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Article

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Experimental and Theoretical Studies on Iron-Promoted Oxidative Annulation of Arylglyoxal with Alkyne: Unusual Addition and Migration on the Aryl Ring

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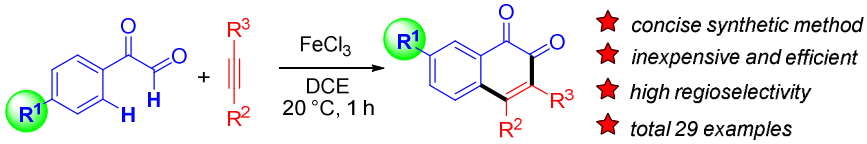
Supporting Information Placeholder

ABSTRACT: An Fe(III)-promoted oxidative annulation reaction was developed for the synthesis of 1,2-naphthoquinones. A variety of substituted arylglyoxals and internal alkynes undergo the transformation in the presence of $FeCl_3$ at room temperature to afford the 1,2-naphthoquinone products in good yields in a short reaction time at room temperature. Interestingly, the products show unusual pseudo-migration of the substituent on the arene ring of arylglyoxals. A possible mechanism involving Fe(III)-promoted formation of a vinyl cation from arylglyoxal and alkyne, electrophilic addition of the vinyl cation to the *ipso* carbon of the aryl group to give a spiral intermediate and then migration of the keto carbon to the *ortho* carbon was proposed as key steps and verified using quantum mechanics.



INTRODUCTION

1,2-Naphthoquinone is an important structural core present in many natural and bioactive compounds (Figure 1).[1] These compounds have been identified as potential candidates for a wide range of pharmacological activities including antitumor, anticancer, antibacterial, anti-diabetic, and antitubercular.[2] In addition, they were found to be useful synthetic intermediates for medicinal and material molecules.[3] Oxidation of naphthols is the most common method used for the preparation of *o*-naphthoquinones.[4] However, this method often gives a mixture of *ortho*- or *para*-quinones. Moreover, the scope is highly limited because of the less availability of the substrates. Considering the large applications of *o*-naphthoquinones in pharmaceuticals and materials, a straightforward approach for their synthesis is highly desirable.

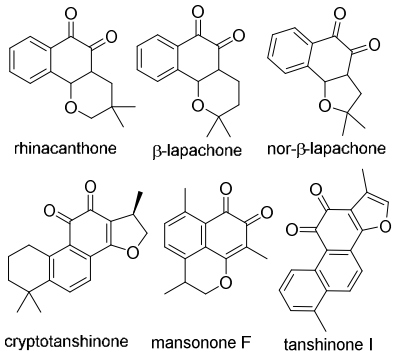
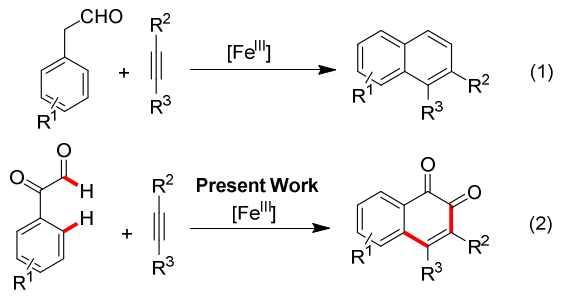


Figure 1. Examples of 1,2-naphthoquinone cored natural and bioactive compounds.

Recently, iron-catalyzed organic transformations received great attentions over the precious metal-catalyzed reactions because of their earth-abundance, lower cost, less/nontoxic, and long-term expediency.[5] Among the various types of organic transformations catalyzed by iron complexes, cyclization/annulation reaction of aldehydes and alkynes is popular for the synthesis of complex aromatic compounds.[6] In particular, iron and Lewis acid (LA) mediated annulation reaction of aryl acetaldehydes and alkynes has proven to be an efficient method to access substituted naphthalenes (Scheme 1, eq 1).[7] This reaction is expected to proceeds via an electrophilic attack of LA-coordinated aldehyde group at the alkyne to form a vinyl cation intermediate, which undergoes intramolecular electrophilic cyclization followed by aromatization to give the final product. We thought that a similar strategy can be used for the synthesis of highly substituted 1,2-naphthoquinones from arylglyoxals and alkynes using an iron catalyst (Schemes 1, eq 2). In this report, we demonstrate the $FeCl_3$-promoted [4 + 2] annulation of arylglyoxals and alkynes to form 1,2-naphthoquinones. To the best of our knowledge, this is the first report that allows to synthesize a variety substituted *β*-naphthoquinone in an effective and concise manner. In addition, the reactions show an interesting pseudo-migration of the

substituent on the arene ring. The observation can be rationalized based on the results of DFT calculations of the system which indicates that the reaction mechanism involves a vinyl cation intermediate and a keto group migration as key steps.

