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Reversible aqueous metathesis reactions for potential application in dynamic combinatorial chemistry

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ABSTRACT

Solutions of heterocycles having an allyl sulfide unit and simple alkenes in 50% *t*-BuOH/H_2O undergo reversible olefin metathesis reactions with the second generation Hoveyda–Grubbs catalyst. The choice of functional groups is limited by competitive chelation of some heterocycles with the catalyst, and other stereoelectronic effects.

Dynamic combinatorial chemistry (DCC) is a powerful method for the formation and amplification of unnatural ligands and receptors in a self-selection process that mirrors the selection processes used in nature.[1] Central to the application of DCC is the incorporation of functional groups that undergo reversible chemistry and deliver an equilibrating mixture of all possible ligands or receptors, or a dynamic combinatorial library (DCL), from a defined set of building blocks. The most common examples of reversible chemistry that have been used in DCC include disulfide formation, Schiff base chemistry, metal ion coordination, and acyl exchange reactions.[1] While the majority of DCC studies have been performed in organic solvents, a number of successful studies with biomolecules under physiologically relevant conditions have illustrated the enormous potential of DCC in biological chemistry.[2–4] Novel ligands for the recognition of quadruplex and duplex DNA have been based on thiol–disulfide exchange reactions, while metal complexes have been used to target RNA.[4] While reversible thiol–disulfide chemistry is well-suited to DCL formation in aqueous solutions, the susceptibility of disulfide linkages to biological redox reactions presents some limitations to the stability of the resultant receptors and ligands for applications in vivo.

Olefin metathesis (Fig. 1a) is a reversible reaction that has been highlighted for potential applications in DCC.[1] The alkene functional group is an attractive feature to incorporate into DCC building blocks because of its high stability under biological conditions, rigidity, and as an isostere of the amide bond.[5] However, there are limited examples of DCC utilizing olefin metathesis, and with the exception of one study that used a phase-transfer catalyst in CH_2Cl_2/H_2O,[6] all examples have been performed in organic solvents.[7] However, recent reports of new catalysts and reaction conditions that allow metathesis chemistry to be performed in water,[8,9] suggest that formation of olefin-based DCLs in water should be possible. For example, Davis and co-workers recently reported that the second generation Hoveyda–Grubbs catalyst is sufficiently stable and active to catalyze cross metathesis (CM) reactions in *t*-BuOH/H_2O mixtures,[9] particularly when one of the coupling substrates is an allyl sulfide (Fig. 1b). Compared with other reported aqueous metathesis reactions, this chemistry is attractive for applications in DCC, as it is not restricted to ring-closing metathesis reactions, homo-coupling reactions are minimized, and less stringent conditions are required that are suitable for applications under biologically relevant conditions. Of particular note is the compatibility of the reaction conditions with proteins,[9] suggesting broader applications in DCC.

Motivated by these recent developments, we decided to investigate whether metathesis-based DCLs could be formed under biologically relevant conditions. The building blocks investigated in this study (Table 1) incorporated functional groups commonly found in DNA-binding compounds,[10] in order to explore the feasibility of generating novel DNA and/or RNA binding compounds using DCC. Allyl sulfide derivatives **2**–**6** contained aromatic chromophores as models for DNA-intercalators.[11] For example, the naturally occurring quinoxaline depsipeptide antitumour antibiotics, as well as the napthalimide derivative, elinafide, interact with DNA by bisintercalation. The CM coupling partners **7**–**10** contain

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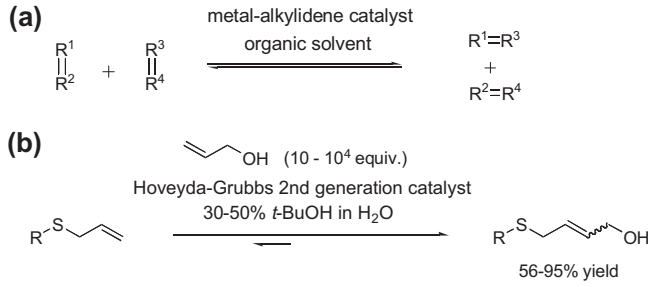


Figure 1. (a) The general olefin cross metathesis reaction. (b) Aqueous CM methodology,[9] employing various allyl sulfide derivatives including *N*-Boc-*S*-allyl cysteine methyl ester (**1**).

functional groups that are typically present in DNA groove binders (e.g., polyamide lexitropsins, carbohydrates, peptides).[12] We envisaged a DCL design in which various intercalator components would be reversibly connected to a variety of groove-binder components to give a dynamic library of olefin-bridged intercalator–groove-binder conjugates. The groove-binder components would be present in large excess in order to avoid homodimerisation of the allyl sulfide-containing intercalator components, and the aromatic chromophores should allow easy identification of the CM conjugates by LC–MS.[13] The allyl sulfide derivatives **2**–**6** were readily prepared by treatment of the appropriate alkyl halides with 2-propen-1-thiol.

