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3-(Triflyloxy)benzynes Enable the Regiocontrolled Cycloaddition of Cyclic Ureas to Synthesize 1,4-Benzodiazepine Derivatives

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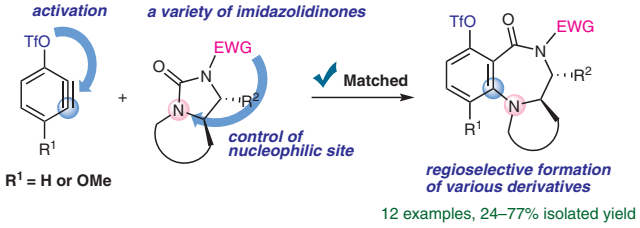

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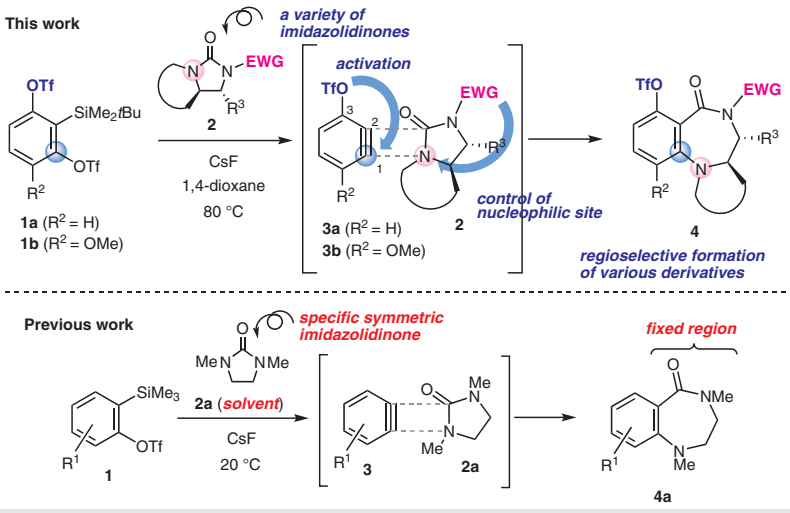
Abstract A versatile synthesis of 1,4-benzodiazepine derivatives through the reaction of various 3-(trifluoromethanesulfonyloxy)benzynes with *N*-(*p*-toluenesulfonyl)imidazolidin-2-ones is reported. This reaction system provides a 1,4-benzodiazepine bearing a trifluoromethanesulfonyloxy group as a single regioisomer among the four possible regioisomers.

Keywords benzodiazepines, benzynes, triflyloxy group, imidazolidinones, regioselectivity, directing group

Benzynes are key reaction intermediates for the synthesis of polysubstituted benzenes and fused aromatic compounds.[1,2] However, regiocontrol of the reactions of unsymmetrically substituted benzynes to afford desired products with high regioselectivity is particularly challenging. Consequently, several benzyne substituents have thus been developed to direct the orientation of such reactions, with the majority of these substituents being introduced at the C-3 position of the benzyne skeleton.[3–5] For example, Hosoya and co-workers[6a] and our group[6b] have reported the introduction of a trifluoromethanesulfonyloxy (triflyloxy) group to impart regioselective control on these cycloaddition reactions. The effect of this group was superior to that of the methoxy group, due to the greater electron-withdrawing nature of the triflyloxy group.[6b] Moreover, the triflyloxy directing group can be easily converted into a range of other substituents through palladium-catalyzed coupling reactions of the benzyne reaction products. Here, we provide tangible evidence for the efficiency of the triflyloxy group in a highly versatile synthesis of 1,4-benzodiazepines **4**, which are important scaffolds for drug discovery.[7–9] We propose that this conversion takes place through a regiocontrolled cycloaddition reaction of 3-(triflyloxy)benzynes **3a** or **3b** with a range of imidazolidin-2-one derivatives **2** (Scheme 1).

