Iron-Catalyzed Three-Component Reaction: Multiple C–C Bond Cleavages and Reorganizations

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ABSTRACT

An unexpected three-component iron-catalyzed reaction, comprising C–C bond cleavages in two components together with three times the cyclopropane formation and ring opening, is developed. The current reaction provides an unprecedented and efficient approach for the synthesis of cyclopen i endienes in high yields.

Reactions involving C–C bond cleavages and reorganizations frequently provide us with unusual but efficient access to molecules that are difficult to reach by routine methods or require multiple steps to synthesis, through confronting the inherent inactivity of C–C bonds.1,2 An eminent example could be the double C–C bond cleavage of a cyclopen i endi enyl ligand, in which the resulting two pieces, a two-carbon unit and a three-carbon unit, were later transformed into a benzene derivative and a pyridine derivative, respectively.3 To date, C–C bond cleavages and recombinations are frequently encountered in strained-ring-opening4 and retro-addition-initiated tandem reactions,5 metathesis of alkenes and alkynes,6 enyne isomerization reactions,7 etc. However, in most


cases, the C–C bond cleavages only occurred in one reaction component. As in a multicomponent reaction, the C–C cleavages of n components will generate 2n reactive intermediates, and then there would be multiple types of recombination possibility. Thus a very high convergence will be required to ensure the reaction proceeds in one direction to deliver the desired product in a high yield. The examples involving C–C splitting of at least two reaction components are rare. The best known reactions of this type involving C–C bond breakage in more than one reaction component could be the alkene cross metathesis, but another molecule of alkene such as ethylene is usually generated besides the desired alkene.6a,8

Recently, we discovered an iron-catalyzed9,10 three-component reaction of crotonate derivatives, diazo acetates, and bromoketones for the synthesis of cyclopentadienes, in which the C–C bonds of the two components were cut and recombined under mild conditions, including cleavages of the C–C double bond in crotonate and the C–C single bond in bromoketones (Scheme 1). Remarkably, mechanistic studies revealed a domino process that involves three times the cyclopropane formation and ring opening, which also represents an unprecedented route to cyclopentadienes. Here, we wish to report this reaction in detail.

Scheme 1. Unexpected C–C Cleavage and Reorganization

During our studies11 on the iron-catalyzed reaction of diazoacetate with ylide 1, we tried to capture the reaction intermediate with 2-bromo-1-phenylethanol. To our great surprise, unanticipated cyclopentadiene 4a was obtained in 29% yield (Scheme 2). The cyclopentadiene structure of 4a was deduced through extensive NMR analyses and further confirmed by the X-ray crystal structures of products 4e and 4f (phenyl with para nitro and trifluoromethyl substitution, respectively). The formation of the cyclopentadiene product is completely unexpected, as the adjacency of the aryl group to the quaternary carbon of the cyclopentadiene suggests an unusual but programmed cleavage and reorganization of the C–C bonds in both bromoaacetophenone 3a and the crotonate-derivative 1.

A possible reaction pathway was proposed as shown in Scheme 3. The cyclopropanation/ring-opening/proton transfer process11b (from 1 to 8) is very likely also involved in the current reaction, and the subsequent proton transfer affords ylide 8 for the following transformation steps. γ-Alkylation of 8 with 2-bromoacetophenone furnishes vinyl phosphonium salt 9 which is subsequently deprotonated to produce enolate 10 under the basic conditions.12 Intramolecular addition of the enolate to vinyl phosphonium provides the second ylidic cyclopropane intermediate 11 which resembles the structure of 6 and should also be prone to undergoing another ylidic carbanion-triggered ring-opening reaction. The subsequent attack to the carbonyl group that arises from 2-bromo-acetophenone affords the third cyclopropane intermediate 13. Then, a negative oxygen anion facilitates the ring-opening reaction of cyclopropane intermediate 13 from the vinyl phosphonium salt side and generates the allylic phosphorus ylide 14. Finally, the cyclopentadiene 4a was formed through an intramolecular Wittig reaction. Consequently, in the whole process, three times the cyclopropane formation and ring opening are involved. Cleavage of the C–C double bond of 1 proceeds via the cyclopropane ring opening of intermediate 6 or 11 which behaves similarly to a D–A cyclopropane with the ylidic carboanion as the donor and one ester group as the acceptor.4a In a similar fashion, the cleavage of the C(CO)–C single bond of acetophenone occurs in the ring-opening step of cyclopropane 13, which is facilitated by the oxygen anion.

Fortunately, we successfully trapped and characterized several key reaction intermediates. When Na2CO3 was employed as a base, vinyl phosphonium salt 9a can be isolated in 82% yield and identified by an X-ray crystal structural analysis (Scheme 4).13 This intermediate can be also obtained in a quantitative yield when no base was used in the reaction. The vinyl phosphonium salt

9a can be converted to the corresponding cyclopentadiene 4a in 86% yield under the standard reaction conditions (Scheme 4). Similarly, intermediate 9f bearing a para-trifluoromethyl phenyl group gave cyclopentadiene 4f in 95% yield. Moreover, in the reaction starting with 9a, the second cyclopropane intermediate ylide 11a can also be trapped by p-nitrobenzaldehyde via an intermolecular Wittig reaction to give vinyl cyclopropane 15 (eq I, Scheme 5).

