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Tertiary Enamide-Triggered S_EAr: Domino Allylation and Enamine-Type Addition

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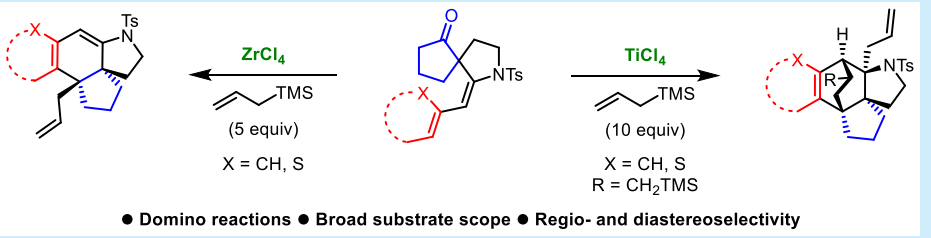
Supporting Information



ABSTRACT: Two unprecedented domino reactions are described, starting from ketospiro-enesulfonamides. By treatment with $ZrCl_4$ and allylsilane, an intramolecular electrophilic aromatic substitution and subsequent allylation is observed. By treatment with $TiCl_4$ and allylsilane, a double enamine-type reaction takes place, thus creating simultaneously four contiguous stereogenic centers diastereoselectively.

Recently, tertiary enamides have become shelf-stable enamine variants. Despite the presence of the electron-withdrawing group, delocalization of the lone-pair electrons of nitrogen into the carbon−carbon double bond remains possible, allowing enamine-type reactivity.[1,2] Thus, these unique synthons in organic synthesis have been successfully used in reactions with epoxides,[3] imines,[4] carbonyls,[5] nitrilium ions,[6] or *N*-acyl iminium ions[7] to access nitrogen-containing frameworks pertinent for assessing biological activities.

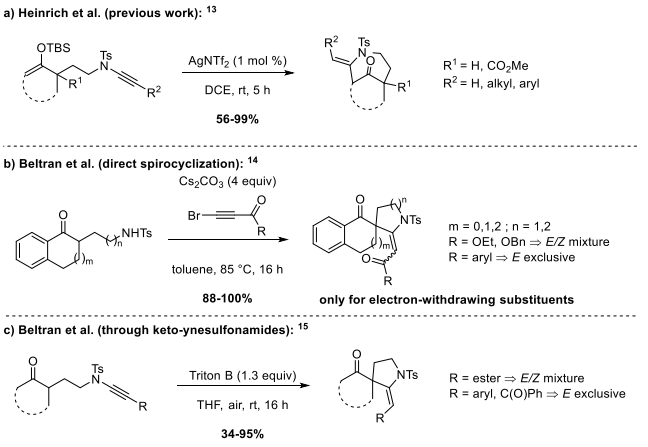
Aromatic organic compounds are ubiquitous in diverse areas of research, from medicinal chemistry to biology and materials science.[8] Often, the building of aromatic systems relies on electrophilic aromatic substitution reactions.[9] Since the pioneering work of Friedel−Crafts,[10] persistent attention has been given to this valuable process.[11]

We present herein an intramolecular electrophilic aromatic substitution promoted by a tertiary enesulfonamide. Using $ZrCl_4$, allylation takes place, generating a tetracyclic system. By contrast, by using $TiCl_4$, allylation and subsequent quenching of β-silylated carbocation by tertiary enamide leads to a spiro pentacyclic scaffold after a second allylation. The former may serve as an analogue of the analgesic metathebainone of the morphinan family.[12]

Our research interest in the chemistry of ketoynamides[13] led us to a direct spirocyclization from ketosulfonamides via ketoynesulfonamides when the ynesulfonamides are substituted by an electron-withdrawing group.[14] Using ynesulfonamides substituted by an aryl group, an ammonium salt-promoted spirocyclization takes place (Scheme 1).[15]

To take advantage of the exclusive *E*-configured tertiary enesulfonamide, i.e., with a vinylogous nitrogen nucleophile present in the aza-spiro compounds **1a**, we speculated that the latter would react with appropriate electrophiles to functionalize the nitrogen-containing framework further (Scheme 2a). Whereas this approach failed, we explored an activation of the carbonyl in the presence of $BF_3{\cdot}OEt_2$ and allylsilane (Scheme 2b).[16] Against all odds, we observed direct intramolecular electrophilic aromatic substitution triggered by enamine-like activity of the nearby tertiary enesulfonamide, providing spiro-tetracyclic fused ring system **2a** diastereoselectively, together with pentacyclic ring-fused system **3a**, resulting from a second intramolecular addition of enamide onto the β-silylated carbocation followed by a second allylation. X-ray analyses of **2a** and **3c** confirmed the structures of

