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# Small-Molecule Inhibitors of Protein Geranylgeranyltransferase Type I

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Research by S. Castellano, H.D.G. Fiji, S.S. Kinderman, M. Watanabe, P. de Leon, F. Tamanoi, and O. Kwon, *J. Am. Chem. Soc.* **2007**, 129, 5843

Condensation and commentary by **Subhasis De** and **Scott R. Gilbertson**, University of Texas Medical Branch

## Condensation of the Research

### Purpose of the Study

*To demonstrate the utility of phosphine-catalyzed additions between polymer bound allenates and imines in the synthesis of libraries for biological screening*

### Background

In recent years, organocatalysis has emerged as a powerful technology, allowing synthetic chemists to perform various types of reactions. The catalytic activity of the process relies on low-molecular-weight organic molecules and does not require involvement of transition or main group metals. The organocatalytic method has become a very attractive strategy, particularly in the synthesis of molecules to be used in biological assays, as it avoids any metal contamination of the product. In many cases, the methods are robust, less sensitive toward moisture and oxygen, inexpensive, and also less toxic. Furthermore, this strategy is useful because of its operational simplicity and applicability in solid-phase synthesis. Among various organic catalysts, nitrogen- and phosphorus-based compounds are widely used, with amine-containing species being more prevalent than their phosphorus counterparts.

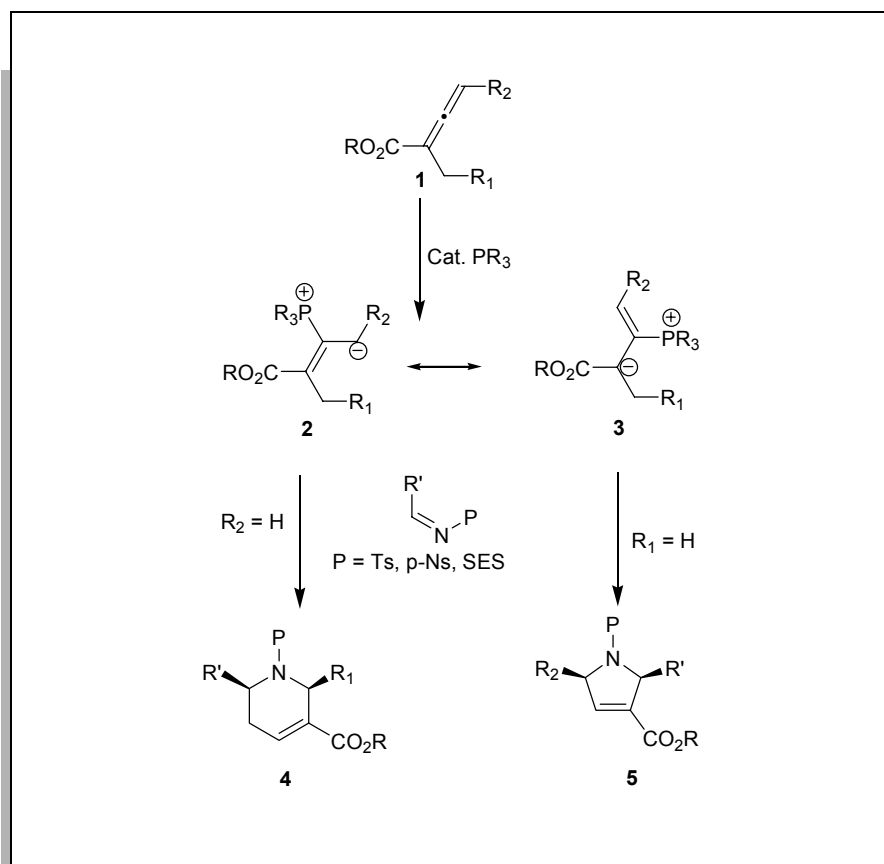
Since the discovery of [3+2] allenolate–acrylate annulation reaction by Lu and coworkers in 1995,<sup>1</sup> numerous reports have been published on formation of functionalized carbocycles and heterocycles using phosphines as nucleophilic catalysts.<sup>2,3</sup> The Zhang and Fu groups have separately demonstrated enantioselective versions of this reaction.<sup>4,5</sup> Several different natural products have also been synthesized by other groups following these

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CHEMTRACTS—ORGANIC CHEMISTRY **20**: 210–219 (2007)

