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# Build/Couple/Pair Strategy Combining the Petasis 3-Component Reaction with Ru-Catalyzed Ring-Closing Metathesis and Isomerization

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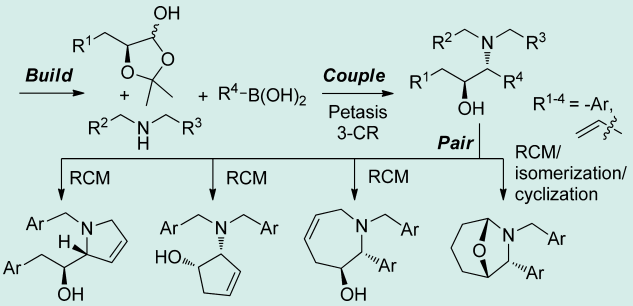
Supporting Information

**ABSTRACT:** A "build/couple/pair" pathway for the systematic synthesis of structurally diverse small molecules is presented. The Petasis 3-component reaction was used to synthesize *anti*-amino alcohols displaying pairwise reactive combinations of alkene moieties. Upon treatment with a ruthenium alkylidene-catalyst, these dienes selectively underwent ring-closing metathesis reactions to form 5- and 7-membered heterocycles and cyclic aminals via a tandem isomerization/*N*-alkyliminium cyclization sequence.




**KEYWORDS:** *Petasis 3-component reaction, ring-closing metathesis, isomerization, build/couple/pair*

In the wake of recent years' discoveries in human genomics, the hunt for small molecule probes with unique biological properties has been intensified in academic laboratories. Affordable screening technologies relying, at least in part, on commercial compound collections now enable life science researchers to rapidly and routinely identify small molecule leads for biological investigation. However, to advance biological probe discovery,[1] it is becoming increasingly accepted that screening collections should include more novel, synthetically tractable molecules of sufficient structural diversity.[2] In this context, innovative synthetic strategies have been proposed for the systematic generation of compound libraries.[3] To more effectively facilitate hit-to-lead processes, such as those encountered during early stage probe development, synthetic concepts that prioritize molecular optimizability more stringently are needed. By emphasizing the access to all stereochemical variants of structurally complex small molecule scaffolds as an optimal coherent design principle and a prerequisite for the development of effective stereostructure activity relations, the recently proposed "build/couple/pair" (B/C/P) strategy has gained some attention.[4,5] In the first phase (*build* phase), building blocks incorporating defined stereogenic units and tailored reactive functionalities are generated asymmetrically. The building blocks are then assembled (*couple* phase) through intermolecular bond-forming processes to yield a complete matrix of stereoisomers of the main carbon framework, prior to intramolecular joining of strategically positioned functional groups (*pair* phase).

We herein report our progress toward a B/C/P pathway that entails the combinatorial pairwise display of alkene moieties around an amino alcohol template (Figure 1). The combination of the Petasis 3-component reaction (Petasis 3-CR) (*couple*)[6,7]

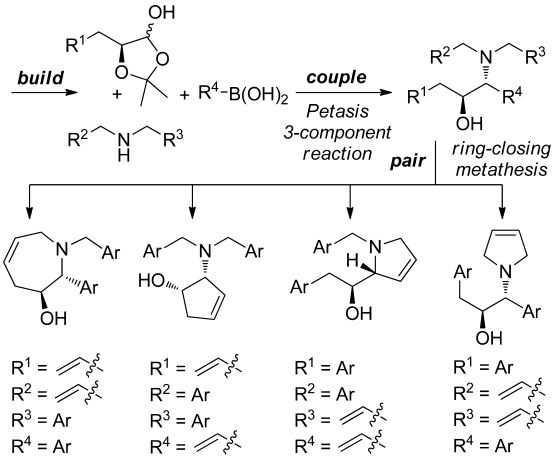



**Figure 1.** Build/couple/pair strategy combining the Petasis 3-component reaction with ring-closing metathesis.

and Ru alkylidene-catalyzed ring-closing metathesis (RCM) (*pair*)[8] would then result in a collection of carbo- and heterocycles of different sizes and appendage modifications.[9] This strategy also opens for the application of a recently discovered Ru alkylidene-catalyzed tandem RCM/isomerization/cyclization reaction to introduce an extra element of skeletal diversity in the *pair* phase (Figure 2).[10]

All desired olefin-containing components (boronic acid, α-hydroxy aldehyde, and amine) were readily synthesized in few

