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Recycling Catalyst as Reactant: A Sustainable Strategy To Improve Atom Efficiency of Organocatalytic Tandem Reactions

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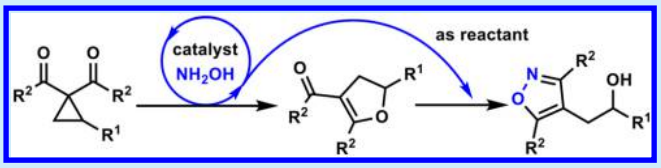
Supporting Information

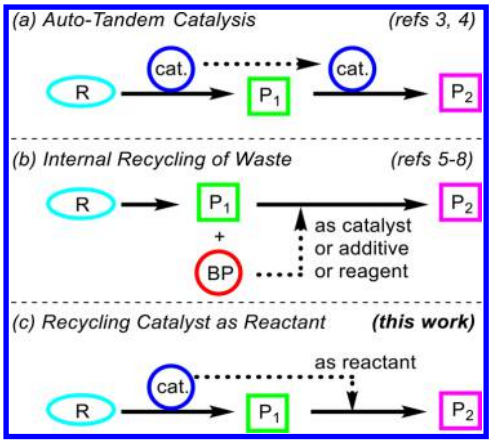
ABSTRACT: A sustainable strategy by internally recycling an organocatalyst as a reactant in a downstream reaction to improve the atom efficiency of organocatalytic tandem reactions is described. Specifically, a one-pot tandem Cloke−Wilson/Boulton−Katritzky reaction of cyclopropylketones with a hydroxylamine has been developed for the synthesis of fully substituted isoxazoles, in which the hydroxylamine serves as both an upstream catalyst and a downstream reactant.



An important goal of synthetic chemistry is to develop green methods that maximize the atom and step economy of organic reactions and minimize the adverse environmental effects.[1] Toward this end, tandem reactions,[2] in which multiple reactions are combined into one operation, have been extensively investigated to enhance the efficiency of the chemical process. The convergent nature of tandem reactions also provides an opportunity for achieving the multifaceted use of the catalysts or reagents to further improve the atom efficiency of the process. For example, the "auto-tandem catalysis"[3] involving a single catalyst to facilitate two or more distinct chemical transformations in a single flask has been applied in a large number of tandem reactions showing great synthetic utility (Scheme 1a).[4] A sustainable strategy of "internal recycling of waste"[5] has also been developed in which the byproduct of a stoichiometric reaction is recycled as a catalyst,[6] additive,[7] or reagent[8] for the following steps (Scheme 1b). Particularly, Shibasaki,[7f] Zhou,[6d,g,7a,c] and Toy[6h,j] have developed sustainable processes based on the Wittig reaction by utilizing the phosphine oxide byproduct to promote an array of downstream transformations. Loh[6o] and Alaimo[6n] have demonstrated that In^0-mediated processes (e.g., Barbier reaction) could be integrated with reactions using an in situ generated In^{III} byproduct as a Lewis acid catalyst. Wu and co-workers[6c,f,i,l] have reported the combination of I_2-mediated iodination of ketones with downstream reactions that were catalyzed by the thus-formed iodine species (e.g., HI, CuI). Recently, a sustainable Mo-catalyzed reduction/annulation process of nitrobenzenes with glycols has been demonstrated by Sanz and co-workers[8a,d] for the synthesis of nitrogenated heterocycles, in which the reduction byproducts of glycols, i.e. aldehydes or ketones, are internally incorporated into the final product. Despite this progress, new strategies to improve the atom efficiency of tandem reactions are still of essential importance.

