 6.1 Hz, 2H), 2.85 (t, J = 6.2 Hz, 2H), 1.41 (bs, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.1, 167.1, 164.5 (d, J = 250.3 Hz), 136.0 (d, J = 124.1 Hz), 129.6, 129.3, 128.6, 127.7, 115.0, 115.1, 93.3, 47.8, 42.5; HRMS (CI) calcd for $C_{17}H_{18}FN_2O$ $[M + H]^+$ 285.1403, found 285.1404.

(2*Z*,2′*Z*)-3,3′-(Ethane-1,2-diylbis(azanediyl))bis(1-(4-fluorophenyl)-3-phenylprop-2-en-1-one) (20a$_2$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 7.87 (dd, J = 8.6, 5.2 Hz, 2H), 7.47−7.37 (m, 3H), 7.29−7.23 (m, 2H), 7.06 (t, J = 8.6 Hz, 2H), 5.69 (s, 1H), 3.34 (t, J = 3.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 166.7, 164.6 (d, J = 250.2 Hz), 135.6 (d, J = 124.0 Hz), 129.6, 129.4, 129.3, 128.7, 127.6, 115.2, 94.3, 44.9; HRMS (CI) calcd for $C_{32}H_{27}F_2N_2O_2$ $[M + H]^+$ 509.2041, found 509.2028.

1-(4-Chlorophenyl)ethanone (21b)[30]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 2.58 (s, 3H).

(*Z*)-3-((2-Aminoethyl)amino)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (21a$_1$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.5 (bs, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.47−7.44 (m, 3H), 7.43−7.39 (m, 2H), 7.36 (d, J = 8.4 Hz, 2H), 5.73 (s, 1H), 3.28 (dt, J = 6.1, 6.1 Hz, 2H), 2.86 (t, J = 6.1 Hz, 2H), 1.41 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 167.3, 138.6, 136.8, 135.5, 129.6, 128.6, 128.5, 128.4, 127.7, 93.3, 47.8, 42.4; HRMS (CI) calcd for $C_{17}H_{18}N_2OCl$ $[M + H]^+$ 301.1108, found 301.1114.

(2*Z*,2′*Z*)-3,3′-(Ethane-1,2-diylbis(azanediyl))bis(1-(4-chlorophenyl)-3-phenylprop-2-en-1-one) (21a$_2$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.30 (s, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 7.4 Hz, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 5.69 (s, 1H), 3.34 (t, J = 3.0 Hz, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 187.3, 166.9, 138.4, 137.0, 134.9, 129.6, 128.7, 128.5, 128.4, 127.6, 94.1, 45.1; HRMS (EI) calcd for $C_{32}H_{26}N_2O_2Cl_2$ $[M]^+$ 540.1371, found 540.1368.

1-(Naphthalen-2-yl)ethanone (22b)[28]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.05−8.02 (m, 1H), 7.98−7.95 (m, 1H), 7.91−7.87 (m, 2H), 7.63−7.54 (m, 2H), 2.73 (s, 3H).

(*Z*)-3-((2-Aminoethyl)amino)-1-(naphthalen-2-yl)-3-phenylprop-2-en-1-one ($22a_1$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.59 (bs, 1H), 8.41 (s, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.9 (d, J = 8.1 Hz, 1H), 7.85 (dd, J = 8.1, 7.5 Hz, 2H), 7.53−7.45 (m, 6H), 5.95 (s, 1H), 3.32 (dt, J = 6.0 Hz, 2H), 2.89 (t, J = 6.0 Hz, 2H), 1.47 (bs, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.3, 167.1, 137.6, 135.8, 134.6, 132.9, 129.5, 129.2, 128.6, 127.8, 127.6, 127.4, 127.1, 94.0, 47.8, 42.5; HRMS (CI) calcd for $C_{21}H_{21}N_2O$ $[M + H]^+$ 317.1654, found 317.1649.