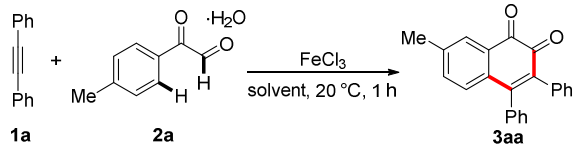
Scheme 1. Iron-Promoted Benzannulation Reactions



RESULTS AND DISCUSSION

The reaction of diphenylacetylene (**1a**) and 4-methylphenylglyoxal (**2a**) in the presence of $FeCl_3$ in 1,2-dichloroethane (DCE) at 20 °C for 1 h gave the annulated 1,2-dione product **3aa** in 82% isolated yield (Table 1, entry 8). Interestingly, the product has methyl substituent *meta* to the keto group instead of *para* to the keto group. The structure was unambiguously confirmed by its single crystal X-ray structure along with the ^1H and ^{13}C NMR and HRMS data.[8] The choice of solvent and concentration of the reaction solution is crucial for the success of the present reaction (Table 1). Among the many tested solvents, CH_2Cl_2, $CHCl_3$, tol-uene, CH_3NO_2, and PhCl were also effective, but gave product **3aa** in lower yields.

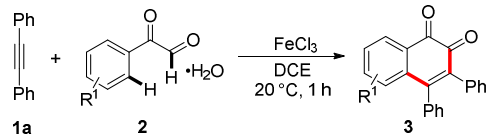
Table 1. Optimization Studies[a]

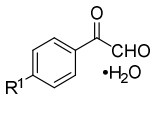
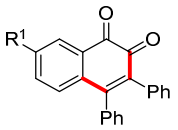
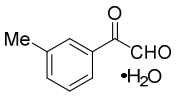
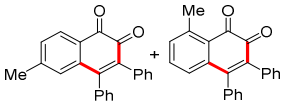
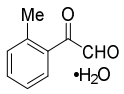
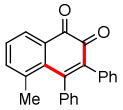
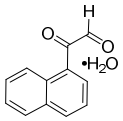
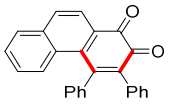
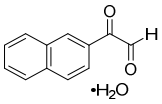
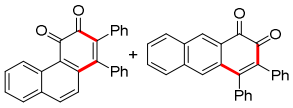
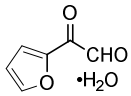
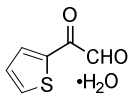


entry	solvent (mL)	yield (%)[b]
1	DCE (2)	72
2	DCM (2)	40
3	$CHCl_3$ (2)	15
4	toluene (2)	29
5	$MeNO_2$ (2)	32
6	PhCl (2)	33
7	DCE (1)	60
8	DCE (3)	83 (82)[c]
9	DCE (4)	77
10	DCE (5)	74

[a]Reactions were performed using diphenylacetylene **1a** (0.20 mmol), 4-methylphenylglyoxal **2a** (0.24 mmol), and $FeCl_3$ (0.60 mmol). [b]Yields were determined by the ^1H NMR integration method using mesitylene as the internal standard. [c]Isolated yield.

Table 2 Scope of the Arylglyoxals in the Synthesis of 1,2-Naphthoquinones[a]



2	product **3**	yield (%)[b]
		
2a: R^1 = Me	**3aa**: R^1 = Me	82
2b: R^1 = H	**3ab**: R^1 = H	45
2c: R^1 = OMe	**3ac**: R^1 = OMe	54
2d: R^1 = *t*-Bu	**3ad**: R^1 = *t*-Bu	53
2e: R^1 = Ph	**3ae**: R^1 = Ph	62
 **2f**	 **3af** + **3af'** (63:37)	57
 **2g**	 **3ag**	43
 **2h**	 **3ah**	46[c]
 **2i**	 **3ai** + **3ai'** (49:51)	65
 **2j**	 **3aj**	45[d]
 **2k**	 **3ak**	90[d,e]

[a]Reactions were performed using diphenylacetylene **1a** (0.20 mmol), arylglyoxals **2** (0.24 mmol), and $FeCl_3$ (0.60 mmol) in 1,2-dichloroethane (3.0 mL) at 20 °C for 1 h. [b]Isolated yields. [c]$Cu(OAc)_2$.(0.10 mmol) was added. [d]$Cu(OAc)_2$.(0.20 mmol) was added. [e]Reaction performed for 3 h.

