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Regioselectivity of the 1,3-dipolar cycloaddition of organic azides to 7-heteronorbornadienes. Synthesis of β-substituted furans/pyrroles

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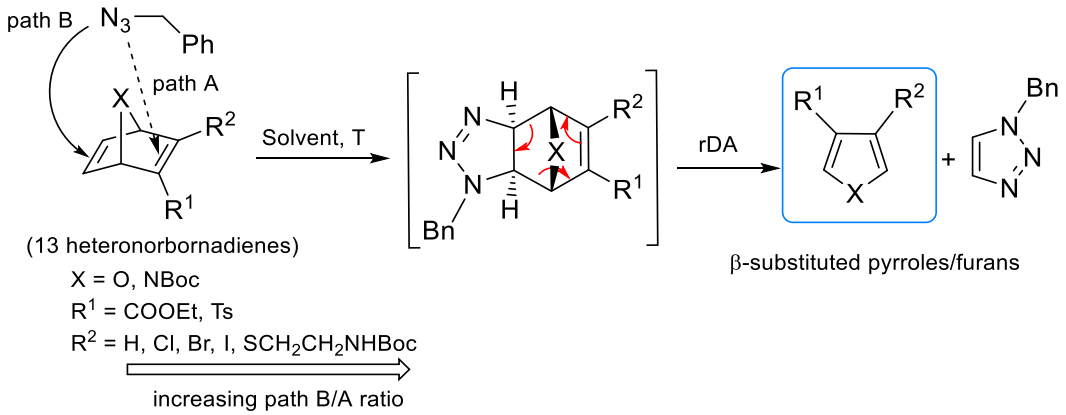
Abstract

An efficient procedure for the preparation of β-substituted furans/pyrroles is presented. The methodology is based on the use of 7-oxa/azanorbornadienes as dipolarophiles in a 1,3-dipolar cycloaddition with benzyl azide. The triazoline cycloadduct thus formed spontaneously decomposes *via* a retro-Diels-Alder (rDA) reaction to afford a β-substituted furan/pyrrole derivative and a stable triazole. The scope of this tandem 1,3-dipolar cycloaddition/rDA reaction was studied with thirteen 7-heteronorbornadienes. This study allowed a deep knowledge of the regioselectivity of the reaction which can be tuned through the substituents of the heteronorbornadienic systems.

Graphical abstract

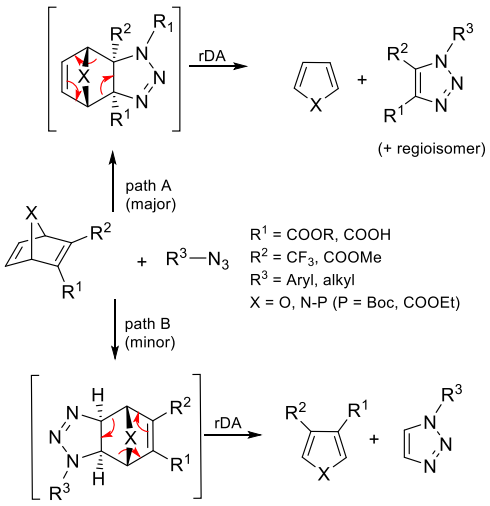


Introduction

Furan and pyrrole motifs are present in many natural products,[1] synthetic materials[2] and pharmaceuticals.[3] Additionally, they are also important reaction intermediates in the preparation of innovative porphyrin dye-sensitized solar cells[4] and biologically relevant compounds.[5] Due to this interest, the development of new methodologies/strategies for the synthesis of β-substituted pyrroles and furans still constitutes an active field in organic chemistry, with relevant publications in the last years.[6] This synthesis still remains a challenge as most reported procedures imply multi-step routes or sophisticated methods.[7] Particularly, β-halo-furans and pyrroles are important intermediates for further functionalization *via* C-C, C-N or C-S bond forming reactions.[8,9,10,11] Taking into account that the direct electrophilic substitution on pyrrole leads to the α-substituted regioisomer as major compound,[12] it is necessary to block the α-position or to introduce a bulky group at the nitrogen atom to achieve the β-substitution. In any case, the use of blocking or directing groups requires derivatization steps that clearly reduces the synthetic efficiency of the route. A similar problem is found in the preparation of β-substituted furans due to the tendency of furans to undergo both metallation and electrophilic reactions at α-position.[13]

7-Heteronorbornadienes (7-heterobicyclo[2.2.1]hepta-2,5-dienes) are systems with a unique geometry that provokes the accumulation of ring strain energy.[14] Double bonds embedded into [2.2.1]bicyclic systems are well known to easily react in cycloaddition reactions.[15] Our research group has recently used this strategy with azanorbornadienes for protein bioconjugation purposes.[16] In accordance to Houk's studies on norbornene systems, the strain results in a predistortion of the alkene, which resembles the transition state geometry of the cycloaddition.[17] This reduces the distortion energy gap to achieve the transition state leading to accelerated reactions. 1,3-Dipolar cycloadditions between (7-hetero)norbornadienes and different dipoles such as nitrile oxides, nitrile imines and azides have been previously

described.[18,19,20,21,22] Organic azides are not as reactive 1,3-dipoles as nitrile oxides or nitrile imines; on the contrary, they are stable molecules that do not need to be *in situ* synthesized. 7-Heteronorbornadienes are easily prepared by Diels-Alder reaction between an electron-deficient alkyne and a furan or pyrrole derivative.[23] It has been reported that the 1,3-dipolar cycloaddition between organic azides and 7-heteronorbornadienes as dipolarophiles can follow two different reaction pathways depending on the site-selective attack of the dipole.[19] On the basis of the frontier orbital theory, the dipole will use its HOMO for the interaction with the LUMO of the bicyclic dipolarophile, which is mainly[24] localized on the electron-deficient alkene (Scheme 1, path A). Alternatively, the dipole can use its LUMO for the interaction with the HOMO of the bicyclic system, which is mainly localized on the electron-rich alkene (Scheme 1, path B). In both cases, the 1,3-dipolar cycloaddition will generate unstable triazoline intermediates that decompose *via* a retro-Diels-Alder (rDA) reaction to afford the corresponding stable triazole and furan or pyrrole derivatives.



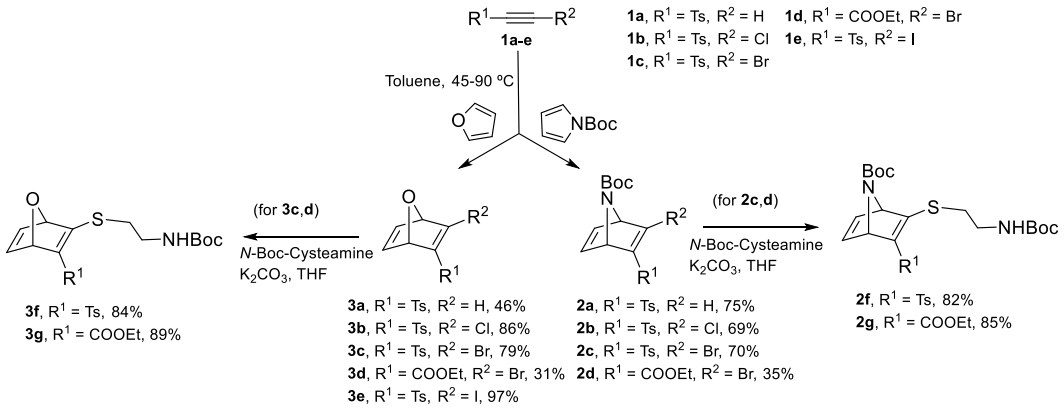
Scheme 1. Proposed reaction pathways for the 1,3-cycloaddition of organic azides to 7-heteronorbornadienes. Path A was always the main pathway in all these previously reported examples.

This tandem 1,3 dipolar cycloaddition-rDA reaction has been explored especially in 7-oxanorbornadienes,[20,22,25] with only a couple of examples in 7-azanorbornadienes.[21,26] In all the reported examples with 7-oxa/azanorbornadienes, path A was the main (or unique) pathway for the reaction. The sequence *via* path A has been exploited by Rutjes and coworkers as an

interesting strategy for metal-free triazole-based protein bioconjugation that has been used in further biological applications.[22] Nevertheless, an exhaustive study of the site-selectivity of this cycloaddition tuning the electronic density of the electron-deficient double bond has not been previously reported. The exploration of the reaction conditions and the substituents on the bicyclic systems that could favour path B is an interesting goal, as this constitutes an efficient strategy for the preparation of β-substituted furans/pyrroles.

Results and discussion.

