ORGANIC
LETTERS

2013
Vol. 15, No. 14
3606–3609

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

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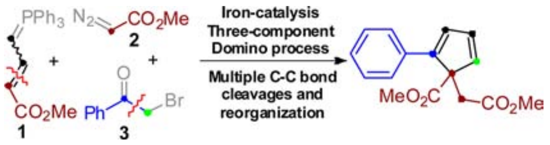
Received May 23, 2013

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 cyclopentadienes 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 synthesize, through confronting the inherent inactivity of C−C bonds.[1,2] An eminent example could be the double C−C bond cleavage of a cyclopentadienyl 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-opening-[4] and retro-addition-initiated tandem reactions,[5] metathesis of alkenes and alkynes,[6] enyne isomerization reactions,[7] etc. However, in most

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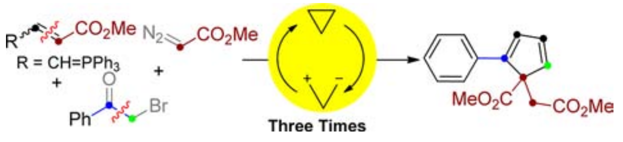
10.1021/ol4014552

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 2*n* 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-catalyzed[9,10] 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 studies[11] on the iron-catalyzed reaction of diazoacetate with ylide **1**, we tried to capture the reaction intermediate with 2-bromo-1-phenylethanone. 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 bromoacetophenone **3a** and the crotonate-derivative **1**.

Scheme 2. Three-Component to Cyclopentadienes

A possible reaction pathway was proposed as shown in Scheme 3. The cyclopropanation/ring-opening/proton transfer process[11b] (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)−Cα 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 Na_2CO_3 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. Furthermore, the vinyl phosphonium salt

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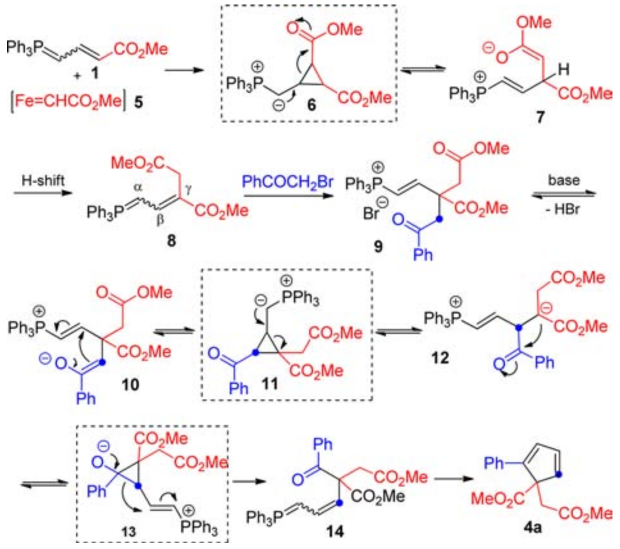
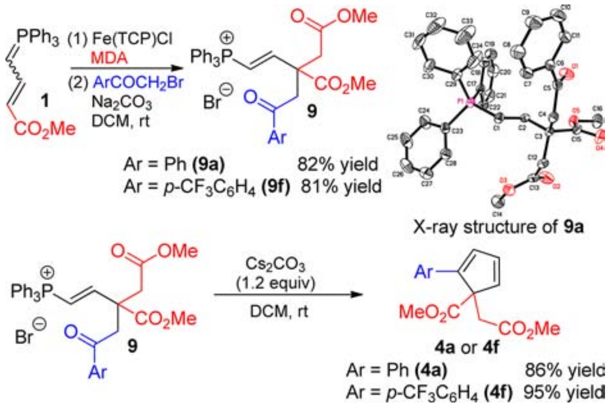
Scheme 3. Proposed Reaction Pathway

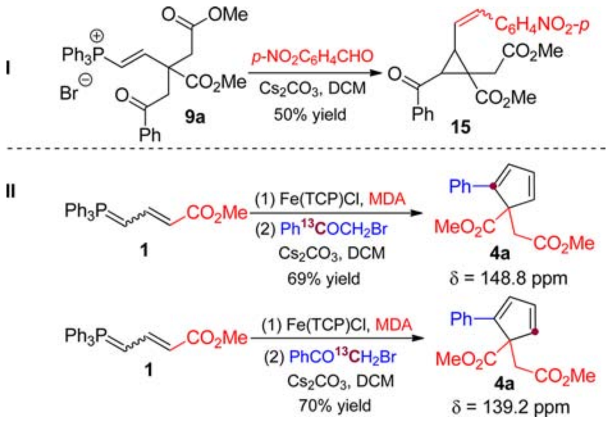


Scheme 4. Isolation of Intermediates and Their Transformation to Cyclopentadienes



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).

