Olefin Metathesis

Template-Assisted Cross Olefin Metathesis**

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Various strategies have been developed for the control of intermolecular association, most of which are based on the design of molecular modules that carry linear arrays of hydrogen-bond donors (D) and acceptors (A).[1] We recently described information-storing hydrogen-bonded duplexes based on linear oligoamide strands that bear arrays of hydrogen-bond donors and acceptors.[2] The formation of such duplexes is highly sequence-specific and involves the pairing of a single strand with another strand of a complementary hydrogen-bonding sequence. These hydrogen-bonded duplexes serve as specific, noncovalent templates for the nucleation of β-sheet structures when attached to natural oligopeptides.[3] The sequence-specificity of our hydrogen-bonded duplexes has prompted us to explore the possibility of directing chemical reactions by using these molecules as templates. In recent years there has been intense interest in the use of duplex DNA as a template for directing chemical reactions.[4,5] Although not yet comparable to the diverse sequence-specificity offered by duplex DNA, the hydrogen-bonded duplexes that we have developed offer some advantages: ready availability in large quantities, much lower molecular weights, and compatibility with a wide variety of organic solvents. We chose the widely utilized olefin metathesis reaction as a demonstration of principle. Specifically, olefin units attached to the same end of a duplex template should be brought into close proximity upon the formation of the hydrogen-bonded duplex in solution. Such a supramolecular event should greatly increase the effective molarity of the olefins that undergo the subsequent cross-metathesis reaction and turn an otherwise intermolecular transformation into one that is intramolecular. Here we report the highly efficient and specific intermolecular cross-metathesis reactions directed by a hydrogen-bonded duplex template.

Since the development of the well-defined catalysts by Schrock[6] and Grubbs,[7] olefin metathesis has become an increasingly powerful tool for carbon–carbon bond formation in organic synthesis.[8] It has been widely used in the total synthesis of a variety of architecturally complex natural products,[9] in polymerization,[10] and in the construction of

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[**] We thank the donors of the Petroleum Research Fund, administered by the ACS, for support of this research (37200-AC4). The NIH, NSF, and ONR are acknowledged for partial funding.

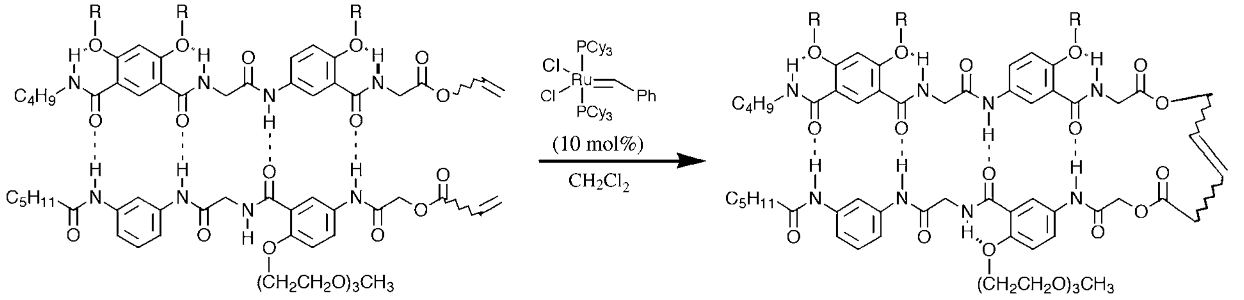
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200461777