Scheme 1. Previous Work on Ketoynamides



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Scheme 2. Enamide Functionalization with Electrophile or Nucleophile

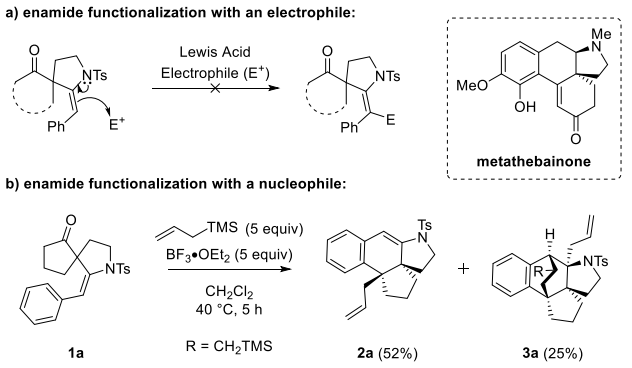
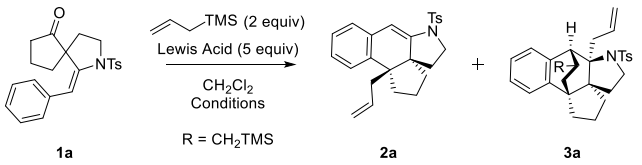


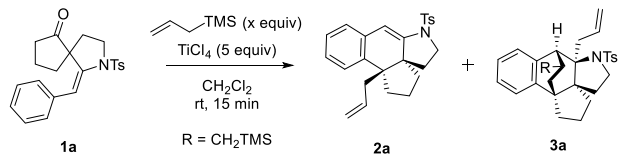
Table 1. Screening of Lewis/Brønsted Acids



entry	Lewis acid	conditions	% yield[a] 2a	% yield[a] 3a
1	$BF_3{\cdot}OEt_2$	7 h, 40 °C	73	14
2	$AlCl_3$	10 min, rt	*c*	*c*
3	Me_3Al	2 h, 40 °C	*b*	*b*
4	$SnCl_2$	2 h, 40 °C	*b*	*b*
5	$InCl_3$	4 h, 40 °C	33	6
6	$FeCl_3$	1 h, 40 °C	*c*	*c*
7	$ZnCl_2$	4 h, 40 °C	*b*	*b*
8	$TiCl_4$	15 min, rt	32	51
9[d]	$ZrCl_4$	1 h, 40 °C	84	5
10	$HfCl_4$	2 h, 40 °C	*b*	*b*
11	$Y(OTf)_3$	5 h, 40 °C	*b*	*b*
12	*p*-TsOH	4 h, 40 °C	*c*	*c*
13	TFA	4 h, 40 °C	*c*	*c*

[a]Yield of isolated compounds. [b]Starting material was totally recovered. [c]Degradation was observed. [d]Concentration in starting material **1a** was 35 mM instead of 70 mM.

Table 2. Optimization of the Formation of Adduct 3a



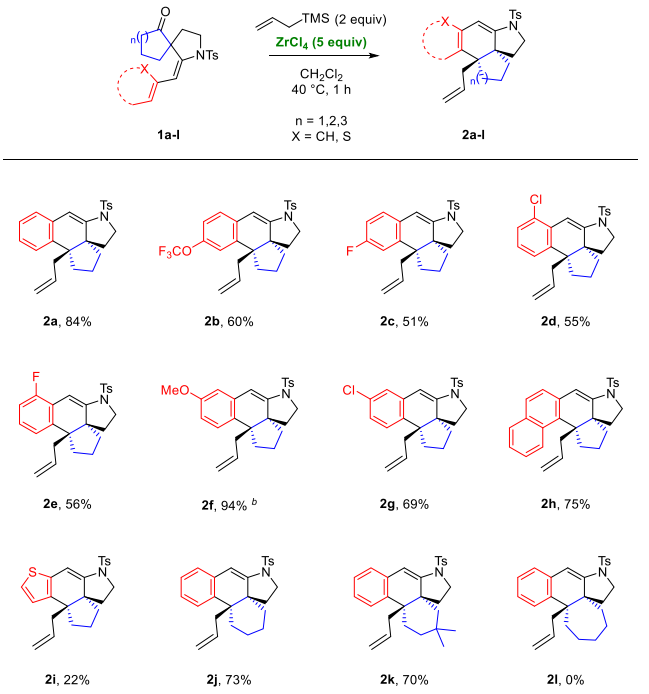
entry	*x* (equiv)	concentration (mM)	% yield[a] 2a	% yield[a] 3a
1	2	70	32	51
2	5	70	15	59
3	5	130	17	62
4	10	130	9	78
5	10	260	8	81

[a]Yield of isolated compounds.

both the tetra- and pentacyclic azaspiro adducts obtained (CCDC 1866279 and CCDC 1895442 contain the supplementary crystallographic data for both structures).