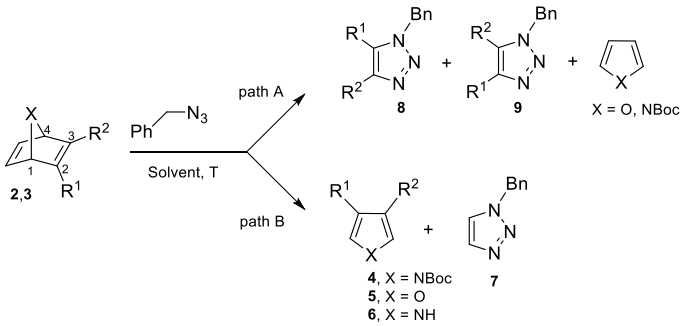
7-Oxa- and 7-azanorbornadienes **2a**-**d** and **3a**-**e** (Scheme 2) can be easily synthesized by Diels-Alder (DA) reaction between furan/*N*-Boc-pyrrole and electron-deficient alkynes (commercially available or easily prepared from commercial alkyne precursors). The Boc group, instead of other acyl groups, was chosen in order to ensure the dienic behaviour of this heterocycle. In most of the cases, the electron-deficient character of the alkyne allowed the DA be efficient, leading to the final cycloadducts in moderate-to-good yields.[27] However, DA reaction with alkynes containing the ethoxycarbonyl group, which is a weaker electron-deficient group than tosyl, led to the corresponding products in poor yield. Thiovinyl derivatives **2f**,**g** and **3f**,**g** can be easily obtained after substitution reaction of cycloadducts **2c**,**d** and **3c**,**d** with *N*-Boc-cysteamine under basic conditions.



Scheme 2. Synthesis of differently substituted 7-heteronorbornadienes.

All these 7-heteronorbornadienes were assayed in the 1,3-dipolar cycloaddition with benzyl azide (Table 1). For comparative purposes, some representative examples of the bibliography were also included in the table (entries 13, 22, 23).

Table 1. Regioselectivity of the 1,3-dipolar cycloaddition between 7-heteronorbornadienes and benzyl azide.



Entry	Bicyclic system	X	R^1	R^2	Solvent	T (°C)	*t* (h)	Paths A:B (%)[a]	Yield (%)[b] heterocycle **4** or **5**	Pyrrole **6** (% *N*-Boc deprotection)[c]
1	**2a**	*N*-Boc	Ts	H	Toluene	110	1	74:26	19	-
2	**2b**	*N*-Boc	Ts	Cl	Toluene	110	2	7:93	66	28
3	**2c**	*N*-Boc	Ts	Br	Toluene	110	3	5:95	54	34
4	**2c**	*N*-Boc	Ts	Br	DMF	110	1	11:89	-	100
5	**2c**	*N*-Boc	Ts	Br	MeOH	65	7	17:83	-	70
6	**2d**	*N*-Boc	COOEt	Br	Toluene	110	3	22:78	59	9
7	**2d**	*N*-Boc	COOEt	Br	DMF	110	1	20:80	-	100
8	**2d**	*N*-Boc	COOEt	Br	MeOH	65	7	29:71	35	48
9	**2f**	*N*-Boc	Ts	$SR^{4[f]}$	Toluene	110	1	27:73	53	19
10	**2f**	*N*-Boc	Ts	$SR^{4[f]}$	Toluene	70	10	4:96	86	1
11	**2f**	*N*-Boc	Ts	$SR^{4[f]}$	Toluene	50	58	0:100	91	0
12	**2g**	*N*-Boc	COOEt	$SR^{4[f]}$	Toluene	110	2	0:100	78	0
13[d]	**2h**	*N*-Boc	COOMe	COOMe	CD_3OD	25	14	100:0	-	-
14	**3a**	O	Ts	H	Toluene	110	1	84:16	-	-
15	**3b**	O	Ts	Cl	Toluene	110	1	15:85	85	-
16	**3c**	O	Ts	Br	Toluene	110	1	15:85	80	-
17	**3d**	O	COOEt	Br	Toluene	110	1	30:70	63	-
18	**3e**	O	Ts	I	Toluene	110	1	9:91	81	-
19	**3e**	O	Ts	I	Toluene	70	5	9:91	-	-

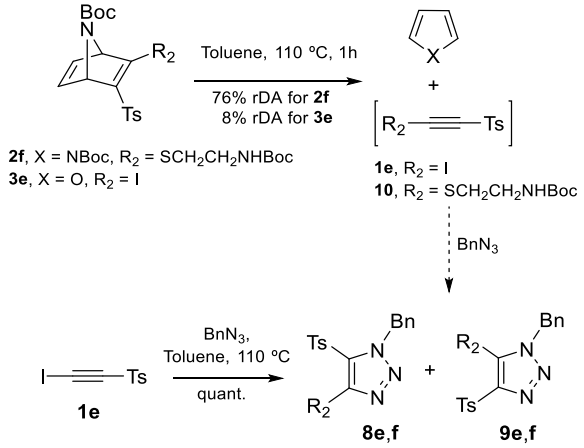
20	**3f**	O	Ts	$SR^{4[f]}$	Toluene	110	1	0:100	90	-
21	**3g**	O	COOEt	$SR^{4[f]}$	Toluene	110	1	0:100	92	-
22[e]	**3h**	O	COOEt	CF_3	CD_3OD	25	-	97:3	-	-
23[e]	**3i**	O	COOMe	COOMe	CD_3OD	25	-	95:5	-	-

[a]Path A/Path B ratio determined by ^{1}H-NMR analysis of the reaction mixtures. The conversion of the substrates was quantitative in all cases. The amount of unprotected pyrrole **6** is incorporated as part of path B. [b] The yield of the β-substituted furan/*N*-Boc-pyrrole after isolation and chromatographic purification is given (except when indicated). [c]% *N*-Boc deprotection measured by ^{1}H-NMR is given. [d]See ref. 26. [e]See ref. 22b. [f]R_4 = -CH_2CH_2NHBoc. -: not determined/not given/not isolated.

All the heteronorbornadiene systems reacted completely with benzyl azide in toluene at 110 °C after 1-3 h. With the exceptions of vinyl sulfones **2a** and **3a** (entries 1 and 14), in all the cases path B was the major pathway of the reaction. The presence of O or *N*-Boc in the bridge did not significantly affect the regioselectivity of the 1,3-dipolar cycloaddition, being the azabicylic systems slightly more prone to react by the path B than the corresponding oxa-analogues (entries 1-3 *vs* entries 14-16). The solvent did not show significant influence on the regioselectivity (entries 3-5 and 6-8), but showed to be crucial on the yield of the final *N*-protected β-substituted pyrroles **4**. *N*-Boc-pyrrole derivatives **4** are completely or significantly converted to the corresponding unprotected derivatives **6** in DMF (entries 4 and 7) and MeOH (entries 5 and 8). For this reason, toluene was chosen as solvent for most of the experiments.[28] The presence of a heteroatom instead of H at C-3 of the bicyclic system, allows electron donation to the electron-poor double bond of the system. This electronic effect increases the energy of the LUMO, which is mainly located on the electron-poor deficient alkene, being detrimental for its interaction with the HOMO of the dipole (path A). Instead, the interaction between the HOMO of the bicyclic system and the LUMO of the azide (path B) turns into the best option. In this sense, all the heteronorbornadiene derivatives containing an halogen at C-3 reacted in the same way, favouring clearly path B over path A (entries 2-5, 6-8, 15-19). A steric influence on the regioselectivity of the reaction should not be discarded, as the size of the halogen atom at

C-3 increases simultaneously with the ability to release electronic density to the π-system of the bicycle. Nevertheless, the electronic effect prevails over the steric one as it is observed for the bicyclic system **3h** with a trifluoromethyl substituent at C-3 (Table 1, entry 22). The trifluoromethyl group exhibits a larger steric demand than a Br or Cl group,[29] however this fact did not lead to a predominance of path B over path A as it would have been expected from a steric point of view. This behaviour can be justified by electronic effects because this group, that exhibits an important inductive electron-withdrawing effect, is not able to release electronic density to the π-system of the bicycle. A similar effect is observed for the examples previously reported in the bibliography, where C-3 is substituted with the methoxycarbonyl group (entries 13 and 23). In this sense, we expected to observe the higher path B/A ratio for dipolarofiles **2f**,**g** and **3f**,**g** that contain a thioether function on C-3, as a consequence of the ability of the sulfur atom to donate electrons to the contiguous π-system. In fact, path B was the only one found for reactions with **2g**, **3f** and **3g** (entries 12, 20 and 21). Surprisingly, for dipolarophile **2f,** the regioselectivity was not as high as expected (path A/B: 27/73, entry 9) under the same reaction conditions and even lower than with halogenated azanorbornadienes **2b** and **2c** (entries 2 and 3). A possible explanation for these results is that a simultaneous *retro*-Diels-Alder (rDA) reaction of **2f** that could compete with the 1,3-dipolar cycloaddition could take place (Scheme 3). The resulting alkyne of this collateral reaction (compound **10**) could directly react with the benzyl azide through a Huisgen cycloaddition to give the regioisomeric 4,5-disubstituted triazoles **8f** and **9f**, what would distort the real path A/B ratio. This hypothesis was explored with the heteronorbornadienes where path A was observed [heteronorbornadiene (% path A): azanorbornadienes **2a** (74%), **2b** (7%), **2c** (5-17%), **2d** (22 -29%), **2f**(2-27%); oxanorbornadienes **3a** (84%), **3b,c** (15%), **3d** (30%), **3e** (9%)]. The major part of these bicyclic systems was stable under refluxing toluene in the period of time needed for the 1,3-dipolar cycloaddition (1-3h). However, partial rDA was detected for oxanorbornadiene **3e** (8% rDA after 1h) and, especially, for azanorbornadiene **2f** (76% rDA after 1 h) (Scheme 3). To confirm the competition of the

Huisgen cycloaddition after the rDA reaction, alkyne **1e** was made react with benzyl azide in toluene at 110 °C. Regioisomeric triazoles **8e** and **9e** were obtained in 1 h after complete conversion. This experiment could not be carried out in the case of **10** because this alkyne could not be isolated nor synthesized separately.