Yoshida and co-workers reported a synthesis of 1,4-benzodiazepines **4a** through the cycloaddition reaction of benzynes **3** with 1,3-dimethylimidazolidin-2-one (**2a**; Scheme 1);[9a] however, examples were limited to the symmetrical imidazolidin-2-one **2a** for the preparation of benzodiazepine **4a**, where **2a** (23 equiv) also acted as the reaction solvent. The application of nonsymmetrical imidazolidin-2-ones in similar reactions with benzyne remains largely unexamined. To address this problem, we report the use of a range of imidazolidin-2-ones **2**, each bearing an electron-withdrawing tosyl group on one of the two nitrogen atoms, to achieve regioselective addition to benzynes through differentiation of the nucleophilicities of the two nitrogen atoms. Our method is expected to be effective due to the presence of the strongly electron-withdrawing triflyloxy group at the C-3 position of the benzynes **3a** and **3b**, which should render the C-1 position more electrophilic, thereby permitting control of the reactive site, and promoting nucleophilic addition of the less-reactive *N*-tosylimidazolidin-2-ones **2** to give **4**.

Initially, we examined the influence of the R^1 substituent at the C-3 position of benzynes **3**, generated from the corresponding 2-(trimethylsilyl)phenyl triflates **1c–f** by reaction with CsF in 1,4-dioxane at 80 °C. The resulting benzynes **3** reacted with 1-methyl-3-(*p*-toluenesulfonyl)imidazolidin-2-one (**2b**; R^3 = Ts), and the results are outlined in Table 1 (entries 1–4). The reactions of the unsubstituted benzyne **3c** (R^1 = H) and the 3-methoxybenzyne **3d** (R^1 = OMe) with **2b** did not produce the desired 1,4-benzodiazepines **4b** and **4c** (Table 1, entries 1 and 2), probably due to the insufficient electrophilicities of **3c** and **3d**. Whereas the reaction of the more electrophilic 3-fluorobenzyne **3e** (R^1 = F) with **2b** provided 6-fluoro-1,4-benzo-



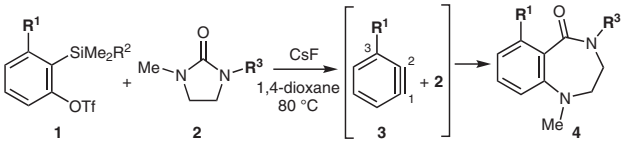
Scheme 1 Comparison of the previous and current work on the reaction of benzynes **3** with imidazolidin-2-ones **2**

diazepine **4d** in 34% isolated yield (entry 3), the reaction with 3-(triflyloxy)benzyne **3a** (R^1 = OTf), generated from **1f**,[6c] gave 6-(triflyloxy)-1,4-benzodiazepine **4e** in a significantly higher yield (65%), along with a small amount of the phenol derivative **4e′** (4%, R^1 = OH) (entry 4). However, a slightly better yield (69%) of **4e** was obtained by using 2-(*tert*-butyldimethylsilyl)phenyl triflate **1a**[6b] (R^2 = *t*-Bu) as a precursor for **3a** (entry 5). Importantly, the regioselectivity of this transformation was successfully controlled by the presence of a triflyloxy group in **3a** and a tosyl group in **2b** to produce **4e** as a single regioisomer.

Note that a similar reaction of **3a** with 1,3-dimethylimidazolidin-2-one (**2a**; R^3 = Me), which should be more nucleophilic than **2b**, produced a lower yield (48%) of the desired product **4f** (Table 1, entry 6) compared with that of **4e**. These contrasting results also indicate the importance of a suitable combination of the less nucleophilic tosyl-containing urea **2b** and the highly electrophilic 3-(triflyloxy)benzyne **3a** (R^1 = OTf) to achieve efficient coupling of these two components. In addition, a similar reaction of 1-benzyl-3-methylimidazolidin-2-one (**2c**; R^3 = Bn) with **3a** gave a mixture of two regioisomers **4g** (43%) and **4g′** (11%) (entry 7). This result clearly indicates that the steric differences between the methyl and benzyl groups of **2c** have no significant effect in determining the nucleophilic site of the urea reagent. Furthermore, the reactions of benzyne **3a** (R^1 = OTf) with imidazolidin-2-ones **2d–f** bearing other electron-withdrawing substituents, such as mesyl (R^3 = Ms), acetyl (R^3 = Ac), or carbobenzyloxy (R^3 = Cbz) groups gave lower yields (23–43%) of the corresponding products **4h–j** (entries 8–10).

