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Gold(I)-Catalyzed Tandem Cycloisomerization and Fluorination of 1,3(4)-Enyne Esters with NFSI: One-Pot Assembly of 5-Fluoro- Cyclopentenones

Xianxiao Chen, Yuanyuan Zhou, Mei Hong, Yuan Ling, Dongliang Yin, Shifa Wang, Xiaoxiang Zhang,* and Weidong Rao*

Jiangsu Key Laboratory of Biomass-based Green Fuels and Chemicals, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China. e-mail: weidong@njfu.edu.cn(W. R); zhangxiaoxiang@njfu.edu.cn (X. Z);
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Abstract. An efficient synthetic approach for the synthesis of 5-fluoro-cyclopentenones containing a fluorine-substituted carbon stereocenter that relies on gold(I)-catalyzed cycloisomerization and fluorination sequence of 1,3(4)-enyne esters with N-fluorbenzensulfonimide (NFSI) is described. This tandem transformation exhibited a broad substrate scope and excellent functional group compatibility, providing a novel protocol for rapid assembly 5-fluoro-cyclopentenones in good to excellent yields under mild reaction conditions. The mechanistic studies revealed that the transformation involves a gold-catalyzed cycloisomerization and electrophilic fluorination cascade to give the 5-fluoro-cyclopentenones.

Keywords: cycloisomerization; fluorination; 5-fluoro-cyclopentenones; gold; enyne esters

Introduction

Fluorine-containing molecules have found a wide range of applications in pharmaceuticals, agrochemicals and material sciences due to their unique physicochemical and biological properties.[1-2] Therefore, the development of efficient synthetic approaches for the introduction of fluorine atoms into diverse organic frameworks has attracted increasing attention.[3] Among various organofluorine molecules, α-fluoroketones are of particular interest because of their potential applications as a versatile building blocks for the synthesis of a wide variety of bioactive compounds such as those illustrated in Figure 1.[4] Consequently, this has led to the establishment of a diverse array of elegant synthetic strategies in recent years towards its construction.[5-12] Including nucleophilic fluorine substitution of α-haloketones or its analogues with fluoride,[5] electrophilic fluorination of ketones enabled by a one-step[6] or two-step process via enolate anion, enamine or imine, enol ether,[7] decarboxylative fluorination of β-ketoacids,[8] fluorine insertion into α-diazocarbonyl compounds,[9] oxidative difunctionalization of phenylethylenes[10] and vinyl azides,[11] and other processes.[12] Despite these advances, current reported approaches are still limited to acyclic α-fluoroketones, and the synthesis of cyclic α-fluoroketones bearing a fluorine-substituted carbon stereocenter [13] from acyclic precursors remains largely elusive.[14]

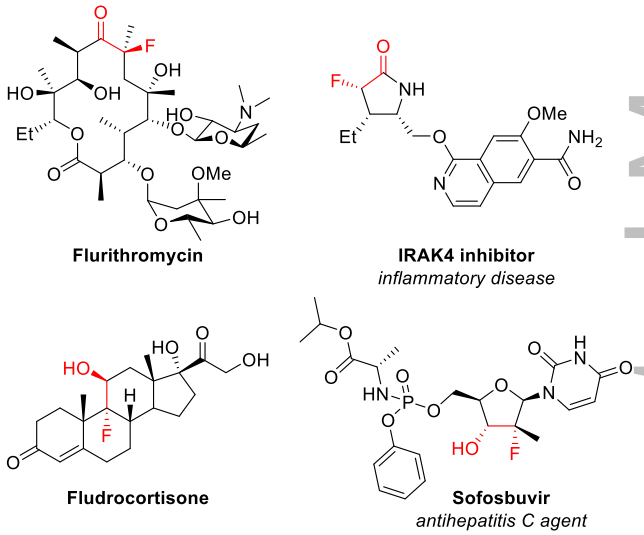
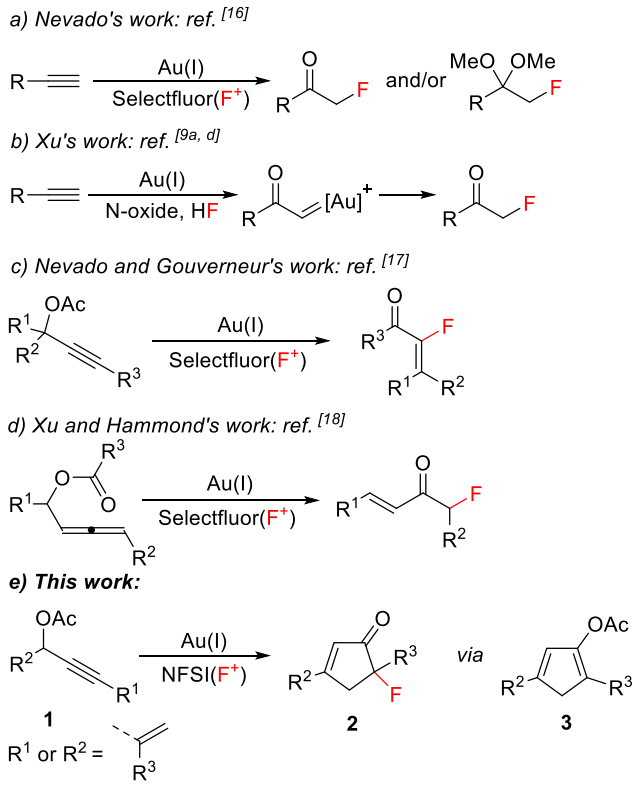


Figure 1. Selected examples of bioactive cyclic α-fluoro ketones and its derivatives

Recently, the combination of gold catalysis with fluorinating reagents has emerged as powerful strategies for the incorporation of fluorine atom into diverse molecules to deliver a number of fluorine-containing organic complexes.[15-18] For instance, Nevado's group developed a novel and efficient protocol for the preparation of α-fluoro ketones or acetals through an alkoxylation−fluorination of alkynes by merging gold catalysis with Selectfluor (Scheme 1a).[16] Very recently, Xu and co-workers have elegantly demonstrated that α-fluoro ketones could be accessed by insertion of HF into the gold carbene, which was generated in-situ from *N*-oxides

and alkynes in the presence of gold catalyst (Scheme 1b).[9a, d] Nevado and Gouverneur have shown that α-fluoroenones can be synthesized from propargylic esters with Selectfluor under gold(I) catalysis, albeit the mechanism involved remains obscure (Scheme 1c).[17] A one-pot, two-step process for the preparation of α-fluoroenones from allenyl carbinol esters has been realized by using gold(I) catalyst with Selectfluor (Scheme 1d).[18] Inspired by these seminal works and as part of ongoing efforts in the field of gold catalysis,[19] we turned our attention to explore the reactivity of 1,3(4)-enyne esters in the presence of the electrophilic fluorinating reagents such as *N*-fluorbenzensulfonimide (NFSI) (Scheme 1e).[20-23] We envisioned that the in-situ generated cyclopentadiene species **3** through a gold-catalyzed cycloisomerization of 1,3(4)-enyne esters **1** might undergo further electrophilic fluorination to afford the desired α-fluoro-cyclopentenone derivatives. Herein, we disclose the details of this chemistry that provides expedient and regioselective access to 5-fluoro-cyclopentenones bearing a fluorine-substituted carbon stereocenter from simple and readily available 1,3(4)-enyne esters with *N*-fluorbenzensulfonimide (NFSI) in one-pot operation.

