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Asymmetric Catalytic Diverse Ring Opening/Cycloadditions of Cyclobutenones with (*E*)-Alkenyloxindoles and (*E*)-Dioxopyrrolidines

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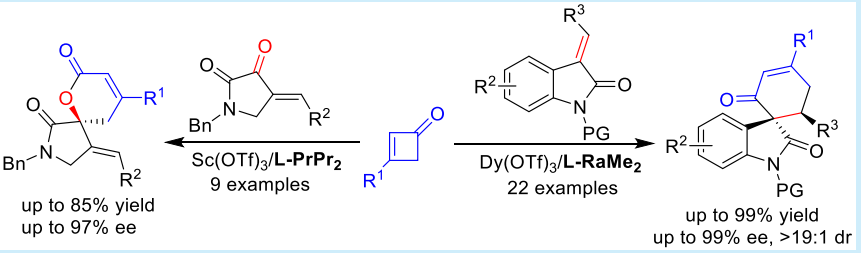
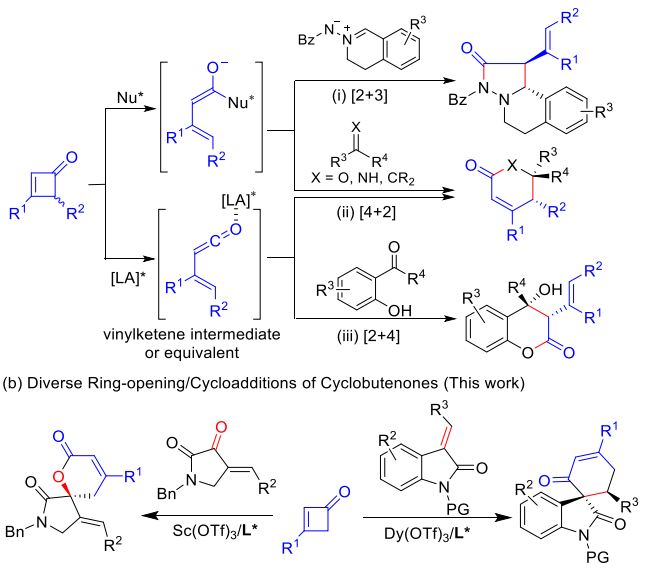


ABSTRACT: Highly enantioselective ring-opening/cycloaddition reactions of cyclobutenones were achieved by employing chiral *N,N′*-dioxide/metal complexes as the catalysts. The Diels–Alder type cycloaddition with (*E*)-alkenyloxindoles yielded spirocyclohexaneoxindoles with excellent results. Meanwhile, a hetero-Diels–Alder process occurred with (*E*)-dioxopyrrolidines to afford spiropyrrolidinone-dihydropyranone derivatives.

Cyclobutenone has been investigated as a versatile synthon in many important organic transformations over the past several decades.[1] Among them, vinylketene intermediates or equivalents, readily available from cyclobutenones under certain conditions,[2] attracted considerable interest due to their utility in the rapid construction of highly valuable cyclic molecules.[2c−j] For instance, nucleophilic organocatalyst mediated asymmetric [4 + 2][3] or [2 + 3][4] cycloadditions of cyclobutenones have been established by the groups of Chi and Zhang (Scheme 1a, paths i and ii). Recently, our group found that chiral Lewis acids were useful to the generation of vinylketene intermediates under mild conditions, thus enabling two interesting ring-formation reactions in an enantioselective manner (Scheme 1a, paths ii and iii).[5] Since multiple possible reaction sites are present in such intermediates, their reaction patterns are underdeveloped and not predictive. Therefore, studies on the reactivity of vinylketene intermediates and further exploration on their application in organic synthesis are highly desirable.

