Literature Report III

A Tandem Dehydrogenation-Driven Cross-Coupling between Cyclohexanones and Primary Amines for Construction of Benzoxazoles

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Checker: Yu-Qing Bai
Date: 2022-08-29

Xu, B.-P., Su, W.-P. *Angew. Chem. Int. Ed.* **2022,** e202203365.

CV of Prof. Wei-Ping Su (苏伟平)

Research Interest:

- Exploration of new organic reactions catalyzed by metal complexes

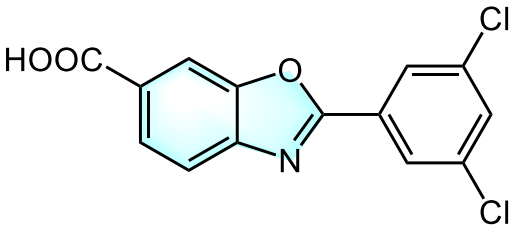
Background:

- **1983-1987** B.S., Hefei Normal University
- **1993-1999** Ph.D., FJIRSM, CAS
- **2000-2001** Postdoc., Harvard University
- **2001-2002** Postdoc., RU
- **2002-2005** Postdoc., ISU
- **2005-now** Researcher, FJIRSM, CAS

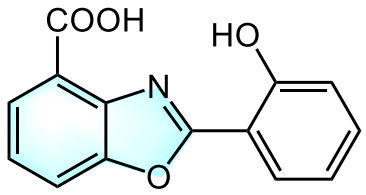
Contents

Introduction

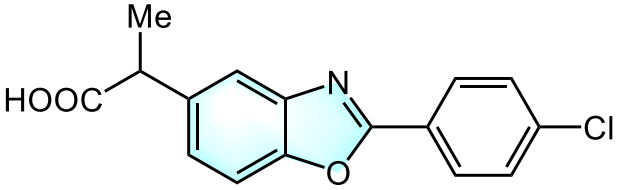
Selected Examples of Bioactive Benzoxazoles



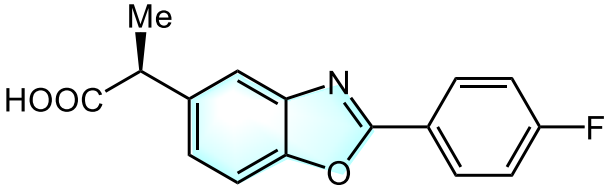
Tafamidis
(deadly neurodegenerative disease)



Caboxamycin
(antibiotic)



Benoxaprofen
(anti-inflammatory drug)



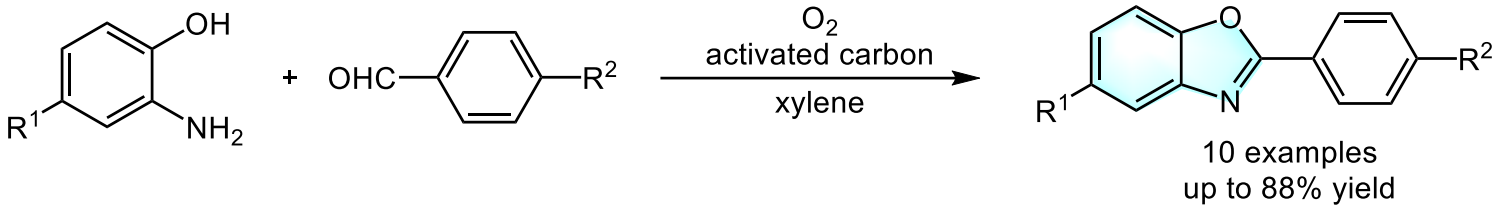
Flunoxaprofen
(anti-inflammatory drug)

Hureau, C. *et al. Chem. Soc. Rev.* **2013**, *42*, 7747.

Introduction

The Conventional Synthesis of Benzoxazoles

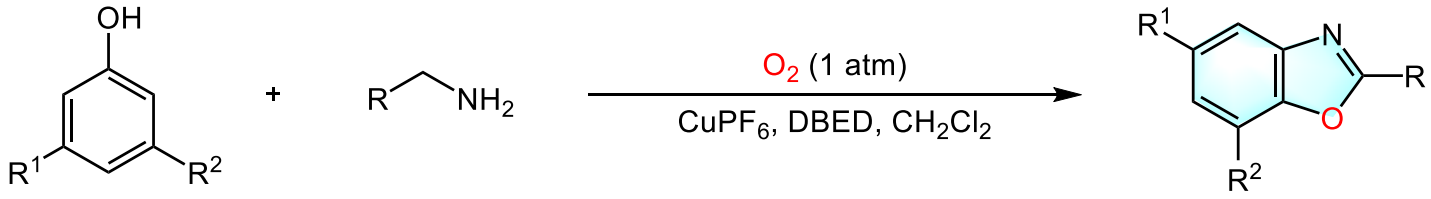
Cyclization



- 2-Aminophenols are Sensitive to Oxygenation

Hayashi, M. *et al*. *Org. Lett*. **2003**, *5*, 3713.

Oxidative *ortho*-Amination



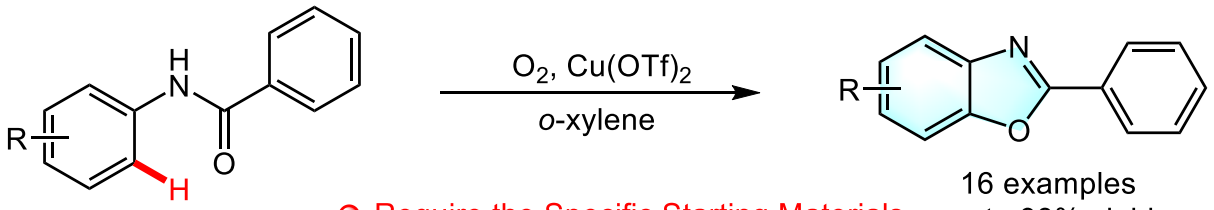
- Narrow Scope of Substrate

Lumb, J. P. *et al*. *Chem.* **2017**, *2*, 533.

Introduction

The Synthesis of Benzoxazoles *via* C-H Functionalization

C-H Functionalization

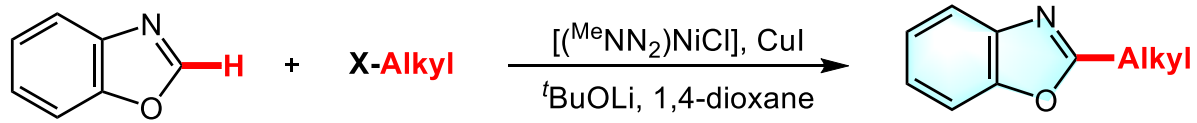


16 examples
up to 93% yield

- Require the Specific Starting Materials

Nagasawa, H. *et al*. *Angew. Chem. Int. Ed*. **2008**, *47*, 6411.