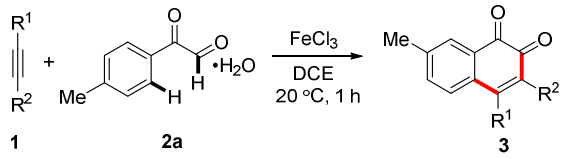
Next, we investigated the scope of arylglyoxals **2** in the iron-promoted annulation reaction with diphenylacetylene (**1a**) (Table 2). Thus, arylglyoxals bearing an electron-donating group (**2a**, **2c**, **2d-e**) proceeded well to give the expected 1,2-naphthoquinones in good yields, while unsubstituted arylglyoxal (**2b**) gave moderate product yield. Treatment of *meta*-methyl substituted substrate **2f** with **1a** afforded two regioisomeric products **3af**+**3af'** in 57% yield. It is noteworthy that the methyl group in the products **3af**+**3af'** is at *para* and *ortho* positions to the 1,2-dione group instead of the *meta* positon shown in substrate **2f**. The reaction of arylglyoxals having an electron-withdrawing group with **1a** gave very low yields of the desired annulation products (*vide infra*).

Structurally hindered *ortho* methyl-substituted glyoxal **2g** also afforded product **3ag** in which the methyl group is *meta* to the dione group in good yield. Notably, this methodology is also compatible with naphthyl glyoxals (**2h-i**), providing phenanthraquinone (**3ah**) and a mixture of anthraquinone and phenanthraquinone derivatives (**3ai**+**3ai'**), respectively. Heterocyclic fused 1,2-dione products (**3aj-k**) could also be formed with good yields using this method.

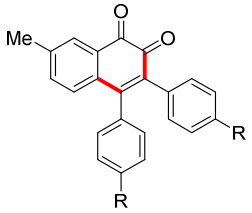
To further understand the generality of the reaction, we examined the reactions of various symmetrical and unsymmetrical alkynes with **2a** under the standard reaction conditions (Table 3). Thus, *para* substituted diarylalkynes, **1b-e**, with the substituents of Me, *t*-Bu, Br, and CF_3, respectively, gave the expected 1,2-naphthoquinone derivatives (**3ba-ea**) in 52-89% yields. The alkynes with an electron-withdrawing substituent appears to give higher product yield. The reaction of *m-Me* and *m-Br* substituted diarylalkynes **1f** and **1g** with **2a** also offered the expected products **3fa** and **3ga** in 80% and 65% yields, respectively. Alkyl substituted alkynes, 3-hexyne (**1h**) and 4-octyne (**1i**) also reacted effectively with **2a** to provide the desired products, **3ha** and **3ia**, respectively, in good yields. In addition, a variety of unsymmetrical alkynes (**1j-s**) underwent annulation efficiently with **2a** to give the respective products in good yields with high regioselectivity. The unsymmetrical alkynes with a phenyl group and a nonaromatic substituent R, where R = alkyl (**1j-1m**), ethoxycarbonyl (**1n**), hydroxymethyl (**1o**) and bromoethyl (**1p**), reacted with **2a** to give highly regioselective products (**3ja-3pa**) with the substituent R close to the dione moiety and the phenyl group near to the aromatic ring of the products. The unsymmetrical alkynes, phenyl aryl acetylene, where aryl = 4-CF_3-C_6H_4 and 3-CF_3-C_6H_4 also underwent the cyclization reaction to give products **3qa** and **3ra** respectively in good yields with very high regioselectivity. The annulation reaction could also tolerate 1-bromosubstituted alkyne, **1s**, to give expected product **3sa** in 67% with high regioselectivity. These observed regioselectivity can be rationalized by the formation of a vinyl cation from **1** and **2** in the presence of $FeCl_3$ (*vide infra*). The vinyl cation could be better stabilized by the terminal phenyl group than by an alkyl, or an electron-withdrawing group.

The synthetic utility of the newly synthesized 1,2-naphthoquinone **3aa** was demonstrated by its divergent transformations to complex heterocyclic compounds (Scheme 2). Thus, the condensation reactions of **3aa** with *o*-phenylenediamine (**4**) and diamin-omaleonitrile (**5**) gave benzophenazine derivatives **6** and **7** in 98%, and 44% yield, respectively. Similarly, substituted dibenzofuran **9** was obtained by treatment of **3aa** with 4-methylcyclohexanone (**8**). A polyannulated imidazole **10** was synthesized by condensation of **3aa** with ammonium acetate and formaldehyde in acetic acid.

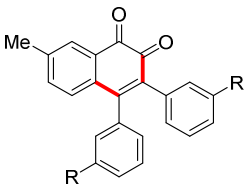
Table 3. Scope of Alkynes in the Iron-Promoted Oxidative Annulation[a]



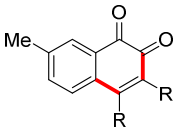
1 2a 3



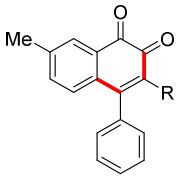
3ba: R = Me; 52%[b]
3ca: R = *t*-Bu; 53%
3da: R = Br; 89%
3ea: R = CF_3; 80%[b]