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CCC 1431-9268



**Scheme 1**

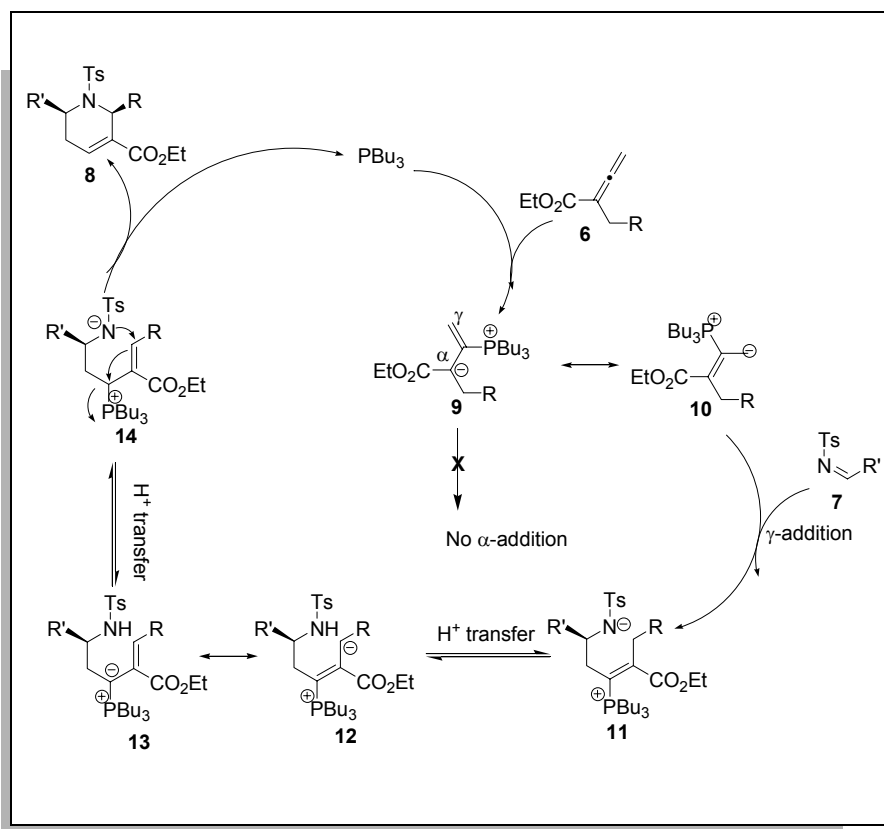
protocols.<sup>6</sup> Recently, the Kwon group has expanded the scope of allenolate annulation strategy toward making libraries of molecules in a combinatorial diversity-oriented synthesis (DOS) mode using nucleophilic phosphines as catalysts.

In 2003, Kwon and coworkers reported a novel and efficient phosphine-catalyzed [4+2] annulation strategy to construct highly functionalized tetrahydropyridines.<sup>3a</sup> Upon mixing protected imines with 2-substituted-2,3-butadienoate and 20% phosphine catalyst substituted tetrahydropyridines were formed. Kwon et al. envisioned that by having a substituent at the 2-position of 2,3-butadienoates the reaction could proceed via  $\gamma$ -addition of the zwitterionic intermediate (**2**) formed with the corresponding imines, rather than following the usual addition at the  $\alpha$  position (Scheme 1). A series of tetrahydropyridine derivatives from mostly aromatic imines were synthesized in excellent yield with complete regioselectivity and high diastereoselectivities using readily available starting materials (Table 1). The authors proposed a catalytic cycle where tri-*n*-butylphosphine nucleophilically triggers the reaction and the resulted zwitterionic intermediate reacts in [4+2] fashion as shown in Scheme 2. After two consecutive proton-transfer steps, the intermediate (**14**) is proposed to close the ring via Michael addition of

