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Self-Selection in Olefin Cross-Metathesis: The Effect of Remote Functionality

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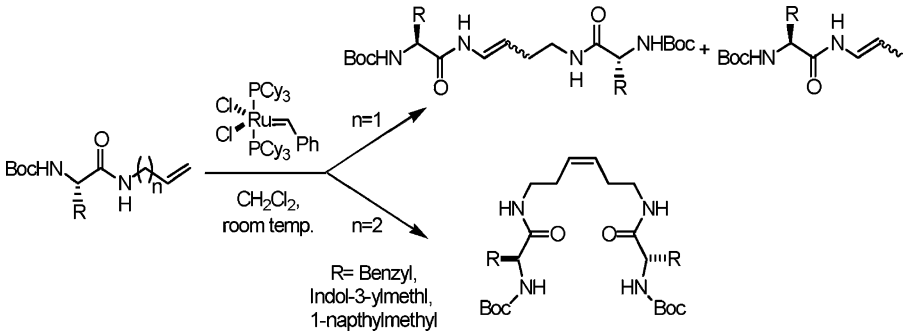
ABSTRACT



Olefin cross-metathesis (CM) is potentially an attractive method for generating dynamic combinatorial libraries (DCLs). In order for the CM reaction to be useful for DCL production, the course of the reaction and product distribution must be relatively insensitive to functionality remote from the reacting centers. We report on the CM of a series of allyl- and homoallylamides that are strongly dependent on remote functionality. This includes an unusual example of a *cis*-selective CM.

Target-oriented chemical synthesis relies on transformations that are selective, specific, and irreversible.[1] Conversely, in the context of a broad program directed toward the design and synthesis of novel high-affinity ligands for biological macromolecules, we have been exploring the use of reversible reactions in the emerging field of dynamic combinatorial chemistry (DCC). DCC attempts to employ the core principles of Darwinian evolution (mutation, selection, and amplification) to select and amplify single compounds from equilibrating mixtures based on their affinity for a target molecule. Dynamic combinatorial libraries (DCLs) rely on reactions that are nonselective and reversible. Such reactions ensure that the evolution of the system is driven primarily by receptor binding and not by differences in the relative kinetic selectivity of the reversible reaction or thermodynamic stabilities of library components (often described as "self-selection"). DCLs have been employed in the identification of DNA binding complexes,[2] thymidate synthetase inhibitors,[3] and a variety of receptors for small molecules.[4]

Over a relatively short period of time, olefin cross-metathesis (CM) has become an important reaction in organic synthesis. CM has been widely used in the synthetic community as a vehicle for elegantly fusing olefinic[5] and

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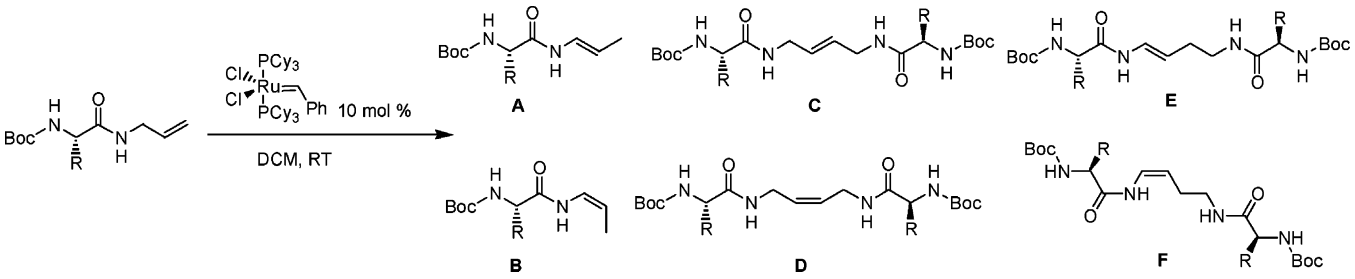
Table 1. Self-Metathesis of Allyl Amides