Organocatalysis[9] has been established as a pivotal methodology due to its versatility and metal-free green nature. Various manifolds of organocatalysis such as nucleophilic catalysis,[10] enamine catalysis,[11] iminium catalysis,[12] NHC catalysis,[13] and Brønsted acid catalysis[14] have flourished in recent decades. In spite of their efficiency,[15] an arguable disadvantage of organocatalysis is the frequent requirement of a high catalyst loading (typically 20 mol %), which compromises the overall atom efficiency and limits its large-scale application in industry. Although several methods for addressing this issue have been attempted, such as recycling[16] and immobilization[17] of the catalyst, the fundamental inefficiency remains. As part of our interest in organocatalysis,[18] we herein report a new sustainable strategy of "recycling the catalyst as the reactant" that internally reuses the organocatalyst as a reactant in a downstream reaction (Scheme 1c). The strategy has the potential to improve the atom efficiency of tandem processes,

Scheme 1. Sustainable Strategies for Tandem Reactions



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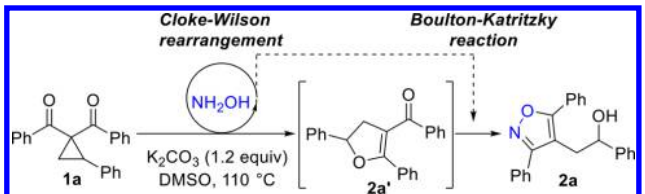
and also circumvents the concern of a large catalyst loading in organocatalysis since all catalyst material is incorporated into the final product. Furthermore, the capacity to use relatively simple and less reactive organocatalysts can be realized, since stoichiometric quantities of reagent compensate for reduced catalytic activity.

In light of our recent studies of organocatalytic ring-opening reactions of cyclopropanes,[18a,b] we envisaged that simple and inexpensive hydroxylamine could not only catalyze the Cloke–Wilson rearrangement[19] of cyclopropylketones, but also promote a subsequent Boulton–Katritzky reaction[20] of the resulting dihydrofurans to finally afford isoxazole products (Scheme 2). Gratifyingly, these two distinct transformations

Scheme 2. Initial Investigation



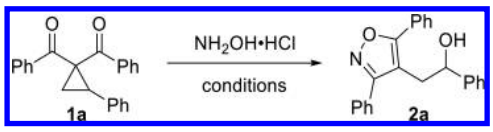
entry	$NH_2OH{\cdot}HCl$	yield of **2a'**	yield of **2a**
1	0.2 equiv	77%	12%
2	1.0 equiv	0%	66%

could be successfully converged into one pot. When cyclopropylketone **1a** was treated with a catalytic amount of hydroxylamine (20 mol %) at 110 °C in DMSO, the reaction produced the dihydrofuran **2a′** in 77% yield together with the desired isoxazole **2a** in 12% yield (Scheme 2, entry 1). Under identical conditions with a stoichiometric amount of hydroxylamine, the reaction produced **2a** in 66% yield as the sole product (Scheme 2, entry 2).[21] Thus, the transformation involves a seamless integration of two reactions utilizing hydroxylamine as both catalyst and reactant, respectively, which presents a new sustainable strategy for tandem reactions.

On the basis of these encouraging results, the conditions of the Cloke–Wilson/Boulton–Katritzky reaction were optimized (Table 1). Among several common bases tested, K_2CO_3 still emerged as the best (entries 1–6). Solvent screening indicated that DMSO was crucial to the reaction, as THF, CH_2Cl_2, CH_3CN, CH_3OH, 1,4-dioxane, and DMF all provided very poor yields (entries 7–12). A survey of temperature found substantially lower yields at a reduced temperature of 90 or 70 °C and an improved yield of 72% at 130 °C (entries 13–15). When the amount of $NH_2OH{\cdot}HCl$ and K_2CO_3 was increased, the yield could be enhanced to 91% (entry 16). Finally, the yield of **2a** could be further improved to 93% when $NH_2OH{\cdot}HCl$ and K_2CO_3 were introduced in two time-separated additions (entry 17). Thus, the optimized condition consists of heating cyclopropylketones at 130 °C in DMSO with 2.0 equiv of $NH_2OH{\cdot}HCl$ and 2.4 equiv of K_2CO_3 added in two portions.