**Table I.** Synthesis of tetrahydropyridines

Entry	R'	R	Product	Yield (%) <sup>a</sup>	dr <sup>b</sup>
1	Ph	H	<b>8a<sup>c</sup></b>	98	—
2	4-OMeC <sub>6</sub> H <sub>4</sub>	H	<b>8b</b>	99	—
3	4-MeC <sub>6</sub> H <sub>4</sub>	H	<b>8c</b>	95	—
4	3-ClC <sub>6</sub> H <sub>4</sub>	H	<b>8d</b>	96	—
5	2-ClC <sub>6</sub> H <sub>4</sub>	H	<b>8e</b>	93	—
6	4-FC <sub>6</sub> H <sub>4</sub>	H	<b>8f</b>	95	—
7	4-CNC <sub>6</sub> H <sub>4</sub>	H	<b>8g</b>	98	—
8	2-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	<b>8h</b>	98	—
9	1-Naphthyl	H	<b>8i</b>	96	—
10	2-Furyl	H	<b>8j</b>	97	—
11	4-Pyridyl	H	<b>8j</b>	92 <sup>d</sup>	—
12	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	H	<b>8k</b>	86	—
13	2-OHC <sub>6</sub> H <sub>4</sub>	H	<b>8l</b>	0	—
14	2-OTBSC <sub>6</sub> H <sub>4</sub>	H	<b>8m</b>	93	—
15	2-Pyrrolyl	H	<b>8n</b>	0	—
16	<i>N</i> -Boc-2-pyrrolyl	H	<b>8o</b>	99	—
17	<i>Trans</i> -styrenyl	H	<b>8p</b>	Trace <sup>e</sup>	—
18	<i>t</i> -Butyl	H	<b>8q</b>	86 <sup>f</sup>	—
19	<i>n</i> -Propyl	H	<b>8r</b>	0 <sup>g</sup>	—
20	Ph	4-CNC <sub>6</sub> H <sub>4</sub>	<b>8s</b>	99	98.2
21	Ph	2-FC <sub>6</sub> H <sub>4</sub>	<b>8t</b>	99	97.3
22	Ph	3-OMeC <sub>6</sub> H <sub>4</sub>	<b>8u</b>	99	98.2
23	Ph	2-MeC <sub>6</sub> H <sub>4</sub>	<b>8v</b>	82	88.12
24	Ph	Ph	<b>8w<sup>c</sup></b>	99	98.2
25	4-OMeC <sub>6</sub> H <sub>4</sub>	Ph	<b>8x</b>	99	97.3
26	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph	<b>8y</b>	90	95.5
27	3-ClC <sub>6</sub> H <sub>4</sub>	4-CNC <sub>6</sub> H <sub>4</sub>	<b>8z</b>	99	98.2
28	2-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-CNC <sub>6</sub> H <sub>4</sub>	<b>8aa</b>	80	90.10
29	2-ClC <sub>6</sub> H <sub>4</sub>	3-OMeC <sub>6</sub> H <sub>4</sub>	<b>8ab</b>	96	83.17
30	4-MeC <sub>6</sub> H <sub>4</sub>	3-OMeC <sub>6</sub> H <sub>4</sub>	<b>8ac</b>	99	98.2

<sup>a</sup> Isolated yields.<sup>b</sup> Diastereomer ratio determined by <sup>1</sup>H NMR (500 MHz).<sup>c</sup> The structure was confirmed by x-ray crystallographic analysis.<sup>d</sup> 30 mol% PBU<sub>3</sub> was used.<sup>e</sup> The product was inseparable from the starting imine.<sup>f</sup> 3 eq of Na<sub>2</sub>CO<sub>3</sub> was added.<sup>g</sup> The imine was decomposed to aldehyde and *p*-toulenesulfonamide.



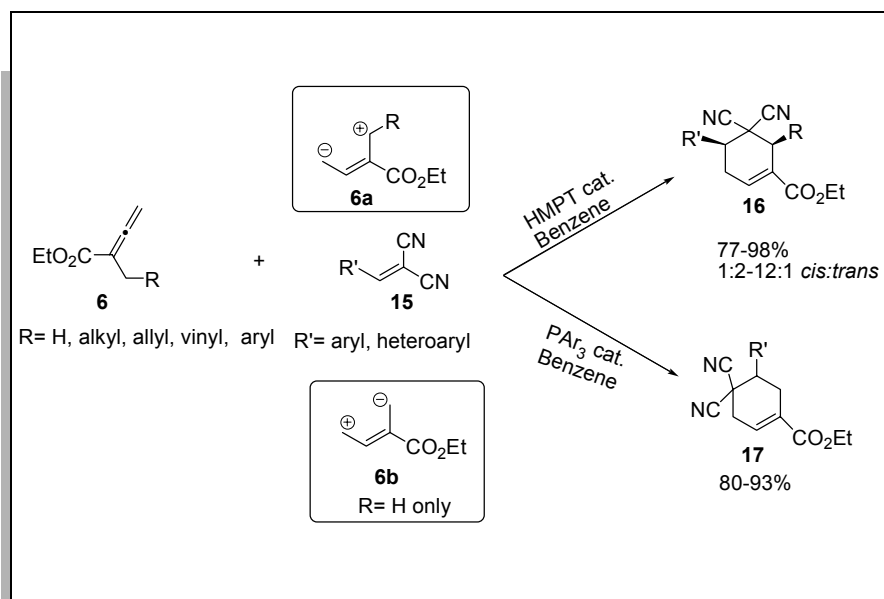
**Scheme 2**

*N*-tosyl with regeneration of the catalyst (**14** to **8**). The methodology was also successfully applied toward the synthesis of medicinally important monoterpenoid indole alkaloids.<sup>3e</sup> In a recent report Kwon and coworkers constructed cyclohexene frameworks following the same strategy using allenolates **6** and electron-deficient alkenes. They also demonstrated that by simply changing nucleophilicity of the phosphine catalyst, the reaction could be directed toward a particular regioisomer (Scheme 3).<sup>3f</sup>

