Development of Fragments Through
a Catalyst-Controlled
Diastereoselective Intramolecular
Oxa-Michael Reaction

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New Molecules Entities Entering the Market vs. Annual Spending on R&D

Conventional HTS Approach vs. Fragment Based Drug Design

~ one million compounds library

Nexium

~ one thousand fragments

Fragment of Nexium
Mission of Our group

Henry Reaction

Mannich Reaction

Michael Reaction

Cancer

Infectious Disease

Psychological Diseases

~1,000 fragments

Objectives

Synthesize morpholine derived fragments using the intramolecular oxa-Michael reaction

- Commercially available amino alcohols
- nitrobenzenesulfonyl (nosyl) amine as a nucleophile and vinyl ketone as an electrophile
- Diastereoselectivity control
Synthesis of Diastereoselective Oxa-Michael Product

Step 1: Protection

\[
\text{BnNH}_2 + \text{ClSO}_2\text{NO}_2 \xrightarrow{\text{DMAP, Et}_3\text{N}} \text{BnNH}_2\text{SO}_2\text{NO}_2
\]

[74-94% yield]

Step 2: Allylation

\[
\text{BnNH}_2\text{SO}_2\text{NO}_2 + \text{BrCH} = \text{CH}_2 \xrightarrow{\text{K}_2\text{CO}_3, \text{DMF}} \text{BnNHCH} = \text{CH}_2\text{SO}_2\text{NO}_2
\]

[64% yield]

Step 3: Akylation; Olefin cross Metathesis

\[
\text{BnNHCH} = \text{CH}_2\text{SO}_2\text{NO}_2 + \text{ClRu=H} \xrightarrow{\text{DCM, 45}^\circ\text{C}} \text{BnNHCH} = \text{CH}_2\text{SO}_2\text{NO}_2
\]

[Enone Product]
Mechanistic Rationale for the Olefin Metathesis

Legend

Metal Carbenoid

Metallocyclobutane intermediate

New Metal Carbenoid
Synthesis of Diastereoselective Oxa-Michael Product: Continues.....

Step 4: intramolecular oxa-Michael reaction

\[
\text{Enone product} \xrightarrow{\text{Me-CCl-Pd-CCl}} \text{Oxa-Michael Product}
\]

\[
\begin{align*}
\text{DCM} & \quad 25^\circ\text{C} \\
\text{Bn} & \quad \text{Me} \\
\text{O}_2\text{N} & \quad \text{N=S=O} \\
\text{O=S=O} & \quad \text{H}_2\text{N}
\end{align*}
\]

Paladium -- Lewis acid to spontaneously produce oxa—Michael product

Step 5: De-protection

\[
\text{Oxa-Michael Product} \xrightarrow{\text{HS-OH}} \text{Oxa-Michael Product}
\]

\[
\begin{align*}
\text{Cs}_2\text{CO}_3 & \quad 3.0 \text{ eq} \\
\text{MeCN} & \quad 23^\circ\text{C} \\
\text{Bn} & \quad \text{Me}
\end{align*}
\]

Prediction for the trans conformation vs. cis conformation

\[
\begin{align*}
\text{cis} & \quad E = \text{very large} \\
\text{trans} & \quad E = 0.0
\end{align*}
\]

The ground state of cyclohexane in a fully staggered conformation is strain free.
To Test the Generality of the Method; Targeted Fragments
Once complete the synthesis of the novel fragment library, we can start to screen known biological targets. This robust screening collection will:

1. Reduce cost (one million compounds in HTS vs. one thousand in FBDD)

2. Facilitate downstream optimization and manufacturing

3. Understand the mechanism of diseases such as cancer, infectious diseases and psychological diseases using these highly selective fragments
• HTS
• FBDD

• robust library: diverse and selective

• Methodology based on the oxa-Michael reaction to synthesizing morpholine derived fragments
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