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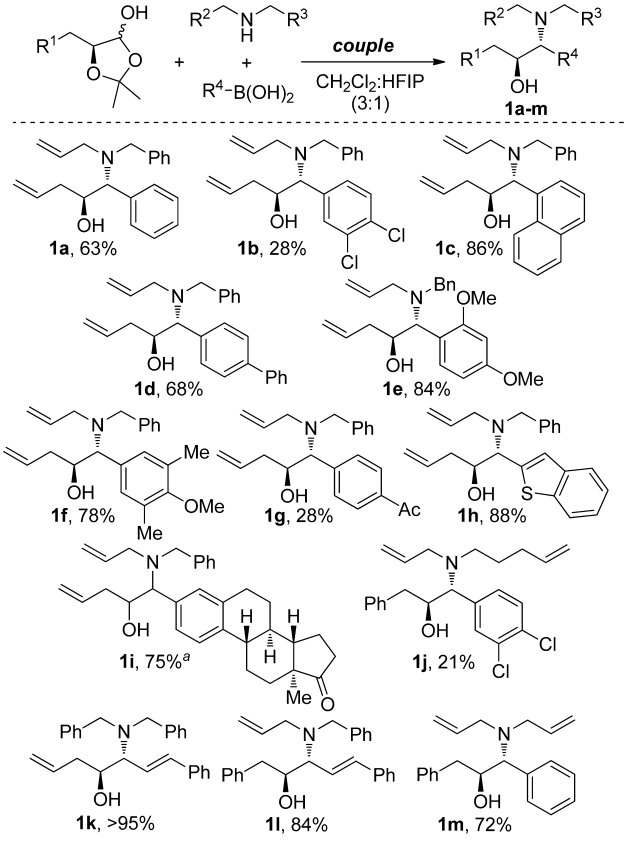
**Scheme 1. *Couple* Phase: Petasis 3-Component Reactions of Olefin-Functionalized Building Blocks[a]**




[a]Product **1i** was obtained as a 1:1 diastereomeric mixture of *anti*-amino alcohols.

steps.[11] Components for the Petasis 3-CR were then matched so that the resulting amino alcohols contained two olefin functionalities aligned to undergo Ru-catalyzed ring-closing metathesis and form small rings. The Petasis 3-CRs were mediated in a mixture of $CH_2Cl_2$ and hexafluoroisopropanol (HFIP) (Scheme 1; *couple* phase) as solvent,[12] generally giving the diasteromerically pure *anti*-amino alcohol products in decent to good yields (>60%). These synthetic transformations were conveniently demonstrated with racemic $\alpha$-hydroxy aldehydes masked as the corresponding lactols, but most