Individual cross metathesis reactions were performed (Table 1) in order to probe the functional group tolerance of the reaction, and to establish the 'start' and 'stop' signals for the reversible chemistry required in DCC.[14] All cross metathesis reactions were initiated by adding the catalyst to a solution of the coupling partners in *t*-BuOH/H_2O according to the reported reaction conditions.[9] The reactions were normally monitored by the color of the reaction mixture: the Hoveyda–Grubbs second generation (pre)catalyst has an intense green color which, during the course of the reaction, changes to yellow once catalysis is initiated, and finally to brown/black when the catalyst has decomposed. The lack of active catalyst effectively acts as the 'stop' signal for the reaction. Reactions were allowed to proceed for 2.5 h, with the addition of a fresh portion of catalyst after 1 h required in order to ensure the reactions went to completion. A control reaction[9] was included (Table 1, entry 1) between *N*-Boc-*S*-allyl cysteine methyl ester (**1**) and allyl alcohol (**7**), which gave the CM product **11** in 72% yield.

Naphthalimide **2** exhibited reasonable solubility in 50% *t*-BuOH/H_2O and cross metathesis reactions proceeded smoothly with allyl alcohol (**7**), β-*O*-allyl glucose (**8**)[9] and *N*-allyl acetamide (**9**)[15] to give the corresponding olefins in >90% yield (Table 1, entries 2–4).[16] However, no reaction was observed between naphthalamide **2** and *N*-allyl-*N*′-methylpiperazine (**10**)[17] (Table 1, entry 5). In a separate experiment, the control reaction between **1** and **7** was shown to be impeded significantly by the presence of 1 equiv of *N*,*N*′-dimethylpiperazine (data not shown), indicating that the piperazine functional group is incompatible with the catalyst. In order to rule out any chelation of the ruthenium catalyst with the piperazine ligand, the reaction between **2** and **10** (Table 1, entry 5) was repeated in the presence of $MgCl_2$, as these conditions have been reported to disrupt unproductive chelation of the catalyst.[9] However, in this case the only reaction observed was formation of a small quantity of the homodimer of **2**.

In the case of quinoline **3**, reaction with 20 equiv of **7** resulted in formation of the desired product **15** in moderate yield (Table 1, entry 6). However, treatment of quinoline **3** with **8** or **10** gave only unreacted starting material (Table 1, entries 7 and 9), while reaction of **3** with a large excess of **9** resulted in consumption of the starting material **3** but none of the desired product was formed and no side-products could be identified (Table 1, entry 8). Reaction of quinoxaline **4** with allyl alcohol **7** under the same conditions resulted in a claret-colored solution that produced the expected product **16** in moderate yield (Table 1, entry 10).

Treatment of phenanthroline **5** with excess **7** in the presence of the catalyst resulted in an immediate color change to red/brown, but no CM reaction had occurred after 2.5 h (Table 1, entry 11). The color change was consistent with the established metal chelator, phenanthroline, forming a complex with the ruthenium catalyst.[18] Heterocycles are known to exchange with ligands attached to the catalyst, sometimes with advantageous effects on reactivity,[19] but the bidentate phenanthroline forms kinetically inert complexes with ruthenium(II)[18] which presumably interferes with catalysis. The control reaction between **1** and **7** was repeated in the presence of 1 equiv of methyl phenathroline-5-carboxylate (data not shown); formation of a deep-red color was again observed, consistent with competitive chelation of the metal catalyst, and no CM product was formed. In contrast, while quinoxaline **4** also formed a red solution consistent with reported complexes between quinoxalines and ruthenium,[20] the quinoxaline complex is evidently sufficiently labile to allow CM metathesis to proceed (Table 1, entry 10).

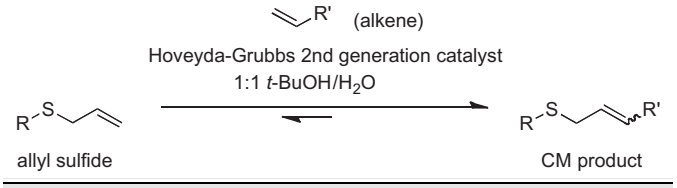
Reaction of acridine **6** with alkenes **7**, **8**, and **9** resulted in products that were tentatively identified as the desired CM conjugates (Table 1, entries 12–14). However, these reactions were complicated by the instability of **6** and its derivatives which were light-sensitive and degraded on standing, and hence pure products were unable to be isolated or fully characterized.

