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Synthesis of 2-Substituted Cyclobutanones by a Suzuki Reaction and Dephosphorylation Sequence

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We report a novel process for the preparation of 2-substituted cyclobutanones. Such a method relies on the cross-coupling reaction of bromocyclobutenyl diethyl phosphate with either boronic acids or organozinc reagents. Dephosphorylation of the prepared 2-substituted cyclobutenyl phosphates affords 2-substituted cyclobutanones. We observed that the course of the dephosphorylation reaction depends on the properties of the substituents found on the cyclobutene nucleus. The presence of groups capable of stabilizing the negative charge is necessary for ring opening of cyclobutanones. The scope of the reported process for the preparation of 2-substituted cyclobutanones has also been extended to the preparation of cyclobutenyl sulfides.

Introduction

A cyclobutane is a kind of naturally occurring four-membered cyclic molecule that exhibits interesting chemical properties.[1] The synthesis and various applications of substituted cyclobutanes have been the subject of several reviews.[2] The tetrasubstituted cyclobutane skeleton represents a key part of both katsumadain C[3] and the palhynosides A-H.[4] Moreover, substituted cyclobutane[5] and the cyclobutene[6] ring have been identified as constituents of the sesquiterpenes. Among the various substituted cyclobutanones,[7] significant research attention has been paid to the synthesis[8] and functionalization of 2-substituted cyclobutanones.[4] The synthetic applications of 2-substituted cyclobutanones also cover natural product synthesis.[9] In relation to the above-mentioned applications of 2-substituted cyclobutanones, it has been reported that 2-alkylated cyclobutanones exhibit both cyto- and genotoxic properties under *in vitro* conditions.[10] As a result, significant attention has been paid to the detection of 2-alkylated cyclobutanones in food.[11] In addition, substituted cyclobutanones have been designed and tested as analogues of various β-lactam antibiotics.[12]

Similar to three-membered carbocycles, the four-membered ring that characterizes cyclobutanones renders them valuable building blocks for ring-opening reactions[9a,13] due to the high ring-strain energy of the cyclobutanone skeleton. Indeed 2,2-dichlorocyclobutanones can be converted into methyl 4,4-dichlorobutanoates by means of sodium methoxide.[14] Similar reactivity was observed by Trost, who proposed that the presence of an electron-stabilizing group could facilitate the cyclobutanone ring-opening process.[15] However, this assumption has not yet been satisfactorily confirmed. Further, Trost also observed that 2,2-diphenylcyclobutanone and 2-phenylcyclobutanone can be opened to the corresponding methyl butanoates via the reaction with sodium methoxide in refluxing methanol.

The ability of 2-substituted cyclobutanones to undergo ring expansion raises the question of how 2-substituted cyclobutanones can be prepared. In fact, two main approaches to the preparation of 2-substituted cyclobutanones have evolved. The first such approach is based on the formation of a cyclobutanone ring by means of ring expansion, ring contraction, and [2+2] cycloadditions. The ring-expansion-based processes of cyclic molecules involve Lewis acid-,[16] oxidative-,[17] and cobalt-[18] or gold-catalyzed[19] rearrangements of the substituted cyclopropanes. Moreover, the microwave-assisted Wolff rearrangement of substituted 2-diazocyclopenta-1,3-diones represents an example of a ring-contraction-based approach for the preparation of cyclobutanones.[20] The concept of using [2+2] cycloadditions for the synthesis of substituted cyclobutanones was first reported in 1964[21] and still counts among the near-endless number of examples of approaches to substituted cyclobutanones synthesis;[17c,22] however, this approach continues to be frequently used for the synthesis of polysubstituted cyclobutanones.[23]

The second approach for the preparation of 2-substituted cyclobutanone bearing alkyl substituents involves the chemical modification of commercially available cyclobutanone (Scheme 1). Aldol-type reactions[24] and Mannich-type reactions[25] are both typical examples of such reactivity (Scheme 1a, Scheme 1b). The direct alkylation of the cyclobutanone-derived enolate provides low product yields (Scheme 1c),[26] likely due to the low stability of the corresponding enolate. Substantially improved yields can be obtained by means of α-allylation via singly occupied molecular orbital (SOMO) alkylation,[27] imine[28] or oxime alkylation,[17c,29] and palladium-catalyzed cyclobutanone alkylation.[30]

The synthesis of 2-arylcyclobutanones is realized by approaches based on ring expansion,[31] general intramolecular

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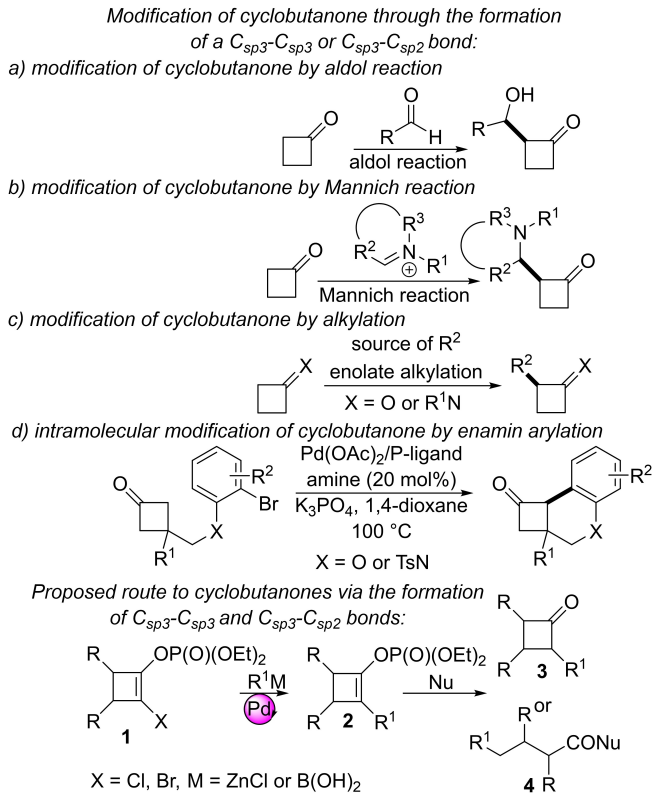
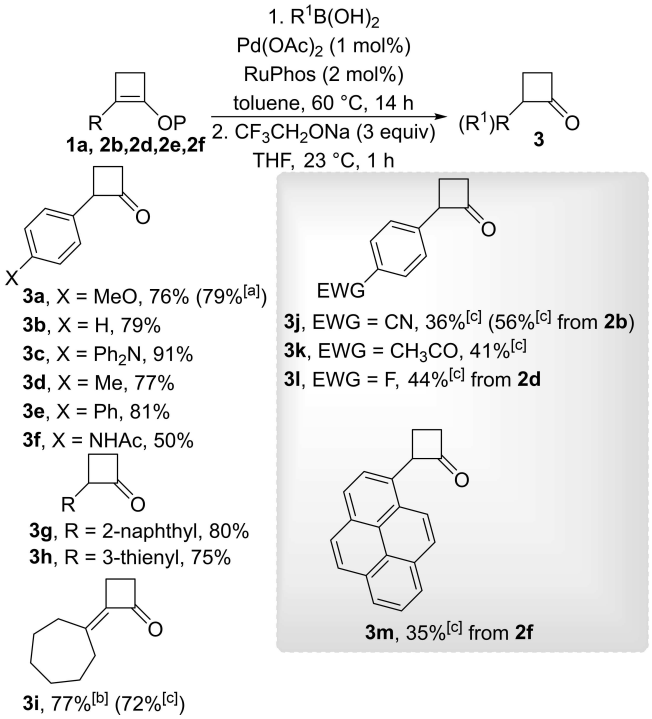


Scheme 1. General scheme representing the aim of our work.