	isolated yield					
starting material	**A**	**B**	**C**	**D**	**E**	**F**
1 (glycine)	28	20	0	0	9	5
2 (phenylalanine)	20	30	0	0	4	22
3 (tryptophan)	22	28	0	0	25	15
4 (N^{Im}-tos)histidine	32	24	0	0	25	15

more recently alkynyl[6] functionality. CM seemingly fills the requirements for an effective DCC reaction, because it provides carbon−carbon double bond formation between readily available alkenes, tolerates a wide range of functionality[7] and is generally reversible for simple olefins. Indeed, Nicolaou and co-workers have employed olefin cross-metathesis in the molecular evolution of vancomycin dimers with high affinity for D-Ala-D-Ala.[8] Similarly, CM reactions driven by internal preorganization have been reported by the Grubbs,[9] Ghadiri,[10] and Sanders groups.[11]

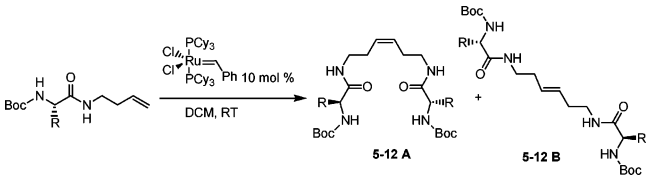
While a variety of researchers have examined the effect of olefin type on CM,[12] few studies have been conducted directed toward systematically studying the effect remote functionality has on overall yield and stereochemical outcome. In addition to general synthetic utility, understanding these effects is a critical prerequisite to furthering the use of CM in DCC experiments. Herein, we report a series of CM experiments employing allyl and homoallyl amino acid derivatives and discuss differences in yield and product ratios based on the identity of remote substituents.

We prepared a series of allyl and homoallylamide derivatives of Boc-protected amino acids using standard coupling conditions. Compounds **1**−**12** were then independently reacted with 10 mol % commercial "first generation" Grubbs' catalyst in anhydrous methylene chloride at room temperature under an atmosphere of nitrogen. The reactions were stopped either when starting material could no longer be detected by TLC or after 12 h, at which time the catalyst had fully decomposed.

Results for CM reactions of Boc-allylamides **1**−**4** are shown in Table 1. Consistent with Alcaide's reports on the behavior of allyl *amines* under metathesis conditions,[13] alkene isomerization was the dominant outcome. However, in contrast to Alcaide's work, the isomerized metathesis products **1E**−**4E** and **1F**−**4F** were also isolated. These presumably derive from the symmetrical metathesis products **1C**−**4C** and **1D**−**4D**.

Initial experiments with the Boc-homoallyl amides **5**−**12** revealed only phenylalanine (**6**), tryptophan (**7**), and naphthylalanine (**10**) derivatives provided the desired cross-metathesis products in good yield as separable *cis*:*trans* mixtures. Conversely, glycine (**5**), (Tos)histidine (**8**), and aliphatic homoallylamides (**9**, **12**) failed to undergo cross-metathesis (Table 2). Assignment of the *cis* and *trans*

Table 2. Self-Metathesis of Homoallyl Amides



		isolated yield (%)	
starting material	amino acid	**A**	**B**
5	glycine	0	0
6	phenylalanine	58	19
7	tryptophan	67	22
8	(N^{Im}-tos)histidine	0	0
9	isoleucine	0	0
10	1-naphthylalanine	56	35
11	pentafluoro phenylalanine	0	0
12	valine	0	0

metathesis products proved troublesome. Therefore, an independent synthesis of **7B**[14] was carried out, subsequently

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providing an HPLC assignment as the minor product from CM of **7**; **7A**, **6A**/**6B**, and **10A**/**10B** were ultimately assigned by analogy.