(2*Z*,2′*Z*)-3,3′-(Ethane-1,2-diylbis(azanediyl))bis(1-(naphthalen-1-yl)-3-phenylprop-2-en-1-one) ($22a_2$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.35 (bs, 1H), 8.37 (s, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.86−7.82 (m, 2H), 7.54−7.45 (m, 3H), 7.42 (dt, J = 7.5, 7.1 Hz, 2H), 7.33 (d, J = 7.1 Hz, 2H), 5.9 (s, 1H), 3.40 (t, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 166.8, 137.4, 135.2, 134.7, 132.8, 129.6, 129.3, 128.7, 127.9, 127.7, 127.6, 127.5, 127.2, 126.3, 124.1, 94.7, 45.4; HRMS (EI) calcd for $C_{40}H_{32}N_2O_2$ $[M]^+$ 572.2464, found 572.2453.

2-Butyl-4,5-dihydro-1*H*-imidazole (23c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (bs, 4H), 2.22 (t, J = 7.0 Hz, 2H), 1.60−1.55 (m, 2H), 1.37−1.32 (m, 2H), 0.89 (t, J = 7.0 Hz, 3H).

(*Z*)-3-((2-Aminoethyl)amino)-1-(4-fluorophenyl)hept-2-en-1-one ($23a_1$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (s, 1H), 7.86 (dd, J = 8.9, 5.6 Hz, 2H), 7.1 (t, J = 8.9 Hz, 2H), 5.63 (s, 1H), 3.28 (dt, J = 6.0, 6.0 Hz, 2H), 2.97 (t, J = 6.2 Hz, 2H), 2.34 (dd, J = 7.7 Hz, 2H), 1.66−1.37 (m, 7H), 0.96 (t, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 169.3, 164.5 (d, J = 250.3 Hz), 136.8, 128.8, 115.1, 114.9, 90.9, 46.0, 42.0, 32.4, 30.3, 22.8, 13.8; HRMS (EI) calcd for $C_{15}H_{22}FN_2O$ $[M + H]^+$ 265.1716, found 265.1710.

(2*Z*,2′*Z*)-3,3′-(Ethane-1,2-diylbis(azanediyl))bis(1-(4-fluorophenyl)hept-2-en-1-one) ($23a_2$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (s, 1H), 7.87 (dd, J = 8.8, 5.5 Hz, 2H), 7.06 (t, J = 8.8 Hz, 2H), 5.65 (s, 1H), 3.58 (d, J = 3.3 Hz, 2H), 2.33 (dd, J = 7.8, 7.8 Hz, 2H), 1.62−1.52 (m, 2H), 1.47−1.38 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 169.0, 164.7 (d, J = 253.7 Hz), 136.4 129.6, 115.2, 114.9, 91.4, 43.4, 32.0, 30.9, 22.6, 13.8; HRMS (CI) calcd for $C_{28}H_{35}F_2N_2O_2$ $[M + H]^+$ 469.2667, found 469.2663.

3-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (24)[31]. Yield 2.23 g (68%), mp 154−156 °C, lit. mp 139−142 °C. IR (cm^{-1}) ν 1664 (C═O), 2194 (C≡C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.9 Hz, 2H), 7.49 (s, 2H), 6.93 (d, J = 8.9 Hz, 2H′), 3.94 (d, J = 4.6 Hz, 9H), 3.81 (s, 3H). Anal. Calcd: C 69.93; H 5.56 $C_{19}H_{18}O_5$. Found: C 70.01; H 5.69.

1-(3,4,5-tTrimethoxyphenyl)ethanone (24b)[32]. IR (neat, cm^{-1}) ν 1680; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 2H), 3.88−3.87 (m, 9H), 2.54 (s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$): 196.8, 153.0, 142.5, 132.4, 105.7, 60.9, 56.2, 26.4; EI-MS m/z (%) 210 (90) $[M]^+$; HRMS calcd for $C_{11}H_{14}O_4$ [M] 210.0892, found 210.0889 $[M]^+$.

2-(4-mMethoxyphenyl)-4,5-dihydro-1*H*-imidazole (24c)[33]. Mp 135−140 °C, lit. mp 138−139 °C.[34] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 3.87 (s, 3H), 3.85 (bs, 4H). MS (ESI): m/z 177.0 $[M + H]^+$.

