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Gold(I)-catalysed cyclisation of (*E*)-ketene-*N*,*O*-acetals: a synthetic route toward spiro-oxazole-γ-lactones†‡

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In this study, we developed a cascade 5,5-cyclisation of internal ketene-*N*,*O*-acetals utilizing homogeneous Au(I) catalysis. This process involves an initial 5-*exo-dig* carbocyclisation, followed by a 5-*exo-dig* heterocyclisation that stereoselectively incorporates the O-atom of a water molecule into an N-tethered propargyl alkyne. This sequential reaction results in the formation of one C–C, two C–O, and two C–I bonds, ultimately leading to the synthesis of spiro-α-iodo-γ-lactone structures featuring oxazole rings in good yields.

Spirocycles[1] are a unique class of molecular structures with prominent three-dimensional characteristics, often found in a variety of natural products and medicinal compounds (Fig. 1a).[2,3] Despite their importance, potential methods for the synthesis of functionalized spirocycles have not been fully explored. Notably, gold-catalysed oxidative cyclisation and cycloisomerisation reactions have played vital roles in the efficient crafting of such complex spirocyclic architectures.

Ynamides, with their unique polarized nature, exhibit both electrophilic and nucleophilic reactive sites.[4] Consequently, alkyne tethered ynamides are amenable to various cyclisation processes. In this context, gold-catalysed activations of alkynes followed by targeted cyclisations have provided a unique means to understand annulation modules (Fig. 1b).[5] In this connection, 6/5-*endo-dig* and 5-*exo-dig* cyclisation/cycloisomerisation reactions of propargyl ynamides have helped build a variety of N-heterocycles such as dihydropyridinones, benzoisoquinolenes, pyrrolidones, spiro-pyrrolidones, and cyclobutene-fused azepines.[5–8] However, the pursuit of a multidirectional strategy, aiming at precise control over specific cyclisation paths among several options, remains a challenging yet promising area for further investigation.

Building upon our recent finding, we hypothesize that subjecting ketene-*N*,*O*-acetals to gold catalysis can result in the

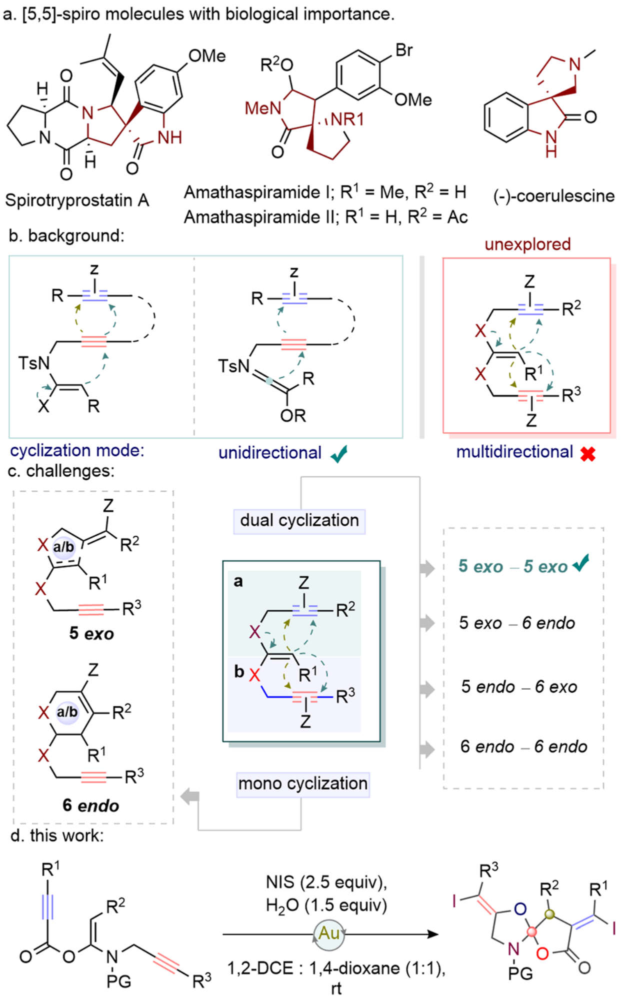

Fig. 1 Background and this work.

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† Dedicated to Prof. Sukh Dev on his 100th birthday for his outstanding scientific contributions to organic chemistry.