Modification of Benzoxazoles



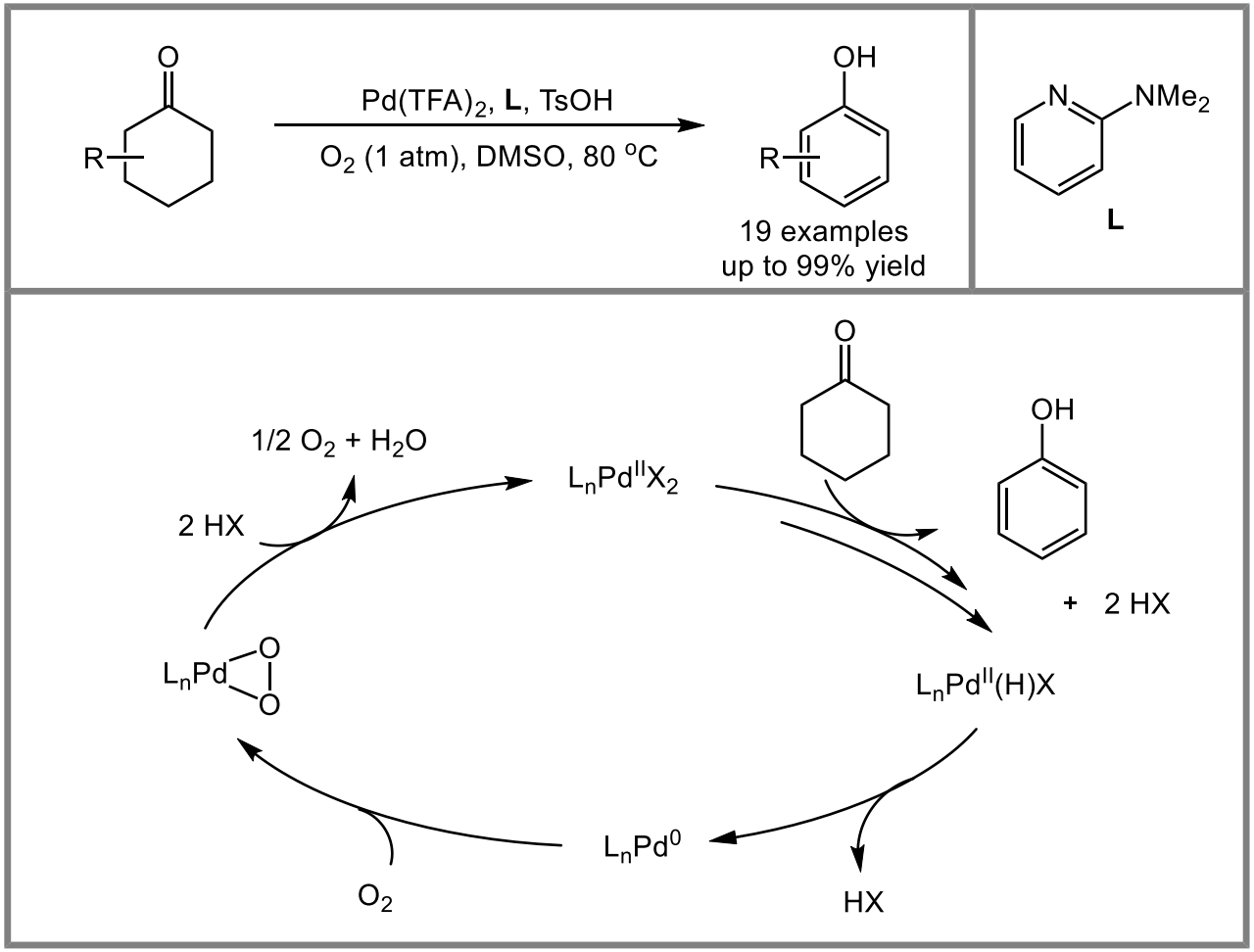
29 examples
up to 86% yield

- The Specific Starting Material is Prepared Through Multistep Procedures

Hu, X.-L. *et al*. *Angew. Chem. Int. Ed.* **2010**, *49*, 3061.

Introduction

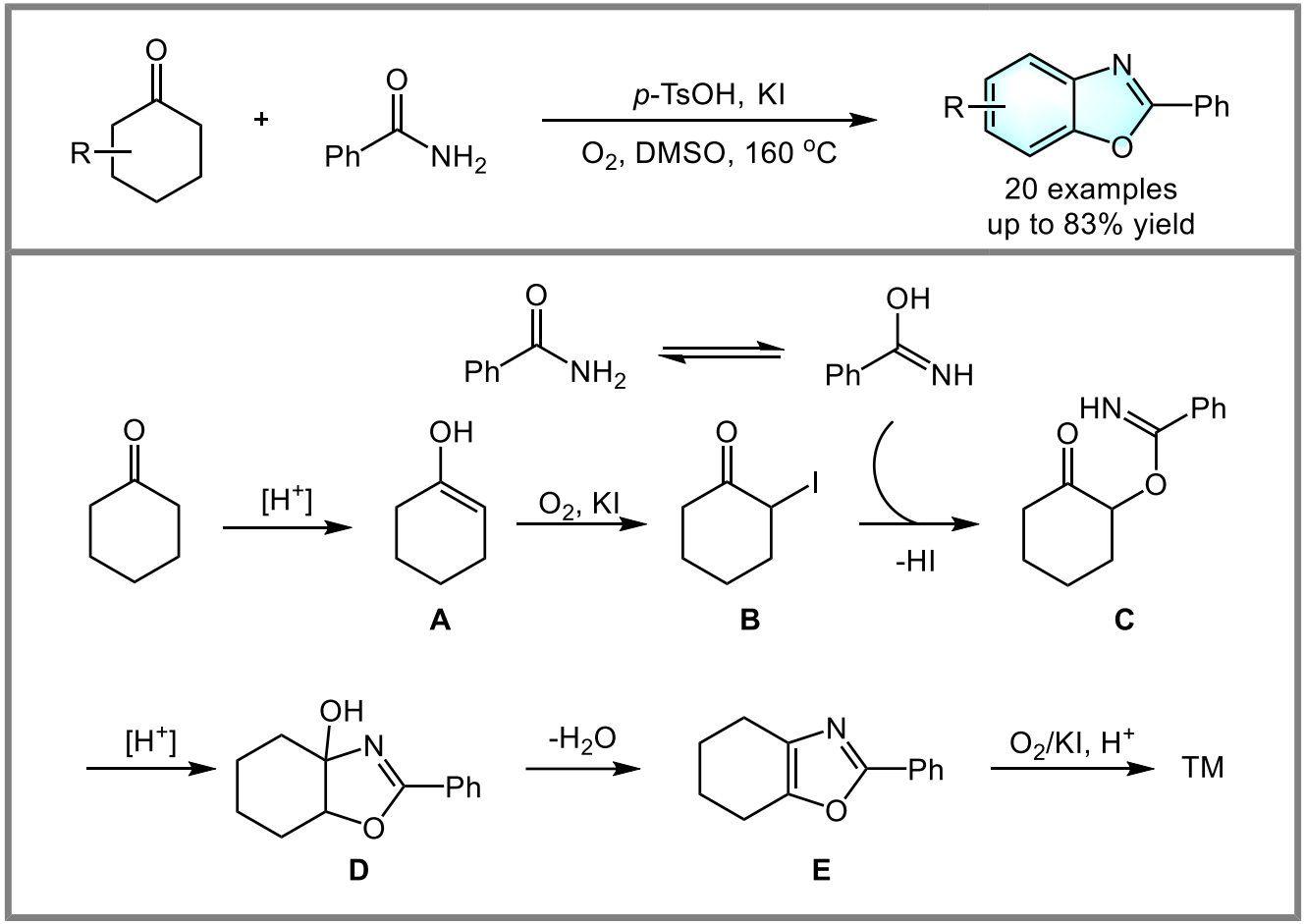
Palladium-Catalyzed Oxidative Dehydrogenation of Cyclohexanones



Stahl, S. S. *et al*. *Science* **2011**, *333*, 209.

Introduction

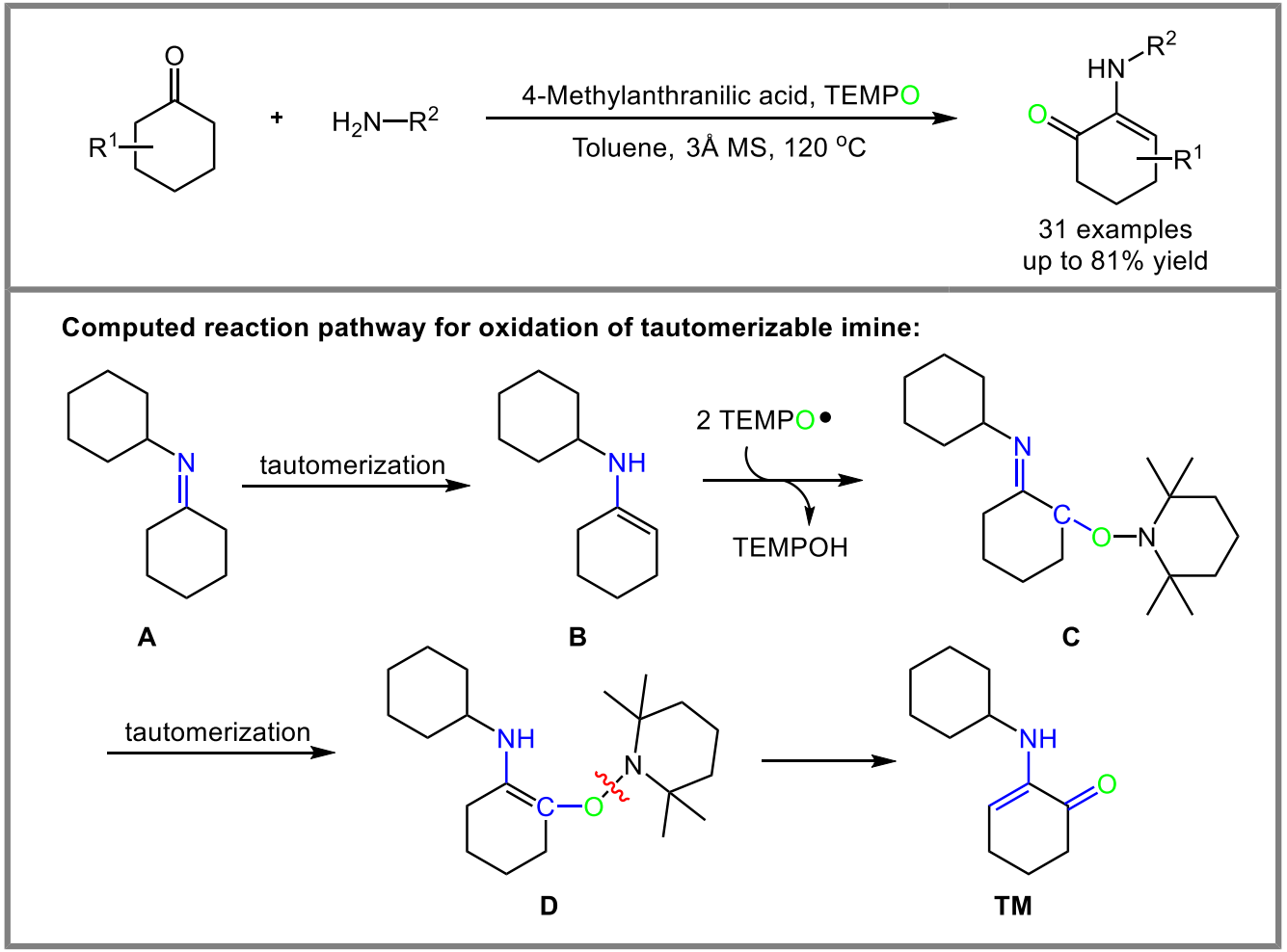
The Synthesis of Benzoxazoles *via* Dehydrogenative Aromatization