Following a protocol similar to Lu's [3+2] cycloaddition, the researchers have also demonstrated formation of 3-carboethoxy-2,5-disubstituted-3-pyrrolines derivatives in excellent yields with high diastereoselectivity using  $\gamma$ -substituted allenolates (Scheme 4).<sup>3b</sup> The proposed mechanism suggests that the zwitterionic phosphonium intermediate undergoes electrophilic addition to the imine at the  $\alpha$  position to form an amide **22** which subsequently cyclizes to **23**. A proton transfer followed by elimination of the catalyst leads the final product (Scheme 5).

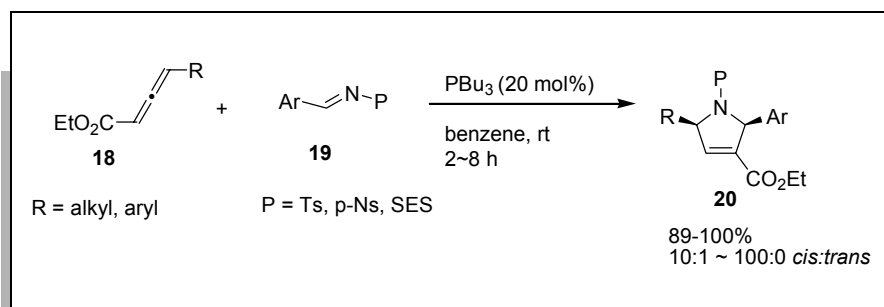
### What Researchers Accomplished

Utilizing the established phosphine-catalyzed annulations methodology, Kwon and coworkers have generated a modest heterocyclic library of compounds that were then screened for their potential as geranylgeranyl-transferase I inhibitors (GGTIs).<sup>7,8</sup> Initially compounds **25** and **26** (Fig. 1)