Additionally, we resubjected each pure homoallylamide tryptophan CM product (**7A** and **7B**) separately to 10 mol % Grubbs' catalyst at room temperature in CH_2Cl_2 for 12 h. Upon workup and concentration, we observed the same 3:1 *cis:trans* ratio (3.6:1 from **7A**; 3.7:1 from **7B**) found in the initial cross-metathesis reaction. This verified that the reaction is at least partially reversible and suggests that it may be under thermodynamic control. Further experiments will be necessary in order to test alternative possibilities. For example, one can also envision kinetic control based on the reactivity of an intermediate ruthenium alkylidene. While a kinetically controlled *cis* selective CM employing conjugated enynes has recently been reported by Chang and coworkers,[15] to our knowledge this is the first report of a *cis* selective CM reaction involving isolated olefins. Interestingly, CM of a related series of compounds on solid phase is *trans* selective.[16]

Given the number of bonds separating the reactive olefins from amino acid side chain functionality, why were moderate *cis* selectivity and good overall yield observed for homoallyl amides **6**, **7**, and **10**, but no reaction observed at all for the other substrates? We reasoned homoallyl amides lacking aromatic side chains might trap the catalyst in an unproductive coordination state such as that shown in Figure 1

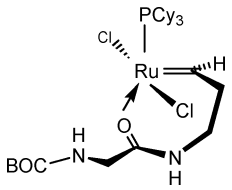

Figure 1. Potential nonproductive chelate of ruthenium carbene.

(although several other geometries are possible). Similar ruthenium coordination by oxygen containing functionality has been observed by Hoveyda[17] and others. Conversely, we reasoned that homoallyl amides bearing aromatic side chains might allow for intramolecular hydrophobic collapse, intermolecular $\pi-\pi$ interactions, or a simple aggregation, thereby interrupting destructive coordination to the catalyst. Subjecting a 1:1 mixture of glycine homoallylamide **5** and phenylalanine homoallylamide **6** to CM conditions provided no self- or cross-metathesis products, supporting the assertion that simple aliphatic substrates may be able to trap the catalyst, preventing CM.

To test the hypothesis that conformational preferences or intermolecular interactions might be responsible for the reactivity of **6**, **7**, and **10**, we examined the ^{1}H NMR spectrum of **6** as a function of temperature.[18] At low temperature, essentially all protons appear as more than one set of distinct resonances, suggesting the existence of multiple conformations undergoing slow interconversion on the NMR time scale. However, coalescence temperatures for each set of related resonances are well below the temperature at which the metathesis reactions are run. This indicates that conformational preferences of the starting material are not a contributing factor in determining whether the metathesis reaction proceeds. Likewise, the rapid conformational mobility of the starting material at the reaction temperature argues against the influence of simple aggregation, hydrophobic collapse, or intermolecular $\pi-\pi$ interactions,[19] which one might expect to be minimal in relatively nonpolar halogenated solvent.[20]

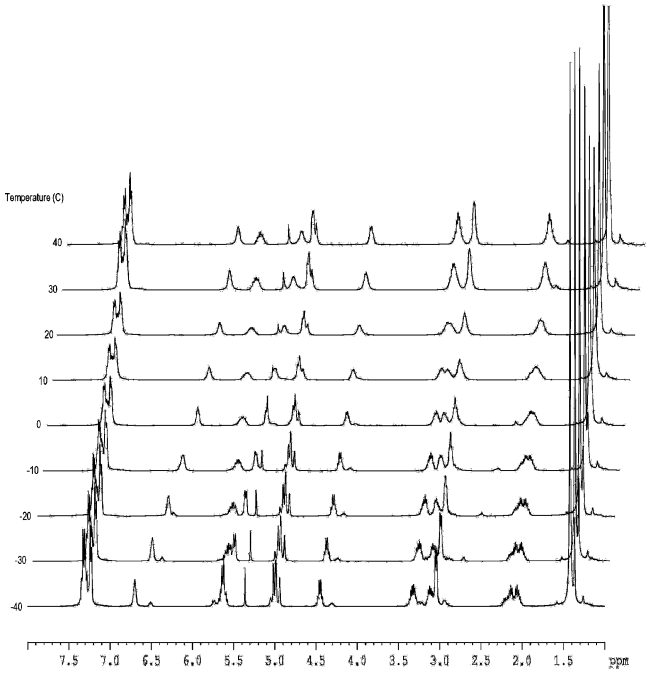

Figure 2. Variable-temperature ^{1}H NMR of **6**.