Scheme 2. The scope of the one-pot two-step procedure for the synthesis of the 2-substituted cyclobutanones **3**. [a] Neopentylglycol boronate was used. [b] The reaction was stirred for 2 h at 60 °C. [c] TBAF (3 equiv.) was used instead of CF_3CH_2ONa and the reaction was stirred 2 h at 23 °C.

palladium-catalyzed enamine arylation (Scheme 1d)[32] and palladium-catalyzed intermolecular arylation of fused cyclobutanones.[33] In addition, there have been no previous reports concerning the transition-metal-catalyzed synthesis of unsubstituted 2-arylated cyclobutanones. The reason why the transition-metal-catalyzed arylation of unsubstituted cyclobutanones has not previously been described may be related to the ability of substituted cyclobutanones to undergo ring-opening reactions under different conditions. Thus, based on our experiences with transition-metal-catalyzed reactions,[34] we proposed a novel approach for the preparation of 2-substituted cyclobutanone that uses the Suzuki and Negishi reactions of the halocyclobutenyl phosphate **1** and the subsequent phosphate group deprotection to the cyclobutanone **3**. Phosphates represented by general structure **1** are examples of the kinds of double electrophilic templates that can be used for the synthesis of tetrasubstituted alkenes.[35] We have previously shown that bromocyclobutenyl phosphate can be used for the synthesis of [3]- and [4]dendralenes through a double cross-coupling reaction.[36] Therefore, a key step in the proposed transformation of the phosphate **2** into the cyclobutanone **3** involves the chemoselective deprotection of the phosphate group with respect to the undesired opening of the cyclobutanone ring to the butanoic acid derivative **4**.

Results and Discussion

At the beginning of our work, we synthesized the phosphates **1a** and **1b** and **2a**–**2f** (Figure 1), which were prepared from the bromocyclobutenyl diethyl phosphate **1a** by means of the Suzuki reaction under previously reported conditions.[36] The same reaction conditions as used for the Suzuki reaction were then used for the one-pot two-step procedure for the synthesis of 2-substituted cyclobutanones (Scheme 2). The isolated phosphate **2a** was treated with different nucleophiles in order to optimize its conversion into the ketone **3a**. The use of

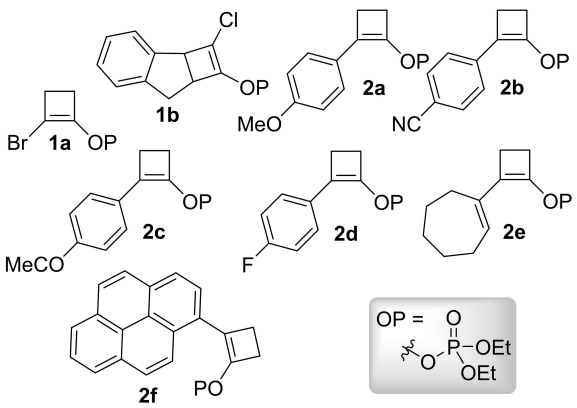


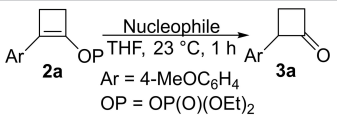
Figure 1. Structures of starting phosphates.

sodium phenoxide resulted in the isolation of the ketone **3a** in a 49% isolated yield (Table 1, entry 1), while the use of potassium hydroxide and acidic hydrolysis failed (Table 1, entries 2 and 3). Potassium carbonate and sodium ethoxide gave only moderate yields of the ketone **3a** (Table 1, entries 4 and 5). Similar reactivity was observed in relation to pure sodium 2,2,2-trifluoroethoxide in tetrahydrofurane (THF), while the use of a 1 M solution of sodium 2,2,2-trifluoroethoxide (TFENa) in 2,2,2-trifluoroethanol (TFE) gave an almost quantitative isolated yield of the ketone **3a** (Table 1, entries 6 and 7).

Following the successful optimization of the reaction conditions, we tested whether it was possible to prepare substituted cyclobutanones without having to separate the product of the Suzuki reaction **2a**. Thus, the phosphate **1a** was reacted with 4-methoxyphenylboronic acid in the presence of palladium acetate and RuPhos as a ligand, thereby affording the desired product **2a**, which was crudely isolated. The isolated crude phosphate was stirred with a 1 M solution of TFENa. The final cyclobutanone **3a** was obtained in a 76% isolated yield (Scheme 2). The other tested boronic acids bearing electron-neutral and electron-rich aryl substituents gave similarly high isolated yields of the cyclobutanones **3b**–**3g**. The 3-thienylboronic acids also gave the ketone **3h** in a high isolated yield over two steps. It is worth noting that no cyclobutane ring opening was observed in either case. In the case of 1-cycloheptenylboronic acid, we observed the isomerization of the double bond to the α,β-unsaturated ketone **3i**, which was obtained in a 77% isolated yield. The use of boronic acids with electron-poor aryl substituents resulted in the opening of the cyclobutene ring. We soon found that a solution of tetrabutylammonium fluoride in THF could be used for the conversion of these phosphates into the cyclobutanones **3j**–**3m** in moderate isolated yields. In addition, tetrabutylammonium fluoride also gave the ketone **3i** in a 72% isolated yield during the deprotection of the phosphate **2e**.

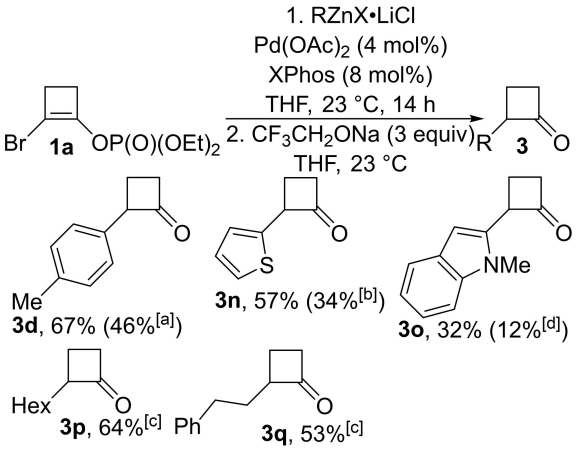
Bromenol phosphate **1a** can also be used in the Negishi reaction to replace the bromine atom with alkyl and aryl groups, as illustrated in Scheme 3. Our recently developed conditions for the Negishi reaction of cyclic bromoenol

Table 1. Condition screening for the phosphate **2a** deprotection.



Entry	Nucleophile	**3a** [%][a]
1	PhONa	49
2	KOH	–[b]
3	H_3PO_4	–[b,c]
4	K_2CO_3	54[d]
5	EtONa[e]	37
6	CF_3CH_2ONa	38
7	CF_3CH_2ONa[f]	91

[a] Isolated yield. [b] Unreacted starting compound was recovered. [c] The reaction was performed in a mixture of THF/H_2O (1:1) at 60 °C. [d] The reaction was stirred for 3 h at 60 °C in methanol. [e] A 1 M solution of EtONa in EtOH was used. [f] A 1 M solution of CF_3CH_2ONa in CF_3CH_2OH was used.



Scheme 3. The Negishi reaction of the phosphate **1a** for the synthesis of the 2-substituted cyclobutanone **3**. [a] The organozinc reagent was prepared from 4-tolylmagnesium chloride. [b] The Negishi reaction was performed at 60 °C. [c] To remove the phosphate group, the prepared phosphate was stirred with TFENa for 2 h at 60 °C. [d] TBAF (3 equiv.) was used instead of CF_3CH_2ONa.

phosphates[34b] proved efficient for the conversion of the phosphate **1a** into the ketone **3d**. This approach is sensitive to the preparation of the organozinc reagent, as shown for the compound **3d**, which was obtained in lower isolated yields when starting from 4-tolylmagnesium chloride. The cyclobutanone **3n** was formed in a lower isolated yield when the Negishi reaction was performed at 60 °C. Aside from the preparation of cyclobutanones with aromatic and heteroaromatic substituents, the Negishi reaction of the bromenol phosphate **1a** is also suitable for the introduction of the alkyl substituents **3p** and **3q** in average isolated yields.