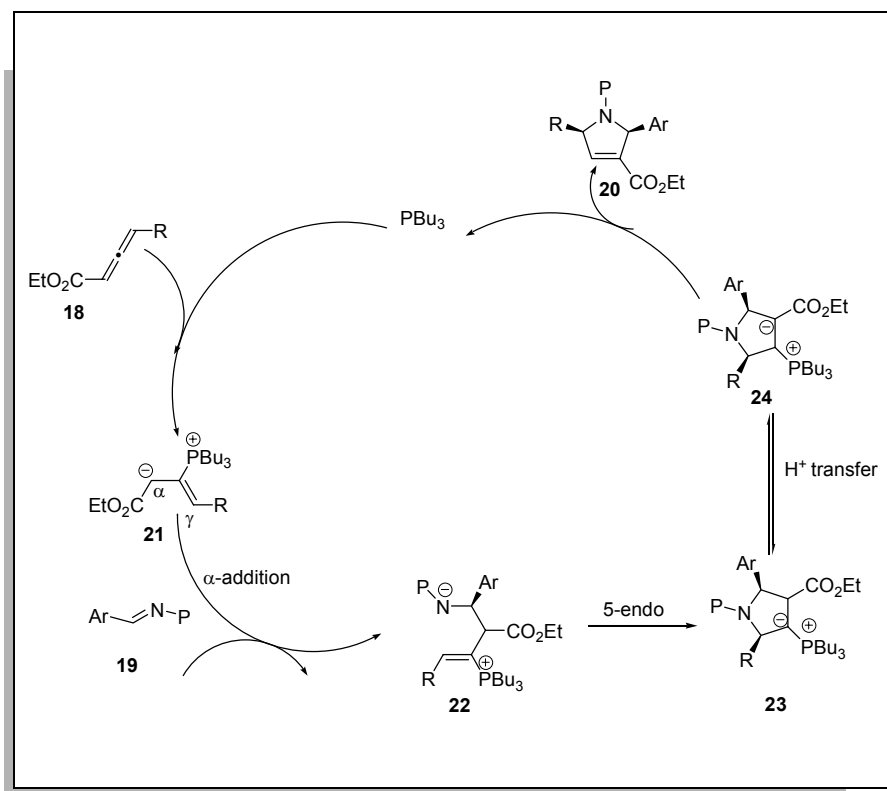


Scheme 3

showed promising inhibitory activity in the micromolar range toward human GGTase I to geranylgeranylate K-Ras4B or RhoA. This motivated the researchers to develop a larger size library. A solid-phase synthetic strategy was adopted where allenoates were directly embedded onto SynPhase lanterns via Mukaiyama's reagent.<sup>3g</sup> The solid supported allenoates (**29a-d**) participated in the phosphine-catalyzed annulations reactions in a similar fashion to the solution-phase examples (Scheme 6). The resin-bound cycloadducts (**30** or **32**) could then be easily detached by trifluoroacetic acid (TFA). Prior to cleavage from the lanterns, the scaffolds could be further diversified by Michael addition of commercially available thiols. Thiol addition took place in a highly diastereoselective fashion for both pyrrolidine (**30**) and piperidine (**32**) derivatives, with the corresponding protonation resulting in *anti* (for **34**) and *syn* (for **35**) modes with respect to the added mercapto groups (Scheme 6).