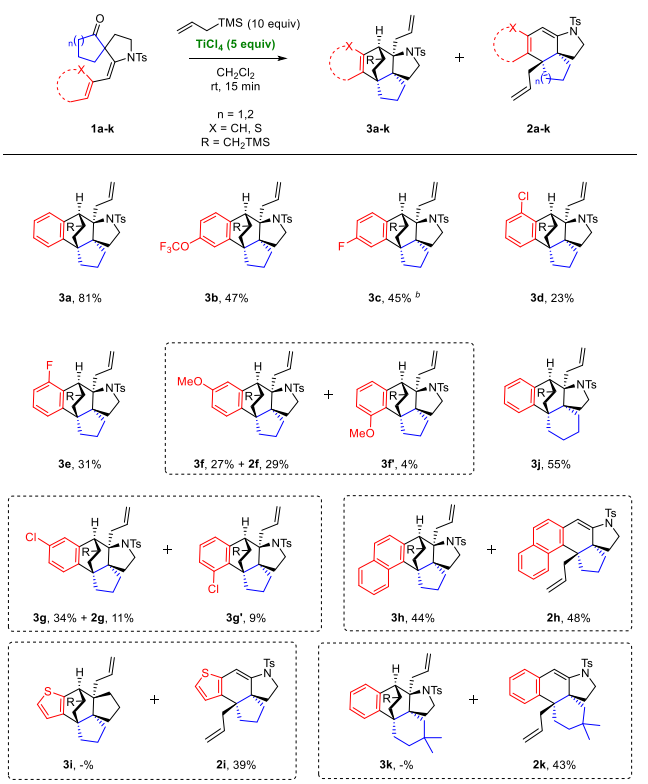
An intramolecular electrophilic aromatic substitution triggered by the delocalization of tertiary enamide electrons into the benzene ring is exceedingly rare. To the best of our knowledge,

Scheme 3. Scope of Electrophilic Aromatic Substitution/Allylation[a]



[a]Yield of isolated compounds. [b]CCDC 1866280 contains the supplementary crystallographic data.

Scheme 4. Scope of the Domino Reaction Providing Pentacyclic Adducts[a]



[a]Yield of isolated compounds. [b]CCDC 1895442 contains the supplementary crystallographic data.

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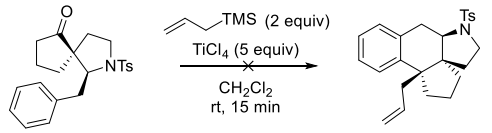
Scheme 5. Attempt To Form the Tetracyclic Adduct



this phenomenon has been observed only once, by the group of Wang, in an *8-endo*-epoxide arene cyclization.[17] Unexpectedly, a second nucleophilic attack of the tertiary enamide took place, providing **3a** with total regio- and diastereoselectivity.

Considering the possibility of a Lewis acid−allylsilylation-promoted sequence to form spirocyclic fused ring systems diastereoselectively, we sought conditions to target the exclusive formation of either the tetracyclic system or the pentacyclic system.

