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# Synthesis of Vinyl-Functionalized Thiazoles by Cross-Metathesis and Tandem Stille Coupling/Cross-Metathesis

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**Abstract:** The application of olefin cross-metathesis to vinyl-functionalized thiazoles and the tandem Stille coupling/cross-metathesis of bis-trifloylthiazoles are reported. These processes offer new opportunities for the synthesis of complex natural products.

**Keywords:** alkenes; heterocycles; homogeneous catalysis; metathesis; Stille coupling; tandem reactions

In the last decade, olefin cross-metathesis (CM) has emerged as a powerful tool for the construction of carbon-carbon double bonds.[1] The commercial availablity of well-defined catalysts such as [Mo]-**I** (Schrock's catalyst),[2] [Ru]-**I** (Grubbs' first generation catalyst),[3] [Ru]-**II** (Grubbs' second generation catalyst),[4] and [Ru]-**III** (Hoveyda–Grubbs' catalyst)[5] (Figure 1) has expanded the variety of functional groups amenable to CM and thus made olefin metathesis practical for application in synthetic organic chemistry. As a consequence, olefin CM has been widely used in the synthesis of complex natural products.[6]

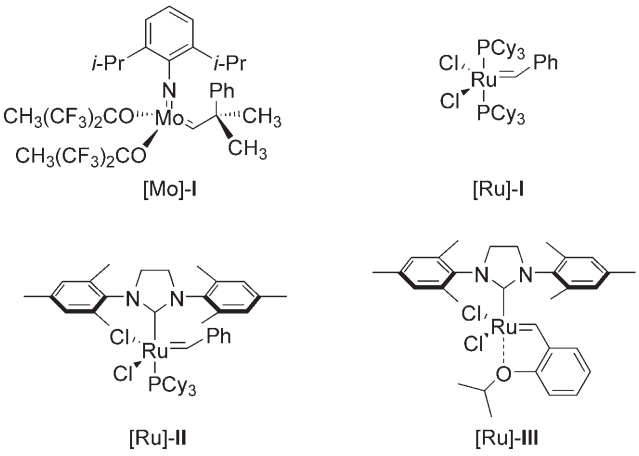



**Figure 1.** Commonly used metathesis catalysts.

Whereas metathesis reactions on substrates bearing a large range of functionalities and heteroatoms are fully documented in the literature, to our knowledge, no examples of substrates containing vinyl-functionalized thiazoles have been reported to date. Functionalized thiazole substructures are present in numerous biologically active natural[7] and non-natural[8] products such as epothilone B or HDAC inhibitor I (Figure 2). It is therefore important to be able to build such substructures in a very versatile and efficient way starting from simple and readily available compounds. Herein, we report a CM reaction involving vinyl-functionalized thiazoles using [Ru]-**II** and [Ru]-**III** catalysts, and a "one-pot" Stille coupling/CM leading to bis-substituted thiazoles of type **A** (Scheme 1).

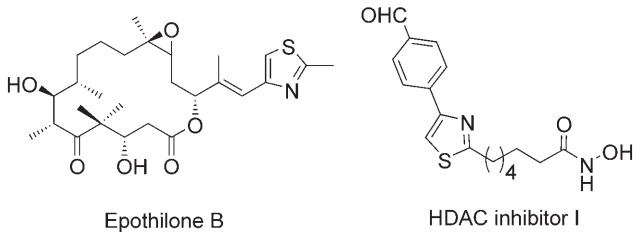
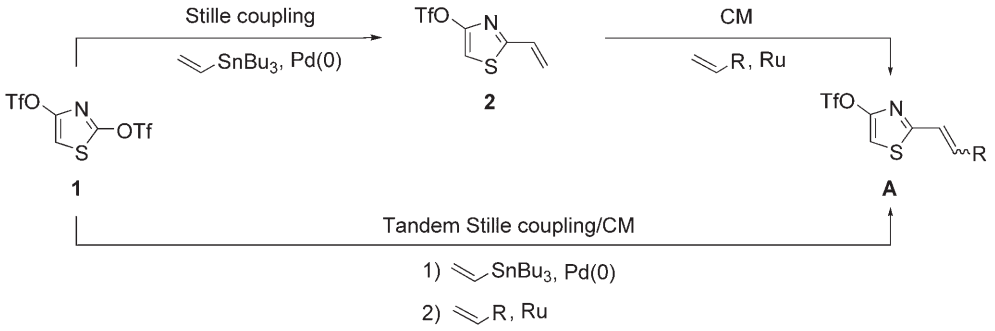