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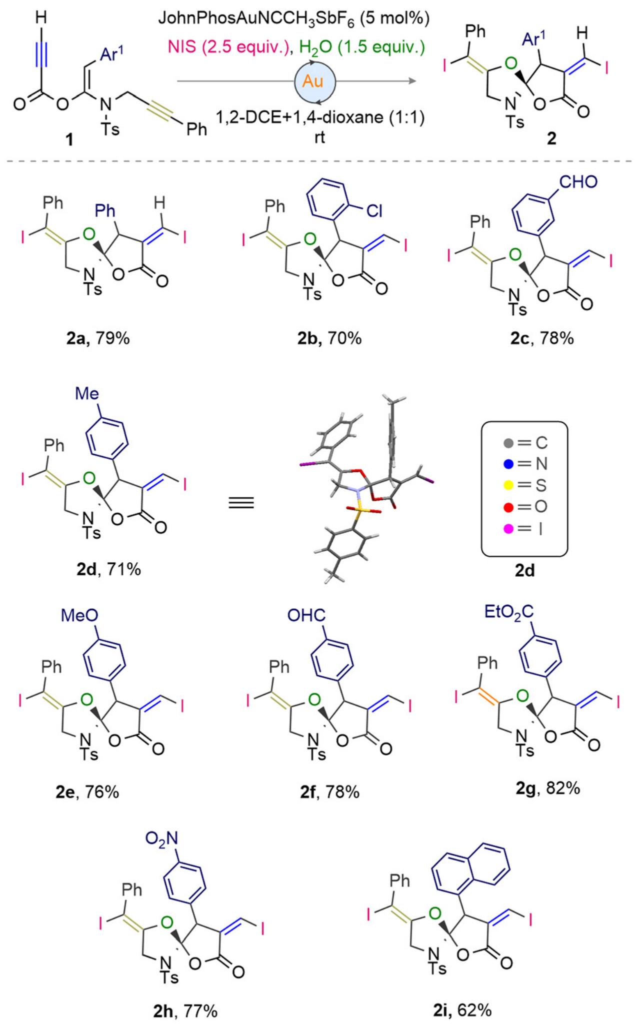
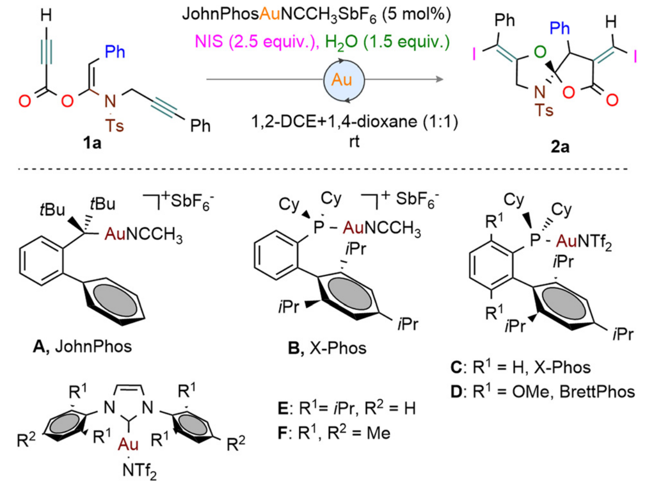
poly-activation of alkyne moieties, paving the way for a multi-directional cyclisation pathway. However, controlling the mono-cyclisation mode (5-*exo*/6-*endo*) for the realization of selective dual cyclisation modes (5-*exo*-5-*exo*, 5-*exo*-6-*endo*, 5-*endo*-6-*exo*, and 6-*endo*-6-*endo*) [Scheme 1c] is challenging. In this study, we introduce a highly regioselective multidirectional 5,5-*exo-dig* cyclisation of di-alkyne tethered ketene-*N*,*O*-acetals catalysed by gold. This strategy enables the efficient synthesis of diverse spiro molecular frameworks from (*E*)-ketene-*N*,*O*-acetals.

The study commenced with the reaction of the ketene-*N*,*O*-acetals **1a** using PPh_3AuCl (5.0 mol%) and $AgSbF_6$ (5.0 mol%) in 1,2-dichloroethane at room temperature, yielding the enediyne-cyclisation product **2a** in a moderate 38% yield (Table 1, entry 1). The employment of $AgNTf_2$ resulted in a lower 26% yield of **2a** and the decomposition of the starting material **1a** (entry 2).



Scheme 1 Substrate scope.[a] Reaction conditions: **1** (0.25 mmol), catalyst (5.0 mol%), NIS (2.5 equiv.), H_2O (1.5 equiv.) in 1,2-DCE : 1,4-dioxane (1 : 1, 0.05 M). [a]Isolated yield.

Table 1 Screening of reaction conditions[a]



Entry	Catalyst	X-source	H_2O equiv.	Solvent	**2a** Yield (%)
1	PPh_3AuCl/ $AgSbF_6$	NIS (2)	2	1,2-DCE	38
2	PPh_3AuCl/ $AgNTf_2$	NIS (2)	2	1,2-DCE	26
3	**A**	NIS (2)	2	1,2-DCE	55
4	**B**	NIS (2)	2	1,2-DCE	39
5	**C**	NIS (2)	2	1,2-DCE	25
6	**D**	NIS (2)	2	1,2-DCE	16
7	**E**	NIS (2)	2	1,2-DCE	Complex
8	**F**	NIS (2)	2	1,2-DCE	Complex
9	**A**	NIS (2)	2	DCM	48
10	**A**	NIS (2)	2	THF	31
11	**A**	NIS (2)	2	CH_3NO_2	24
12	**A**	NIS (2)	2	1,4-Dioxane	57
13	**A**	NIS (2)	2	DCE/dioxane (1 : 1)	69
14	**A**	NIS (2.5)	2	DCE/dioxane (1 : 1)	77
15	**A**	NIS (2.5)	1.5	DCE/dioxane (1 : 1)	79

Reaction conditions: **1** (0.25 mmol), catalyst (5.0 mol%) in 1,2-DCE : 1,4-dioxane (1 : 1, 0.05 M). [a] Isolated yields.

A significant improvement was achieved with the JohnPhos ligated gold(I) catalyst **A**, leading to 55% yield of the desired product **2a** (entry 3).