Scheme 3. Collateral rDA reaction of **2f** and **3e** and subsequent Huisgen cycloaddition.

With these results in hand, we decided to perform the 1,3-dipolar cycloaddition in toluene with **2f** and **3e** at lower temperature (entries 10, 11 and 19), in order to avoid the collateral rDA. At 70 °C, the extension of the rDA was clearly slowed down in the case of **2f** (4% conversion after 4h) and abolished for **3e** (no rDA was detected after 4h). To our delight, at 70 °C the 1,3-dipolar cycloaddition between **2f** and benzyl azide, although considerably slower, was clearly more regioselective than at 110 °C (entry 9 *vs* entry 10). At the same temperature, in the case of **3e** the regioselectivity was not improved (entries 18 and 19, highly regioselective for both 110° and 70 °C), what indicates that in this case the effect of the rDA should not be really significant. At 50 °C, the 1,3-dipolar cycloaddition between **2f** and benzyl azide showed total regioselectivity (entry 11).

In summary, in this work we have demonstrated that the regioselectivity of the 1,3-dipolar cycloaddition between 7-heteronorbornadienes and benzyl azide can be efficiently controlled by tuning the electronic density of the electron-poor double bond of the bicyclic system. The

bicyclic dipolarophile promoted a spontaneous rDA reaction of the intermediate cycloadducts that directly afforded functionalized furans or pyrroles. Thus, the synthetic sequence that implies a Diels-Alder reaction between electron-poor alkynes and furan/*N*-Boc-pyrrole, followed by a 1,3-dipolar cycloaddition of the resulting heteronorbornadiene with benzyl azide, showed to be a versatile approach for the preparation of β-substituted furans and pyrroles. In particular, this methodology constitutes an efficient strategy for the synthesis of β-halo-furans and pyrroles. Altogether, this sequence allows the incorporation of the substituents previously present in the initial alkyne to the β-positions of a furan or pyrrole.

Experimental section

General methods

Infrared spectra were recorded with a Jasco FTIR-410 spectrophotometer. ^{1}H- and ^{13}C{^{1}H}-NMR spectra were recorded with a Bruker AMX300 spectrometer for solutions in $CDCl_3$, CD_3OD and DMSO-d_6. δ are given in ppm and *J* in Hz. *J* are assigned and not repeated. All the assignments were confirmed by 2D spectra (COSY and HSCQ). HMBC and NOE experiments were performed when necessary. High resolution mass spectra were recorded on a Orbitrap Elite spectrometer with an ion trap mass analyser. For reactions that require heating, aluminium heating blocks with magnetic stirring were used. TLC was performed on silica gel 60 F_{254} (Merck), with detection by UV light charring with *p*-anisaldehyde and $KMnO_4$. Silica gel 60 (Merck, 40-60 and 63-200 μm) was used for preparative chromatography.

[2-(Iodo)ethynyl] *p*-tolyl sulfone (1e). To a solution of commercial *p*-tolyl [2-(trimethylsilyl)ethynyl] sulfone (1.54 g, 6.11 mmol) in acetone (45 mL), *N*-iodosuccinimide (1.59 g, 6.72 mmol) and $AgNO_3$ (104 mg, 0.611 mmol) were added in darkness. After stirring for 1.5 h at r.t., the mixture was filtered through celite and the solvent removed under reduced pressure. The resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:5) to give **1e** (1.72 g, 5.61 mmol, 92%) as a white solid. IR (ῡ) 2922, 2118 (C≡C), 1593, 1323,

1083, 795 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90-7.86 (m, 2H, H-Ar), 7.40-7.37 (m, 2H, H-Ar), 2.47 (s, 3H, C*H*$_3$ of Ts). $^{13}C\{^1H\}$-NMR (75.4 MHz, $CDCl_3$) δ 146.0 (C_q-Ar), 138.1 (C_q-Ar), 130.3, 127.8 (C-Ar), 92.0 (C_q of alkyne), 23.9 (C_q of alkyne), 21.9 (*C*H_3 of Ts). HRESIMS *m/z* found 328.9101 calcd. for $C_9H_7IO_2NaS$ $(M+Na)^+$: 328.9104.

(*rac*)-(1*R*,4*S*)-*N*-Boc-2-chloro-3-tosyl-7-azabicyclo[2.2.1]hepta-2,5-diene (2b). To a solution of alkyne **1b**[30] (309 mg, 1.44 mmol) in toluene (2 mL), commercial *N*-Boc-pyrrole (1.2 mL, 7.2 mmol) was added and the reaction mixture was stirred at 80 °C for 1 d. Then, the solvent was evaporated and the resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:8) to give **2b** (381 mg, 0.998 mmol, 69%) as a yellow oil. IR (ū) 2984, 1718 (C=O), 1581, 1318, 1154, 828 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-*d*$_6$, 353 K) δ 7.77-7.73 (m, 2H, H-Ar), 7.50-7.47 (m, 2H, H-Ar), 7.11-7.06 (m, 2H, H-5, H-6), 5.32 (td, 1H, $J_{H,H}$ = 2.3, $J_{H,H}$ = 1.1, H-1 or H-4), 5.11 (td, 1H, $J_{H,H}$ = 2.3, $J_{H,H}$ = 1.0, H-4 or H-1), 2.43(s, 3H, C*H*$_3$ of Ts), 1.30 (s, 9H, -C(C*H*$_3$)$_3$). $^{13}C\{^1H\}$-NMR (75.4 MHz, DMSO-*d*$_6$, 353 K) δ 156.6, 146.7 (C-2, C-3), 152.8 (C=O, Boc), 144.8 (C_q-Ar), 142.7, 139.2 (C-5, C-6), 135.7 (C_q-Ar), 129.8, 126.9 (C-Ar), 80.9 (-*C*$(CH_3)_3$), 73.4, 68.7 (C-1, C-4), 27.2 (-C(*C*H_3)$_3$), 20.6 (*C*H_3 of Ts). HRESIMS *m/z* found 404.0691 calcd. for $C_{18}H_{20}ClNO_4NaS$ $(M+Na)^+$: 404.0694.

(*rac*)-(1*R*,4*S*)-2-Chloro-3-tosyl-7-oxabicyclo[2.2.1]hepta-2,5-diene (3b). To a solution of alkyne **1b**[30] (312 mg, 1.45 mmol) in toluene (3 mL), furan (1.3 mL, 18 mmol) was added and the reaction mixture was stirred at 45 °C for 1 d. Then, the solvent was evaporated and the resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:5) to give **3b** (350 mg, 1.24 mmol, 86%) as a brown solid. IR (ū) 2925, 1587, 1329, 1149, 870 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79-7.75 (m, 2H, H-Ar), 7.37-7.34 (m, 2H, H-Ar), 7.10-7.05 (m, 2H, H-5, H-6), 5.59-5.58 (m, 1H, H-1 or H-4), 5.25 (ap. t, 1H, H-4 or H-1), 2.45 (s, 3H, C*H*$_3$ of Ts). $^{13}C\{^1H\}$-NMR (75.4 MHz, $CDCl_3$) δ 157.7, 146.8 (C-2, C-3), 145.4 (C_q-Ar), 144.3, 140.2 (C-5, C-6), 136.4 (C_q-Ar), 130.2, 127.8 (C-Ar), 88.9, 85.0 (C-1, C-4), 21.8 (*C*H_3 of Ts). HRESIMS *m/z* found 305.0009 calcd. for $C_{13}H_{11}ClO_3NaS$ $(M+Na)^+$: 305.0010.

(*rac*)-(1*R*,4*S*)-2-Iodo-3-tosyl-7-oxabicyclo[2.2.1]hepta-2,5-diene (3e). To a solution of **1e** (305 mg, 0.996 mmol) in toluene (2 mL), furan (0.88 mL, 12 mmol) was added and the reaction mixture was stirred at 45 °C for 1 d. Then, the solvent was evaporated and the resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:4→1:2) to give **3e** (362 mg, 0.968 mmol, 97%) as a pale yellow solid. IR (ū) 2920, 1547, 1306, 1146, 874 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80-7.77 (m, 2H, H-Ar), 7.36 (d, 2H, $J_{H,H}$ = 8.0, H-Ar), 7.06 (dd, 1H, $J_{H,H}$ = 5.3, $J_{H,H}$ = 1.8, H-5 or H-6), 6.98 (dd, 1H, $J_{H,H}$ = 5.3, $J_{H,H}$ = 1.8, H-6 or H-5), 5.51 (ap. t, 1H, H-1 or H-4), 5.47 (ap. t, 1H, H-4 or H-1), 2.44 (s, 3H, CH_3 of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 157.0, (C-3), 145.4 (C_q-Ar), 143.1, 140.4 (C-5, C-6), 135.9 (C_q-Ar), 130.2, 127.9 (C-Ar), 117.5 (C-2), 94.1, 84.9 (C-1, C-4), 21.9 (*C*H_3 of Ts). HRESIMS *m/z* found 396.9361 calcd. for $C_{13}H_{11}IO_3NaS$ $(M+Na)^+$: 396.9366.

