

# Dearomative [4 + 3] cycloaddition of furans with vinyl-*N*-triflylhydrazones by silver catalysis: stereoselective access to oxa-bridged seven-membered bicycles

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## Article

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# Abstract

The first example of dearomative [4 + 3] cycloaddition between furans and vinyl-*N*-sulfonylhydrazones as vinylcarbene precursors is reported. The merger of silver catalysis and easily decomposable vinyl-*N*-triftosylhydrazones enabled the efficient synthesis of a variety of skeletally and functionally diverse oxa-bridged seven-membered bicyclic compounds with complete and predictable stereoselectivity. The combination of experimental studies and DFT calculations disclosed that the silver-catalyzed reaction proceeds via a concerted [4 + 3] cycloaddition mechanism, rather than the generally accepted cyclopropanation / Cope rearrangement pathway by rhodium catalysis.

## Introduction

Seven-membered carbocycles, especially those embedded in oxa-bridged bicyclic scaffolds, are privileged structural motifs widely found in natural products and synthetic drugs.<sup>1-7</sup> Over the past few decades, the [4 + 3] cycloaddition between 1,3-dienes and vinylcarbenes has been established as the most promising strategy for the stereoselective synthesis of these complex ring systems, as demonstrated by a variety of complex natural products synthesis.<sup>8-13</sup> Major efforts in this arena so far have been dedicated to the use of vinyl diazo compounds,<sup>14-18</sup> propargyl esters,<sup>19-21</sup> 4-alkenyl-1,2,3-triazoles,<sup>22,23</sup> enynes,<sup>24-27</sup> allenes,<sup>28,29</sup> and 7-vinyl-1,3,5-cycloheptatrienes<sup>30</sup> as the sources of vinylcarbene partners to access 1,4-cycloheptadienes (Fig. 1a). However, the use of furans as cyclic 1,3-diene equivalents in such [4 + 3] cycloaddition reactions to construct oxa-bridged seven-membered bicyclic skeletons remained a challenging task, mainly due to the unfavorable entropic and transannular interaction.<sup>31</sup> After the seminal contribution from the group of Davies in 1985, the few available examples in the literature are limited to the use of hazardous vinyl diazoacetates as donor-acceptor vinylcarbene precursors through a rhodium-catalyzed cyclopropanation / Cope rearrangement sequence (Fig. 1b). While the rhodium-catalyzed protocol has been applied in the total syntheses of several natural products,<sup>36-39</sup> this method is still problematic in terms of efficiency and practicality, including (i) delivering a mixture of cycloadduct and triene byproduct, which is highly dependent on the substitution pattern of furans,<sup>36,37</sup> and (ii) unsuitable for alkyl- and unsubstituted vinyl diazo compounds. Moreover, the use of other vinylcarbene precursors such as cyclopropenes and propargylic carboxylates all exclusively resulted in trienes through the carbene-triggered ring-opening of furans.<sup>40-42</sup> Therefore, a new catalytic approach to achieve the stereoselective synthesis of seven-membered oxa-bridged bicycles by the [4 + 3] cycloaddition of furans with vinylcarbenes is highly in demand.

As part of our continued efforts in the design and application of functionalized *N*-triftosylhydrazones,<sup>43-46</sup> we were intrigued by the possibility of applying this approach to solve the aforementioned issues in the [4 + 3] cycloaddition methodology. Here we report a silver-catalyzed dearomative [4 + 3] cycloaddition of furans using the easily decomposable vinyl-*N*-triftosylhydrazones as donor and donor-acceptor vinylcarbene precursors (Fig.1c). The use of vinyl-*N*-sulfonylhydrazones as vinylcarbene precursors is known to be challenging because they easily tend to form pyrazoles by self-cyclization.<sup>47,48</sup> We

speculated that this could be addressed by the combined use of silver catalysis and vinyl-*N*-triftosylhydrazones. Moreover, mechanistic investigations reveal that the silver-catalyzed reaction proceeds through a concerted [4 + 3] cycloaddition, rather than the cyclopropanation / Cope rearrangement sequence by rhodium catalysis, thus mechanically avoiding the formation of triene byproducts.

## Results

The study began by determining the optimal conditions for the cycloaddition of vinyl-*N*-triftosylhydrazone **1a** with furan using NaH as the base in the presence of varied catalyst and solvent (Table 1). The use of AgOTf as a catalyst in CHCl<sub>3</sub> at 60 °C ensued the desired product **2** in 24% yield, with a carbene dimer as the major product (Entry 1). The product yield could be substantially improved when using weakly coordinating trispyrazolylborate silver(I),<sup>49-51</sup> especially Tp<sup>(CF<sub>3</sub>)<sub>2</sub></sup>Ag affording **2** in 91% yield, with only a trace amount of undesired triene byproduct (entries 2 and 3). In contrast, Rh<sub>2</sub>(OAc)<sub>4</sub><sup>14</sup> and Cu(hfacac)<sub>2</sub>,<sup>18</sup> the most commonly used catalysts in the [4 + 3] cycloaddition of 1,3-dienes with vinyl diazoacetates, led to low yield, whereas Pd(OAc)<sub>2</sub> only enabled the carbene dimerization and the self-cyclization to pyrazole (entries 4-6). Further, the screening on solvents disclosed that CH<sub>2</sub>Cl<sub>2</sub> and PhCF<sub>3</sub> were less effective than CHCl<sub>3</sub>, whereas 1,4-dioxane was completely ineffective (entries 7-9). Vinyl-*N*-tosylhydrazone **1b** as vinylcarbene source, instead of the easily decomposable vinyl-*N*-triftosylhydrazone **1a**, afforded **2** in a far low yield (40%), owing to the self-cyclization to pyrazole (entry 10). The structural configuration of **2** was unambiguously established by the X-ray crystallographic analysis.<sup>52</sup>