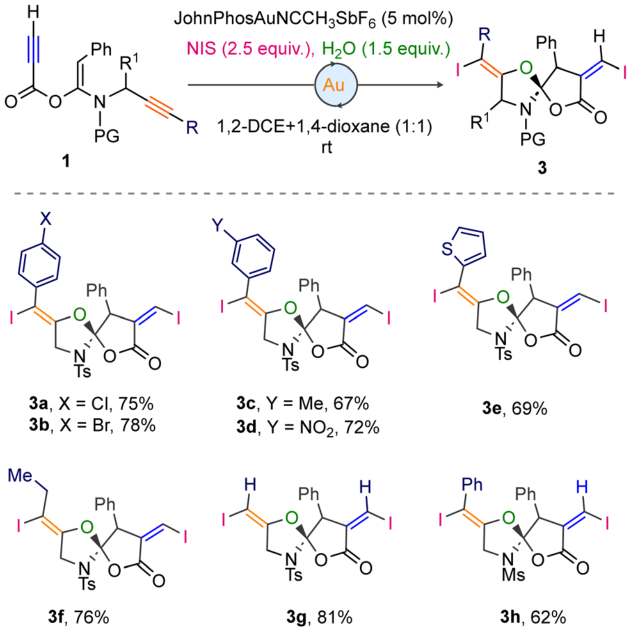
However, the use of other Au-catalysts, such as CyJohnPhosgold-SbF_6 (**B**), and those with bulkier phosphine ligands, such as Xphosgold-NTf_2 (**C**) and Brettphosgold-NTf_2 (**D**), did not enhance the yield (entries 4–6). Attempts with the N-heterocyclic carbene (NHC)-based gold catalysts **E** and **F** provided a complex mixture (entries 7 and 8). Various parameters were tested, including the water-to-enyne ratio, *N*-iodosuccinimide (NIS) concentration, solvents, and reaction concentration (Table 1, entries 9–12). The addition of 2.0 equiv. of NIS and 2.0 equiv. of water in 1,4-dioxane improved the yield to 57% (entry 12). Optimally, a 1 : 1 mixture of DCE : 1,4-dioxane with 2.5 equiv. of NIS and 1.5 equiv. of water yielded 79% of the enediyne-cyclisation product **2a** (entry 15). Substituting NIS with NBS resulted in a complex reaction profile, whereas other iodine sources failed to produce the desired product.[10]

Having established the optimized conditions, we proceeded to investigate the substrate scope and functional-group tolerance of the cyclisation reaction of the propiolic acid derived ketene-*N*,*O*-acetals that offers access to the synthesis of peripherally-decorated 1,6-dioxa-4-azaspiro[4.4]nonan-7-one skeletons. We began by testing substrates with modifications at the enamide–alkene terminus. The outcome showed that ketene-*N*,*O*-acetals with both electron-neutral and electron-donating groups (*p*-Me and *p*-OMe) and electron-withdrawing groups (*o*-Cl, *m*-CHO, *p*-CHO, *p*-CO_2Et, and *p*-NO_2) on the aryl ring successfully yielded the desired [5,5]-spiro compounds **2a–h** in 70–82% yields. The crystal structure of **2d** was verified using SC-XRD analysis (CCDC 2120244‡). Additionally, ketene-*N*,*O*-acetals featuring bulky 1-naphthyl substitutions at the ynamide terminus were compatible, producing compound **2i** in a good yield (Scheme 1).

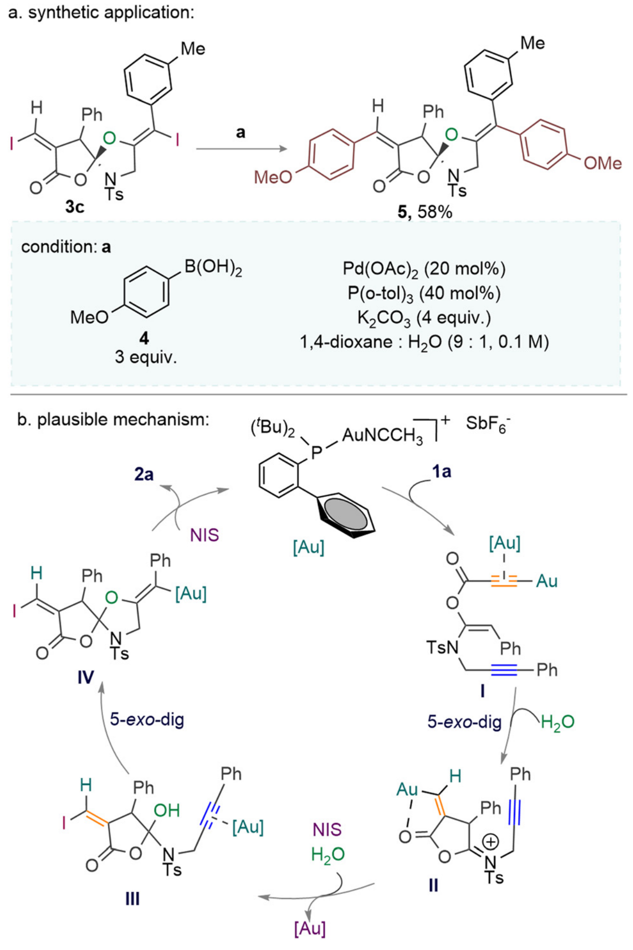
Next, we explored the reactivity of ketene-*N*,*O*-acetals with varied substitutions on the propargyl terminus. Substrates with halo and electron-withdrawing substituents at the aryl ring (*p*-Cl, *p*-Br, *m*-Me, and *m*-NO_2) produced the corresponding products **3a** (75%), **3b** (78%), **3c** (67%), and **3d** (72%). The 1-thienyl-based ketene-*N*,*O*-acetal is not the exception, delivering 69% yield of the desired product **3e**. Likewise, the spiro compounds **3f** and **g** were obtained from the alkyl substituted and unsubstituted propargyl terminus of the respective ketene-*N*,*O*-acetals in good yields.

