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Note

Transferring Substituents from Alkynes to Furans and Pyrroles through Heteronorbornadienes as Intermediates: Synthesis of β-Substituted Pyrroles/Furans

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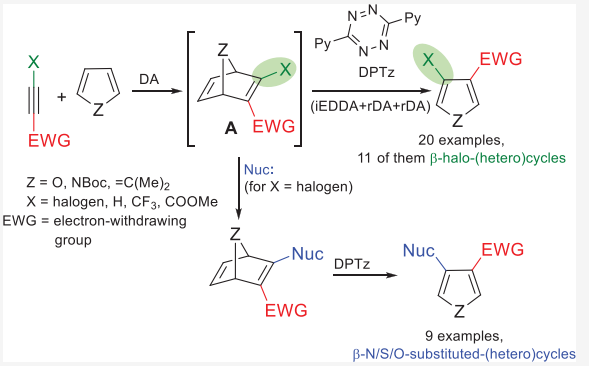
ABSTRACT: The use of 7-oxa/azanorbornadienes as synthetic intermediates for the preparation of 3/4-substituted (β-substituted) furans/pyrroles is presented. The method lies in the inverse electron demand Diels−Alder (iEDDA) cycloaddition between a substituted heteronorbornadiene and an electron-poor tetrazine followed by spontaneous fragmentation of the resulting cycloadduct *via* two retro-Diels−Alder (rDA) reactions affording a β-substituted furan/pyrrole. The scope of this tandem iEDDA/rDA/rDA reaction was explored in the preparation of 29 heterocycles. A one-pot procedure starting directly from the alkyne precursors of the heteronorbornadiene intermediates is also described.



Furan and pyrrole are two of the most representative five-membered heterocycles. Both structural motifs are ubiquitously present in natural products or pharmaceuticals with high biological activity[1] and compounds of significance for material sciences.[2] Both heterocycles can incorporate up to four substituents (five in the case of *N*-substituted pyrroles), however, the most challenging substitution pattern is 3,4-disubstitution (β-substitution).[3] In fact, the regioselective synthesis of β-substituted furans/pyrroles continues to attract the attention of researchers in the last years.[4] Classic syntheses of furan and pyrrole derivatives from acyclic carbonyl precursors, such as Paal-Knorr, Feist-Benary, and Hantzsch procedures, among others, generally work best for fully substituted heterocycles or for 2,5-disubstituted systems.[3a,5] Procedures based on the electrophilic aromatic substitution of preformed heterocycles are not a good alternative for the 3,4-substituted derivatives as C-2 is usually much more reactive toward electrophiles.[6] Moreover, lithiation of furans or *N*-protected pyrroles also occurs preferentially at C-2 and C-5.[7] We have recently reported the tandem regioselective 1,3-dipolar cycloaddition and subsequent retro-Diels−Alder reaction between organic azides and 7-heteronorbornadienes (Scheme 1a).[4b] This procedure allowed us to carry out efficiently the preparation of a small library of 3,4-disubstituted heterocycles. The regioselectivity of the 1,3-cycloaddition was controlled by tuning the electronic density of the electron-poor double bond using the adequate substituents (R^1 and R^2) on the heteronorbornadiene.

As part of our program for the use of heteronorbornadienic systems in the selective modification of proteins, we have recently found that the treatment of an azanorbornadiene-modified protein with the electron-deficient 3,6-di(2-pyridyl)-*s*-tetrazine (DPTz) afforded the β-substituted pyrrole-modified protein (Scheme 1b) under mild conditions and with total regioselectivity.[8] This transformation took place through a three-step cascade reaction: (i) ligation between a tetrazine and the available electron-rich alkene of the azanorbornadiene system through an inverse electron demand Diels−Alder (iEDDA) cycloaddition; (ii) first retro-Diels−Alder reaction (rDA) with extrusion of N_2; (iii) second rDA with extrusion of 3,6-dipyridyl pyridazine. A similar reaction had been previously used by Warrener and co-workers for the preparation of isoindoles and isobenzofurans by reaction of heterobenzonorbornadienes with DPTz.[9] The procedure was also exploited for the preparation of substituted cyclopentadienes from norbornadiene derivatives, however, the inherent instability of the resulting cyclopentadienes complicated their characterization.[10]

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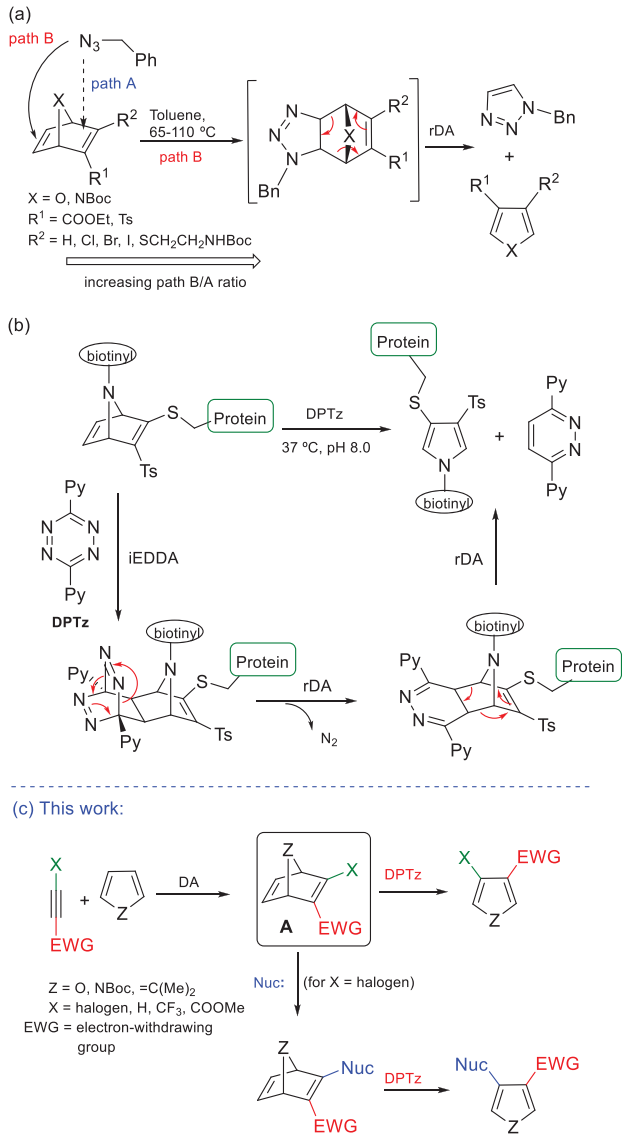
Scheme 1. Our Previous Work on the Synthesis of β-Substituted Pyrroles/Furans through Heteronorbornadienic Intermediates and the New Proposal



With these results in hand, in this work we envisaged that heteronorbornadienes of type **A** could be versatile substrates for the preparation of β-substituted(halo) pyrroles/furans (Scheme 1c). Bicyclic systems **A** contain an electron-poor and an electron-rich double bond, being the latter the only one able to react in the initial iEDDA that guarantees the regioselectivity of the process. Heteronorbornadienes of type **A** can be easily prepared from the adequate electron-deficient alkyne and furan/pyrrole via Diels–Alder (DA) cycloaddition. All together this strategy implies the transfer of the substituents of the activated alkyne (X and EWG) to the furan or pyrrole skeleton. When X = halogen, valued β-halopyrroles/furans are the resulting products. These compounds have special interest as direct precursors of metalated heterocycles that are excellent synthetic intermediates in C–C and C–S bond forming reactions.[7,11] Moreover, halo-pyrroles/furans are also employed in C–N bond formation as they are substrates for the palladium-catalyzed amination.[12] Additionally, the functionalization of halo-heteronorbornadienes of type **A** will be also explored in order to expand the scope of this methodology.