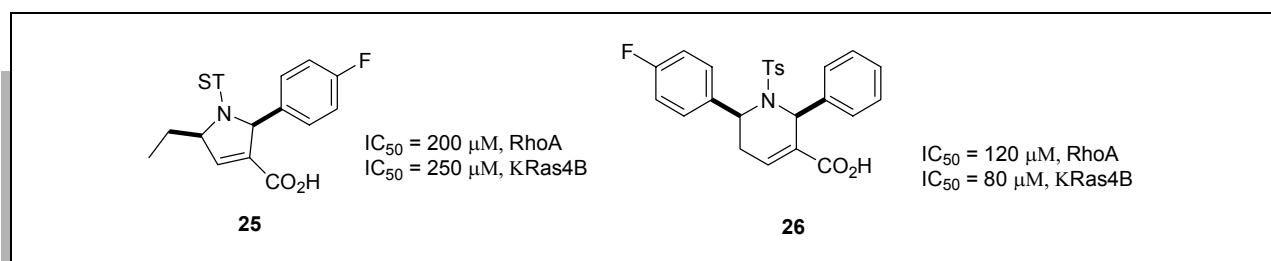


Scheme 4

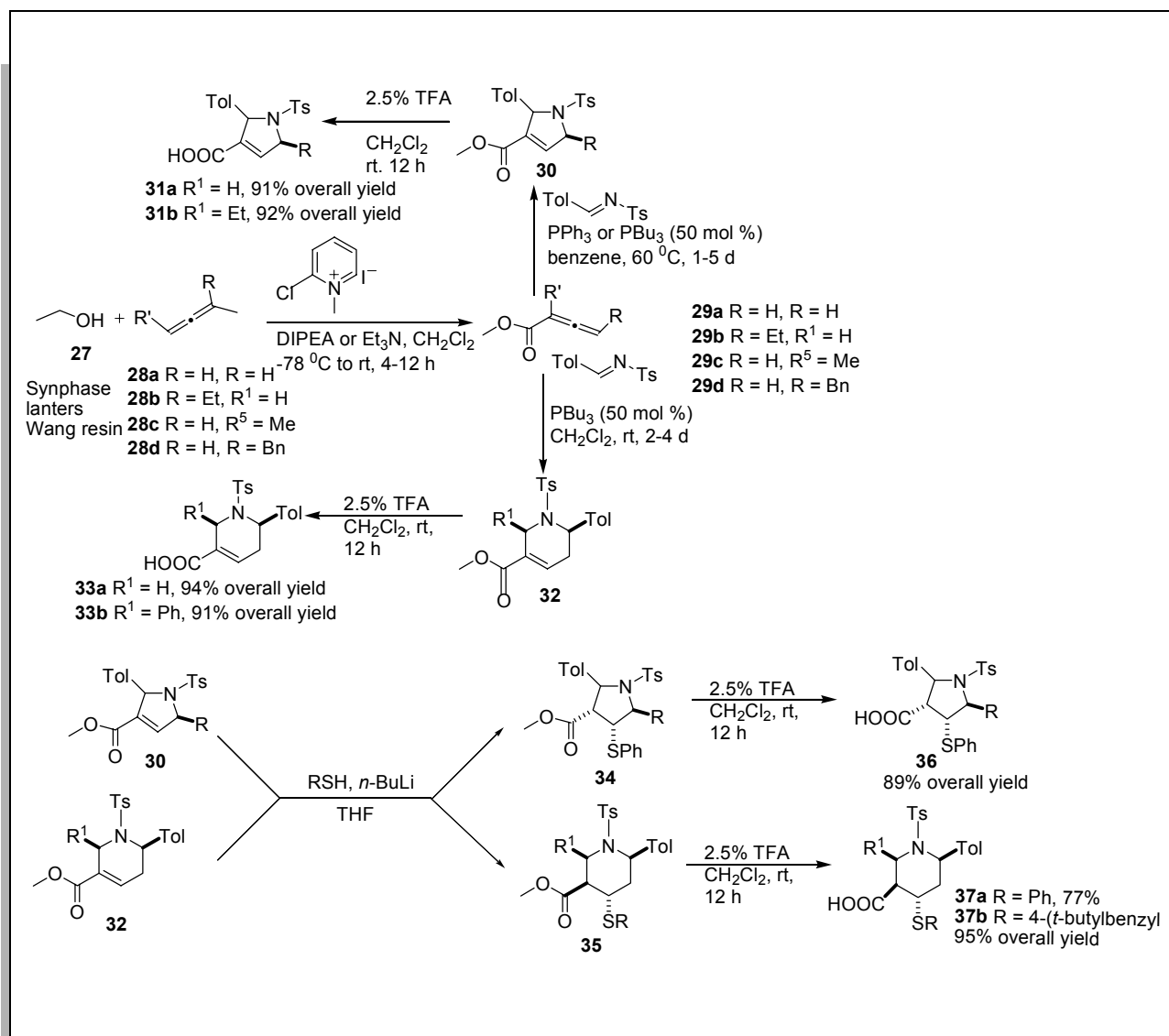


**Scheme 5**

In this synthetic procedure  $\alpha$ - and  $\gamma$ -substituted allenoic acid (Fig. 2) and *N*-sulfonylimines (Fig. 3) were prepared following standard literature protocol,<sup>9-11</sup> while all the thiols (Fig. 4) used in the process were commercially available. After several rounds of optimization, 4288 compounds were generated in split-pool fashion from these building blocks. Each of the compounds were transferred into 96 well plates and screened for activity against GGTase I. Screening results identified compounds **38** and **39** as potent inhibitors of GGTase I with  $IC_{50}$  values in the submicromolar range (Fig. 5). The inhibitory effects of these compounds were then validated by *in vivo* studies.



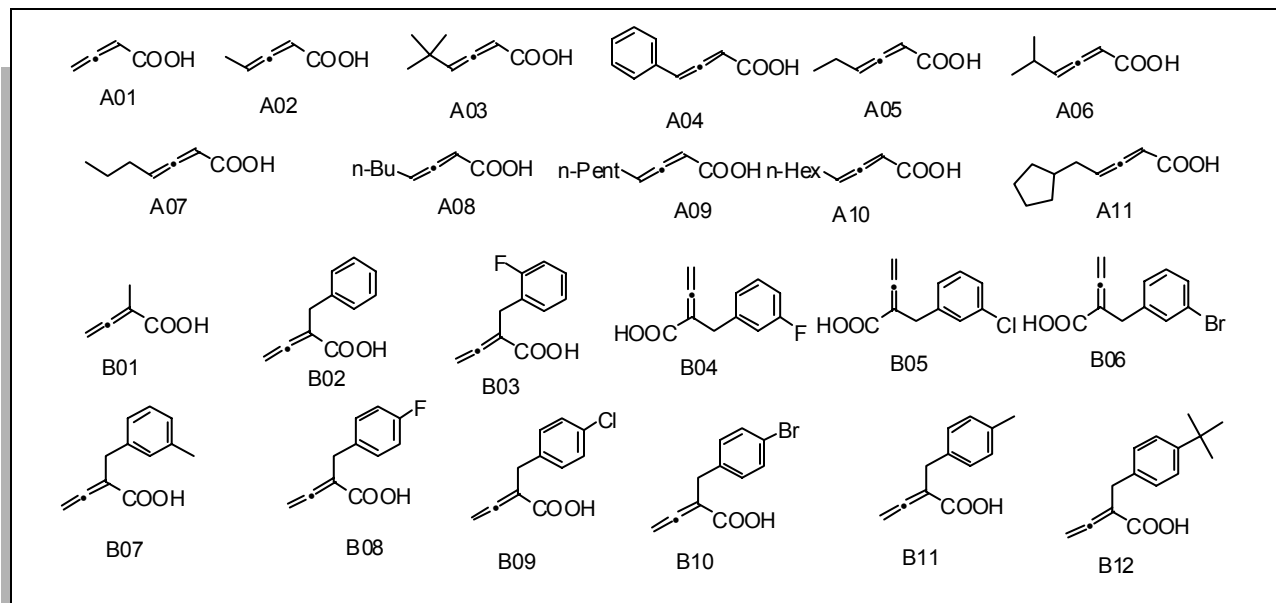
**Figure 1.** Promising GGTIs.