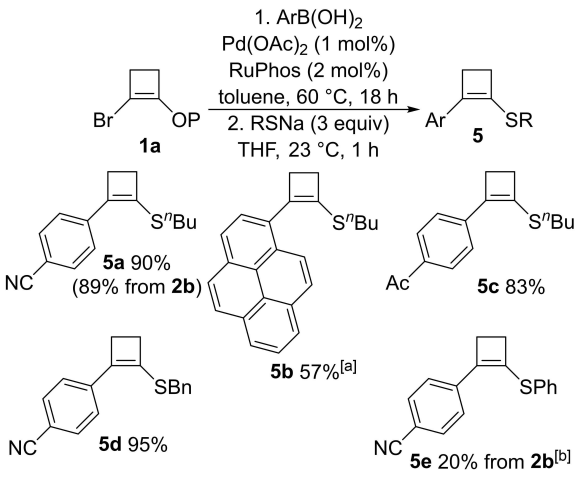
During the preparation of the cyclobutanone **3j**, we observed the opening of the formed cyclobutanone to the corresponding butanoate by means of a base. Thus, we studied the effect of cyclobutane ring substitution on the course of the dephosphorylation process (Scheme 4). A two-step procedure starting from the bromocyclobutenyl phosphate **1a** gave the corresponding 2,2,2-trifluoroethyl butanoates **4a** and **4b** in high isolated yields, albeit only for those boronic acids with electron-withdrawing groups. We also succeeded in converting the phosphate **2b** into the methyl ester **4c** using a 1 M solution of sodium methoxide in methanol at room temperature. The protocol is also suitable for the synthesis of trisubstituted butanoates, as represented by the ester **4d**. Scheme 2 shows that boronic acids with electron-donating substituents are resistant to cyclobutanone ring opening even at elevated reaction temperatures. Yet, in the case of both 1-pyrenylboronic acid and 2-benzothienylboronic acid, the smooth opening of the cyclobutanone moiety occurred during the dephosphorylation process to give the esters **4e** and **4f**. This procedure should enable the synthesis of other carboxylic acid derivatives, although the dephosphorylation process represents the key step in the transformation. We initially started with the synthesis of the morpholine amide **4g** from phosphate **2b**, but all attempts to use the morpholine, or a combination of

morpholine with a base, proved unsuccessful. However, a mixture of TFENa with morpholine resulted in the isolation of the amide **4g** in a 60% isolated yield. This result indicates that morpholine under basic conditions is unable to remove the phosphate moiety, although TFENa-mediated dephosphorylation and ring-opening reactions followed by the conversion of the formed ester into the final amide accomplished the synthesis of the amide **4g**. The synthesis of the primary amide **4h** was achieved in a similar isolated yield.

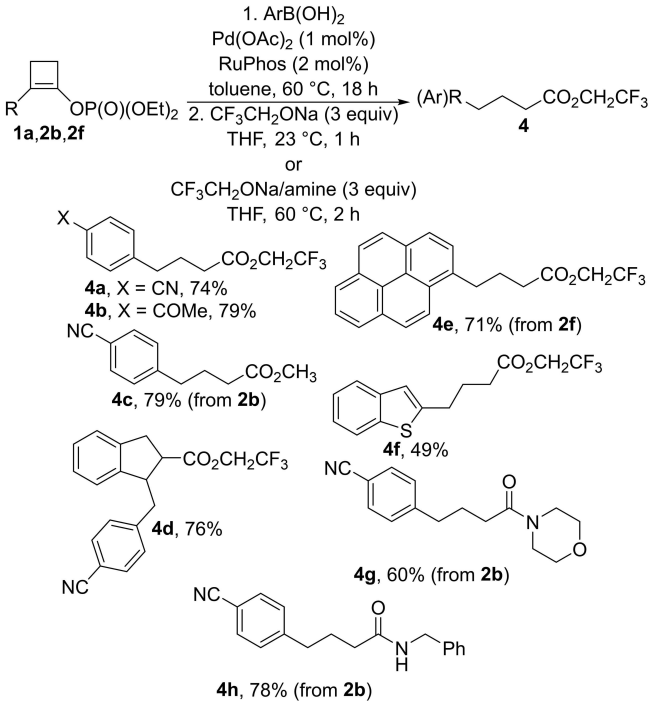
We also demonstrated the broader scope of our methodology through the synthesis of the sulfide **5** (Scheme 5). The phosphate **1a** was cross-coupled with boronic acids and the crudely isolated phosphates was treated with three equivalents of sodium thiolate in the presence of the corresponding thiol. Although the reaction is limited to cyclobutenyl phosphates with substituents capable of stabilizing the negative charge, which allows for phosphate substitution by means of the preferential addition–elimination mechanism, we synthesized the series of sulfides **5a**–**5d**. The use of thiophenol proved less efficient, affording the sulfide **5e** in a 20% isolated yield.

Conclusion

We have developed a novel process for the preparation of substituted cyclobutanones that relies on the cross-coupling reaction of bromocyclobutenyl phosphate with either boronic acids or organozinc reagents. The resulting cyclobutenyl phosphate is then dephosphorylated by means of 2,2,2-trifluoroethanol at room temperature. This process allows for the preparation of cyclobutanones with electron-rich and electron-neutral substituents. For those substituents with the ability to stabilize the negative charge, the preparation of cyclobutanones is performed via the reaction with TBAF in dry tetrahydrofuran. We observed that the groups capable of stabilizing the negative charge facilitated the opening of the cyclobutanones to γ-substituted butanoates and butanamides. This approach for the preparation of 2-substituted cyclobutanones has a broader scope because it also allows for the synthesis of cyclobutenyl sulfides by means of the reaction of sodium thiolates with cyclobutenyl phosphate in tetrahydrofuran at room temperature.



Scheme 5. The synthesis of sulfides when starting from the cyclobutenyl phosphates **1a**, **2b**, and **2c**. [a] Reaction time for the phosphate group substitution was 18 h. [b] Reaction time for the phosphate group substitution was 3 h.



Scheme 4. Preparation of butanoic acid derivatives when starting from the phosphates **1a**, **2b**, and **2f**.

Experimental Section

General Information All reactions were performed under argon atmosphere. NMR spectra were measured on Varian MercuryPlus 300 (^{1}H, 300.13 MHz; ^{13}C, 75.46 MHz), Agilent 400MR DD2 (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) spectrometer at 298 K. Mass spectra were measured on ZAB-SEQ (VG Analytical). The dry and degassed THF was prepared by PureSolv MD7. Silica gel (Merck, Silica Gel 60, 40–63 μm or Merck Silica Gel 60, 63–200 μm) was used for column chromatography. The synthesis of starting phospates **1a**, **2a**–**2g** was accomplished according to published procedure.[36] *n*-BuLi (2.5 M solution in hexane), and other compounds were purchased from Sigma-Aldrich, FLuorochem and Acros Organics. Concentration of BuLi was determined by titration using menthol and 1,10-phenanthroline before use.

General procedure for „one-pot" two-step synthesis of cyclobutanones by the Suzuki reaction of bromocyclobutenyl diethyl phosphate (GP1)

Toluene (4 mL/1 mmol) was added to a mixture of 2-bromocyclobuten-1-yl diethyl phosphate (1.0 equiv) (**1a**), boronic acid or boronic acid ester (1.3 equiv), palladium acetate (1 mol%) and RuPhos (2 mol%). The reaction mixture was stirred for 1 min at 23 °C, and then 2 M K_3PO_4 (3 equiv) was added at once. The

reaction mixture was stirred for 18 h at 60 °C. The reaction mixture was diluted with ether, washed with 1 M KOH (10 mL/1 mmol), water (10 mL/1 mmol), brine (10 mL/1 mmol) and then the organic phase was dried over $MgSO_4$. The solvents were evaporated under reduce pressure and the crude phosphate was dried under reduce pressure. A solution of the crude phosphate in dry THF (3 mL/1 mmol) was added to a solution of CF_3CH_2ONa (3 equiv) in dry CF_3CH_2OH (3 mL/1 mmol) and THF (2 mL/1 mmol) at 23 °C, and the resultant mixture was stirred for 1 h at 23 °C. In the case of TBAF dephosphorylation TBAF (3 equiv, 1 M solution in THF) was added to a solution of the crude phosphate (1 equiv) in dry THF (6 mL/1 mmol) The crude reaction mixture was diluted with ether (30 mL/1 mmol), washed with water (10 mL/1 mmol) and brine (10 mL/1 mmol) and the organic layer was dried over $MgSO_4$. The solvents were evaporated under reduce pressure and column chromatography (Silica gel) gave the final product.

