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Ring-Opening Formal Hetero-[5+2] Cycloaddition of 1-Tosyl-2,3-dihydro-1*H*-pyrroles with Terminal Alkynes: Entry to 1-Tosyl-2,3-dihydro 2,3-Dihydro-1*H*-azepines

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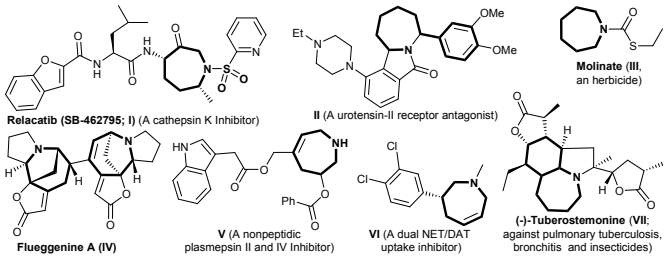
A new Lewis acid catalysed formal hetero-[5+2] cycloaddition of 2,3-dihydro-1*H*-pyrroles to terminal alkynes is described. By employing a $FeCl_3$ and $BF_3{\cdot}OEt_2$ co-catalytic strategy, the ring-opening of 1-tosyl-2,3-dihydro-1*H*-pyrroles by selective cleavage of the C(sp^2)-N bond and subsequent annulation have been achieved to access 1-tosyl 2,3-dihydro-1*H*-azepines with excellent regioselectivity, offering a new avenue for cycloaddition through the ring-opening of non-strained-ring-based units.

The cycloaddition reaction is commonly utilized in synthesis to build diverse complex ring systems, and it continues to attract attention.[1-3] However, the development of such a cycloaddition reaction capable of constructing seven-membered to larger ring systems is generally hindered by a combination of entropic factors and the presence of non-bonding interactions in the transition states preferentially leading to five- or six-membered ring products instead. In past decades, selective cycloaddition strategies that proceed by ring-opening to access seven-membered or larger ring systems in-situ by cyclometallation and/or heteroatom coordination have been developed to overcome the complications caused by the aforementioned disadvantageous entropic factors and non-bonding interactions.[1-3]

Among them, the [5+2] cycloaddition of ring-based five-atom units to π systems (e.g., alkynes, alkenes and allenes) by ring-opening and annulation to efficiently access seven-membered carbo- and heterocyclic compounds has been the focus of attention. However, the vast majority of such reactions have employed strained-ring-based five-atom units that are less accessible and versatile as synthetic building blocks.[2-4] Examples of intermolecular ring-opening and hetero-[5+2] cycloaddition reactions with alkynes are rare,[4] although they represent straightforward synthetic strategies for the construction of valuable seven-membered heterocycles, such as azepine derivatives,[5,6] which show strong bioactivity as potent inhibitors of protein kinase C, nonpeptidic plasmepsin II/IV and dual NET/DAT uptake, as well as urotensin-II receptor antagonists and herbicides (Scheme 1).[6] Stogryn[4a] and



Scheme 1. Important examples of bioactive azepine derivatives.

Hassner[4b] and their co-workers independently developed catalyst-free three-membered ring-opening and hetero-[5+2] reactions of vinylaziridines with electron-poor perfluorobut-2-yne and dimethyl but-2-ynedioate, respectively, by cleavage of the C(sp^3)-N bond for the synthesis of 2,5-dihydro-1*H*-azepines (Scheme 2a top). Recently, the Zhang and co-workers illustrated a new rhodium catalysis that made such a strategy applicable to a wide range of both vinylaziridines and alkynes (Scheme 2a bottom).[4c] We have reported a $FeCl_3$ and $BF_3{\cdot}OEt_2$ co-catalysed ring-opening and [5+2] heteroannulation of 2-(2-aminoethyl)oxiranes with alkynes for the synthesis of 2,3-dihydro-1*H*-azepines by the cleavage of two C(sp^3)-O bonds (Scheme 2b).[4d] Two protocols for the hetero-[5+2] cycloaddition reactions initiated by ring-opening by cleavage of a C-C bond have been established in which only highly active electron-poor alkynes are viable (Scheme 2c-d).[4e-g] More promisingly, less strained 2,3-dihydro-1*H*-pyrroles[4g] have been employed in hetero-[5+2] cycloaddition reactions in which the C=C bond was selectively broken, although this approach is limited to special 2,3-dihydro-1*H*-pyrroles and electron-poor alkynes (Scheme 2d). On this basis, we envisioned that by utilizing a potent catalytic system, common 2,3-dihydro-1*H*-pyrroles might undergo ring-opening by the selectively