The labile N-Ms-protected spiro compound **3h** is synthesized in 62% yield (Scheme 2). To further expand the structural diversity of the spirocycles, a Pd-catalyzed Suzuki cross-coupling of the iodo-moiety of spirocycle **3c** with the *p*-methoxyphenyl-boronic acid **4** was performed, which led to the successful synthesis of compound **5** in 58% yield (Scheme 3a).

Based on the observed reactivity, we propose a plausible catalytic cycle (Scheme 3). The reaction begins with the coordination of the cationic JohnPhosAuNCCH_3SbF_6 catalyst with the nucleophilic terminal alkyne of ketene-*N*,*O*-acetal **1a** to form the gold-acetylide.[9] We believe the gold-acetylide formation through σ-activation of the terminal alkyne is facile compared to the π-activation of the internal alkyne.[9] Meanwhile, the simultaneous π-activation by the carbophilic gold-catalyst could provide the dual activated [Au]-species **Int-I;** although the formation of such an intermediate is less probable, it cannot be ruled out.[9] Consequently, the intramolecular 5-*exo-dig* cyclisation of **Int-I** provides the vinyl-[Au] intermediate **II.**[11] The trap of water by the iminium-moiety and the deaurative iodination of vinyl-[Au] of **Int-II** then forms **Int-III.** Next, the intramolecular 5-*exo-dig* hetero-cyclisation of aminol to the [Au]-activated alkyne yields the core spirocyclic-vinyl-[Au] intermediate **IV.** Finally, a second deaurative iodination of **Int-IV** produces the spirocyclic product **2a** with the regeneration of the active gold species.



Scheme 2 Substrate scope.[a] Reactions conditions: **1** (0.25 mmol), catalyst (5.0 mol%), NIS (2.5 equiv.), H_2O (1.5 equiv.) in 1,2-DCE : 1,4-dioxane (1 : 1, 0.05 M). [a]Isolated yield.



Scheme 3 Synthetic application and plausible mechanism.

Conclusions

In summary, we have established a protocol for an Au(I)-catalysed cascade double-5-*exo-dig* cyclisation utilizing ketene-*N*,*O*-acetals. This method facilitates the synthesis of α-methylene-γ-amino-butyrolactones by incorporating isoxazole moieties. Operating under mild conditions, this process demonstrates compatibility with various functional groups and the reaction is scalable. We believe that these spiro-bicyclic lactones hold promise for applications in the pharmaceutical industry, owing to their unique structural characteristics and potential pharmacological relevance.

Experimental

Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. 1,4-Dioxane, dichloromethane (CH_2Cl_2; DCM), toluene, acetonitrile (CH_3CN), 1,2-dichloroethane (DCE), and acetone were distilled over CaH_2. THF was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. All the gold catalysts were purchased from Sigma Aldrich Ltd and used as received. Silver salts such as $AgSbF_6$, $AgNTf_2$, $AgBF_4$, and NIS were purchased from Aldrich Ltd and used as received. PPh_3, DEAD, $CuSO_4·H_2O$, 1,10-phenanthroline, K_3PO_4, Na_2CO_3, and $Na_2S_2O_3·5H_2O$ were purchased from Merck. The aryl iodides were purchased from Aldrich and used. Analytical and spectral data of all those known compounds matched exactly with the reported values.

Experimental procedures

General procedure for the Au-catalyzed cascade double 5-*exo-dig* cyclization of 1: (GP-4)

To a screw capped tube were added, under an argon atmosphere, a solution of **1** (0.25 mmol) in 1,4-dioxane (3.0 mL) and NIS (2.5 equiv.). The catalyst JohnphosAuSbF_6 (**A**; 7.6 mg, 5 mol%) in DCE (3.0 mL) was next introduced along with 1.5 equiv. of H_2O. The reaction mixture was stirred for 6–8 h. The reaction progress was periodically monitored by TLC. After 8 h, the reaction mixture was quenched with saturated sodium thiosulfate solution and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/EtOAc) to afford the expected products **2a–2i** and **3a–3h**.

(2*E*,8*Z*)-2-(Iodo(phenyl)methylene)-8-(iodomethylene)-9-phenyl-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (2a)

2a was obtained in 79% yield as a pale-yellow solid; R_f = 0.45 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 2983, 1735, 1376, 1214, 1179, 1135, 1099, 865, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8 Hz, 2H), 7.41–7.34 (m, 3H), 7.29–7.26 (m, 1H), 7.26–7.23 (m, 2H), 7.21–7.16 (m, 3H), 7.00–6.91 (m, 2H), 5.41 (d, J = 2.8 Hz, 1H), 4.41 (d, J = 13.6 Hz, 1H), 4.18 (d, J = 13.6 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.8, 145.3, 143.6, 136.5, 133.4, 133.3, 133.1, 130.2, 129.9, 128.8, 128.6, 128.4, 128.0, 127.8, 128.4, 125.3, 117.6, 101.6, 54.0, 49.4, 21.6. HRMS (ESI): m/z calcd for $C_{27}H_{21}I_2NNaO_5S$ (M + Na)$^+$: 747.9127, found: 747.9121.