After the successful reaction of 3-(triflyloxy)benzyne (**3a**) with 1-tosyl-1,3-imidazolidin-2-one (**2b**), we examined the scope and limitations of a range of 1-tosylimidazolidin-2-ones **2g–j** in the reaction with 3-(triflyloxy)benzyne (**3a**). The reactions of imidazolidin-2-ones bearing benzyl and allyl groups instead of methyl groups on their nitrogen atoms (**2g** and **2h**) gave the corresponding benzodiazepines **4k** and **4l** (Table 2, entries 1 and 2), albeit in slightly lower yields (43 and 30%, respectively) than that of **4e** (Table 1,

Table 1 Optimization of the R^1 and R^3 Substituents of Benzyne **3** and Imidazolidin-2-one **2**[a]

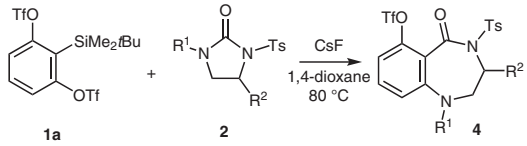


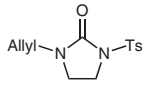
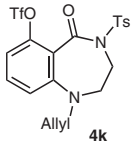
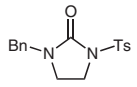
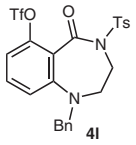
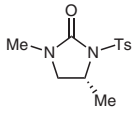
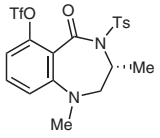
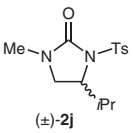
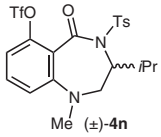
Entry	R^1	R^2	1	R^3	2	3	4	Yield[b] (%)
1	H	Me	**1c**	Ts	**2b**	**3c**	**4b**	0[c]
2	OMe	Me	**1d**	Ts	**2b**	**3d**	**4c**	0[c]
3	F	Me	**1e**	Ts	**2b**	**3e**	**4d**	34
4	OTf	Me	**1f**	Ts	**2b**	**3a**	**4e**	65 (4)[d]
5	OTf	*t*-Bu	**1a**	Ts	**2b**	**3a**	**4e**	69[e]
6	OTf	*t*-Bu	**1a**	Me	**2a**	**3a**	**4f**	48
7[f]	OTf	*t*-Bu	**1a**	Bn	**2c**	**3a**	**4g**	43 (11)[g]
8	OTf	*t*-Bu	**1a**	Ms	**2d**	**3a**	**4h**	43
9	OTf	*t*-Bu	**1a**	Ac	**2e**	**3a**	**4i**	42
10	OTf	*t*-Bu	**1a**	Cbz	**2f**	**3a**	**4j**	23

[a] Reaction conditions: **1** (1.0 equiv), **2** (3.0 equiv), CsF (3.0 equiv), 1,4-dioxane, 80 °C, 40–60 min.
[b] Isolated yield.
[c] No benzodiazepines were observed.
[d] In addition to **4e**, the hydrolyzed benzodiazepine **4e′** (R^1 = OH) was also isolated in 4% yield.
[e] The hydrolyzed benzodiazepine **4e′** (R^1 = OH) was not observed.
[f] Reaction at r.t. for 3 h.
[g] In addition to **4g**, 1-benzyl-4-methyl-6-(triflyloxy)-1,4-benzodiazepine (**4g′**) was also isolated in 11% yield.

entry 5). This is probably due to steric hindrance; however, these protecting groups can be easily cleaved when required. We then examined the reactions of **2i** and **2j** bearing alkyl substituents (methyl or isopropyl) at the C-5 position. In this case, the desired products **4m** and **4n** were obtained in 44 and 24% isolated yields, respectively. Furthermore, the chiral integrity of the optically active (*R*)-**2i** (89% ee) was maintained during the cycloaddition reaction to produce (*R*)-**4m** (89% ee) (entry 3). Unfortunately, a similar reaction of **3a** with the six-membered urea, 1-tosyltetrahydropyrimidin-2-one, did not provide the desired 1,4-benzodiazocine.

Table 2 Synthesis of 1,4-Benzodiazepines **4** with Various Monocyclic Ureas **2**: Scope and Limitations[a]