Most (hetero)norbornadienes were prepared by DA cycloaddition between furan/*N*-Boc-pyrrole and activated alkynes (commercial or synthetically achievable) as it was reported in previous works.[13] Bicyclic bromovinyl phosphonates **9j–9m** were prepared here for the first time. With this (hetero)norbornadienic substrates in hand, we decided to explore the tandem iEDDA/rDA/rDA by reaction with DPTz as it is shown in Scheme 2 (Procedure A). Additionally, in order to simplify the experimental procedure, two additional approaches were assayed in selected cases: (i) reaction of the alkyne with a mixture of the cyclic diene and DPTz (Procedure B, only used when the heteronorbornadienes are efficiently obtained under mild conditions); (ii) synthesis of the heteronorbornadienic intermediate and subsequent addition of the tetrazine in one-pot (Procedure C).

In general, all the five-membered heterocycles (and carbacycle **10t**) were obtained in excellent yields under mild conditions (25–45 °C) following the procedure A. Furan **10d**, **10f**, and **10h** were obtained in moderate-to-good yields using the procedure B. The procedure B could not be used in the synthesis of pyrrole derivatives because the Diels–Alder that leads to the formation of the azanorbornadienic intermediates requires higher temperature (~90 °C) than for the oxa-analogues and, unfortunately, DPTz was unstable at this temperature. The procedure C was successfully assayed for the synthesis of pyrrole derivative **10q** and oxa-analogues **10b–10d**. It is important to highlight that the iEDDA reaction was totally regioselective, in contrast to the 1,3-dipolar cycloaddition of our previous strategy (Scheme 1a) where the regioselectivity was highly dependent on the substituents of the heteronorbornadiene. In addition, as the temperature required for the new experiments is lower than the one required for our previous strategy,[4b] no Boc deprotection was observed for *N*-Boc pyrrole derivatives.[14]

Then we decided to exploit the presence of the halogen into the heteronorbornadienic system in order to increase the scope of the methodology. Thus, the bromo-azabicyclic system **9o**, that we had previously used for the modification of proteins,[8] was first selected to explore the thio-functionalization of the C2 position. As expected, this compound reacted efficiently with *N*-Boc cysteamine under mild conditions (Scheme 3); a similar behavior was observed for the reaction of the oxa-analogues **9b,j,k** and carba-analogue **9t** with *N*-acetylcysteamine. The resulting thiovinyl sulfones/phosphonates **12-16** were isolated and subsequently made to react with DPTz under mild conditions affording β-thio(hetero)cycles **17-21** in excellent yields. Next, we explored the incorporation of *N*- and *O*-based nucleophiles (Scheme 4). Thus, bicyclic systems **9b** and **9o** reacted with diethylamine in the presence of triethylamine in a fast and clean reaction. The resulting enamines were not isolated and reacted with DPTz in a one-pot procedure furnishing the corresponding β-aminoheterocycles **22** and **23** in 46 and 51% yield (two steps), respectively. Following a similar strategy, the pyridinum salt **24** was also prepared from oxanorbornadiene **9b**, as the bromovinyl sulfone functionality is electrophilic enough to accept the attack of pyridine. Finally, the introduction of oxygenated nucleophiles was first attempted with oxabicyclic bromovinyl sulfone **9b**, using MeOH in the presence of DBU. However, besides the nucleophilic substitution, the conjugate addition also took place, affording undesired ketal **25** in excellent yield.

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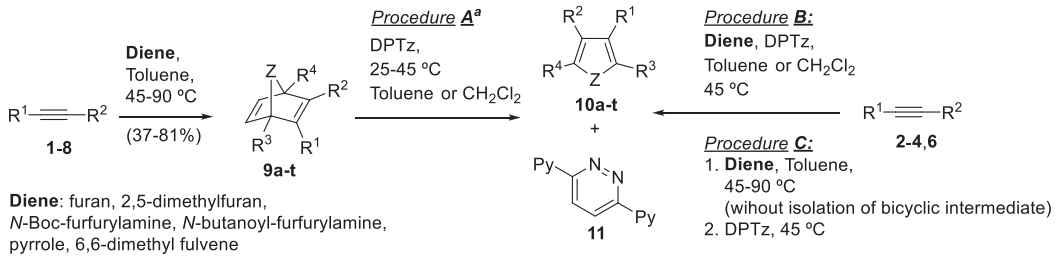
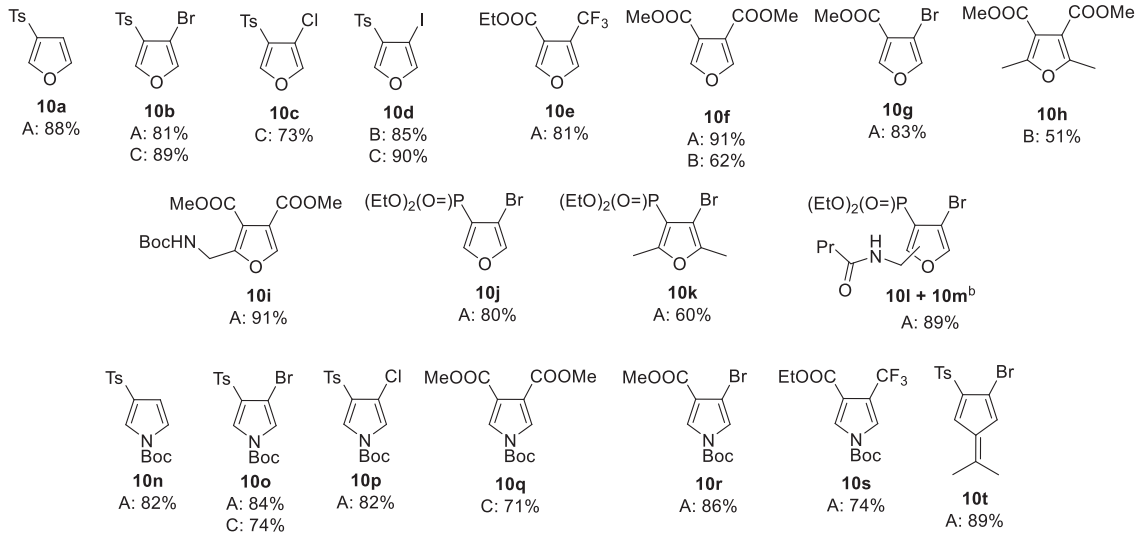
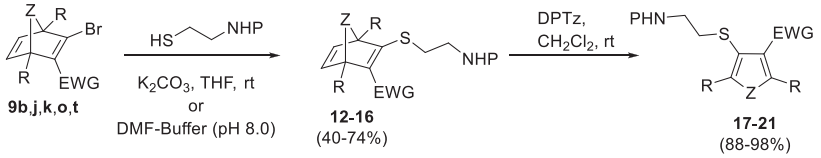
Scheme 2. Synthesis of β-Substituted Furans/Pyrroles/Fulvenes via (Hetero)norbornadiene Intermediates[a,b]





[a]Yields corresponding to Procedure A are referred exclusively to the iEDDA/rDA/rDA step from pure heteronorbornadienes **9a-t**. [b]Regioisomers **10l** and **10m**, obtained from a regioisomeric mixture of oxanorbornadienes **9l** and **9m**, could be separated.

Scheme 3. Thio-functionalization of (Hetero)norbornadienes 9b,j,k,o,t at C2 Position: Synthesis of β-Thio-heterocycles



9b,**12**,**17**; Z = O, EWG = Ts, P = Ac, R = H
9o,**13**,**18**; Z = NBoc, EWG = Ts, P = Boc, R = H
9k,**14**,**19**; Z = C=C(Me)$_2$, EWG = Ts, P = Ac, R = H
9j,**15**,**20**; Z = O, EWG = P(=O)(OEt)$_2$, P = Ac, R = H
9t,**16**,**21**; Z = O, EWG = P(=O)(OEt)$_2$, P = Ac, R = Me

Replacement of the tosyl electron-withdrawing group by a diethyl phosphonate decreased the reactivity of the oxanorbornadiene system and enol ether derivative **26** was obtained under the same reaction conditions. Treatment of **26** wih DPTz afforded the corresponding β-methoxyfuran **27**.