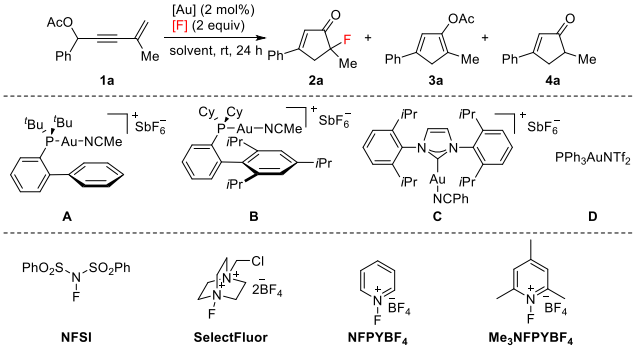


Scheme 1. Synthesis of α-fluoroketones by merging gold catalysis and fluorinating reagents

Results and Discussion

We began our studies by examining the gold-catalyzed cycloisomerization and electrophilic fluorination cascade of 1,3-enyne ester **1a** in the presence of electrophilic fluorinating reagents to establish the optimum reaction conditions (Table 1).[24] This initially revealed that treating **1a** with 2 mol% of gold(I) phosphine catalyst **A**[24a] and NFSI (2 equiv.) in 1,2-dichloroethane at room temperature for 24 h afforded 5-fluorinated cyclopentenone **2a** and **4a** in 28% and 53% yields, respectively (Table 1, entry 1). The structure of 5-fluorinated cyclopentenone **2a** was unambiguously ascertained by NMR measurements and X-ray crystallographic analysis.[25] A similar results were observed upon repeating the reaction in toluene instead of 1,2-dichloroethane as the solvent (entry 2). However, switching the solvent to CH_3CN was found to result in no reaction observed based on TLC and ^1H NMR analysis (entry 3). Gratifyingly, we found that the reaction proceeded efficiently, leading to the desired 5-fluorinated cyclopentenone **2a** as the sole product in 86% and 81% yields and without the formation of **3a** and **4a** upon changing the solvent from DCE to MTBE and THF (entries 4-5). On the contrary, only cyclopentadiene **3a** was obtained in 89-95% yields when other commercially fluorinating reagents such as Selectfluor, $NFPYBF_4$ and $Me_3NFPYBF_4$ were used (entries 6-8). It was then found that replacement of gold(I) complex **A** with gold(I) complex **B**,[24b] **C** [24c] and PPh_3AuNTf_2[24d] gave the product **2a** in lower yields (entries 9-11). In addition, using 1.5 equivalents instead of 2 equivalents of NFSI gave the

Table.1 Optimization of Reaction Conditions[a]



Entry	[Au]	[F]	Solvent	Yield [%]		
				2a	**3a**	**4a**
1	**A**	NFSI	DCE	28	-	53
2	**A**	NFSI	toluene	29	-	50
3	**A**	NFSI	CH_3CN	[b]	-	-
4	**A**	**NFSI**	**MTBE**	**86**	-	-
5	**A**	NFSI	THF	81	-	-
6	**A**	SelectFluor	MTBE	-	95	-
7	**A**	$NFPYBF_4$	MTBE	-	93	-
8	**A**	$Me_3NFPYBF_4$	MTBE	-	89	-
9	**B**	NFSI	MTBE	83	-	-
10	**C**	NFSI	MTBE	81	-	-
11	**D**	NFSI	MTBE	62	-	-
12[c]	**A**	NFSI	MTBE	79	-	-

[a]All reactions were performed with **1** (0.3 mmol), gold(I) complex **A** (2 mol %) and **[F]** source (0.6 mmol) in solvent (6 mL) at room temperature for 24 h. [b]No reaction. [c]Reaction performed with NFSI (0.45 mmol, 1.5 equiv).

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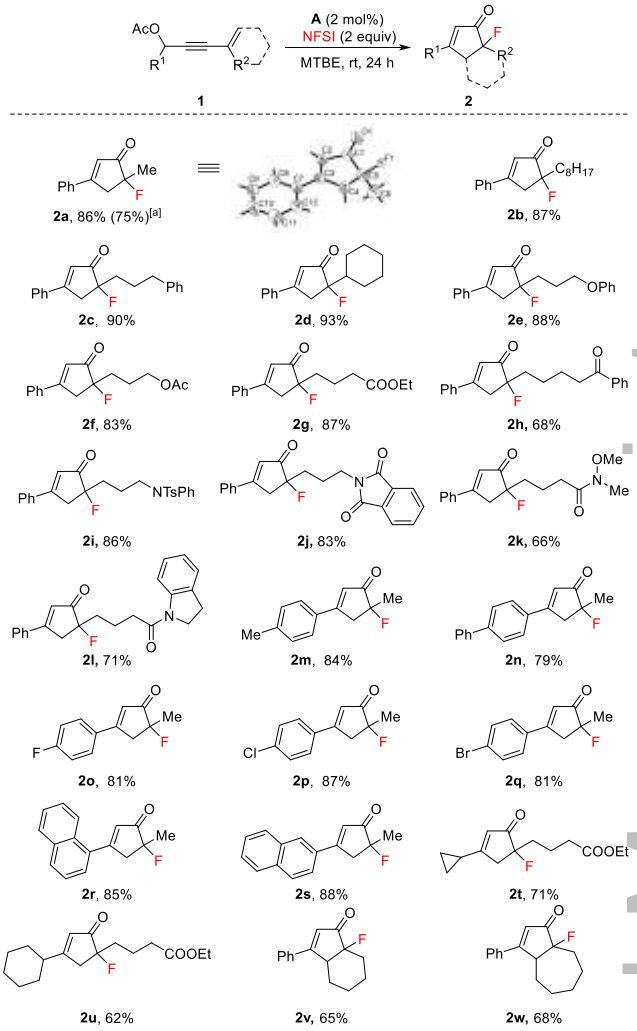
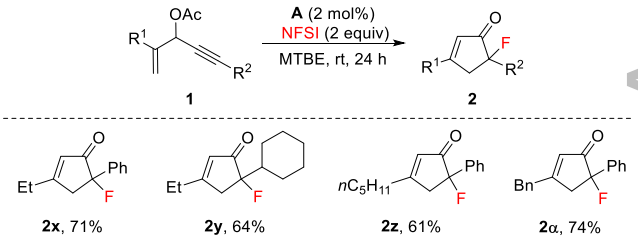
product **2a** in 79% yield (entry 12). On the basis of the above results, reaction of **1a** with NFSI (2 equiv) in the presence of 2 mol% of gold(I) phosphine catalyst **A** in MTBE at room temperature for 24 h was deemed to provide the optimum conditions.

With the optimal conditions in hand, we set out to evaluate the generality of the present protocol with a variety of 1,3-enyne acetates, and the results are summarized in Scheme 2. Overall, the tandem reaction conditions were found to be broad, providing a diverse array of 5-fluoro-cyclopentenone derivatives bearing a fluorine-substituted carbon stereocenter with a variety of substitution patterns in 65-93% yield from the corresponding substrates **1a-w.** Substrates containing a linear or cyclic alkyl groups such as cyclohexyl at the R^2 position were found to proceed well under the optimal conditions, affording the products **2b**, **2c** and **2d** in 87%, 90% and 93% yields, respectively. Pleasingly, substrates bearing a variety of functional groups such as phenyl ether (**1e**), esters (**1f**, **g**), ketone (**1h**), sulfonamide (**1i**), phthalimide (**1j**), weinreb or indoline amides (**1k, l**) were proven to be compatible with this tandem process, providing the corresponding fluorinated products **2e-l** in 66-88% yields. Likewise, 1,3-enyne acetates having electron-donating (**1m-n**) as well as electron-withdrawing (**1o-q**) substituents at *para*-position of the phenyl moiety were well tolerated and furnished the desirable products **2m-q** in excellent yields. Similarly, the reaction of **1r** and **1s** containing a 1-naphthyl or 2-naphthyl group at the R^1 position furnished **2r** and **2s** in 85% and 88% yields, respectively. Furthermore, our protocol is not restricted to the substrates of 1,3-enyne acetates with aryl substituents at R^1 position and can be applied to the substrates of aliphatic substituents at both $R^1$and R^2 positions as well. For instance, **1t** and **1u** were smoothly converted to the corresponding fluorinated products **2t-u** in 62-71% yields. Additionally, the tandem reactions of 1,3-enyne acetates incorporating cyclic alkenes such as cyclohexene (**1v**) and cycloheptene (**1w**) produced the fluorinated bicyclic cyclopentenones **2v** and **2w** in 65% and 68% yields. It is noteworthy that a gram-scale reaction of **1a** (5 mmol, 1.07 g) with NFSI in the presence of 1 mol% gold(I) catalyst **A** was also successful and provided **2a** in a slightly diminished yield of 75% (0.71 g), demonstrating the scalability and practicality of the present protocol.