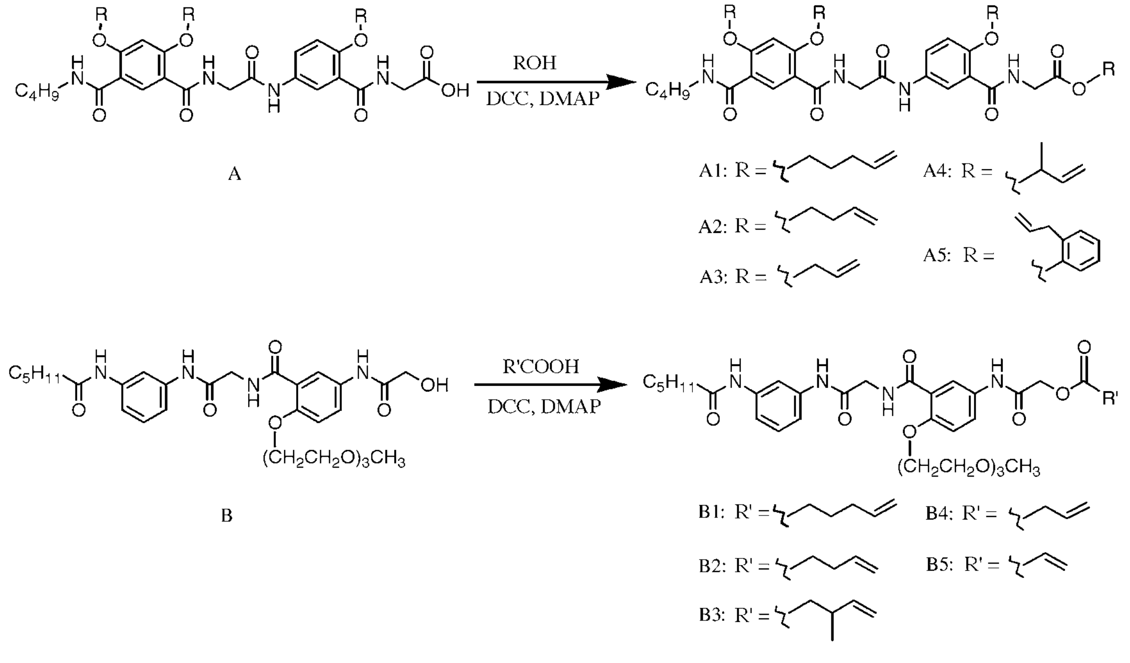
peptides.[11] The metathesis reaction is routinely carried out for the generation of C–C double bonds by using either the cross-metathesis of two acyclic alkenes or the ring-closing metathesis (RCM) of a diene. Efforts have been made to improve the chemical selectivity of intramolecular metathesis (RCM) by controlling the concentrations of the reactants.[12] Relative to olefin RCM, intermolecular cross-metathesis reactions, particularly those which involve two different olefins, have received less attention even though they offer great potential for a range of intermolecular C–C bond constructions. The main reason for this may be a lack of selectivity, especially because the intermolecular cross-metathesis reaction often proceeds to yield three products: two unwanted homodimeric self-metathesis products along with the desired heterodimeric product.[13] Several methods have recently been reported in which selective cross-metathesis reactions can be achieved when olefins of high reactivity are treated with bulky, electron-deficient olefins of lower reactivity.[14] Except for strategies that are based on intramolecular RCM,[12] highly selective cross-metathesis reactions of olefins that exhibit similar reactivities have yet to be developed.

To test the strategy outlined above, a quadruply hydrogen-bonded duplex, which consists of two different but complementary oligoamide strands that carry the unsymmetrical hydrogen-bonding sequences ADAA and DADD, respectively, was chosen as the template (Scheme 1). Alkenyl alcohols or acids were tethered to A or B by means of DCC (dicyclohexyl carbodiimide) coupling[15] to yield the desired strands A 1–5 and B 1–5 (Scheme 2). Combination of strands A 1–5 with strands B 1–5 should lead to 25 different A·B pairs. To demonstrate the feasibility of this approach, pair A3·B2 was first examined in detail. By using commercially available polystyrene molecular-weight standards, vapor pressure osmometry (VPO) studies at 37 °C in $CHCl_3$ over the concentration range of 5–50 mM consistently gave an apparent molecular weight of 1471 ± 5% that corresponds to A3·B2. The presence of the dimeric A3·B2 species in solution was also supported by ^1H NMR spectroscopic studies in $CDCl_3$ (5 mM) that revealed significant downfield shifts of the signals of the aniline NH group ($\delta = 9.97$, 9.65, and 9.53 ppm) relative to that of the single strand 1c ($\delta = 7.62$ ppm).[2,3]

A solution of A3·B2 in chloroform (2 mM) was then treated with Grubbs' catalyst[7] under heating at reflux. The



Scheme 1. Cross-metathesis of oligoamide-tethered olefins. R = n-C_8H_{17}.