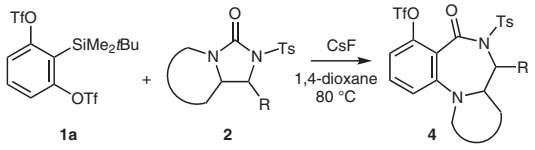


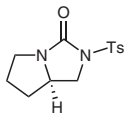
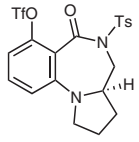
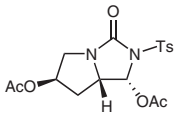
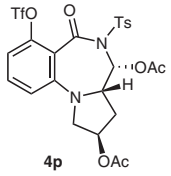
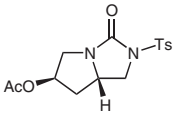
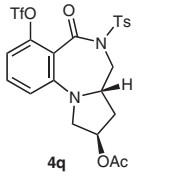
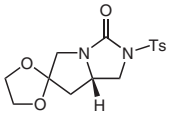
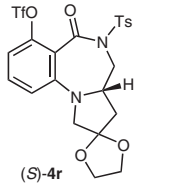
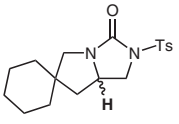
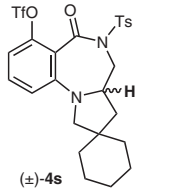
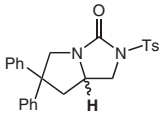
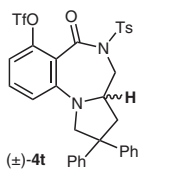
Entry	Cyclic amide **2**	Product **4**	Yield[b] (%)
1	 **2g**	 **4k**	43 (11)[c]
2	 **2h**	 **4l**	30
3	 (*R*)-**2i** (89% ee)	 (*R*)-**4m** (89% ee)	44
4	 (±)-**2j**	 Me (±)-**4n**	24

[a] Conditions: **1a** (1.0 equiv), **2** (3.0 equiv), CsF (3.0 equiv), 1,4-dioxane, 80 °C, 40–50 min.
[b] Isolated yield.
[c] In addition to **4k**, the hydrolyzed benzodiazepine **4k′** bearing a phenolic hydroxyl group was also isolated in 11% yield.

The reactions of fused bicyclic imidazolidin-2-ones **2k–p** with 3-(triflyloxy)benzyne (**3a**), generated from **1a**, provided the desired pyrrolo-1,4-benzodiazepines **4o–t** (Table 3). Interestingly, the resulting products were obtained in greater yields (49–77%) than those of the 1,4-benzodiazepines **4e** and **4k–n** from the corresponding monocyclic substrates **2b** and **2g–j** (Tables 1 and 2). This improvement can be accounted for by firstly considering

Table 3 Synthesis of Pyrrolo-1,4-benzodiazepines **4** by Using Fused Cyclic Ureas **2**: Scope and Limitations[a]

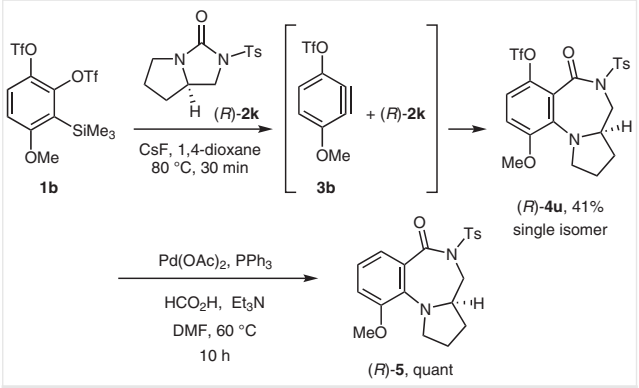


Entry	Fused cyclic urea **2**	Product **4**	Yield[b] (%)
1	 (*R*)-**2k** (88% ee)	 (*R*)-**4o** (88% ee)	70
2	 **2l**	 **4p**	63
3	 **2m**	 **4q**	73
4	 (*S*)-**2n**	 (*S*)-**4r**	77
5	 (±)-**2o**	 (±)-**4s**	75
6	 (±)-**2p**	 (±)-**4t**	49

[a] Conditions: **1a** (1.0 equiv), **2** (3.0 equiv), CsF (3.0 equiv), 1,4-dioxane, 80 °C, 40–50 min.
[b] Isolated yield.