(2*Z*,2′*Z*)-3,3′-(Ethane-1,2-diylbis(azanediyl))bis(3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one) ($24a_2$). Mp 223−225 °C; IR (cm^{-1}) ν 1592 (C═O), 3440 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 7.22 (d, J = 8.5 Hz, 2H), 7.10 (s, 2H), 6.92 (d, J = 8.5 Hz, 2H), 5.66 (s, 1H), 3.85 (d, J = 8.5 Hz, 12H), 3.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 166.5, 160.5, 152.8, 140.50, 135.5, 128.2, 127.2, 114.0, 104.2, 93.8, 60.7, 56.1, 55.2, 44.9; HRMS found m/z 712.2979 $[M]^+$, $C_{40}H_{44}O_{10}N_2$, calcd M = 712.2990.

3-([1,1′-Biphenyl]-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (25). Yield 2 g (53%), mp 160−162 °C; IR (cm^{-1}) ν 1627 (C═O), 2202 (C≡C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.72 (m, 2H), 7.68−7.60 (m, 4H), 7.53 (s, 2H), 7.50−7.45 (m, 2H), 7.43−7.39 (m, 1H), 3.97 (s, 6H), 3.96 (s, 3H); HRMS found m/z 372.1360 $[M]^+$, $C_{24}H_{20}O_4$, calcd M = 372.1356.

2-([1,1′-Biphenyl]-4-yl)-4,5-dihydro-1*H*-imidazole (25c)[35]. Mp 200−201 °C, lit. mp 177−179 °C;[36] IR (cm^{-1}) ν 1618 (C═N), 3423 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.63 (t, J = 8 Hz, 4H), 7.45 (t, J = 7.5 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 3.81 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 143.2, 140.1,; 129.2, 128.7, 127.7, 127.3, 127.0, 126.9. Anal. Calcd for $C_{15}H_{14}N_2$: C 81.05; H 6.35; N 12.60. Found: C 81.44; H 6.76; N 12.18.

(2*Z*,2′*Z*)-3,3′-(Ethane-1,2-diylbis(azanediyl))bis(3-([1,1′-biphenyl]-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one) ($25a_2$). Mp 253−255 °C; IR, cm^{-1}, ν 1664 (C═O), 3430 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H), 7.58 (t, J = 8.5 Hz, 4H), 7.46−7.33 (m, 5H), 7.12 (s, 2H), 5.73 (s, 1H), 3.87 (s, 3H), 3.85 (s, 6H), 3.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 166.2, 152.8, 142.4, 140.6, 140.5, 135.4, 133.7, 128.8, 128.1, 127.8, 127.4, 127.3, 104.2, 93.9, 60.8, 56.1, 45.1.

3-Phenyl-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (26)[37]. Yield 1.1 g (47%), mp 87−89 °C, lit. mp 94−95 °C. IR (cm^{-1}) ν 1731 (C═O), 2207 (C≡C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.63 (d, J = 7.3 Hz, 2H), 7.47−7.41 (m, 5H), 3.94 (s, 9H).

(2*Z*,2′*Z*)-3,3′-(Ethane-1,2-diylbis(azanediyl))bis(3-phenyl-1-(3,4,5-trimethoxyphenyl) prop-2-en-1-one) ($26a_2$). Mp 202−204 °C; IR (cm^{-1}) ν 3437 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (s, 1H), 7.44 (m, 3H), 7.26 (m, 2H), 7.12 (s, 2H), 5.68 (s, 1H), 3.88 (s, 9H), 3.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 166.5, 152.8, 140.5, 135.4, 134.9, 129.4, 128.6, 127.5, 104.2, 93.8, 60.8, 56.1, 44.9. Anal. Calcd for $C_{38}H_{40}N_2O_8$: C, 69.96; H, 6.18; N, 4.29. Found: C, 69.94; H, 6.17; N, 4.35.