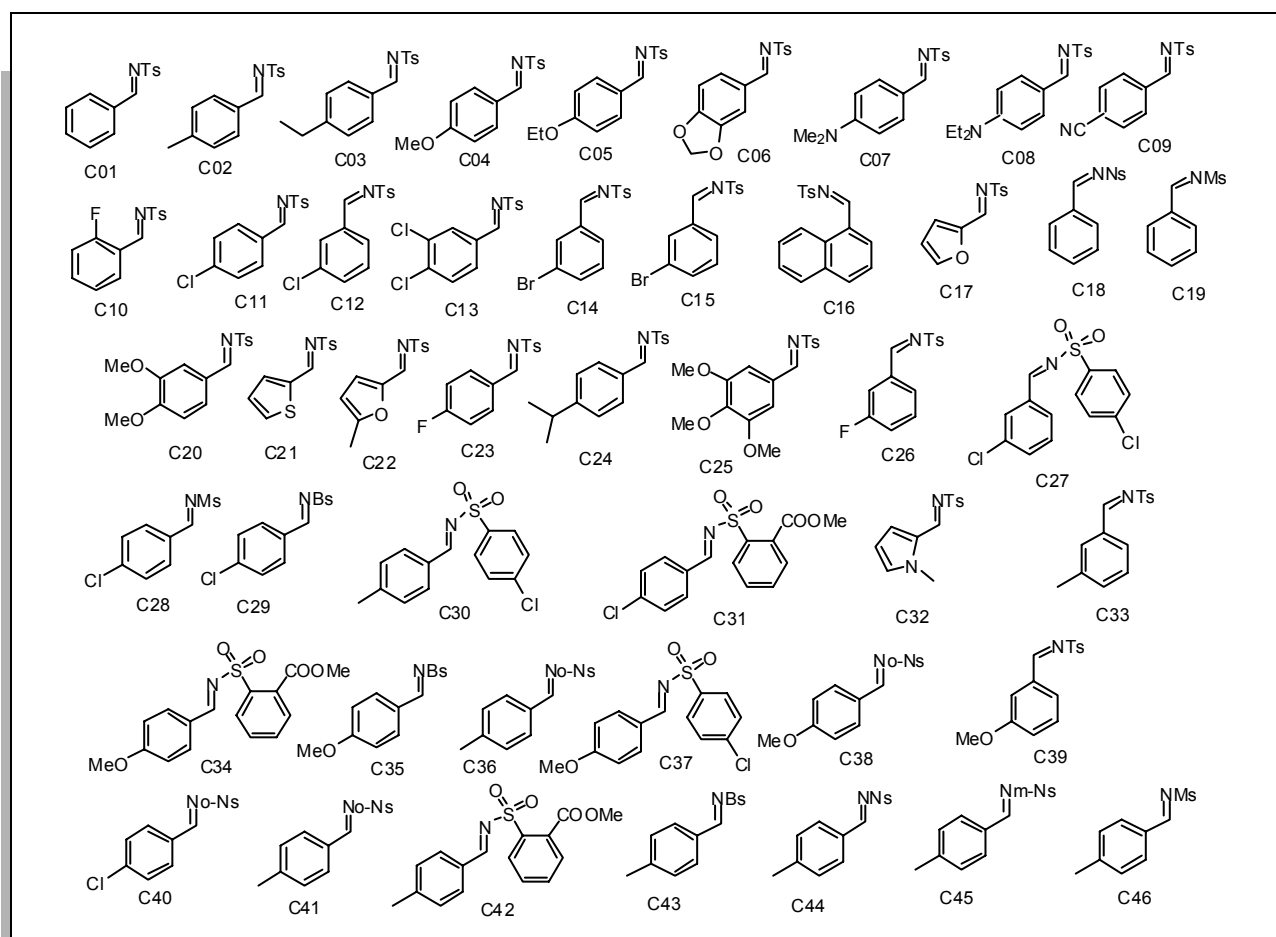
Scheme 6

## Commentary on the Research

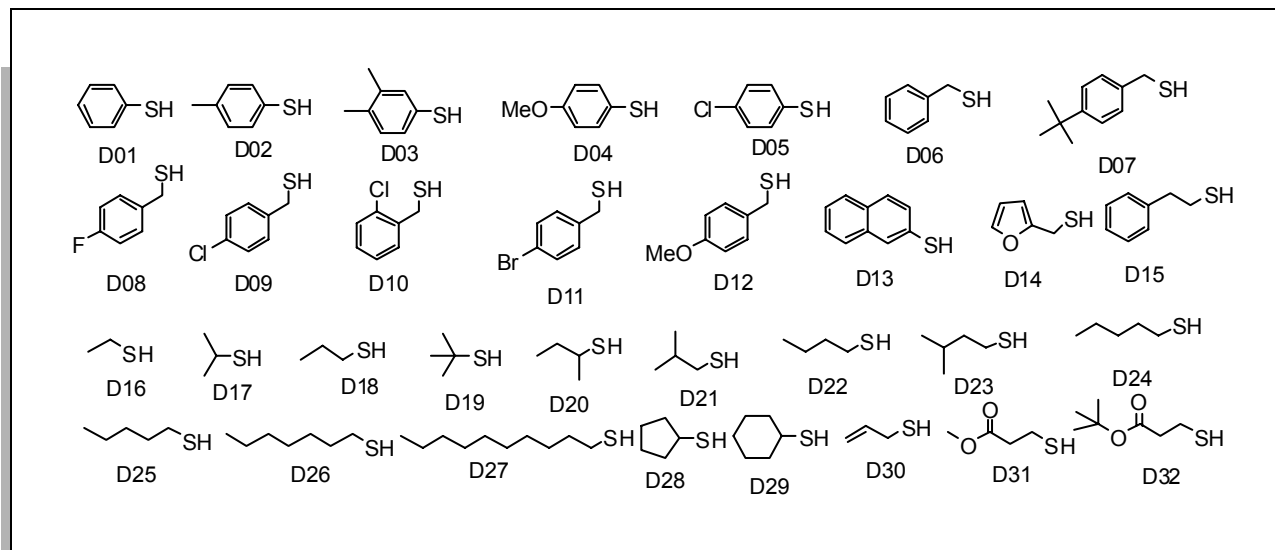
The authors have successfully demonstrated that allenolate annulations on solid support can be used to establish a small-molecule heterocyclic library. The identification of active lead compounds illustrated the potential usefulness of the overall process. So far the reactions are mostly limited to aromatic protected imines. Catalysts that allow for greater substrate tolerance