**Scheme 2. *Pair* Phase: Functional-Group Pairing of Alkene-Containing Amino Alcohols**

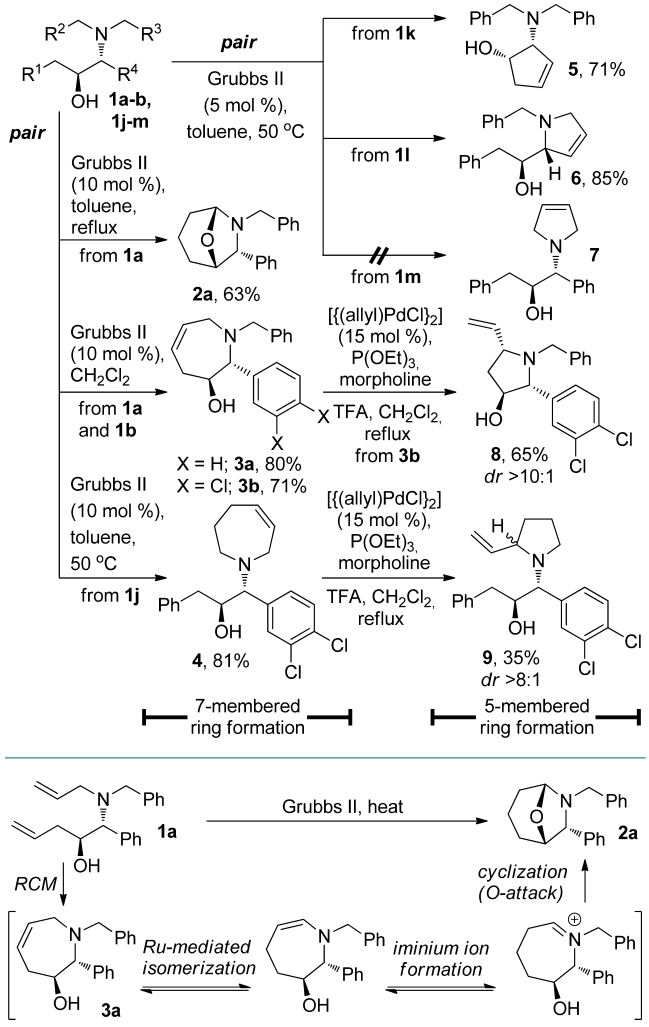


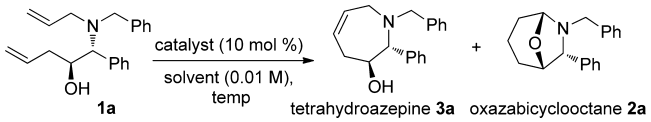




**Figure 2.** Mechanism for the Formation of Oxazabicyclooctane **2a**.

enantiopure aldehyde components would be accessible from readily available $\alpha$-hydroxy carboxylic acid derivatives.[13a] For example, the metal-catalyzed asymmetric allylation of glyoxylic acid derivatives could be an important step (*build*) in the generation of a stereochemically complete assembly of

**Table 1. Catalyst and Reaction Conditions for the Selective Formation of Tetrahydroazepines (Selected Results)[a]**




| entry | catalyst | solvent (temp) | ratio **1a**:**3a**:**2a** (1 h)[a−c] | ratio **1a**:**3a**:**2a** (24 h)[a−c] |
|---|---|---|---|---|
| 1 | Grubbs I | $CH_2Cl_2$ (rt) | NA[d] | 52:48:0 |
| 2 | Grubbs II | $CH_2Cl_2$ (rt) | NA | 1:98:1 |
| 3 | Hoveyda−Grubbs II | $CH_2Cl_2$ (rt) | NA | 17:82:1 |
| 4 | Grubbs II | $CH_2Cl_2$ (reflux) | 6:73:20 | 5:68:27 |
| 5 | Grubbs II | toluene (reflux) | 3:10:87[e,f] | NA |
| 6 | Hoveyda−Grubbs I | toluene (reflux) | 1:45:54[e] | NA |
| 7 | Hoveyda−Grubbs II | toluene (reflux) | 1:3:96[e] | NA |

[a]Consult the Supporting Information for a full account on all catalyst optimization experiments. [b]Determined by RP-HPLC (215 nm). [c]Reaction mixtures were generally clean (>85% of **1a**, **3a**, and **2a**). [d]NA: Not available. [e]Reactions run at 0.03 M concentration. [f]Complex reaction mixture (<70% of **1a**, **3a**, and **2a**).


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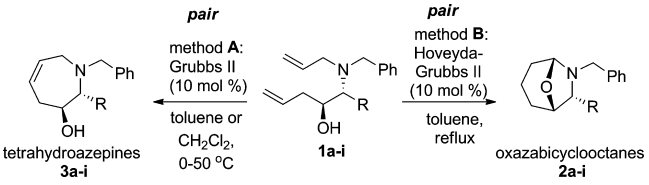
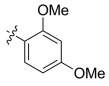
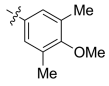
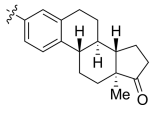
**Table 2. *Pair* Phase: Selective Formation of Tetrahydroazepines and Oxazabicyclooctanes**




| entry | R | tetrahydroazepine (method **A**), yield (%)[a,b] | oxazabicyclooctane (method **B**), yield (%)[a] |
|---|---|---|---|
| 1 |  | **3a**, 80 | **2a**, 82 |
| 2 |  | **3b**, 71 | **2b**, 41 |
| 3 |  | **3c**, 76 | **2c**, 37 |
| 4 |  | **3d**, 77 | **2d**, 58 |
| 5 |  | **3e**, 90 | **2e**, 68 |
| 6 |  | **3f**, 74 | **2f**, 78 |
| 7 |  | **3g**, 71 | **2g**, 85 |
| 8 |  | **3h**, 79 | **2h**, 64 |
| 9 |  | **3i**, 67[c] | **2i**, 66[c] |

[a]Isolated yield after flash column chromatography. [b]See Supporting Information for detailed reaction conditions. [c]Products **3i**/**2i**, were obtained as 1:1 diastereomeric mixtures of *anti*-amino alcohols/ethers.

alkene-containing building blocks.[13b] Notably, the use of *trans*-phenylvinylboronic acid enabled the introduction of an alkene moiety via the boronic acid component (compounds **1k**–**l**). Products resulting from the reaction of electron-deficient arylboronic acids (**1b**, **1g**, and **1j**) were not surprisingly obtained in lower yields.