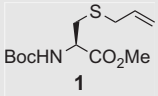
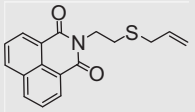
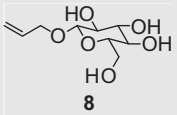
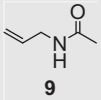
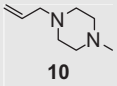
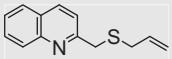
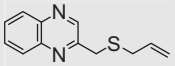
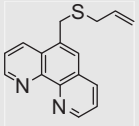
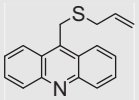
Having performed this initial exploration of the scope of the aqueous CM reaction, attention was next turned towards establishing conditions for generating a DCL. Naphthalimide **2** was treated with 20 equiv each of **7**, **8**, and **9** in the presence of ~25 mol % catalyst in 50% *t*-BuOH/H_2O at 32 °C (Table 2, entry 1).[21] The initial green color of the reaction mixture changed to yellow within a few minutes, and then gradually darkened as expected. The reaction mixture was analyzed by LC–MS at regular time intervals, which showed that all three expected CM conjugates (**12**–**14**) started to appear within 5 min. However, the reaction stopped within 20 min, and a second addition of catalyst was necessary to achieve complete consumption of starting material and a stable product distribution. Repeating the experiment with different catalyst loadings gave consistent, reproducible final ratios of products **12**–**14** (Table 2, entry 1).

In order to confirm that the DCL system was reversible and had reached equilibrium within the experimental time, a second experiment was performed in which the conjugate **12** was used as the initial substrate rather than **2** (Table 2, entry 2). LC–MS analysis showed a product distribution that was approximately the same as the DCL obtained with substrate **2** (Table 2, entry 1), that is, the system reached the same product distribution regardless of which starting material was used. This result indicates that the system is dynamic and reaches equilibrium within the experimental time, and consistent with this result, varying the initial DCL component concentrations resulted in changed distributions of the products **12**–**14** as expected (Table 2, entries 3 and 4).

The results summarized in Table 1 demonstrate that there are subtle, and as yet not completely understood, electronic and metal co-ordination chemistry effects that influence the outcome of the reaction and limit the building block design. CM reactions in organic solvents with different catalysts have also highlighted a lack of predictability in product selectivity and stereoselectivity, but extensive studies have allowed development of a general model for selectivity in olefin CM reactions.[22] CM reactions with allyl sulfides under the conditions used in this study, have been performed with a protein containing an allyl-Cys residue,[9] suggesting that

Table 1
Cross metathesis reactions[a]



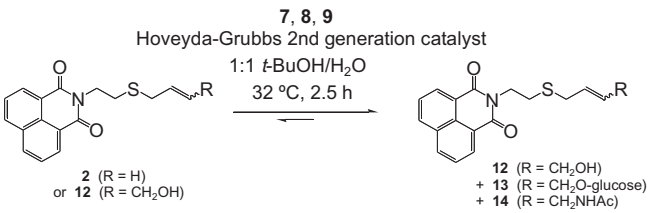
Entry	Allyl sulfide	Alkene	Product and yield (%)
1	 **1**	 **7**	**11** 72
2		**7**	**12** 94
3	 **2**	 **8**	**13** >90
4		 **9**	**14** 96
5		 **10**	0
6		**7**	**15** 53[b]
7	 **3**	**8**	0
8		**9**	0
9		**10**	0
10	 **4**	**7**	**16** 31(51)[c]
11	 **5**	**7**	0
12	 **6**	**7**	~65[d]
13		**8**	LC–MS[e]
14		**9**	~30[d]

[a] General conditions: 1 equiv allyl sulfide derivative, 10–50 equiv coupling partner alkene, 2 × 10 mol % Hoveyda–Grubbs second generation catalyst, 1:1 *t*-BuOH/H_2O (1.5 mL), 32 °C, atm, 2.5 h.
[b] 20 equivalents of **7** used; if 10 equiv of **7** used, then the homodimer of **3** was the only product.
[c] 51 percent based on consumed starting material, 31% isolated yield.
[d] Unstable product, not fully purified.
[e] Product identified by LC–MS only.

amine, guanidinium, carboxylate, and other amino acid side-chain functional groups would be tolerated in the allyl sulfide CM partner, provided $MgCl_2$ is present to disrupt nonproductive chelation of the catalyst. In this study, however, the potential chelating functional groups in the alkene coupling partner (e.g., **10**) are present in a large molar excess, which would favor the formation of complexes between the alkene and the catalyst. Under these conditions 'Lewis acid rescue' of the catalyst by addition of $MgCl_2$ may not be possible.