3-(4-Nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (27)[38]. Mp 206−207 °C; IR (cm^{-1}) ν 1646 (C═O), 2214 (C≡C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.7, 2H), 7.8 (d, J = 8.7, 2H), 7.4 (s, 2H), 3.93 (s, 3H), 3.92 (s, 6H). Anal. Calcd for $C_{18}H_{15}NO_6$: C 63.36; H 4.51; N 4.22. Found: C 63.34; H 4.43; N 4.10.

2-(4-Nitrophenyl)-4,5-dihydro-1*H*-imidazole (27c)[33]. Mp 242−244 °C, lit. mp 242−243 °C;[34] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H), 3.95−3.88 (m, 4H); MS (ESI): m/z 191.9 $[M+ H]^+$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Detailed experimental procedures for synthesis, ^{1}H and ^{13}C NMR spectroscopic data, MS, total energy and Cartesian coordinates for each optimized stationary structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) *Acetylene Chemistry: Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005.

(2) Four C−C bonds: (a) Zeidan, T. A.; Kovalenko, S. V.; Manoharan, M.; Clark, R. J.; Ghiviriga, I.; Alabugin, I. V. *J. Am. Chem. Soc.* **2005**, *127*, 4270–4285. One C═C and two C−H bonds: (b) Alabugin, I. V.; Kovalenko, S. V. *J. Am. Chem. Soc.* **2002**, *124*, 9052–9053. (c) Breiner, B.; Schlatterer, J. C.; Kovalenko, S. V.; Greenbaum, N. L.; Alabugin, I. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3666–3670. (d) Yang, W.-Y.; Breiner, B.; Kovalenko, S. V.; Ben, C.; Singh, M.; LeGrand, S. N.; Sang, Q.-X.; Strouse, G. F.; Copland, J. A.; Alabugin, I. V. *J. Am. Chem. Soc.* **2009**, *131*, 11458–11470. Two C═C bonds: (e) Alabugin, I. V.; Gilmore, K.; Patil, S.; Manoharan, M.; Kovalenko, S. V.; Clark, R. J.; Ghiviriga, I. *J. Am. Chem. Soc.* **2008**, *130*, 11535–11545. One C═C bond, one C-C bond, and one C-H bond: (f) Pal, R.; Clark, R. J.; Manoharan, M.; Alabugin, I. V. *J. Org. Chem.* **2010**, *75*, 8689–8692.

(3) For the intricate metal-catalyzed cascade reactions of alkynes, creating multiple new C−C bonds, see also: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *103*, 813–834. (c) Moreau, X.; Goddard, J.-P.; Bernard, M.; Lemière, G.; López-Romero, J. M.; Mainetti, E.; Marion, N.; Mouriès, V.; Thorimbert, S.; Fensterbank, L.; Malacriaa, M. *Adv. Synth. Catal.* **2008**, *350*, 43–48. (d) Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2007**, *72*, 2651–2654. (e) Barluenga, J.; Riesgo, L.; Vicente, R.; Lopez, L. A.; Tomas, M. *J. Am. Chem. Soc.* **2007**, *129*, 7772–7773. (f) Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2005**, *70*, 9345–9353. (g) Blaszykowski, C.; Harrak, Y.; Gonalves, M.-H.; Cloarec, J.-M.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 3771–3774. (h) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouris, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656–8657. (i) Mamane, V.; Gress, T.; Krause, H.; Förstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655.

(4) (a) Bluthe, N.; Gorë, J.; Malacria, M. *Tetrahedron* **1986**, *42*, 1333–1344. (b) Fehr, C.; Vuagnoux, M.; Sommer, H. *Chem.—Eur. J.* **2011**, *17*, 3832–3836. (c) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129–4132.

(5) Vasilevsky, S. F.; Baranov, D. S.; Mamatyuk, V. I.; Gatilov, Y. V.; Alabugin, I. V. *J. Org. Chem.* **2009**, *74*, 6143–6150.