Deng, G.-J. *et al*. *Green Chem*. **2014**, *16*, 4644.

Introduction

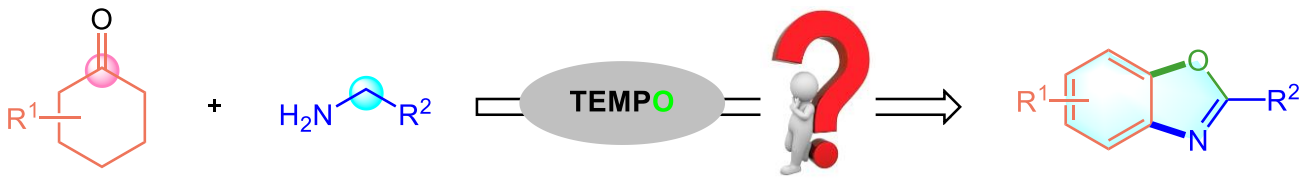
α-Oxygenation of Imine by TEMPO



Su, W,-P. *et al. Nat. Commun.* **2018**, *9*, 5002.

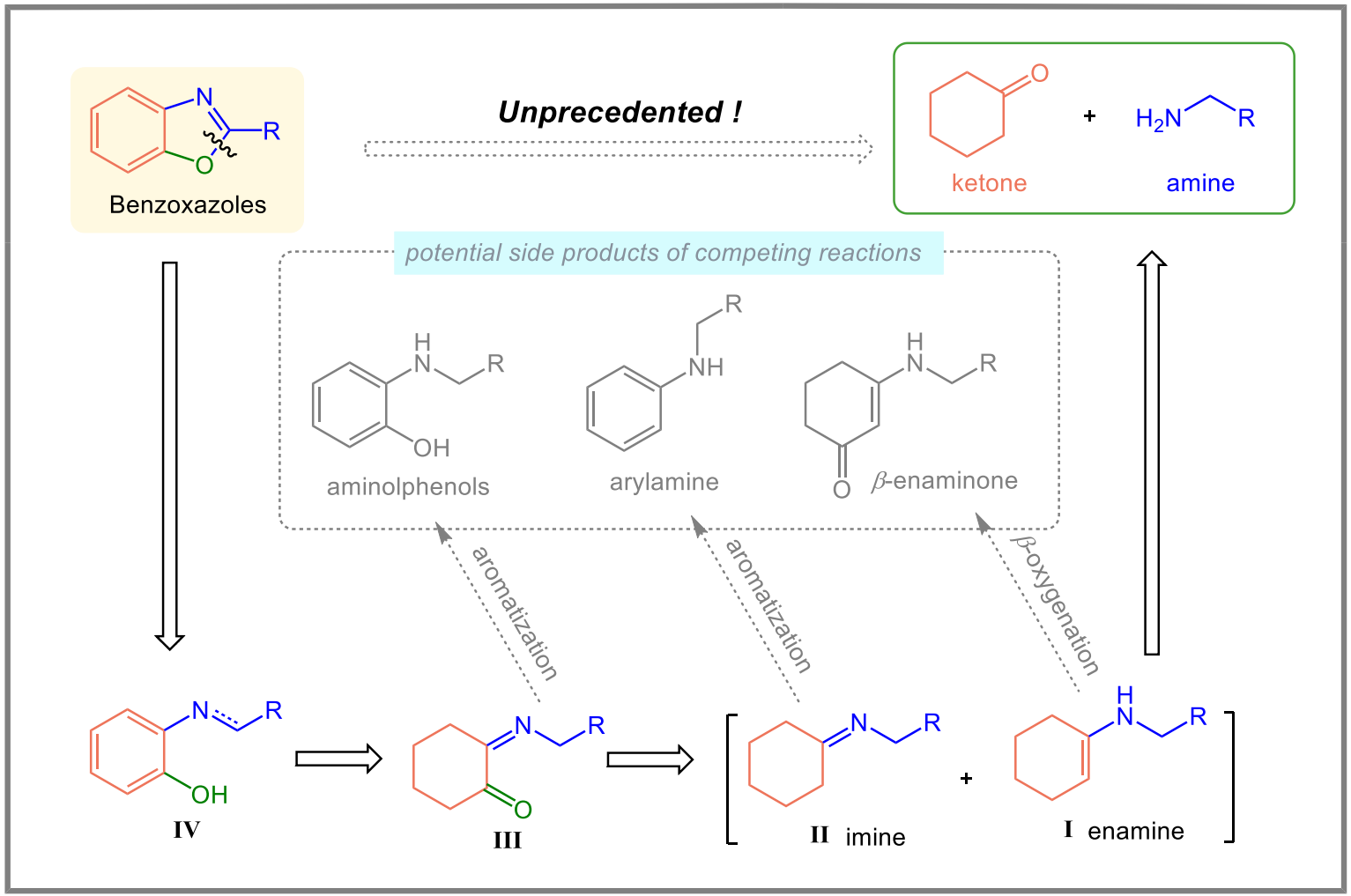
Dehydrogenation-driven Coupling

Dehydrogenation-driven Coupling

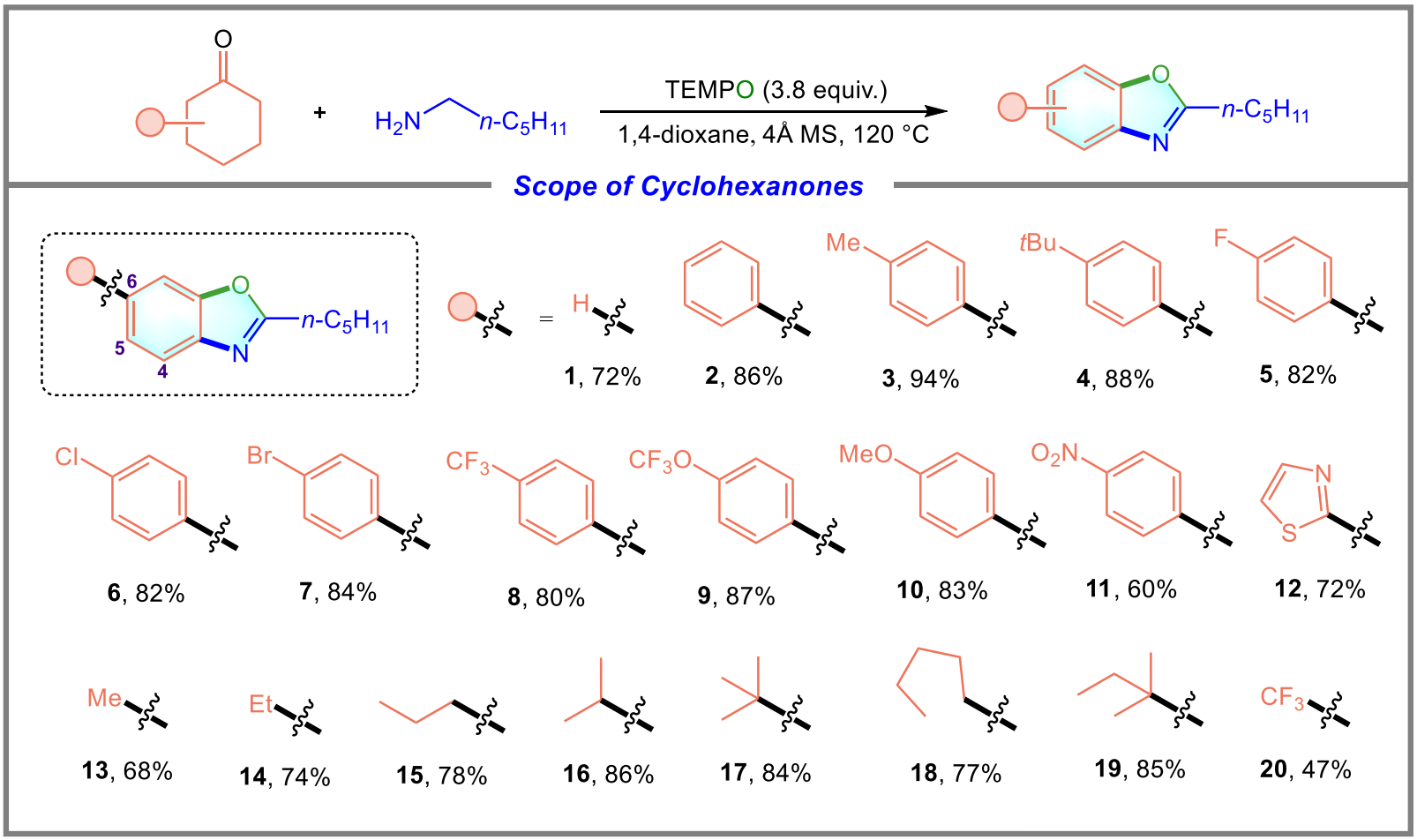