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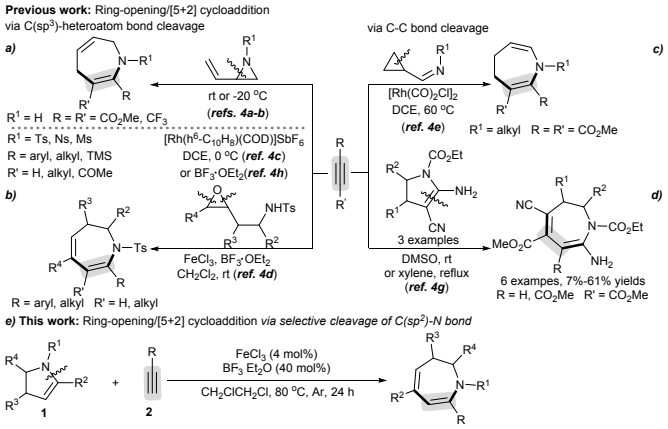
cleavage of a chemical bond to enable formal hetero-[5+2] cycloaddition reactions with various π systems.

Thus, we report herein a new Lewis acid catalysed ring-opening and formal [5+2] cycloaddition of 1-tosyl-2,3-dihydro-1*H*-pyrroles to terminal alkynes by C(sp^2)-N bond cleavage (Scheme 2e). An inexpensive $FeCl_3$/$BF_3{\cdot}Et_2O$ co-catalytic system[7] proved effective for the conversion of various common 1-tosyl-2,3-dihydro-1*H*-pyrroles into 1-tosyl-2,3-dihydro-1*H*-azepines by ring-opening and annulation with alkynes, thus providing a catalytic hetero-[5+2] cycloaddition triggered by selective cleavage of the C(sp^2)-N bond[8] using a two Lewis acids co-catalysed strategy.

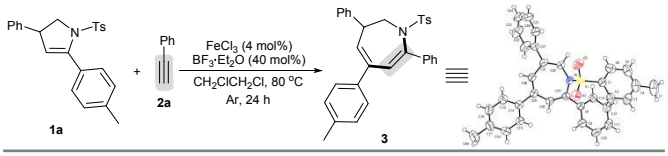


Scheme 2. [5+2] Cycloaddition *via* ring-opening.

We started our investigation initiated by exploring the ring-opening/formal [5+2] cycloaddition reaction between 3-phenyl-5-(*p*-tolyl)-1-tosyl-2,3-dihydro-1*H*-pyrrole (**1a**) and phenylacetylene (**2a**) using different Lewis acid catalysts (Table 1). The reaction was efficiently catalysed by combining 4 mol% $FeCl_3$ and 40 mol% $BF_3{\cdot}Et_2O$ in CH_2ClCH_2Cl at 80 °C, which gave the desired 1-tosyl-2,3-dihydro-1*H*-azepine **3** in 73% yield (entry 1), whose structure was unambiguously confirmed by X-ray crystallography analysis.[9] It was noted that the reaction could afford **3** in the absence of either $BF_3{\cdot}Et_2O$ or $FeCl_3$ (entries 2 and 4), albeit in a lower yield. Increasing the amount of $BF_3{\cdot}Et_2O$ and $FeCl_3$, respectively, did not improve the yield (entries 3 and 5). A series of Lewis acids, including $Fe(OTf)_3$, $Fe(acac)_3$, $AgSbF_6$, $CuCl_2$, $Sc(OTf)_3$, $InCl_3$ and $AlCl_3$, were examined. Both $Fe(OTf)_3$ (entry 6) and $AgSbF_6$ (entry 8) displayed high catalytic efficiency, giving fairly good yields of the product, but $Fe(acac)_3$ was less effective (entry 7). The other Lewis acids (entry 9) gave similar results to that obtained in the absence of $FeCl_3$ (entry 4). However, by using only $Sc(OTf)_3$ as the catalyst (entry 10), the amount of azepine 3 was negligible after this reaction. When the reaction was performed in two other solvents, namely CH_2Cl_2 and $MeNO_2$, lower yields were obtained (entries 11 and 12). Reducing the temperature (60 °C) had a negative effect (entry 13), whereas raising the temperature (100 °C) led to a similar yield to that obtained at 80 °C (entry 14). The optimal reaction conditions were suitable for scaling up the reaction of 1-tosyl-2,3-dihydro-1*H*-pyrrole **1a** to 1 mmol, giving azepine **3** in good yield (entry 15).