Encouraged by the above success, we next turned our attention to examine whether the present protocol could also be applied to 1,4-enyne acetates, which the cycloisomerization chemistry has been well documented. [23] Gratifyingly, the present approach could be applied to 1,4-enyne acetates, allowed for the regiospecific construction of 5-fluoro-cyclopentenones containing a fluorine-substituted carbon stereocenter in satisfactory yields with a variety of substitution patterns (Scheme 3). Notably, it was found that the 1,4-enyne acetates with a cyclohexyl substitution at the alkyne terminus, was also compatible in the gold(I)-catalyzed cycloisomerization and fluorination cascade reaction to afford the corresponding 5-fluoro-cyclopentenone **2y** in good yield.

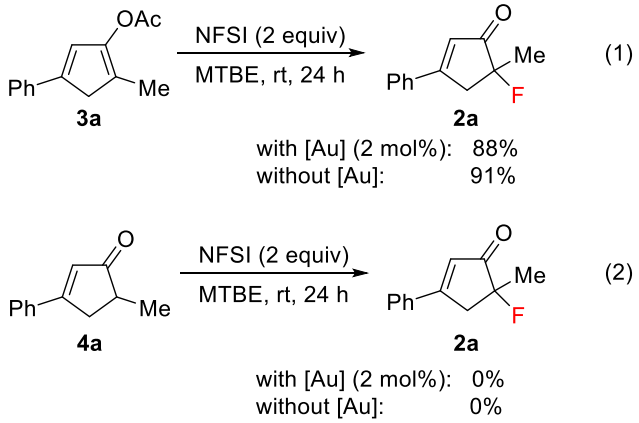


Scheme 2. Gold(I)-catalyzed tandem cycloisomerization and fluorination of 1,3-enyne esters **1a-w** with NFSI. All reactions were performed with **1**(0.3 mmol), gold(I) complex **A** (2 mol %) and NFSI (0.6 mmol) in MTBE (6 mL) at room temperature for 24 h. [a]The reactions was conducted on 5.0 mmol scale with 1 mol% of gold(I) complex **A**.



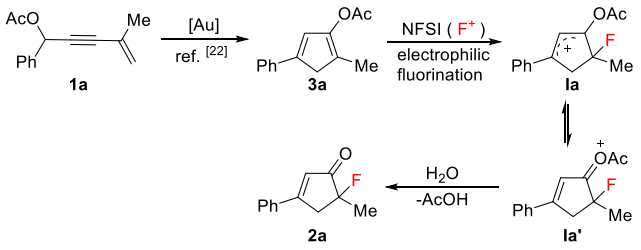
Scheme 3. Gold(I)-catalyzed tandem cycloisomerization and fluorination of 1,4-enyne esters **1x-α** with NFSI. All reactions were performed with **1**(0.3 mmol), gold(I) complex **A** (2 mol %) and NFSI (0.6 mmol) in MTBE (6 mL) at room temperature for 24 h.

The isolation of **4a** and **3a** under certain conditions described in Table 1 led us to evaluate on their possible involvement as intermediates in this tandem process. To support this hypothesis and gain more insight into the reaction mechanism, several control experiments were performed as described in Scheme 4. First, subjecting **3a** with NFSI in MTBE in the presence and absence of the gold(I) catalyst **A** (2 mol%) at room temperature for 24 h provided the desired product **2a** in respective yields of 88% and 91% (Scheme 4, eq 1). We next investigated the analogous reaction of **4a** and NFSI under the above mentioned conditions. These experiments showed that there was no formation of 5-fluorinated cyclopentenone **2a** by TLC and ^{1}H NMR analysis, and starting material **4a** were recovered in near quantitative yield in both cases (Scheme 4, eq 2). These results clearly indicated that cyclopentenone **4a** was not the productive intermediate and the formation of cyclopentadiene **3a** intermediate must be involved in this transformation.



Scheme 4. Control Experiments

On the basis of the above results and the literature precedents,[22] a plausible mechanism for the gold(I)-catalyzed 1,3(4)-enyne ester cycloisomerization and fluorination reaction in the presence of NFSI is illustrated in Scheme 5. With 1,3-enyne ester **1a** as a representative example, this initially involves a gold-catalyzed 1,3-acyloxy migration/Nazarov cyclization to produce the cyclopentadiene **3a**.[22] The resulting electron-rich cyclopentadiene intermediate **3a** may then undergo a direct, nongold-catalyzed electrophilic fluorination with NFSI to afford the allylic cation species **Ia** or its resonance structure **Ia'**. Upon hydrolysis with trace amounts of H_2O from the reaction media MTBE would furnish 5-fluoro-cyclopentenone **2a.** The formation of 5-fluoro-cyclopentenone **2x-α** from 1,4-enyne ester **1x-α** could be derived from the initially Rautenstrauch rearrangement[26] followed by electrophilic fluorination and hydrolysis. However, the competitive formation of unfluorinated cyclopentenone **4a** could be due to protonolysis of cyclopentadiene **3a.**[22e]



Scheme 5. Proposed mechanism

Conclusion

In summary, we have developed an efficient protocol for the synthesis of 5-fluorocyclopentenone possessing a fluorine-substituted carbon stereocenter from gold(I)-catalyzed cycloisomerization and fluorination sequence of 1,3(4)-enyne esters with NFSI under mild reaction conditions in one-pot operation. The present fluorination methodology also exhibited high regioselectivity and excellent functional group compatibility. Efforts to explore the synthetic applications of the one-pot fluorination reactions are currently underway and will be reported in due course.

Experimental Section

Representative Experimental Procedure for Gold(I) Complex A-Catalyzed Tandem Cycloisomerization and Fluorination of 1,3(4)-Enyne Esters with NFSI

To a solution of 1,3(4)-enyne acetate **1** (0.3 mmol) and **NFSI** (0.36 mmol) in MTBE (6 mL) was added gold(I) complext **A** (2 mol%) under an argon atmosphere. The reaction mixture was stirred at room temperature for 12-24 h. Upon completion, the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether:EtOAc =50:1 as eluent) furnished the product **2a**.

5-Fluoro-5-methyl-3-phenylcyclopent-2-en-1-one (2a): Yield: 86% (49 mg), colorless solid, mp 105-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67-7.65 (m, 2H), 7.55-7.46 (m, 3H), 6.58 (m, 1H), 3.41-3.30 (ddd, 1H, J = 19.8, 18.0, 1.6 Hz), 3.20-3.12 (ddd, 1H, J = 12.0, 10.4, 1.7 Hz), 1.61 (d, 3H, J = 22.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.9 (d, 1C, J = 18.2 Hz), 169.9 (d, 1C, J = 3.3 Hz), 133.1, 132.1, 129.1, 127.1, 123.7, 93.9 (d, 1C, J = 182.0 Hz), 42.3 (d, 1C, J = 25.0 Hz), 21.6 (d, 1C, J = 27.0 Hz); ^{19}F NMR (376 MHz, CDCl3) δ = –150.2 (s); HRMS (ESI) calcd for $C_{12}H_{11}FONa$ $[M+Na]^+$: 213.0686, found: 213.0692.

5-Fluoro-5-octyl-3-phenylcyclopent-2-en-1-one (2b): Yield: 87% (75 mg), pale-yellow solid, mp 58-60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68-7.65 (m, 2H), 7.55-7.46 (m, 3H), 6.59 (d, 1H, *J* = 1.3 Hz), 3.25 (dd, 1H, *J* = 4.8, 1.7 Hz), 3.21 (d, 1H, *J* = 1.7 Hz), 2.05-1.95 (m, 1H), 1.84-1.68 (m, 1H), 1.52-1.15 (m, 12H), 0.87 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.3 (d, 1C, *J* = 18.2 Hz), 170.3, 133.1, 132.1, 129.1, 127.1, 124.4, 96.2 (d, 1C, *J* = 183.0 Hz), 40.2 (d, 1C, *J* = 25.0 Hz), 34.9 (d, 1C, *J* = 24.0 Hz), 31.8, 29.8, 29.3, 29.1, 23.0 (d, *J* = 6.1 Hz), 22.6, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –154.9 (s); HRMS (ESI) calcd for $C_{19}H_{26}FO$ $[M+H]^+$: 289.1962, found: 289.1976.

