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Solid-Phase Olefin Cross-Metathesis Promoted by a Linker

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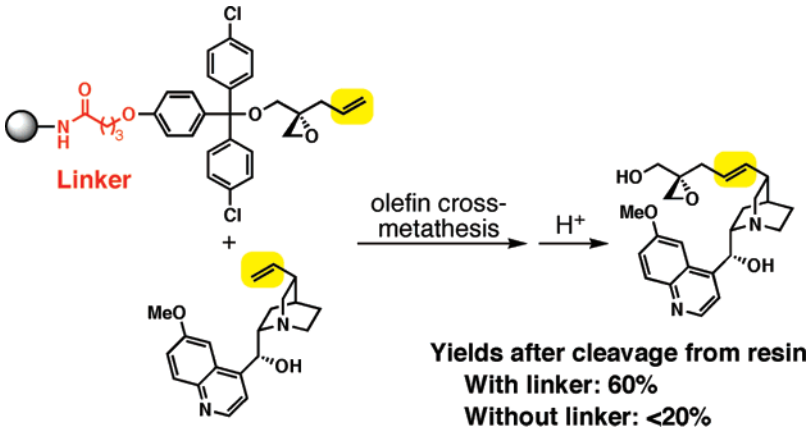
ABSTRACT



Olefin cross-metathesis couples two alkenes to form complex molecules and has been widely used in solution-phase organic synthesis. However, this powerful method has rarely been used in solid-phase organic synthesis. Herein we report that olefin cross-metathesis is a synthetically viable method particularly when a traceless longer linker is inserted between solid support and reacting olefins.

Carbon-carbon double bond formations are important in organic synthesis. Among these reactions is olefin metathesis, which is a very powerful method for the construction of complex alkenes.[1] As such, olefin metathesis has been used in the syntheses of a variety of molecules in solution phase.[2] In solid-phase synthesis, although ring-closing olefin metathesis has been widely used,[3] olefin cross-metathesis has been rarely used[4,5] despite its potential for the convergent synthesis of complex alkenes. In a rare example, Testero and Mata showed that β-lactam analogues could be prepared on solid support using olefin cross-metathesis between alkenes on polymer and alkenes in solution, in which the yields of the metathesis ranged from 35 to 78%.[4] As apparent in our study described below, their success may be due to the large distance between the polymer and the reacting olefins, which may not apply to other cases. In related cases, two spatially separated alkenes, both on the same solid support, were coupled by olefin metathesis, but these examples are, strictly speaking, intramolecular reactions.[6] Broadly applicable solid-phase olefin cross-metathesis would be valuable because homodimers and byproducts in solution can easily be removed by simple filtration and the process can be

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(5) Chang, S.; Na, Y.; Shin, H. J.; Choi, E.; Jeong, L. S. *Tetrahedron Lett.* **2002**, *43*, 7445.

(6) (a) Blackwell, H. E.; Clemons, P. A.; Schreiber, S. L. *Org. Lett.* **2001**, *3*, 1185. (b) Liao, Y.; Fathi, R.; Yang, Z. *J. Comb. Chem.* **2003**, *5*, 79. (c) Olenyuk, B.; Jitianu, C.; Dervan, P. B. *J. Am. Chem. Soc.* **2003**, *125*, 4741. (d) Tang, Q.; Wareing, J. R. *Tetrahedron Lett.* **2001**, *42*, 1399.

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automated.[5] Herein, we report a general solution to the challenging solid-phase olefin cross-metathesis.

In our synthetic efforts toward the development of biologically active compounds on solid support, we chose olefin cross-metathesis as a convergent coupling method. Olefin cross-metathesis is a mild transformation catalyzed by various ruthenium reagents such as **1a**[7] and **1b**[8] (Figure 1) and

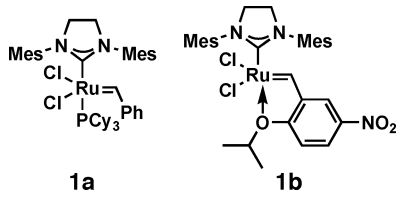
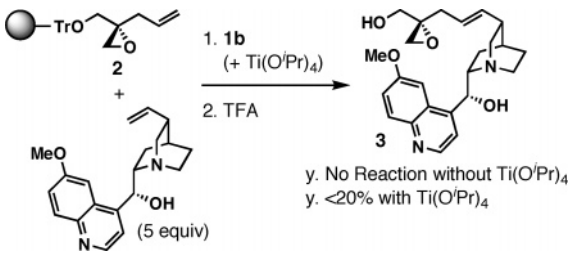