With the optimal conditions in hand, we explored the scope of this ring-opening/formal [5+2] cycloaddition reaction of 3-phenyl-5-(*p*-tolyl)-1-tosyl-2,3-dihydro-1*H*-pyrrole (**1a**) with a wide range of alkynes **2** (Scheme 3). The reactions proceeded well with electron-rich

Table 1 Screening of optimal reaction conditions[a]



Entry	Variation from the standard conditions	Yield (%)[b]
1	none	73
2	without $BF_3{\cdot}Et_2O$	36
3	$BF_3{\cdot}Et_2O$ (80 mol%)	68
4	without $FeCl_3$	50
5	$FeCl_3$ (6 mol%)	71
6	$Fe(OTf)_3$ instead of $FeCl_3$	70
7	$Fe(acac)_3$ instead of $FeCl_3$	59
8	$AgSbF_6$ instead of $FeCl_3$	72
9	$CuCl_2$, $Sc(OTf)_3$, $InCl_3$ or $AlCl_3$ instead of $FeCl_3$	46-51
10	$Sc(OTf)_3$ instead of the $FeCl_3$/$BF_3{\cdot}Et_2O$ system	trace
11	CH_2Cl_2 instead of CH_2ClCH_2Cl	52
12	$MeNO_2$ instead of CH_2ClCH_2Cl	53
13	At 60 °C	38
14	At 100 °C	68
15[c]	none	62

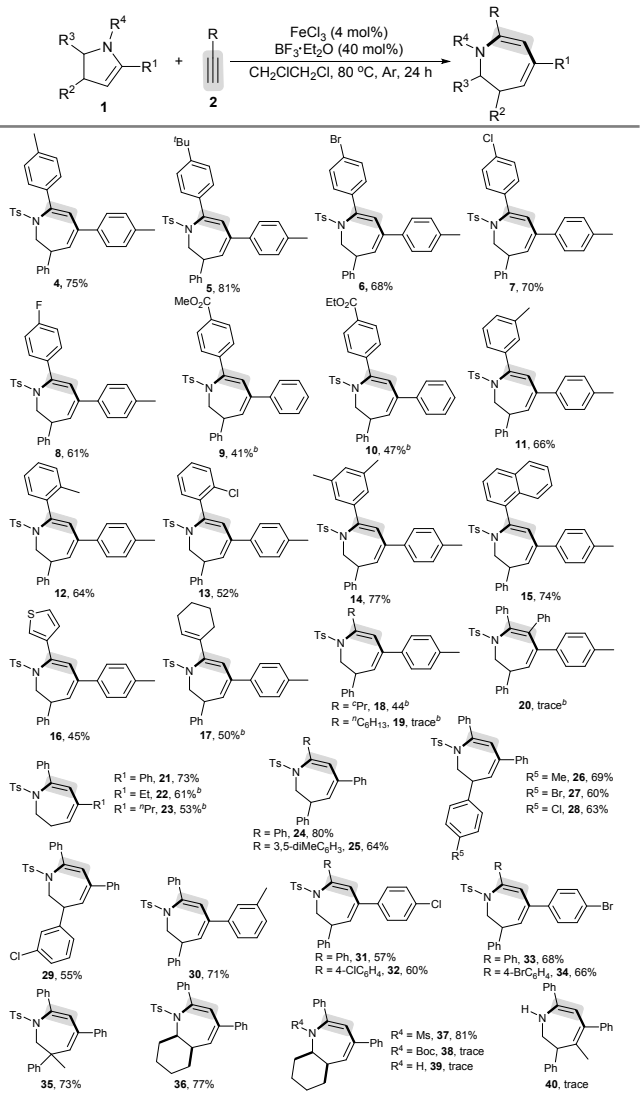
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (4 equiv), $FeCl_3$ (4 mol%), $BF_3{\cdot}Et_2O$ (40 mol%), CH_2ClCH_2Cl (anhydrous; 2 mL), argon, 80 °C, and 24 h. [b] Isolated yield. [c] **1a** (1 mmol) and 48 h.