and run with a low loading will enhance what is already a useful method. Additionally, it will be very interesting to see if nucleophiles other than thiols can eventually be added to the initially formed  $\alpha,\beta$ -unsaturated esters.



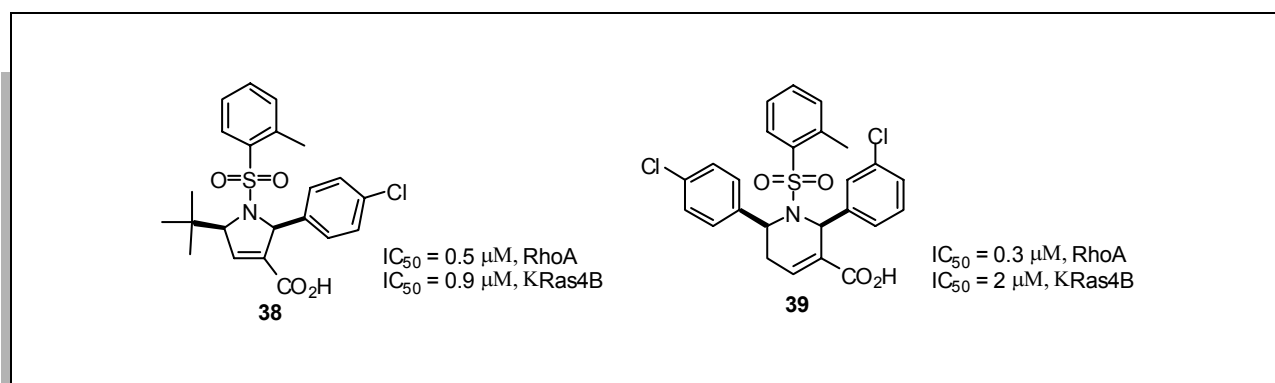
**Figure 2.** Allenoic acids.



**Figure 3.** N-sulfonylimines.



**Figure 4.** Thiols.



**Figure 5.** Highest potency exhibited by **38** and **39** as GGTIs.

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