With the optimized conditions in hand (Table 1, entry 3), the substrate scope of this reaction with a series of furans was then investigated. As shown in Fig. 2, furans with various substituents at 2-position, including alkyl, alkenyl, alkynyl, and (hetero)aryl as well as bromo, tributylstannyl, siloxy, allyl, and benzyl ether, ester, and ketone functional groups reacted smoothly with phenyl vinyl-*N*-triftosylhydrazone **3** to afford the corresponding products (**4-18**) in 44-90% yield. We were pleased to find that the substrates bearing a carbon-carbon double/triple bond and an activated C(sp<sup>3</sup>)-H bond (**15-18**) did not undergo competitive [2 + 1] cycloaddition<sup>53-55</sup> and C-H insertion,<sup>10</sup> thus achieving high chemoselectivity. The relatively low yields observed in some cases were ascribed to the ring-opening of furans to trienes and the carbene dimerization to olefins. In comparison, 2-substituted furans resulted in trienes as the major product in rhodium-catalyzed [4 + 3] cycloaddition with alkenyl diazoacetates.<sup>[12a-c]</sup> In addition, the steric hindrance of furans had no apparent effect on the reaction, for instance, di- and tri-substituted furans reacted efficiently with **3**, providing multi-substituted oxa-bridged bicycles **19-23** in 55-87% yield.

Next, we investigated the reaction scope with respect to vinyl-*N*-triftosylhydrazones. As summarized in Fig. 2, a broad range of β-aryl vinyl-*N*-triftosylhydrazones with both electron-donating groups (e.g., Me and OMe) and -withdrawing groups (e.g., halogen, CN, NO<sub>2</sub>, CO<sub>2</sub>Et, and CF<sub>3</sub>) at various positions of aryl ring afforded the corresponding oxa-bridged bicyclic products (**24-35**) in 68-85% yield. Similarly, vinyl-*N*-triftosylhydrazones bearing an indolyl, thienyl, or furyl group at β-position all efficiently reacted with furan

to afford the heteroaryl-substituted products (**36-38**) in 72-81% yield, whereas a ferrocenyl-substituted substrate led to the product (**39**) in a moderate yield (45%). The tolerance of strongly coordinated heteroatoms renders this silver-based catalytic approach particularly useful for the construction of medicinally relevant heterocyclic molecules. Moreover, the reaction of *N*-triftosylhydrazones derived from 2,4-dienals produced 4-vinyl oxa-bridged bicycles (**40-42**) in good yield, and the vinyl group present in the reaction products allows further orthogonal derivatization. In addition, an ester-containing product (**43**, 54% yield) was readily accessed from the carbethoxy-substituted vinyl-*N*-triftosylhydrazone. Alkyl-substituted vinyl diazomethanes are known to be prone to spontaneous cyclization to pyrazoles within hours even stored at -20 °C.<sup>21,56</sup> By using the strategy of the merge of silver catalysis and vinyl-*N*-triftosylhydrazones, we were pleased to find that  $\beta$ -alkyl vinyl-*N*-triftosylhydrazones smoothly reacted with furan to give the corresponding 4-alkyl-8-oxabicyclo[3.2.1]oct-2,6-dienes (**44-49**, 62-85% yield), in which the common functional groups, including ester (OAc, **47**), benzyloxy (OBn, **48**), and dimethyltertbutylsilyloxy (OTBS, **49**), were well tolerated. Furthermore, the substitution at  $\alpha$ -position with an alkyl or halogen atom did not affect the efficiency and stereoselectivity (**50-53**, 67-84% yield). *N*-triftosylhydrazones derived from  $\alpha,\beta$ -unsaturated ketones also underwent this reaction, even though an electron-withdrawing substituent at carbene carbon is required to suppress the self-cyclization to pyrazoles (**54-61**, 53-94% yield).<sup>2</sup> Note that the compounds **60** and **61** could be prepared by rhodium-catalyzed method, albeit slow addition of styryldiazoacetate was required to achieve good efficiency.<sup>35</sup> Furthermore, unsubstituted allyl aldehyde-derived *N*-triftosylhydrazone was examined in the current protocol; to our delight, the desired oxa-bridged bicyclic product **62** was obtained in 72% yield. This achievement clearly demonstrated the superiority of current method, as unsubstituted vinyl carbenes underwent self-condensation more easily than the substituted ones.<sup>56,57</sup> Overall, the results summarized in Fig. 2 clearly demonstrated the superior features of silver-catalyzed [4 + 3] cycloaddition between furans and vinyl-*N*-triftosylhydrazones, namely the broad substrate scope, good functional group tolerance, excellent chemo-, regio- and *endo*-stereoselectivity, and good to high yield, thereby constituting a versatile method for the stereoselective synthesis of a wide range of *endo* oxa-bridged 1,4-cycloheptadienes.