General procedure for „one-pot" two-step synthesis of cyclobutanones by the Negishi reaction of bromocyclobutenyl diethyl phosphate (GP2)

A solution of organozinc reagent (1.3 equiv) was added to a solution of 2-bromocyclobuten-1-yl diethyl phosphate (1.0 equiv) (**1 a**), palladium acetate (4 mol %) and XPhos (8 mol %). The reaction mixture was stirred for 18 h at 23 °C. The reaction mixture was diluted with ether (30 mL/1 mmol), washed with water (10 mL/1 mmol), brine (10 mL/1 mmol) and the organic phase was dried over $MgSO_4$. The solvents were evaporated under reduce pressure and the crude phosphate was dried under reduce pressure. A solution of the crude phosphate in dry THF (3 mL/1 mmol) was added to a solution of CF_3CH_2ONa (3 equiv) in dry CF_3CH_2OH (3 mL/1 mmol) and THF (2 mL/1 mmol) at 23 °C, and the resultant mixture was stirred for 1 h at 23 °C. The crude reaction mixture was diluted with ether (30 mL/1 mmol), washed with water (10 mL/1 mmol) and brine (10 mL/1 mmol) and the organic layer was dried over $MgSO_4$. The solvents were evaporated under reduce pressure and column chromatography (Silica gel) gave the final product.

General procedure for „one-pot" two-step synthesis of butanoates (GP3)

Toluene (4 mL/mmol) was added to a mixture of 2-bromocyclobuten-1-yl diethyl phosphate (1.0 equiv) (**1 a**), boronic acid or boronic acid ester (1.3 equiv), palladium acetate (1 mol %) and RuPhos (2 mol %). The reaction mixture was stirred for 1 min at 23 °C, and then 2 M K_3PO_4 (3 equiv) was added at once. The reaction mixture was stirred for 18 h at 60 °C. The reaction mixture was diluted with ether, washed with 1 M KOH (10 mL/1 mmol), water (10 mL/1 mmol), brine (10 mL/1 mmol) and then the organic phase was dried over $MgSO_4$. The solvents were evaporated under reduce pressure and the crude phosphate was dried under reduce pressure. A solution of the crude phosphate (1.0 equiv) in dry THF (3 mL/1 mmol) was added to a solution of CF_3CH_2ONa (3 equiv) in dry CF_3CH_2OH (3 mL/1 mmol) and THF (2 mL/1 mmol) at 23 °C, and the resultant mixture was stirred for 1 h at 23 °C. The crude reaction mixture was diluted with ether (30 mL/mmol), washed with water (10 mL/1 mmol) and brine (10 mL/1 mmol) and the organic layer was dried over $MgSO_4$. The solvents were evaporated under reduce pressure and column chromatography (Silica gel) gave the final product.

General procedure for „one-pot" two-step synthesis of butanamides (GP4)

Toluene (4 mL/mmol) was added to a mixture of 2-bromocyclobuten-1-yl diethyl phosphate (1.0 equiv) (**1 a**), boronic acid or boronic ester (1.3 equiv), palladium acetate (1 mol %) and RuPhos (2 mol %). The reaction mixture was stirred for 1 min at 23 °C, and then 2 M K_3PO_4 (3 equiv) was added at once. The reaction mixture was stirred for 18 h at 60 °C. The reaction mixture was diluted with ether, washed with 1 M KOH (10 mL/1 mmol), water (10 mL/1 mmol), brine (10 mL/1 mmol) and then the organic phase was dried over $MgSO_4$. The solvents were evaporated under reduce pressure and the crude phosphate was dried under reduce pressure. A solution of crudely isolated phosphate (1.0 equiv) in dry THF (3 mL/1 mmol) was added to a solution of CF_3CH_2ONa (3 equiv) in dry CF_3CH_2OH (3 mL/1 mmol), THF (4 mL/1 mmol) and amine (3.0 equiv) at 23 °C, and the resultant mixture was stirred for 2 h at 60 °C. The crude reaction mixture was diluted with ether (30 mL/1 mmol), washed with 1 M HCl (5 mL/1 mmol), water (20 mL/1 mmol) and brine (20 mL/1 mmol) and the organic layer was dried over $MgSO_4$. The solvents were evaporated under reduce pressure and column chromatography (Silica gel) gave the final product.

General procedure (GP5) for the synthesis of cyclobutenyl sulfides

Toluene (4 mL/mmol) was added to a mixture of 2-bromocyclobuten-1-yl diethyl phosphate (1.0 equiv) (**1 a**), boronic acid or boronic ester (1.3 equiv), palladium acetate (1 mol %) and RuPhos (2 mol %). The reaction mixture was stirred for 1 min at 23 °C, and then 2 M K_3PO_4 (3 equiv) was added at once. The reaction mixture was stirred for 18 h at 60 °C. The reaction mixture was diluted with ether, washed with 1 M KOH (10 mL/1 mmol), water (10 mL/1 mmol), brine (10 mL/1 mmol) and then the organic phase was dried over $MgSO_4$. The solvents were evaporated under reduce pressure and the crude phosphate was dried under reduce pressure. Thiol (6 equiv) was added to a suspension of NaH (3 equiv) in dry THF (4 mL/mmol) cooled to 0 °C. The resultant mixture was stirred for 30 min at 23 °C followed by addition of a solution of crude phosphate (1.0 equiv) in dry THF (2 mL/1 mmol) and the reaction mixture was stirred for 1 h at 23 °C. The crude mixture was diluted with ether (30 mL/1 mmol), washed with water (10 mL/1 mmol) and brine (10 mL/1 mmol) and the organic layer was dried over $MgSO_4$. The solvents were removed under reduce pressure and column chromatography (Silica gel) gave the final product.

2-Chloro-2 a, 7 a-dihydro-7H-cyclobuta[a]inden-1-yl diethyl phosphate (1 b)

Toluene (20 mL) was added to 2,2-dichloro-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-one (1.28 g, 5.64 mmol). Then triethyl phosphite (1.125 g, 6.77 mmol) was added and the reaction mixture was stirred for 18 h at 80 °C. The solvent and an excess of triethyl phosphite was removed under reduce pressure and column chromatography (Hexane/AcOEt 3:1, $R_f = 0.21$) gave 1.353 g (73 %) of the title compound as a yellowish liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.31 (m, 1H), 7.23–7.17 (m, 3H), 4.26–4.16 (m, 4H), 4.10–4.08 (m, 1H), 3.94–3.89 (m, 1H), 3.23–3.18 (m, 1H), 3.01–2.94 (m, 1H), 1.39–1.33 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.7, 140.4 (d, $J = 7.5$ Hz), 140.1, 127.9, 126.7, 126.6, 125.0, 110.5 (d, $J = 11.1$ Hz), 65.1 (dd, $J = 6.1$, 3.0 Hz), 52.7, 47.6 (d, $J = 3.0$ Hz), 30.3, 16.2 (dd, $J = 6.8$, 2.3 Hz). HRMS (APCI) $[M+H]^+$ Calcd for $C_{15}H_{18}ClO_4P$: 329.0704; found: 329.0710.