Spirocyclohexaneoxindole structures are commonly found in a variety of natural products as well as biologically active compounds,[6] as exemplified by gelsemine, MDM2-p53 interaction inhibitor, satavaptan, and so on (Figure 1). In the past decades, many efforts have been devoted to their synthesis.[7] However, to the best of our knowledge, only a few examples were related to the construction of optically active spirocyclohexaneoxindole derivatives.[7g−q] As part of our ongoing interest in the concise synthesis of chiral spiro-compounds[8] as well as the reactivity[5] of cyclobutenones, we

Scheme 1. Asymmetric Transformations of Cyclobutenones



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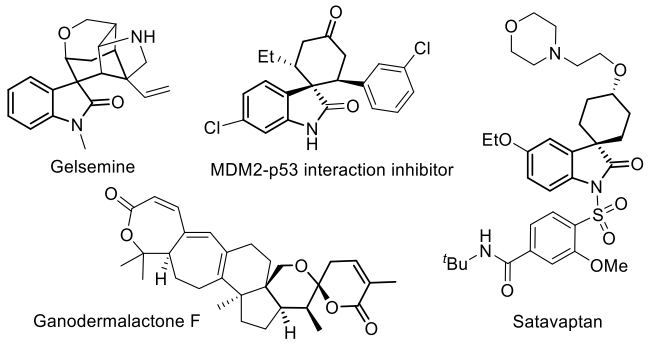
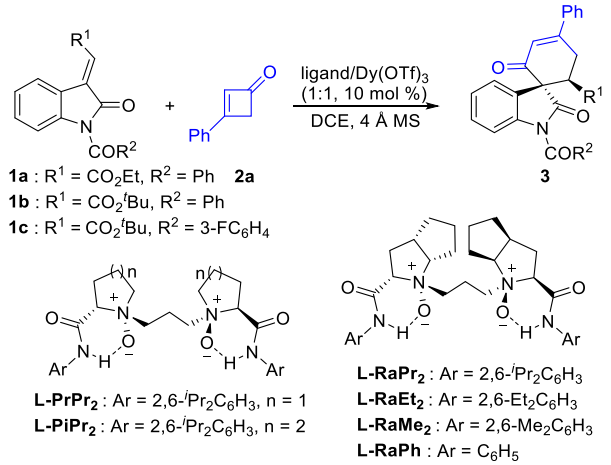


Figure 1. Selected medicinally important spirocyclohexaneoxindole and spiro-δ-lactone skeletons.

carried out the systemic examination of substrates using well-defined chiral *N,N′*-dioxide/metal salt complex as the catalyst.[9] Herein, we report our results in this area that chiral spirocyclohexaneoxindoles were readily available from (*E*)-alkenyloxindoles via a highly diastereo- and enantioselective [4 + 2] cycloaddition. A hetero-Diels−Alder reaction occurred at the C═O bond of (*E*)-dioxopyrrolidines,[10] affording spiro-δ-lactones with good results (up to 85% yield, 97% ee). In addition, a [2 + 2] cycloaddition performed from isatin-derived imine rather than an aza-[4 + 2] process[3a] generated a β-lactam adduct in high yield with moderate enantiomeric excess (ca. 60% ee).

Initially, the ring-opening/cycloaddition of cyclobutenone **2a** with (*E*)-alkenyloxindole **1a** was selected as the model reaction to optimize the reaction conditions (Table 1). A variety of metal salts were examined by coordinating with L-proline derived *N,N′*-dioxide L-**PrPr$_2$** in DCE at 60 °C (see the SI for more details). It was found that the complex of Dy(OTf)$_3$ with L-**PrPr$_2$** could promote the reaction smoothly to afford the corresponding [4 + 2] cycloaddition product (**3aa**) in 55% yield, 85:15 dr and 39% ee (Table 1, entry 1). In sharp contrast, Sc(OTf)$_3$ as the metal precursor only gave the racemic product (Table 1, entry 2). As such, Dy(OTf)$_3$ was chosen as the central metal to screen the chiral *N,N′*-dioxide ligands. It was indicated that L-**RaPr$_2$** derived from L-ramipril was superior to L-**PrPr$_2$** and L-pipecolic acid derived L-**PiPr$_2$** in terms of enantioselectivities (Table 1, entry 4 vs entries 1 and 3). Interestingly, decreasing the steric hindrance of the amide substituents from 2,6-^{i}Pr$_2$C$_6$H$_3$ to 2,6-Et$_2$C$_6$H$_3$ (L-**RaEt$_2$**) or 2,6-Me$_2$C$_6$H$_3$ (L-**RaMe$_2$**) led to higher enantioselectivity, but with reversal configuration, and L-**RaMe$_2$** exhibited a better performance (Table 1, entry 6, 59% yield, 94:6 dr, and 72% ee).[11] However, the use of L-**RaPh** with a simple phenyl group delivered a racemic product (Table 1, entry 7), implying the important role of the 2,6-substituents at the phenyl group. Increasing the amount of 4 Å molecular sieves enhanced both the isolated yield and enantioselectivity (Table 1, entry 8 vs entry 6). Other parameters such as solvents and additives were investigated as well; however, no better results were achieved (see the SI for details). When the substrate **1b** bearing a large *tert*-butyl ester group was used instead of **1a** at 50 °C for 48 h, the corresponding spirocyclohexaneoxindole **3ba** was obtained in 75% yield and improved enantiomeric excess (87% ee; Table 1, entry 9). To our delight, a better result was afforded when **1c** with a 3-fluoro-substituted benzoyl group at nitrogen was employed (92% ee; Table 1, entry 10). Finally, enhancing the reaction concentration (0.2 M) and using slightly excessive amount of cyclobutenone **2a** (1.5 equiv) resulted in an obvious