Figure 1. Metathesis catalysts.

tolerates many functional groups.[9] Olefins themselves are stable for long-term storage and compatible with many synthetic transformations such as carbonyl addition reactions. In addition to carbon−carbon double bonds as key retrosynthetic disconnection sites, we became interested in epoxides as featured synthetic intermediates and final products. As intermediates, the regioselectivity of nucleophilic additions to sterically and/or stereoelectronically differentiated epoxides is predictable. As final compounds for biological screenings, since epoxides are present in over eight thousand biologically active natural products and can specifically form covalent bonds with proteins,[10] they should facilitate subsequent chemical genetic studies (e.g., trapoxin B,[11] fumagillin,[12] epoxomicin).[13] Furthermore, a range of enantiomerically enriched epoxides is synthetically available.[14]

Our epoxide-based library synthesis project commenced with trityl ether **2** (Scheme 1), which was derived from trityl

Scheme 1. Solid-Phase Olefin Cross-Metathesis with Epoxide **2**

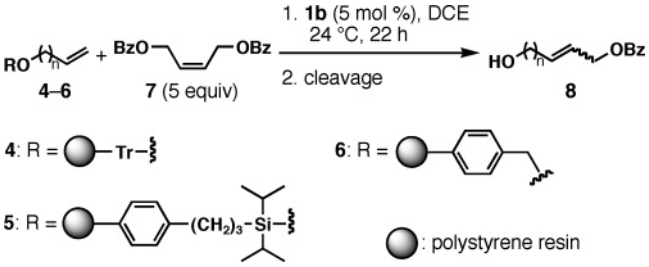


chloride resin and the corresponding epoxy alcohol. The epoxy alcohol was prepared according to our previous work (see Supporting Information).[15] A trityl ether was chosen because the readily cleavable linker provided a handle for the analysis of compounds synthesized on the solid support upon cleavage. As a complex olefin in solution, we chose quinine because it presents high functionality, is commercially available, and has been used as an antimalarial drug.[16] Unexpectedly, treatment of **2** with quinine (5.0 equiv) and **1b** (5 mol %) at 40 °C did not yield the desired alkene **3** as determined by crude ^{1}H NMR analysis (Scheme 1). We speculated that the ruthenium alkylidene complex of **2** might be catalytically inactive because of chelation with the epoxide oxygen atom. On the basis of this speculation, the above reaction of **2** and quinine was employed in the presence of Ti(O^{i}Pr)$_4$ (20 mol %),[17] which proceeded but to less than 20% which was still unsatisfactory. No intrabead homodimerization was observed in either of these experiments.

In light of these poor results and the lack of systematic studies in the literature, we decided to study cross-metathesis reactions using model systems on solid support to further the use of this method in solid-phase organic synthesis. We noted that the olefin in **2** was much closer to the polymer than those substrates reported in the literature.[4] Although change in linker length has been shown to be nonessential in other solid-phase reactions,[18] the proximity of the olefin to the solid support could impact cross-metathesis because the steric bulk of the polymer may block the catalyst's access to the olefin and the steric bulk of the catalyst may prevent it from entering further into the polymer to react with shorter carbon chains. Conversely, too long of a carbon chain would facilitate the formation of undesired homodimers on the same bead as previously shown by others.[6]

To study the distance-dependent solid-phase olefin cross-metathesis, we prepared compounds **4a**−**d** (Table 1). For

Table 1. Proximity Effect on Solid-Supported Olefin Cross-Metathesis



entry	substrate	n	% yield
1	**4a**	1	12 (<10[a])
2	**4b**	2	62 (48[a])
3	**4c**	3	70[b] (52[a])
4	**4d**	4	>95[c] (60[a])
5	**5a**	1	37
6	**5b**	2	52
7	**5c**	3	80[b]
8	**5d**	4	83[c]
9	**6a**	1	37
10	**6b**	2	42
11	**6c**	3	50[b]
12	**6d**	4	70[c]

[a] Yield using **1a** instead of **1b**. [b] Yield, 6:1 *E*:*Z*. [c] Yield, 5:1 *E*:*Z*.