or electron-deficient terminal arylalkynes, affording diversely tetrasubstituted 2,3-dihydro-1*H*-azepines **4-16** in moderate-to-good yields. The results showed that various substituents, including Me, *t*-Bu, Br, Cl, F, CO_2Me and CO_2Et, on the aryl ring of terminal alkynes were well tolerated, but the electronic nature and position of the substituent affected the yield. Electron-rich *para*-alkyl (e.g., Me, *t*-Bu)-substituted aryl alkynes efficiently generated azepines **4** and **5**, respectively, in high yields (75 and 81%), whereas arylalkynes bearing either an electron-deficient *para*-substituent (e.g., ester) or a *meta*- *or ortho*-substituent (e.g., Me, Cl) delivered the corresponding products **9-13** in moderate yields (41-66%). Gratifyingly, the halo groups, such as Br, Cl and F, were also tolerated in this reaction (**6-8**, **13**). The reaction could also be performed smoothly with alkynes possessing other functional groups, such as 1-naphthalenyl (**15**), 3-thiophenyl (**16**) and cyclohex-1-enyl (**17**). Cyclopropylacetylene, an alkylalkyne, was also a viable cycloaddition partner (**18**). However, this cycloaddition reaction was not compatible with a common linear aliphatic terminal alkyne (**19**) and internal alkyne (**20**).

We next assessed the generality of this formal cycloaddition protocol with regard to 2,3-dihydro-1*H*-pyrroles **1** (Scheme 3). The reaction was applicable to a variety of 1-tosyl-2,3-dihydro-1*H*-pyrroles (**21-36**). 1-Tosyl-2,3-dihydro-1*H*-pyrroles possessing a phenyl or an alkyl group at the 5 position were viable five-atom units, giving azepines **21-23** in good yields. The reaction with 3,5-disubstituted 2,3-dihydro-1*H*-pyrroles efficiently produced azepines **24-34** in yields of 55-80% depending on the nature of the substituent and the alkyne. 3,5-Diphenyl-1-tosyl-2,3-dihydro-1*H*-pyrrole reacted with phenylacetylene (**2a**) to afford **24** in 80% yield, but the reaction with 1-ethynyl-3,5-dimethylbenzene gave **25** in a

reduced yield of 64%. An array of aryl groups, including Ph, *para*-MeC_6H_4, *para*-BrC_6H_4, *para*-ClC_6H_4 and *meta*-ClC_6H_4, placed at the

Scheme 3. Variation of the 2,3-dihydro-1*H*-pyrroles (**1**) and alkynes (**2**)[a]

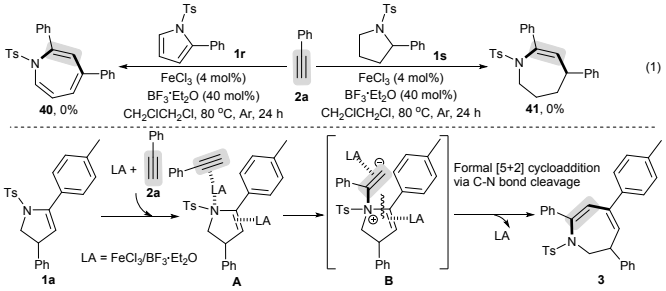


[a] Reaction conditions: **1a** (0.2 mmol), **2** (4 equiv), $FeCl_3$ (4 mol%), $BF_3{\cdot}Et_2O$ (40 mol%), CH_2ClCH_2Cl (anhydrous; 2 mL), argon, 80 °C, and 24 h. [b] $AgSbF_6$ (30 mol%) instead of $FeCl_3$ for 60 h.