Encouraged by the above achievements, we then turned our attention towards the synthesis of fused [5.n.0] bicyclic systems, a challenging target that has attracted the interest of synthetic and medicinal chemists due to their structural diversity and biological relevance (Fig. 3).<sup>1,58</sup> First, we explored the [4 + 3] cycloaddition of furan with cyclic vinyl-*N*-triftosylhydrazones derived from cyclic enals, which were easily prepared by the one-carbon homologation reaction from commercially available cyclic ketones.<sup>59</sup> A series of cyclic vinyl-*N*-triftosylhydrazones, having 6 to 8 membered rings, were found to be suitable in this reaction, affording the desired fused [5.4.0], [5.5.0], and [5.6.0] bicyclic compounds (**63-66**) in 53-78% yield. Furthermore, several commercially available 2,3-fused cyclic furans were suitable for this [4 + 3] cycloaddition, delivering the corresponding oxa-bridged [5.4.0] bicyclic compounds (**67-70**) in 49-80% yield. Finally, the intramolecular [4 + 3] cycloaddition of diverse vinyl-*N*-triftosylhydrazones bearing a tethered furan was rationally designed and applied to prepare benzannulated bicyclic compounds, which are the common structural core of several biologically active natural products.<sup>60</sup> We were pleased to find

that these intramolecular [4 + 3] cycloaddition reactions proceeded smoothly under the silver-catalyzed conditions, affording the desired benzannulated bicyclic compounds (**71-74**) in 60-76% yield. To the best of our knowledge, this is the first example of an intramolecular type I [4 + 3] cycloaddition between vinylcarbenes and furans.<sup>61</sup>

To demonstrate the practicality of the protocol, a gram-scale reaction between hydrazone **75** and furan was performed under standard conditions, affording the product **50** in 80% yield (1.05 g) that is comparable to that obtained on small scale (Fig. 4). Further, the silver-catalyzed [4 + 3] cycloaddition protocol was applied to the late-stage modification of drug molecules, such as Aspirin, Indomethacin, and Fenbufen bearing a furan motif. All these compounds reacted smoothly with vinyl-*N*-triflylhydrazone **3** and gave the corresponding oxa-bridged [3.2.1] bicyclic compounds (**76-78**) in synthetically useful yield.

Based on related precedents,<sup>8,13,30,32</sup> this transformation may proceed via a tandem cyclopropanation / Cope rearrangement sequence. Therefore, our initial mechanistic studies aimed to distinguish a direct [4 + 3] cycloaddition pathway and a tandem [2 + 1] cycloaddition followed by a divinylcyclopropane [3,3]-rearrangement. To address this, we first tried to capture the furanocyclopropane intermediate by shortening the reaction time or performing the reaction at a low temperature (0 °C), but all failed (for details, see Fig. S1). Fortunately, the use of vinyl-*N*-triflylhydrazone **79** in the reaction with furan produced a mixture of vinylcyclopropane **80** (which would correspond to the putative intermediates of the stepwise process)<sup>13,32</sup> and triene **81**, along with a trace amount of 1,4-cycloheptadiene **82**. When the isolated compound **80** was heated at 160 °C for 12 hours, only a triene **81** was isolated in 90% yield by the ring-opening of furanocyclopropane intermediate, whereas no rearrangement product **82** was observed (Fig. 5a). This result is different from the Rh-catalyzed [4 + 3] cycloaddition of 1,3-dienes with vinylcarbenoids.<sup>13,30,32</sup> Finally, we got a circumstantial evidence from the analysis of regioselectivity in the reaction of 3-phenylfuran with vinyl-*N*-triflylhydrazone **3**, which afforded a 1:1 mixture of **83** to **83'**. However, this is not consistent with the stereospecificity resulting from a tandem cyclopropanation / Cope rearrangement, where the initial cyclopropanation should selectively occur at the double bond with less sterical hindrance.<sup>13,30,32</sup> Hence, the involvement of a concerted [4 + 3] cycloaddition is more possible than a step-wise tandem cyclopropanation / Cope rearrangement.