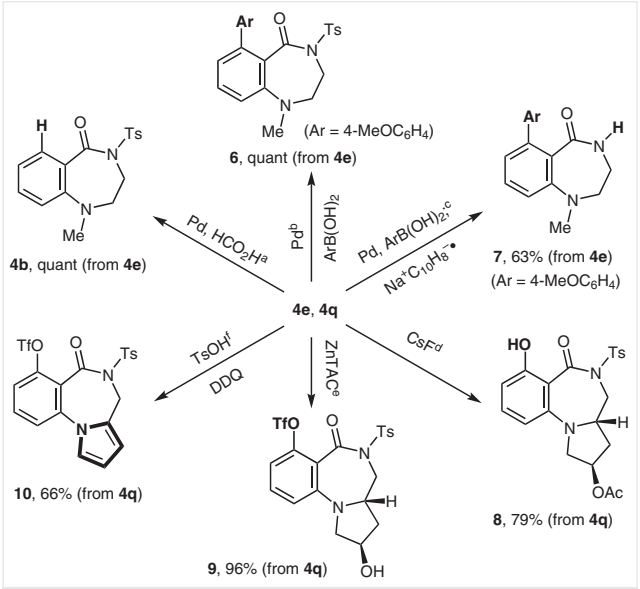
that the orbitals for the lone-pair of electrons on the nitrogen atoms at the ring junctions in **2k–p** should have more s-character, due to the presence of two fused five-membered rings, thereby producing less conjugation with the carbonyl group (see calculated data for the s-character in the Supporting Information). Additionally, it should also be considered that the 5,5-fused ring systems of **2k–p** should be fixed in the *cis*-configuration at the ring junctions, thereby hampering inversion of the nitrogen center. For these two reasons, the lone pair of electrons on the nitrogen atom should be more nucleophilic. We also found that the substituents present on **2** had no significant effect on the yields of **4o–t** (Table 3, entries 2–6). Additionally, both the acetoxy group (entries 2 and 3) and the acetal moiety (entry 4) were tolerated under the reaction conditions that were used.

We then examined the reaction of **2k** with 3-methoxy-6-(triflyloxy)benzyne (**3b**), generated from 1,2-bis(triflyloxy)-4-methoxy-3-(trimethylsilyl)benzene (**1b**), which gave the 9-methoxy-6-(triflyloxy)-1,4-benzodiazepine **4u** in 41% isolated yield as a single regioisomer (Scheme 2). This result clearly indicates that the triflyloxy group exerts a significantly stronger directing effect than the methoxy group in the reaction of benzynes. Following the successful preparation of **4u**, the triflyloxy group was effectively removed by a palladium catalyst in the presence of formic acid to give 9-methoxy-1,4-benzodiazepine **5** quantitatively. The 1,4-benzodiazepine **5** bearing an oxygen substituent at the C-9 position is regiocomplementary to **4o** synthesized from **1a**.



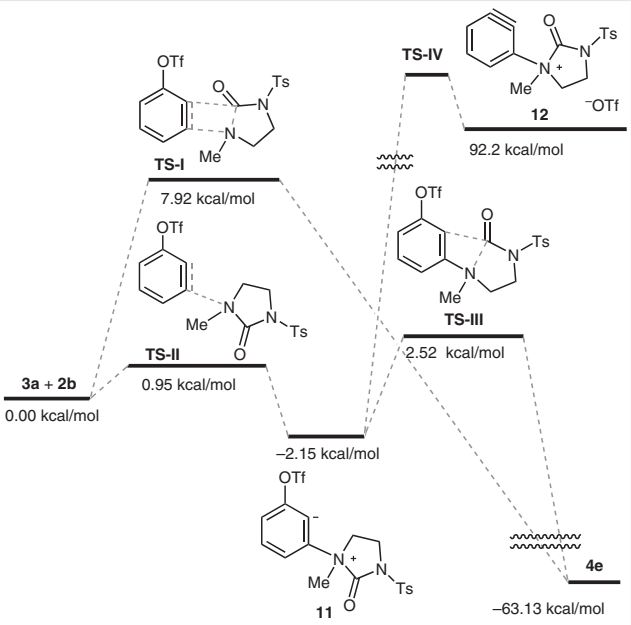
Scheme 2 Regiocontrolled synthesis of 9-methoxy-1,4-benzodiazepine **5**