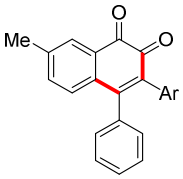
3fa: R = Me; 80%[b]
3ga: R = Br; 65%



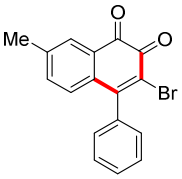
3ha: R = Et; 46%
3ia: R = *n*-Pr; 60%



3ja: R = Me; 40% (94:6)[d]
3ka: R = Et; 45% (95:5)[d]
3la: R = *n*-Bu; 51%[b] (96:4)[d]
3ma: R = cyclohexyl; 53%[b] (>10:1)[c]
3na: R = CO_2Et; 34%[e] (99:1)[d]
3oa: R = CH_2OH; 31%[f] (95:5)[c]
3pa: R = CH_2CH_2Br; 23%[g] (99:1)[c]



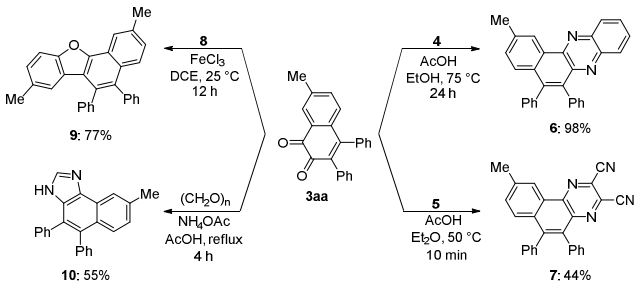
3qa: Ar = 4-$CF_3C_6H_4$; 75% (94:6)[c]
3ra: Ar = 3-$CF_3C_6H_4$; 71% (94:6)[c]



3sa, 67% (93:7)[c]

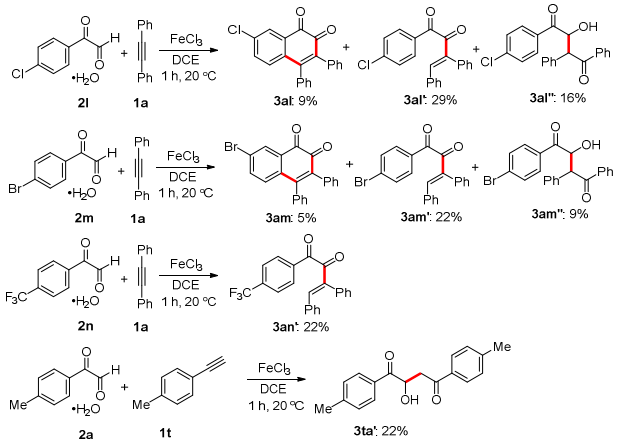
[a]Reactions were performed using alkyne **1** (0.20 mmol), glyoxals **2a** (0.24 mmol), and $FeCl_3$ (0.60 mmol) in 1,2-dichloroethane (3.0 mL) at 20 °C for 1 h. Isolated yields. [b]2.0 mL DCE was used. [c]Regioisomers were determined by ^1H NMR and the major isomer was shown. [d]Regioisomers were determined by LC-MS (Supporting Information p. 91- 98) and the major isomer was shown. [e]$Cu(OAc)_2$ (0.20 mmol) was added. [f]$FeCl_3$ (0.80 mmol) was used. [g]**1s** (0.30 mmol) and **2a** (0.20 mmol) was used.