An alternative hypothesis is that homoallylamides bearing aromatic groups might participate in a relatively weak π-ruthenium interaction, thereby prohibiting the relatively strong (and destructive) carbonyl coordination and ultimately permitting cross-metathesis. Changing the electron density on the aromatic ring has a strong impact, as indicated by the inability of pentafluorophenylalanine homoallylamide **11** to undergo CM. Steric effects are also important; the histidine-derived substrate **8** is potentially prevented from

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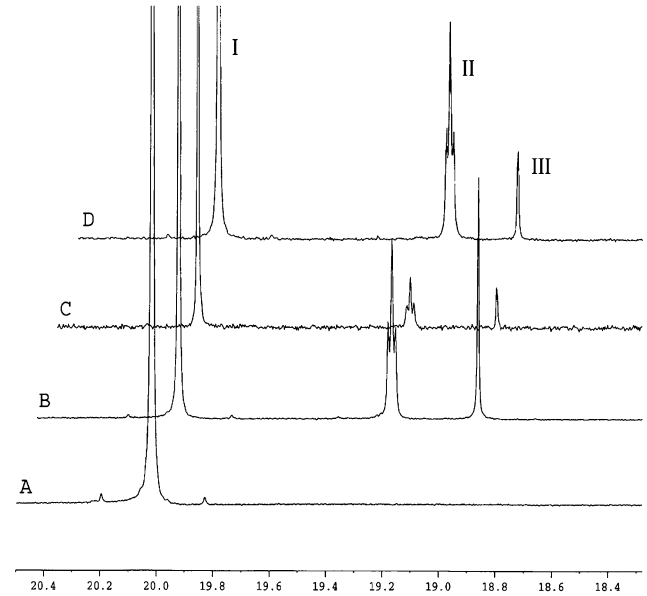

A= Grubbs' catalyst, B= Phenylalanine (**6**),
C= Pentafluorophenylalanine (**11**), D= Valine (**12**)

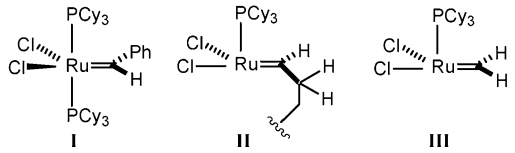

Figure 3. ^{1}H NMR spectra and carbenoid species formed by addition of Grubbs' catalyst to compounds **6**, **11**, and **12**.

participating in π-ruthenium interactions because of its bulky tosyl protecting group.

In an attempt to gain greater insight into the mechanism of catalyst consumption, time-dependent proton NMR experiments were performed on the homoallyl derivatives **6**, **11**, and **12** in the presence of stoichiometric catalyst. Almost immediately, we observed formation of a triplet at 19.2 ppm and a singlet at 18.9 ppm. The triplet is consistent with formation of carbene **II** from the homoallylamide, while the singlet is consistent with previously reported spectral data for methylene carbene (**III**).[21] Additionally, we are able in all cases to observe olefin peaks consistent with metathesis products. These data suggest that regardless of side chain all homoallyl amides initiate, and some fraction of the starting material does undergo metathesis. ^{1}H NMR and HPLC analysis of the reaction mixture indicates this is less than 5% of total material for **11** and **12**, however.

In conclusion, we have demonstrated the importance of remote functionality in the olefin cross-metathesis reaction and its influence on reaction progress and stereochemical outcome. While this does not preclude use of cross-metathesis in dynamic combinatorial experiments, it is an important factor to consider in library design and in the analysis of DCC results. Further efforts, designed to expand on these results and apply CM in DCC experiments, are in progress.

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Supporting Information Available: Spectral data for all previously unknown compounds, HPLC analysis of CM products **7A** and **7B**, and full experimental procedures. This material is vailable free of charge via the Internet at http://pubs.acs.org.

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