Table 1. Optimization of the Reaction Conditions



entry[a]	1	ligand	yield[a] (%)	dr[a] (%)	ee[a] (%)
1	**1a**	L-**PrPr$_2$**	55 (**3aa**)	85:15	−39
2[b]	**1a**	L-**PrPr$_2$**	32 (**3aa**)	84:16	0
3	**1a**	L-**PiPr$_2$**	50 (**3aa**)	>19:1	−34
4	**1a**	L-**RaPr$_2$**	32 (**3aa**)	92:8	−48
5	**1a**	L-**RaEt$_2$**	56 (**3aa**)	>19:1	61
6	**1a**	L-**RaMe$_2$**	59 (**3aa**)	94:6	72
7	**1a**	L-**RaPh**	76 (**3aa**)	92:8	0
8[c]	**1a**	L-**RaMe$_2$**	64 (**3aa**)	94:6	73
9[c,d]	**1b**	L-**RaMe$_2$**	75 (**3ba**)	>19:1	87
10[c,d]	**1c**	L-**RaMe$_2$**	72 (**3ca**)	>19:1	92
11[c,d,e]	**1c**	L-**RaMe$_2$**	99 (**3ca**)	>19:1	93

[a]The reactions were performed with **L**/Dy(OTf)$_3$ (10 mol %), **1a** (0.10 mmol), **2a** (1.0 equiv), and 4 Å MS (50 mg) in DCE (0.1 M) at 60 °C for 16 h. Isolated yield of the product. The dr values were determined by ^{1}H NMR analysis, and ee values were determined by HPLC analysis on a chiral stationary phase. [b]Sc(OTf)$_3$ instead of Dy(OTf)$_3$. [c]4 Å MS (80 mg). [d]At 50 °C for 48 h. [e]DCE (0.2 M), **2a** (1.5 equiv).

increase of the yield (99%) with 93% ee (Table 1, entry 11). Therefore, the optimal reaction conditions were established as **1c**, **2a** (1.5 equiv), Dy(OTf)$_3$/L-**RaMe$_2$** (1:1, 10 mol %), 4 Å MS, in DCE (0.2 M) at 50 °C for 48 h.

Under the optimized reaction conditions, the scope of (*E*)-alkenyloxindoles was then investigated with cyclobutenone **2a**. As depicted in Table 2, the position of substitution on the phenyl ring had a significant influence on the enantioselectivity of the reaction. First, variant of the groups at C5- and C6-positions in (*E*)-alkenyloxindoles exhibited that regardless of electronic nature of the substituents all of the reactions proceeded well, delivering the desired products **3da**−**3ka** in good yields (86−99%) with moderate to high enantioselectivities (79−92% ee) (Table 2, entries 2−9). However, when C4- and C7-substituted (*E*)-alkenyloxindoles **1l**−**1n** were subjected into the current system, only moderate enantioselectivities (48−79% ee) were observed, probably due to the effect of steric hindrance (Table 2, entries 10−12). Additionally, when R^1 was CO$_2$Et or COPh, the product **3oa** or **3pa** was obtained in good results (**3oa**, 88% yield, 86% ee; **3pa**, 99% yield, 91% ee; Table 2, entries 13 and 14). The gram-scale reaction of **1c** (3.0 mmol) and **2a** (4.5 mmol) proceeded well under the optimized reaction conditions, delivering the corresponding product **3ca** in 99% yield (>19:1 dr, 1.53 g) with 93% ee (Table 2, entry 1). Furthermore, the absolute configuration of