**Figure 2.** Thiazole-containing natural products.

The synthesis of compound **2** was achieved starting from the corresponding 2,4-bis-trifloylthiazole **1**[9] in 76% yield using the standard Stille conditions[10] [vinylstannane (1 equiv.), $Pd(PPh_3)_4$ (5 mol%), LiCl (5 equivs.), dioxane, 80 °C, 4 h]. In order to determine the best conditions for the CM reaction, compound **2** was then subjected to a series of CM experiments in the presence of carbene ruthenium complexes [Ru]-**I**, [Ru]-**II**, and [Ru]-**III**, and 4-methylpent-1-ene **3a**




**Scheme 1.** CM and tandem Stille coupling/CM of bis-functionalized thiazoles.

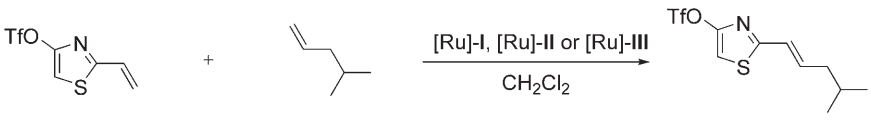
(3 equivs.) as the coupling partner. The results are reported in Table 1.

When 10 mol% of [Ru]-**I** were used and the reaction performed at room temperature for 24 h, the disubstituted olefin **4a** was isolated in 53% yield as a single isomer (Table 1, entry 1). The (*Z*)-isomer was not detected by either $^{1}H$ or $^{13}C$ NMR thus suggesting a selectivity superior to 95/5 in favor of the (*E*)-isomer. It is noteworthy that under these conditions only 66% of the starting material **2** were converted. By performing the reaction in refluxing $CH_2Cl_2$ under otherwise identical conditions, the conversion of **2** was increased to 90%, while the yield in **4a** was increased to 67% (Table 1, entry 2). The use of 10 mol% of [Ru]-**II** at room temperature led to complete conversion of the starting material after only 0.5 h, and compound **4a** was isolated in 92% yield as the (*E*)-isomer (Table 1, entry 3). To allow direct comparison with the previous set of conditions, the reaction was run in refluxing $CH_2Cl_2$ in the presence of 10 mol% of [Ru]-**II**. Under these conditions, **4a** was isolated in 91% yield as the (*E*)-isomer (Table 1, entry 4). By decreasing the amount of [Ru]-**II** catalyst to 5 mol%, **4a** was isolated in 81% (Table 1, entry 5). Similar yields were obtained when the reaction was performed with 5 mol% of [Ru]-**III** in $CH_2Cl_2$ as the quasi complete disappearance of **2** took place in 12 h at room temperature and in 1 h in refluxing $CH_2Cl_2$ to produce **4a** in 83% and 84% yield respectively (Table 1, entries 6 and 7).

The above experiments led us to select [Ru]-**II** and [Ru]-**III** over [Ru]-**I** as the catalyst candidates. A series of CM experiments was therefore carried out between **2** and a series of electron-rich olefinic partners in order to explore the scope and limitation of the reaction. Typically, the CM were performed in refluxing $CH_2Cl_2$ using 10 mol% of [Ru]-**II** and 5 mol% of [Ru]-**III**.[11] The results are summarized in Table 2.

The reaction of compound **2** with 3 equivalents of **3b** using the two selected catalysts, [Ru]-**II** and [Ru]-**III**, afforded the desired product **4b** in 79% to 82% isolated yield as the (*E*)-isomer (Table 2, entries 1 and 2). Similarly, **2** reacted with **3c** to give the desired product **4c** in 86% to 89% yield (Table 2, entries 3 and 4). For olefins such as allyltrimethylsilane **3d**, bu-