The successful identification of the two key intermediates 9 and 11 strongly supports the proposed mechanism in the whole reaction (Scheme 3).

As proposed in Scheme 3, the C–C bond break of acetophenone happens in the transformation of intermediate 12 into intermediate 14. To verify this proposal, we performed 13C-labeled experiments with the 13C label located at the carbonyl- and α-carbon of 2-bromoacetophenone, respectively, to track the phenyl migration. As shown in Scheme 5, the 13C-labeled carbonyl carbon was found still linked to the phenyl group (δ 148.8 ppm), while α-13C-labeled 2-bromoacetophenone gave the final cyclopentadiene product bearing the 13C-labeled carbon at the position away from the phenyl group (δ 139.2 ppm). These 13C-labeled experiments confirmed that the cleavage of the C(CO)–α bond instead of the C(CO)–C(Ph) bond occurred in this domino process, just as proposed. Therefore, the whole reaction pathway proposed in Scheme 3 has been established. Impressively, there are three times carbon–carbon bond cleavages in the reaction. The high convergence method to the final cyclopentadiene product over a sequential domino process is rare and remarkable.

The current reaction represents a novel and facile synthetic route to useful cyclopentadienes with a quaternary carbon atom. We then moved to the optimization of reaction parameters, such as solvents, bases, and reagent loadings. Finally, using Cs2CO3 as the base and CH2Cl2 as the solvent with 2.0 equiv of methyl 2-diazoacetate (MDA), the desired cyclopentadiene product 4a can be obtained in a good yield (entry 1, Table 1). The generality of this domino reaction was thus evaluated next. As shown in Table 1, various acetophenone bromides are suitable substrates, leading to the desired products in moderate to excellent yields. The electronic nature of the substituents on the benzene ring greatly influenced the yield (entries 1–10). In general, the substrates with electron-withdrawing groups at the para position provided better yields than those with electron-donating groups. The ortho and meta bromo-substituted bromides gave similar results to the para bromo-substituted acetophenone (entry 4 vs entries 11 and 12). A 74% yield was obtained in the reaction of 2-bromoacetophenone (entry 13). Notably, the bromides bearing a heteroaromatic ring, such as 2-benzofuranyl and 4-pyridyl, are also suitable for this reaction, giving

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the corresponding cyclopentadienes in 72% and 85% yield respectively (entries 14 and 15). It is worth noting that lower yields in the cases of electron-rich substrates is consistent with the mechanism, because in the formation of the third cyclopropane intermediate 13, an electron-rich substituent will decrease the electrophilicity of the carbonyl group.

Cyclopentadiene is a useful type of feedstock and has been widely employed in a variety of transformations. Our current reaction also provides a new approach for the synthesis of cyclopentadiene derivatives, and the products can be readily converted into other useful compounds as shown in Scheme 6. Hydrogenation of the products gave the substituted cyclopentane 16 in 94% yield. Selective reduction of the ester group with DIBAL-H led to 2-oxaspiro-[4.4]-lactone 17 in 95% yield (based on the recovered starting material). Acid 18 was obtained in 83% yield after saponification with NaOH, which can be further transformed to the bicyclo[3.3.0] lactone 19 in 80% yield in the presence of a catalytic amount of Cu(OTf)$_2$.

In conclusion, an iron-catalyzed novel carbon—carbon bond programmed cleavage and reorganization reaction leading to cyclopentadienes under mild conditions was discovered and further developed. The reaction proceeds by rolling over three times the cyclopropane forming and ring-opening process, and involves three carbon—carbon bond cleavages and six carbon—carbon bond formations. It is potentially useful for the development of a new C—C bond cleavage reaction. $^{13}$C-labeled experiments, along with the isolation and capture of different reaction intermediates, were carried out to establish the reaction pathway. The current domino reaction also provides an unprecedented and efficient approach for the synthesis of cyclopentadienes.

### Table 1. Reaction Scope

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<tr>
<th>entry</th>
<th>R</th>
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<th>yield (%)</th>
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<tr>
<td>1</td>
<td>Ph-</td>
<td>4a</td>
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<tr>
<td>2</td>
<td>$p$-FC$_6$H$_4$-</td>
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<td>24</td>
</tr>
<tr>
<td>3</td>
<td>$p$-ClC$_6$H$_4$-</td>
<td>4c</td>
<td>24</td>
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<tr>
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<tr>
<td>7</td>
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<tr>
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<td>4i</td>
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<tr>
<td>10</td>
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<td>2-naphanyl-</td>
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<td>14</td>
<td>2-benzofuranyl-</td>
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<tr>
<td>15</td>
<td>4-pyridyl-</td>
<td>4o</td>
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$^*$Ylide 1 (259.2 mg, 0.72 mmol), Fe(TCP)Cl (1.7 mg, 0.002 mmol), MDA (67 $\mu$L, 0.8 mmol), RCOCH$_2$Br (0.4 mmol), Cs$_2$CO$_3$ (156 mg, 0.48 mmol), CH$_2$Cl$_2$ (4.0 mL), rt. $^\beta$The reaction time was not optimized. $^\gamma$Isolated yield

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Supporting Information Available. Experimental procedures, spectral data, and X-ray crystallographic data of 4e, 4f, and 9a are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.