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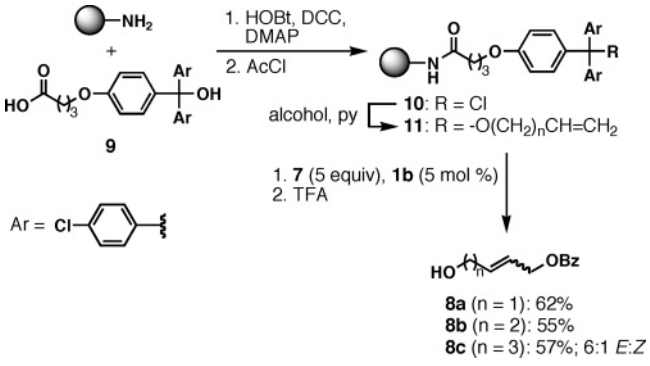
our model studies, we chose alkene **7** as a symmetrical alkene in solution.[19] Metathesis reactions were performed between alkenes **4a**−**d** and alkene **7** (5.0 equiv) using precatalyst **1b** (5 mol %) in DCE at 24 °C for 22 h. Following cleavage with TFA, alcohols **8a**−**d** were isolated (entries 1−4).[20] All reaction yields were quantified based on an external standard method (see Supporting Information). Indeed, reaction yields were strongly influenced by the carbon chain length; ether **4a** ($n = 1$) afforded alcohol **8a** in 12% yield (entry 1), while ether **4d** ($n = 4$) gave alcohol **8d** in nearly quantitative yield. The low yield of **8a** is not due to the steric hindrance imposed by the trityl group because a control cross-coupling between allyl trityl ether and **7** (5 equiv) catalyzed by **1b** (5 mol %) afforded the corresponding metathesis product in 61% yield. Also, no intrabead homodimerization was observed for each carbon chain length. We found that catalyst **1b** consistently gave higher yields than catalyst **1a** (entries 1−4; brackets), which is reminiscent of a report by the Schreiber group.[21] Thus, we concluded that **1b** was superior to **1a** in solid-phase olefin cross-metathesis.

To determine the generality of this proximity effect we also loaded each alkenyl alcohol onto alkylsilyl resin[22] and Merrifield resin to generate compounds **5a**−**d** and **6a**−**d**, respectively. Metathesis reactions were performed in a similar manner as described above, and products **8a**−**d** were isolated after cleavage.[20] These experiments revealed a similar proximity effect; silyl ethers **5a**−**d** produced the corresponding alcohols **8a**, **8b**, **8c**, and **8d** in 37% (entry 5), 52% (entry 6), 80% (entry 7), and 83% yield (entry 8), respectively. Benzyl ethers **6a**−**d** produced alcohols **8a**, **8b**, **8c**, and **8d** in 37% (entry 9), 42% (entry 10), 50% (entry 11), and 70% (entry 12), respectively. Again, intrabead homodimerization did not occur. These solid-phase experiments showed that increasing the distance between the reacting olefin and the resin improved the efficiency of olefin cross-metathesis.

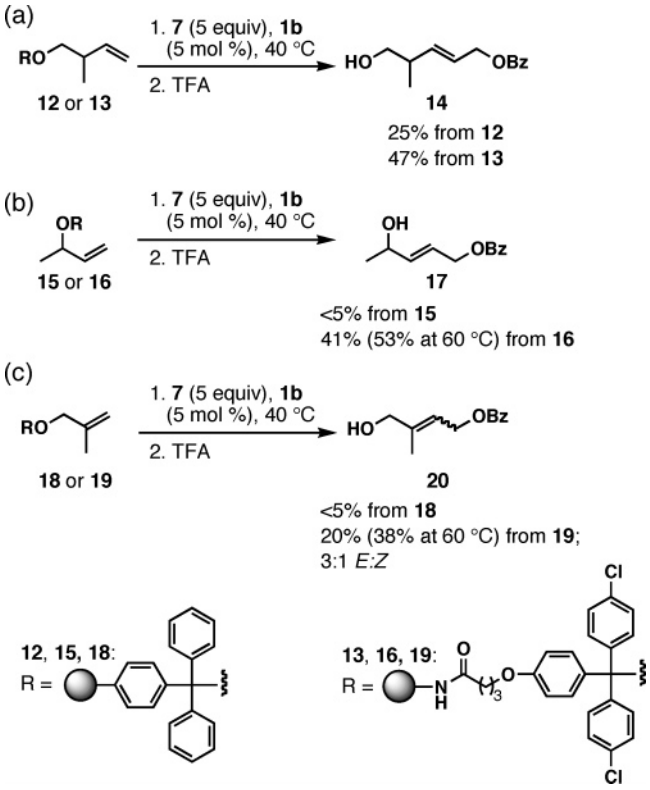
While these studies provided insight, the addition of carbons in the substrate and product is not always acceptable in organic synthesis. Therefore, on the basis of the proximity effect and the necessity for a traceless linker, we turned our attention to the commercially available trityl alcohol **9** (Scheme 2). Although **9** contains a chlorotrityl moiety instead of trityl, the chlorine atoms should only affect cleavage and have no effect on the olefin's reactivity. This alcohol was loaded onto aminomethyl polystyrene resin via a standard amide forming method, and the resulting compound was converted to trityl chloride **10** by the action of acetyl chloride. This trityl chloride was reacted with alkenyl alcohols to form trityl ethers **11a**−**11c** ($n = 1$−3). To our delight, metathesis of **11a** with **7** (5.0 equiv) using **1b** followed by cleavage (5% TFA in CH_2Cl_2) provided the desired product **8a** in 62% yield. Similar yields were observed from **11b** and **11c** with the linker (55 and 57% yield). These data indicate that with an additional linker between the trityl moiety and polymer, more consistent yields can be obtained (cf. Table 1, entries 1−3).