Scheme 2. Preparation of strands A 1–5 and B 1–5. R = n-C_8H_{17}, DCC = dicyclohexyl carbodiimide, DMAP = 4-dimethylaminopyridine.

progress of the reaction was monitored by using ESI-MS (Figure 1). Upon completion of the reaction (5 h), new peaks with m/z values of 1536 $[M+H]^+$ and 1557 $[M+Na]^+$ appeared (Figure 1 b). The net loss of 28 ($CH_2{=}CH_2$) relative to the m/z values of the starting duplex (1563 $[M+H]^+$ and 1585 $[M+Na]^+$, Figure 1 a) suggested that the duplex A3·B2 underwent an intermolecular cross-metathesis reaction to afford the desired product A3=B2. Product A3=B2 was isolated in 92 % yield as a mixture of E and Z isomers (E/Z = 8:1, determined by ^1H NMR spectroscopy).[16]

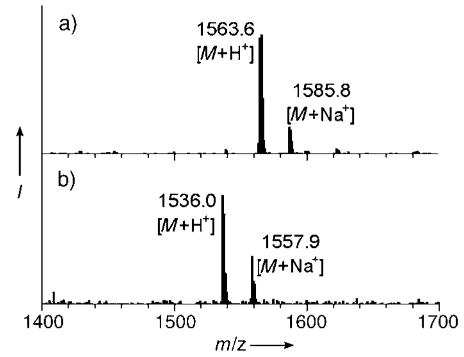


Figure 1. ESI mass spectra of a) the duplex A3·B2 and b) the product A3=B2 after the cross-metathesis reaction.

On the basis of the results obtained from the pair A3·B2, we extended this template-directed approach to the metathesis reactions of all 25 combinations (Scheme 2), the results of which are listed in Table 1. In the presence of Grubbs' catalyst, each of the 25 pairs was heated at reflux in CH_2Cl_2 during 3–6 h to afford 20 of the 25 possible products. The products formed were those expected from the cross-metathesis reactions and were all obtained as inseparable mixtures of E and Z isomers[16] with yields ranging from 36–99 %. Among the combinations, duplexes that comprised the strands A1 and B1–4 gave products A1=B1, A1=B2, A1=B3, and A1=B4 in yields ranging from 91–98 %. The combinations of A2/A3/A4 with B1/B2/B3/B4 led to their products in 83–99 % yields. Compared with the duplexes that contained A1, A3, and A5, those that contained A4, that is, A4·B1, A4·B2, and A4·B3, gave slightly lower yields that ranged from 83 to 87 %. The two products from the cross-metathesis reactions that involved B5 were obtained in lower yields (A1=B5: 36 %; A5=B5: 77 %), whereas no other products were obtained from the other three combinations involving B5. Similarly, the products A3=B4 and A4=B4 that should have resulted from the cross-metathesis of pairs A3·B4 and A4·B4 were not obtained. Examination of the structures of those pairs which either did not react or which gave products in low yields revealed that the spacers between the terminal vinyl moieties and the template strands were much shorter than for those combinations which resulted in efficient reactions. This suggests that for the cross-metathesis reaction to proceed, the two vinyl moieties in a duplex need to reach each other and adopt the proper orientation, which in turn requires spacers of sufficient length. Furthermore, the major stereoisomers for all transformations were consistently the thermodynamically more stable E isomers, which reflects the reversible nature of the metathesis reactions. The highest stereoselectivity was observed for the product A4=B1 with an E/Z ratio of 20:1 and a yield of 87 %.[16]

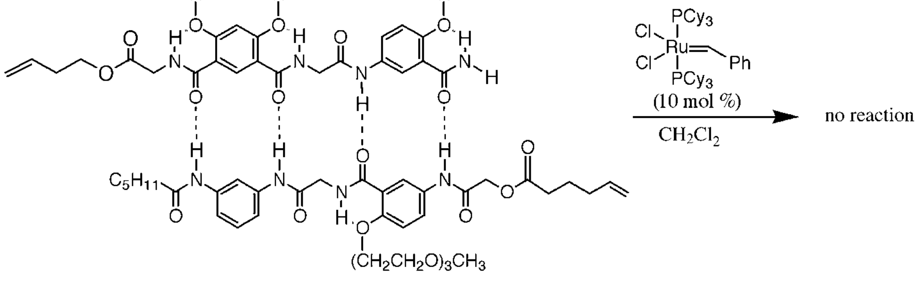
Table 1: Template-assisted olefin cross-metathesis.[a]

Strands	B1	B2	B3	B4	B5
A1	98 (1.6:1)	97 (3:1)	91 (2:1)	94 (6:1)	36 (8:1)
A2	97 (9:1)	94 (5:1)	93 (2:1)	83 (4:1)	nr[b]
A3	99 (14:1)	99 (8:1)	97 (3:1)	nr[b]	nr[b]
A4	87 (20:1)	84 (7:1)	83 (4:1)	nr[b]	nr[b]
A5	96 (11:1)	89 (5:1)	65 (4:1)	85 (3:1)	77 (7:1)

[a] All reactions were carried out at a concentration of 2 mM in CH_2Cl_2 in the presence of the catalyst (10 mmol %). The yields and E/Z ratios (quoted in brackets) were determined by ^1H NMR spectroscopy. [b] No reaction.