CONCLUSIONS

In summary, we have demonstrated that differently functionalized heteronorbornadienes react with an electron-poor tetrazine through a tandem iEDDA/rDA/rDA sequence affording β-substituted furans/pyrroles in excellent yields. As the heteronorbornadienes are prepared *via* DA reaction between electron-poor alkynes and cyclic dienes, the resulting bicyclic adducts always contain two double bonds with very different electronic density, that guarantees the total regioselectivity in the further iEDDA with the electron-poor tetrazine. The halovinyl sulfone/ester/phosphonate embedded in the bicyclic system allows the easy functionalization of the structure, expanding the scope of the methodology. When the initial DA reaction that leads to the heteronorbornadienes is feasible under mild conditions, the tandem process can be extended (DA/iEDDA/rDA/rDA) thus simplifying the experimental to a unique step. Altogether, the one-pot or the step-by-step procedure, allows the transfer of the substituents of the starting activated alkyne into the β-positions of a furan or pyrrole. The presence of a halogen on the activated alkyne offers an added value to the strategy given that the halovinyl sulfone embedded into the bicycle can easily accept the attack of different nucleophiles expanding the scope of β-substituents on the final heterocycle. This methodology constitutes one of the very few examples reported for the preparation of synthetically valuable β-halopyrroles/furans.

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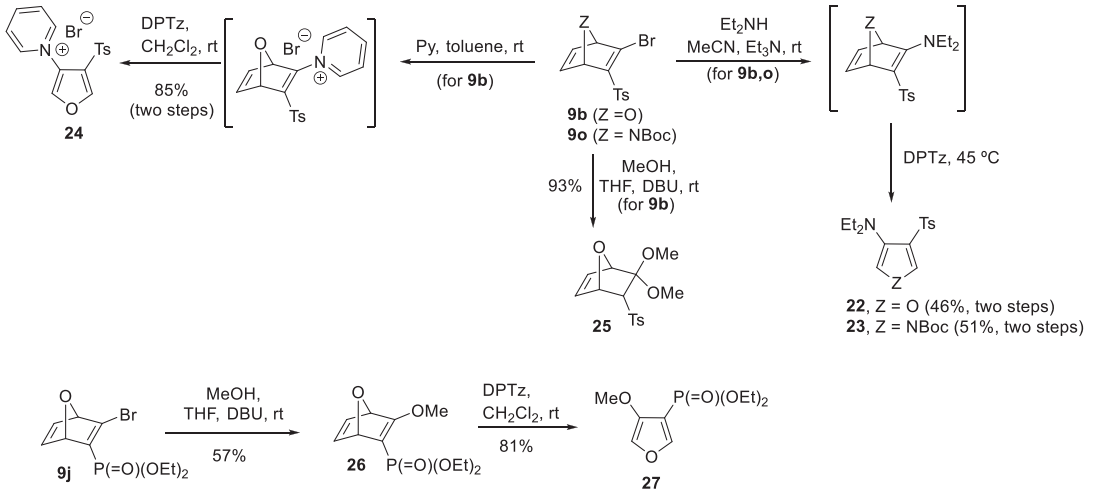
Scheme 4. *N*/*O*-Functionalization of (Hetero)norbornadienes 9b,j,o at C2 Position: Synthesis of *β*-Amino/pyridinium/alkoxy-heterocycles



EXPERIMENTAL SECTION

General Methods. ^{1}H- and ^{13}C NMR spectra were recorded with a Bruker AMX300 spectrometer for solutions in $CDCl_3$ and CD_3OD. δ are given in ppm and J in Hz. Chemical shifts are calibrated using residual solvent signals. High resolution mass spectra were recorded on a Q-exactive-quadrupole mass spectrometer. TLC was performed on silica gel 60 F_{254} (Merck), with detection by UV light charring with *p*-anisaldehyde, $KMnO_4$, ninhydrin, phosphomolybdic acid, or with reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Purification by silica gel chromatography was carried out using either hand-packed glass columns (Silica gel 60 Merck, 40−60 and 63−200 μm) or Puriflash XS520 Plus Interchim system with prepacked cartridges.

Synthesis of *β*-Substituted Furans/Pyrroles/Fulvene Derivatives 10a−t, 17−24, and 27. *General Procedure A.* To a solution of the corresponding 7-heteronorbornadiene (0.083 M) in the indicated solvent (3 mL/0.25 mmol) for each case (see Supporting Information, SI), 3,6-di-2-pyridyl-1,2,4,5-tetrazine (DPTz) (0.28−0.50 mmol, 1.1−2.0 equiv) was added. The reaction was vigorously stirred at 25−45 °C for the time indicated (5−24 h). Then, the solvent was removed under reduced pressure and purified by column chromatography on silica gel to afford the targeted furan/*N*-Boc-pyrrole derivatives.

General Procedure B. To a solution of the corresponding alkyne derivative (0.083 M) and furan or 2,5-dimethylfuran (3.0 mmol, 12 equiv) in the indicated solvent (3 mL/0.25 mmol of alkyne) for each case (see SI), DPTz (0.28−0.50 mmol, 1.1−2.0 equiv) was added. The reaction was vigorously stirred at 45 °C for 1−2 d. Then, the solvent was removed under reduced pressure and purified by column chromatography on silica gel to afford the targeted furan derivatives.

General Procedure C. A solution of the corresponding alkyne derivative (0.083 M) and furan/*N*-Boc-pyrrole (3.0 mmol, 12 equiv) in the indicated solvent (3 mL/0.25 mmol of alkyne) for each case, was vigorously stirred at 45 °C overnight. Then, DPTz (0.28−0.50 mmol, 1.1−2.0 equiv) was added, and the mixture stirred at 25−45 °C for 10−24 h. After that, the solvent was removed under reduced pressure and purified by column chromatography on silica gel to afford the targeted furan/*N*-Boc-pyrrole derivatives.

3-Tosylfuran (10a).[4b] General procedure A was followed starting from **9a** (75 mg, 0.30 mmol) and DPTz (78 mg, 0.33 mmol) in toluene (3 mL) for 5 h at r.t. Purification by column chromatography (EtOAc:Cy, 1:4 → 1:1), afforded **10a** (59 mg, 0.27 mmol, 88%, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.97−7.96 (m, 1H), 7.84−7,81 (m, 2H), 7.42−7.41 (m, 1H), 7.32−7.29 (m, 2H), 6.58−6.57 (m, 1H), 2.42 (s, 3H).

3-Bromo-4-tosylfuran (10b).[4b] General procedure A was followed starting from **9b** (75 mg, 0.23 mmol) and DPTz (108 mg, 0.46 mmol) in toluene (3 mL) for 18 h at r.t. Purification by flash automated chromatography (EtOAc:Cy, 1:24 → 5:3), afforded **10b** (56 mg, 0.19 mmol, 81%, white solid).

General procedure C was followed starting from **2** (60 mg, 0.23 mmol) and furan (0.2 mL, 2.8 mmol) in toluene (3 mL) for 1 d at 45 °C (oil bath). Then, DPTz (109 mg, 0.461 mmol) was added, stirring at r.t. for 15 h. Purification by column chromatography (EtOAc:Cy 1:8 → 1:3), afforded **10b** (62 mg, 0.21 mmol, 89%, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 8.06 (d, 1H, $J_{H,H}$ = 1.8), 7.92−7.89 (m, 2H), 7.44 (d, 1H, $J_{H,H}$ = 1.8), 7.34−7.31 (m, 2H), 2.42 (s, 3H).

3-Chloro-4-tosylfuran (10c).[4b] General procedure C was followed starting from **3** (50 mg, 0.23 mmol) and furan (0.2 mL, 2.8 mmol) in toluene (3 mL) for 20 h at 45 °C (oil bath). Then, DPTz (110 mg, 0.465 mmol) was added, stirring at r.t. for 19 h. Purification by column chromatography (EtOAc:Cy, 1:10 → 1:1), afforded **10c** (43 mg, 0.17 mmol, 73%, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 8.04 (d, 1H, $J_{H,H}$ = 1.9), 7.92−7.89 (m, 2H), 7.43 (d, 1H, $J_{H,H}$ = 1.9), 7.34−7.32 (m, 2H), 2.43 (s, 3H).