5-Fluoro-3-phenyl-5-(3-phenylpropyl)cyclopent-2-en-1-one (2c): Yield: 90% (80 mg), colorless solid, mp 88-90 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.68-7.66 (m, 2H), 7.59-7.47 (m, 3H), 7.31-7.28 (m, 2H), 7.24-7.16 (m, 3H), 6.60 (d, 1H, *J* = 1.2 Hz), 3.30-3.17 (m, 2H), 2.75-2.65 (m, 2H), 2.13-2.03 (m, 1H), 1.92-1.71 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.0 (d, 1C, *J* = 18.2 Hz), 170.3 (d, 1C, *J* = 3.4 Hz), 141.5, 133.0, 132.2, 129.1, 128.4, 127.1, 126.0, 124.3, 96.0 (d, 1C, *J* = 184.8 Hz), 40.2 (d, 1C, *J* = 25.4 Hz), 35.9, 34.4 (d, 1C, *J* = 24.8 Hz), 24.9 (d, 1C, *J* = 5.8 Hz); ^{19}F NMR (564 MHz, $CDCl_3$) δ = –155.1 (s); HRMS (ESI) calcd for $C_{20}H_{19}FONa$ $[M+Na]^+$: 317.1312, found: 317.1307.

5-Cyclohexyl-5-fluoro-3-phenylcyclopent-2-en-1-one (2d): Yield: 93% (72 mg), pale-yellow solid, mp 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69-7.66 (m, 2H), 7.55-7.46 (m, 3H), 6.59 (d, 1H, *J* = 1.2 Hz), 3.29-3.21 (ddd, 1H, *J* = 18.3, 11.4, 1.7 Hz), 3.14-3.03 (ddd, 1H, *J* = 22.8, 18.3, 1.8 Hz), 2.16-2.04 (qd, 1H, *J* = 10.7, 3.2 Hz), 2.00 (d, 1H, *J* = 12.6 Hz), 1.82 (dd, 1H, *J* = 12.9, 1.8 Hz), 1.70 (d, 2H, *J* = 11.0 Hz), 1.49 (d, 1H, *J* = 12.8 Hz), 1.36-1.07 (m, 4H), 0.89 (qd, 1H, *J* = 12.5, 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.9 (d, 1C, *J* = 18.0 Hz), 170.9 (d, 1C, *J* = 3.5 Hz), 133.1, 132.1, 129.1, 127.1, 125.2, 98.2 (d, 1C, *J* = 184.0 Hz), 42.1 (d, 1C, *J* = 23.0 Hz), 37.6 (d, 1C, *J* = 26.0 Hz), 26.4 (d, 1C, *J* = 9.0 Hz), 26.3, 26.1 (d, 1C, *J* = 3.0 Hz), 25.7, 25.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –156.6 (s); HRMS (ESI) calcd for $C_{17}H_{19}FONa$ $[M+Na]^+$: 281.1312, found: 281.1305.

5-Fluoro-5-(3-phenoxypropyl)-3-phenylcyclopent-2-en-1-one (2e): Yield: 88% (82 mg), pale-yellow solid, mp 105-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74-7.66 (m, 2H), 7.61-7.48 (m, 3H), 7.35-7.23 (m, 2H), 7.01-6.94 (m, 1H), 6.90 (dd, 2H, *J* = 8.7, 0.9 Hz), 6.64 (d, 1H, *J* = 1.3 Hz), 4.12-3.97 (m, 2H), 3.33 (dd, 1H, *J* = 4.6, 1.7 Hz), 3.29 (d, 1H, *J* = 1.7 Hz), 2.30-2.17 (m, 1H), 2.12-1.92 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.8 (d, 1C, *J* = 18.2 Hz), 170.4 (d, 1C, *J* = 3.4 Hz), 158.8, 133.1, 132.3, 129.5, 129.2, 127.2, 124.3, 120.8, 114.5, 95.9 (d, 1C, *J* = 185.3 Hz), 67.3, 40.4 (d, 1C, *J* = 25.2 Hz), 31.7 (d, 1C, *J* = 25.2 Hz), 23.2 (d, 1C, *J* = 5.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –156.4 (s); HRMS (ESI) calcd for $C_{20}H_{19}FO_2Na$ $[M+Na]^+$: 333.1261, found:333.1269.

3-(1-Fluoro-2-oxo-4-phenylcyclopent-3-en-1-yl)propyl acetate (2f): Yield: 83% (69 mg), pale-yellow solid, mp 71-72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69-7.62 (m, 2H), 7.56-7.44 (m, 3H), 6.59 (d, 1H, *J* = 1.3 Hz), 4.17-4.02 (m, 2H), 3.34-3.13 (m, 2H), 2.16-1.97 (m, 4H), 1.87-1.73 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.6 (d, 1C, *J* = 18.4 Hz), 171.0, 170.3 (d, 1C, *J* = 3.2 Hz), 132.9, 132.3, 129.1, 127.1, 124.2, 95.6 (d, 1C, *J* = 185.5 Hz), 64.0, 40.2 (d, 1C, *J* = 25.3 Hz), 31.5 (d, 1C, *J* = 25.2 Hz), 22.5 (d, 1C, *J* = 5.7 Hz), 20.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –156.6 (s); HRMS (ESI) calcd for $C_{16}H_{18}FO_3$ $[M+H]^+$: 277.1234, found: 277.1219.

Ethyl 4-(1-fluoro-2-oxo-4-phenylcyclopent-3-en-1-yl)butanoate (2g): Yield: 87% (76 mg), pale-yellow solid, mp 40-42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68-7.65 (m, 2H), 7.58-7.43 (m, 3H), 6.59 (d, 1H, *J* = 1.3 Hz), 4.11 (q, 2H, *J* = 7.1 Hz), 3.28 (d, 1H, *J* = 1.7 Hz), 3.24 (t, 1H, *J* = 1.9 Hz), 2.48-2.30 (m, 2H), 2.08-2.00 (m, 1H), 1.90-1.61 (m, 3H), 1.24 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.7 (d, 1C, *J* = 18.1 Hz), 173.1, 170.5 (d, 1C, *J* = 3.3 Hz), 133.0, 132.2, 129.1, 127.1, 124.2, 95.8 (d, 1C, *J* = 180.0Hz), 60.4, 40.1(d, 1C, *J* = 25.0Hz), 34.2, 33.9, 18.5 (d, 1C, *J* = 6.2 Hz), 14.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ= –155.9 (s); HRMS (ESI) calcd for $C_{17}H_{20}FO_3$ $[M+H]^+$: 291.1391, found: 291.1384.

5-fluoro-5-(5-oxo-5-phenylpentyl)-3-phenylcyclopent-2-en-1-one (2h): Yield: 68% (69 mg), colorless solid, mp 82-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95-7.93 (m, 2H), 7.67-7.65 (m, 2H), 7.57-7.43 (m, 6H), 6.59 (d, 1H, *J* = 1.2 Hz), 3.26 (dd, 1H, *J* = 4.3, 1.7 Hz), 3.22 (d, 1H, *J* = 1.7 Hz), 3.00 (t, 2H, *J* = 7.2 Hz), 2.07 (ddd, 1H, *J* = 25.1, 13.4, 4.8 Hz), 1.92-1.75 (m, 3H), 1.66-1.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.1, 199.9, 170.5, 136.9, 133.1, 133.0, 132.2, 129.1, 128.6, 128.0, 127.2, 124.3, 95.9 (d, 1C, *J* = 184.9 Hz), 40.2 (d, 1C, *J* = 25.3 Hz), 38.1, 34.7 (d, 1C, *J* = 24.7 Hz), 24.2, 22.7 (d, 1C, *J* = 6.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –155.4 (s); HRMS (ESI) calcd for $C_{22}H_{22}FO_2$ $[M+H]^+$: 337.1598, found: 337.1606.

***N*-(3-(1-Fluoro-2-oxo-4-phenylcyclopent-3-en-1-yl)propyl)-4-methyl-N-phenylbenzenesulfonamide (2i):** Yield: 86% (120 mg), colorless solid, mp 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68-7.61 (m, 2H), 7.59-7.43 (m, 5H), 7.32-7.25 (m, 5H), 7.06-7.03 (m, 2H), 6.56 (d, 1H, *J* = 1.2 Hz), 3.61 (t, 2H, *J* = 6.8 Hz), 3.26-3.06 (m, 2H), 2.44 (s, 3H), 2.15-2.00 (m, 1H), 1.97-1.79 (m, 1H), 1.78-1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.6 (d, 1C, *J* = 18.3 Hz), 170.3 (d, 1C, *J* = 3.0 Hz), 143.4, 138.9, 135.0, 132.9, 132.2, 129.4, 129.1, 128.7, 128.0, 127.7, 127.1, 124.1, 95.7 (d, 1C, *J* = 185.0 Hz), 50.3, 40.3 (d, 1C, *J* = 25.0 Hz), 31.8 (d, 1C, *J* = 25.0 Hz), 22.0 (d, 1C, *J* = 5.1 Hz), 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –157.1 (s); HRMS (ESI) calcd for $C_{27}H_{26}FNO_3SNa$ $[M+Na]^+$: 486.1510, found: 486.1507.