To support our hypothesis concerning the involvement of a concerted [4 + 3] cycloaddition, in which silver vinylcarbenes act as a delocalized 2π system,<sup>62</sup> density functional theory (DFT) calculations were carried out for a model reaction, namely the silver-catalyzed reaction of 2-methylfuran with vinyl-*N*-triflylhydrazone **3** (for computational details see Fig. S2-S5 in supporting information). First, the diazo compound **Int1**, generated in situ from the decomposition of **3**, coordinates to Tp<sup>(CF<sub>3</sub>)<sub>2</sub></sup>Ag and then releases a N<sub>2</sub> molecule to generate a silver carbene **Int2** with an energy barrier of 11.3 kcal/mol (Fig. S3). Subsequently, a concerted [4 + 3] cycloaddition of **Int2** with 2-methylfuran occurs affording 1,4-cycloheptadiene products **4**, **4'**, and **4''**, respectively, due to the approach of carbene intermediate **Int2** to 2-methylfuran from different orientations (Fig. 5b and Fig. S4). The energy barrier for the generation of the

desired product **4** from **Int3-B1** via **TS2-4** is only 1.8 kcal/mol, which is 12.0 and 23.4 kcal/mol lower than those for the formation of regioisomer **4'** via **TS2-4'** from **Int3-B2** and stereoisomer **4''** via **TS2-4''** from **Int3-C**. To investigate the origin of the regio- and stereoselectivity, NCI and frontier molecular orbital analyses of transition states were performed (Fig. 5c and Fig. S2).<sup>63,64</sup> A secondary orbital interaction exists in the boat form of transition states **TS2-4** and **TS2-4'**, and remarkably lowers the energy barriers for the generation of *endo* products and determines the stereoselectivity of this silver-catalyzed [4 + 3] cycloaddition. Furthermore, due to the C–H··· $\pi$  interactions between methyl and phenyl groups in **TS2-4** and the steric exclusion between the methyl group and the bulky  $\text{Tp}^{(\text{CF}_3)_2}$  ligand of carbene moiety in **TS2-4'** (Figure 2c, for details see Figure S2), the secondary orbital interaction in **TS2-4'** is weaker than that in **TS2-4**. This result provides a suitable rationale for high regioselectivity observed in the experiment. By comparison, the DFT calculations for the tandem cyclopropanation / Cope rearrangement pathway have been carried out, but this process entails an energy barrier (14.1 kcal/mol) that is higher than that for concerted [4 + 3] cycloaddition pathway (1.8 kcal/mol) (see Fig. S5). At this moment, we cannot rule out completely that a tandem cyclopropanation / Cope rearrangement pathway is involved, but the experimental results and theoretical calculations indicate that a concerted [4 + 3] cycloaddition pathway is more favorable.

## Discussion

In conclusion, we have developed a novel dearomative [4 + 3] cycloaddition of furans with donor and donor-acceptor vinylcarbenes by the combination of silver catalysis and vinyl-*N*-triflylhydrazones. This reaction features broad substrate scope, excellent functional group tolerance, complete and predictable chemo-, regio- and stereoselectivity, thus constituting a powerful method for the synthesis of skeletally and functionally diverse oxa-bridged [3.2.1] bicyclic compounds from simple starting materials under mild conditions. Investigation of the mechanism by experimental studies and DFT calculations disclosed a concerted [4 + 3] cycloaddition pathway. Investigations into further extensions to other heteroaromatic molecules as well as into the development of an asymmetric version are ongoing in our laboratory.

## Declarations

Data availability

Complete experimental procedures and compound characterization data are available in the Supplementary Information or from the corresponding author upon request

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## Author contributions

Z.L., Y.Y. and X.J. contributed equally to this work. Z.L., Y.Y., X.J., Q.S., and S.L. performed the experimental investigations and theoretical calculations. Z.L. and X.B. conceived the concept, designed the project, analyzed the data, and together with G.Z. discussed the results and prepared this manuscript.

## Competing interests

The authors declare no competing interests.

## Additional information

**Supplementary information** The online version contains supplementary material available at <https://doi.org>

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## Tables

Table 1 is in the supplementary files section.