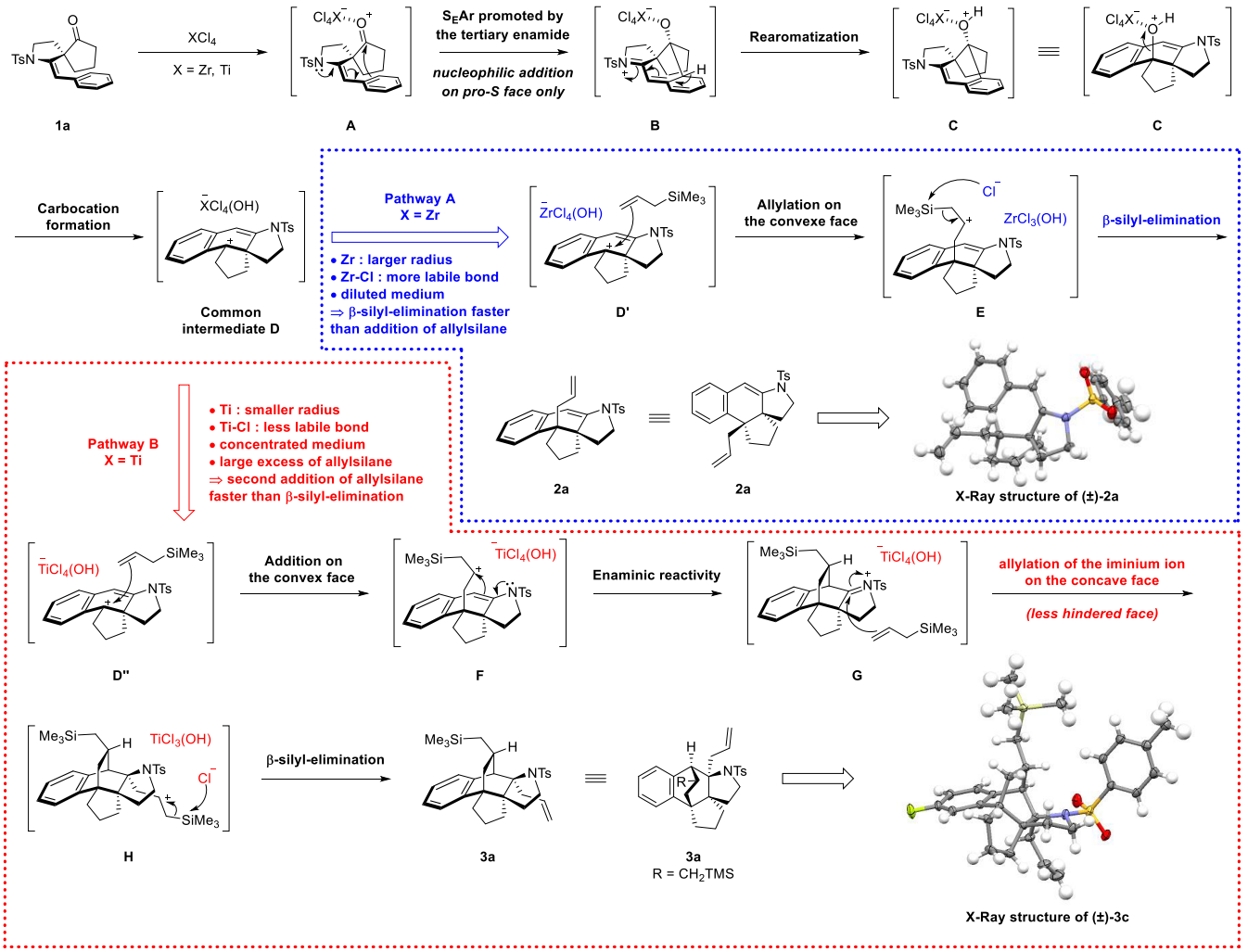
To do so, we screened several Lewis acids as well as Brønsted acids (Table 1).

Among the tested Lewis acids, only $BF_3{\cdot}OEt_2$ (Table 1, entry 1), $InCl_3$ (Table 1, entry 5), $TiCl_4$ (Table 1, entry 8), and $ZrCl_4$[18] (Table 1, entry 9) led to both tetracyclic adduct **2a** and pentacyclic compound **3a**. Other Lewis acids, such as $AlCl_3$, Me_3Al, $SnCl_2$, $ZnCl_2$, $FeCl_3$, and $HfCl_4$ (Table 1, entries 2, 3, 4, 6, 7, and 10), as well as Brønsted acids (Table 1, entries 12 and 13) were not beneficial for this reaction. Finally, $ZrCl_4$ promotes the selective formation of tetracyclic compound **2a**, whereas the pentacyclic adduct **3a** predominated by treatment of **1a** with the stronger Lewis acid $TiCl_4$. It should be noted that the formation of the pentacyclic fused ring system **3a** occurred in a totally diastereoselective and regioselective manner, creating four new contiguous stereogenic centers in one strike. Having found that $TiCl_4$ favors the formation of pentacyclic adduct **3a**, we tried to optimize this reaction further (Table 2).

Although increasing the amount of allylsilane (Table 2, entry 2) favored bridged compound **3a**, enhancing the concentration of the substrate and using 5 equiv of allylsilane (Table 2, entry 3) led to more pentacyclic derivative **3a**, albeit with a lower selectivity. Enhanced selectivity (**3a** vs **2a**) could be obtained by increasing the amount of allylsilane (Table 2, entry 4). Quadrupling the concentration of spiro-enesulfonamide **1a** and working with 10 equiv of allylsilane (Table 2, entry 5) was the most efficient way to obtain bridged compound **3a** with the highest yields and selectivity. With suitable reaction conditions for high selectivity in hand, we explored first the scope of the sequential electrophilic aromatic substitution reaction/allylation reaction (Scheme 3).