**Table 1.** Olefin cross-metathesis reaction of 2-vinyl-4-trifloylthiazole.[a]



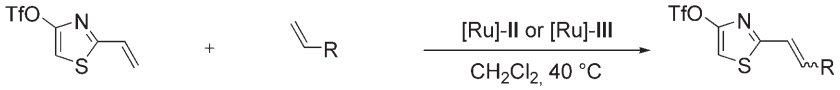

**2** **3a** **4a**

| Entry | Catalyst | Temperature [°C] | Time [h] | Conversion [%][b] | Yield [%][c] | *E*/*Z*[d] |
|---|---|---|---|---|---|---|
| 1 | **I** (10 mol%) | 24 | 24 | 66 | 53 | >20:1 |
| 2 | **I** (10 mol%) | 40 | 18 | 90 | 67 | >20:1 |
| 3 | **II** (10 mol%) | 24 | 0.5 | 100 | 92 | >20:1 |
| 4 | **II** (10 mol%) | 40 | 0.5 | 100 | 91 | >20:1 |
| 5 | **II** (5 mol%) | 24 | 12 | 95 | 81 | >20:1 |
| 6 | **III** (5 mol%) | 24 | 12 | 95 | 83 | >20:1 |
| 7 | **III** (5 mol%) | 40 | 1 | 100 | 84 | >20:1 |

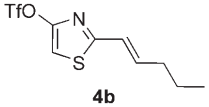
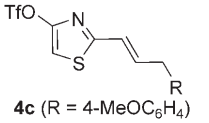
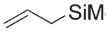
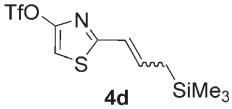
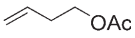
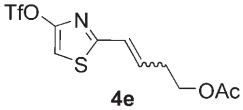
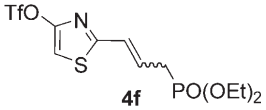
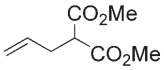
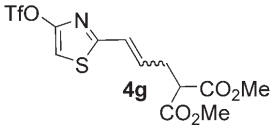
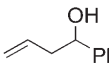
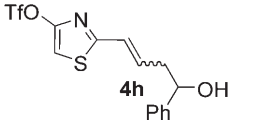
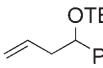
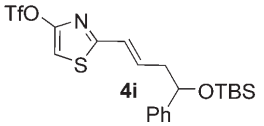
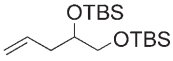
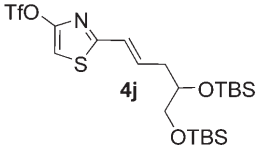
[a] All reactions were carried out on a 0.11 mmol scale using 3 equivs. of **3a** in $CH_2Cl_2$.
[b] Conversion determined by $^{1}H$ NMR of the crude reaction mixture.
[c] Isolated yield.
[d] *E*/*Z* ratio determined by $^{1}H$ NMR of the crude reaction mixture.

**Table 2.** Olefin cross-metathesis of 2-vinyl-4-trifloylthiazole.[a]




**2** **3a – j** **4a – j**

| Entry | Olefin | Catalyst | Time [h] | Conversion [%][b] | Product | Yield [%][c] | *E*/*Z*[d] |
|---|---|---|---|---|---|---|---|
| 1 |  | **II** (10 mol%) | 4 | 100 |  | 82 | >20:1 |
| 2 | **3b**[e] | **III** (5 mol%) | 8 | 100 | **4b** | 79 | >20:1 |
| 3 |  | **II** (10 mol%) | 12 | 100 |  | 89 | >20:1 |
| 4 | **3c** (R = 4-MeOC$_6$H$_4$) | **III** (5 mol%) | 24 | 100 | **4c** (R = 4-MeOC$_6$H$_4$) | 86 | >20:1 |
| 5 |  | **II** (10 mol%) | 2 | 100 |  | 89 | 5:1 |
| 6 | **3d**[e] | **III** (5 mol%) | 12 | 100 | **4d** | 83 | 5:1 |
| 7 |  | **II** (10 mol%) | 18 | 80 |  | 63 | 8:1 |
| 8 | **3e** | **III** (5 mol%) | 24 | 67 | **4e** | 58 | 7:1 |
| 9 |  | **II** (10 mol%) | 24 | 50 |  | 43 | 5:1 |
| 10 | **3f** | **III** (5 mol%) | 24 | 42 | **4f** | 37 | 7:1 |
| 11 |  | **II** (10 mol%) | 24 | 50 |  | 46 | 4:1 |
| 12 | **3g** | **III** (5 mol%) | 24 | 67 | **4g** | 54 | 3:1 |
| 13 |  | **II** (10 mol%) | 24 | 27 |  | 22 | 4:1 |
| 14 | **3h** | **III** (5 mol%) | 24 | 25 | **4h** | 19 | 3:1 |
| 15 |  | **II** (10 mol%) | 12 | 80 |  | 65 | >20:1 |
| 16 | **3i** | **III** (5 mol%) | 24 | 100 | **4i** | 83 | >20:1 |
| 17 |  | **II** (10 mol%) | 18 | 86 |  | 57 | >20:1 |
| 18 | **3j** | **III** (5 mol%) | 8 | 77 | **4j** | 51 | >20:1 |