Amino alcohols **1a**–**b** and **1j**–**m** were then subjected to Ru alkylidene-catalysis (Scheme 2; *pair* phase). The 5-membered ring systems **5** and **6**, were smoothly obtained (71% and 85%, respectively) in the presence of Grubbs' second generation catalyst (Grubbs II). Disappointingly, diallylamine **1m** could not be transformed into the desired 5-membered pyrrolidine **7**. Even the addition of catalytic amounts of Ti(*i*-PrO)$_4$, previously reported to enable the RCM reaction of diallylamines, proved unsuccessful.[14] Substrate **1j** was transformed into the 7-membered RCM product **4** with Grubbs II at slightly elevated temperature (50 °C), whereas tetrahydroazepines **3a**–**b** could be efficiently obtained using the same catalyst at room temperature. An additional mode of skeletal diversification was demonstrated by subjecting RCM products **3b** and **4** to Pd-catalyzed ring-contraction reactions,[15] which afforded two new 5-membered rings (**8** and **9**, respectively) in acceptable yields and in a highly diastereoselective fashion (>10:1 and >8:1, respectively).

We have previously described the Ru alkylidene-mediated formation of 8-oxa-6-azabicyclo[3.2.1]octane (oxazabicyclooctane) **2a** from substrate **1a** at elevated temperature (Scheme 2).[10] We speculated that the formation of **2a** was the result of a metal-assisted double bond isomerization of the RCM product **3a** to an iminium intermediate, subsequently trapped by the tethered *O*-nucleophile (Figure 2). Although processes involving tandem RCM/isomerization have been reported,[16] the concomitant isomerization to synthetically useful iminium ions has only been marginally explored.[10,17]

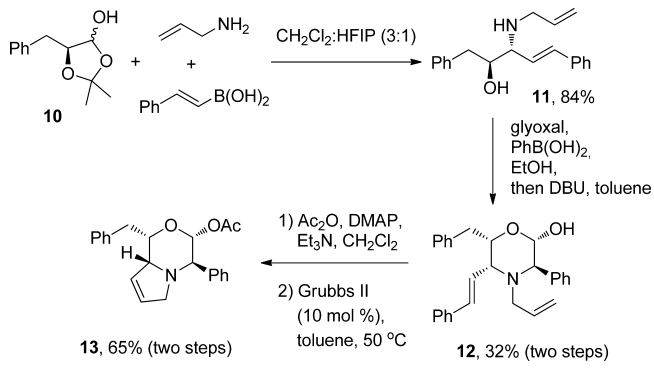
To provide synthetically useful protocols for the selective formation of tetrahydroazepine and oxazabicyclooctane ring systems, an extensive optimization study was carried out (Table 1, selected results), the challenge being to identify reaction conditions that provide minimal or maximal postmetathesis olefin isomerization.

To this end, a range of ruthenium catalysts, temperatures, and reactant stoichiometries were thoroughly examined. When running the reactions at room temperature (entries 1–3), the Grubbs II catalyst was sufficiently efficient for the RCM reaction, while still keeping formation of the oxazabicyclooctane at satisfyingly low levels (entry 2). The results clearly revealed the superiority of the Hoveyda–Grubbs II catalyst (entry 7) and the necessity of elevated temperatures (entries 4–7) for the initiation of oxazabicyclooctane formation.

In general, the developed protocols proved highly efficient when applied to a range of diene-containing amino alcohols (**1a**–**i**), as evidenced by the formation of tetrahydroazepines and oxazabicyclooctanes in good to excellent yields (Table 2). Compared to our previous findings,[10] the conversion of **1a** into oxazabicyclooctane **2a** was improved from 63% to 82% when using method **B** (Table 2, entry 1). In a few instances, substrates only reluctantly underwent RCM reaction, necessitating the use of higher reaction temperatures.

In a final stage toward more complex structures, an approach taking advantage of two consecutive Petasis 3-CRs of a parent amine was investigated. Allylamine was treated with lactol **10** and *trans*-phenylvinylboronic acid to give *anti*-amino alcohol **11**, followed by reaction with glyoxal and phenylboronic acid to provide a tertiary amine as a mixture of diastereomers, which, upon treatment with DBU, equilibrated to diastereomerically pure **12** (29% yield, 3 steps).[18] Compound **12** was then acetylated and subjected to RCM to provide bicyclic compound **13** in decent yield (65%, 2 steps).

**Scheme 3. Consecutive Petasis 3-CR and RCM Reactions**





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In conclusion, important steps toward a B/C/P strategy relying on the strategic positioning of olefin moieties around an amino alcohol template, effectively combining the Petasis 3-CR (*couple*) with Ru-catalyzed RCM and isomerization reactions (*pair*), have been taken. By mix-matching combinations of olefin-containing components, this modular strategy rapidly grants access to skeletally diverse molecules. To provide an element of skeletal diversification control, catalysts and reaction conditions for the selective formation of tetrahydroazepines and azabicyclooctanes have been developed. In the future, we hope to bring *syn*-selective Petasis reactions into the scope of the present methodology and thereby provide a more complete B/C/P pathway.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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