2-(4-Methoxyphenyl)cyclobutan-1-one (3 a)

GP1 starting from **1 a** (288 mg, 1.0 mmol), 4-methoxyphenylboronic acid (197 mg, 1.3 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), RuPhos (9.3 mg, 0.02 mmol), K_3PO_4 (1.5 mL, 3.0 mmol), CF_3CH_2ONa (367 mg, 3.0 mmol) gave (Hexane/AcOEt 20:1, R_f = 0.26), 136 mg (76 %) yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 4.48 (tt, *J* = 8.2, 2.7 Hz, 1H), 3.79 (s, 3H), 3.22 (dddd, *J* = 17.6, 10.6, 8.3, 2.4 Hz, 1H), 3.01 (dddd, *J* = 17.7, 9.7, 4.9, 2.6 Hz, 1H), 2.52 (dtd, *J* = 11.2, 10.5, 4.9 Hz, 1H), 2.18 (ddt, *J* = 11.2, 9.7, 8.3 Hz, 1H), in accordance with literature.[22a]

2-Phenylcyclobutan-1-one (3 b)

GP1 starting from **1 a** (285 mg, 1.0 mmol), phenylboronic acid (160 mg, 1.3 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), RuPhos (9.3 mg, 0.02 mmol), K_3PO_4 (1.5 mL, 3.0 mmol), CF_3CH_2ONa (367 mg, 3.0 mmol) gave (Hexane/AcOEt 20:1, Rf = 0.26) 115 mg (79 %) of the title compound as an yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.30 (m, 2H), 7.29–7.14 (m, 3H), 4.55 (tt, *J* = 8.3, 2.6 Hz, 1H), 3.24 (dddd, *J* = 17.9, 10.6, 8.3, 2.5 Hz, 1H), 3.04 (dddd, *J* = 17.5, 9.9, 5.1, 2.6 Hz, 1H), 2.55 (qd, *J* = 10.7, 4.9 Hz, 1H), 2.25 (ddt, *J* = 11.3, 9.8, 8.2 Hz, 1H), in accordance with literature.[37]

2-(4-(Diphenylamino)phenyl)cyclobutan-1-one (3 c)

GP1 starting from **1 a** (143 mg, 0.5 mmol), 4-(diphenylamino) phenylboronic acid (188 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), CF_3CH_2ONa (183 mg, 1.5 mmol) gave (Hexane/AcOEt 20:1, R_f = 0.25), 142.0 mg (91 %) of the title compound as an orange oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.20 (m, 6H), 7.12–6.97 (m, 8H), 4.52–4.45 (m, 1H), 3.29–3.16 (m, 1H), 3.09–2.97 (m, 1H), 2.59–2.46 (m, 1H), 2.27–2.14 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 208.5, 147.9, 146.9, 130.8, 129.3, 128.0, 124.4, 124.3, 122.9, 64.3, 44.9, 18.0. HRMS (APCI) $[M+H]^+$ Calcd for $C_{22}H_{19}NO$: 314.1539; found: 314.1541.

2-(p-Tolyl)cyclobutan-1-one (3 d)

GP1 starting from **1 a** (145 mg, 0.5 mmol), 4-tolylboronic acid (88 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), CF_3CH_2ONa (183 mg, 1.5 mmol) gave (Hexane/AcOEt 20:1, R_f = 0.25), 63 mg (77 %) of the title compound as an yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (m, 4H), 4.54–4.47 (m, 1H), 3.28–3.16 (m, 1H), 3.08–2.96 (m, 1H), 2.59–2.46 (m, 1H), 2.33 (s, 3H), 2.29–2.15 (m, 1H), in accordance with literature.[22a]

2-([1,1′-Biphenyl]-4-yl)cyclobutan-1-one (3 e)

GP1 starting from **1 a** (145 mg, 0.5 mmol), 4-biphenylboronic acid (129 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), CF_3CH_2ONa (183 mg, 1.5 mmol) gave (Hexane/AcOEt 20:1, R_f = 0.28), 91 mg (81 %) white solid, mp = 88.5–89.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 4H), 7.47–7.43 (m, 2H), 7.38–7.33 (m, 3H), 4.63–4.57 (m, 1H), 3.32–3.22 (m, 1H), 3.12–3.03 (m, 1H), 2.63–2.54 (m, 1H), 2.34–2.25 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.9, 140.9, 140.1, 135.6, 128.9, 127.5, 127.5, 127.4, 127.2, 64.4, 45.0, 17.8. HRMS (APCI) $[M+H]^+$ Calcd for $C_{16}H_{14}O$: 221.0972; found: 221.0971.

N-(4-(2-Oxocyclobutyl)phenyl)acetamide (3 f)

GP1 starting from **1 a** (144 mg, 0.5 mmol), 4-acetamidophenylboronic acid (116 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), CF_3CH_2ONa (183 mg, 1.5 mmol) gave (Hexane/AcOEt 1:1, R_f = 0.21) 51 mg (50 %) of the title compound as an orange oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (br s, 1H), 7.45–7.43 (m, 2H), 7.17–7.15 (m, 2H), 4.51–4.47 (m, 1H), 3.27–3.17 (m, 1H), 3.06–2.97 (m, 1H), 2.57–2.48 (m, 1H), 2.24–2.14 (m, 1H overlapping with s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 208.2, 168.4, 136.8, 132.3, 127.5, 120.1, 64.0, 44.8, 24.5, 17.8. HRMS (APCI) $[M+H]^+$ Calcd for $C_{12}H_{13}NO_2$: 204.1019; found: 204.1020.

2-(Naphthalen-2-yl)cyclobutan-1-one (3 g)

GP1 starting from **1 a** (144 mg, 0.5 mmol), 2-naphthylboronic acid (112 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), CF_3CH_2ONa (183 mg, 1.5 mmol) gave (Hexane/AcOEt 20:1, R_f = 0.22) 79 mg (80 %) of the title compound as a white solid, mp = 86.0–86.4 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.84–7.79 (m, 3H), 7.71 (s, 1H), 7.48–7.44 (m, 2H), 7.39–7.36 (m, 1H), 4.75–4.68 (m, 1H), 3.36–3.23 (m, 1H), 3.16–3.05 (m, 1H), 2.69–2.57 (m, 1H), 2.43–2.30 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 208.0, 134.1, 133.5, 132.6, 128.5, 127.9, 127.8, 126.4, 125.9, 125.5, 125.5, 64.8, 45.1, 17.9. HRMS (APCI) $[M+H]^+$ Calcd for $C_{14}H_{12}NO$: 197.1507; found: 197.1508.

2-(Thiophen-3-yl)cyclobutan-1-one (3 h)

GP1 starting from **1 a** (146 mg, 0.5 mmol), 3-thienylboronic acid (83 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), CF_3CH_2ONa (183 mg, 1.5 mmol), (Hexane/AcOEt 20:1, R_f = 0.30), 59 mg (75 %) yellowish oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.30 (m, 1H), 7.13–7.11 (m 1H), 7.01–6.99 (m, 1H), 4.58–4.52 (m, 1H), 3.29–3.16 (m, 1H), 3.12–3.00 (m, 1H), 2.61–2.48 (m, 1H), 2.23–2.10 (m, 1H), in accordance with literature.[22a]

2-Cycloheptylidenecyclobutan-1-one (3 i)

GP1 starting from **1 a** (148 mg, 0.5 mmol), CF_3CH_2ONa (183 mg, 1.5 mmol), the reaction was stirred for 2 h at 60 °C, gave (Hexane/AcOEt 30:1, R_f = 0.30) 62 mg (77 %) of the title compound as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.82–2.72 (m, 4H), 2.50–2.44 (m, 2H), 2.29–2.23 (m, 2H), 1.69–1.51 (m, 8H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 199.5, 153.0, 141.6, 42.4, 33.6, 32.6, 30.13, 30.06, 27.5, 26.5, 20.0. HRMS (APCI) $[M+H]^+$ Calcd for $C_{11}H_{16}O$: 165.1274; found: 165.1276.

4-(2-Oxocyclobutyl)benzonitrile (3 j)

GP1 starting from **1 a** (142 mg, 0.5 mmol), 4-cyanophenylboronic acid (96 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), TBAF (1.5 mL, 1.5 mmol), THF (3 mL) gave (Hexane/AcOEt 4:1, R_f = 0.29) 31 mg (36 %) of the title compound as a yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 4.61–4.57 (m, 1H), 3.33–3.23 (m, 1H), 3.09–3.00 (m, 1H), 2.63–2.54 (m, 1H), 2.29–2.20 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 205.8, 141.6, 132.5, 127.8, 118.9, 111.0, 64.1, 45.2, 17.3. HRMS (APCI) $[M+H]^+$ Calcd for $C_{11}H_9NO$: 172.0757; found: 172.0757.