(*rac*)-(1*R*,4*S*)-*N*-Boc-2-[(2-(*N*-Boc-amino)ethyl)thio]-3-tosyl-7-azabicyclo[2.2.1]hepta-2,5-diene (2f). To a solution of azabicycle **2c**[27d] (241 mg, 0.566 mmol) in THF (1 mL), a solution of *N*-Boc-cysteamine (84 mg, 0.47 mmol) in THF (1.4 mL), K_2CO_3 (198 mg, 1.42 mmol, in three portions, one portion every 30 minutes) and H_2O (0.8 mL) were added. After stirring for 1.5 h at r.t., the reaction mixture was diluted with CH_2Cl_2 and the organic phase was washed twice with H_2O and brine. The resulting organic phase was dried over Na_2SO_4, filtered and evaporated. Chromatographic purification on silica gel (EtOAc:cyclohexane 1:3) afforded **2f** (202 mg, 0.386 mmol, 82%) as a pale yellow solid. IR (ū) 3378 (NH), 2979, 1706 (C=O), 1519, 1253, 1148, 871 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6, 353 K) δ 7.72-7.68 (m, 2H, H-Ar), 7.42 (d, 2H, $J_{H,H}$ = 8.1, H-Ar), 6.99-6.96 (m, 1H, H-5 or H-6), 6.93-6.90 (m, 1H, H-6 or H-5), 6.83 (bs, 1H, NH), 5.61 (ap. t, 1H, H-1 or H-4), 5.23-5.21 (m, 1H, H-4 or H-1), 3.33-3.03 (m, 4H, -CH_2CH_2NHBoc), 2.41 (s, 3H, CH_3 of Ts), 1.42 (s, 9H, -C(CH_3)$_3$), 1.27 (s, 9H, -C(CH_3)$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, DMSO-d_6, 353 K) δ 166.7 (C-2), 155.1, 152.7 (C=O, Boc), 143.7 (C_q-Ar), 142.0, 138.5 (C-5, C-6), 139.1 (C-3), 137.1 (C_q-Ar), 129.4, 126.3 (C-Ar), 80.5, 77.8 (-*C*(CH$_3$)$_3$), 70.3, 68.5 (C-1, C-4), 40.7 (-CH$_2$*C*H$_2$NHBoc), 31.2 (-

CH_2CH_2NHBoc), 27.8, 27.2 (-C(*C*$H_3)_3$), 20.6 (*C*H_3 of Ts). HRESIMS *m/z* found 545.1751 calcd. for $C_{25}H_{34}N_2O_6NaS_2$ $(M+Na)^+$: 545.1750.

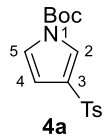
(*rac*)-(1*R*,4*S*)-*N*-Boc-2-[(2-(*N*-Boc-amino)ethyl)thio]-3-ethoxycarbonyl-7-azabicyclo[2.2.1]hepta-2,5-diene (2g). This compound was synthesized following the previous procedure described for **2f**, using azabicycle **2d**[27b] (119 mg, 0.346 mmol) as starting material. Chromatographic purification on silica gel (EtOAc:cyclohexane 1:4) afforded **2g** (108 mg, 0.245 mmol, 85%) as a pale yellow oil. IR (ῡ) 3369 (NH), 2978, 1687 (C=O), 1507, 1366, 1161, 729 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6, 353K) δ 7.13-7.08 (m, 2H, H-5, H-6), 6.81 (bs, 1H, NH), 5.56 (bs, 1H, H-1 or H-4), 5.31 (td, 1H, $J_{H,H}$ = 2.1, $J_{H,H}$ = 1.1, H-4 or H-1), 4.21-4.09 (m, 2H, -C*H*$_2$CH$_3$), 3.35-3.10 (m, 4H, -C*H*$_2$C*H*$_2$NHBoc), 1.42 (s, 9H, -C(C*H*$_3)_3$), 1.37 (s, 9H, -C(C*H*$_3)_3$), 1.23 (t, 3H, $J_{H,H}$ = 7.1, -CH$_2$C*H*$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, DMSO-d_6, 353K) δ 169.2 (C-2), 162.4 (C=O, COOEt), 155.1, 153.1 (C=O, Boc), 142.8, 140.0 (C-5, C-6), 132.1 (C-3), 80.0, 77.7 (-*C*$(CH_3)_3$), 69.4, 67.4 (C-1, C-4), 59.2 (-*C*H$_2$CH$_3$), 40.9 (-CH$_2$*C*H$_2$NHBoc), 31.0 (-*C*H$_2$CH$_2$NHBoc), 27.8, 27.4 (-C(*C*H$_3)_3$), 13.8 (-CH$_2$*C*H$_3$). HRESIMS *m/z* found 463.1871 calcd. for $C_{21}H_{32}N_2O_6NaS$ $(M+Na)^+$: 463.1873.

(*rac*)-(1*R*,4*S*)-2-[(2-(*N*-Boc-amino)ethyl)thio]-3-tosyl-7-oxabicyclo[2.2.1]hepta-2,5-diene (3f). This compound was synthesized following the previous procedure described for **2f**, using oxabicycle **3c**[27d] (240 mg, 0.733 mmol) as starting material. Chromatographic purification on silica gel (EtOAc:cyclohexane 1:2) afforded **3f** (216 mg, 0.511 mmol, 84%) as a pale yellow solid. IR (ῡ) 3379 (NH), 2979, 1702 (C=O), 1523, 1251, 1147, 881 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (d, 2H, $J_{H,H}$ = 8.3, H-Ar), 7.32 (d, 2H, H-Ar), 6.99-6.93 (m, 2H, H-5, H-6), 5.78 (bs, 1H, H-4), 5.51 (bs, 1H, H-1), 5.00 (bs, 1H, NH), 3.39-3.23 (m, 2H, -CH$_2$C*H*$_2$NHBoc), 3.18-2.99 (m, 2H, -C*H*$_2$CH$_2$NHBoc), 2.42 (s, 3H, C*H*$_3$ of Ts), 1.43 (s, 9H, -C(C*H*$_3)_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 165.9 (C-2), 155.9 (C=O, Boc), 144.6 (C_q-Ar), 143.6, 139.7 (C-5, C-6), 140.5 (C-3), 137.3 (C_q-Ar), 130.0, 127.2 (C-Ar), 86.5 (C-4), 85.1 (C-1), 80.1 (-*C*$(CH_3)_3$), 41.7 (-CH$_2$*C*H$_2$NHBoc), 32.3 (-*C*H$_2$CH$_2$NHBoc), 28.5 (-C(*C*H$_3)_3$), 21.8 (*C*H$_3$ of Ts). HRESIMS *m/z* found 446.1060 calcd. for $C_{20}H_{25}NO_5NaS_2$ $(M+Na)^+$: 446.1066.

(*rac*)-(1*R*,4*S*)-2-[(2-(*N*-Boc-amino)ethyl)thio]-3-ethoxycarbonyl-7-oxabicyclo[2.2.1]hepta-2,5-diene (3g). This compound was synthesized following the previous procedure described for **2f**, using oxabicycle **3d**[27e] (175 mg, 0.714 mmol) as starting material. Chromatographic purification on silica gel (EtOAc:cyclohexane 1:4) afforded **3g** (182 mg, 0.533 mmol, 89%) as a colorless oil. IR (ū) 3361 (NH), 2979, 1682 (C=O), 1507, 1366, 1270, 878 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, 1H, $J_{6,5}$ = 5.4, $J_{6,1}$ = 1.7, H-6), 7.09 (dd, 1H, $J_{5,4}$ = 1.8, H-5), 5.74-5.71 (m, 2H, H-1, H-4), 4.99 (bs, 1H, NH), 4.27-4.11 (m, 2H, -C*H*$_2$CH$_3$), 3.38-3.31 (m, 2H, -CH$_2$C*H*$_2$NHBoc), 3.20-3.03 (m, 2H, -C*H*$_2$CH$_2$NHBoc), 1.44 (s, 9H, -C(C*H*$_3$)$_3$), 1.29 (t, 3H, $J_{H,H}$ = 7.1, -CH$_2$C*H*$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 169.2 (C-2), 163.7 (C=O, COOEt), 155.9 (C=O, Boc), 144.6 (C-6), 140.8 (C-5), 133.9 (C-3), 85.7, 84.5 (C-1, C-4), 80.0 (-*C*(CH$_3$)$_3$), 60.4 (-*C*H$_2$CH$_3$), 41.7 (-CH$_2$*C*H$_2$NHBoc), 32.2 (-*C*H$_2$CH$_2$NHBoc), 28.5 (-C(*C*H$_3$)$_3$), 14.5 (-CH$_2$*C*H$_3$). HRESIMS *m/z* found 364.1188 calcd. for $C_{16}H_{23}NO_5NaS$ $(M+Na)^+$: 364.1189.

General procedure for the 1,3-dipolar cycloaddition between 7-heteronorbornadienes and benzyl azide. To a solution of the corresponding 7-heteronorbornadiene (1.0 eq) in the solvent indicated for each case (Table 1), a solution of benzyl azide (1.5 eq) in the same solvent was added (final concentration: 0.23 M). The reaction was stirred at the desired temperature for the time indicated for each assay and the solvent was removed under reduced pressure. The crude reaction mixture was then analysed by ^{1}H-NMR (Figures S1 and S2, Supporting information) and purified by chromatography column on silica gel to afford the corresponding furan/*N*-Boc-pyrrole derivatives **4** or **5**. Unprotected pyrroles **6**, triazoles **7**, **8** and **9** could be isolated only in the cases where the estimated amount of these product was appreciable (≥10 mg).