- Differentiate the reactivity of reaction intermediates
- Promote preferentially α-oxygenation of the imine
- Be simultaneously compatible with the following dehydrogenative aromatization and intramolecular oxidative C-H phenoxylation processes

Retrosynthetic Disconnection Design



Substrate Scope



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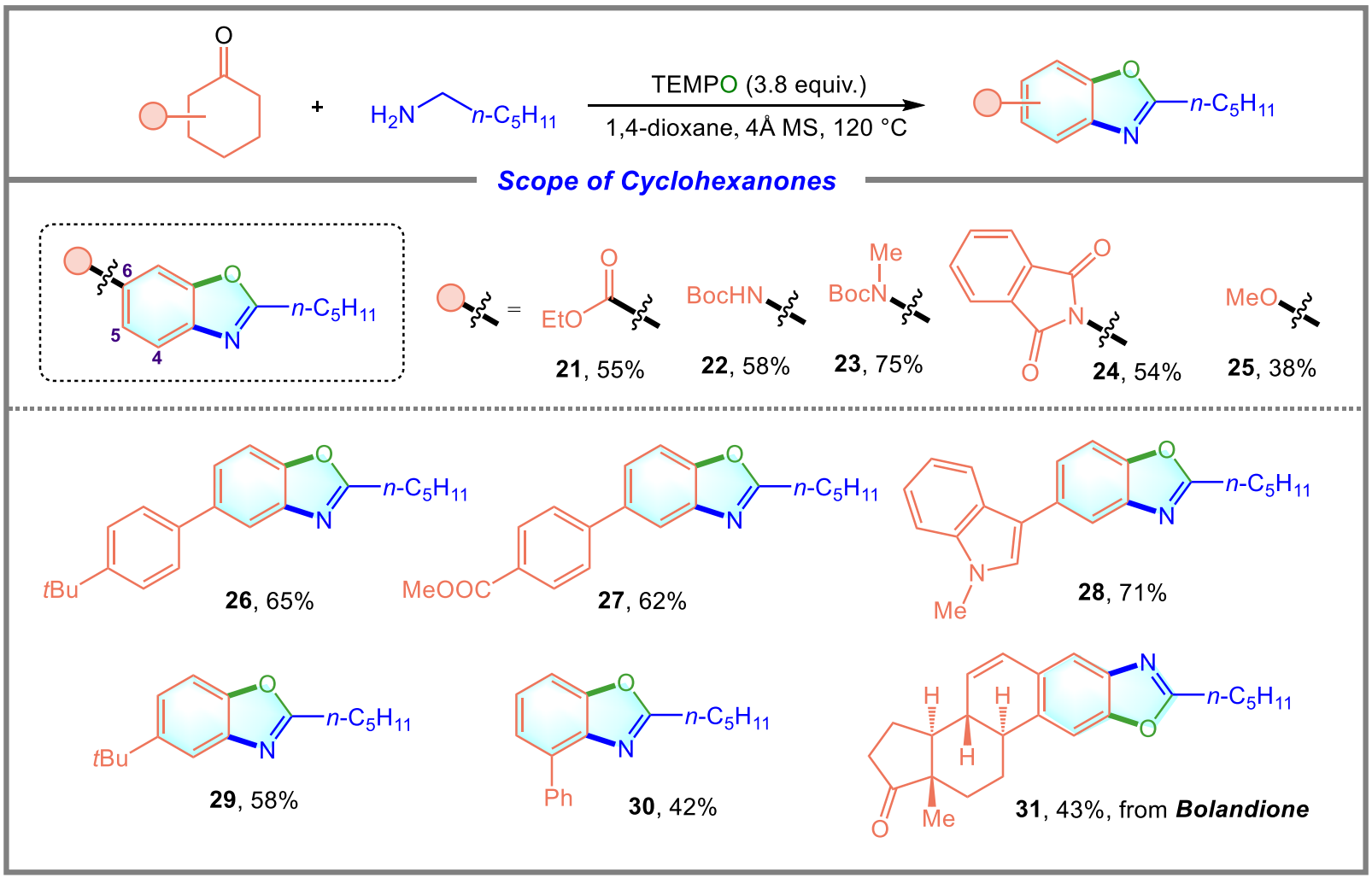