We next investigated more substituted alcohols on solid support. With trityl ethers **12**, **15**, and **18** without the linker and trityl ethers **13, 16**, and **19** with the linker (Scheme 3),

Scheme 2. Cross-Metathesis with Linker



Scheme 3. Cross-Metathesis with Substituted Alcohols



metathesis reactions were carried out using **7** (5 equiv) and **1b** (5 mol %). In general, raising the temperature from 24 to 40 °C increased isolated yields by approximately 2 fold,

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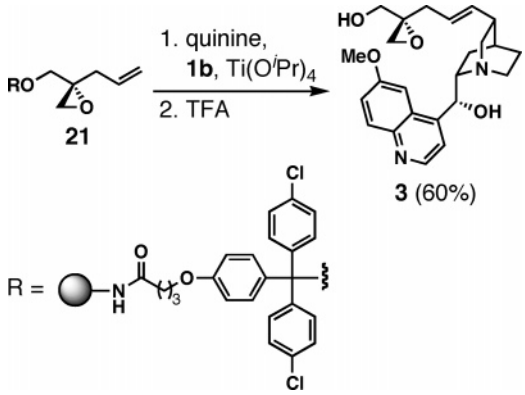
thus the yields at 40 °C are shown here. With the substituted homoallylic ethers **12** and **13**, the reaction was again more efficient with the linker (25% vs 47% yield). With the substituted allylic ether **15** without the linker, the reaction essentially did not proceed. In contrast, the allylic ether **16** with the linker underwent olefin metathesis with **7** to form **17** in 41% yield. This coupling could be improved to 53% yield when the reaction mixture was heated to 60 °C. In the case of type III olefins,[23] **18** and **19**, the reaction was also more efficient with the linker (<5% vs 20%). Similar to **16** the coupling was further improved to 38% when the reaction mixture was heated to 60 °C. With these more substituted allylic and homoallylic alcohols, the linker effect is prominent.

Having established the olefin cross-metathesis technology on solid support, we revisited our initial problem depicted in Scheme 1. The epoxyalcohol was loaded onto linker resin **10** to generate trityl ether **21**. Metathesis of **21** with quinine (5 equiv) was performed using **1b** and $Ti(O^iPr)_4$ at 40 °C for 24 h. NMR analysis of the crude material cleaved from the resin revealed that the quinine derivative **3** was formed in 60% yield (Scheme 4). In the absence of $Ti(O^iPr)_4$, the

Scheme 4. Cross-Metathesis with Solid-Supported Epoxide



reaction again did not proceed validating our initial claim of catalyst inactivation by the epoxide. These results clearly demonstrate the merit of linker **9** in performing metathesis reactions on solid support. Moreover, the quinine example illustrates that the solid-phase olefin cross-metathesis could be applied to the synthesis of morphed drugs/natural products with new properties.

In summary, olefin cross-metathesis in solid phase was strongly influenced by the proximity between the olefin of the substrate and polymer. On the basis of this insight, a linker was used to increase the distance between the polymer and the reacting olefins, which enabled cross-metathesis to be successfully performed. This method could be applied to both the primary and secondary alkenyl alcohols on the resin and quinine in solution. The linker on solid-support should now enable olefin cross-metathesis of a wide range of alkenes.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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