(2*E*,8*Z*)-9-(2-Chlorophenyl)-2-(iodo(phenyl)methylene)-8-(iodomethylene)-3-methyl-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (2b)

2b was obtained in 70% yield as a pale-yellow gummy liquid; R_f = 0.58 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 2977, 1766, 1385, 1209, 1176, 1112, 1067, 852, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.4 Hz, 2H), 7.48 (m, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 2.8 Hz, 1H), 7.32–7.26 (m, 2H), 7.16–7.08 (m, 3H), 7.02–6.97 (m, 1H), 6.99 (dd, J = 7.5, 1.5 Hz, 1H), 6.84–6.82 (m, 1H), 5.98 (d, J = 3.0 Hz, 1H), 4.46 (d, J = 14.0 Hz, 1H), 4.13 (d, J = 14.0 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.3, 145.5, 144.5, 136.6, 136.2, 135.7, 133.2, 132.5, 131.4, 130.0, 129.8, 129.6, 129.3, 129.2, 129.1 128.9, 127.9, 127.7, 127.6, 126.9, 116.3, 92.7, 70.4, 54.5, 53.5, 21.7. HRMS (ESI): m/z calcd for $C_{27}H_{21}ClI_2NO_5S$ (M + H)$^+$: 759.8918; found: 759.8912.

3-((2*E*,8*Z*)-2-(Iodo(phenyl)methylene)-8-(iodomethylene)-7-oxo-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-9-yl)benzaldehyde (2c)

2c was obtained in 78% yield as a pale-yellow gummy liquid; R_f = 0.51 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 2964, 1443, 1388, 1218, 1105, 1037, 865, 744 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.71 (s, 1H), 7.83 (m, 1H), 7.79 (d, J = 2.5 Hz, 2H), 7.59 (s, 1H), 7.48–7.44 (m, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.20 (m, 1H), 7.14–7.09 (m, 3H), 6.92–6.86 (m, 2H), 5.41 (d, J = 2.5 Hz, 1H), 4.34 (d, J = 14.0 Hz, 1H), 4.01 (d, J = 14.0 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.4, 163.1, 145.8, 143.9, 136.9, 136.7, 135.8, 133.9, 132.9, 132.0, 130.1, 129.6, 129.4, 129.3, 129.0, 128.3, 128.1, 116.2, 92.0, 70.5, 57.3, 53.9, 21.7. HRMS (ESI): m/z calcd for $C_{28}H_{22}I_2NO_6S$ (M + H)$^+$: 753.9257; found: 753.9262.

(2*E*,8*Z*)-2-(Iodo(phenyl)methylene)-8-(iodomethylene)-9-(*p*-tolyl)-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (2d)

2d was obtained in 71% yield as a pale brown semi solid; R_f = 0.52 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 2987, 1753, 1382, 1242, 1139, 1090, 1053, 879, 723 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, J = 8 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.0 Hz, 1H), 7.25–7.17 (m, 5H), 7.15 (d, J = 8.0 Hz, 2H), 7.04–6.98 (m, 2H), 5.38 (d, J = 3.0 Hz, 1H), 4.43 (d, J = 14.0 Hz, 1H), 4.11 (d, J = 14.0 Hz, 1H), 2.51 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.5, 145.6, 144.2, 138.7, 136.8, 136.3, 133.0, 130.5, 130.1, 129.54, 129.46 129.4, 128.9, 128.1, 127.8, 116.8, 91.5, 70.2, 57.2, 54.0, 21.7, 21.2. HRMS (ESI): m/z calcd for $C_{28}H_{24}I_2NO_5S$ (M + H)$^+$: 739.9465; found: 739.9458.

(2*E*,8*Z*)-2-(Iodo(phenyl)methylene)-8-(iodomethylene)-9-(4-methoxyphenyl)-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (2e)

2e was obtained in 76% yield as a pale brown semi solid; R_f = 0.52 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 3049, 2972, 1740, 1354, 1159, 1148, 1073, 852, 698 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.84 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.26–7.20 (m, 4H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.06–7.02 (m, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.34 (d, *J* = 3.0 Hz, 1H), 4.41 (d, *J* = 14.0 Hz, 1H), 4.10 (d, *J* = 14.0 Hz, 1H), 3.84 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ = 163.5, 159.9, 145.6, 144.2, 136.8, 136.5, 133.0, 131.8, 130.0, 129.5, 128.9, 128.1, 127.8, 124.2, 116.8, 114.1, 91.3, 70.1, 56.9, 55.3, 53.9, 21.7. HRMS (ESI): *m*/*z* calcd for $C_{28}H_{24}I_2NO_6S$ (M + H)$^+$: 755.9414 found: 755.9422.

4-((2*E*,8*Z*)-2-(Iodo(phenyl)methylene)-8-(iodomethylene)-7-oxo-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-9-yl)benzaldehyde (2f)

2f was obtained in 78% yield as a pale-yellow semi solid; R_f = 0.41 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 2238, 1756, 1735, 1510, 1371, 1174, 1092 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.84 (s, 1H), 7.90 (m, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.65 (s, 1H), 7.55–7.50 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 3.0 Hz, 1H), 7.22–7.15 (m, 3H), 6.98–6.94 (m, 2H), 5.48 (d, *J* = 3.0 Hz, 1H), 4.41 (d, *J* = 13.5 Hz, 1H), 4.08 (d, *J* = 13.5 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ = 191.5, 163.1, 145.83, 143.8, 136.9, 136.7, 135.8, 133.8, 132.8, 132.0, 130.1, 129.6, 129.4, 129.3, 129.0, 128.3, 128.1, 116.2, 92.0, 70.5, 57.2, 53.8, 21.7. HRMS (ESI): *m*/*z* calcd for $C_{28}H_{22}I_2NO_6S$ (M + H)$^+$: 753.9257; found: 753.9260.