The prepared 1,4-benzodiazepines **4e** and **4q** were then easily converted into a range of derivatives **4b** and **6–10,** as outlined in Scheme 3. For example, reductive cleavage of the triflyloxy group of **4e** gave benzodiazepine **4b**, attempts at the preparation of which from the unsubstituted benzyne **3c** and **2b** had previously proved unsuccessful (Table 1, entry 1). In addition, we also demonstrated the successful replacement of the triflyloxy group of **4e** with an aromatic substituent under Suzuki coupling conditions to provide the 6-aryl-1,4-benzodiazepine **6** in quantitative yield. The tosyl group of **6** was then removed by using sodium naphthalenide to provide **7**. Interestingly, the triflyl group of **4q** was easily hydrolyzed to give phenol **8** with the acetoxy group intact; this was achieved under the same reaction conditions employed for benzyne generation using CsF, but with a longer reaction time. Furthermore, treatment of **4q** with $Zn_4(OCOCF_3)_6O$ (ZnTAC)[10] resulted in the selective cleavage of the acetoxy group of **4q**, although the triflyloxy group remained intact to give **9** in 96% isolated yield. Moreover, the fused benzodiazepine **4q** was transformed into the aromatized pyrrolo-1,4-benzodiazepine **10** by a deacetoxylation/oxidation sequence.



Scheme 3 Transformations of the triflyloxy-containing 1,4-benzodiazepines **4e** and **4q.** *Reagents and conditions*: [a] **4e**, Pd(OAc), PPh_3, Et_3N, HCO_2H, DMF, 60 °C, 10 h; [b] **4e**, $Pd(PPh_3)_4$, $4\text{-MeOC}_6H_4B(OH)_2$, K_2CO_3, DMF, 80 °C, 15 h; [c] **4e**, $Pd(PPh_3)_4$, $4\text{-MeOC}_6H_4B(OH)_2$, K_2CO_3, DMF, 80 °C, 15 h, then $Na^+C_{10}H_8^{-\bullet}$, THF, r.t., 10 min; [d] **4q**, CsF, 1,4-dioxane, 80 °C, 13 h; [e] **4q**, ZnTAC, MeOH, reflux, 9 h; [f] **4q**, $TsOH{\cdot}H_2O$, DDQ, MeCN, r.t., 36 h.

Finally, we proposed two plausible mechanisms (a non-synchronous concerted mechanism and a stepwise mechanism) for the reaction between 3-(triflyloxy)benzyne (**3a**) and imidazolidin-2-one **2b**, as outlined in Scheme 4. Density functional theory (DFT) calculations were performed to study these two proposed mechanisms. The B3LYP-D3 functional with 6-31G(d) basis set was utilized for the calculations with *Gaussian09* software.[11] The structures of reactants **3a** and **2b**, product **4e**, intermediate **11**, and transition states **TS-I** to **TS-III** were optimized, and the nature of these structures were confirmed by frequency calculations.



Scheme 4 Plausible reaction mechanisms for the formation of benzodiazepines **4** via benzynes **3a**

Interestingly, the calculated activation energy for the concerted mechanism (7.92 kcal/mol) was higher than that for the stepwise mechanism (4.67 kcal/mol), and the calculated activation energy for the second step of the stepwise mechanism (4.67 kcal/mol) was significantly higher than that of the first step (0.95 kcal/mol). The DFT results, therefore, indicate that the reaction probably proceeds by a stepwise mechanism via intermediate **11**, with the rate-limiting step being the second cyclization step. In this case, the cyclization step might potentially be accelerated by the electron-withdrawing *p*-toluenesulfonyl group present on the nitrogen atom of **11**.

Although the intermediate **11** might possibly be converted into another benzyne **12** through the elimination of the triflyloxy group, the energy of **12** (92.2 kcal/mol) is too high to be reached from **11** (–2.15 kcal/mol), and therefore this conversion can be ruled out under the present reaction conditions. The stepwise mechanism, therefore, accounts for the successful preparation of the desired 1,4-benzodiazepine **4e** without the observed formation of benzyne **12**.

In summary, we have successfully developed a novel modular approach to the synthesis of 1,4-benzodiazepines through the cycloaddition reactions of 3-(triflyloxy)-benzynes with 1-(*p*-toluenesulfonyl)imidazolidin-2-ones.[12–14] The combination of highly electrophilic 3-(triflyloxy)benzynes with weakly nucleophilic imidazolidin-2-ones was the key to the success of this process. DFT calculations indicated that the reactions between 3-(triflyloxy)benzynes and cyclic ureas proceeded in a stepwise manner. Subsequent transformations of the cycloaddition products provided a range of substituted 1,4-benzodiazepines, thereby expanding the scope of this reaction. Indeed, it should be emphasized that the fused imidazolidin-2-ones provided improved yields of pyrrolo-1,4-benzodiazepines, which are found in many pharmaceutical products and drug candidates. We therefore believe that our proposed method might be suitable for application in drug-discovery programs. Further studies into the potential synthetic applications of this process, in addition to detailed mechanistic investigations, are currently underway in our laboratory, and the results will be presented in due course.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591924.

