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A cascade approach to fused indolizinones through Lewis acid–copper(I) relay catalysis†

Cite this: DOI: 10.1039/c3cc40643a

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Received 25th January 2013,
Accepted 5th March 2013

DOI: 10.1039/c3cc40643a

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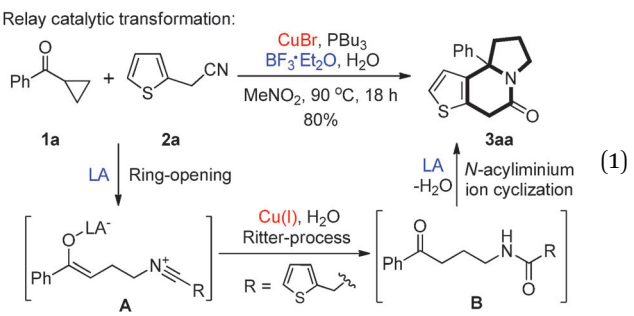
A relay catalytic cascade process involving Lewis acid triggered ring-opening of cyclopropyl ketones with nitriles, the copper(I)-catalyzed Ritter process, and acid-promoted *N*-acyliminium ion cyclization is described, which efficiently provides thieno-, furano-, and benzo-indolizinones in moderate to good yields.

The indolizine structural motif forms the core of many natural products, pharmaceuticals, and functional materials.[1,2] In particular, ring-fused indolizidines[3] represent an important class of bioactive compounds, such as crispine A,[3g] a phenyl-fused indolizidine with cytotoxic activity against HeLa human cancer cell lines, and cocculolidine,[3i] a polycyclic alkaloid possessing insecticidal and antihypertensive activities. Other well-known examples also include bioactive harmicine[3h] and mearsamine.[3j] Because of the structural diversity and the broad range of biological activities, extensive efforts have been directed toward the synthesis of indolizidines in the past decades, and a number of methods have been reported.[4] For instance, *N*-acyliminium ion cyclizations[5] have provided direct access to benzo-,[5a–d] indolo-,[5e,f] and thieno-indolizidines.[5g,h] Yet, a mild and general approach for the construction of bicyclic indolizidine scaffolds from easy-to-assemble substrates in one single operation is still of great interest. In this context, a cascade approach involving *in situ* preparation of the precursors by relay catalytic transformation to the biologically important indolizidines would be very meaningful, offering opportunities to achieve desirable synthetic convergence, flexibility and improve overall efficiency.

On the other hand, donor–acceptor (D–A) cyclopropanes have attracted much attention as flexible building blocks owing to their controllable reactivity and selectivity.[6] Recently, a diversity of heterocyclic compounds have been accessed *via* Lewis acid-catalyzed cycloadditions of D–A cyclopropanes with unsaturated partners, such as aldehydes,[7] imines,[8] nitriles,[9] and nitrones.[10] Synthesis of pyran and pyrrole derivatives *via* [3+3] cycloaddition of D–A cyclopropanes with propargyl alcohols and propargyl amines has also been reported.[11] Meanwhile, cyclopropyl ketones were found to be efficient four-carbon building blocks to construct heterocycles.[12] While intermolecular reactions of D–A cyclopropanes and other reagents for mono-heterocycles have been intensively investigated, few examples designed towards polycyclic patterns,[13] although some intramolecular reactions affording polycyclic heterocycle products have been known.[14] Herein, we describe a binary catalytic system consisting of a Lewis acid and a copper(I) catalyst for construction of fused indolizinone compounds. The proposed sequential transformation involves a three step relay catalysis, where (i) ring-opening reaction of cyclopropane **1a** with nitrile **2a** is trigged by Lewis acid; (ii) a subsequent Ritter process to obtain an amine intermediate **B** is relayed by a copper(I) complex; and (iii) the catalytic sequence is terminated by *N*-acyliminium ion cyclization under the influence of the Lewis acid catalyst, affording indolizinone **3aa** in 80% yield [eqn (1)]. The present method would enable the generation of reactive precursors **B**, thus allowing efficient synthesis of fused indolizinones from readily available cyclopropyl ketones and nitriles in a one-pot reaction.