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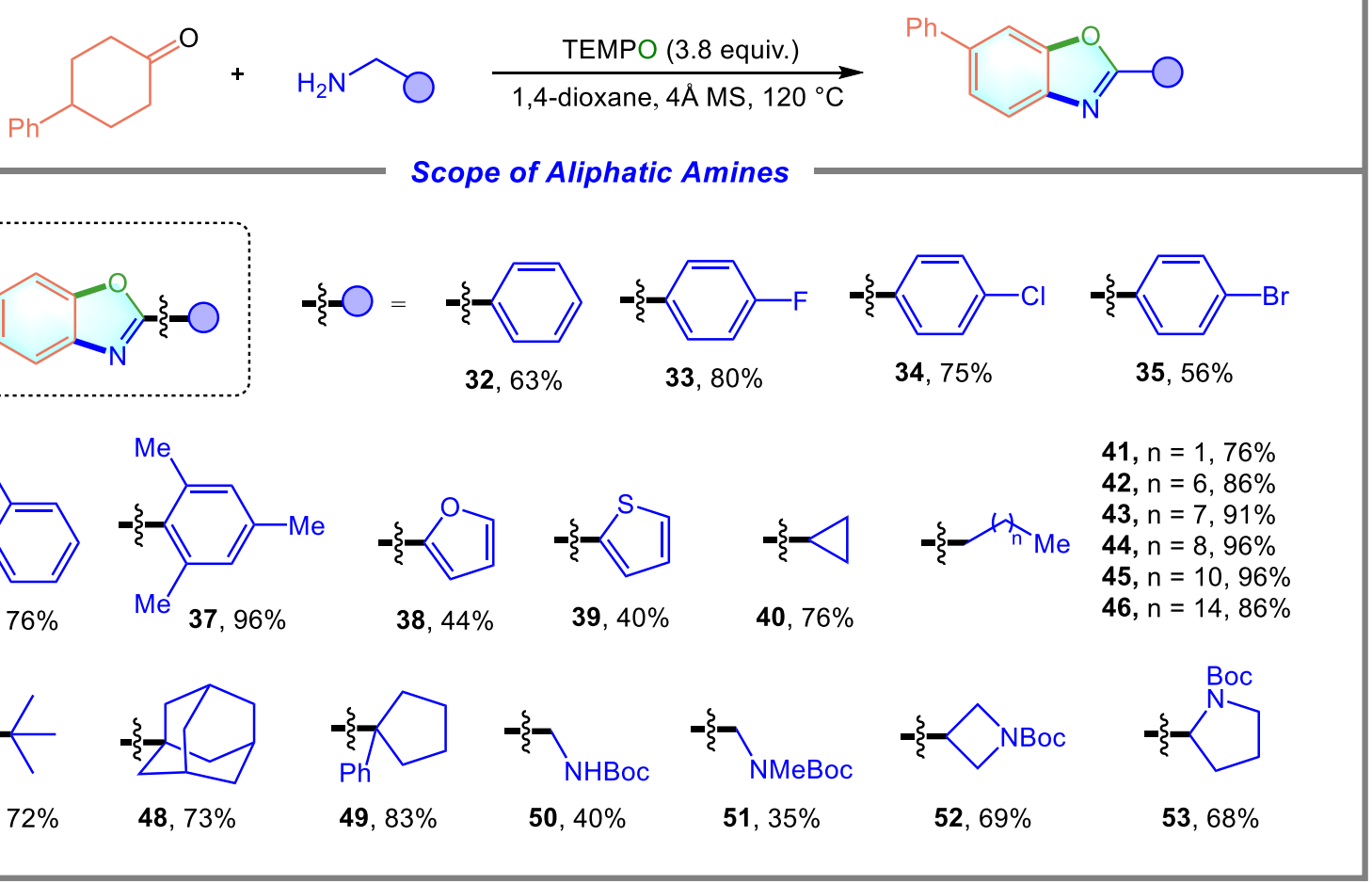
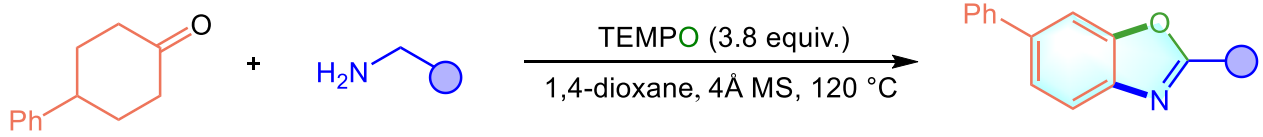
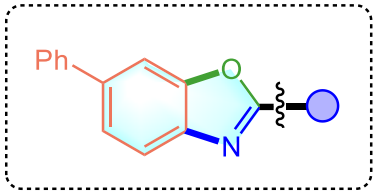
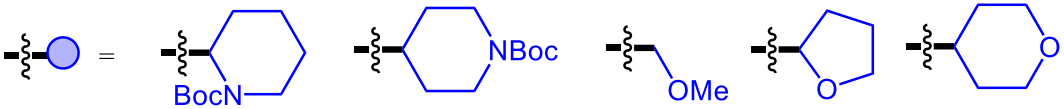


Substrate Scope

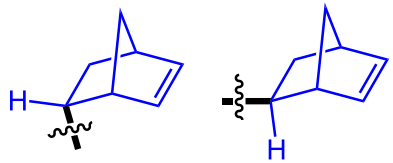


Scope of Aliphatic Amines



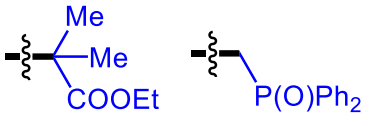


54, 70% **55**, 83% **56**, 58% **57**, 73% **58**, 82%

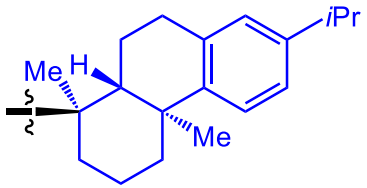


59 (endo) **60** (exo)

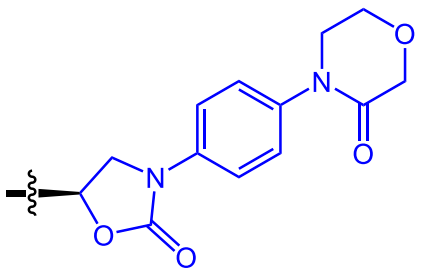
59+60, 72%
(**59:60** = 2.4:1)