In summary, conditions have been established for reversible aqueous metathesis chemistry between an *S*-allyl naphthalimide derivative and various other alkenes. Functional group tolerance

Table 2
Equilibrium mixtures of metathesis conjugates **12**–**14**



Entry	Starting material	Molar excess of **7**/**8**/**9**	Product ratio[a] **12**:**13**:**14**
1	**2**	20/20/20	22:20:58
2	**12**	20/20/20	24:18:58
3	**2**	40/20/5	48:27:25
4	**2**	5/20/40	7:9:84

[a] Determined by LC–MS.

is a limiting feature of this chemistry, and further work is required to fully understand the different reactivities observed in this study. However, our results show that given suitable substrates, a metathesis-based DCL can rapidly reach equilibrium in solvent mixtures containing 50% water, conditions that may be used in applications with water-soluble substrates.

Acknowledgment

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Malkinson, J. P.; Paumier, D.; Searcey, M. *Nat. Prod. Rep.* **2007**, *24*, 109–126; (d) Brana, M. F.; Cacho, M.; Ramos, A.; Dominguez, M. T.; Pozuelo, J. M.; Abradelo, C.; Rey-Stolle, M. F.; Yuste, M.; Carrasoco, C.; Bailly, C. *Org. Biomol. Chem.* **2003**, *1*, 648–654.