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(12) **1,4-Benzodiazepines 4; General Procedure**
CsF (3.0 equiv) was flame-dried under reduced pressure in a flask equipped with a three-way stopcock, and the flask was backfilled with argon. Cyclic urea **2** (3.0 equiv) and a magnetic stirrer bar were loaded into the flask, which was subject to three cycles of evacuation and backfilling with argon. 1,4-Dioxane (one-fifth of the total volume of the solvent) was added to the flask from a syringe. A solution of the appropriate precursor **1a–f** (1.0 equiv) in anhyd 1,4-dioxane (one-fifth of total volume) was added to the flask through a cannula, which was washed with 1,4-dioxane (three-fifth of total volume). The mixture was then stirred at 80 °C for 30–60 min until the benzyne reaction was complete (TLC). The reaction was then quenched by addition of H_2O. The aqueous phase was extracted with EtOAc (×3), and the organic phases were combined, washed with sat. brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, hexane–EtOAc).

(13) **1-Methyl-5-oxo-4-tosyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-6-yl Triflate (4e; Table 1, Entry 5)**
By following the general procedure, a mixture of CsF (46 mg, 0.30 mmol), 1-methyl-3-tosyl-2-imidazolidone (**2b**; 76 mg, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**1a**; 50 mg, 0.10 mmol) was stirred in 1,4-dioxane (1.0 mL) for 40 min at 80 °C. The crude product was purified by column chromatography [silica gel, EtOAc–hexane (1:2)] to give a colorless solid; yield: 33 mg (69%); mp 47–50 °C. IR (neat): 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 2.87 (s, 3 H), 3.36 (t, *J* = 5.5 Hz, 2 H), 4.11 (t, *J* = 5.5 Hz, 2 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 1 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 7.42 (dd, *J* = 8.0, 8.0 Hz, 1 H), 7.97 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 40.5, 44.1, 58.6, 115.6, 118.4 (q, *J* = 319 Hz), 118.6, 122.7, 128.8, 129.3, 133.1, 135.3, 145.1, 147.3, 149.4, 164.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.0. HRMS (MALDI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{17}F_3N_2NaO_6S_2$: 501.0372; found: 501.0371.
The regiochemistry of **4e** was determined by NOE experiments.

(14) **(3a*R*)-6-Oxo-5-tosyl-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-yl Triflate [(*R*)-4o; Table 3, Entry 1]**
By following the general procedure, a mixture of CsF (46 mg, 0.30 mmol), (*R*)-2-tosylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazole-3-one [(*R*)-**2k**] (84 mg, 0.30 mmol), and 2-(*tert*-butyldimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene (**1a**; 50 mg, 0.10 mmol) in 1,4-dioxane (1.0 mL) was stirred for 40 min at 80 °C. The crude product was purified by column chromatography [silica gel, EtOAc–hexane (2:3)] to give a yellow solid; yield: 35 mg (70%); mp 141–143 °C; $[\alpha]_D^{20}$ +5.5 (*c* 0.15, $CHCl_3$). IR (neat): 1699, 1684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.86–1.98 (m, 2 H), 2.05–2.16 (m, 2 H), 2.43 (s, 3 H), 3.24–3.35 (m, 2 H), 3.48–3.52 (m, 1 H), 4.07 (dd, *J* = 4.5, 16.0 Hz, 1 H), 4.24 (dd, *J* = 3.0, 16.0 Hz, 1 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 6.75 (d, *J* = 8.5 Hz, 1 H), 7.29–7.34 (m, 3 H), 7.95 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 22.1, 29.5, 45.1, 48.9, 65.8, 112.6, 116.0, 117.3, 118.4 (q, *J* = 319 Hz), 129.1, 129.2, 132.7, 135.2, 145.0, 146.4, 148.6, 164.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.1. HRMS (MALDI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{19}F_3N_2NaO_6S_2$: 527.0529; found: 527.0519.
The enantiomeric excess of the product (*R*)-**4o** was determined to be 88% by HPLC on CHIRALCEL AD-3 [hexane–*i*-PrOH (90:10), flowrate: 1.0 mL/min]; t_R [(*R*)-isomer] = 30.0 min, t_R [(*S*)-isomer] = 33.0 min. The absolute configuration was assigned on the basis of that of (*R*)-**2k**, synthesized from D-proline.