## Figures

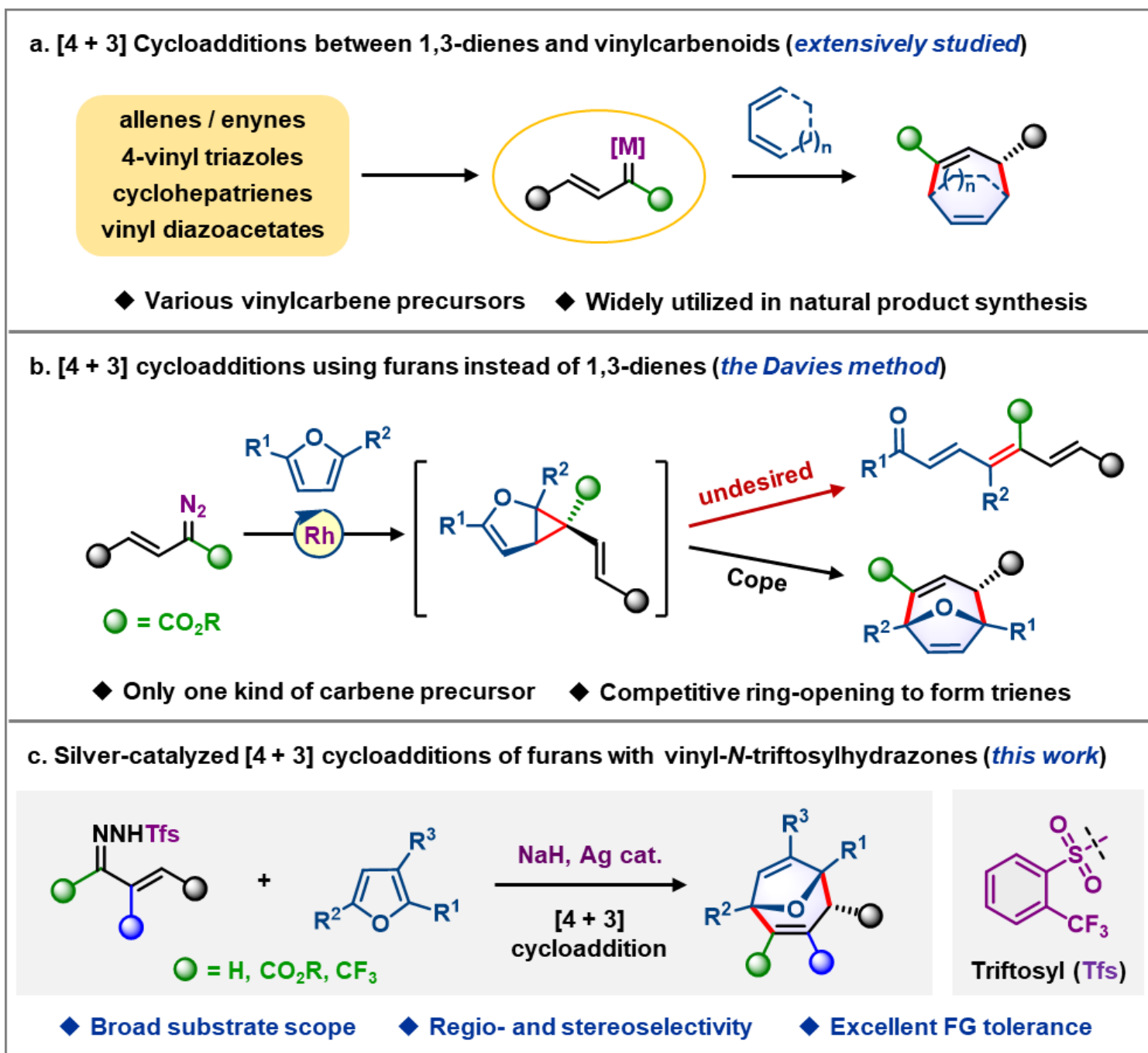
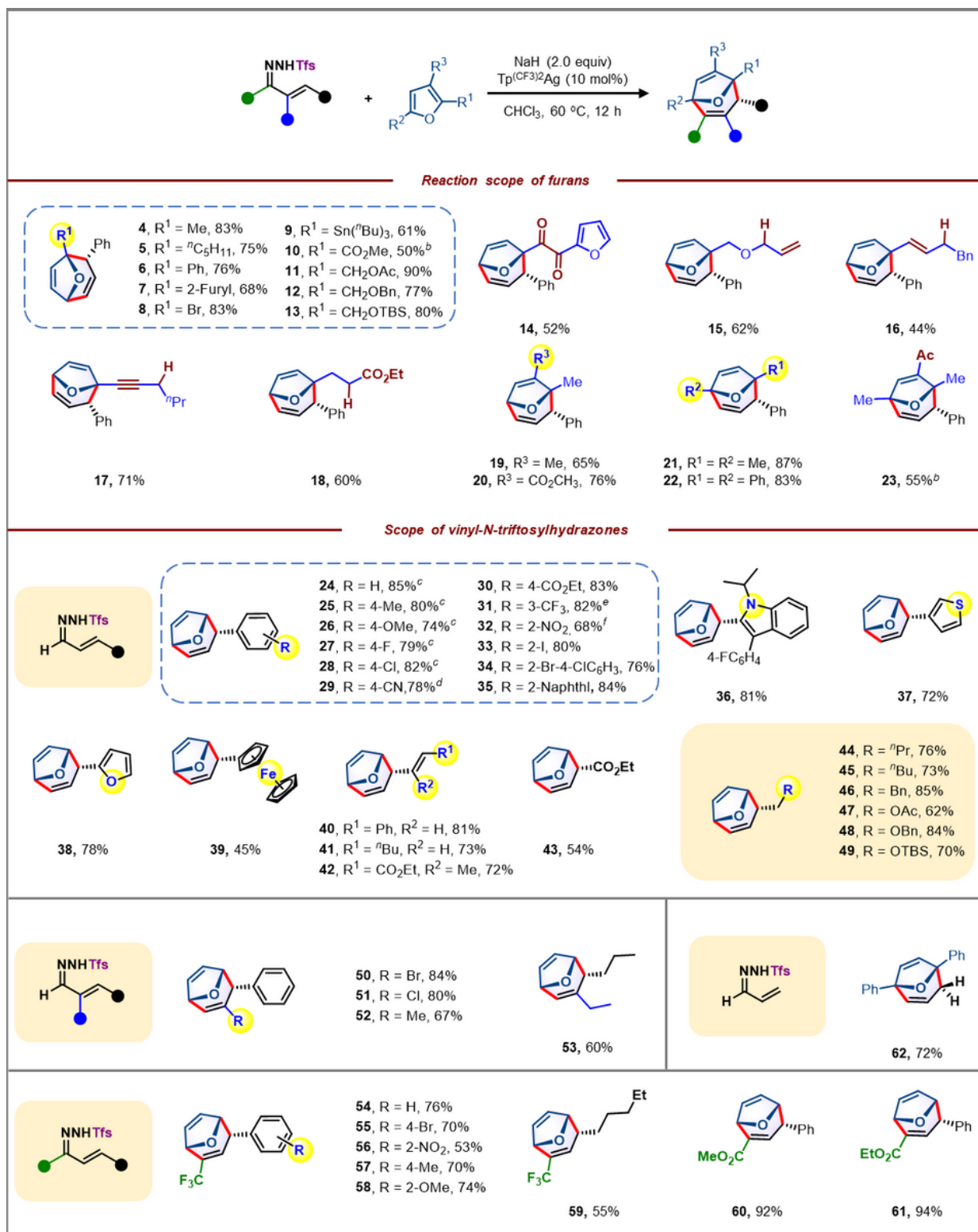