1,3-Dipolar cycloaddition of 2a with benzyl azide (Table 1, entry 1).

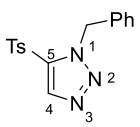


4a

Following the general procedure and starting from **2a**[27a] (100 mg, 0.29 mmol) in toluene for 1 h at 110 °C, pyrrole **4a** (18 mg, 0.056 mmol, 19%, brown oil) and triazoles **8a** (54 mg, 0.17 mmol, 58%, brown solid) and **9a** (13 mg, 0.042

mmol, 14%, brown solid) were isolated after chromatographic purification (EtOAc:cyclohexane 1:10→1:5→1:1).

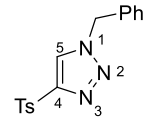
Data for **4a**: IR (ū) 3170, 2980, 1752 (C=O), 1594, 1536, 1086, 974, 820 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H, H-Ar), 7.79-7.78 (m, 1H, H-2 or H-4 or H-5) 7.31-7.28 (m, 2H, H-Ar), 7.23-7.21 (m, 1H, H-2 or H-4 or H-5), 6.45-6.43 (m, 1H, H-2 or H-4 or H-5), 2.40 (s, 3H, C*H*$_3$ of Ts), 1.59 (s, 9H, -C(C*H*$_3$)$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 147.6 (C=O, Boc), 144.0 (C_q-Ar), 139.6 (C_q-Ar), 129.9 (C-Ar), 129.2 (C_q-Ar), 127.4, 123.4, 122.0, 110.3 (C-Ar), 86.0 (-*C*(CH$_3$)$_3$), 28.0 (-C(*C*H$_3$)$_3$), 21.7 (*C*H$_3$ of Ts). HRESIMS *m/z* found 344.0920, calcd. for $C_{16}H_{19}NO_4NaS$ $(M+Na)^+$: 344.0927.



8a

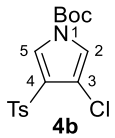
Data for **8a**: IR (ū) 2922, 2851, 1598, 1099, 969, 858, 651 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H, H-4), 7.50-7.47 (m, 2H, H-Ar), 7.27-7.21 (m, 3H, H-Ar), 7.14-7.12 (m, 2H, H-Ar), 7.06-7.04 (m, 2H, H-Ar), 5.82 (s, 2H, C*H*$_2$Ph), 2.36 (s, 3H, C*H*$_3$ of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 145.8 (C_q-Ar), 137.8 (C-4), 137.6, 136.4, 133.9 (C_q-Ar), 130.1, 128.9, 128.5, 127.8, 127.7 (C-Ar), 53.3 (*C*H$_2$Ph), 21.8 (*C*H$_3$ of Ts). HRESIMS *m/z* found 336.0781, calcd. for $C_{16}H_{15}N_3O_2NaS$ $(M+Na)^+$: 336.0777.

Data for **9a**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (bs, 1H, H-Ar), 7.95-7.92 (m, 2H, H-Ar), 7.41-7.37 (m, 3H, H-Ar), 7.33-7.27 (m, 4H, H-Ar), 5.52 (s, 2H, *CH*$_2$Ph), 2.41 (s, 3H, CH$_3$ of Ts). Its spectroscopic data are in accordance with those described in the bibliography.[31]



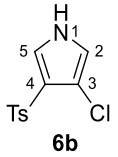
9a

1,3-Dipolar cycloaddition of 2b with benzyl azide (Table 1, entry 2).



4b

Following the general procedure and starting from **2b** (150 mg, 0.393 mmol) in toluene for 2 h at 110 °C, pyrrole **4b** (92 mg, 0.26 mmol, 66%) was isolated after chromatographic purification (EtOAc:cyclohexane 1:5) as a yellow oil. Unprotected pyrrole **6b** was detected, but could not be isolated. This compound was prepared separately following the general procedure: A



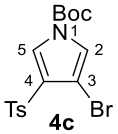
6b

solution of the corresponding β-substituted *N*-Boc-pyrrole (**4b** in this case, 81 mg, 0.23 mmol) in MeOH (final concentration: 0.08 M) was refluxed for 24 h. Then, the solvent was removed under reduced pressure and the resulting crude product was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:1) to give pure **6b** (58 mg, 0.23 mmol, quant.) as a white solid.

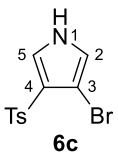
Data for **4b**: IR (ū) 2981, 1759 (C=O), 1532, 1325, 1251, 812 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91-7.87 (m, 2H, H-Ar), 7.86 (d, 1H, $J_{H,H}$ = 2.7, H-2 or H-5), 7.32-7.29 (m, 2H, H-Ar), 7.18 (d, 1H, H-5 or H-2), 2.41 (s, 3H, CH_3 of Ts), 1.59 (s, 9H, -C(CH_3)$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 146.7 (C=O, Boc), 144.5, 138.3 (C_q-Ar), 129.8, 128.0 (C-Ar), 126.5 (C_q-Ar), 124.4, 119.7 (C-2, C-5), 113.3 (C_q-Ar), 86.8 (-*C*$(CH_3)_3$), 27.9 (-C(*C*H_3)$_3$), 21.7 (*C*H_3 of Ts). HRESIMS *m/z* found 378.0530, calcd. for $C_{16}H_{18}ClNO_4NaS$ $(M+Na)^+$: 378.0537.

Data for **6b**: IR (ū) 3309 (NH), 2919, 1527, 1289, 1142, 810 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.82 (d, 2H, $J_{H,H}$ = 8.3, H-Ar), 7.44 (d, 1H, $J_{H,H}$ = 2.4, H-2 or H-5), 7.33 (d, 2H, H-Ar), 6.83 (d, 1H, H-5 or H-2), 2.38 (s, 3H, CH_3 of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, CD_3OD) δ 145.3, 140.9 (C_q-Ar), 130.6, 128.4 (C-Ar), 125.1, 120.2 (C-2, C-5), 122.5, 111.0 (C_q-Ar), 21.5 (*C*H_3 of Ts). HRESIMS *m/z* found 278.0015 calcd. for $C_{11}H_{10}ClNO_2NaS$ $(M+Na)^+$: 278.0013.

1,3-Dipolar cycloaddition of 2c with benzyl azide (Table 1, entry 3).



4c



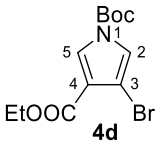
6c

Following the general procedure and starting from **2c**[27d] (110 mg, 0.259 mmol) in toluene for 3 h at 110 °C, pyrrole **4c** (55 mg, 0.14 mmol, 54%) was isolated after chromatographic purification (EtOAc:cyclohexane 1:10→1:5) as a yellow oil. Unprotected pyrrole **6c** was detected, but could not be isolated. Compound **6c** (64 mg, 0.21 mmol, 88%) was obtained separately following the procedure reported for **6b** after chromatographic purification (EtOAc:cyclohexane 1:1) as a white solid.

Data for **4c**: IR (ῡ) 2922, 1752 (C=O), 1522, 1366, 1237, 816 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92-7.89 (m, 3H, H-Ar, H-2 or H-5), 7.32-7.29 (m, 2H, H-Ar), 7.25 (d, 1H, $J_{H,H}$ = 2.6, H-5 or H-2), 2.41 (s, 3H, C*H*$_3$ of Ts), 1.59 (s, 9H, -C(C*H*$_3$)$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 146.6 (C=O, Boc), 144.4, 138.2 (C_q-Ar), 129.7, 128.2 (C-Ar), 127.7 (C_q-Ar), 125.1, 122.5 (C-2, C-5), 97.6 (C_q-Ar), 86.8 (-*C*(CH$_3$)$_3$), 27.9 (-C(*C*H$_3$)$_3$), 21.7 (*C*H$_3$ of Ts). HRESIMS *m/z* found 422.0024 calcd. for $C_{16}H_{18}BrNO_4NaS$ $(M+Na)^+$: 422.0032.

Data for **6c**: IR (ῡ) 3333 (NH), 2921, 1527, 1293, 1131, 809 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.83 (d, 2H, $J_{H,H}$ = 8.3, H-Ar), 7.50 (d, 1H, $J_{H,H}$ = 2.3, H-2 or H-5), 7.32 (d, 2H, H-Ar), 6.88 (d, 1H, H-5 or H-2), 2.38 (s, 3H, C*H*$_3$ of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, CD_3OD) δ 145.2, 140.7 (C_q-Ar), 130.6, 128.5 (C-Ar), 125.9, 123.0 (C-2, C-5), 123.8, 94.8 (C_q-Ar), 21.5 (*C*H$_3$ of Ts). HRESIMS *m/z* found 321.9506 calcd. for $C_{11}H_{10}BrNO_2NaS$ $(M+Na)^+$: 321.9508.

1,3-Dipolar cycloaddition of 2d with benzyl azide (Table 1, entry 6).



4d

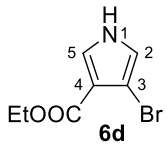
Following the general procedure and starting from **2d**[27b] (146 mg, 0.423 mmol) in toluene for 3 h at 110 °C, pyrrole **4d** (81 mg, 0.25 mmol, 59%) was isolated after chromatographic purification (EtOAc:cyclohexane 1:20→1:10) as a white solid.