Scheme 2. Synthetic Applications of Compound 3aa

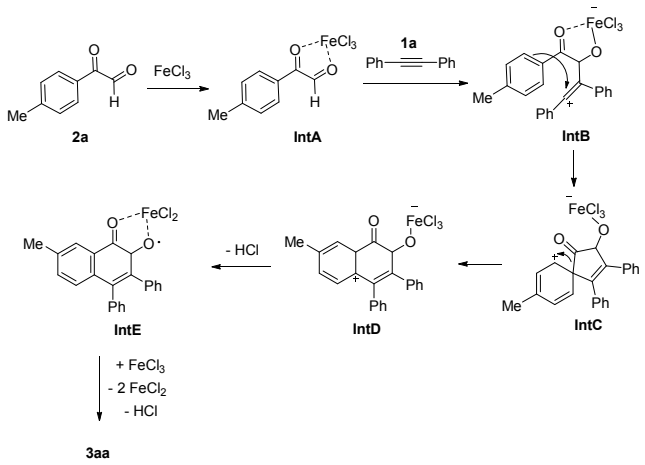


Arylglyoxals having an electron-withdrawing substituent **2l-n** also reacted with **1a** under the standard reaction conditions to give the oxidative annulation products, **3al** and **3am**, respectively, albeit in very low yields. In addition, diketo-vinyl (**3al'**, **3am'** and **3an'**) or diketoalcohol (**3al''** and **3am''**) products were observed (Scheme 3). The observation of these products supported that the transformation presumably proceeded through a common vinyl cation intermediate. Based on the above observation and the known literature results, a mechanism for this transformation is proposed in Scheme 4.[7,9-10] First, coordination of the carbonyl groups of glyoxal to Fe(III) forms glyoxal-Fe(III) adduct **IntA**. Regioselective electrophilic addition of the aldehyde group of complex **IntA** to diphenylacetylene (**1a**) forms **IntB**.[9] Next, the intramolecular 5-exo dearomatizing spirocyclization[10] provides the spirocyclic cationic species **IntC**. The migration of the keto group from *ipso* to an *ortho* carbon of the aryl ring affords **IntD**. Hydrogen elimination of **IntD** affords **IntE** in which the coordinated alkoxide is oxidized to a radical and Fe(III) is reduced to Fe(II). Further oxidation and hydrogen elimination by another $FeCl_3$ gives the final product **3aa** and the release of HCl and $FeCl_2$. The proposed mechanism is validated by the DFT calculation shown below.