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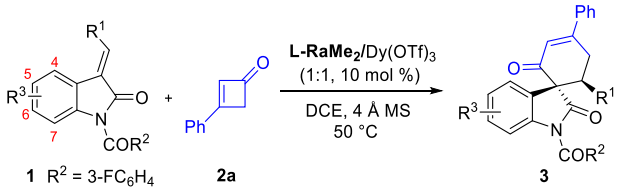
Table 2. Substrate Scope for (*E*)-Alkenyloxindoles



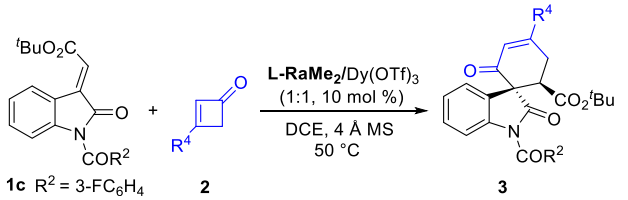
entry[a]	R^1	R^3	yield[b] (%)	dr[c] (%)	ee[d] (%)
1[e]	$CO_2{}^tBu$	H	99 (**3ca**)	>19:1	93
2	$CO_2{}^tBu$	5-F	99 (**3da**)	>19:1	91
3	$CO_2{}^tBu$	5-Cl	99 (**3ea**)	>19:1	91
4	$CO_2{}^tBu$	5-Br	99 (**3fa**)	>19:1	90
5	$CO_2{}^tBu$	5-I	96 (**3ga**)	>19:1	84
6	$CO_2{}^tBu$	5-NO_2	92 (**3ha**)	>19:1	79
7	$CO_2{}^tBu$	5-Me	94 (**3ia**)	>19:1	85
8	$CO_2{}^tBu$	5-OMe	86 (**3ja**)	>19:1	90
9	$CO_2{}^tBu$	6-Cl	99 (**3ka**)	>19:1	92
10	$CO_2{}^tBu$	7-F	94 (**3la**)	19:1	48
11	$CO_2{}^tBu$	4-Cl	92 (**3ma**)	19:1	79
12	$CO_2{}^tBu$	4-Br	88 (**3na**)	>19:1	55
13	CO_2Et	H	88 (**3oa**)	>19:1	86
14	COPh	H	99 (**3pa**)	>19:1	91

[a]The reactions were performed with **1** (0.1 mmol), **2a** (1.5 equiv), 4 Å MS (80 mg), and catalyst L-**RaMe$_2$**/Dy(OTf)$_3$ (1:1, 10 mol %) in DCE (0.2 M) at 50 °C for 48 h. [b]Yield of the isolated product. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC analysis on a chiral stationary phase. [e]**1c** (3.0 mmol), **2a** (4.5 mmol), 4 Å MS (2.40 g).

3fa was determined as (1*R*,2*R*) by the X-ray diffraction analysis, and other products were assigned by analogy.

Subsequently, the scope of cyclobutenones **2** was examined. As shown in Table 3, the reactions of cyclobutenones **2c**−**2i** with (*E*)-alkenyloxindole **1c** took place smoothly, giving the expected spirooxindole derivatives **3cc**−**3ci** in moderate to good yields with high enantioselectivities (79−99% yields, > 19:1 dr, 87−99% ee; Table 3, entries 2−8). However, under above conditions, 2-fluorophenyl-substituted **2b** transformed into the desired product **3cb** with lower yield and enantiomeric excess (69% yield, 66% ee; Table 3, entry 1).