Figure 1

Assembly of seven-membered carbocycles by [4 + 3] cycloaddition of 1,3-dienes/furans with vinylcarbenes.



**Figure 2**

**Substrate scope for intramolecular [4 + 3] cycloaddition.** <sup>a</sup>Reaction conditions: Vinyl-*N*-triflylhydrazone (0.3 mmol), furan (0.6 mmol), NaH (0.6 mmol), Tp(CF<sub>3</sub>)<sub>2</sub>Ag (10 mol%) in CHCl<sub>3</sub> (3.0 mL) was stirred at 60 °C for 12 h under argon atmosphere. Isolated yield. <sup>b</sup>20 mol% Tp(CF<sub>3</sub>)<sub>2</sub>Ag in CHCl<sub>3</sub> at 60 °C for 24 h. <sup>c</sup>5 h. <sup>d</sup>24 h. <sup>e</sup>at 80 °C for 24 h. <sup>f</sup>in PhCF<sub>3</sub> at 60 °C for 24 h.

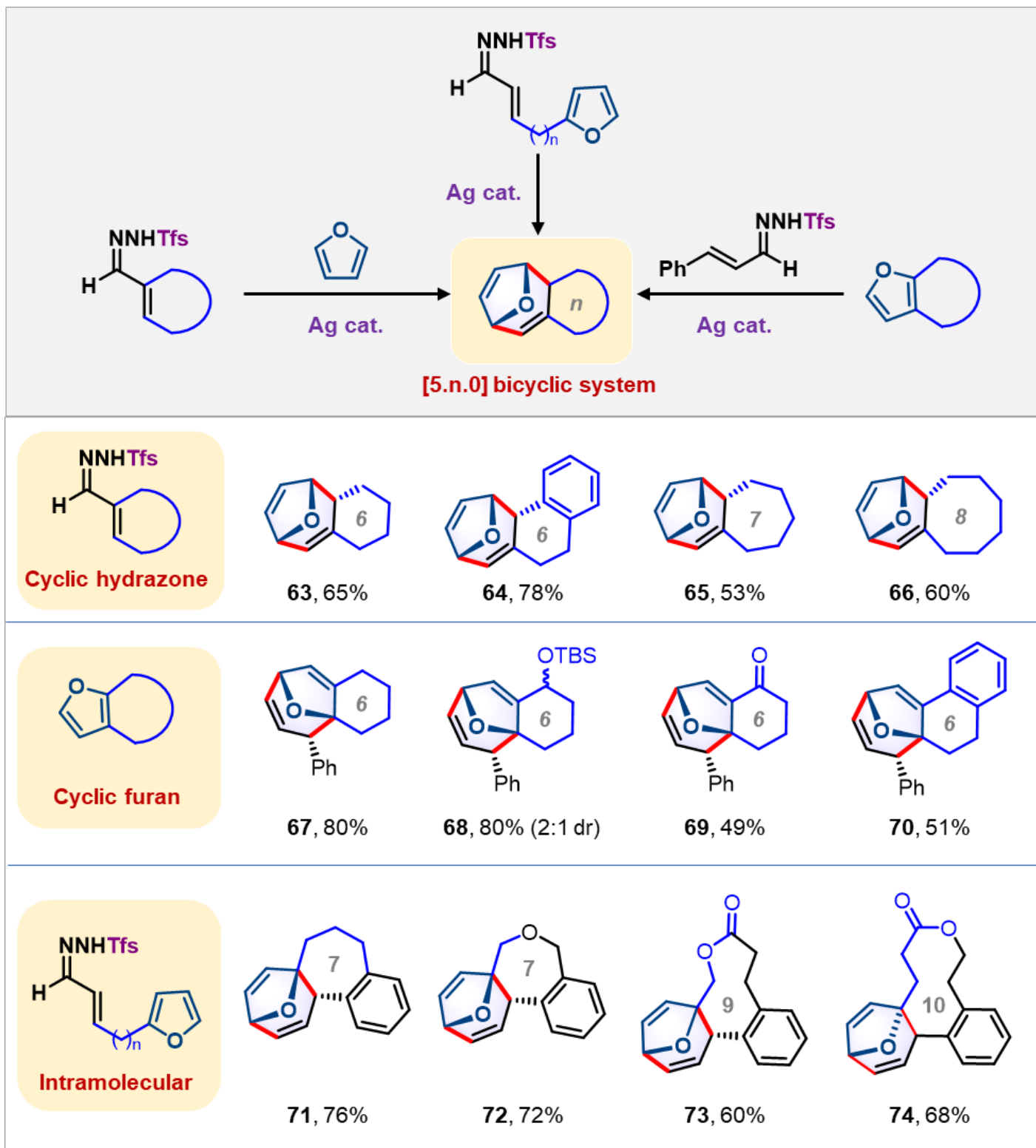


Figure 3

Collective synthesis of oxa-bridged bicyclo[5.n.0] ring systems.