2-(4-Acetylphenyl)cyclobutan-1-one (3 k)

GP1 starting from **1 a** (143 mg, 0.5 mmol), 4-acetylphenylboronic acid (107 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), TBAF (1.5 mL, 1.5 mmol), THF (3 mL) gave (Hexane/AcOEt 4:1, $R_f = 0.31$) 39 mg (41%) of the title compound as a yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94–7.92 (m, 2H), 7.37–7.35 (m, 2H), 4.64–4.59 (m, 1H), 3.33–3.24 (m, 1H), 3.11–3.02 (m, 1H), 2.64–2.54 (m, 1H) overlapping with 2.59 (s, 3H), 2.33–2.24 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 206.6, 197.8, 141.7, 135.9, 128.8, 127.2, 64.4, 45.1, 26.7, 17.4. HRMS (APCI) $[M+H]^+$ Calcd for $C_{12}H_{12}O_2$: 189.0910; found: 189.0910.

2-(4-Fluorophenyl)cyclobutan-1-one (3 l)

GP1 starting from **1 a** (142 mg, 0.5 mmol), 4-fluorophenylboronic acid (91 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), TBAF (1.5 mL, 1.5 mmol), THF (3 mL) gave (Hexane/AcOEt 20:1, $R_f = 0.21$) 36 mg (44%) of the title compound as a yellowish oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.19 (m, 2H), 7.05–6.99 (m, 2H), 4.54–4.48 (m, 1H), 3.31–3.18 (m, 1H), 3.09–2.97 (m, 1H), 2.62–2.49 (m, 1H), 2.26–2.13 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.7, 162.0 (d, J = 245.4 Hz), 132.4 (d, J = 3.1 Hz), 128.6 (d, J = 8.0 Hz), 115.6 (d, J = 21.4 Hz), 63.8, 45.0, 18.0, in accordance with literature.[38] ^{19}F NMR (282 MHz, $CDCl_3$) δ −116.11 (s).

2-(Pyren-1-yl)cyclobutan-1-one (3 m)

GP1 starting from **1 a** (144 mg, 0.5 mmol), 1-pyrenylboronic acid (160 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), TBAF (1.5 mL, 1.5 mmol), THF (3 mL) gave (Hexane/AcOEt 20:1, $R_f = 0.15$) 48 mg (35%) of the title compound as a yellow solid, mp = 116.0–117.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20–8.10 (m, 5H), 8.04–7.99 (m, 4H), 5.47–5.41 (m, 1H), 3.43–3.34 (m, 1H), 3.25–3.16 (m, 1H), 2.86–2.77 (m, 1H), 2.48–2.39 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 208.2, 131.4, 130.9, 130.7, 130.6, 128.5, 127.8, 127.5, 127.3, 126.1, 125.4, 125.2, 125.0, 124.8, 123.9, 123.3, 62.6, 45.0, 19.1. HRMS (APCI) $[M+H]^+$ Calcd for $C_{20}H_{14}O$: 271.1117; found: 271.1118.

2-(Thiophen-2-yl)cyclobutan-1-one (3 n)

GP2 starting from **1 a** (143 mg, 0.5 mmol), 2-thienylzinc(II) chloride (1.35 mL, 0.65 mmol, 0.48 M), $Pd(OAc)_2$ (4.4 mg, 4 mol%, 0.02 mmol), XPhos (19 mg, 8 mol%, 0.04 mmol), THF (3 mL), CF_3CH_2ONa (183 mg, 1.5 mmol), CF_3CH_2OH (1.5 mL), THF (1 mL) gave (Hexane/AcOEt 20:1, $R_f = 0.13$) 44 mg (57%) of the title compound as a yellowish oil. $^1H\{^1H\}$ NMR (300 MHz, $CDCl_3$) δ 7.22–7.20 (m, 1H), 6.99–6.97 (m, 1H), 6.93–6.91 (m, 1H), 4.73–4.66 (m, 1H), 3.32–3.19 (m, 1H), 3.16–3.04 (m, 1H), 2.68–2.56 (m, 1H), 2.27–2.15 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.9, 138.6, 127.2, 124.4, 124.4, 59.8, 45.1, 19.8. HRMS (APCI) $[M+H]^+$ Calcd for C_8H_8OS: 153.0369; found: 153.0370.

2-(1-Methyl-1*H*-indol-2-yl)cyclobutan-1-one (3 o)

GP2 starting from **1 a** (145 mg, 0.5 mmol), (1-methyl-1*H*-indol-2-yl) zinc(II) chloride (1.38 mL, 0.65 mmol, 0.47 M), $Pd(OAc)_2$ (4.4 mg, 4 mol%, 0.02 mmol), XPhos (19 mg, 8 mol%, 0.04 mmol), THF (3 mL), CF_3CH_2ONa (183 mg, 1.5 mmol), CF_3CH_2OH (1.5 mL), THF (1 mL) gave (Hexane/AcOEt 20:1, $R_f = 0.15$) 32 mg (32%) of the title compound as a reddish brown solid mp = 70.0–70.8 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57–7.55 (m, 1H), 7.30–7.28 (m, 1H), 7.21–7.17 (m, 1H), 7.10–7.07 (m, 1H), 6.40 (s, 1H), 4.74–4.70 (m, 1H), 3.75 (s, 3H), 3.33–3.14 (m, 2H), 2.64–2.55 (m, 1H), 2.43–2.31 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 205.2, 138.0, 135.4, 127.6, 121.6, 120.4, 119.6, 109.2, 99.1, 57.9, 45.5, 30.3, 16.7. HRMS (APCI) $[M+H]^+$ Calcd for $C_{13}H_{13}NO$: 200.1070; found: 200.1069.

2-Hexylcyclobutan-1-one (3 p)

GP2 starting from **1 a** (143 mg, 0.5 mmol), hexylzinc(II) chloride (1.58 mL, 0.65 mmol, 0.41 M), $Pd(OAc)_2$ (4.4 mg, 4 mol%, 0.02 mmol), XPhos (19 mg, 8 mol%, 0.04 mmol), THF (3 mL), CF_3CH_2ONa (183 mg, 1.5 mmol), CF_3CH_2OH (1.5 mL), THF (1 mL), the dephosphorylation was stirred for 2 h at 60 °C, gave (Hexane/AcOEt 20:1, $R_f = 0.24$) 49 mg (64%) of the title compound as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 3.32–3.22 (m, 1H), 3.06–2.86 (m, 2H), 2.21–2.12 (m, 1H), 1.72–1.59 (m, 2H), 1.52–1.42 (m, 1H), 1.38–1.20 (m, 8H), 0.89–0.85 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 212.8, 60.8, 44.5, 31.8, 29.7, 29.3, 27.1, 22.7, 17.0, 14.2, in accordance with literature.[22a]

2-Phenethylcyclobutan-1-one (3 q)

GP2 starting from **1 a** (142 mg, 0.5 mmol), phenethylzinc(II) chloride (1.86 mL, 0.65 mmol, 0.35 M), $Pd(OAc)_2$ (4.4 mg, 4 mol%, 0.02 mmol), XPhos (19 mg, 8 mol%, 0.04 mmol), THF (3 mL), CF_3CH_2ONa (183 mg, 1.5 mmol), CF_3CH_2OH (1.5 mL), THF (1 mL), the dephosphorylation was stirred for 2 h at 60 °C, gave (Hexane/AcOEt 20:1, $R_f = 0.32$) 46 mg (53%) of the title compound as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 7.21–7.17 (m, 3H), 3.31–3.24 (m, 1H), 3.08–2.68 (m, 2H), 2.70 (t, J = 7.70 Hz, 2H), 2.22–2.12 (m, 1H), 2.08–1.99 (m, 1H), 1.86–1.76 (m, 1H), 1.70–1.61 (m, 1H), HRMS (APCI) $[M-H]^-$ Calcd for $C_{12}H_{14}NO$: 173.0972; found: 173.0970.