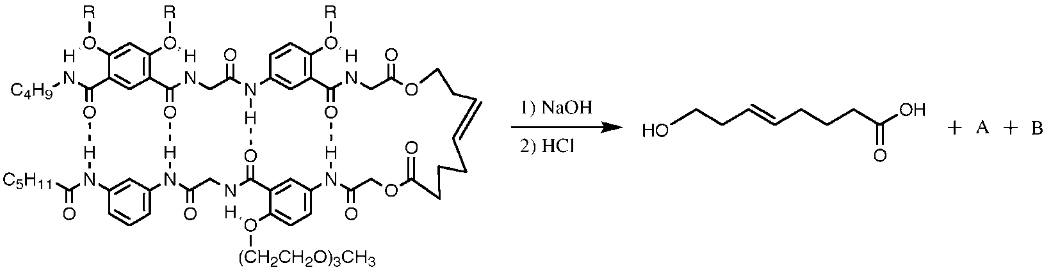
As a control, compound C, in which the olefin unit was attached to the "wrong" side of the template strand, was synthesized and then mixed with compound B1 (Scheme 3). The formation of duplex B1·C was confirmed by both NMR spectroscopy and VPO experiments. In duplex B1·C, the vinyl moieties would not be able to react with each other because they are located at the two remote ends of the duplex template. Indeed, when a solution of duplex B1·C was subjected to cross-metathesis in the presence of Grubbs' catalyst, the metathesis reaction did not occur. The hydrogen-bonded duplex B1·C was the only species detected by NMR spectroscopy or ESI-MS before and after the reaction. These results further confirmed the template-dependence of the above metathesis reactions, in which the reactions took place only when the two olefin units were brought into close proximity by the duplex template.

As shown in Scheme 1 and Scheme 2, all of the olefin units were attached to the template through an ester linkage that should be cleaved under basic conditions. To test if the desired



B1·C

Scheme 3. Attempted cross-metathesis reaction of distant olefins in B1·C. R = n-C_8H_{17}.



Scheme 4. Cleavage of product from A2=B1. R = n-C_8H_{17}.

products could be cleaved from the template, product A2=B1 was treated with an aqueous solution of NaOH. After completion of the reaction, the insoluble residue was filtered, and the acidified aqueous layer was extracted with CH_2Cl_2 to yield the desired 8-hydroxyoct-5-enoic acid (Scheme 4).[16]

In conclusion, we have shown that a quadruply hydrogen-bonded duplex can act as a sequence-specific template to direct the cross-metathesis of different olefins that are tethered to this duplex. These templated metathesis reactions occur with extremely high selectivity, with no homodimeric products observed. Compared to strategies that directly tether two olefin units together, our approach has the advantage of being combinatorial. By simply mixing the complementary A and B strands, a large number of A·B combinations were easily obtained. Thus, the combination (mixing) of a group of five tethered olefins with another group of five olefins lead to a total of 25 combinations. In contrast, with covalently linked olefins, all 25 possibilities have to first be synthesized before they can be tested. Obviously, the number of combinations based on our approach increases rapidly as the number of tethered olefins increases. Coupled with NMR spectroscopic and mass spectrometric methods, our template-directing method can be used to probe a large number of combinations that would otherwise be difficult to examine based on previous methods. After cleavage from the template, the desired products can be easily obtained and the template can also be recycled. It is envisaged that our current strategy will serve as a useful tool to broaden the scope of cross-metathesis reactions. The approach described here should also be generally applicable to other types of bimolecular reactions.

Received: August 24, 2004
Revised: October 5, 2004

Keywords: alkenes · C–C coupling · hydrogen bonds · noncovalent interactions · template synthesis

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[15] See Supporting Information for details.

[16] The conformations of double bonds were determined from the coupling constants J measured from ^{1}H NMR spectra, and the major E isomer was found to have $J > 15$ Hz (see Supporting Information).