3-Iodo-4-tosylfuran (10d).[4b] General procedure B was followed starting from **4** (75 mg, 0.24 mmol), furan (0.2 mL, 2.8 mmol) and DPTz (116 mg, 0.490 mmol) in toluene (3 mL) for 2 d at 45 °C (oil bath) in a pressure tube. Purification by column chromatography (Et_2O:Cy, 1:4 → 2:1), afforded **10d** (70 mg, 0.204 mmol, 85%, white solid).[15]

General procedure C was followed starting from 4 (77 mg, 0.25 mmol) and furan (0.420 mL, 6.0 mmol) in toluene (3 mL) for 1 d at 45 °C (oil bath). Then, DPTz (90 mg, 0.38 mmol) was added, stirring at r.t. for 17 h. Purification by column chromatography (DCM: Cy 2:1), afforded **10d** (79 mg, 0.23 mmol, 90%, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 8.08 (d, 1H, $J_{H,H}$ = 1.8), 7.94−7.91 (m, 2H), 7.43 (d, 1H, $J_{H,H}$ = 1.8), 7.34−7.31 (m, 2H), 2.43 (s, 3H).

Ethyl 4-(Trifluoromethyl)furan-3-carboxylate (10e).[13c,16] General procedure A was followed starting from **9e** (54 mg, 0.23 mmol) and DPTz (109 mg, 0.461 mmol) in DCM (3 mL) for 6 h at r.t. Purification by column chromatography (DCM:*n*-pentane, 1:1), afforded **10e** (39 mg, 0.19 mmol, 81%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 8.06−8.05 (m, 1H), 7.79−7.78 (m, 1H), 4.33 (q, 2H, $J_{H,H}$ = 7.1), 1.35 (t, 3H, $J_{H,H}$ = 7.1).

Dimethyl Furan-3,4-dicarboxylate (10f).[17] General procedure A was followed starting from **9f** (75 mg, 0.36 mmol) and DPTz (93 mg, 0.39 mmol) in toluene (3 mL) for 10 h at r.t. Purification by flash automated chromatography (Et_2O:Cy 1:10 → 9:1), afforded **10f** (60 mg, 0.32 mmol, 91%, white solid).

General procedure B was followed starting from **6** (40 mg, 0.28 mmol), furan (0.24 mL, 3.36 mmol) and DPTz (133 mg, 0.563 mmol) in toluene (3 mL) for 22 h at 45 °C (oil bath) in a pressure

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J. Org. Chem. 2023, 88, 13331−13338

tube. Purification by column chromatography (Et_2O:Cy, 1:2 → 2:1) afforded **10f** (32 mg, 0.17 mmol, 62%, white solid). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.93 (s, 2H), 3.84 (s, 6H).

Methyl 4-Bromofuran-3-carboxylate (10g).[4b] General procedure A was followed starting from **9g** (98 mg, 0.42 mmol) and DPTz (130 mg, 0.550 mmol) in DCM (3 mL) for 1 d at r.t. Purification by column chromatography (Et_2O:*n*-pentane, 1:2), afforded **10g** (72 mg, 0.35 mmol, 83%, white solid). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.97 (d, 1H, $J_{H,H}$ = 1.9), 7.46 (d, 1H, $J_{H,H}$ = 1.9), 3.85 (s, 3H).

Dimethyl 2,5-dimethylfuran-3,4-dicarboxylate (10h).[18] General procedure B was followed starting from **6** (50 mg, 0.35 mmol), 2,5-dimethylfuran (0.2 mL, 1.8 mmol) and DPTz (108 mg, 0.457 mmol) in DCM (3 mL)) for 18 h at 45 °C (oil bath) in a pressure tube. Purification by column chromatography (Et_2O:*n*-pentane, 1:3), afforded **10h** (38 mg, 0.18 mmol, 51%, yellowish oil). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 3.75 (s, 6H), 2.36 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 164.0, 155.8, 113.4, 51.7, 13.1. HRESIMS m/z: found, 235.0576; calcd. for $C_{10}H_{12}O_5Na$ $[M + Na]^+$, 235.0577.

Dimethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)furan-3,4-dicarboxylate (10i). General procedure A was followed starting from **9i** (100 mg, 0.29 mmol) and DPTz (91 mg, 0.38 mmol) in DCM (3 mL) for 1 d at r.t. Purification by column chromatography (Et_2O:Cy, 1:4 → 2:1), afforded **10i** (84 mg, 0.27 mmol, 91%, white solid). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.79 (s, 1H), 5.17 (br. s, 1H), 4.48 (d, 1H, $J_{H,H}$ = 5.9), 3.86 (s, 3H), 3.81 (s, 3H), 1.41 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 163.1, 162.1, 158.6, 155.5, 146.4, 118.8, 114.1, 80.0, 52.2, 52.0, 36.9, 28.3. HRESIMS m/z: found, 336.1051; calcd. for $C_{14}H_{19}O_7NNa$ $[M + Na]^+$, 336.1054.

Diethyl (4-Bromofuran-3-yl)phosphonate (10j). General procedure A was followed starting from **9j** (100 mg, 0.324 mmol) and DPTz (99 mg, 0.42 mmol) in DCM (3 mL) for 4 h at r.t. Purification by column chromatography (DCM → DCM:Acetone, 9:1), afforded **10j** (73 mg, 0.26 mmol, 80%, colorless oil). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.81 (t, 1H, $J_{H,H}$ = 1.9), 7.50 (dd, 1H, $J_{H,H}$ = 2.4, 1.8), 4.24–4.03 (m, 4H), 1.33 (m, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 151.6 (d, 1C, $J_{C,P}$ = 22.7), 143.1 (d, 1C, $J_{C,P}$ = 12.8), 114.9 (d, 1C, $J_{C,P}$ = 216.4), 100.3 (d, 1C, $J_{C,P}$ = 7.9), 62.5 (d, 2C, $J_{C,P}$ = 5.4), 16.2 (d, 2C, $J_{C,P}$ = 6.6). HRESIMS m/z: found, 282.9736; calcd. for $C_8H_{13}O_4{}^{79}BrP$ $[M + H]^+$, 282.9740.

3-Bromo-2,5-dimethyl-4-tosylfuran (10k). General procedure A was followed starting from **9k** (100 mg, 0.297 mmol) and DPTz (91 mg, 0.39 mmol) in DCM (3 mL) for 1 d at r.t. Purification by column chromatography (DCM → DCM:Acetone, 15:1), afforded **10k** (56 mg, 0.18 mmol, 60%, colorless oil). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 4.20–3.98 (m, 4H), 2.53 (d, 3H, $J_{H,H}$ = 2.2), 2.24 (s, 3H), 1.33 (t, 6H, $J_{H,H}$ = 7.1). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 160.6 (d, 1C, $J_{C,P}$ = 25.1), 148.9 (d, 1C, $J_{C,P}$ = 13.0), 108.0 (d, 1C, $J_{C,P}$ = 216.6), 96.9 (d, 1C, $J_{C,P}$ = 8.1), 62.0 (d, 2C, $J_{C,P}$ = 5.1), 16.2 (d, 2C, $J_{C,P}$ = 6.8), 14.1, 11.6. HRESIMS m/z: found, 311.0048; calcd. for $C_{10}H_{17}O_4{}^{79}BrP$ $[M + H]^+$, 311.0053.

Diethyl (4-Bromo-2-(butyramidomethyl)furan-3-yl)-phosphonate (10l) and Diethyl (4-Bromo-5-(butyramidomethyl)-furan-3-yl)phosphonate (10m). General procedure A was followed starting from a 5:1 regioisomeric mixture of **9l** and **9m** (100 mg, 0.245 mmol) and DPTz (75 mg, 0.32 mmol) in DCM (3 mL) for 6 h at r.t. Purification by flash automated chromatography (DCM:MeOH:NH_4OH, 150:1:0.1 → 85:14:1), afforded **10l** (72 mg, 0.19 mmol, 77%), and **10m** (11 mg, 0.029 mmol, 12%), both as colorless oils.