2,2,2-Trifluoroethyl 4-(4-cyanophenyl)butanoate (4 a)

GP3 starting from **1 a** (141 mg, 0.5 mmol), 4-cyanophenylboronic acid (96 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), RuPhos (4.7 mg, 0.01 mmol), K_3PO_4 (0.75 mL, 1.5 mmol), CF_3CH_2ONa (183 mg, 1.5 mmol), CF_3CH_2OH (1.5 mL), THF (1 mL) gave (Hexane/AcOEt 20:1 → 9:1, $R_f = 0.09$) 99 mg (74%) of the title compound as a yellowish liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 4.47 (q, J = 8.5 Hz, 2H), 2.75–2.71 (m, 2H), 2.45 (t, J = 7.3 Hz, 2H), 2.04–1.96 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.5, 146.7, 132.5, 129.4, 123.0 (q, J = 277.3 Hz), 119.1, 110.3, 60.4 (q, J = 36.6 Hz) 35.1, 32.9, 25.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.30 (t, J = 8.4 Hz). HRMS (APCI) $[M+H]^+$ Calcd for $C_{13}H_{12}F_3NO_2$: 272.0893; found: 272.0894.

2,2,2-Trifluoroethyl 4-(4-acetylphenyl)butanoate (4 b)

GP3 starting from **1 a** (142 mg, 0.5 mmol), 4-acetylphenylboronic acid (107 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 1 mol%), RuPhos (4.7 mg, 2 mol%), K_3PO_4 (0.75 mL), toluene (2 mL), CF_3CH_2ONa (183 mg, 1.5 mmol), CF_3CH_2OH (1.5 mL), THF (1 mL) gave (Hexane/AcOEt 20:1→9:1, $R_f = 0.08$) 110 mg (79%) of the title compound as a yellowish liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–7.82 (m, 1H), 7.28–7.26 (m, 1H), 4.60–4.37 (m, 1H), 2.78–2.70 (m, 1H), 2.59 (s, 1H), 2.44 (t, J = 7.4 Hz, 1H), 2.10–1.94 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.9, 171.7, 146.8, 135.5, 128.8, 128.8, 123.1 (q, J = 277.2 Hz), 60.4 (q, J = 36.5 Hz), 35.0, 32.9, 26.7, 26.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.29 (t, J = 8.5 Hz). HRMS (APCI) $[M+H]^+$ Calcd for $C_{14}H_{15}F_3O_3$: 289.1046; found: 289.1047.

Methyl 4-(4-cyanophenyl)butanoate (4c)

A solution of sodium methoxide (1.5 mL, 1.5 mmol, 1 M in MeOH) was added to a solution of 2-(4-cyanophenyl)cyclobut-1-en-1-yl diethyl phosphate (**2b**) (146 mg, 0.5 mmol) in dry THF (6 mL/1 mmol) and the resultant mixture was stirred for 1 h at 23 °C. Then the reaction mixture was diluted with ether (30 mL), washed with water (20 mL) and brine (20 mL) and the organic layer was dried over $MgSO_4$. The solvents were evaporated under reduce pressure and column chromatography (Hexane/AcOEt 9:1, R_f = 0.23) gave 71 mg (79%) of the title compound as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.56 (m, 2H), 7.30–7.27 (m, 2H), 3.67 (s, 3H), 2.74–2.69 (m, 2H), 2.36–2.31 (m, 2H), 2.01–1.91 (m, 2H), in accordance with literature.[39]

2,2,2-Trifluoroethyl 1-(4-cyanobenzyl)-2,3-dihydro-1H-indene-2-carboxylate (4d)

GP3 starting from **1b** (157 mg, 0.5 mmol), 4-cyanophenylboronic acid (96 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 1 mol%), RuPhos (4.7 mg, 2 mol%), K_3PO_4 (0.75 mL), toluene (2 mL), CF_3CH_2ONa (183 mg, 1.5 mmol), CF_3CH_2OH (1.5 mL), THF (1 mL) gave (Hexane/AcOEt 9:1, R_f = 0.40) 130 mg (76%) of the title compound as a white solid, mp = 90.5–91.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.53 (m, 2H), 7.26–7.16 (m, 2H), 7.11–7.08 (m, 2H), 7.02–6.98 (m, 1H), 6.40–6.38 (m, 1H), 4.59–4.42 (m, 2H), 3.77–3.71 (m, 1H), 3.64–3.57 (m, 1H), 3.43–3.36 (m, 1H), 3.11–3.05 (m, 1H), 3.00–2.95 (m, 1H), 2.68–2.63 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.6, 144.9, 143.1, 140.6, 132.1, 130.5, 127.7, 126.3, 124.9, 124.8, 123.1 (d, *J* = 277.1 Hz), 119.0, 110.4, 60.4 (q, *J* = 36.5 Hz), 48.5, 48.1, 37.2, 33.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.99 (t, *J* = 8.6 Hz). HRMS (APCI) $[M+H]^+$ Calcd for $C_{20}H_{16}F_3NO_2$: 360.1206; found: 360.1213.

2,2,2-Trifluoroethyl 4-(pyren-1-yl)butanoate (4e)

GP3 starting from **1a** (145 mg, 0.5 mmol), 1-pyrenylboronic acid (150 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 1 mol%), RuPhos (4.7 mg, 2 mol%), K_3PO_4 (0.75 mL), toluene (2 mL), CF_3CH_2ONa (183 mg, 1.5 mmol), CF_3CH_2OH (1.5 mL), THF (1 mL) gave (Hexane/AcOEt 20:1, R_f = 0.18) 133 mg (71%) of the title compound as a yellow solid, mp = 98.3–99.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29–8.27 (m, 1H), 8.20–8.11 (m, 4H), 8.04–7.99 (m, 3H), 7.86–7.84 (m, 1H), 4.51 (q, *J* = 8.5 Hz, 1H), 3.42–3.38 (m, 2H), 2.56 (t, *J* = 7.2 Hz, 1H), 2.27–2.20 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.0, 135.3, 131.5, 131.0, 130.2, 128.9, 127.6, 127.6, 127.5, 126.9, 126.0, 125.2, 125.1, 125.1, 125.0, 125.0, 123.3, 120.4 (q, *J* = 277.6 Hz), 119.0, 60.4 (q, *J* = 36.5 Hz), 33.3, 32.7, 26.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.24 (t, *J* = 8.5 Hz). HRMS (APCI) $[M+H]^+$ Calcd for $C_{22}H_{17}F_3O_2$: 371.1253; found: 371.1256.

2,2,2-Trifluoroethyl 4-(benzo[b]thiophen-2-yl)butanoate (4f)

GP3 starting from **1a** (143 mg, 0.5 mmol), $Pd(OAc)_2$ (4.5 mg, 1 mol%, 0.02 mmol), XPhos (19 mg, 8 mol%, 0.04 mmol), benzothiophen-2-ylzinc(II) chloride (1.67 mL, 0.65 mmol, 0.39 M), THF (3 mL), CF_3CH_2ONa (183 mg, 1.5 mmol), CF_3CH_2OH (1.5 mL), THF (1 mL) gave (Hexane/AcOEt 20:1, R_f = 0.28) 74 mg (49%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.34–7.25 (m, 2H), 7.03 (s, 1H), 4.47 (q, *J* = 8.4 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 2.51 (t, *J* = 7.4 Hz, 2H), 2.15–2.08 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.7, 144.67, 140.2, 139.5, 124.3, 123.8, 123.0, 122.3, 121.5, 60.4 (q, *J* = 36.5 Hz), 32.7, 29.9, 26.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.30 (t, *J* = 8.4 Hz). HRMS (APCI) $[M+H]^+$ Calcd for $C_{14}H_{13}F_3O_3S$: 319.0610; found: 319.0614.