Utilizing these conditions, the scope of the tandem Cloke–Wilson/Boulton–Katritzky reaction was probed (Scheme 3). First, a range of cyclopropylketones bearing various aromatic substitutions (R^1, R^2 = aryl) proved to work well in the tandem reaction, giving the desired isoxazoles **2a–h** in good to excellent yields (65–97%). The product structure was unequivocally established by X-ray crystallography (for **2c**, CCDC: 1861088; **2f**, CCDC: 1861089; see Supporting

Table 1. Optimization on Reaction Conditions[a]



entry	base/equiv	equiv of $NH_2OH{\cdot}HCl$	solvent	temp (°C)	yield[b] (%)
1	K_2CO_3/1.2	1.0	DMSO	110	66
2	Na_2CO_3/1.2	1.0	DMSO	110	60
3	Cs_2CO_3/1.2	1.0	DMSO	110	45
4	DBU/1.2	1.0	DMSO	110	46
5	K_3PO_4/1.2	1.0	DMSO	110	10
6	^{t}BuOK/1.2	1.0	DMSO	110	trace
7	K_2CO_3/1.2	1.0	THF	reflux	trace
8	K_2CO_3/1.2	1.0	CH_2Cl_2	reflux	trace
9	K_2CO_3/1.2	1.0	CH_3CN	reflux	trace
10	K_2CO_3/1.2	1.0	CH_3OH	reflux	<5
11	K_2CO_3/1.2	1.0	dioxane	60	trace
12	K_2CO_3/1.2	1.0	DMF	110	trace
13	K_2CO_3/1.2	1.0	DMSO	70	trace
14	K_2CO_3/1.2	1.0	DMSO	90	38
15	K_2CO_3/1.2	1.0	DMSO	130	72
16	K_2CO_3/2.4	2.0	DMSO	130	91
17[c]	K_2CO_3/2.4	2.0	DMSO	130	93

[a]Under N_2 and at indicated temperature, to a solution of **1a** (0.2 mmol) in the solvent (2.0 mL) were added the base and $NH_2OH{\cdot}HCl$, and the mixture was stirred for 24 h. [b]Isolated yield. [c]K_2CO_3 and $NH_2OH{\cdot}HCl$ were added in two portions in 20% and 80%, respectively, over 24 h interval.

Information). Vinyl substituted cyclopropylketones (R^1 = vinyl) were also effective which produced the corresponding allylic alcohol products **2i–n** in 40–78% yields. Substrates containing aliphatic ketones (R^2 = Me) were well tolerated in these cases. In addition, alkyl substituted cyclopropylketones (R^1 = Me) were competent providing isoxazoles **2o–q** in good yields (56–78%) under our standard conditions. Furthermore, nonsubstituted cyclopropylketones (R^1 = H) also reacted smoothly to afford products **2r–t** bearing a primary alcohol in high yields (79–90%). Of note, cyclopropylketone **1u**, bearing two different ketone moieties, delivered a pair of regioisomeric isoxazoles **2u** and **2u′** in a 3:1 ratio and 55% combined yield. Taken together, the above results suggest a broad scope of the tandem Cloke–Wilson/Boulton–Katritzky reaction, which includes aryl-, alkyl-, vinyl-, and nonsubstituted cyclopropylketones featuring either aromatic or aliphatic ketones. To demonstrate the practicality, a scale-up reaction of **1a** (3.0 mmol) was conducted which afforded the product **2a** in 0.76 g, 78% yield.

Subsequently, we probed the possibility of using hydrazine as both a catalyst and reactant to mediate the Cloke–Wilson/Boulton–Katritzky reaction of cyclopropylketones to generate the corresponding pyrazoles. However, this attempt was not successful because hydrazine failed to catalyze the Cloke–Wilson rearrangement. Alternatively, when DABCO was employed as the organocatalyst, the desired pyrazoles **3** could be generated in one pot in excellent yields from representative cyclopropylketones **1** (Scheme 4). This result, however, corroborates the dual role of hydroxylamine as both catalyst and reactant in the Cloke–Wilson/Boulton–Katritzky reaction.