2-(3-(1-Fluoro-2-oxo-4-phenylcyclopent-3-en-1-yl)propyl)isoindoline-1,3-dione (2j): Yield: 83% (91 mg), colorless solid, mp 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84-7.81 (m, 2H), 7.76-7.67 (m, 2H), 7.67-7.59 (m, 2H), 7.56-7.40 (m, 3H), 6.57 (d, 1H, *J* = 1.2 Hz), 3.82- 3.67 (m, 2H), 3.31-3.14 (m, 2H), 2.14-2.03 (m, 1H), 1.98-1.73 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.4 (d, 1C, *J* = 200.0 Hz), 170.2 (d, 1C, *J* = 3.0 Hz), 168.3, 134.0, 132.9, 132.2, 132.0, 129.1, 127.1, 124.2, 123.2, 95.5 (d, 1C, *J* = 185.8 Hz), 40.2 (d, 1C, *J* = 25.2 Hz), 37.8, 32.3 (d, 1C, *J* = 25.3 Hz), 22.5 (d, 1C, *J* = 5.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –156.3 (s); HRMS (ESI) calcd for $C_{22}H_{18}FNO_3Na$ $[M+Na]^+$: 386.1163, found: 396.1163.

4-(1-Fluoro-2-oxo-4-phenylcyclopent-3-en-1-yl)-*N*-methoxy-*N*-methylbutanamide (2k): Yield: 66% (61 mg), pale-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74-7.60 (m, 2H), 7.58-7.40 (m, 3H), 6.58 (d, 1H, *J* = 1.2 Hz), 3.67 (s, 3H), 3.37-3.22 (m, 2H), 3.16 (s, 3H), 2.60-2.43 (m, 2H), 2.11-1.98 (m, 1H), 1.89-1.70 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.0 (d, 1C, *J* = 18.2 Hz), 170.7 (d, 1C, *J* = 3.3 Hz), 133.0, 132.2, 129.1, 127.2, 124.2, 96.0 (d, 1C, *J* = 183.0 Hz), 61.2, 40.0 (d, 1C, *J* = 25.0 Hz), 34.1 (d, 1C, *J* = 25.0 Hz), 32.1, 31.4, 18.1 (d, *J* = 6.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –155.4 (s); HRMS (ESI) calcd for $C_{17}H_{20}FNO_3Na$ $[M+Na]^+$: 328.1319, found: 328.1328.

5-Fluoro-5-(4-(indolin-1-yl)-4-oxobutyl)-3-phenylcyclopent-2-en-1-one (2l): Yield: 71% (77 mg), brown solid, mp 119-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 (d, 1H, *J* = 8.3 Hz), 7.68 (dd, 2H, *J* = 8.1, 1.4 Hz), 7.57-7.43 (m, 3H), 7.17 (t, 2H, *J* = 6.7 Hz), 7.00 (t, 1H, *J* = 7.4 Hz), 6.60 (d, 1H, *J* = 1.2 Hz), 4.04 (t, 2H, *J* = 8.5 Hz), 3.44-3.26 (m, 2H), 3.20 (t, 2H, *J* = 8.5 Hz), 2.59-2.44 (m, 2H), 2.14-2.08 (m, 1H), 1.96-1.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.0 (d, 1C, *J* = 18.0 Hz), 170.6 (d, 1C, *J* = 41.2 Hz), 142.9, 133.0, 132.2, 131.0, 129.1, 127.5, 127.2, 124.5, 124.2, 123.6, 116.9, 96.1 (d, 1C, *J* = 184.4 Hz), 47.9, 40.0 (d, 1C, *J* = 25.3 Hz), 35.4, 34.1 (d, 1C, *J* = 24.7 Hz), 28.0, 18.2 (d, 1C, *J* = 6.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –155.2 (s); HRMS (ESI) calcd for $C_{23}H_{22}FNO_2Na$ $[M+Na]^+$: 386.1527, found: 386.1519.

5-Fluoro-5-methyl-3-(p-tolyl)cyclopent-2-en-1-one (2m): Yield: 84% (52 mg), yellow solid, mp 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, 2H, *J* = 8.2 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 6.54 (d, 1H, *J* = 1.3 Hz), 3.38-3.28(ddd, 1H, *J* = 19.7, 18.0, 1.6 Hz), 3.18-3.10 (ddd, 1H, *J* = 18.0, 10.4, 1.7 Hz), 2.42 (s, 3H), 1.60 (d, *J* = 22.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0 (d, 1C, *J* = 18.3 Hz), 170.0, 143.0, 130.4, 129.8, 127.1, 122.9, 94.0 (d, 1C, *J* = 182.8 Hz), 42.3 (d, 1C, *J* = 25.1 Hz), 21.7 (d, 1C, *J* = 27.0 Hz), 21.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –150.1

(s); HRMS (ESI) calcd for $C_{13}H_{13}FONa$ $[M+Na]^+$: 227.0843, found: 227.0851.

3-([1,1'-Biphenyl]-4-yl)-5-fluoro-5-methylcyclopent-2-en-1-one (2n): Yield: 79% (63 mg), colorless solid, mp 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75-7.70 (m, 4H), 7.65-7.63 (m, 2H), 7.53-7.46 (m, 2H), 7.44-7.40 (m, 1H), 6.63 (d, 1H, J = 1.3 Hz), 3.44-3.34 (ddd, 1H, J = 21.5, 18.0, 1.6 Hz), 3.24-3.16 (ddd, 1H, J = 18.0, 10.4, 1.7 Hz), 1.63 (d, 3H, J = 22.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.9 (d, 1C, J = 18.8 Hz), 169.5, 144.9, 139.6, 131.9, 129.0, 128.3, 127.7, 127.6, 127.1, 123.5, 94.0 (d, 1C, J = 182.9 Hz), 42.3 (d, 1C, J = 25.2 Hz), 21.7 (d, 1C, J = 26.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –150.1(s); HRMS (ESI) calcd for $C_{18}H_{15}FONa$ $[M+Na]^+$: 289.0999, found: 289.0994.

5-Fluoro-3-(4-fluorophenyl)-5-methylcyclopent-2-en-1-one (2o): Yield: 81% (51 mg), colorless solid, mp 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71-7.62 (m, 2H), 7.22-7.13 (m, 2H), 6.53 (d, 1H, J = 1.3 Hz), 3.40-3.25 (ddd, 1H, J = 19.8, 18.0, 1.7 Hz), 3.17-3.09 (ddd, 1H, J = 18.0, 10.5, 1.7 Hz), 1.61 (d, 3H, J = 22.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.7 (d, 1C, J = 18.4 Hz), 168.5 (d, 1C, J = 3.4 Hz), 165.0 (d, 1C, J = 253.0 Hz), 129.5 (d, 1C, J = 2.6 Hz), 129.3 (d, 1C, J = 8.9 Hz), 123.5, 116.4 (d, 1C, J = 22.0 Hz), 93.9 (d, 1C, J = 183.2 Hz), 42.4 (d, 1C, J = 25.2 Hz), 21.6 (d, 1C, J = 26.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.2 (s), –149.9 (s); HRMS (ESI) calcd for $C_{12}H_{11}F_2O$ $[M+H]^+$: 209.0772, found: 209.0775.

3-(4-Chlorophenyl)-5-fluoro-5-methylcyclopent-2-en-1-one (2p): Yield: 87% (59 mg), colorless solid, mp 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66-7.54 (m, 2H), 7.50-7.41 (m, 2H), 6.57 (d, 1H, J = 1.3 Hz), 3.44-3.24 (ddd, 1H, J = 19.8, 18.1, 1.8 Hz), 3.16-3.09 (ddd, 1H, J = 18.0, 10.5, 1.7 Hz), 1.61 (d, J = 22.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.7 (d, 1C, J = 26.9 Hz), 168.4 (d, 1C, J = 3.4 Hz), 138.4, 131.6, 129.5, 128.3, 124.1, 93.8 (d, 1C, J = 183.3 Hz), 42.3 (d, 1C, J = 25.3 Hz), 21.6 (d, 1C, J = 26.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –150.0 (s); HRMS (ESI) calcd for $C_{12}H_{10}{}^{35}ClFONa$ $[M+Na]^+$: 247.0296, found: 247.0287.