Table 3. Substrate Scope for Cyclobutenones

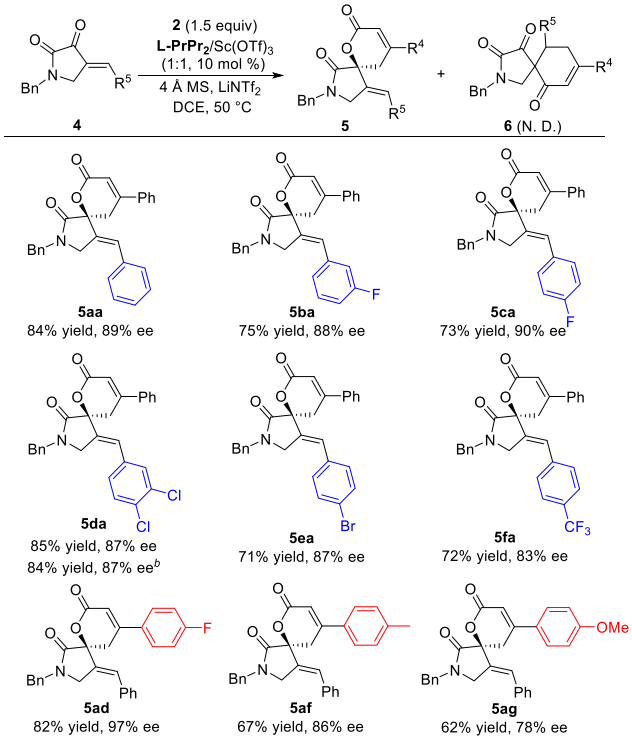


entry[a]	R^4	yield[b] (%)	dr[c] (%)	ee[d] (%)
1[e]	2-FC_6H_4	69 (**3cb**)	>19:1	66
2	3-FC_6H_4	99 (**3cc**)	>19:1	92
3	4-FC_6H_4	99 (**3cd**)	>19:1	87
4	3-MeC_6H_4	99 (**3ce**)	>19:1	90
5	4-MeC_6H_4	79 (**3cf**)	>19:1	88
6	4-$MeOC_6H_4$	99 (**3cg**)	>19:1	87
7	4-PhC_6H_4	99 (**3ch**)	>19:1	99
8	4-BrC_6H_4	99 (**3ci**)	>19:1	87

[a−d]Unless otherwise stated, all of the reactions were same as the footnotes in Table 2. [e]72 h.

Encouraged by these results, we tried to expand the substrate scope by searching other unsaturated compounds in place of alkenyloxindoles **1**. When (*E*)-dioxopyrrolidine **4a** bearing both C═O and C═C double bonds was subjected into the standard conditions, the ring-opening/oxa-[4 + 2] cycloaddition product **5aa** was afforded exclusively rather than [4 + 2] product **6aa** (Scheme 2). A subsequent detailed examination indicated that Sc(OTf)$_3$/L-**PrPr$_2$** was the best catalyst (see the SI for details), and the desired spiropyrrolidinone **5aa** was isolated in 84% yield and 89% ee. Then representative (*E*)-dioxopyrrolidines **4** as well as cyclobutenones **2** were tested, and the desired products **5** were provided in good yields and enantioselectivities (62−85% yield, 78−97% ee; Scheme 2). In addition, a gram-scale synthesis of **5da** was also carried out successfully (Scheme 2, 84% yield, 87% ee). Furthermore, the absolute configuration of **5da** was determined as (*S*) by the X-ray diffraction analysis, and other products were assigned by analogy.

Scheme 2. Substrate Scope for (*E*)-Dioxopyrrolidines[a]



[a]The reactions were performed with **4** (0.1 mmol), **2** (1.5 equiv), 4 Å MS (80 mg), $LiNTf_2$ (30 mol %), and L-**PrPr$_2$**/Sc(OTf)$_3$ (1:1, 10 mol %) in DCE (0.2 M) at 50 °C for 72 h, and yields of the isolated products are shown. Chiral HPLC analysis was used to determine ee values. [b]**4d** (2.5 mmol), **2a** (3.75 mmol), 4 Å MS (2.0 g).

Surprisingly, when isatin-derived imine **7** was employed, aza-[2 + 2] cycloaddition reaction took place instead of aza-[4 + 2] cycloaddition. Preliminary studies suggested that Zn(OTf)$_2$/L$_2$-**PrPr$_3$** could promote the aza-[2 + 2] reaction smoothly. Nevertheless, removal of the Boc group occurred simultaneously.[8g] The reaction gave *N*-Boc spiro[azetidine-2,3′-indoline]-2′,4-dione **8** and N−H product **9** in total 95% yield with 60% ee and 63% ee, respectively (Scheme 3a). The deprotection of the product **3ca** was carried out in the presence of ammonium hydroxide, delivering the product **11** in good result (88% yield, 93% ee, >19:1 dr) (Scheme 3b).