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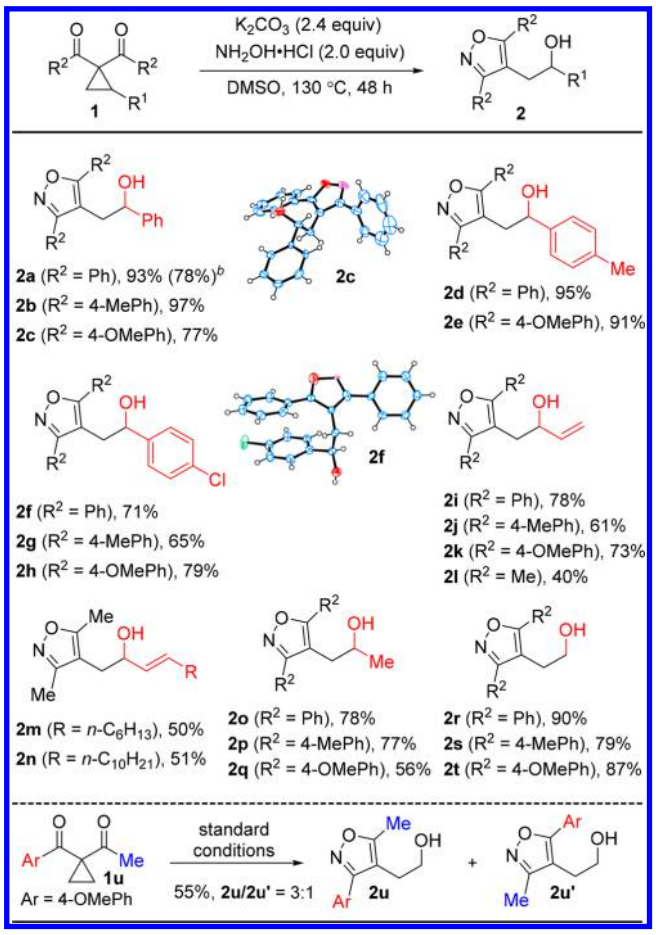
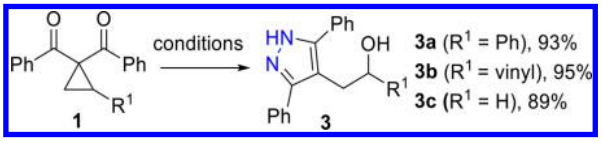
Scheme 3. Substrate Scope[a]



[a]Under N_2 and at 130 °C, to a solution of cyclopropylketone **1** (0.2 mmol) in DMSO (2.0 mL) were added $NH_2OH{\cdot}HCl$ (0.04 mmol) and K_2CO_3 (0.04 mmol). After the mixture stirred for 24 h, remaining $NH_2OH{\cdot}HCl$ (0.36 mmol) and K_2CO_3 (0.44 mmol) were added, and the mixture was stirred for an additional 24 h. [b]Yield from 3.0 mmol scale.

Scheme 4. One-Pot Synthesis of Pyrazoles 3[a]

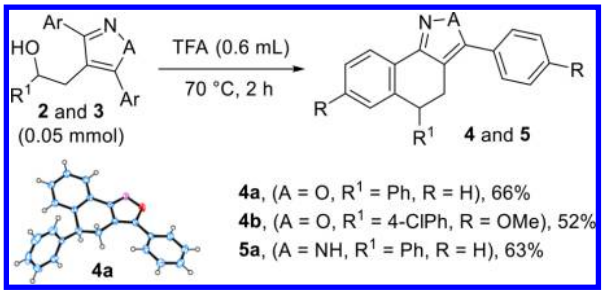


[a]Conditions: DABCO (0.5 equiv), DMSO, 120 °C, 24 h, then $NH_2NH_2{\cdot}H_2O$ (2.0 equiv), K_2CO_3 (2.4 equiv), 24 h.