3-(4-Bromophenyl)-5-fluoro-5-methylcyclopent-2-en-1-one (2q): Yield: 81% (65 mg), colorless solid, mp 102-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, 2H, J = 8.6 Hz), 7.51 (d, 2H, J = 8.6 Hz), 6.57 (d, 1H, J = 1.3 Hz), 3.42-3.21 (ddd, 1H, J = 19.8, 18.0, 1.7 Hz), 3.16-3.09 (ddd, 1H, J = 18.0, 10.6, 1.7 Hz), 1.60 (d, 3H, J = 22.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 202.7 (d, 1C, J = 19.0 Hz), 168.5, 132.4, 132.0, 128.5, 126.8, 124.1, 93.8 (d, 1C, J = 183.5 Hz), 42.2 (d, 1C, J = 25.3 Hz), 21.5 (d, 1C, J = 26.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –150.0 (s); HRMS (ESI) calcd for $C_{12}H_{10}{}^{79}BrFONa$ $[M+Na]^+$: 290.9791, found: 290.9779.

5-Fluoro-5-methyl-3-(naphthalen-1-yl)cyclopent-2-en-1-one (2r): Yield: 85% (61 mg), pale-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12-8.10 (m, 1H), 7.99-7.94 (m, 2H), 7.67-7.50 (m, 4H), 6.57 (d, 1H, J = 1.4 Hz), 3.65-3.47 (ddd, 1H, J = 19.8, 18.0, 1.8 Hz), 3.23 (ddd, 1H, J = 18.4, 10.5, 1.8 Hz), 1.72 (d, 3H , J = 22.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.8 (d, 1C, J = 18.3 Hz), 171.1 (d, 1C, J = 3.4 Hz), 133.9, 133.0, 131.1, 130.0, 129.8, 129.0, 127.4, 126.5, 125.0, 125.0, 124.5, 93.6 (d, 1C, J = 183.4 Hz), 45.9 (d, 1C, J = 24.6 Hz), 21.5 (d, 1C, J = 26.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –151.3 (s); HRMS (ESI) calcd for $C_{16}H_{13}FONa$ $[M+Na]^+$: 263.0843, found: 263.0848.

5-Fluoro-5-methyl-3-(naphthalen-2-yl)cyclopent-2-en-1-one (2s): Yield: 88% (63 mg), yellow solid, mp 137-139 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.09 (s, 1H), 7.95-7.86 (m, 3H), 7.75 (dd, 1H, J = 8.6, 1.8 Hz), 7.61-7.56 (m, 2H), 6.70 (d, 1H, J = 1.3 Hz), 3.52-3.45 (ddd, 1H, J = 24.0, 18.0, 6.0 Hz), 3.31 (ddd, 1H, J = 17.8, 10.5, 1.7 Hz), 1.65 (d, J = 22.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 202.9 (d, 1C, J = 18.3 Hz), 169.6, 134.9, 132.9, 130.5, 129.1, 128.9, 128.3, 127.8, 127.6, 127.1, 124.0, 123.7, 94.0 (d, 1C, J = 183.1 Hz), 42.4 (d, 1C, J = 25.2 Hz), 21.7 (d, 1C, J = 27.0 Hz); ^{19}F NMR (565 MHz, $CDCl_3$) δ = –149.8 (s); HRMS (ESI) calcd for $C_{16}H_{13}FONa$ $[M+Na]^+$: 263.0843, found: 263.0836.

Ethyl 4-(4-cyclopropyl-1-fluoro-2-oxocyclopent-3-en-1-yl)butanoate (2t): Yield: 71% (54 mg), colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.91 (d, 1H, J = 1.4 Hz), 4.09 (q, 2H, J = 7.1 Hz), 2.62 (dd, 2H, J = 15.6, 1.4 Hz), 2.40-2.24 (m, 2H), 1.95 -1.81 (m, 2H), 1.75-1.55 (m, 3H), 1.22 (t, 3H, J = 7.1 Hz), 1.14-1.09 (m, 2H), 0.96-0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.3 (d, 1C, J = 18.1 Hz), 182.7 (d, 1C, J = 3.3 Hz), 173.1, 124.3, 95.5 (d, 1C, J = 184.9 Hz), 60.4, 39.6 (d, 1C, J = 25.1 Hz), 33.9, 33.8 (d, 1C, J = 24.0 Hz), 18.5 (d, 1C, J = 6.4 Hz), 15.3, 14.2, 10.5, 10.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –157.0 (s); HRMS (ESI) calcd for $C_{14}H_{20}FO_3$ $[M+H]^+$: 255.1391, found: 255.1384.

Ethyl 4-(4-cyclohexyl-1-fluoro-2-oxocyclopent-3-en-1-yl)butanoate (2u): Yield: 62% (55 mg), colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.91 (t, 1H, J = 1.1 Hz), 4.10 (q, 2H, J = 7.1 Hz), 2.84-2.73 (m, 2H), 2.39-2.22 (m, 2H), 1.94-1.57 (m, 9H), 1.39-1.13 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.6 (d, 1C, J = 18.2 Hz), 184.4, 173.1, 125.1, 95.6 (d, 1C, J = 185.1 Hz), 60.4, 42.0, 40.9 (d, 1C, J = 24.5 Hz), 34.0, 33.9, 33.8, 30.8, 30.7, 25.9, 25.8 (d, 1C, J = 2.3 Hz), 18.6 (d, 1C, J = 6.4 Hz), 14.2; ^{19}F NMR (376 MHz, CDCl3) δ = –158.0 (s); HRMS (ESI) calcd for $C_{17}H_{26}FO_3$ $[M+H]^+$: 297.1860, found: 297.1871.

7a-Fluoro-3-phenyl-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one (2v): Yield: 65% (45 mg), pale-yellow solid, mp 49-50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65-7.58 (m, 2H), 7.52-7.43 (m, 3H), 6.47 (s, 1H), 3.49-3.39 (ddd, 1H, J = 21.3, 8.9, 6.8 Hz), 2.27-2.12 (m, 2H), 1.99-1.85 (m, 1H), 1.85-1.73 (m, 1H), 1.58-1.41 (m, 2H), 1.37-1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.4 (d, 1C, J = 18.4 Hz), 176.4, 132.9, 131.6, 129.1, 127.6, 123.9, 95.9 (d, 1C, J = 181.2 Hz), 46.5 (d, 1C, J = 22.0 Hz), 28.2 (d, 1C, J = 3.7 Hz), 27.0 (d, 1C, J = 23.6 Hz), 20.8, 19.1 (d, 1C, J = 7.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –143.8 (s); HRMS (ESI) calcd for $C_{15}H_{15}FONa$ $[M+Na]^+$: 253.0999, found: 253.0996.

8a-Fluoro-3-phenyl-4,5,6,7,8,8a-hexahydroazulen-1(3aH)-one (2w): Yield: 68% (50 mg), pale-yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.60-7.42 (m, 5H), 6.44 (s, 1H), 3.62-3.56 (ddd, 1H, J = 25.4, 10.4, 2.0 Hz), 2.39-2.27 (m, 1H), 2.11-2.01 (m, 1H), 1.85-1.60 (m, 5H), 1.55-1.45 (m, 1H), 1.41-1.34 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 202.8 (d, 1C, J = 17.5 Hz), 177.2, 133.4, 131.3, 129.0, 127.5, 125.7, 98.9 (d, 1C, J = 178.9 Hz), 53.0 (d, 1C, J = 25.0 Hz), 31.7 (d, 1C, J = 24.8 Hz), 30.8, 29.8, 27.9, 22.6 (d, 1C, J = 5.2 Hz); ^{19}F NMR (565 MHz, $CDCl_3$) δ = –142.6 (s); HRMS (ESI) calcd for $C_{16}H_{17}FONa$ $[M+Na]^+$: 267.1156, found: 267.1153.