(6) (a) Seminal work: Eschenmoser, A.; Frey, A. *Helv. Chim. Acta* **1952**, *35*, 1660–1666. (b) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1–15. (c) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254–3257. (d) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943–3946. (e) Recent review: Prantz, K.; Mulzer, J. *Chem. Rev.* **2010**, *110*, 3741–3766. Representative recent examples: (f) Alkynogenic fragmentations: Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028–5029. Jones, D. M.; Lisboa, M. P.; Kamijo, S.; Dudley, G. B. *J. Org. Chem.* **2010**, *75*, 3260–3267. Tummatorn, J.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 1572–1575. (g) Allenogenic fragmentations: Kolakowski, R. V.; Manpadi, M.; Zhang, Y.; Emge, T. J.; Williams, L. J. *J. Am. Chem. Soc.* **2009**, *131*, 12910–12911. (h) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 8962–8965. (i) Shifting unfavorable equilibrium in 1,2-C,O transpositions: Baroudi, A.; Mauldin, J.; Alabugin, I. V. *J. Am. Chem. Soc.* **2010**, *132*, 967–979. (j) Baroudi, A.; Alicea, J.; Alabugin, I. V. *Chem.—Eur. J.* **2010**, *16*, 7683–7687. Baroudi, A.; Flack, P.; Alabugin, I. V. *Chem.—Eur. J.* **2010**, *16*, 12316–12320. (k) Baroudi, A.; Alicea, J.; Flack, P.; Kirincich, P.; Alabugin, I. V. *J. Org. Chem.* **2011**, *76*, 1521–1537. Other interesting examples: (l) Prantz, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5030–5033. (m) El Kaïm, L.; Grimaud, L.; Wagschal, S. *Chem. Commun.* **2011**, *47*, 1887–1889. (n) Sword, R.; Baldwin, L. A.; Murphy, J. A. *Org. Biomol. Chem.* **2011**, *9*, 3560–3570.

(7) See for example: (a) Hamidane, H. B.; He, H.; Tsybin, O. Y.; Emmett, M. R.; Hendrickson, C. L.; Marshall, A. G.; Tsybin, Y. O. *J. Am. Soc. Mass Spectrom.* **2009**, *20*, 1182–1192. (b) Zubarev, R. A.; Kelleher, N. L.; McLafferty, F. W. *J. Am. Chem. Soc.* **1998**, *120*, 3265–3266. (c) Zubarev, R. A. *Mass Spectrom. Rev.* **2003**, *22*, 57–77. (d) Syka, J. E. P.; Coon, J. J.; Schroeder, M. J.; Shabanowitz, J.; Hunt, D. F. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 9528–9533. (e) Coon, J. J.; Ueberheide, B.; Syka, J. E. P.; Dryhurst, D. D.; Ausio, J.; Shabanowitz, J.; Hunt, D. F. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 9463–9468. (f) Stenson, A. C.; Marshall, A. G.; Cooper, W. T. *Anal. Chem.* **2003**, *75*, 1275–1284.

(8) (a) Kottani, R.; Valiulin, R. A.; Kutateladze, A. G. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 13917–13921. (b) Kottani, R. R.; Majjigapu, J. R. R.; Kurchan, A. N.; Majjigapu, K.; Gustafson, T. P.; Kutateladze, A. G. *J. Am. Chem. Soc.* **2006**, *128*, 14794–14795. (c) Mitkin, O.; Wan, Y.; Kurchan, A.; Kutateladze, A. *Synthesis* **2001**, *8*, 1133–1142. (d) Gustafson, T. P.; Metzel, G. A.; Kutateladze, A. G. *Org. Biomol. Chem.* **2011**, *9*, 4752–4755.

(9) (a) Preliminary report: Davydova, M. P.; Vasilevskii, S. F.; Tolstikov., G. A. *Izv. Akad. Nauk. Ser. Khim.* **2011**, *1*, 180–181.