IR (ῡ) 2983, 1748, 1724 (C=O), 1507, 1373, 1253, 848 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79 (d, 1H, $J_{H,H}$ = 2.6, H-2 or H-5), 7.25 (d, 1H, H-5 or H-2), 4.29 (q, 2H, $J_{H,H}$ = 7.1, -C*H*$_2$CH$_3$), 1.59 (s, 9H, -C(C*H*$_3$)$_3$), 1.34 (t, 3H, -CH$_2$C*H*$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 162.6 (C=O, COOEt), 147.2 (C=O, Boc), 125.7, 121.5 (C-2, C-5), 117.8, 100.3 (C-3, C-4), 86.0 (-*C*(CH$_3$)$_3$), 60.5 (-*C*H$_2$CH$_3$), 27.9 (-C(*C*H$_3$)$_3$), 14.4 (-CH$_2$*C*H$_3$). HRESIMS *m/z* found 340.0150 calcd. for $C_{12}H_{16}BrNO_4Na$ $(M+Na)^+$: 340.0155.

1,3-Dipolar cycloaddition of 2d with benzyl azide (Table 1, entry 8).

Following the general procedure and starting from **2d**[27b] (136 mg, 0.395 mmol) in MeOH for 7 h at 65 °C, pyrrole **4d** (43 mg, 0.14 mmol, 35%, white solid) and unprotected pyrrole **6d** (31 mg,

0.14 mmol, 35%, brown solid) were isolated after chromatographic purification (EtOAc:cyclohexane 1:20→1:10→1:5→1:2).

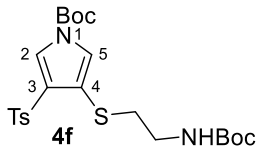


6d

IR (ū) 3247 (NH), 2917, 1719, 1682 (C=O), 1512, 1320, 1158, 722 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.07 (bs, 1H, NH), 7.41-7.40 (m, 1H, H-2 or H-5), 6.82 (ap. t, 1H, H-5 or H-2), 4.30 (q, 2H, $J_{H,H}$ = 7.1, -C*H*$_2$CH$_3$), 1.35 (t, 3H, -CH$_2$C*H*$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 163.9 (C=O), 124.9, 120.4 (C-2, C-5), 114.7, 97.4 (C-3, C-4), 60.2 (-*C*H$_2$CH$_3$), 14.5 (-CH$_2$*C*H$_3$). HRESIMS *m/z* found 239.9627 calcd. for $C_7H_8BrNO_2Na$ $(M+Na)^+$: 239.9631.

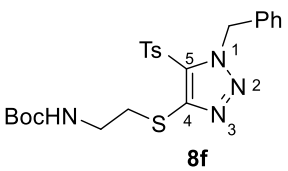
1,3-Dipolar cycloaddition of 2f with benzyl azide (Table 1, entry 9).

Following the general procedure and starting from **2f** (149 mg, 0.286 mmol) in toluene for 1 h at 110 °C, pyrrole **4f** (72 mg, 0.15 mmol, 53%, colorless oil) and triazoles **8f** (20 mg, 0.042 mmol, 15%, yellow oil) and **9f** (15 mg 0.030 mmol, 11%, yellow solid) were isolated after chromatographic purification (EtOAc:cyclohexane 1:4). Unprotected pyrrole **6f** was detected but could not be isolated. Compound **6f** (46 mg, 0.12 mmol, 92%) was obtained separately following the procedure reported for **6b** after chromatographic purification (EtOAc:cyclohexane 1:1) as a white solid.



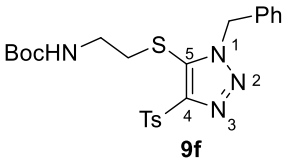
4f

Data for **4f**: IR (ū) 3391 (NH), 2979, 1757, 1704 (C=O), 1507, 1365, 1243, 841 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (d, 2H, $J_{H,H}$ = 8.3, H-Ar), 7.89 (d, 1H, $J_{H,H}$ = 2.5, H-2 or H-5), 7.30-7.26 (m, 3H, H-Ar, H-5 or H-2), 5.14 (bs, 1H, NH), 3.26-3.20 (m, 2H, -CH$_2$C*H*$_2$NHBoc), 2.85 (t, 2H, $J_{H,H}$ = 6.2, -C*H*$_2$CH$_2$NHBoc), 2.40 (s, 3H, C*H*$_3$ of Ts), 1.59 (s, 9H, -C(C*H*$_3$)$_3$), 1.42 (s, 9H, -C(C*H*$_3$)$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 155.9, 146.8 (C=O, Boc), 144.3, 138.6, (C_q-Ar), 130.0 (C-3), 129.6, 128.1 (C-Ar), 125.9, 125.8 (C-2, C-5), 114.8 (C-4), 86.6, 79.4 (-*C*(CH$_3$)$_3$), 39.4 (-CH$_2$*C*H$_2$NHBoc), 36.7 (-*C*H$_2$CH$_2$NHBoc), 28.5, 27.9 (-C(*C*H$_3$)$_3$), 21.7 (*C*H$_3$ of Ts). HRESIMS *m/z* found 519.1592 calcd. for $C_{23}H_{32}N_2O_6NaS_2$ $(M+Na)^+$: 519.1594.



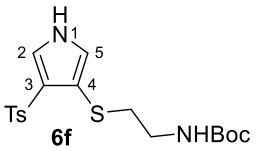
8f

Data for **8f**: IR (ū) 3357 (NH), 2929, 1704 (C=O), 1454, 1248, 1161, 813 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.43-7.38 (m, 2H, H-Ar), 7.33-7.25 (m, 3H, H-Ar), 7.16-7.13 (m, 2H, H-Ar), 7.10-7.07 (m, 2H, H-Ar), 5.87 (s, 2H, C*H*$_2$Ph), 5.04 (bs, 1H, NH), 3.46-3.40 (m, 2H, -CH_2C*H*$_2$NHBoc), 3.33-3.29 (m, 2H, -C*H*$_2$$CH_2$NHBoc), 2.35 (s, 3H, C*H*$_3$ of Ts), 1.44 (s, 9H, -C(C*H*$_3$)$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 155.9 (C=O), 146.4 (C-4), 145.8, 136.7, 134.3 (C_q-Ar), 132.3 (C-5), 129.9, 129.0, 128.6, 127.9, 127.4 (C-Ar), 79.6 (-*C*(CH$_3$)$_3$), 54.3 (*C*H$_2$Ph), 40.3 (-CH_2*C*H$_2$NHBoc), 32.5 (-*C*H$_2$$CH_2$NHBoc), 28.5 (-C(*C*H$_3$)$_3$), 21.8 (*C*H$_3$ of Ts). HRESIMS *m/z* found 511.1438 calcd. for $C_{23}H_{28}N_4O_4NaS_2$ $(M+Na)^+$: 511.1444.



9f

Data for **9f**: IR (ū) 3391 (NH), 2926, 1707 (C=O), 1497, 1250, 1145, 814 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00-7.96 (m, 2H, H-Ar), 7.35-7.31 (m, 5H, H-Ar), 7.30-7.25 (m, 2H, H-Ar), 5.62 (s, 2H, C*H*$_2$Ph), 5.19 (bs, 1H, NH), 3.14 (q, 2H, $J_{H,H}$ = 5.7, -CH_2C*H*$_2$NHBoc), 2.80 (t, 2H, -C*H*$_2$$CH_2$NHBoc), 2.42 (s, 3H, C*H*$_3$ of Ts), 1.44 (s, 9H, -C(C*H*$_3$)$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 155.9 (C=O), 151.2 (C-4), 145.5, 137.1, 134.0 (C_q-Ar), 131.4 (C-5), 130.0, 129.3, 129.1, 128.5, 128.1 (C-Ar), 79.7 (-*C*(CH$_3$)$_3$), 52.8 (*C*H$_2$Ph), 39.6 (-CH_2*C*H$_2$NHBoc), 37.5 (-*C*H$_2$$CH_2$NHBoc), 28.5 (-C(*C*H$_3$)$_3$), 21.8 (*C*H$_3$ of Ts). HRESIMS *m/z* found 511.1438 calcd. for $C_{23}H_{28}N_4O_4NaS_2$ $(M+Na)^+$: 511.1444.



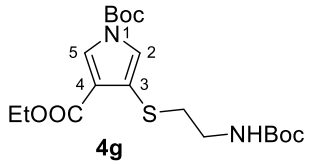
6f

Data for **6f**: IR (ū) 3334 (NH), 2976, 1683 (C=O), 1516, 1365, 1254, 813 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.87 (d, 2H, $J_{H,H}$ = 8.3, H-Ar), 7.50 (d, 1H, $J_{H,H}$ = 2.3, H-2 or H-5), 7.34-7.31 (m, 2H, H-Ar), 6.98 (d, 1H, H-5 or H-2) 3.07 (t, 2H, $J_{H,H}$ = 6.7, -CH_2C*H*$_2$NHBoc), 2.62 (t, 2H, -C*H*$_2$$CH_2$NHBoc), 2.38 (s, 3H, C*H*$_3$ of Ts), 1.42 (s, 9H, -C(C*H*$_3$)$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, CD_3OD) δ 158.2 (C=O, Boc), 145.0, 141.2 (C_q-Ar), 130.4, 128.6 (C-Ar), 128.0, 126.5 (C-2, C-5), 126.7 (C-3), 111.7 (C-4), 80.1 (-*C*(CH$_3$)$_3$), 40.5 (-CH_2*C*H$_2$NHBoc), 37.2 (-*C*H$_2$$CH_2$NHBoc), 28.8 (-C(*C*H$_3$)$_3$), 21.5 (*C*H$_3$ of Ts). HRESIMS *m/z* found 419.1063 calcd. for $C_{18}H_{24}N_2O_4NaS_2$ $(M+Na)^+$: 419.1070.