Ethyl 4-((2*E*,8*Z*)-2-(Iodo(phenyl)methylene)-8-(iodomethylene)-7-oxo-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-9-yl)benzoate (2g)

2g was obtained in 82% yield as a pale-yellow gummy liquid; R_f = 0.45 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 1787, 1706, 1443, 1360, 1159, 1092, 911, 823 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.89–7.82 (m, 4H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.48–7.38 (m, 3H), 7.32 (d, *J* = 3.0 Hz, 1H), 7.27–7.22 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.43 (d, *J* = 5.0 Hz, 1H), 4.42 (d, *J* = 14.0 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 4.10 (d, *J* = 14.0 Hz, 1H), 2.49 (s, 3H), 1.40 (t, *J* = 7.5 Hz, 3H).^{13}C NMR (126 MHz, CDCl$_3$): δ = 165.9, 163.3, 145.7, 145.5, 141.0, 135.7, 132.8, 132.3, 130.5, 130.0, 129.5, 129.0, 128.91, 128.87, 116.8, 92.2, 68.6, 61.1, 57.5, 54.1, 21.7, 14.3. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{26}I_2NO_7S$ (M + H)$^+$: 797.9519, found 797.9519.

(2*E*,8*Z*)-2-(Iodo(phenyl)methylene)-8-(iodomethylene)-9-(4-nitrophenyl)-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (2h)

2h was obtained in 77% yield as a thick yellow liquid; R_f = 0.56 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 2231, 1768, 1489, 1243, 1119, 1187, 890 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.12 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.32 (bd, *J* = 3.0 Hz, 1H), 7.24–7.18 (m, 3H), 6.97–6.89 (m, 2H), 5.49 (d, *J* = 3.0 Hz, 1H), 4.43 (d, *J* = 13.5 Hz, 1H), 4.05 (d, *J* = 13.5 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ = 162.8, 148.1, 145.9, 143.6, 139.8, 136.6, 135.3, 132.7, 131.4, 130.2, 129.2, 128.9, 128.4, 128.0, 123.8, 115.8, 92.7, 70.7, 57.2, 53.6, 21.7. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{21}I_2N_2O_7S$ (M + Na)$^+$: 770.9159; found: 770.9160.

(2*E*,8*Z*)-2-(Iodo(phenyl)methylene)-8-(iodomethylene)-9-(naphthalen-1-yl)-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (2i)

2i was obtained in 74% yield as a pale-yellow thick liquid; R_f = 0.54 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 2935, 1796, 1623, 1448, 1233, 1032, 868 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.49 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.93–7.90 (m, 3H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.51–7.47 (m, 2H), 7.45–7.40 (m, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.17–7.08 (m, 3H), 6.63 (d, *J* = 7.5 Hz, 2H), 6.31 (d, *J* = 2.5 Hz, 1H), 4.35 (d, *J* = 14.0 Hz, 1H), 4.09 (d, *J* = 13.5 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 163.6, 145.7, 144.1, 136.7, 136.4, 133.8, 133.0, 130.6, 130.1, 129.3, 129.2, 129.10, 129.08, 129.0, 128.2, 127.9, 127.7, 127.5, 126.4, 125.1, 122.8, 116.7, 92.9, 70.3, 53.6, 53.1, 21.7. HRMS (ESI): *m*/*z* calcd for $C_{31}H_{24}I_2NO_5S$ (M + H)$^+$: 775.9465; found: 775.9465.

(2*E*,8*Z*)-2-((4-Chlorophenyl) iodomethylene)-8-(iodomethylene)-9-phenyl-4-tosyl-1,6-dioxa-4-azaspiro[4.4] nonan-7-one (3a)

3a was obtained in 75% yield as a pale-yellow thick liquid; R_f = 0.60 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 2919, 1775, 1558, 1448, 1362, 1238, 1089, 809, 744 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.84 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.41–7.37 (m, 3H), 7.32 (d, *J* = 2.5 Hz, 1H), 7.26–7.23 (m, 2H), 7.17–7.13 (m, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.41 (d, *J* = 3.0 Hz, 1H), 4.40 (d, *J* = 14.0 Hz, 1H), 4.06 (d, *J* = 14 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ = 163.3, 145.7, 144.8, 135.8, 135.2, 133.8, 132.9, 132.6, 130.8, 130.5, 130.1, 129.0, 128.9, 128.1, 116.7, 92.2, 68.4, 57.5, 53.9, 21.8. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{20}ClI_2NNaO_5S$ (M + Na)$^+$: 781.8738, found: 781.8738.

(2*E*,8*Z*)-2-((4-Bromophenyl) iodomethylene)-8-(iodomethylene)-9-phenyl-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (3b)

3b was obtained in 78% yield as a pale-yellow thick liquid; R_f = 0.60 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max} 2929, 1768, 1597, 1478, 1448, 1362, 1089, 887, 736, 680 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.86 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.44–7.39 (m, 3H), 7.36–7.30 (m, 3H), 7.29–7.24 (m, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.43 (d, *J* = 2.5 Hz, 1H), 4.41 (d, *J* = 14.0 Hz, 1H), 4.08 (d, *J* = 14.0 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ = 163.3, 145.7, 144.8, 135.9, 135.7, 130.0, 132.6, 131.1, 131.0, 130.4, 130.0, 129.2, 129.1, 128.9, 128.9, 122.0, 116.7, 92.0, 68.4, 57.5, 53.9, 21.7. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{20}BrI_2NNaO_5S$ (M + Na)$^+$: 825.8233; found 825.8238.