Scheme 3. Mechanistic Studies



Scheme 4. Possible Reaction Mechanism

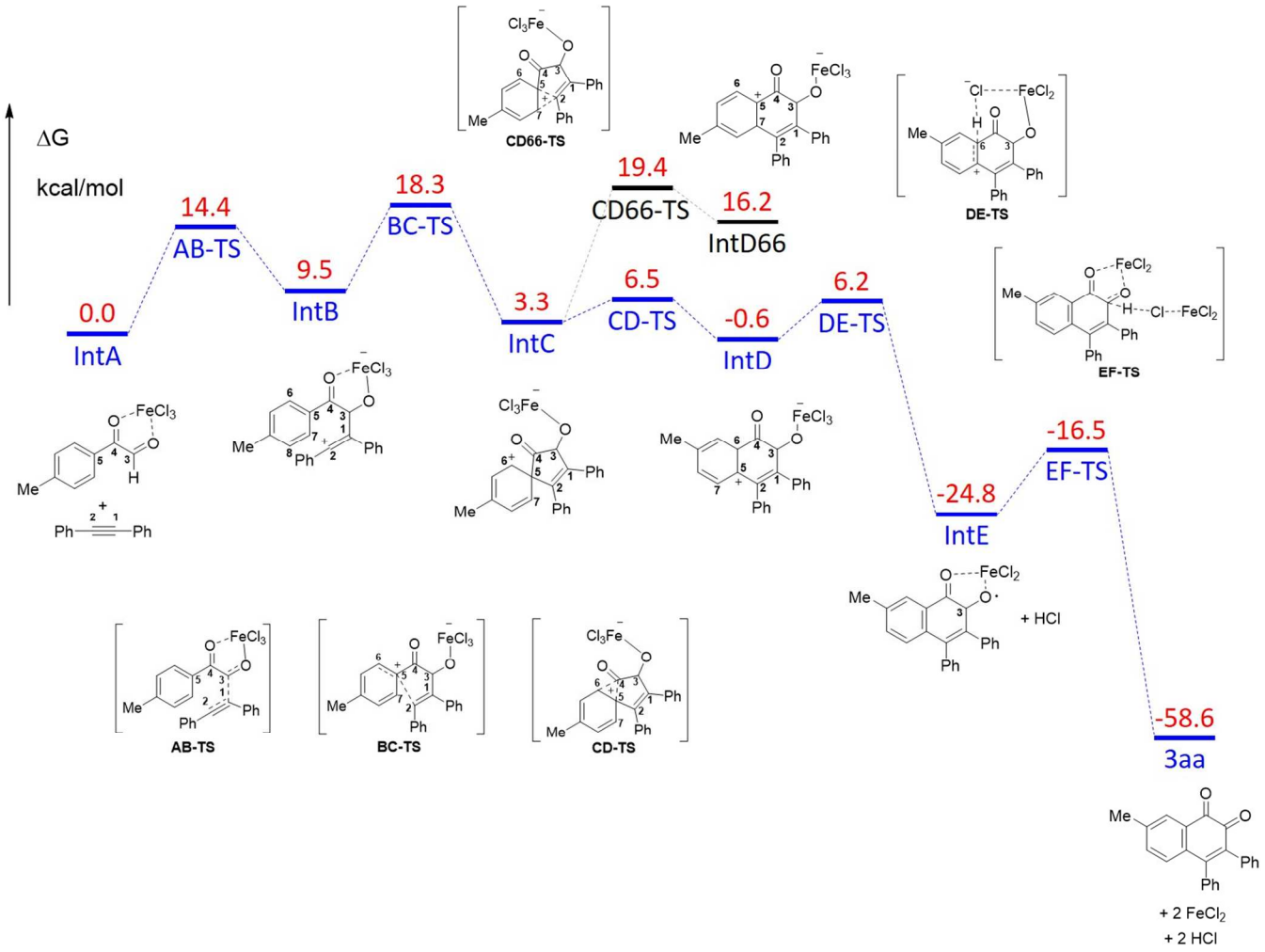


To gain more insight into this system, we performed DFT calculations at the B3LYP level[11] including Poisson-Boltzmann continuum solvation[12] to obtain Gibbs free energies at 298 K (full details in the Supporting Information). We found that C^1-C^3 coupling between **IntA** and diphenylacetylene led to the formation of **IntB** with a kinetic barrier of 14.4 kcal/mol and reaction energy of 9.5 kcal/mol (Scheme 5). This was followed by electrophilic addition of the C^2 cation to the *ipso* carbon C^5 of the aryl group to give a spirocyclic intermediate **IntC** with a barrier of 8.8 kcal/mol and reaction energy of -6.2 kcal/mol. Starting from this intermediate, two pathways were identified. **IntC** → **CD-TS** → **IntD** represented the more energetically favorable one, in which C^4-C^6 coupling took place with a barrier of only 3.2 kcal/mol and reaction energy of -3.9 kcal/mol. In contrast, the other pathway (**IntC** → **CD66-TS** → **IntD66**, through C^2-C^7 coupling) has a barrier of 16.1 kcal/mol and reaction energy of 12.9 kcal/mol, indicating that this route is kinetically inaccessible and thermodynamically unfavorable. Therefore, our theoretical investigation suggests that the methyl substituent prefers to be at the *meta* rather than *para* position to the keto group in the products, consistent with the experimental observations.

Finally, two hydrogen atoms were eliminated consecutively by Cl of the bound $FeCl_3$ (H on C^6, **IntD** → **IntE**) and Cl of a free $FeCl_3$ (H on C^3, **IntE** → **3aa**) to form the product plus two HCl and two $FeCl_2$. The free energy barriers are 6.8 kcal/mol for the first hydrogen elimination and 8.3 kcal/mol for the second one. For the overall reaction, the free energy barrier is 18.3 kcal/mol with **IntB** → **BC-TS** → **IntC** being the rate determining step, and the reaction free energy is -58.6 kcal/mol.

To understand the effect of solvent on the reaction, we perform DFT calculation of the reaction using different solvents. Similar free energy surfaces but higher barriers for the rate-determining step were found, for example, 20.4 kcal/mol for $CHCl_3$, 20.5 kcal/mol for $MeNO_2$, and 20.3 kcal/mol for PhCl. The results are consistent with our experiments.

Scheme 5. Gibbs Free Energy Surface Calculated Using Quantum Mechanics (unit in kcal/mol). Carbon atoms involved in the reaction are labeled with numbers.



Our attempts to locate a direct pathway from **IntB** to **IntD66** failed. Analyzing the molecular orbitals (MOs) of **IntB**, we found that there are two MOs involving $-PhCH_3$ (HOMO-1 and HOMO-4, Figure 2) have energies close to HOMO. HOMO-1 (Figure 2(a)) has MO localized mostly at C^5 of $-PhCH_3$ and is 4.0 kcal/mol higher in energy than HOMO-4 (Figure 2(b)), which has MO localized majorly at C^6 and C^7 (Figure 2). This means that the coupling of C^2 to C^5 is energetically more favorable than the coupling of C^2 to C^6 (or C^7), explaining why there is only a pathway for **IntB** → **IntC** but no pathway for **IntB** → **IntD66**.[10]

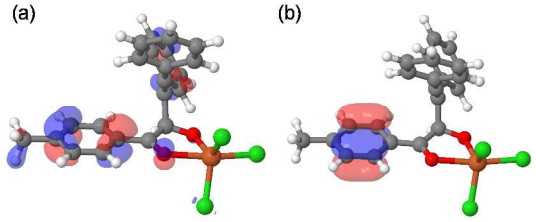
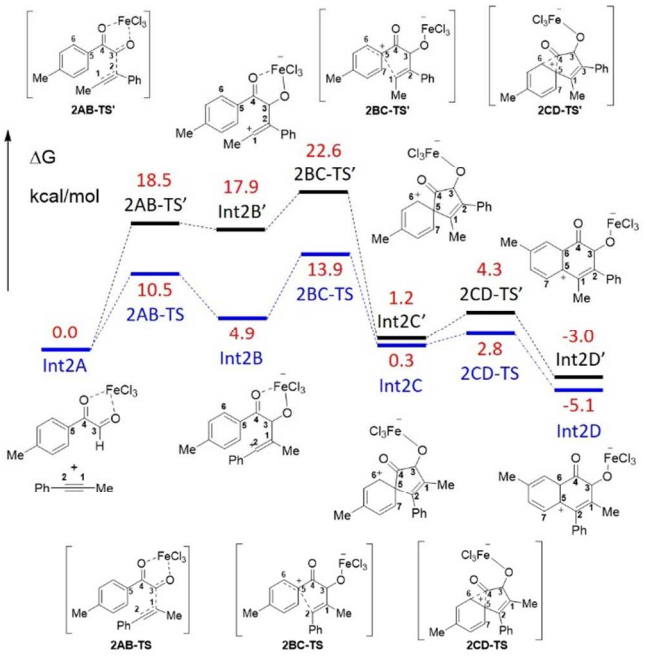


Figure 2. Calculated HOMO-1 and HOMO-4 of majority spin for IntB.