1,3-Dipolar cycloaddition of 2f with benzyl azide (Table 1, entry 11).

Following the general procedure and starting from **2f** (150 mg, 0.287 mmol) in toluene for 58 h at 50 °C, pyrrole **4f** (129 mg, 0.260 mmol, 91%) was isolated after chromatographic purification (EtOAc:cyclohexane 1:4) as a colorless oil.

1,3-Dipolar cycloaddition of 2g with benzyl azide (Table 1, entry 12).

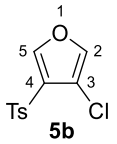


4g

Following the general procedure and starting from **2g** (149 mg, 0.337 mmol) in toluene for 2 h at 110 °C, pyrrole **4g** (108 mg, 0.262 mmol, 78%) was isolated after chromatographic purification (EtOAc:cyclohexane 1:5) as a white solid.

IR ($\bar{\upsilon}$) 3417 (NH), 2979, 1746, 1705 (C=O), 1509, 1370, 1255, 836 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.77 (d, 1H, $J_{H,H}$ = 2.4, H-2 or H-5), 7.32 (d, 1H, H-5 or H-2), 7.04 (t, 1H, $J_{H,H}$ = 5.6, NH), 4.20 (q, 2H, $J_{H,H}$ = 7.1, -CH_2CH$_3$), 3.17-3.10 (m, 2H, -CH$_2$CH_2NHBoc), 2.88-2.83 (m, 2H, -CH_2CH$_2$NHBoc), 1.58 (s, 9H, -C(CH_3)$_3$), 1.38 (s, 9H, -C(CH_3)$_3$), 1.26 (t, 3H, -CH$_2$CH_3). ^{13}C{^{1}H}-NMR (75.4 MHz, DMSO-d_6) δ 162.4 (C=O, COOEt), 155.6, 146.9 (C=O, Boc), 125.7, 117.34 (C-2, C-5), 120.0 (C-3), 117.27 (C-4), 85.4, 77.8 (-*C*(CH$_3$)$_3$), 59.9 (-*C*H$_2$CH$_3$), 39.0 (-CH$_2$*C*H$_2$NHBoc), 31.5 (-*C*H$_2$CH$_2$NHBoc), 28.2, 27.4 (-C(*C*H$_3$)$_3$), 14.2 (-CH$_2$*C*H$_3$). HRESIMS *m/z* found 437.1713 calcd. for $C_{19}H_{30}N_2O_6NaS$ $(M+Na)^+$: 437.1717.

1,3-Dipolar cycloaddition of 3b with benzyl azide (Table 1, entry 15).

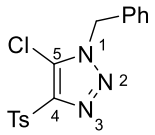


5b

Following the general procedure and starting from **3b** (157 mg, 0.554 mmol) in toluene for 1 h at 110 °C, furan **5b** (120 mg, 0.468 mmol, 85%, white solid) and triazole **9b** (24 mg, 0.069 mmol, 12%, pale yellow oil) were isolated after chromatographic purification (EtOAc:cyclohexane 1:5).

Data for **5b**: IR ($\bar{\upsilon}$) 3153, 1595, 1325, 1148, 817 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.03 (d, 1H, $J_{H,H}$ = 1.9, H-2 or H-5), 7.92-7.88 (m, 2H, H-Ar), 7.43 (d, 1H, H-5 or H-2), 7.35-7.32 (m, 2H, H-Ar), 2.43 (s, 3H, CH_3 of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 147.5, 141.8 (C-2, C-5), 145.1, 137.6 (C_q-Ar),

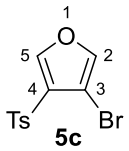
130.0 (C-Ar), 128.3 (C_q-Ar), 128.2 (C-Ar), 113.7 (C_q-Ar), 21.8 (*C*H_3 of Ts). HRESIMS *m/z* found 278.9855 calcd. for $C_{11}H_9ClO_3NaS$ $(M+Na)^+$: 278.9853.



9b

IR (ū) 3032, 1595, 1335, 1166, 813 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98-7.94 (m, 2H, H-Ar), 7.37-7.31 (m, 5H, H-Ar), 7.30-7.26 (m, 2H, H-Ar), 5.49 (s, 2H, C*H*$_2$Ph), 2.42 (s, 3H, C*H*$_3$ of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 145.5 (C_q-Ar), 143.8 (C-4 or C-5), 137.2, 132.5 (C_q-Ar), 130.1, 129.29, 129.27, 128.3 (C-Ar), 127.4 (C-5 or C-4), 52.8 (*C*H_2Ph), 21.8 (*C*H_3 of Ts). HRESIMS *m/z* found 370.0385 calcd. for $C_{16}H_{14}ClN_3O_2NaS$ $(M+Na)^+$: 370.0387.

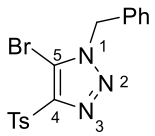
1,3-Dipolar cycloaddition of 3c with benzyl azide (Table 1, entry 16).



5c

Following the general procedure and starting from **3c**[27d] (119 mg, 0.364 mmol) in toluene for 1 h at 110 °C, furan **5c** (86 mg, 0.29 mmol, 80%, white solid) and triazole **9c** (14 mg, 0.035 mmol, 10%, pale yellow oil) were isolated after chromatographic purification (EtOAc:cyclohexane 1:5→1:2).

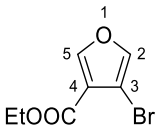
Data for **5c**: IR (ū) 3127, 1594, 1323, 1148, 870 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07-8.06 (m, 1H, H-2 or H-5), 7.93-7.91 (m, 2H, H-Ar), 7.45-7.44 (m, 1H, H-5 or H-2), 7.35-7.32 (m, 2H, H-Ar), 2.44 (s, 3H, C*H*$_3$ of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 148.0, 144.0 (C-2, C-5), 145.1, 137.5 (C_q-Ar), 129.9, (C-Ar), 129.4 (C_q-Ar), 128.4 (C-Ar), 97.7 (C_q-Ar), 21.8 (*C*H_3 of Ts). HRESIMS *m/z* found 322.9347 calcd. for $C_{11}H_9BrO_3NaS$ $(M+Na)^+$: 322.9348.



9c

IR (ū) 2923, 1595, 1338, 1157, 815 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99-7.95 (m, 2H, H-Ar), 7.37-7.30 (m, 5H, H-Ar), 7.29-7.26 (m, 2H, H-Ar), 5.54 (s, 2H, C*H*$_2$Ph), 2.42 (s, 3H, C*H*$_3$ of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 146.7 (C-4), 145.5, 137.2 (C_q-Ar), 132.7 (C_q-Ar), 130.1, 129.3, 129.2, 128.3, 128.26 (C-Ar), 113.5 (C-5), 53.6 (*C*H_2Ph), 21.8 (*C*H_3 of Ts). HRESIMS *m/z* found 413.9879 calcd. for $C_{16}H_{14}BrN_3O_2NaS$ $(M+Na)^+$: 413.9882.

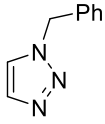
1,3-Dipolar cycloaddition of 3d with benzyl azide (Table 1, entry 17).



5d

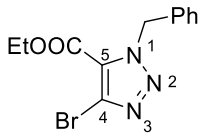
Following the general procedure and starting from **3d**[27e] (140 mg, 0.572 mmol) in toluene for 1 h at 110 °C, furan **5d** (78 mg, 0.36 mmol, 63%, colorless oil) and triazoles **7** (61 mg, 0.38 mmol, 66%, white solid), **8d** (11 mg, 0.036 mmol, 6%, yellow oil) and **9d** (43 mg, 0.14 mmol, 24%, white solid) were isolated after chromatographic purification (EtOAc:cyclohexane 1:20→1:10→1:5→1:1→EtOAc).

Data for **5d**: IR (ῡ) 2982, 1729, 1715 (C=O), 1566, 1309, 1037, 875 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1H, $J_{2,5}$ = 1.8, H-2), 7.46 (d, 1H, H-5), 4.31 (q, 1H, $J_{H,H}$ = 7.1, -CH_2CH$_3$), 1.34 (t, 3H, -CH$_2$CH_3). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 161.6 (C=O), 149.0 (C-2), 143.1 (C-5), 118.6 (C-4), 99.8 (C-3), 60.8 (-*C*H$_2$CH$_3$), 14.3 (-CH$_2$*C*H$_3$). HRESIMS *m/z* found 218.9648 calcd. for $C_7H_8BrO_3$ $(M+H)^+$: 218.9651.