(2*E*,8*Z*)-2-(Iodo(phenyl)methylene)-8-(iodomethylene)-9-(*m*-tolyl)-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (3c)

3c was obtained in 67% yield as a pale brown semi solid; R_f = 0.52 (4 : 1 hexane/EtOAc); [Silica, UV and I_2]. IR (Neat)ν_{max}

2985, 1753, 1382, 1245, 1139, 1090, 1053, 910, 719 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ = 7.87 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.45–7.37 (m, 3H), 7.30–7.25 (m, 3H), 7.11 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.91 (s, 1H), 6.77 (d, J = 7.7 Hz, 1H), 5.43 (d, J = 3.0 Hz, 1H), 4.41 (d, J = 13.8 Hz, 1H), 4.11 (d, J = 13.8 Hz, 1H), 2.51 (s, 3H), 2.33 (s, 3H).^{13}C NMR (126 MHz, CDCl$_3$): δ = 163.4, 145.6, 144.0, 137.5, 136.8, 136.2, 133.2, 132.4, 130.6, 130.0, 130.0, 129.0, 128.9, 128.9, 128.8, 127.7, 126.7, 116.7, 91.3, 70.6, 57.5, 54.0, 21.7, 21.3. HRMS (ESI): *m/z* calcd for $C_{28}H_{24}I_2NO_5S$ (M + H)$^+$: 739.9465; found: 739.9458.

(2*E*,8*Z*)-2-(Iodo(3-nitrophenyl)methylene)-8-(iodomethylene)-9-phenyl-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (3d)

3d was obtained in 72% yield as a pale-yellow gummy liquid; R_f = 0.48 (4 : 1 hexane/EtOAc); [Silica, UV and I$_2$]. IR (Neat)ν_{max} 3059, 2971, 2227, 1779, 1597, 1370, 1169, 1122, 760 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.06 (dt, J = 7.5 Hz, 1H), 7.99 (s, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.47–7.37 (m, 6H), 7.34 (d, J = 3 Hz, 1H), 7.32–7.26 (m, 3H), 5.42 (d, J = 2.5 Hz, 1H), 4.42 (d, J = 14.0 Hz, 1H), 4.13 (d, J = 14.0 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 163.2, 147.9, 146.5, 145.8, 138.4, 135.63, 135.55, 133.0, 132.0, 130.4, 130.1, 129.1, 128.97, 128.90, 124.1, 122.9, 117.0, 92.1, 66.5, 57.5, 54.2, 21.7. HRMS (ESI): *m/z* calcd for $C_{27}H_{20}I_2N_2O_7S$ (M + Na)$^+$: 792.8978, found: 792.8970.

(2*E*,8*Z*)-2-(Iodo(thiophen-2-yl)methylene)-8-(iodomethylene)-9-phenyl-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (3e)

3e was obtained in 69% yield as a pale-yellow gummy liquid; R_f = 0.48 (4 : 1 hexane/EtOAc); [Silica, UV and I$_2$]. IR (Neat)ν_{max} 2227, 1722, 1586, 1460, 1228, 1168, 1075, 755 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.84 (d, J = 8.5 Hz, 2H), 7.30–7.24 (m, 7H), 7.18–7.11 (m, 2H), 7.00 (d, J = 3.5 Hz, 1H), 6.94 (t, J = 5.0 Hz, 1H), 5.06 (d, J = 18 Hz, 1H), 4.69 (dd, J = 17.5, 1.5 Hz, 1H), 4.57 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ = 166.8, 145.3, 141.0, 136.6, 134.7, 134.1, 129.4, 129.3, 129.2, 128.7, 128.4, 128.2, 127.4, 126.7, 126.5, 88.1, 58.2, 58.0, 21.7. HRMS (ESI): *m/z* calcd for $C_{25}H_{20}I_2NO_5S_2$ (M + H)$^+$: 731.8872, found 731.8879.

(2*E*,8*Z*)-8-(Iodomethylene)-2-(1-iodopropylidene)-9-phenyl-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (3f)

3f was obtained in 76% yield as a pale brown semi solid; R_f = 0.57 (4 : 1 hexane/EtOAc); [Silica, UV and I$_2$]. IR (Neat)ν_{max} 2971, 2227, 1792, 1630, 1453, 1229, 1163, 1091, 808 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.82 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.39–7.33 (m, 5H), 7.27 (d, J = 3.0 Hz, 1H), 5.36 (d, J = 3.2 Hz, 1H), 4.15 (d, J = 16.5 Hz, 1H), 3.84 (d, J = 16.5 Hz, 1H), 2.48 (s, 3H), 2.25–2.06 (m, 2H), 0.75 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 163.7, 145.4, 142.7, 136.5, 133.1, 132.2, 130.6, 129.9, 128.88, 128.78, 128.75, 116.0, 91.0, 77.9, 57.9, 52.5, 28.7, 21.7, 13.9. HRMS (ESI): *m/z* calcd for $C_{23}H_{21}I_2NO_5S$ (M + H)$^+$: 677.9308; found 677.9310.