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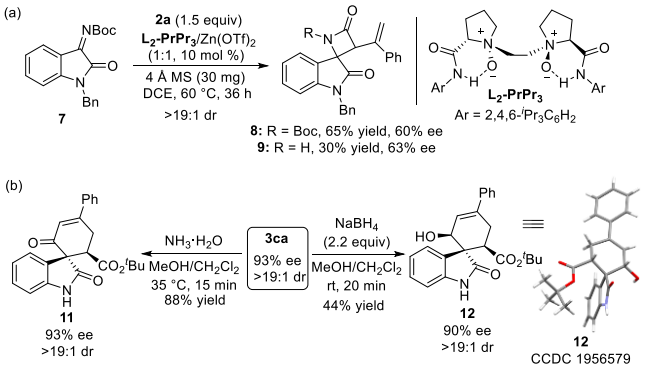
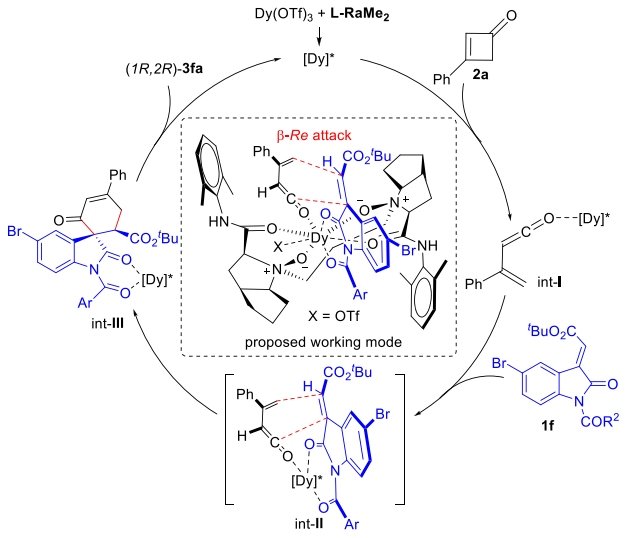
Scheme 3. [2 + 2] Cycloaddition and Transformations



Furthermore, treatment of **3ca** with 2.2 equiv sodium borohydride could yield the product **12** in 44% yield with >19:1 dr and 90% ee (Scheme 3b), and its absolute configuration was confirmed by diffraction analysis as well.

On the basis of previous reports and X-ray crystal structures of product **3fa** and catalyst ($Dy(OTf)_3$/L-**RaEt$_2$**), a possible mechanism was proposed to understand the process of the reaction (Scheme 4). In the presence of chiral Lewis acid

Scheme 4. Proposed Catalytic Cycle



$Dy(OTf)_3$/L-**RaMe$_2$** catalyst, vinylketene intermediate was generated through ring-opening of cyclobutenone **2a**. Meanwhile, (*E*)-alkenyloxindole **1f** was activated by bidentate coordination with Dy^{III}-L-**RaMe$_2$**. The *β-Si* face of compound **1f** was shielded by the nearby 2,6-dimethyl phenyl group of L-**RaMe$_2$**. Therefore, the in situ formed vinylketene intermediate could approach **1f** from its *β-Re* face, followed by a rapid ring-closing step, to generate the (1*R*,2*R*)-**3fa** as the major product.

In summary, we have developed diverse enantioselective ring-opening/cycloadditions of cyclobutenones with (*E*)-alkenyloxindoles, (*E*)-dioxopyrrolidines, or isatin-derived imine by using chiral *N*,*N*′-dioxide/metal complexes as catalysts. This strategy provided a highly efficient method for the synthesis of various spiro products in excellent yields (up to 99%) and high enantioselectivities (up to 99% ee) under mild conditions. Furthermore, a possible catalytic cycle was provided to elucidate the enantioselective control of the reaction. Further investigation on the reaction mechanism and other relative reactions of cyclobutenones are undergoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00608.

Experimental details; characterization data (copies of ^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H} NMR, HPLC and HRMS data) (PDF)

Accession Codes

CCDC 1956579−1956580, 1977127, and 1989600 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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