Data for compound **10l**: ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.38 (d, 1H, $J_{H,P}$ = 2.2), 7.13 (br. s, 1H), 4.63 (dd, 2H, J = 6.3, 1.4), 4.21–4.00 (m, 4H), 2.14 (t, 2H, $J_{H,H}$ = 7.3), 1.62 (sextet, 2H, $J_{H,H}$ = 7.5), 1.34 (t, 6H, $J_{H,H}$ = 7.1), 0.90 (t, 3H, $J_{H,H}$ = 7.4). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 172.6, 163.1 (d, 1C, $J_{C,P}$ = 25.7), 140.7 (d, 1C, $J_{C,P}$ = 12.8), 109.5 (d, 1C, $J_{C,P}$ = 213.9), 101.0 (d, 1C, $J_{C,P}$ = 7.4), 62.5 (d, 2C, $J_{C,P}$ = 5.2), 38.4, 36.2, 18.9, 16.3 (d, 2C, $J_{C,P}$ = 6.8), 13.8. Data for compound **10m**: ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.78 (d, 1H, $J_{H,P}$ = 2.3), 5.83 (br. s, 1H), 4.50 (d, 2H, $J_{H,H}$ = 5.6), 4.24–4.05 (m, 4H), 2.19 (t, 2H, $J_{H,H}$ = 7.3), 1.74–1.61 (m, 2H), 1.35 (t, 6H, $J_{H,H}$ = 7.1), 0.94 (t, 3H, $J_{H,H}$ = 7.4). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 172.9, 151.1 (d, 1C, $J_{C,P}$ = 12.5), 150.4 (d, 1C, $J_{C,P}$ = 22.2), 115.6 (d, 1C, $J_{C,P}$ = 216.7), 98.6 (d, $J_{C,P}$ = 7.8), 62.6 (d, 2C, $J_{C,P}$ = 5.4), 38.4, 34.4, 19.0, 16.3 (d, 2C, $J_{C,P}$ = 6.7), 13.7. HRESIMS m/z: found, 382.0405; calcd. for $C_{13}H_{21}O_5N^{79}BrP$ $[M + H]^+$, 382.0413.

***tert*-Butyl 3-tosyl-1H-pyrrole-1-carboxylate (10n).**[4b] General procedure A was followed starting from **9n** (75 mg, 0.22 mmol) and DPTz (56 mg, 0.24 mmol) in toluene (3 mL) for 1 d at 45 °C (oil bath). Purification by column chromatography (EtOAc:Cy, 1:4 → 1:1), afforded **10n** (59 mg, 0.18 mmol, 82%, white solid). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.84–7.80 (m, 2H), 7.78 (ap. dd, 1H, $J_{H,H}$ = 1.8, $J_{H,H}$ = 2.2), 7.30–7.27 (m, 2H), 7.21 (dd, 1H, $J_{H,H}$ = 2.2, $J_{H,H}$ = 3.4), 6.43 (dd, 1H, $J_{H,H}$ = 1.8, $J_{H,H}$ = 3.4), 2.39 (s, 3H), 1.58 (s, 9H).

***tert*-Butyl 3-bromo-4-tosyl-1H-pyrrole-1-carboxylate (10o).**[4b] General procedure A was followed starting from **9o** (100 mg, 0.23 mmol) and DPTz (73 mg, 0.30 mmol) in toluene (2 mL) and DCM (1 mL) for 16 h at 45 °C. Purification by column chromatography (DCM:Cy, 1:1), afforded **10o** (79 mg, 0.20 mmol, 84%, yellowish solid).

General procedure C was followed starting from **2** (65 mg, 0.25 mmol) and *N*-Boc-pyrrole (0.5 mL, 3.0 mmol) in toluene (3 mL) for 6 h at 70 °C. Then, DPTz (120 mg, 0.51 mmol) was added, stirring at 45 °C for 22 h. Purification by column chromatography (Et_2O:Cy 1:2), afforded **10o** (74 mg, 0.19 mmol, 74%, yellowish solid). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.91–7.88 (m, 3H), 7.31–7.28 (m, 2H), 7.26–7.25 (d, 1H, $J_{H,H}$ = 2.6), 2.40 (s, 3H), 1.59 (s, 9H).

***tert*-Butyl 3-chloro-4-tosyl-1H-pyrrole-1-carboxylate (10p).** General procedure A was followed starting from **9p** (103 mg, 0.27 mmol) and DPTz (82 mg, 0.35 mmol) in toluene (2 mL) and DCM (1 mL) for 17 h at 45 °C (oil bath). Purification by column chromatography (DCM:Cy, 1:1), afforded **10p** (79 mg, 0.22 mmol, 82%, yellowish oil). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.89 (ap. d, 2H, $J_{H,H}$ = 8.3), 7.86 (d, 1H, $J_{H,H}$ = 2.6), 7.30 (ap. d, 2H, $J_{H,H}$ = 8.0), 7.18 (d, 1H, $J_{H,H}$ = 2.6), 2.40 (s, 3H), 1.59 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 146.5, 144.3, 138.1, 129.6, 127.8, 126.4, 124.2, 119.6, 113.1, 86.6, 27.7, 21.5. HRESIMS m/z: found, 378.0530; calcd. for $C_{16}H_{18}O_4N^{35}ClNaS$ $[M + Na]^+$, 378.0537.

1-(*tert*-butyl) 3,4-dimethyl 1H-pyrrole-1,3,4-tricarboxylate (10q).[13g] General procedure C was followed starting from **6** (43 μL, 0.35 mmol) and *tert*-butyl 1H-pyrrole-1-carboxylate (0.70 mL, 4.2 mmol) in toluene (3 mL) for 1 d at 45 °C (oil bath). Then, DPTz (92 mg, 0.39 mmol) was added and stirred at 45 °C for 22 h. Purification by flash automated chromatography (EtOAc:Cy, 1:24 → 4:1), afforded **10q** (70 mg, 0.25 mmol, 71%, yellowish oil). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.73 (s, 2H), 3.84 (s, 6H), 1.61 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 163.2, 147.1, 125.9, 118.1, 86.2, 51.8, 27.8. HRESIMS m/z: found, 306.0941; calcd. for $C_{13}H_{17}O_6NNa$ $[M + Na]^+$, 306.0948.

1-(*tert*-Butyl) 3-Methyl 4-bromo-1H-pyrrole-1,3-dicarboxylate (10r). General procedure A was followed starting from **9r** (70 mg, 0.21 mmol) and DPTz (100 mg, 0.423 mmol) in toluene (3 mL) for 1 d at r.t. Purification by column chromatography (DCM:Cy, 2:1), afforded **10r** (55 mg, 0.18 mmol, 86%, yellowish solid). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.79 (d, 1H, $J_{H,H}$ = 2.6), 7.26 (d, 1H, $J_{H,H}$ = 2.6), 3.83 (s, 1H), 1.59 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 162.8, 146.9, 125.6, 121.3, 117.2, 100.0, 85.8, 51.3, 27.7. HRESIMS m/z: found, 325.9993; calcd. for $C_{11}H_{14}O_4N^{79}BrNa$ $[M + Na]^+$, 325.9998.

1-(*tert*-Butyl) 3-Ethyl 4-(trifluoromethyl)-1H-pyrrole-1,3-dicarboxylate (10s). General procedure A was followed starting from **9s** (77 mg, 0.23 mmol) and DPTz (71 mg, 0.30 mmol) in toluene (3 mL) for 16 h at 45 °C (oil bath). Purification by column chromatography (DCM:Cy, 1:1), afforded **10s** (53 mg, 0.17 mmol, 74%, white solid). ^1H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.89–7.88 (m, 1H), 7.57–7.56 (m, 1H), 4.32 (q, $J_{H,H}$ = 7.1, 2H), 1.63 (s, 9H), 1.35 (t, 3H, $J_{H,H}$ = 7.1). $^{13}C\{^1H\}$ NMR (75 MHz,

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J. Org. Chem. 2023, 88, 13331–13338

$CDCl_3$, 298 K, δ ppm, J Hz): δ 161.9, 147.0, 127.2, 122.0 (q, 1C, $J_{C,F}$ = 6.6), 121.9 (q, 1C, $J_{C,F}$ = 267.2), 116.8 (q, 1C, $J_{C,F}$ = 37.6), 116.29−116.27 (m, 1C), 86.5, 60.7, 27.7, 14.0. HRESIMS m/z: found, 330.0924; calcd. for $C_{13}H_{16}O_4NF_3Na$ $[M + Na]^+$, 330.0924.