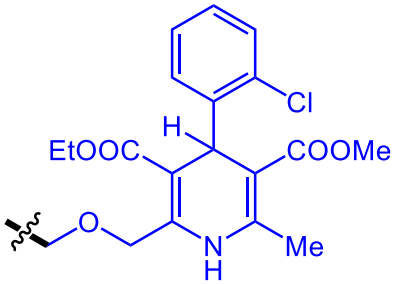
61, 76% **62**, 52%



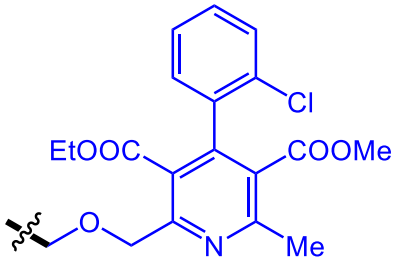
63, 85%
from ***Leelamine***



64, 62%
from ***Rivaroxaban*** *fragment*



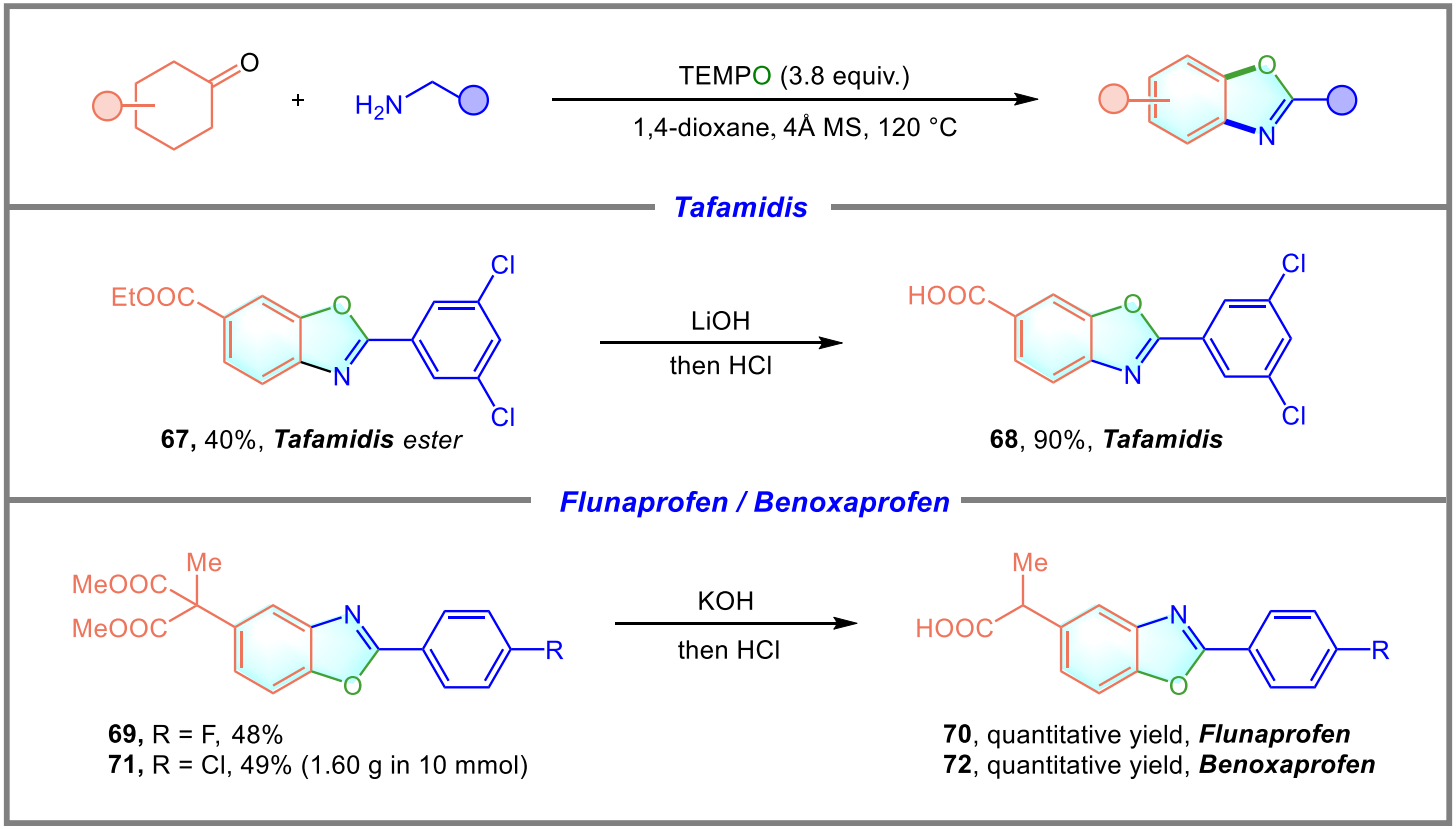
65



66

65+66, 82%
(**65:66** = 1:0.4)
from ***Amlodipine***

Synthetic Applications



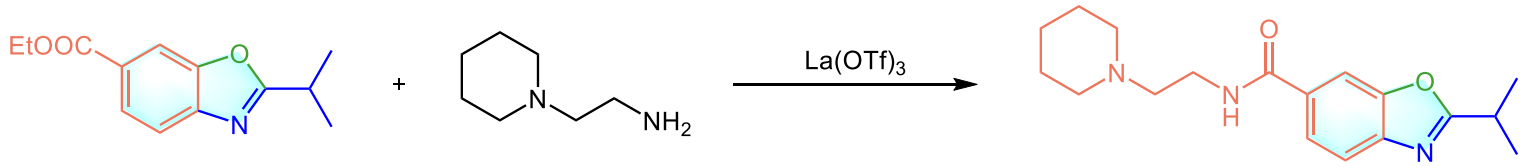
Synthetic Applications

JTP 426457

73, 70%

74, 81%, ***JTP 426457***

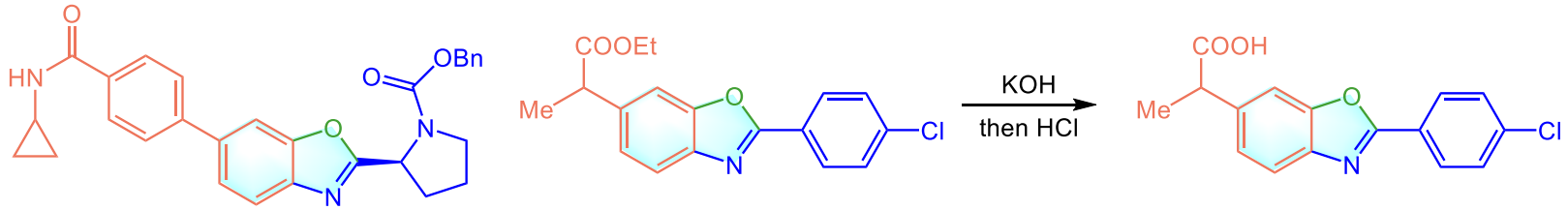
***TLR7*-antagonist**



75, 49%

76, 58%, ***TLR7*-antagonist**

HCV inhibitor / ***Benoxaprofen analogue***



77, 74%, HCV inhibitor

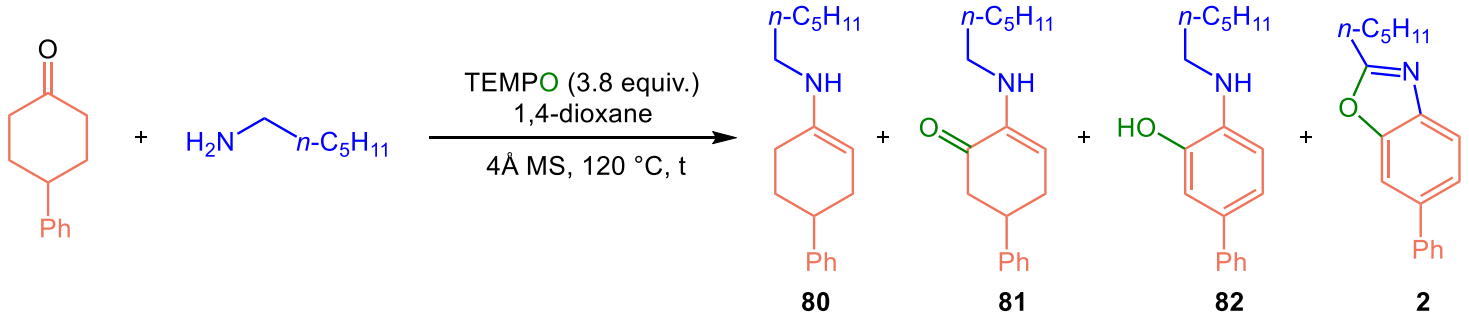
78, 41%

79, 82%, ***Benoxaprofen analogue***

Experimental Mechanistic Studies

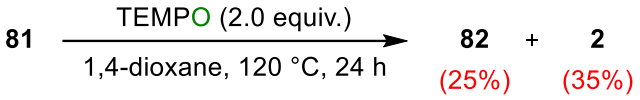
Mechanistic Investigations

a



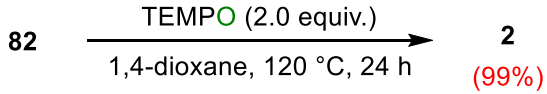
Validation of The Possible Intermediate 81