(10) TB interaction: (a) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1–9. (b) Gleiter, R.; Paddon-Row, M. N. *Angew. Chem., Int. Ed.* **2003**, *13*, 696–701. Charged species: (c) Alabugin, I. V.; Manoharan, M. *J. Am. Chem. Soc.* **2003**, *125*, 4495–4509. (d) Alabugin, I. V.; Manoharan, M. *J. Org. Chem.* **2004**, *69*, 9011–9024. Radicals: (e) Schottelius, M. J.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896–4903. (f) Pickard, F. C., I. V.; Shepherd, R. L.; Gillis, A. E.; Dunn, M. E.; Feldgus, S.; Kirschner, K. N.; Shields, G. C.; Manoharan, M.; Alabugin, I. V. *J. Phys. Chem. A.* **2006**, *110*, 2517–2526.

(11) (a) Ci, X.; Lee, L. Y. C.; Whitten, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 2536–2538. (b) Ci, X.; Whitten, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 7215–7217. (c) Ci, X.; Kellett, M. A.; Whitten, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3893–3904.

(12) Facilitating effect of this bond weakening in anionic oxy-Cope rearrangements: (a) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766. (b) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877–1884. (c) Evans, D. A.; Ballallargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242–2244. (d) Transition to the dissociative mechanism: Black, K. A.; Wilsey, S.; Houk, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 5622–5627. (e) Hi, Y. Y.; Houk, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 205–206. (f) Black, K. A.; Wilsey, S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 6715–6725. (g) Synergestic effect of two alkoxy groups on the fragmentations: ref 2f and references therein.

(13) (a) Alabugin, I. V.; Manoharan, M.; Zeidan, T. A. *J. Am. Chem. Soc.* **2003**, *125*, 14014–14031. (b) Alabugin, I. V.; Manoharan, M.; Buck, M.; Clark, R. J. *THEOCHEM* **2007**, *813*, 21–27. (c) Alabugin, I. V.; Gilmore, K. M.; Peterson, P. W. *WIREs Comp. Mol. Sci.* **2011**, *1*, 109–141.

(14) Karpov, A. S.; Muller, T. J. J. *Org. Lett.* **2003**, *5*, 3451–3454.

(15) Spectroscopic data of the known products were identical to those reported in the literature: (a) Wu, X. F.; Sundararaju, B.; Neumann, H.; Dixneuf, P. H.; Beller, M. *Chem.—Eur. J.* **2011**, *17*, 106–110. (b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2010**, *16*, 12104–12107. (c) Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2071–2073.

(16) (a) Baldwin, J. E. *J. Chem. Soc. Chem. Commun* **1976**, 734–736. (b) Alabugin, I.; Gilmore, K.; Manoharan, M. *J. Am. Chem. Soc.* **2011** Epub ahead of print, DOI: 10.1021/ja203191f. (c) Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011** In process, DOI:10.1021/cr200164y.

(17) Although we refer to this step as retro-Mannich,[27] the formal oxidation state at the fragmentation site in our starting material is greater than that in the typical aldol product. Such reactions has been classified under the general umbrella of Mannich reactions in the literature: (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070. (b) Schleimer, R.; Würthwein, E.-U. *Chem. Ber.* **1994**, *127*, 1437–1440.

(18) Nenajdenko, V. G.; Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Kondrashov, E. V.; Ushakov, I. A.; Rulev, A. Y. *J. Org. Chem.* **2010**, *75*, 5679–5688.

(19) (a) Becke, A. D. *Phys. Rev. A.* **1988**, *38*, 3098–3100. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (c) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.

(20) We have used this level of theory earlier for anionic cyclizations of N-nucleophiles:Vasilevsky, S. F.; Mikhailovskaya, T. F.; Mamatyuk, V. I.; Bogdanchikov, G. A.; Manoharan, M.; Alabugin, I. V. *J. Org. Chem.* **2009**, *74*, 8106–8117.

(21) Frisch, M. J. et al. *Gaussian 03, revision C.01*; Gaussian, Inc.: Wallingford, CT, 2004. See Supporting Information for complete reference.