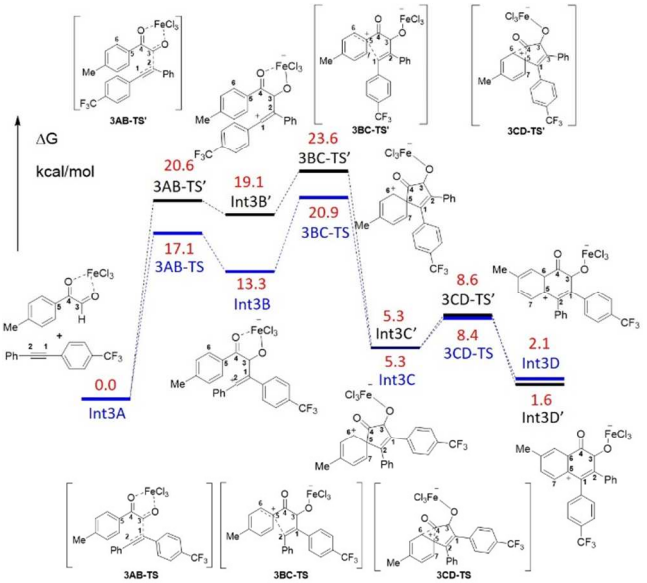
To further verify the proposed mechanism, we calculated the free energy surfaces for the reaction of 4-methylphenylglyoxal (**2a**) with 1-phenyl-1-propyne (**1j**). Our experiments showed that the ratio of the major and minor product for this particular reaction is 94:6 (**3ja**, Table 3). We found that all the intermediates and transition states on the path to the major product are more stable than those on the path to the minor product (Scheme 6), and importantly, the barrier for the rate-determining step for the major product is only 13.9 kcal/mol, much lower than that for the minor product (22.6 kcal/mol).

Based on the experimentally measured ratio (94:6), the difference in the kinetic barriers for the rate-determining step (RDS, Int2B→Int2C) of the two isomers is 1.63 kcal/mol. Although our DFT calculations predict that the free energy surface for the major isomer formation is indeed energetically more stable than that for the other, the difference in the kinetic barriers for the RDS is 8.70 kcal/mol, which is 7.07 kcal/mol larger than the experimental value. This means that our DFT results are qualitatively consistent with the experiments but not quantitatively.

Scheme 6. Gibbs Free Energy Surface for the reaction of 4-methylphenylglyoxal (2a) with 1-phenyl-1-propyne (1j) promoted by $FeCl_3$ calculated using quantum mechanics (unit in kcal/mol). Carbon atoms involved in the reaction are labeled with numbers.



Scheme 7. Gibbs Free Energy Surface for the reaction of 4-methylphenylglyoxal (2a) with 1-(phenylethynyl)-4-(trifluoromethyl)benzene (1q) promoted by $FeCl_3$ calculated using quantum mechanics (unit in kcal/mol). Carbon atoms involved in the reaction are labeled with numbers.



We believe that **Int2B**, **2AB-TS**, and **2BC-TS** are lower in energy than the corresponding **Int2B'**, **2AB-TS'**, and **2BC-TS'**, because Ph- is able to better stabilize the positive charge on C^2 formed after C-C coupling (due to the resonance of the charge in Ph-) than CH_3-. Therefore, for **Int2B'**, **2AB-TS'**, and **2BC-TS'**, the additional stabilization provided by solvent molecules becomes important. However, since we used an implicit solvent model rather than an explicit solvent, the stabilization from solvent may not be as large as it should be. For example, explicit solvent molecules (1,2-dichloroethane) may be able to use its lone pairs on Cl to stabilize C^+, and this effect is missing in the implicit solvation model. We therefore used another substrate PhC≡CAr (Ar = 4-$CF_3C_6H_4$), in which both sides of the C≡C triple bond contain a Ph-like substituent. Examining the calculated Gibbs free energy surface for the two isomers, we found that the difference for the RDS is 2.7 kcal/mol (Scheme 7), which is much closer to the experimental value.