1-((5-Bromo-3-(propan-2-ylidene)cyclopenta-1,4-dien-1-yl)sulfonyl)-4-methylbenzene (10t). General procedure A was followed starting from **9t** (85 mg, 0.23 mmol) and DPTz (60 mg, 0.26 mmol) in toluene (2 mL) and DCM (1 mL) for 14 h at r.t. Purification by column chromatography (DCM:Cy, 2:1), afforded **10t** (70 mg, 0.21 mmol, 89%, brownish solid). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.90−7.87 (m, 2H), 7.44 (d, 1H, $J_{H,H}$ = 2.8), 7.29 (ap. d, 2H, $J_{H,H}$ = 8.0), 6.67 (d, 1H, $J_{H,H}$ = 2.8), 2.40 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 162.9, 144.1, 140.5, 138.1, 137.7, 129.1, 128.6, 128.3, 124.0, 113.9, 23.9, 23.5, 21.6. HRESIMS m/z: found, 360.9868; calcd. for $C_{15}H_{15}O_2{}^{79}BrNaS$ $[M + Na]^+$, 360.9874.

***N*-(2-((4-Tosylfuran-3-yl)thio)ethyl)acetamide (17).** General procedure A was followed starting from **12** (85 mg, 0.23 mmol) and DPTz (110 mg, 0.466 mmol) in water (3 mL) for 18 h at r.t. Purification by flash automated chromatography (EtOAc:Cy, 1:8 → 9:1), afforded **17** (60 mg, 0.18 mmol, 76%, brownish oil). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 8.03 (d, 1H, $J_{H,H}$ = 1.8), 7.92−7.89 (m, 2H), 7.52 (d, 1H, $J_{H,H}$ = 1.8), 7.33−7.30 (m, 2H), 6.62 (br. s, 1H), 3.35 (q, 2H, $J_{H,H}$ = 6.2), 2.87 (t, 2H, $J_{H,H}$ = 6.2), 2.40 (s, 3H), 1.96 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 170.5, 148.2, 148.1, 145.0, 137.7, 131.2, 129.8, 127.0, 114.8, 38.0, 36.6, 23.2, 21.7. HRESIMS m/z: found, 362.0485; calcd. for $C_{15}H_{17}O_4NNaS_2$ $[M + Na]^+$, 362.0491.

***tert*-Butyl-3-((2-((*tert*-butoxycarbonyl)amino)ethyl)thio)-4-tosyl-1H-pyrrole-1-carboxylate (18).**[4b] General procedure A was followed starting from **13** (125 mg, 0.239 mmol) and DPTz (73 mg, 0.31 mmol) in DCM (3 mL) for 11 h at r.t. Purification by column chromatography (EtOAc:Cy, 1:6), afforded **18** (108 mg, 0.22 mmol, 91%, yellowish oil). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.92 (ap. d, 2 H, $J_{H,H}$ = 8.3), 7.88 (d, 1H, $J_{H,H}$ = 2.5), 7.30−7.27 (m, 3H), 5.14 (br. s, 1H), 3.23−3.19 (m, 2H), 2.84 (t, 2H, $J_{H,H}$ = 6.3), 2.39 (s, 3H), 1.59 (s, 9H), 1.42 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 155.8, 146.8, 144.2, 138.5, 129.9, 129.5, 128.0, 125.8, 125.7, 114.7, 85.4, 79.2, 39.3, 36.6, 28.4, 27.8, 21.5. HRESIMS m/z: found, 519.1590; calcd. for $C_{23}H_{32}O_6N_2NaS_2$ $[M + Na]^+$, 519.1594.

***N*-(2-((3-(Propan-2-ylidene)-5-tosylcyclopenta-1,4-dien-1-yl)thio)ethyl)acetamide (19).** General procedure A was followed starting from **14** (405 mg, 1.00 mmol) and DPTz (261 mg, 1.10 mmol) in DCM (12 mL) for 5.5 h at r.t. Then, DCM was added and the organic layer was washed with 1 M aq. HCl and brine. The organic layer was dried on anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc), afforded **19** (336 mg, 0.890 mmol, 89%, orange solid). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.90−7.87 (m, 2H), 7.40 (d, 1H, $J_{H,H}$ = 2.6), 7.29 (ap. d, 2H, $J_{H,H}$ = 8.1), 6.50 (d, 1H, $J_{H,H}$ = 2.6), 6.35 (br. s, 1H, $J_{H,H}$ = 5.8), 3.48−3.41 (m, 2H), 2.96 (t, 2H, $J_{H,H}$ = 6.4), 2.40 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 1.93 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 170.4, 159.5, 144.1, 141.9, 138.5, 138.0, 133.0, 129.53, 129.50, 128.0, 119.2, 37.9, 33.8, 23.7, 23.5, 23.1, 21.6. HRESIMS m/z: found, 400.1004; calcd. for $C_{19}H_{23}O_3NNaS_2$ $[M + Na]^+$, 400.1012.

Diethyl (4-((2-Acetamidoethyl)thio)furan-3-yl)phosphonate (20). General procedure A was followed starting from **15** (50 mg, 0.14 mmol) and DPTz (44 mg, 0.19 mmol) in DCM (3 mL) for 4 h at r.t. Purification by column chromatography (DCM → DCM:MeOH, 50:1), afforded **20** (41 mg, 0.13 mmol, 93%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.73 (t, 1H, $J_{H,H}$ = 1.8), 7.61−7.58 (m, 2H), 4.23−4.14 (m, 4H), 3.35−3.30 (m, 2H), 2.92−2.88 (m, 2H), 1.96 (s, 3H), 1.36 (t, 6H, $J_{H,H}$ = 7.1). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 170.7, 150.2 (d, 1C, $J_{C,P}$ = 22.7), 148.0 (d, 1C, $J_{C,P}$ = 14.7), 117.2 (d, 1C, $J_{C,P}$ = 217.9), 116.6 (d, 1C, $J_{C,P}$ = 12.4), 62.7 (d, 2C, $J_{C,P}$ = 5.9), 37.9, 37.4, 23.0, 16.4 (d, 2C, $J_{C,P}$ = 6.5). HRESIMS m/z: found, 322.0884; calcd. for $C_{12}H_{21}O_5NPS$ $[M + H]^+$, 322.0876.

Diethyl (4-((2-Acetamidoethyl)thio)-2,5-dimethylfuran-3-yl)phosphonate (21). General procedure A was followed starting from **16** (50 mg, 0.13 mmol) and DPTz (41 mg, 0.17 mmol) in DCM (3 mL) for 18 h at r.t. Purification by flash automated chromatography (DCM:MeOH:NH_4OH, 150:1:0.1 → 85:14:1), afforded **21** (32 mg, 0.091 mmol, 69%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.84 (br. s, 1H), 4.19−4.09 (m, 4H), 3.27 (q, 2H, $J_{H,H}$ = 5.7), 2.78−2.74 (m, 2H), 2.42 (d, 3H, $J_{H,H}$ = 2.3), 2.31 (s, 3H), 1.96 (s, 3H), 1.35 (t, 6H, $J_{H,H}$ = 7.1). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 170.6, 158.1 (d, 1C, $J_{C,P}$ = 24.3), 156.1 (d, 1C, $J_{C,P}$ = 15.0), 111.0 (d, 1C, $J_{C,P}$ = 218.8), 110.8 (d, 1C, $J_{C,P}$ = 12.9), 62.2 (d, 2C, $J_{C,P}$ = 5.8), 37.8, 36.3, 23.2, 16.4 (d, 2C, $J_{C,P}$ = 6.8), 14.1, 11.7. HRESIMS m/z: found, 350.1197; calcd. for $C_{14}H_{25}O_5NPS$ $[M + H]^+$, 350.1187.