(22) (a) Pollack, R. M.; Ritterstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 5064–5069. (b) Pollack, R. M.; Cooper, J. D. *J. Org. Chem.* **1973**, *38*, 2689–2692. (c) Añez, R.; Izquierdo, R.; Vidal, A.; Cordova, T.; Sierraalta, A.; Chuchani, G. *J. Phys. Org. Chem.* **2006**, *19*, 836–840.

(23) Dipole moments of reactants were 2.5 and 2.7 D and transition states 5.0 and 5.1 D for the Ph- and Me-substrates, respectively.

(24) Hansen, D. W.; Sinsheimer, J. E.; Burckhalter, J. H. *J. Org. Chem.* **1976**, *41*, 3556–3559.

(25) Importance of rehybridization in organic structure and reactivity: Alabugin, I. V.; Manoharan, M. *J. Comput. Chem.* **2007**, *28*, 373–390.

(26) (a) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Paolini, F.; Schütz, J. *Angew. Chem, Int. Ed.* **2004**, *43*, 5896–5911. (b) Wanzlick, H. W. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 75. (c) Lemal, D. M.; Lovald, R. A.; Kawano, K. I. *J. Am. Chem. Soc.* **1964**, *86*, 2518–2519.

(27) For recent examples of retro-Mannich reactions, see: (a) White, J. D.; Li, Y.; Ihle, D. C. *J. Org. Chem.* **2010**, *75*, 3569–3577. (b) Chen, P.; Carroll, P. J.; Sieburth, S. M. *Org. Lett.* **2009**, *11*, 4540–4543. (c) White, J. D.; Ihle, D. C. *Org. Lett.* **2006**, *8*, 1081–1084. (d) Cramer, N.; Juretschke, J.; Laschat, S.; Baro, A.; Frey, W. *Eur. J. Org. Chem.* **2004**, *7*, 1397–1400. (e) Page, P. C. B.; Heaney, H.; McGrath, M. J.; Sampler, E. P.; Wilkins, R. F. *Tetrahedron Lett.* **2003**, *44*, 2965–2970. (f) Winkler, J. D.; Siegel, M. G.; Stelmach, J. E. *Tetrahedron Lett.* **1993**, *34*, 6509–6512.

(28) Ruan, J.; Iggo, J. A.; Berry, N. G.; Xiao, J. *J. Am. Chem. Soc.* **2003**, *132*, 16689–16699.

(29) Nenajdenko, V. G.; Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Kondrashov, E. V.; Ushakov, I. A.; Rulev, A. Y. *J. Org. Chem.* **2010**, *75*, 5679–5688.

(30) Sharghi, H.; Jokar, M.; Doroodmand, M. M.; Khalifeh, R. *Adv. Synth. Catal.* **2010**, *352*, 3031–3044.

(31) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377–4380.

(32) Liu, M.; Hyder, Z.; Sun, Y.; Tang, W.; Xu, L.; Xiao, J. *Org. Biomol. Chem.* **2010**, *8*, 2012–2015.

(33) Chen, J.; Wang, Z.; Li, C.-M.; Lu, Y.; Vaddady, P. K.; Meibohm, B.; Dalton, J. T.; Miller, D. D.; Li, W. *J. Med. Chem.* **2010**, *53*, 7414–7427.

(34) Piskov, V. B.; Kasperovich, V. P.; Yakovleva, L. M. *Chem. Heterocycl. Compd.* **1976**, *12*, 917–923.

(35) Anastassiadou, M.; Danoun, S.; Crane, L.; Baziard-Mouysset, G.; Payard, M.; Caignard, D-H; Rettori, M.-C.; Renard, P. *Bioorg. Med. Chem.* **2001**, *9*, 585–592.

(36) Hill, A. J.; Johnston, J. V. *J. Am. Chem. Soc.* **1954**, *76*, 922–923.

(37) Edwards, M. L.; Stemerick, D. M.; Sunkara, P. S. *J. Med. Chem.* **1990**, *33*, 1948.

(38) Vasilevsky, S. F.; Davydova, M. P.; Tolstikov, G. A. *Chem. Heterocycl. Compd. (N.Y.)* **2008**, *44*, 1257–1261.