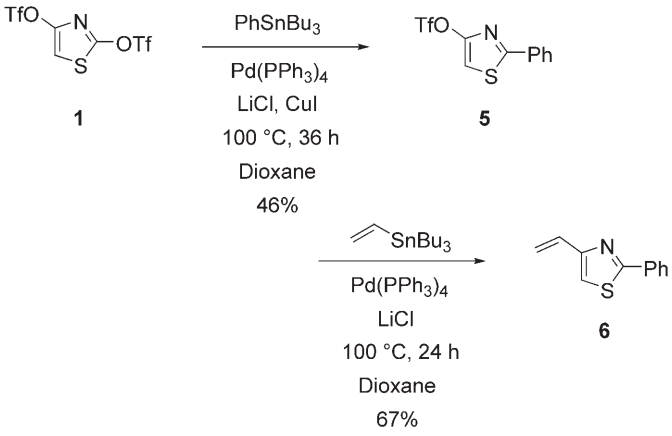
[a] All reactions were carried out on a 0.11 mmol scale using 1.5 equivs. of olefin (unless otherwise specified) in $CH_2Cl_2$ at 40 °C.
[b] Conversion determined by $^1$H NMR of the crude reaction mixture.
[c] Isolated yield.
[d] *E*/*Z* ratio determined by $^1$H NMR of the crude reaction mixture.
[e] Reaction performed using 3 equivs. of the olefin partner.

tenyl acetate **3e**, allyl diethylphosphonate **3f**, and allyl dimethylmalonate **3g**, chemical yields were ranging from 37% to 89% while the *E*/*Z* stereoselectivity of products **4d–g** ranged from 3/1 to 8/1 in favor of the (*E*)-isomer (Table 2, entries 5–12). Interestingly, **3h** bearing a free hydroxy group led to low yields of the desired coupled product, as **4h** was isolated in only 19% to 22% yield as a mixture of (*E*)- and (*Z*)-stereoisomers (Table 2, entries 13 and 14). In comparison, the corresponding *tert*-butyldimethylsilyl protect-

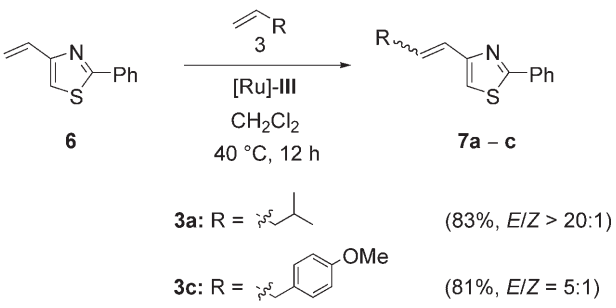
ed alcohol **3i** gave the desired coupled product as a single isomer in 83% yield when [Ru]-**III** was used (Table 2, entry 16). Similarly, olefin **3j** gave the desired CM-product **4j** in both good yield and good stereoselectivity (51% to 57% yield) (Table 2, entries 17 and 18). It is worth noting that vinyl-functionalized thiazole **2** behaves as an olefin substituted with an electron-withdrawing group and does not undergo any homodimerization under the reaction conditions.

The CM could also be applied to 4-substituted vinylthiazoles such as **6** which was prepared from bis-trifloylthiazole **1** following two subsequent Stille couplings in 30% overall yield (Scheme 2). Thus, the reaction of 4-vinylthiazole **6** with olefin **3a** and **3c** in the presence of 10 mol% of [Ru]-**III** in refluxing $CH_2Cl_2$ for 12 h afforded the desired products **7a** and **7c** in 83% and 81% isolated yield respectively (Scheme 3).