Within the aryl unit, electron-withdrawing 4-OCF_3 (**2b**), 4-F (**2c**), 2-Cl (**2d**), and 2-F (**2e**) substitutions were tolerated. Naphthyl enesulfonamide **1h** and heteroaryl compound **1i** were

Scheme 6. Proposed Mechanisms



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suitable candidates, although the latter led to polycyclic derivative **2i** with a moderate yield. Surprisingly, unsymmetrically aryl-substituted compounds (meta derivatives **1f** and **1g**) underwent enamide-triggered aromatic substitution and subsequent allylation in a totally regioselective manner, affording exclusively 9-hexahydro-1*H*-benzo[*f*]cyclopenta[*d*]indoles **2f** and **2g** with good yields. The protocol was extended to spiro-enesulfonamides derived from cyclohexanones (**1j** and **1k**), wherein fused spirocyclic ring systems **2j** and **2k** could be obtained with 73 and 70% yield, respectively. Spiro-enesulfonamide **1l** containing a 7−5 ring system did not undergo cyclization, probably because of the increased distance between the two carbons of the new C−C bond to be formed, thus delineating one limitation of this reaction.

Successful formation of pentacyclic adduct **3a** with $TiCl_4$ and allylsilane prompted us to investigate the pertinence of this domino reaction (Scheme 4). Within the aryl unit, electron-withdrawing 4-OCF_3 (**1b**), 4-F (**1c**), 2-Cl (**1d**), and 2-F (**1e**) substitution was tolerated, providing bridged compounds **3a**−**e**.

Although the domino reaction proceeded with unsymmetrically substituted aryl compounds (meta derivatives **1f** and **1g**), in this case moderate yields of **3f**, **3f′** and **3g**, **3g′** were obtained with moderate selectivity. Cyclohexyl derivative **3j** was found to be a good candidate for this reaction, whereas *gem*-dimethyl derivative **1k** met with less success, undergoing only electrophilic aromatic substitution and subsequent allylation. Likewise, 2-thienyl adduct **2i** was obtained exclusively by treatment with $TiCl_4$. With naphthyl spiro-enesulfonamide **1h**, an erosion of selectivity with respect to the formation of polycyclic compounds formed was observed, and in this case, **3h** and **2h** were isolated by treatment with $TiCl_4$.

With respect to the mechanism of this process and to verify whether enesulfonamide is essential for the reaction to proceed, reduced **4**[19] was treated with $TiCl_4$ and allylsilane. Intramolecular cyclization reaction was not observed, and only starting material was recovered (Scheme 5).

To explain the formation of these spiro-polycyclic-fused ring systems, the mechanism outlined in Scheme 6 is proposed. Activation of ketone **1a** by a Lewis acid provides alkoxide **A**. Subsequent intramolecular electrophilic aromatic substitution assisted by the tertiary spiro-enesulfonamide affords imidium intermediate **B** followed by rearomatization to afford **C**.

Ionization of the alkoxide/Lewis acid complex of **C** leads to tertiary carbocation **D**.[16] At this point, two pathways can be considered, depending on the Lewis acid involved:[18,20] Pathway A involves allylsilane addition on the convex face of molecule **D′**. Because zirconium(IV) has an ionic radius much larger than that of titanium(IV),[21] the Zr−Cl bond may be more labile, promoting β-silyl elimination to form polycyclic system **2a**. In pathway B, allylsilane adds to **D″**, providing **F**. In this case, the enamine-like reactivity of **F** is faster than β-elimination of the silicon moiety, thus leading to bridged compound **G**. A second molecule of allylsilane subsequently adds to the iminium ion from the less hindered side of **G**, thus ending with the production of **3a** after β-silyl elimination.

In conclusion, we have developed a tandem intramolecular electrophilic aromatic substitution followed by allylation to form aza-tetracyclic fused spiranic ring systems diastereoselectively by treatment with $ZrCl_4$. A diverse array of various aryl-substituted fused spiro-enesulfonamides were obtained. Unsymmetrically substituted aryl compounds led to 9-hexahydro-1*H*-benzo[*f*]-cyclopenta[*d*]indoles exclusively. Cyclization with $TiCl_4$ and allylsilane afforded pentacyclic bridged derivatives with complete diastereoselectivity by consecutive electrophilic aromatic substitution/enamine-like addition/allylation, where four contiguous stereogenic centers were created simultaneously.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03987.

Experimental procedures, synthesis of starting materials, and compound characterization data (PDF)

^{1}H and ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 1866279−1866280 and 1895442 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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