b

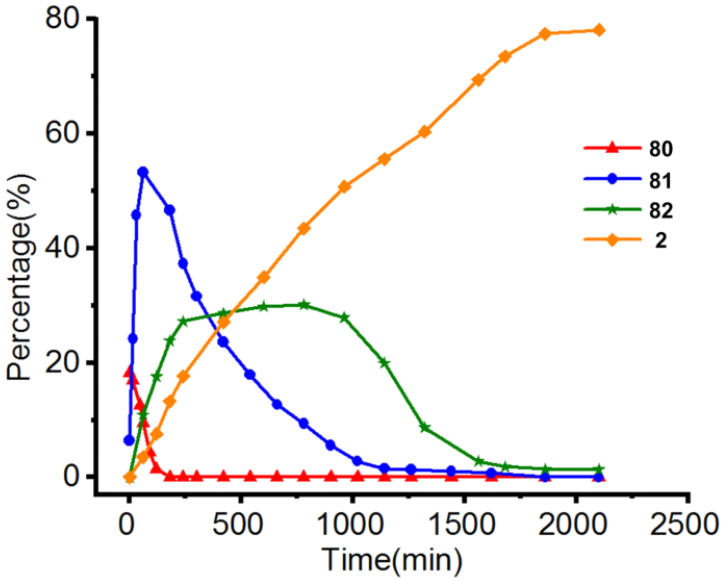


Validation of The Possible Intermediate 82

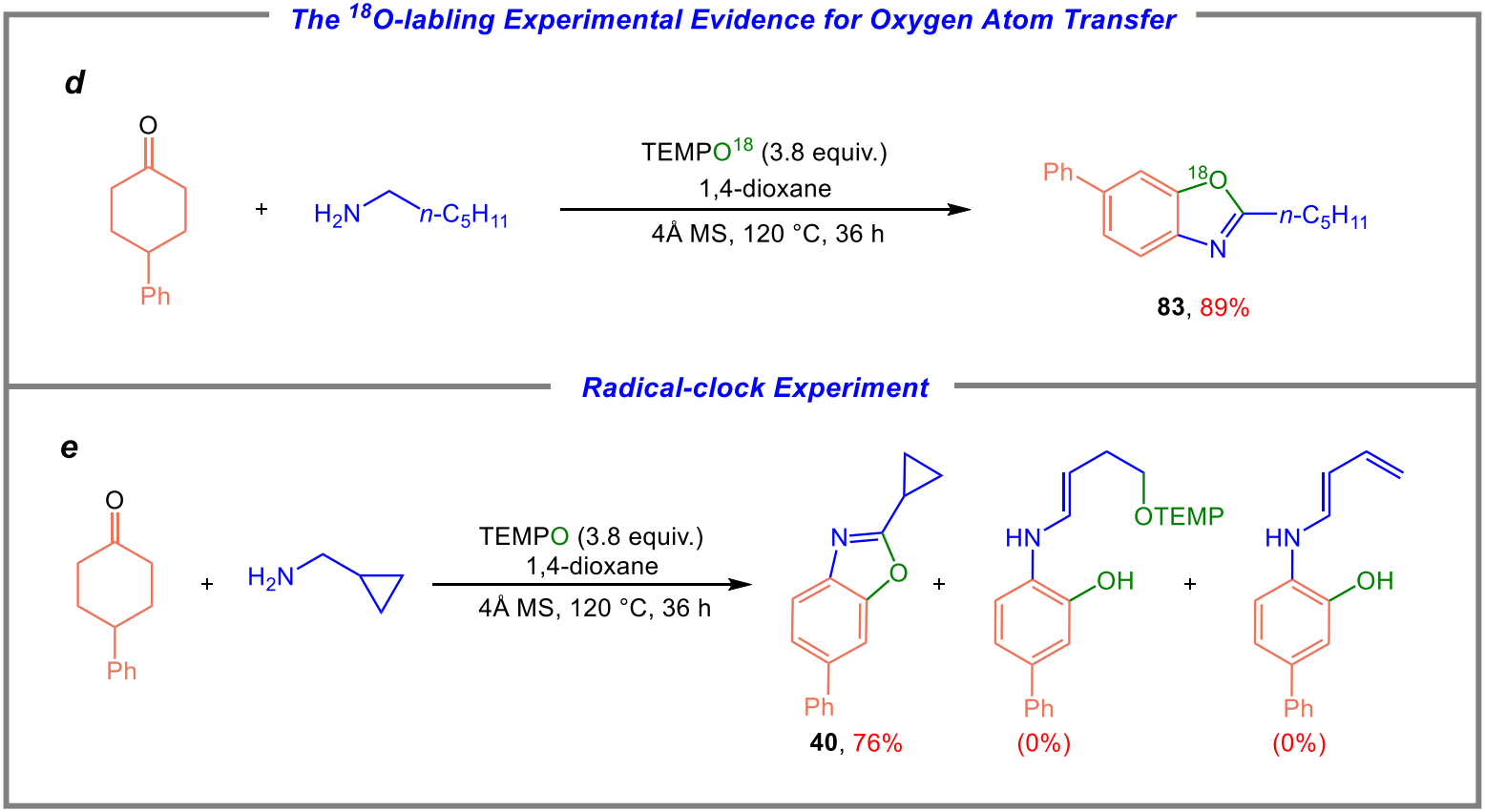
c



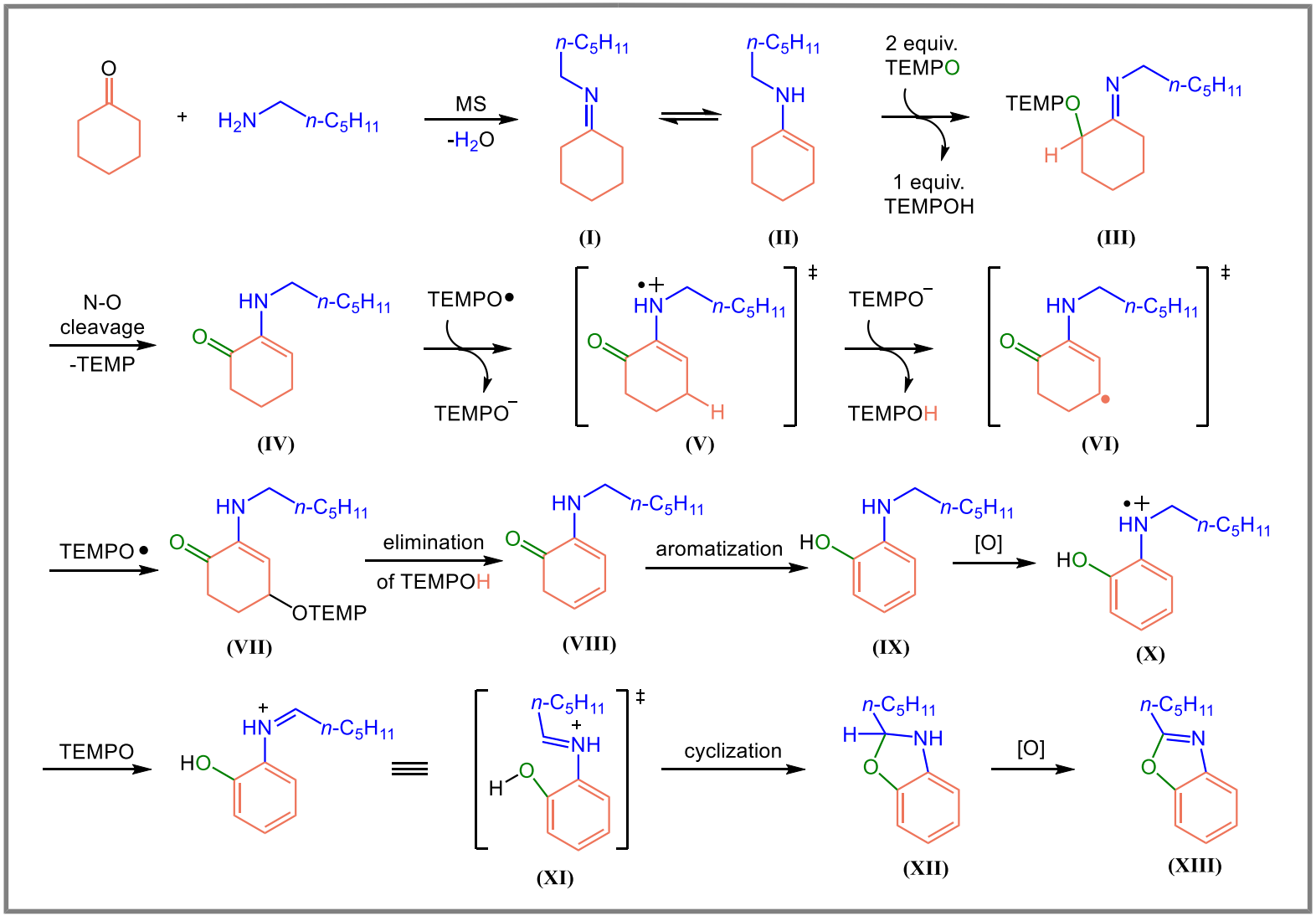
The Reaction Time Course



Experimental Mechanistic Studies

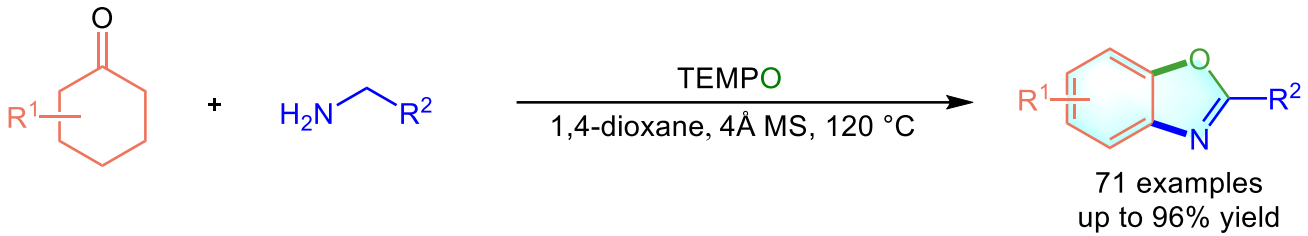


Proposed Mechanism



Summary

Dehydrogenation-driven Coupling Synthesis of Benzoxazoles

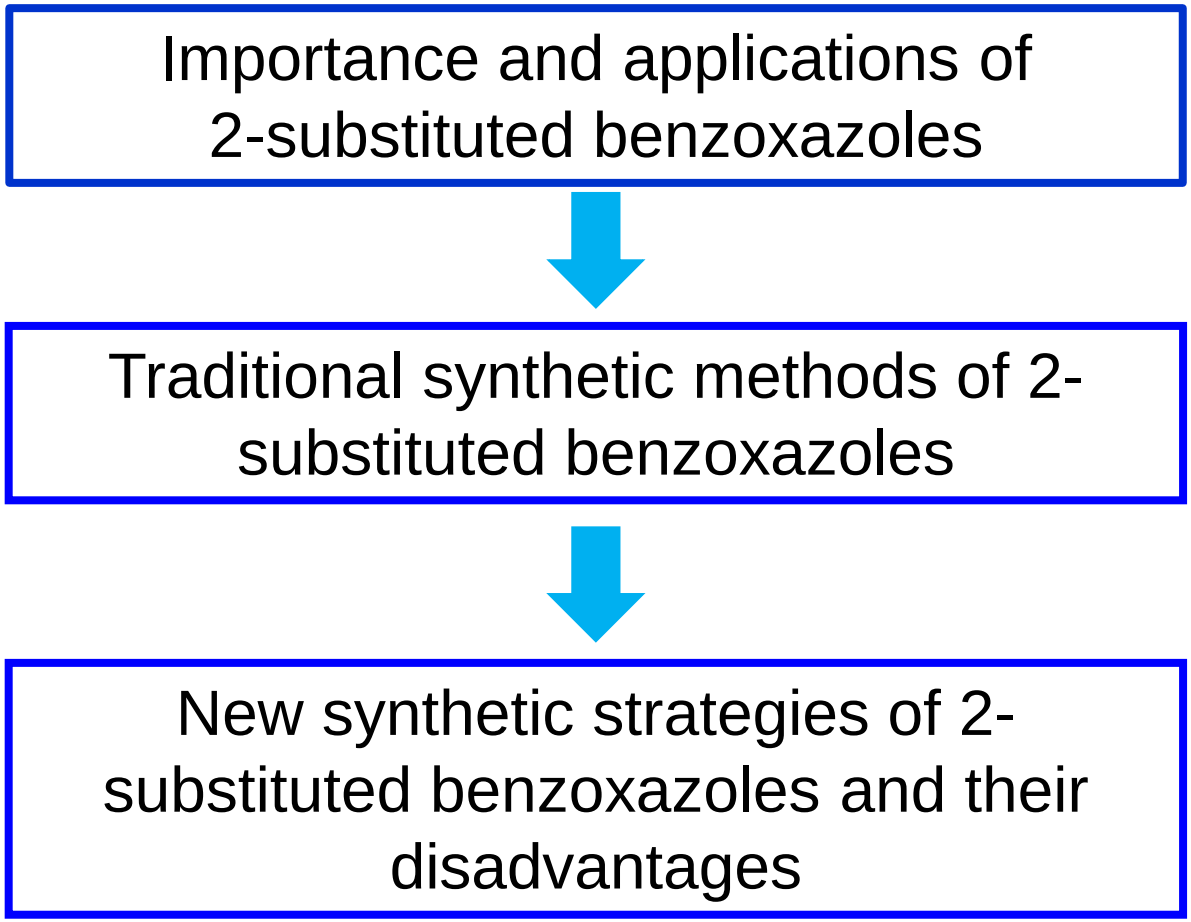


71 examples
up to 96% yield

- Transition metal-free
- Oxygen atom transfer
- Readily available reactants
- High functional groups tolerance
- Orchestration of multiple oxidation steps

- 71 examples
- Good to excellent yields
- Simplified synthesis of drugs and drug candidates
- Late-stage modification of drugs and natural products

Writing Strategy



The First Paragraph

2-Substituted benzoxazoles represents a class of key structural components that are prevalent in various natural products, bioactive compounds and drugs, and intensive efforts have been spurred to develop the methods for syntheses and derivatizations of these compounds. The conventional synthesis of 2-substituted benzoxazoles is the cyclization of 2-aminophenols with carbonyl compounds such as carboxylic acid derivatives or aldehydes, which has promoted the exploration on chemistries and biological activities of benzoxazoles. However, this conventional synthetic method suffers from the limited availability of 2-aminophenols because 2-aminophenols are sensitive to oxygenation.

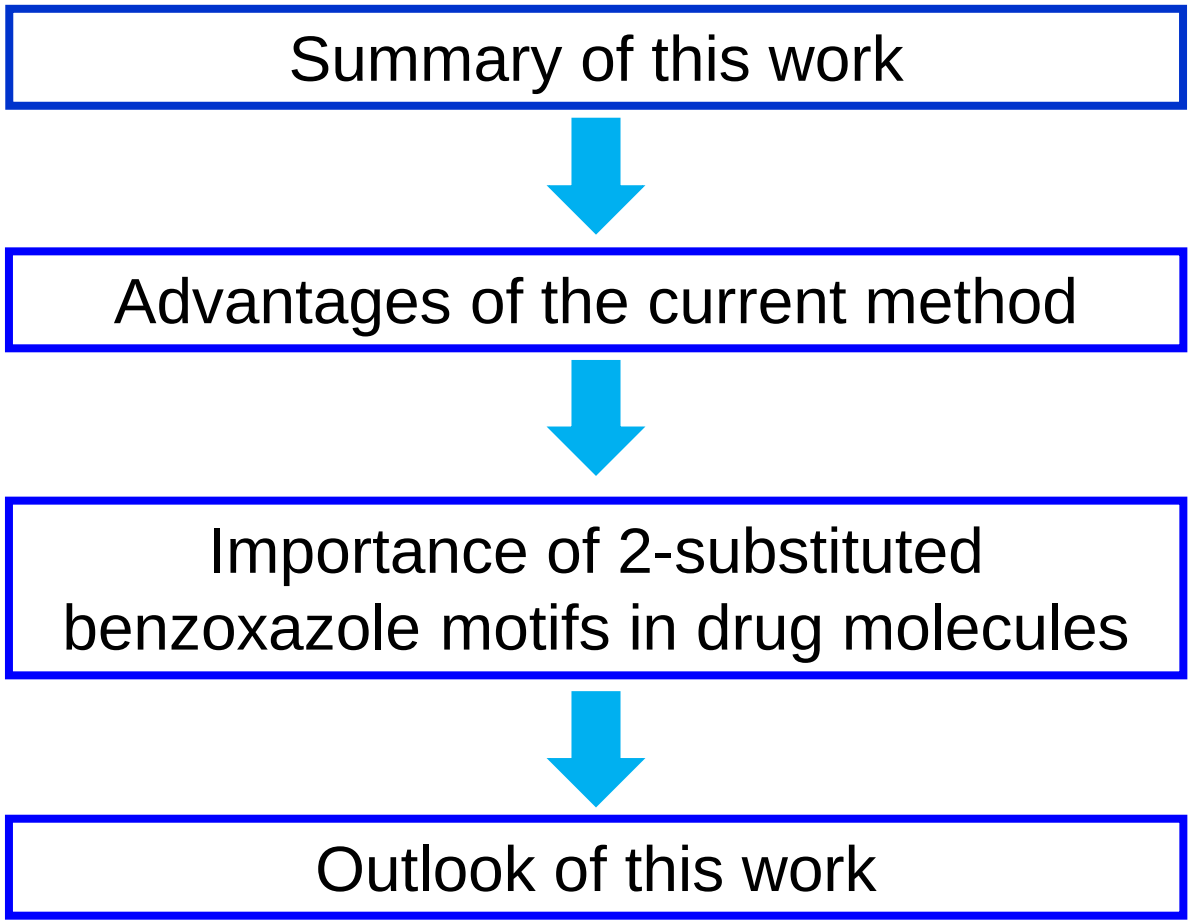
The First Paragraph

Although the metal-catalyzed method for oxidative *ortho*-amination reaction of phenols provides a novel approach to syntheses of 2-substituted benzoxazoles without the need for pre-preparation of 2-aminophenol reactants, currently, such a kind of method only works for a few phenols bearing two bulky substituents on 3- and 5-positions of phenyl ring. Recently, the strategy for transition metal-catalyzed C-H functionalization has been applied to modification of benzoxazoles by introducing substituents at their 2-positions, and synthesis of 2-substituted benzoxazoles via intramolecular C-H bond oxygenation, offering alternative accesses to 2-substituted benzoxazoles. These catalytic methods, nevertheless, require the specific starting materials such as benzanilides and 2-unsubstituted benzoxazoles that are prepared through multistep procedures.

The First Paragraph