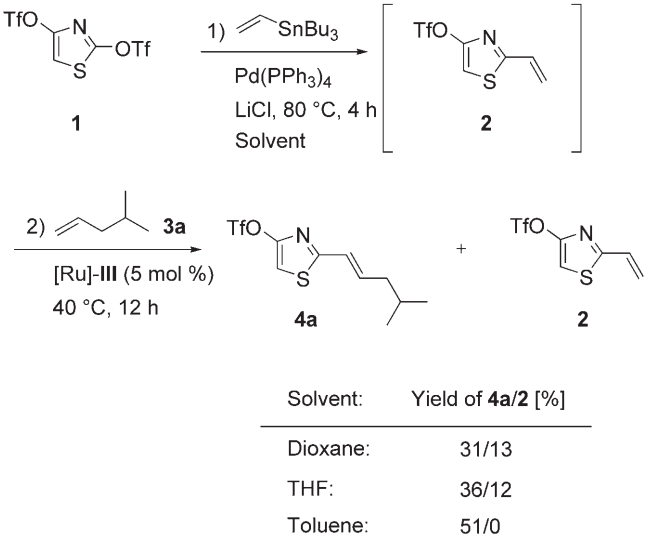



**Scheme 2.** Synthesis of 4-vinyl-functionalized thiazole.

The sequential use of reactions, also called "tandem reactions", allows to circumvent the time and yield loss associated with the isolation and purification of intermediates in a multistep sequence.[12] In a more practical sense, it allows one to perform multiple transformations in a single reaction vessel thus leading to a more environmentally friendly chemistry. In this context, we were able to perform a "one-pot" Stille coupling/CM starting from bis-trifloylthiazole **1** (Scheme 4). Thus, treatment of **1** with 5 mol% of Pd-$(PPh_3)_4$ in the presence of LiCl (4 equivs.) and vinyltributylstannane (1.0 equiv.) at 80°C followed, after complete conversion of the starting material, by the addition of 5 mol% of [Ru]-**III** and olefin **3a** led, after 12 h at 40°C, to the desired product **4a** in moderate to good yield depending on the nature of the solvent used. Thus, when the reaction was performed in either dioxane or THF, **4a** was isolated with yields ranging from 31% to 36%. On the other hand, when the reaction was performed in toluene, **4a** was isolated in 51% yield which can be compared favorably with the standard two-step procedure.




**Scheme 3.** CM of 4-vinyl-functionalized thiazole.




**Scheme 4.** Tandem Stille coupling/CM of bis-trifloylthiazole **1**.

In conclusion, we have shown that vinyl-functionalized thiazoles could undergo CM with a variety of electron-rich olefins of Type **1**[1c] using ruthenium catalysts [Ru]-**II** and [Ru]-**III** to afford the desired coupled products in good to excellent yield. Moreover, we have developed a very selective tandem Stille coupling/CM process which provides an easy access to functionalized thiazoles. The application of this methodology to the synthesis of natural products is currently underway in our laboratory and the results will be reported in due course.

## Experimental Section

### Typical Procedure for the CM of Vinyl-Functionalized Thiazoles with Various Olefins

To a stirred solution of vinyl-functionalized thiazole **2** (0.11 mmol) and olefin **4** (0.165 mmol, 1.5 equivs.) in $CH_2Cl_2$ (1 mL) was added either [Ru]-**II** (0.01 mmol, 10 mol%) or

[Ru]-**III** (0.005 mmol, 5 mol%). The reaction mixture was heated under $N_2$ at 40 °C (the reaction was monitored by TLC). The solvent was then removed under reduced pressure, and the residue purified by flash column chromatography on silica gel (EtOAc/hexanes = 1/99 to 5/95).

Fully detailed experimental procedures and compound characterization data can be found in the electronic Supporting Information.

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[10] For reviews, see : a) J. K. Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; b) J. K. Stille, *Pure Appl. Chem.* **1985**, *57*, 1771–1780; c) F. Diederich, P. J. Stang, *Metal-Catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1998**.

[11] As a general trend, all reactions were performed using 1.5 equivalents of olefin. In the case of volatile olefins, 3 equivalents were used instead.

[12] For a recent review on tandem catalysis, see: J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; see also: a) G. H. Posner, *Chem. Rev.* **1986**, *86*, 831–844; b) T.-L. Ho, *Tandem Organic Reactions*, Wiley-Interscience : New York, **1992**; c) N. Hall, *Science* **1994**, *266*, 32–34; d) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136.


  