3-Ethyl-5-fluoro-5-phenylcyclopent-2-en-1-one (2x): Yield: 71% (44 mg), yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43-7.28 (m, 5H), 6.08 (q, 1H, J = 1.6 Hz), 3.29-3.06 (m, 2H), 2.55 (q, 2H, J = 7.3 Hz), 1.28 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.7 (d, 1C, J = 20.0 Hz), 181.8 (d, 1C, J = 3.6 Hz), 137.8 (d, 1C, J = 24.2 Hz), 128.6, 128.4, 125.9, 124.1 (d, 1C, J = 8.6 Hz), 96.0 (d, 1C, J = 188.5 Hz), 46.5 (d, 1C, J = 24.4 Hz), 27.0, 11.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –157.2 (s); HRMS (ESI) calcd for $C_{13}H_{13}FONa$ $[M+Na]^+$: 227.0846, found: 227.0851.

5-Cyclohexyl-3-ethyl-5-fluorocyclopent-2-en-1-one (2y): Yield: 64% (40 mg), colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.97-5.96 (m, 1H), 2.78 (dd, 1H, J = 18.7, 11.5 Hz), 2.70 -2.56 (m, 1H), 2.43 (q, 2H, J = 7.3 Hz), 2.05-1.86 (m, 2H), 1.85-1.75 (m, 1H), 1.69 (d, 2H, J = 12.1 Hz), 1.46-1.37 (m, 1H), 1.33-0.99 (m, 7H), 0.87-0.77 (ddd, 1H, J = 24.8, 12.4, 3.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ =

204.4 (d, 1C, *J* = 18.4 Hz), 181.9 (d, 1C, *J* = 3.2 Hz), 126.8 (d, 1C, *J* = 1.1 Hz), 98.2 (d, 1C, *J* = 184.3 Hz), 41.7 (d, 1C, *J* = 23.1 Hz), 40.1 (d, 1C, *J* = 25.1 Hz), 26.9, 26.4 (d, 1C, *J* = 8.7 Hz), 26.3, 26.0 (d, 1C, *J* = 3.9 Hz), 25.7, 25.6, 11.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –158.1 (s); HRMS (ESI) calcd for $C_{13}H_{19}FONa$ $[M+Na]^+$: 233.1312, found: 233.1303.

5-Fluoro-3-pentyl-5-phenylcyclopent-2-en-1-one (2z): Yield: 61% (45 mg), pale-yellow solid, mp 48-50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41-7.29 (m, 5H), 6.07 (d, 1H, *J* = 1.4 Hz), 3.28-3.04 (m, 2H), 2.52 (t, 2H, *J* = 7.6 Hz), 1.72-1.60 (m, 2H), 1.46-1.31 (m, 4H), 0.93 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.7 (d, 1C, *J* = 19.9 Hz), 180.8, 137.8 (d, 1C, *J* = 24.2 Hz), 128.6 (d, 1C, *J* = 0.7 Hz), 128.3 (d, 1C, *J* = 1.2 Hz), 126.6, 124.1 (d, 1C, *J* = 8.6 Hz), 95.9 (d, 1C, *J* = 188.7 Hz), 46.5 (d, 1C, *J* = 24.3 Hz), 33.8, 31.4, 26.3, 22.3, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –157.3(s); HRMS (ESI) calcd for $C_{16}H_{20}FO$ $[M+H]^+$: 247.1493, found: 247.1489.

3-Benzyl-5-fluoro-5-phenylcyclopent-2-enone (2 α): Yield: 74% (59 mg), yellow solid, mp 76-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.23 (m, 10H), 6.02-6.03 (m, 1H), 3.85 (d, 1H, *J* = 16.1 Hz), 3.80 (d, 1H, *J* = 16.1 Hz), 3.22-3.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.5 (d, 1C, *J* = 20.0 Hz), 178.4 (d, 1C, *J* = 4.0 Hz), 137.6 (d, 1C, *J* = 24.0 Hz), 135.6, 129.1 (d, 1C, *J* = 3.0 Hz), 128.6 (d, 1C, *J* = 1.0 Hz), 128.4 (d, 1C, *J* = 1.0 Hz), 127.7 (d, 1C, *J* = 1.0 Hz), 127.5, 124.1 (d, 1C, *J* = 9.0 Hz), 96.1 (d, 1C, *J* = 188.0 Hz), 45.9 (d, 1C, *J* = 25.0 Hz), 40.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –156.7(s) . HRMS (ESI) calcd for $C_{18}H_{15}FONa$ $[M+Na]^+$: 289.0999, found: 289.0987..

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References

[1] a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, 2nd ed.*; Wiley-VCH: Weinheim, Germany, **2013**. b) V. Gouverneur, *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications, 1st ed.* (Eds.: K. Müller), Imperial College Press, London, **2012**.

[2] a) J. Wang, M. Sanchez-Roselló, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432. b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470. c) V. V. Grushin, *Acc. Chem. Res.* **2010**, *43*, 160. d) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320. e) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308. f) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881. g) H. J. Bohm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Muller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637.

[3] a) P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738. b) Y. Gao, B. Twamley, J. M. Shreeve, *Org. Biomol. Chem.* **2009**, *7*, 1716. c) T. Furuya, C. A. Kuttruff, T. Ritter, *Curr. Opin. Drug.Discovery Dev.* **2008**, *11*, 803. d) E. Belanger, K. Cantin, O. Messe, M. Tremblay, J.-F. Paquin, *J. Am. Chem. Soc.* **2007**, *129*, 1034. e) R. D. Chambers, *Fluorine in Organic Chemistry;* Blackwell, **2004**.

[4] a) S. D. Putnam, M. Castanheira, G. J. Moet, D. J. Farrell, R. N. Jones, Diagn. *Microbiol. Infect. Dis.* **2010**, *66*, 393. b) P. Hewawasam, V. K. Gribkoff, Y. Pendri, S. I. Dworetzky, N. A. Meanwell, E. Martinez, C. G. Boissard, D. J. Post-Munson, J. T. Trojnacki, K. Yeleswaram, L. M. Pajor, J. Knipe, Q. Gao, R. Perrone, J. E. Starrett Jr, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1023.

[5] For selected examples: a) R. P. Singh, J. L. Martin, *J. Fluorine Chem.* **2016**, *181*, 7. b) W. Borzęcka, I. Lavandera, V. Gotor, *J. Org. Chem.* **2013**, *78*, 7312. c) Y. He, X. Zhang, Na. Shen, X. Fan, *J. Fluorine Chem.* **2013**, *156*, 9. d) Z. Chen, W. Zhu, Z. Zheng, X. Zou, *J. Fluorine Chem.* **2010**, *131*, 340. e) K. Y. Kim, B. C. Kim, H. B. Lee, H. Shin, *J. Org. Chem.* **2008**, *73*, 8106. f) D. W. Kim, C. E. Song, D. Y. Chi, *J. Am. Chem. Soc.* **2002**, *124*, 10278.

[6] For selected examples: a) J. L. Howard, Y. Sagatov, L. Repusseau, C. Schotten, D. L. Browne, *Green Chem.* **2017**, *18*, 2798. b) T. Kitamura, K. Muta, K. Muta, *J. Org. Chem.* **2014**, *79*, 5842. c) T. Kitamura, S. Kuriki, M. H. Morshed, Y. Hori, *Org. Lett.* **2011**, *13*, 2392. d) G. Stavber, M. Zupan, S. Stavber, *Synlett* **2009**, 589. e) S. Stavber, M. Jereb, M. Zupan, *Chem. Commun.* **2000** *1323*. f) S. Stavber, M. Zupan, *Tetrahedron Lett.* **1996**, *37*, 3591.

[7] a) E. Fuglseth, T. H. K. Thvedt, M. F. Møll, B. H. Hoff, *Tetrahedron* **2008**, *64*, 7318. b) W. Peng, J. M. Shreeve, *J. Org. Chem.* **2005**, *70*, 5760. c) G. Verniest, E. V. Hende, R. Surmont, N. De Kimpe, *Org. Lett.* **2005**, *70*, 5760. d) S. Sato, M. Yoshida, S. Hara, *Synthesis* **2005**, *15*, 2602. e) L. Zoute, C.Audouard, J.-C. Plaquevent, D. Cahard, *Org. Biomol. Chem.* **2003**, *1*, 1833. f) S. Stavber, B. Sket, B. Zajc, M. Zupan, *Tetrahedron* **1989**, *45*, 6003.