3 and 5 positions were tolerated (**26-34**). Notably, both halogen atoms (e.g., Br, Cl) and the C=C bond were incorporated into the resulting products (**27-29, 31-34**), which have potential for substituent modification to access new azepine derivatives. A 1-tosyl-2,3-dihydro-1*H*-pyrrole bearing three substituents, two phenyl and a methyl group, was converted into pentasubstituted azepine **35** with a quaternary carbon centre. Interestingly, the reaction was applicable to the construction of bicyclic compounds **36** and **37**. Employing 1-tosyl-3a,4,5,6,7,7a-hexahydro-1*H*-indole gave access to six-membered-ring-fused azepine **36** in 77% yield. The 2,3-dihydro-1*H*-pyrrole with *N*-Ms instead of *N*-Ts showed high reactivity (**37**), but the corresponding pyrroles with *N*-Boc and free *N*-H did not lead to the formation of azepines (**38** and **39**). Both conformations of azepines **36** and **37** adopt *cis*-form, which is the assumed relative configuration from the starting materials.[10] Moreover, 4-methyl-3,5-diphenyl-1-tosyl-2,3-dihydro-1*H*-pyrrole was also inert due to steric hindrance to inhibiting coordination with the Lewis acids.

As shown in Scheme 4, neither 2-phenyl-1-tosyl-1*H*-pyrrole [**1r;** (Eqn (1), left)] nor 2-phenyl-1-tosylpyrrolidine [**1s;** (Eqn (2), right)] showed any reactivity in this ring-opening/cycloaddition protocol. because both compounds have very stable five-membered-heterocyclic rings: the C(sp^2)-N bond in 1*H*-pyrrole **1r** has a very high dissociation energy and its cleavage requires a challenging dearomatization process, and the C(sp^3)-N bond in pyrrolidine **1s** is extremely stable as it adopts puckered conformation to reduce the torsional strain and small ring strain.

A possible mechanism for this ring-opening/formal hetero-[5+2] cycloaddition protocol is proposed in Scheme 4.[1-4,7,8] Initially, complexation of the Lewis acids ($FeCl_3$ and $BF_3{\cdot}Et_2O$)[7] with both 1-tosyl-2,3-dihydro-1*H*-pyrrole **1a** (through the C=C bond and the nitrogen atom) and alkyne **2a** (through the C≡C bond) affords the intermediate **A**, and subsequent addition of the nitrogen atom to the C≡C bond of alkyne **2a** leads to the intermediate **B**. Finally, formal hetero-[5+2] annulation of the intermediate **B** through C(sp^2)-N bond cleavage[8] generates 1-tosyl-2,3-dihydro-1*H*-azepine **3**.



Scheme 4. Other pyrrole derivatives and possible mechanism.

In summary, we have developed a general, highly effective ring-opening/formal hetero-[5+2] cycloaddition protocol for selectively accessing 2,3-dihydro-1*H*-azepines, in which two new chemical bonds, namely a C(sp^2)-N bond and a C(sp^2)-C(sp^2) bond, have been formed smoothly by means of two non-precious $FeCl_3$ and $BF_3{\cdot}Et_2O$ double-activation catalysts. It is the first example of a Lewis acid co-catalysed formal hetero-[5+2] cycloaddition reaction of 1-tosyl-2,3-dihydro-1*H*-pyrroles (acting effectively as non-strained-ring-based five-atom units) with terminal alkynes. In addition, the reaction shows high selectivity and a broad scope. Studies on how to selectively cleave of the C(sp^2)-N bonds of 1-tosyl-2,3-dihydro-1*H*-pyrroles and the utility of this formal hetero-[5+2] cycloaddition strategy are underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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9 CCDC 1867336 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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