The art of total synthesis through cascade reactions

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The growing importance of cascade reactions reflects and imparts advances in the state of the art of organic synthesis and underscores the desire of synthetic chemists to achieve higher levels of elegance and efficiency. Besides their esthetic appeal, cascade processes offer economical and environmentally friendly means for generating molecular complexity. Because of their many advantages, these reactions have found numerous applications in the synthesis of complex molecules, both natural and designed. In this tutorial review, we highlight the design and execution of cascade reactions within the context of total synthesis as demonstrated with selected examples from these laboratories.
Scheme 2  Biomimetic cascade total synthesis of endiandric acids A (21), D (19), and E (20) methyl esters.
Fig. 10  Retrosynthetic analysis of BE-43472B (6).
Scheme 15  Diels–Alder/$S_6(Ar)$ cascade synthesis of the BE-43472B skeleton (99 and 107).
CeCl₃·7H₂O Catalyzed C–C and C–N Bond-Forming Cascade Cyclization with Subsequent Side-Chain Functionalization and Rearrangement: A Domino Approach to Pentasubstituted Pyrrole Analogues

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Supporting Information

ABSTRACT: CeCl₃·7H₂O is found as an efficient catalyst for new intermolecular domino reactions of three-, four- and seven-component assemblies of common precursors under benign reaction conditions. Generation of enaminoesters from β-keto esters and primary amines, activation of their allylic sp³ C–H, vinylic sp² C–H and N–H bonds, multi C–C and C–N bond-forming cascade cyclization with 1,2-diketones and subsequent side-chain alkylation have been developed to construct functionalized pentasubstituted pyrroles and their chiral analogues. The scope of the domino reaction is successfully explored toward synthesis of highly aryl-substituted pyrroles, pentasubstituted pyrroles bearing C2-olefinic side-chain and spiro-2-pyrrolirones and their chiral analogues via unusual side-chain amination, elimination and ring contraction. The new domino reaction is operationally simple, robust, substrate specific, selective and high yielding.
Four Component Domino Reaction with Side-Chain Alkylation

\[
\text{R}_1= \text{alkyl}; \text{R}_2= \text{H}; \text{R}_3= \text{alkyl}; \text{R}_4= \text{alkyl}; \text{R}_5= \text{CO}_2\text{R} \& \text{R}_6= \text{alkyl}
\]
Three Component Domino Reaction with Side-Chain Elimination

\[
\begin{align*}
\text{R}_2\text{H}_2\text{C} & \quad \text{CO} \quad \text{OEt} \quad 1 \\
\text{R}_3\text{-NH}_2 & \quad 2 \\
\text{CO} \quad \text{O} \quad 3 \\
\end{align*}
\]

\[
\text{CeCl}_3\cdot 7\text{H}_2\text{O} (5 \text{ mol}\%) \quad \text{KI, THF, MgSO}_4, \text{rt}
\]

\[
\begin{align*}
\text{L}_n\text{M} \quad & \quad \text{OH} \\
\text{R}_3 & \quad \text{N} \\
\text{R}_4 & \quad \text{R}_1 \\
\text{H} & \quad \text{R}_3 \quad \text{N} \quad \text{R}_4 \\
\text{Me} & \quad \text{R}_3 \quad \text{N} \quad \text{R}_4 \\
\text{CO}_2\text{Et} & \quad \text{R}_1 \\
\end{align*}
\]

\[
\begin{align*}
7 & \quad \text{R}_4 \quad \text{R}_3 \quad \text{N} \quad \text{R}_4 \\
7a (\text{time: 42 h}; \text{yield: 82\%}) & \quad 7b (\text{time: 45 h}; \text{yield: 79\%}) \\
7c (\text{time: 48 h}; \text{yield: 76\%}) & \quad 7d (\text{time: 47 h}; \text{yield: 82\%}) \\
7e (\text{time: 44 h}; \text{yield: 81\%}) & \quad \text{XRD structure of 7e}
\end{align*}
\]

R_1 = alkyl; R_2 = Et; R_3 = alkyl; R_4 = alkyl or aryl
Three Component Domino Reaction with Ring Contraction

\[
\begin{align*}
R_1 &= \text{Et; } R_2 &= \text{Et; } R_3 = \text{alkyl; } R_4, R_4' &= (\text{CH}_2)_4
\end{align*}
\]

\[
\text{1} + \text{2} + \text{3} \xrightarrow{\text{CeCl}_3 \cdot 7\text{H}_2\text{O}(5 \text{ mol\%}), \ K\text{I, THF, MgSO}_4, \ rt} \text{II}
\]

Path d

\[
\text{III} \xrightarrow{L_nM^-} \text{8}
\]

8a (time: 42 h; yield: 85%)
8b (time: 48 h; yield: 74%)
8c (time: 40 h; yield: 78%)
8d (time: 47 h; yield: 82%)
8e (time: 45 h; yield: 92%)

XRD structure of 8e