(2*E*,8*Z*)-2,8-Bis(iodomethylene)-9-phenyl-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (3g)

3g was obtained in 81% yield as a pale brown gummy liquid; R_f = 0.43 (4 : 1 hexane/EtOAc); [Silica, UV and I$_2$]. IR (Neat)ν_{max}, 2925, 2232, 1778, 1556, 1347, 1285, 1170, 1089, 777 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.86 (d, J = 8.4 Hz, 1H), 7.46–7.27 (m, 7H), 7.19 (d, J = 2.68 Hz, 1H), 5.40 (d, J = 2.8 Hz, 1H), 5.26 (s, 1H), 4.19 (d, J = 16.5, 2.0 Hz, 1H), 3.90 (d, J = 13.5, 2.4 Hz, 1H), 2.51 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 163.4, 149.7, 145.6, 136.3, 133.1, 131.7, 130.7, 130.0, 128.9, 128.8, 116.2, 90.9, 57.6, 51.3, 47.5, 21.7. HRMS (ESI): *m/z* calcd for $C_{21}H_{17}I_2NNaO_5S$ (M + Na)$^+$: 671.8814; found 671.8808.

(2*E*,8*Z*)-2-(Iodo(phenyl)methylene)-8-(iodomethylene)-4 (methylsulfonyl)-9-phenyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (3h)

3h was obtained in 62% yield as a pale-yellow gummy liquid; R_f = 0.38 (4 : 1 hexane/EtOAc); [Silica, UV and I$_2$]. IR (Neat)ν_{max} 2228, 1727, 1598, 1371, 1324, 1264, 1123, 887 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.41–7.36 (m, 3H), 7.28–7.24 (m, 4H), 7.22 (dd, J = 7.56, 1.44 Hz, 2H), 7.09–7.05 (m, 2H), 5.20 (d, J = 2.8 Hz, 1H), 4.40 (q, J = 27.6, 14.4 Hz, 2H), 3.23 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ = 163.3, 143.6, 136.7, 135.8, 130.6, 129.6, 128.9, 128.8, 128.3, 128.0, 116.4, 92.2, 70.8, 57.2, 54.4, 38.7. HRMS (ESI): *m/z* calcd for $C_{21}H_{17}I_2NO_5S$ (M + Na)$^+$: 671.8814; found: 671.8819.

(5*R*,*E*)-8-((*Z*)-4-Methoxybenzylidene)-2-((4-methoxyphenyl)(phenyl)methylene)-9-(*m*-tolyl)-4-tosyl-1,6-dioxa-4-azaspiro[4.4]nonan-7-one (5)

To a mixture of spirocycle **2e** (100 mg, 0.14 mmol, 1.0 equiv.), *p*-methoxy phenyl boronic acid (**4**; 52 mg, 0.33 mmol, 3.0 equiv.), K_2CO_3 (93 mg, 0.40 mmol, 3.0 equiv.), (p-tol)$_3$P (17 mg, 0.05 mmol, 0.4 equiv.) and Pd (OAc)$_2$ (6.0 mg, 0.027 mmol, 0.2 equiv.) was added 1,4-dioxane : H$_2$O (9 : 1, 0.1 M, 1.4 mL). The reaction mixture was stirred at 40 °C using a preheated heating block for 12 h. The reaction progress was periodically monitored by TLC. Upon complete consumption of **2e**, the reaction mixture was diluted with 3 mL of ethyl acetate and filtered through a small pad of Celite. The solvent was concentrated and the crude reaction mixture was purified by column chromatography on silica to afford **5** in 58% yield as a pale-yellow gummy liquid; R_f = 0.2 (4 : 1 hexane/EtOAc); [Silica, UV and I$_2$]. IR (Neat)ν_{max} 2924, 1712, 1599, 1359, 1246, 1088, 905, 727 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ = 7.94 (d, J = 8.9 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.49–7.43 (m, 2H), 7.44–7.37 (m, 5H), 7.05 (t, J = 7.7 Hz, 1H), 6.98–6.89 (m, 3H), 6.92–6.85 (m, 2H), 6.87–6.80 (m, 2H), 6.74 (d, J = 3.0 Hz, 2H), 6.63 (d, J = 7.7 Hz, 1H), 5.78 (d, J = 2.8 Hz, 1H), 4.14 (d, J = 13.2 Hz, 1H), 4.07 (d, J = 13.3 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 2.49 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ = 165.3, 161.8, 159.1, 145.5, 143.6, 141.8, 137.7, 137.5, 134.9, 134.1, 133.9, 131.5, 131.4, 131.1, 130.2, 130.1, 129.9, 129.8, 129.3, 129.0, 128.7, 127.9, 127.9, 127.8, 126.8, 126.5, 123.4, 116.9, 114.5, 114.1, 77.7, 77.4, 77.2, 56.0, 55.8, 55.6, 49.4, 30.1, 22.1, 21.8. HRMS (ESI): *m*/*z* calcd for $C_{42}H_{39}NO_7S$ $(M + H)^+$: 700.2364; found: 700.2367.

Data availability

The ESI‡ contains method description, product characterization data, and NMR spectra.

Author contributions

All authors have given approval to the final version of the manuscript. A. K. S. and R. P. conceived the idea and R. P. and S. K. performed the experiments. The manuscript and the ESI‡ data writing, and execution were done by M. S. and S. K. Review, editing, and supervision were done by A. K. S.

Conflicts of interest

There are no conflicts to declare.

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