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13. This strategy is analogous to the disulfide DCL design employed by Nielsen and Ulven outlined in Ref.2b.
14. Typical procedure: Hoveyda–Grubbs second generation catalyst (1.5 mg, 2.5 μmol) was dissolved in *t*-BuOH (0.25 mL) by repeated sonication and vortexing. The resultant clear green solution was added to a stirred mixture of the allyl sulfide (41 μmol), allyl alcohol (**7**) (57 μL, 0.82 mmol), *t*-BuOH (0.25 mL) and in-house Milli-Q® water (0.5 mL) at 32 °C, and the mixture was stirred at 32 °C for 1 h. During this time the reaction mixture changed from a green color to a yellow color within a few minutes, then more gradually to a brown/black color. A second solution of Hoveyda–Grubbs second generation catalyst (1.5 mg, 2.5 μmol) in *t*-BuOH (0.25 mL) was added followed by Milli-Q® water (0.25 mL), and the mixture was stirred at 32 °C for 1.5 h. The mixture was concentrated to give the crude product which was purified by chromatography.
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16. Selected data: Compound **12** IR (neat) (cm^{-1}) 3437, 2954, 2923, 2855, 1699, 1658, 1591, 1515, 1457, 1438, 1383, 1235; ^1H NMR (300 MHz) ($CDCl_3$) δ 8.60 (dd, J = 7.4, 0.8 Hz, 2H), 8.23 (dd, J = 8.3, 0.8 Hz, 2H), 7.77 (dd, J = 8.3, 7.4 Hz, 2H), 5.93 (m, 1H), 5.73 (m, 1H), 4.33 (m, 2H), 4.20 (m, 2H), 3.27 (d, J = 7.1 Hz, 2H), 2.81 (m, 2H); MS (ESI, +ve) m/z 328 ($M+H^+$, 10%); HRMS (ESI, +ve) $C_{18}H_{17}NO_3S$ $(M+Na)^+$ requires m/z 350.0827, found 350.0821; Compound **13** IR (neat) (cm^{-1}) 3365, 2956, 2925, 2856, 1698, 1656, 1589, 1440, 1384, 1260, 1027; ^1H NMR (300 MHz) (MeOD/$CDCl_3$) δ 8.56 (dd, J = 7.4, 1.0 Hz, 2H), 8.29 (dd, J = 8.2, 1.0 Hz, 2H), 7.78 (dd, J = 8.2, 7.4 Hz, 2H), 5.87–5.69 (m, 2H), 4.40–4.30 (m, 4H), 4.15 (dd, J = 12.0, 4.6 Hz, 1H), 3.85 (dd, J = 12.0, 2.5 Hz, 1H), 3.68 (dd, J = 12.0, 5.3 Hz, 1H), 3.40–3.20 (m, 6H), 2.80 (m, 2H); MS (ESI, +ve) m/z 490 ($M+H^+$, 60%); HRMS (ESI, +ve) $C_{24}H_{27}NO_8S$ $(M+Na)^+$ requires m/z 512.1355, found 512.1351; Compound **14** IR (neat) (cm^{-1}) 3261, 1695, 1657, 1631, 1590, 1539, 1429, 1379, 1333, 1254, 1231, 1169, 1141, 1100; ^1H NMR (300 MHz) ($CDCl_3$) δ 8.60 (dd, J = 7.2, 0.9 Hz, 2H), 8.26 (dd, J = 8.2, 0.9 Hz, 2H), 7.79 (dd, J = 8.2, 7.2 Hz, 2H), 6.52 (br s, 1H), 5.81–5.63 (m, 2H), 4.33 (m, 2H), 3.94 (m, 2H), 3.26 (d, J = 5.8 Hz, 2H), 2.79 (m, 2H), 2.09 (s, 3H); MS (ESI, +ve) m/z 369 ($M+H^+$, 100%); HRMS (ESI, +ve) $C_{20}H_{20}N_2O_3S$ $(M+Na)^+$ requires m/z 391.1092, found 391.1086; Compound **15** IR (neat) (cm^{-1}) 3284, 3058, 2913, 2857, 1710, 1618, 1598, 1564, 1504, 1427, 1310, 1215, 1089, 1008; ^1H NMR (300 MHz) ($CDCl_3$) δ 8.19–8.08 (m, 2H), 7.82 (dd, J = 8.2, 1.1 Hz, 1H), 7.71 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.60–7.52 (m, 2H), 5.81–5.60 (m, 2H), 4.10 (d, J = 4.8 Hz, 2H), 4.00 (s, 2H), 3.12 (d, J = 6.3 Hz, 2H), 2.35 (br s, 1H); MS (ESI, +ve) m/z 246 ($M+H^+$, 100%); HRMS (ESI, +ve) $C_{14}H_{15}NOS$ $(M+H)^+$ requires m/z 246.0947, found 246.0948; Compound **16** IR (KBr) (cm^{-1}) 3296, 3027, 2926, 2851, 1716, 1557, 1496, 1409, 1378, 1301, 1202, 1090, 984, 965; ^1H NMR (300 MHz) ($CDCl_3$) δ 8.94 (s, 1H), 8.07 (m, 2H), 7.76 (m, 2H), 5.84–5.75 (m, 1H), 5.70–5.60 (m, 1H), 4.09 (d, J = 5.2 Hz, 2H), 3.99 (s, 2H), 3.16 (d, J = 7.8 Hz, 2H); MS (ESI, +ve) m/z 247 ($M+H^+$, 100%); HRMS (ESI, +ve) $C_{13}H_{14}N_2OS$ $(M+H)^+$ requires m/z 247.0905, found 247.0880.
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21. A solution of Hoveyda–Grubbs second generation catalyst (0.75 mg, 1 μmol) in *t*-BuOH (0.125 mL) was added to a mixture of naphthalimide **2** (1.5 mg, 5 μmol), allyl alcohol (**7**) (6.88 μL, 0.10 mmol), β-*O*-allyl glucose (**8**) (22 mg, 0.10 mmol), *N*-allyl acetamide (**9**) (10 μL, 0.10 mmol), *t*-BuOH (0.125 mL) and Milli-Q® water (0.25 mL) at 32 °C, and the resulting mixture was stirred at 32 °C for 1 h. During this time the reaction mixture turned from green to yellow within a few minutes, then more gradually to brown/black. A second portion of catalyst (0.75 mg in 0.125 mL *t*-BuOH) was added, followed by Milli-Q® water (0.125 mL), and the mixture was stirred at 32 °C for 1.5 h. At time intervals, an aliquot (10 μL) was withdrawn from the reaction mixture, diluted with MeOH (190 μL), and analyzed directly by LC–MS [20–100% MeCN over 30 min]. The LC–MS result corresponding to a 2.5 h reaction time showed the presence of CM conjugates **12**, **13**, and **14** (confirmed by MH^+ molecular ions and by comparison with standard samples) plus additional peaks attributed to catalyst degradation products (e.g., M^+ = 307, attributed to free carbene ligand, which co-elutes with **12**). The relative amounts of **12**, **13**, and **14** were determined by integrating separate plots of the corresponding molecular ions over time. Data for **12**: retention time 16.6 min, m/z 328 [MH^+], relative area 22%. Data for **13**: retention time 12.9 min, m/z 490 [MH^+], relative area 20%. Data for **14**: retention time 16.1 min, m/z 369 [MH^+], relative area 58%.
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