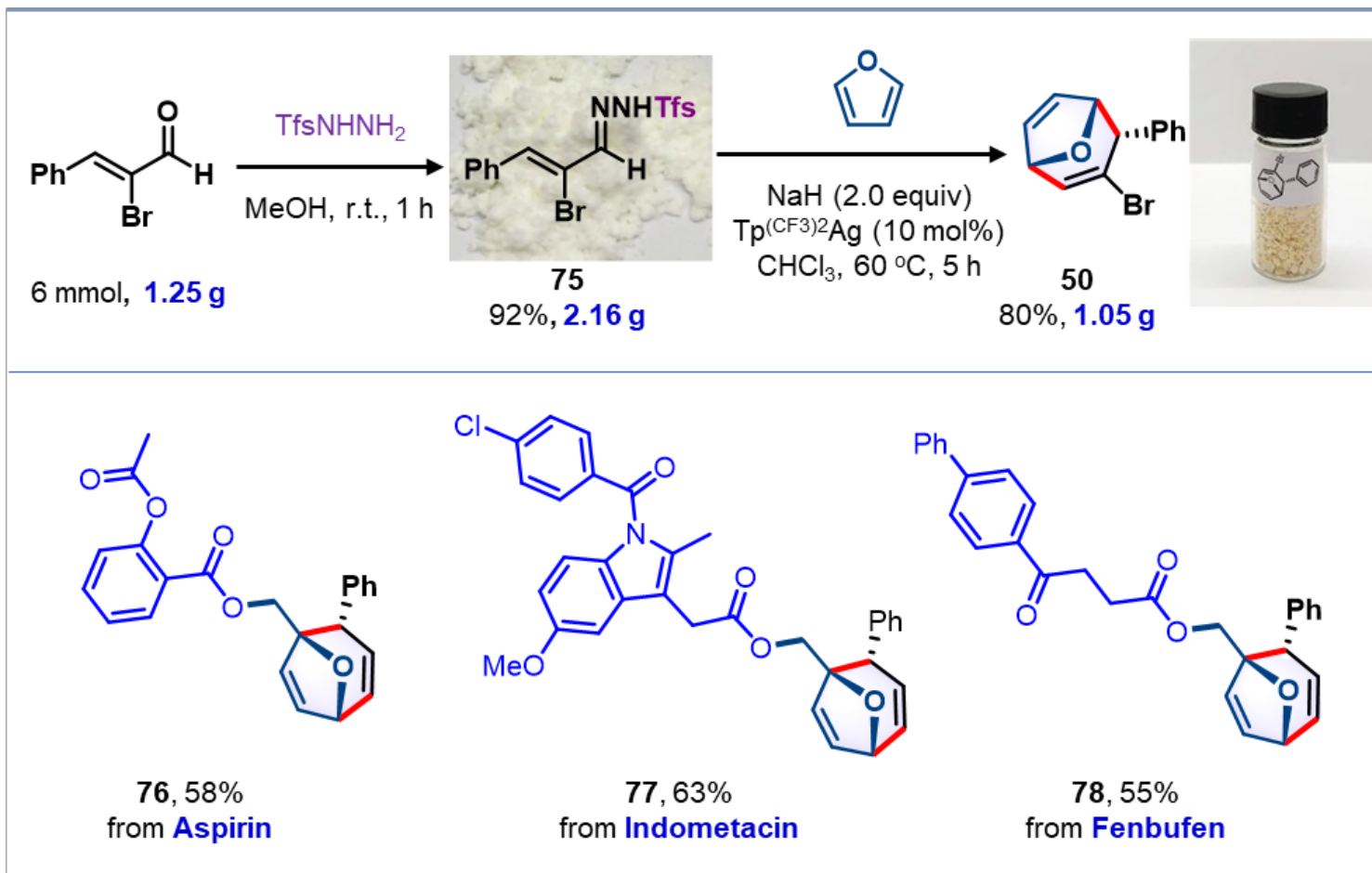
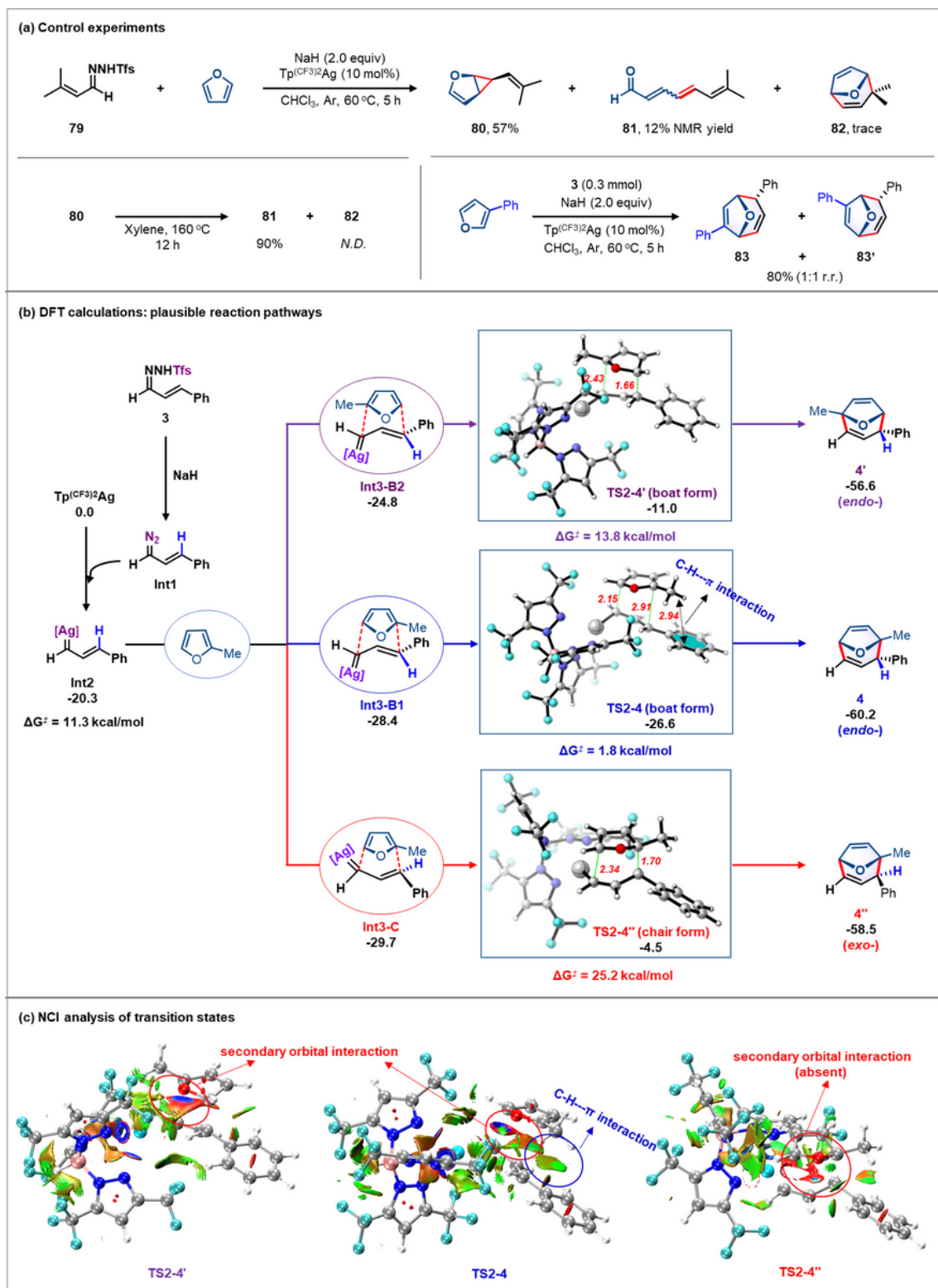


Figure 4

Gram-scale reaction and late-stage modifications.



**Figure 5**

**Mechanistic investigations.** (a) Control experiments. (b) A concerted [4 + 3] cycloaddition was proposed by computational studies at the B3LYP-D3(BJ)//6-31G(d,p)-SDD(Ag) level of theory. The relative Gibbs free energies are given in kcal/mol (black); the distances are given in angstroms (red). (c) NCI analysis of transition states for [4 + 3] cycloadditions. Blue: attraction; green: weak interaction; red: steric effect.



## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.docx](#)
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