CONCLUSIONS

In summary, we have developed a novel method for the synthesis of 1,2-naphthoquinones from arylglyoxals and alkynes. The new reaction system features an inexpensive iron catalyst, ambient reaction temperature, short reaction time, and ample substrate scope. Interestingly, an unusual keto migration was observed at room temperature under the reaction conditions. A possible mechanism involving a vinyl cation and a spiral intermediate and migration of the keto carbon to the *ortho* carbon was proposed as key steps and verified using quantum mechanics. Furthermore, the synthetic applications of this methodology were demonstrated.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Product 3. A sealed tube containing alkynes **1** (0.20 mmol) and arylglyoxals **2** (0.24 mmol) was evacuated and purged with nitrogen gas three times. A solution of $FeCl_3$ (97.4 mg, 0.60 mmol) in 1,2-dichloroethane (3.0 mL) was added to the system via syringe under a nitrogen atmosphere and the reaction mixture was stirred at 20 °C for 1 h. When the reaction was completed, the mixture was diluted with EtOAc, quenched with H_2O (2 mL), extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered through a Celite pad and the solvents were removed in vacuum to give the crude product, which was purified by column chromatography using a mixture of ethyl acetate/*n*-hexane as eluent to afford the corresponding 1,2-naphthoquinone **3** as orange to red solid.

Compound **3aa**. Red solid, 82% yield (53 mg); m.p. 243-244 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1 H), 7.30-7.24 (m, 4 H), 7.13-7.06 (m, 5 H), 6.95-6.89 (m, 3 H), 2.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.6 (*C*O), 179.3 (*C*O), 152.9 (C), 140.9 (C), 137.5 (C), 135.9 (*C*H), 135.7 (C), 134.1 (C), 133.5 (C), 130.9 (C), 130.8 (*C*H), 130.3 (2 *C*H), 130.2 (*C*H), 129.0 (2 *C*H), 128.1 (2 *C*H), 128.1 (*C*H), 127.4 (2 *C*H), 127.2 (*C*H), 21.0 (*C*H$_3$); HRMS (EI$^+$) calcd for $C_{23}H_{16}O_2$ 324.1150, found 324.1153; IR (KBr, cm^{-1}): 3054, 1650, 1604, 1342, 1272.

COMPUTATIONAL DETAILS

The geometry optimizations and zero-point vibrational energies (ZPVE) were carried out using the B3LYP functional.[11] For the choice of basis set, we used the 6-31G** basis set for C, O, H, and Cl atoms,[13] while for Fe the first two shells of core electrons were described by the Los Alamos angular momentum projected effective core potential (ECP) using the double- ζ contraction of valence functions (denoted as LACVP**).[14] Single-point energy calculations were per-

formed using B3LYP/LACVP** optimized structures and the same functional with a larger basis set: Fe was described with the triple-ζ contraction of valence functions and the core electrons were described by the same ECP, and the other atoms were described with the 6-311++G** basis set.[15] Open-shell wave functions were used to describe all intermediate and transition states, and all possible spin state were considered. The energetics reported here was based on the most stable spin state, which is the sextet state for all stationary points. All of the calculations were performed under the influence of implicit solvents, which were described using the Poisson-Boltzmann self-consistent polarizable continuum method[12] implemented in Jaguar (for 1,2-dichloroethane, nitromethane, chloroform, and chlorobenzene, the corresponding dielectric constants are 10.36, 35.87, 2.52, and 5.708, respectively, and effective radii are 2.33, 2.73, 2.52, and 2.72 Å, respectively).[12]

All energies discussed in this work are free energies, calculated as

$$G298K = E_{elec} + G_{solv} + ZPVE + \sum_{\nu} \frac{h\nu}{e^{h\nu/kT}-1} + \frac{n}{2}kT - T(S_{vib} + S_{rot} + S_{trans}),$$

where n = 12 accounts for the potential and kinetic energies of the translational and rotational modes and T = 298K.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. General experimental procedures, characterization details and ^{1}H and ^{13}C NMR spectra of new compounds (PDF). Supplementary crystallographic data (CIF). Computational details, electronic energies and coordinates for optimized structures.

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Notes

The authors declare no competing financial interest.

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graphic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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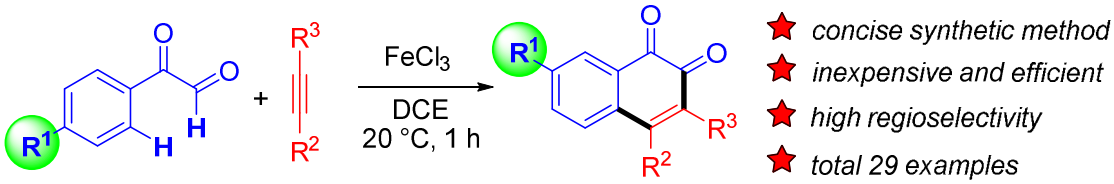
R1
O
H
O
+
R3
R2
FeCl3
DCE
20 °C, 1 h
R1
O
O
R3
R2
concise synthetic method
inexpensive and efficient
high regioselectivity
total 29 examples