To streamline synthesis of valuable 2-substituted benzoxazoles, the development of efficient methods that directly convert simple, readily available starting materials into 2-substituted benzoxazoles by a concise process is highly desired. Such a kind of straightforward method has the potential to bypass the issue regarding substrate limitation encountered in the previously established methods by following the different reaction mechanism, and accelerate the development of the 2-substituted benzoxazole-based pharmaceuticals.

Writing Strategy



The Last Paragraph

A transition metal-free, operationally simple method has been developed for the dehydrogenation-driven coupling reactions between cyclohexanones and aliphatic primary amines via a cascade reaction sequence using TEMPO as a mild oxidant. Owing to the moderate oxidative property of TEMPO under neutral condition, this type of transformations both tolerate the substrates with a broad scope of structural scaffolds and functional groups, thus providing the general methods for streamlined syntheses of structurally complicated but important 2-substituted benzoxazoles from readily available reactants.

The Last Paragraph

Importantly, this method offers straightforward access to the highly complex products that are conventionally unattainable by the existing methods and allows for the late-stage modification of the functionally concentrated drug molecules and natural products. The gram-scale experiments, ready availability and low-cost of reactants show the great potential of this method for discovery and development of 2-substituted benzoxazole-derived drugs, given the prevalence of 2-substituted benzoxazole motifs in drug molecules and bioactive compounds, the scarcity of general methods for rapid syntheses of these compounds.

Representative Examples

To streamline synthesis of valuable 2-substituted benzoxazoles, the development of efficient methods that directly convert simple, readily available starting materials into 2-substituted benzoxazoles by a concise process is highly desired. **(**为了简化…合成**)**

Actually, the α-oxygenation of the imine to α-imino-cyclohexanone is likely interfered by the following two competing processes. **(**受干扰，被影响**)**

The multiple reactivity modes of TEMPO the involved cascade reactions are sequenced and compatible with each other, which is key to achieving the high efficiency in the implementation of this dehydrogenation-driven coupling reaction. (实现高效执行的关键…)

Thanks
for your attention