[8] a) R. Zhang, C. Ni, Z. He, J. Hu. *J. Fluorine Chem.* **2017**, *203*, 166. b) J. Li, Y.-L. Li, N. Jin, A.-L. Ma, Y.-N. Huang, J. Deng, *Adv. Synth. Catal.* **2015**, *357*, 2474.

[9] a) X. Zeng, S. Liu, G. B. Hammond, B. Xu, *Chem. Eur. J.* **2017**, *23*, 11977. b) W. Yuan, K. J. Szabó, *ACS Catal.* **2016**, *6*, 6687. c) E. E. Gray, M. K. Nielsen, K. A. Choquette, J. A. Kalow, T. J. A. Graham, A. G. Doyle, *J. Am. Chem. Soc.* **2016**, *138*, 10802. d) X. Zeng, S. Liu, Z. Shi, G. Liu, B. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 10032. e) G. Chen, J. Song, Y. Yu, X. Luo, C. Li, X. Huang, *Chem. Sci.* **2016**, *7* , 1786.

[10] Q. Yang, L.-L. Mao, B. Yang, S.-D. Yang, *Org. Lett.* **2014**, *16*, 3460.

[11] S.-W.Wu, F. Liu, *Org. Lett.* **2016**, *18*, 3642.

[12] a) P. Wang, J. Wang, L. Wang, D. Li, K. Wang, Y. Liu, H. Zhu, X. Liu, D. Yang, R. Wang, *Adv. Synth. Catal.* **2018**, *360*, 401. b) F.-H. Li, Z.-J. Cai, L. Yin, J.

Li, S.-Y. Wang, S.-J. Ji, *Org. Lett.* **2017**, *19*, 1662. c) E. K. Raja, D. A. Klumpp, *Tetrahedron Lett.* **2011**, *52*, 5170.

[13] For leading review: Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho, F. D. Toste, *Chem. Rev.* **2018**, *118*, 3887.

[14] a) F. Li, J. Nie, J.-W. Wu, Y. Zheng, J.-A. Ma, *J. Org. Chem.* **2012**, *77*, 2398. b) Y. Liu, J. Zhu, J. Qian, Z. Xu, *J. Org. Chem.* **2012**, *77*, 5411. c) M. Kawatsura, K. Kajita, S. Hayase, T. Itoh, *Synlett* **2010**, *8*, 1243. d) H.-F. Wang, H.-F. Cui, Z. Chai, P. Li, C.-W. Zheng, Y.-Q. Yang, G. Zhao, *Chem. Eur. J.* **2009**, *15*, 13299. e) J. Nie, H.-W. Zhu, H.-F. Cui, M.-Q. Hua, J.-A. Ma, *Org. Lett.* **2007**, *9*, 3053.

[15] For leading review: J. Miro, C. del Pozo, *Chem. Rev.* **2016**, *116*, 11924.

[16] T. Harode, C. Nevado, *Adv. Synth. Catal.* **2010**, *352*, 2767.

[17] a) T. de Haro, C. Nevado, *Chem Comm.* **2011**, *47*, 248. b) M. N. Hopkinson, G. T. Giuffredi, A. D. Gee, V. Gouverneur, *Synlett* **2010**, *18*, 2737.

[18] Z. Jin, R. S. Hidinger, B. Xu, G. B. Hammond, *J. Org. Chem.* **2012**, *77*, 7725.

[19] a) C. Chen, X. Chen, X. Zhang, S. Wang, W. Rao, P. W. H. Chan, A*dv. Synth. Catal.* **2017**, *359*, 4359. b) C. Chen, Y. Zou, X. Chen, X. Zhang, W. Rao, P. W. H. Chan, *Org. Lett.* **2016**, *18*, 4730. c) W. Rao, J. W. Boyle, P. W. H. Chan, *Chem. Eur. J.* **2016**, *22*, 6532. d) X. Zhang, X. Sun, H. Fan, C. Lyu, P. Li, H. Zhang, W. Rao, *RSC Adv.* 2016, *6* , 56319. e) X. Zhang, X. Sun, H. Fan, P. Li, C. Lyu, W. Rao, Eur. *J. Org. Chem.* **2016**, 4265.

[20] Selected general reviews on gold catalysis: a) W. Li, J. Zhang, *Chem. Eur. J.* **2017**, *23*, 467. b) D. P. Day, P. W. H. Chan, *Adv. Synth. Catal.* **2016**, *358*, 1368. c) M. Jia, M. Bandini, *ACS Catal.* **2015**, *5*, 1638. d) *Gold Catalysis: A Homogeneous Approach*, F. D. Toste, V. Michelet, Eds.; Imperial College Press: London, **2014**. e) C. M. Friend, A. S. K. Hashmi, *Acc. Chem. Res.* **2014**, *47*, 729. f) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448. g) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994. h) A. Corma, A. Leyva-Perez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657. i) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208. j) D. J. Gorin, B. J. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351.

[21] For selected reviews on gold-catalyzed 1,n-enyne cycloisomerizations: a) A. M. Asiria, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 4471. b) B. J. Ayers, P. W. H. Chan, *Synlett* **2015**, 1305. c) L. Fensterbank, M. Malacria, *Acc. Chem. Res.* **2014**, *47*, 953. d) S. R. Kazem, V. Gevorgyan, *Chem. Soc. Rev.* **2013**, *42*, 4991. e) S. K. Hashmi, *Angew. Chem., Int. Ed.* **2010**, *49*, 5232. f) E. Jiménez-Núnez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326. g) N. Marion, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2750. h) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271.

[22] Selected examples of cyclopentadiene species involved in gold(I)-catalyzed cycloisomerization of 1,3-enyne esters, see: 19c and a) D. Scarpi, M. Petrović, B. Fiser, E. Gómez-Bengoa, E. G. Occhiato, *Org. Lett.* **2016**, *18*, 3922. b) W. Rao, D. Susanti, B. J. Ayers, P. W. H. Chan, *J. Am. Chem. Soc.* **2015**, *137*, 6350. c) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2009**, *131*, 2993. d) G. Lemière, V. Gandon, K. Cariou, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *Org. Lett.* **2007**, *9*, 2207. e) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442.

[23] Selected examples of cyclopentadiene species involved in gold(I)-catalyzed cycloisomerization of 1,4-enyne esters, see: a) J. Zhao, S. Yang, X. Xie, X. Li, Y. Liu, *J. Org. Chem.* **2018**, *83*, 1287. b) X. Chen, D. P. Day,W. T. Teo, P. W. H. Chan, *Org. Lett.* **2016**, *18*, 5936. c) C. Bürki, A. Whyte, S. Arndt, A. S. K. Hashmi, M. Lautens, *Org. Lett.* **2016**, *18*, 5058. d) D. Susanti, L.-J. Liu, W. Rao, S. Lin, D.-L. Ma, C.-H. Leung, P. W. H. Chan, *Chem. Eur. J.* **2015**, *21*, 9111. e) R. Kazem Shiroodi, M. Sugawara, M. Ratushnyy, D. C. Yarbrough, D. J. Wink, V. Gevorgyan, *Org. Lett.* **2015**, *17*, 4062. f) X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, 127, 5802. g) N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133.

[24] For the synthesis of starting materials **1** see the Supporting Information for details, for the synthesis of gold(I) complexes **A**–**D**, see: a) E. Herrero-Gólmez, C. Nieto-Oberhuber, S. López, J. Benet-Buchholz, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5455. b) V. López-Carrillo, A. M. Echavarren, *J. Am. Chem. Soc.* **2010**, 132, 9292. c) C. H. M. Amijs, V. López-Carrillo, M. Raducan, P. Pérez-Galán, C. Ferrer, A. M. Echavarren, *J. Org. Chem.* **2008**, *73*, 7721. d) N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133.

[25] CCDC 1845001 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif .

[26] V. Rautenstrauch. *J. Org. Chem.* **1984**, *49*, 950. For DFT study on gold(I)-catalyzed Rautenstrauch rearrangement, see: O. N. Faza, C. S. López, R. Álvarez, A. R. de Lera, *J. Am. Chem. Soc.* **2006**, 128, 2434.

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FULL PAPER

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