4-(4-Morpholino-4-oxobutyl)benzonitrile (4g)

GP4 starting from phosphate **2b** (95 mg, 0.3 mmol), CF_3CH_2ONa (113 mg, 0.93 mmol), CF_3CH_2OH (0.9 mL), morpholine (81 mg, 0.93 mmol) and THF (1 mL) gave (Hexane/AcOEt 2:1, R_f = 0.17) 48 mg (60%) of the title compound as a white solid, mp = 55.0–56.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.53 (m, 2H), 7.29–7.27 (m, 2H), 3.65–3.57 (mm, 6H), 3.40–3.37 (m, 2H), 2.73–2.70 (m, 2H), 2.32–2.28 (m, 2H), 2.00–1.91 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 147.5, 132.3, 129.3, 119.1, 109.9, 66.9, 66.6, 45.9, 42.0, 35.4, 31.9, 26.0. HRMS (APCI) $[M+H]^+$ Calcd for $C_{15}H_{18}N_2O_2$: 259.1441; found: 259.1444.

N-Benzyl-4-(4-cyanophenyl)butanamide (4h)

GP4 starting from phosphate **2b** (140 mg, 0.5 mmol), CF_3CH_2ONa (183 mg, 1.5 mmol), CF_3CH_2OH (1.5 mL), benzylamine (161 mg, 1.5 mmol) and THF (2.0 mL) gave (Hexane/AcOEt 2:1→1:2, R_f = 0.12) 99 mg (78%) of the title compound as a white solid, mp = 103.0–103.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.53 (m, 2H), 7.35–7.25 (m, 7H), 5.82 (brs, 1H), 4.42 (d, *J* = 5.7 Hz, 1H), 2.71 (t, *J* = 7.7 Hz, 1H), 2.21 (t, *J* = 7.4 Hz, 1H), 2.03–1.96 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.0, 147.4, 138.3, 132.3, 129.4, 128.9, 128.0, 127.7, 119.1, 110.0, 43.7, 35.6, 35.4, 26.6. HRMS (APCI) $[M - H]^-$ Calcd for $C_{18}H_{18}N_2O$: 277.1346; found: 277.1347.

4-(2-(Butylthio)cyclobut-1-en-1-yl)benzonitrile (5a)

GP5 starting from **1a** (141 mg, 0.5 mmol), 4-cyanophenylboronic acid (96 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 1 mol%), RuPhos (4.7 mg, 2 mol%), K_3PO_4 (0.75 mL), toluene (2 mL), NaH (60 mg, 1.5 mmol), 1-butanethiol (270 mg, 3.0 mmol), THF (2 mL) gave (Hexane/AcOEt 20:1, R_f = 0.43) 108 mg (90%) of the title compound as a yellow solid, mp = 50.5–51.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.57 (m, 2H), 7.39–7.36 (m, 2H), 2.88–2.72 (m, 6H), 1.70–1.62 (m, 2H), 1.50–1.41 (m, 2H), 0.96–0.92 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 139.2, 138.8, 135.4, 132.3, 125.5, 119.6, 108.9, 33.0, 31.4, 29.9, 26.1, 21.9, 13.8. HRMS (APCI) $[M+H]^+$ Calcd for $C_{15}H_{17}NS$: 244.1155; found: 244.1160.

Butyl(2-(pyren-1-yl)cyclobut-1-en-1-yl)sulfane (5b)

GP5 starting from **1a** (145 mg, 0.5 mmol), 1-pyrenylboronic acid (160 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 1 mol%), RuPhos (4.7 mg, 2 mol%), K_3PO_4 (0.75 mL), toluene (2 mL), NaH (60 mg, 1.5 mmol), 1-butanethiol (270 mg, 3.0 mmol), THF (2 mL) gave (Hexane→hexane/DCM 15:1, R_f = 0.18) 98 mg (57%) of the title compound as a yellow solid, mp = 113.8–114.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56–8.53 (m, 1H), 8.17–7.97 (m, 8H), 3.32–3.30 (m, 2H), 2.94–2.92 (m, 2H), 2.85 (t, *J* = 7.3 Hz, 1H), 1.70–1.67 (m, 2H), 1.47–1.42 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.4, 135.2, 131.6, 131.1, 130.6, 130.2, 127.8, 127.5, 127.2, 127.1, 126.0, 125.6, 125.2, 125.12, 125.05, 124.82, 124.80, 32.9, 31.2, 31.2, 30.7, 22.0, 13.8. HRMS (APCI) $[M+H]^+$ Calcd for $C_{24}H_{22}S$: 343.1515; found: 343.1519.

1-(4-(2-(Butylthio)cyclobut-1-en-1-yl)phenyl)ethan-1-one (5c)

GP5 starting from **1a** (143 mg, 0.5 mmol), 4-acetylphenylboronic acid (107 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 1 mol%), RuPhos (4.7 mg, 2 mol%), K_3PO_4 (0.75 mL), toluene (2 mL), NaH (60 mg, 1.5 mmol), 1-butanethiol (270 mg, 3.0 mmol), THF (2 mL) gave (Hexane/AcOEt 20:1, R_f = 0.39) 109 mg (83%) of the title compound as a yellow solid, mp = 34.2–35.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 2.87–2.83 (m, 2H),

2.78–2.75 (m, 4H), 2.57 (s, 3H), 1.70–1.63 (m, 2H), 1.50–1.41 (m, 2H), 0.94 (t, $J=7.3$ Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.6, 139.5, 137.2, 136.2, 134.5, 128.7, 125.1, 33.0, 31.3, 29.8, 26.7, 26.2, 21.9, 13.8. HRMS (APCI) $[M+H]^+$ Calcd for $C_{16}H_{20}OS$: 261.1308; found: 261.1314.

4-(2-(Benzylthio)cyclobut-1-en-1-yl)benzonitrile (5 d)

GP5 starting from **1 a** (142 mg, 0.5 mmol), 4-cyanophenylboronic acid (96 mg, 0.65 mmol), $Pd(OAc)_2$ (1.2 mg, 1 mol%), RuPhos (4.7 mg, 2 mol%), K_3PO_4 (0.75 mL), toluene (2 mL), NaH (60 mg, 1.5 mmol), 1-butanethiol (270 mg, 3.0 mmol), THF (2 mL) gave (Hexane/AcOEt 20:1, $R_f=0.29$) 131 mg (95%) of the title compound as a yellow solid, mp = 96.0–97.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58–7.55 (m, 2H), 7.40–7.26 (m, 7H), 4.11 (s, 2H), 2.78–2.77 (m, 2H), 2.73–2.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 137.7, 137.4, 135.8, 132.2, 128.8, 128.7, 127.5, 125.5, 119.4, 109.0, 36.0, 30.3, 26.3. HRMS (APCI) $[M+H]^+$ Calcd for $C_{18}H_{15}NS$: 278.0998; found: 278.1002.

4-(2-(Phenylthio)cyclobut-1-en-1-yl)benzonitrile (5 e)

Thiophenol (330 mg, 3.0 mmol) was added to a suspension of NaH (60 mg, 1.5 mmol) in dry THF (4 mL/mmol) cooled to 0 °C. The resultant mixture was stirred for 30 min at 23 °C followed by addition of a solution of phosphate **2 b** (144 mg, 0.5 mmol) in THF (2 mL/1 mmol) and the reaction mixture was stirred for 3 h at 23 °C. The crude mixture was diluted with ether (30 mL/1 mmol), washed with water (10 mL/1 mmol) and brine (10 mL/1 mmol) and the organic layer was dried over $MgSO_4$. The solvents were removed under reduce pressure and column chromatography (Hexane/AcOEt 20:1, $R_f=0.37$) gave 25 mg (20%) of the title compound as a yellow solid, mp = 134.7–136.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.61 (m, 2H), 7.51–7.47 (m, 4H), 7.39–7.35 (m, 3H), 2.75–2.74 (m, 2H), 2.55–2.54 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.8, 138.2, 136.2, 133.1, 132.4, 131.1, 129.3, 128.5, 125.9, 119.4, 109.7, 30.4, 26.3. HRMS (APCI) $[M+H]^+$ Calcd for $C_{17}H_{13}NS$: 264.0842; found: 264.0843.

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Conflict of Interest

The authors declare no conflict of interest.

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