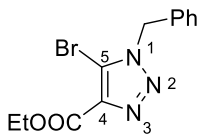
7

Data for **7**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H, H-Ar), 7.41 (bs, 1H, H-Ar), 7.31-7.25 (m, 3H, H-Ar), 7.19-7.16 (m, 2H, H-Ar), 5.48 (s, 2H, CH_2Ph). Its spectroscopic data are in accordance with those described in the bibliography.[32]



8d

Data for **8d**: IR (ῡ) 2922, 1722 (C=O), 1512, 1328, 1274, 1102, 839 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H, H-Ar), 5.91 (s, 2H, CH_2Ph), 4.37 (q, 2H, $J_{H,H}$ = 7.1, -CH_2CH$_3$), 1.37 (t, 3H, -CH$_2$CH_3). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 157.7 (C=O), 134.6 (C_q-Ar), 131.1 (C-4), 129.0, 128.8, 128.1 (C-Ar), 126.1 (C-5), 62.4 (-*C*H$_2$CH$_3$), 55.0 (*C*H$_2$Ph), 14.1 (-CH$_2$*C*H$_3$). HRESIMS *m/z* found 310.0184 calcd. for $C_{12}H_{13}BrN_3O_2$ $(M+H)^+$: 310.0186.

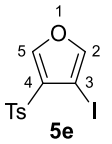


9d

Data for **9d**: IR (ῡ) 2921, 1731 (C=O), 1505, 1343, 1278, 1197, 844 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H, H-Ar), 5.60 (s, 2H, CH_2Ph), 4.42 (q, 2H, $J_{H,H}$ = 7.1, -CH_2CH$_3$), 1.40 (t, 3H, -CH$_2$CH_3). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 159.9 (C=O), 138.0 (C-4), 133.3 (C_q-Ar), 129.1, 128.9, 128.0 (C-Ar), 116.2 (C-5), 61.6 (-*C*H$_2$CH$_3$),

53.2 (*C*H_2Ph), 14.3 (-CH_2*C*H_3). HRESIMS *m/z* found 310.0184 calcd. for $C_{12}H_{13}BrN_3O_2$ $(M+H)^+$: 310.0186.

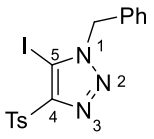
1,3-Dipolar cycloaddition of 3e with benzyl azide (Table 1, entry 18).



5e

Following the general procedure and starting from **3e** (151 mg, 0.403 mmol) in toluene for 1 h at 110 °C, furan **5e** (113 mg, 0.326 mmol, 81%, pale yellow solid) and triazole **9e** (14 mg, 0.033 mmol, 8%, pale yellow oil) were isolated after chromatographic purification (EtOAc:cyclohexane 1:5→1:2).

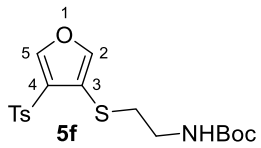
Data for **5e**: IR (ū) 2922, 1592, 1313, 1139, 810 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 1H, $J_{H,H}$ = 1.8, H-2 or H-5), 7.94-7.90 (m, 2H, H-Ar), 7.43 (d, 1H, H-5 or H-2), 7.34-7.31 (m, 2H, H-Ar), 2.42 (s, 3H, C*H*$_3$ of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 148.8, 148.1 (C-2, C-5), 144.9, 137.4 (C_q-Ar), 131.0 (C-4), 129.8, 128.5 (C-Ar), 62.1 (C-3), 21.8 (*C*H_3 of Ts). HRESIMS *m/z* found 370.9204 calcd. for $C_{11}H_9IO_3NaS$ $(M+Na)^+$: 370.9209.



9e

IR (ū) 2921, 1595, 1329, 1152, 813 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 2H, $J_{H,H}$ = 8.3, H-Ar), 7.35-7.33 (m, 5H, H-Ar), 7.28-7.26 (m, 2H, H-Ar), 5.59 (s, 2H, C*H*$_2$Ph), 2.42 (s, 3H, C*H*$_3$ of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 151.2 (C-4), 145.4, 137.2, 133.1 (C_q-Ar), 130.1, 129.2, 129.1, 128.4, 128.2 (C-Ar), 81.8 (C-4), 55.0 (*C*H_2Ph), 21.8 (*C*H_3 of Ts). HRESIMS *m/z* found 461.9740 calcd. for $C_{16}H_{14}IN_3O_2NaS$ $(M+Na)^+$: 461.9744.

1,3-Dipolar cycloaddition of 3f with benzyl azide (Table 1, entry 20).



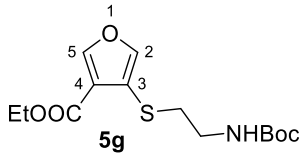
5f

Following the general procedure and starting from **3f** (151 mg, 0.355 mmol) in toluene for 1 h at 110 °C, furan **5f** (127 mg, 0.320 mmol, 90%) was isolated after chromatographic purification (EtOAc:cyclohexane 1:3) as a yellow oil.

IR (ū) 3386 (NH), 2977, 1700 (C=O), 1504, 1319, 1148, 872 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 1H, $J_{H,H}$ = 1.7, H-2 or H-5), 7.93 (d, 1H, $J_{H,H}$ = 8.3, H-Ar), 7.50 (ap. s, 1H, H-5 or H-2), 7.32 (d, 2H, H-Ar), 5.05 (bs, 1H, NH), 3.24 (q, 2H, $J_{H,H}$ = 6.0, -CH_2C*H*$_2$NHBoc), 2.85 (t, 2H, -C*H*$_2$$CH_2$NHBoc),

2.42 (s, 3H, CH_3 of Ts), 1.43 (s, 9H, -C(CH_3)$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 155.9 (C=O, Boc), 148.4, 147.7 (C-2, C-5), 144.9, 137.9, 131.1 (C_q-Ar), 129.8, 128.2 (C-Ar), 114.4 (C_q-Ar), 79.6 (-*C*(CH$_3$)$_3$), 39.4 (-CH$_2$*C*H$_2$NHBoc), 36.1 (-*C*H$_2$CH$_2$NHBoc), 28.5 (-C(*C*H$_3$)$_3$), 21.8 (*C*H$_3$ of Ts). HRESIMS *m/z* found 420.0906 calcd. for $C_{18}H_{23}NO_5NaS_2$ $(M+Na)^+$: 420.0910.

1,3-Dipolar cycloaddition of 3g with benzyl azide (Table 1, entry 21).



5g

Following the general procedure and starting from **3g** (150 mg, 0.440 mmol) in toluene for 1 h at 110 °C, furan **5g** (128 mg, 0.405 mmol, 92%) was isolated after chromatographic purification (EtOAc:cyclohexane 1:5) as a colorless oil.

IR (ῡ) 3379 (NH), 2983, 1687 (C=O), 1567, 1322, 1154, 880 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (d, 1H, $J_{H,H}$ = 1.7, H-2 or H-5), 7.43 (d, 1H, H-5 or H-2), 5.09 (bs, 1H, NH), 4.29 (q, 1H, $J_{H,H}$ = 7.1, -C*H*$_2$CH$_3$), 3.30 (bs, 2H, -CH$_2$C*H*$_2$NHBoc), 2.92 (t, 2H, $J_{H,H}$ = 6.5, -C*H*$_2$CH$_2$NHBoc), 1.41 (s, 9H, -C(C*H*$_3$)$_3$), 1.33 (t, 3H, -CH$_2$C*H*$_3$). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 162.6 (C=O, COOEt), 155.9 (C=O, Boc), 149.6, 143.3 (C-2, C-5), 119.4, 117.4 (C-3, C-4), 79.6 (-*C*(CH$_3$)$_3$), 60.7 (-*C*H$_2$CH$_3$), 39.3 (-CH$_2$*C*H$_2$NHBoc), 34.3 (-*C*H$_2$CH$_2$NHBoc), 28.5 (-C(*C*H$_3$)$_3$), 14.4 (-CH$_2$*C*H$_3$). HRESIMS *m/z* found 338.1029 calcd. for $C_{14}H_{21}NO_5NaS$ $(M+Na)^+$: 338.1033.

Huisgen cycloaddition between 1e and benzyl azide: synthesis of triazoles 8e and 9e. To a solution of **1e** (50 mg, 0.16 mmol) in toluene (0.4 mL), a solution of benzyl azide (32 mg, 0.24 mmol) in toluene (0.3 mL) was added and the reaction mixture was stirred at 110 °C for 1 h. Then, the solvent was evaporated and the resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:5→1:2) to give regioisomeric triazoles **8e** (39 mg, 0.090 mmol) and **9e** (35 mg, 0.079 mmol) as yellow oils in quantitative yield.

Data for **8e**: IR (ῡ) 2921, 1593, 1334, 1141, 814 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H, H-Ar), 7.20-7.16 (m, 2H, H-Ar), 7.11-7.08 (m, 2H, H-Ar), 6.01 (s, 2H, -C*H*$_2$Ph), 2.35 (s, 3H, C*H*$_3$ of Ts). ^{13}C{^{1}H}-NMR (75.4 MHz, $CDCl_3$) δ 146.1 (C_q-Ar), 137.6 (C-5), 136.2 (C_q-Ar), 134.2 (C_q-Ar),

129.9, 129.1, 128.7, 128.0 (C-Ar), 94.8 (C-4), 55.0 (-*C*H_2Ph), 21.8 (*C*H_3 of Ts). HRESIMS *m/z* found 461.9743 calcd. for $C_{16}H_{14}IN_3O_2NaS$ $(M+Na)^+$: 461.9744.

Supporting information.

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

Example of the determination of the Path A/Path B ratio by ^{1}H-NMR analysis of the cycloaddition crude mixture.

Example of the determination of the percentage of N-Boc deprotection in β-substituted pyrroles.

^{1}H- and ^{13}C-NMR spectra for new compounds.

^{1}H-NMR spectra for known compounds.

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