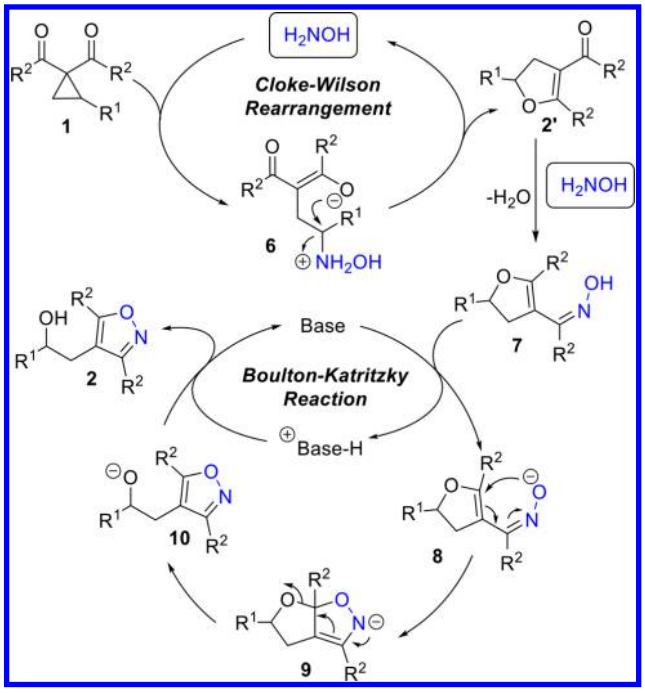
Isoxazoles[22] and pyrazoles[23] are privileged heterocycles embedded in a large number of biologically active molecules and pharmaceuticals. The above Cloke–Wilson/Boulton–Katritzky reactions thus provide an efficient and convenient route to these hetereocycles. The homobenzylic alcohol unit of the products offers a good opportunity for further elaboration. To demonstrate the potential, Friedel–Crafts alkylations of the products in the presence of TFA[24] were achieved to access tricyclic skeletons **4** and **5** in good yields (Scheme 5). The structure of **4a** was confirmed by X-ray crystallography (CCDC: 1861090).

A plausible mechanism for the Cloke–Wilson/Boulton–Katritzky tandem reaction is proposed in Scheme 6. For the initial Cloke–Wilson rearrangement,[18b] nucleophilic attack of

Scheme 5. Elaboration of Products for the Synthesis of Tricyclic Heterocycles



Scheme 6. Proposed Mechanism



NH_2OH on cyclopropane **1** via a homoconjugate addition pathway[25] produces an enolate intermediate **6**. The anion then undergoes a favorable 5-*exo*-tet cyclization to give the dihydrofuran **2′** and release the NH_2OH catalyst. The subsequent Boulton–Katritzky reaction initiates when NH_2OH acts as a reactant to condense with the dihydrofuran **2′** to afford oxime **7**, which is deprotonated by a catalytic amount of base (e.g., K_2CO_3) to give intermediate **8**. Cyclization then occurs to generate **9**, which undergoes fragmentation and protonation to afford the aromatic heterocycle **2**. The isolation of intermediate **2a′**, as shown in Scheme 2, entry 1, suggests the rate of the Cloke–Wilson rearrangement should be significantly faster than the downstream Boulton–Katritzky reaction.

In summary, we have described a new sustainable strategy of "recycling catalyst as reactant" which holds great promise for improving the atom efficiency of organocatalytic tandem reactions. Specifically, a hydroxylamine-mediated Cloke–Wilson/Boulton–Katritzky reaction of cyclopropylketones has been developed for the efficient assembly of fully substituted isoxazoles, wherein the hydroxylamine serves as both the catalyst for the Cloke–Wilson rearrangement and a reactant for the downstream Bouton–Katritzky reaction. By recovering the catalyst as a reactant, the strategy may

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circumvent the concern of a high catalyst loading of organocatalysis. In addition, utilizing stoichiometric amounts of catalyst allows the use of relatively simple and less reactive organocatalysts to promote the reaction. Efforts are underway in our laboratory to evaluate this strategy in other tandem organocatalytic reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02898.

Experimental procedures, analytical data, NMR spectra, and crystallographic information (PDF)

Accession Codes

CCDC 1861088−1861090 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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