***N,N*-Diethyl-4-tosylfuran-3-amine (22).** To a stirred solution of **9b** (100 mg, 0.31 mmol) in anhydrous MeCN (3 mL) under Ar, Et_3N (47 μL, 0.34 mmol) and Et_2NH (36 μL, 0.34 mmol) were added. The reaction mixture was stirred for 40 min at r.t. Then, DPTz (110 mg, 0.466 mmol) was added and the reaction mixture was heated to 45 °C (oil bath) and vigorously stirred for 18 h. The solvent was removed under reduced pressure and the crude was purified by chromatography column on silica gel (EtOAc:Cy, 1:8) to afford **22** (41 mg, 0.14 mmol, 46%, orange solid). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.90−7.86 (m, 3H), 7.29−7.26 (m, 2H), 7.05 (s, 1H), 2.98 (q, 4H, $J_{H,H}$ = 7.1), 2.40 (s, 3H), 0.86 (t, 6H, $J_{H,H}$ = 7.1). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 147.8, 144.0, 138.7, 135.6, 135.3, 129.3, 127.7, 126.3, 47.0, 21.6, 11.3. HRESIMS m/z: found, 294.1160; calcd. for $C_{15}H_{20}NO_3S$ $[M + H]^+$, 294.1158.

***tert*-Butyl 3-(diethylamino)-4-tosyl-1H-pyrrole-1-carboxylate (23).** To a stirred solution of **9o** (150 mg, 0.35 mmol) in anhydrous MeCN (2 mL) under Ar, Et_3N (53 μL, 0.38 mmol) and Et_2NH (40 μL, 0.38 mmol) were added. The reaction mixture was stirred for 2 h. Then, DPTz (110 mg, 0.466 mmol) was added and the reaction mixture was heated to 45 °C (oil bath) and vigorously stirred for 6 h. The solvent was removed under reduced pressure and the crude was purified by chromatography column on silica gel (Et_2O:Cy, 1:1) to afford **23** (70 mg, 0.18 mmol, 51%, orange oil). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.89 (ap. d, 2H, $J_{H,H}$ = 8.4), 7.77 (d, 1H, $J_{H,H}$ = 2.6), 7.25 (ap. d, 2H, $J_{H,H}$ = 8.2), 6.77 (d, 1H, $J_{H,H}$ = 2.3), 2.96 (q, 4H, $J_{H,H}$ = 7.1), 2.39 (s, 3H), 1.60 (s, 9H), 0.84 (t, 6H, $J_{H,H}$ = 7.1). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm): δ 147.6, 143.5, 139.2, 136.7, 129.0, 127.6, 125.0, 124.3, 112.2, 85.3, 47.4, 27.8, 26.9, 21.5, 11.4. HRESIMS m/z: found, 393.1835; calcd. for $C_{20}H_{29}N_2O_4S$ $[M + H]^+$, 393.1843.

1-(4-Tosylfuran-3-yl)pyridin-1-ium Bromide (24). To a solution of pyridine (32 μL, 0.39 mmol) in toluene (1 mL), a solution of **9b** (75 mg, 0.23 mmol) in toluene (1 mL) was added. The reaction was stirred at r.t. overnight and concentrated under reduced pressure. Then, the residue was dissolved in DCM (3 mL) and DPTz (108 mg, 0.457 mmol) was added. The reaction was vigorously stirred at r.t. for 2.5 h. The reaction mixture was filtered to afford **24** (74 mg, 0.195 mmol, 85%, white solid). ^{1}H NMR (300 MHz, CD_3OD, 298 K, δ ppm, J Hz): δ 9.04−9.01 (m, 2H), 8.92 (tt, 1H, $J_{H,H}$ = 8.0, $J_{H,H}$ = 1.3), 8.64 (d, 1H, $J_{H,H}$ = 1.7), 8.51 (d, 1H, $J_{H,H}$ = 1.7), 8.33−8.29 (m, 2H), 7.55−7.52 (m, 2H), 7.42−7.39 (m, 2H), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD, 298 K, δ ppm): δ 148.2, 148.1, 146.8, 145.6, 142.9, 136.4, 129.7, 127.3, 126.5, 126.1, 125.1, 19.6. HRESIMS m/z: found, 300.0681; calcd. for $C_{16}H_{14}O_3NaS$ $[M\text{-}Br]^+$, 300.0689.

Diethyl (4-Methoxyfuran-3-yl)phosphonate (27). General procedure A was followed starting from **26** (45 mg, 0.17 mmol) and DPTz (53 mg, 0.22 mmol) in DCM (3 mL) for 4 h at r.t. Then, it was diluted with DCM, washed with 1M HCl (×5), with sat. aq. $NaHCO_3$ and with brine. The organic layer was dried with Na_2SO_4, filtered and concentrated in vacuo to afford **27** (33 mg, 0.14 mmol, 81%, brownish oil). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 7.61 (t, 1H, $J_{H,H}$ = 1.9), 7.10 (dd, 1H, $J_{H,H}$ = 2.8, 1.7), 4.21−4.02 (m, 4H), 3.73 (s, 3H), 1.31 (t, 6H, $J_{H,H}$ = 7.1). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K, δ ppm, J Hz): δ 150.1 (d, 1C, $J_{C,P}$ = 21.0), 149.8 (d, 1C, $J_{C,P}$ = 3.1), 124.4 (d, 1C, $J_{C,P}$ = 4.4), 106.8 (d, 1C, $J_{C,P}$ = 212.0),

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62.4 (d, 2C, $J_{C,P}$ = 5.4), 58.6, 16.3 (d, 2C, $J_{C,P}$ = 6.5). HRESIMS *m/z*: found, 235.0729; calcd. for $C_9H_{16}O_5P$ $[M + H]^+$, 235.0730.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its SI.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c01145.

Details of the experimental procedures for the preparation of heteronorbornadienes and NMR spectra for the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Mateev, E.; Georgieva, M.; Zlatkov, A. Pyrrole as an Important Scaffold of Anticancer Drugs: Recent Advances. *J. Pharm. Pharm. Sci.* **2021**, *25*, 24−40. (b) Singh, N.; Singh, S.; Kohli, S.; Singh, A.; Asiki, H.; Rathee, G.; Chandra, R.; Anderson, E. A. Recent Progress in the Total Synthesis of Pyrrole Containing Natural Products (2011−2020). *Org. Chem. Front.* **2021**, *8*, 5550−5573. (c) Khajuria, R.; Dham, S.; Kapoor, K. K. Active Methylenes in the Synthesis of a Pyrrole Motif: an Imperative Structural Unit of Pharmaceuticals, Natural Products and Optoelectronic Materials. *RSC Adv.* **2016**, *6*, 37039−37066. (d) Boto, A.; Álvarez, L. Heterocycles in Natural Products Synthesis; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; pp 99−152. (e) Sperry, J. B.; Wright, D. L. Furans, Thiophenes and Related Heterocycles in Drug Discovery. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723−740.

(2) (a) Post, C.; Maniar, D.; Voet, V. S. D.; Folkersma, R.; Loos, K. Biobased 2,5-Bis(hydroxymethyl)furan as a Versatile Building Block for Sustainable Polymeric Materials. *ACS Omega* **2023**, *8*, 8991−9003. (b) Karlinskii, B. Y.; Ananikov, V. P. Recent Advances in the Development of Green Furan Ring-Containing Polymeric Materials Based on Renewable Plant Biomass. *Chem. Soc. Rev.* **2023**, *52*, 836−862. (c) Fathi, P.; Pan, D. Current Trends in Pyrrole and Porphyrin-Derived Nanoscale Materials for Biomedical Applications. *Nanomedicine* **2020**, *15*, 2493−2515.

(3) (a) Leeper, F. J.; Kelly, J. M. Synthesis of 3,4-Disubstituted Pyrroles. A Review. *Org. Prep. Proced. Int.* **2013**, *45*, 171−210. (b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. Regioselective Synthesis of Substituted Furans. *Tetrahedron* **1998**, *54*, 1955−2020.