Scheme 5. Trapping of **11a** with Aldehyde and ^{13}C-Labeled Experiments



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 ^{13}C-labeled experiments with the ^{13}C label located at the carbonyl- and α-carbon of 2-bromoacetophenone, respectively, to track the phenyl migration. As shown in Scheme 5, the ^{13}C-labeled carbonyl carbon was found still linked to the phenyl group (δ 148.8 ppm), while α-^{13}C-labeled 2-bromoacetophenone gave the final cyclopentadiene product bearing the ^{13}C-labeled carbon at the position away from the phenyl group (δ 139.2 ppm). These ^{13}C-labeled experiments confirmed that the cleavage of the C(CO)−Cα 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[12,14] with a quaternary carbon atom. We then moved to the optimization of reaction parameters, such as solvents, bases, and reagent loadings.[13] Finally, using Cs_2CO_3 as the base and CH_2Cl_2 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-bromoacetonaphthalenone (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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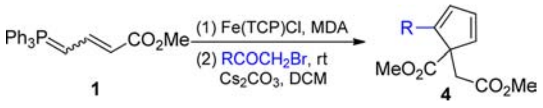
the corresponding cyclopentadienes in 72% and 85% yield respectively (entries 14 and 15). It is worth noting that lower yields in the cases of electron-rich substrates is consistent with the mechanism, because in the formation of the third cyclopropane intermediate **13**, an electron-rich substituent will decrease the electrophilicity of the carbonyl group.

Table 1. Reaction Scope



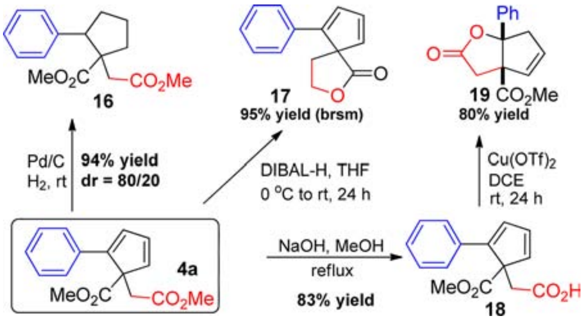
entry[a]	R		*t* (h)[b]	yield (%)[c]
1	Ph-	**4a**	24	71
2	*p*-FC_6H_4-	**4b**	24	53
3	*p*-ClC_6H_4-	**4c**	24	71
4	*p*-BrC_6H_4-	**4d**	24	77
5	*p*-$NO_2C_6H_4$-	**4e**	24	86
6	*p*-$CF_3C_6H_4$-	**4f**	24	88
7	*p*-CNC_6H_4-	**4g**	24	93
8	3,4-$Cl_2C_6H_3$-	**4h**	26	90
9	*p*-C_6H_5-C_6H_4-	**4i**	41	53
10	*p*-$CH_3C_6H_4$-	**4j**	24	40
11	*o*-BrC_6H_4-	**4k**	24	76
12	*m*-BrC_6H_4-	**4l**	24	75
13	2-naphanyl-	**4m**	24	74
14	2-benzofuranyl-	**4n**	24	72
15	4-pyridyl-	**4o**	37	85

[a] Ylide **1** (259.2 mg, 0.72 mmol), Fe(TCP)Cl (1.7 mg, 0.002 mmol), MDA (67 μL, 0.8 mmol), $RCOCH_2Br$ (0.4 mmol), Cs_2CO_3 (156 mg, 0.48 mmol), CH_2Cl_2 (4.0 mL), rt. [b] The reaction time was not optimized. [c] Isolated yield

Cyclopentadiene is a useful type of feedstock and has been widely employed in a variety of transformations.[14] 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[14] 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.

Scheme 6. Chemical Transformations of the Cyclopentadiene Product



Acknowledgment. We are grateful for the financial support from the Natural Sciences Foundation of China (Nos. 21121062, 20932008, and 21272248), the Major State Basic Research Development Program (Grant No. 2009CB825300), and the Chinese Academy of Sciences.

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.