(4) Selected references in the last five years: (a) Chu, X.-Q.; Cai, S.-Z.; Chen, J.-W.; Yu, Z.-L.; Ma, M.; Walsh, P. J.; Shen, Z.-L. Defluorophosphorylation of Fluoroalkyl Peroxides for the Synthesis of Highly Substituted Furans. *Green Chem.* **2023**, *25*, 2000−2010. (b) Gil de Montes, E.; Martınez-Bailén, M.; Carmona, A. T.; Robina, I.; Moreno-Vargas, A. J. Regioselectivity of the 1,3-Dipolar Cycloaddition of Organic Azides to 7-Heteronorbornadienes. Synthesis of *β*-Substituted Furans/Pyrroles. *J. Org. Chem.* **2020**, *85*, 8923−8932. (c) Gao, X.; Wang, P.; Wang, Q.; Chen, J.; Lei, A. Electrochemical Oxidative Annulation of Amines and Aldehydes or Ketones to Synthesize Polysubstituted Pyrroles. *Green Chem.* **2019**, *21*, 4941−4945. (d) Muralirajan, K.; Kancherla, R.; Rueping, M. Dehydrogenative Aromatization and Sulfonylation of Pyrrolidines: Orthogonal Reactivity in Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2018**, *57*, 14787−14791. (e) Manasa, K. L.; Sastry, K. N. V.; Tangella, Y.; Babu, B. N. Tandem Synthesis of 3,4-Disubstituted Pyrroles from Aldehydes, 1,3-Diketones and TosMIC Under Metal-Free Conditions. *ChemistrySelect* **2018**, *3*, 2730−2733.

(5) Ferreira, V. F.; de Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. Recent Advances in the Synthesis of Pyrroles. *Org. Prep. Proced. Int.* **2001**, *33*, 411−454.

(6) (a) Bergman, J.; Janosik, T.Five-Membered Heterocycles: Pyrrole and Related Systems. In Modern Heterocyclic Chemistry; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, 2011; Vol. *1*, pp 269−375. (b) Eicher, T.; Hauptmann, S.; Speicher, A.Five-Membered Heterocycles. *The Chemistry of Heterocycles*, 2nd Ed.; Wiley-VCH: Weinheim, 2003; pp 61−79.

(7) Chinchilla, R.; Nájera, C.; Yus, M. Metalated Heterocycles and Their Applications in Synthetic Organic Chemistry. *Chem. Rev.* **2004**, *104*, 2667−2722.

(8) Gil de Montes, E.; Istrate, A.; Navo, C. D.; Jimenez-Moreno, E.; Hoyt, E. A.; Corzana, F.; Robina, I.; Jimenez-Oses, G.; Moreno-Vargas, A. J.; Bernardes, G. J. L. Stable Pyrrole-Linked Bioconjugates through Tetrazine-Triggered Azanorbornadiene Fragmentation. *Angew. Chem., Int. Ed.* **2020**, *59*, 6196−6200.

(9) (a) Priestley, G. M.; Warrener, R. N. A New route to Isoindole (Benzo[c]indole) and its Derivatives. *Tetrahedron Lett.* **1972**, *13*, 4295−4298. (b) Warrener, R. N. Isolation of Isobenzofuran, a Stable but Highly Reactive Molecule. *J. Am. Chem. Soc.* **1971**, *93*, 2346−2348.

(10) Dalkilic, E.; Dastan, A. Synthesis of Cyclopentadiene Derivatives by Retro-Diels-Alder Reaction of Norbornadiene Derivatives. *Tetrahedron* **2015**, *71*, 1966−1970.

(11) Alvarez-Ibarra, C.; Quiroga, M. L.; Toledano, E. Synthesis of Polysubstituted 3-Thiofurans by Regiospecific Mono-*Ipso*-Substitution and Ortho-Metallation from 3,4-Dibromofuran. *Tetrahedron* **1996**, *52*, 4065−4078.

(12) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. Scope and Mechanism of Palladium-Catalyzed Amination of Five-Membered Heterocyclic Halides. *J. Org. Chem.* **2003**, *68*, 2861−2873.
(13) (a) For the synthesis of **9a**, **9c**, **9d**, **9p**, and **9r**, see references 4b and 8; oxanorbornadienes **9f** and **9h** are commercially available. (b) For the synthesis of **9b** and **9o**, see: Zhang, C.; Ballay II, C. J.; Trudell, M. L. 2-Bromoethynyl Aryl Sulfones as Versatile Dienophiles: a Formal Synthesis of Epibatidine. *J. Chem. Soc., Perkin Trans. 1* **1999**, 675−676. (c) For the synthesis of **9e**, see: van Berkel, S. S.; Dirks, A. J.; Debets, M. F.; van Delft, F. L.; Cornelissen, J. J. L. M.; Nolte, R. J. M.; Rutjes, F. P. J. T. Metal-Free Triazole Formation as a Tool for Bioconjugation. *ChemBioChem.* **2007**, *8*, 1504−1508. (d) For the synthesis of **9g** and **9t**, see: Moreno-Clavijo, E.; Moreno-Vargas, A. J.; Carmona, A. T.; Robina, I. Strain-Promoted Retro-Dieckmann-Type Condensation on [2.2.2]- and [2.2.1]Bicyclic Systems: a Fragmentation Reaction for the Preparation of Functionalized Heterocycles and Carbocycles. *Org. Biomol. Chem.* **2013**, *11*, 7016−7025. (e) For the synthesis of **9i**, see: Kislukhin, A. A.; Higginson, C. J.; Finn, M. G. Aqueous-Phase Deactivation and Intramolecular [2 + 2+2] Cycloaddition of Oxanorbornadiene Esters. *Org. Lett.* **2011**, *13*, 1832−1835. (f) For the synthesis of **9n**, see: Gil de Montes, E.; Jiménez-Moreno, E.; Oliveira, B. L.; Navo, C. D.; Cal, P. M. S. D.; Jiménez-Osés, G.; Robina, I.; Moreno-Vargas, A. J.; Bernardes, G. J. L. Azabicyclic Vinyl Sulfones for Residue-Specific Dual Protein Labelling. *Chem. Sci.* **2019**, *10*, 4515−4522. (g) For the synthesis of **9q**, see: Keana, J. F. W.; Heo, G. S.; Mann, J. S.; Van Nice, F. L. V.; Lex, L.; Prabhu, V. S.; Ferguson, G. Synthesis and Chemistry of *N*-Oxygenated Pyrroles: Crystal and Molecular Structure of a Highly Stable *N*-Hydroxypyrrole 18-Crown Ether Hydrate. *J. Org. Chem.* **1988**, *53*, 2268−2274. (h) For the synthesis of **9s**, see: Troelsen, N. S.; Shanina, E.; Gonzalez-Romero, D.; Dankova, D.; Jensen, I. S. A.; Sniady, K. J.; Nami, F.; Zhang, H.; Rademacher, C.; Cuenda, A.; Gotfredsen, C. H.; Clausen, M. H. The 3F Library: Fluorinated Fsp^3-Rich Fragments for Expeditious ^{19}F-NMR Based Screening. *Angew. Chem., Int. Ed.* **2020**, *59*, 2204−2210.
(14) Partial or total *N*-Boc deprotection of *β*-substituted pyrroles was observed in our previous strategy (ref. 4b), where the reaction conditions require high temperature (70−110 °C).
(15) Reaction of compound **4** (1.0 mmol scale) afforded **10d** (243 mg, 0.70 mmol, 70%) following this procedure.
(16) Barlow, M. G.; Suliman, N. N. E.; Tipping, A. E. A High-Yield Synthesis of 3-Carboethoxy-4-trifluoromethylfuran and some Diels-Alder Reactions of this Furoate with Acetylenic Dienophiles. *J. Fluor. Chem.* **1995**, *70*, 59−69.
(17) Deshpande, A. M.; Natu, A. A.; Argade, N. P. A New Strategy for the Synthesis of Furan-3,4-dicarboxylic Acid. *Synthesis* **2002**, *8*, 1010−1012.
(18) Wong, H. N. C.; Xing, Y. D.; Zhou, Y. F.; Gong, Q. Q.; Zhang, C. Synthesis of Benzene Derivatives via Deoxygenation by Low Valent Titanium. *Synthesis* **1984**, *9*, 787−790.

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