(1)

A broad range of cyclopropyl ketones and nitriles were investigated to afford fused indolizinone compounds under the optimized conditions.[15] As shown in Table 1, the phenyl cyclopropyl ketones reacted smoothly with **2a** to give the corresponding thieno-fused indolizinones in excellent yields (**3aa**–**3ga**), allowing –F, –Cl, $–CF_3$, and methyl substituents on the phenyl group to be tolerated. Cyclopropyl naphthalen-1-yl ketone also transformed into the corresponding product in 55% yield. However,

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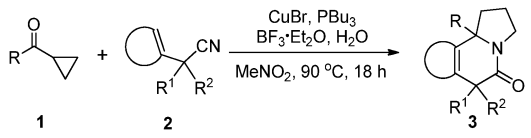
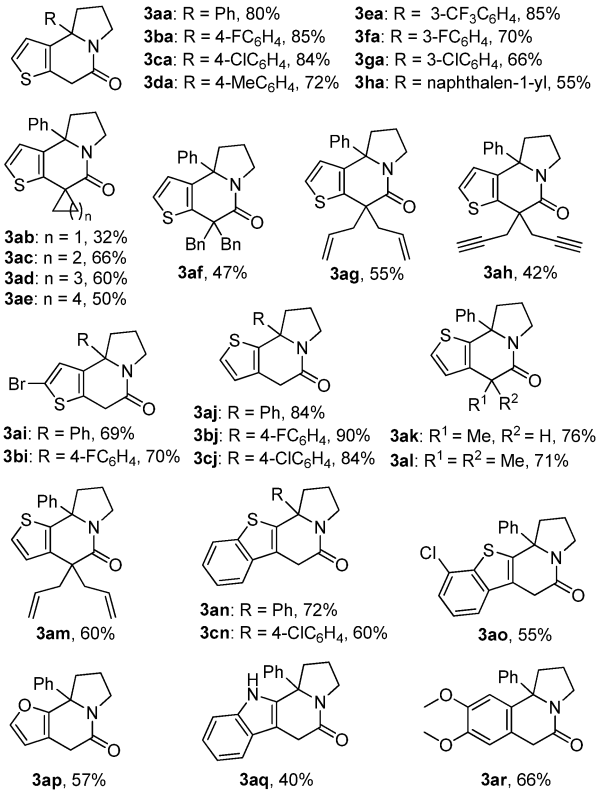
† Electronic supplementary information (ESI) available. CCDC 873749. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc40643a

Table 1 Substrate scope of the binary catalytic reaction[a]



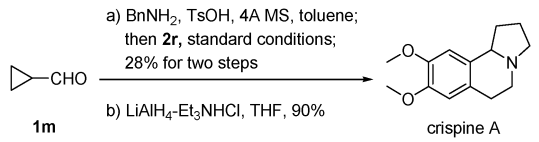


[a] *Reaction conditions*: **1** (0.2 mmol), **2** (1.2 equiv.), $BF_3{\cdot}Et_2O$ (1 equiv.), CuBr (5 mol%), and PBu_3 (10 mol%) in solvent (1.5 mL) under air at 90 °C for 18 h.

cyclopropyl-, methyl- and bicyclopropyl-ketone did not work in this reaction system. Interestingly, instead of the desired products, both 1-acetyl-1-benzoylcyclopropane and 1,1-dibenzoylcyclopropane exclusively afforded **3aa** with deacetylation and debenzoylation, respectively.[15]

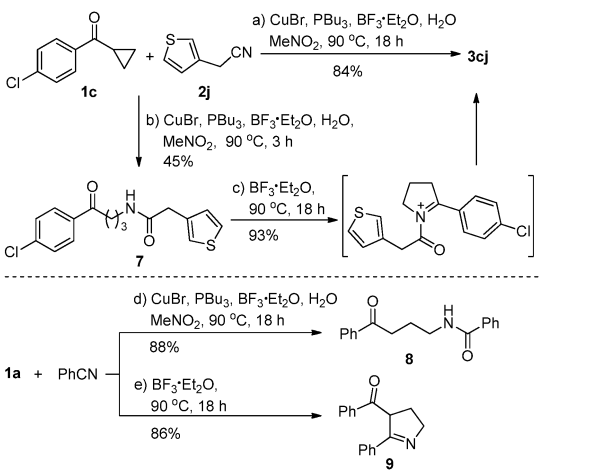
The substrate scope of this transformation was further expanded to different kinds of nitriles (Table 1). Various substituents at the α-position of 2-(thiophen-2-yl)acetonitriles, such as alkyl, benzyl, allyl, and propargyl groups were tolerated well, allowing the generation of a range of indolizinone moieties in good yields (**3ab–3ah**), including spiro-indolizinone derivatives (**3ab–3ae**). Also, bromine substitution at the 5-position of thiophene was tolerated (**3ai–3bi**). It should be noted that 2-(thiophen-3-yl)-acetonitriles showed similar reactivity in this reaction system, affording the expected thieno-indolizinones **3aj–3am** in good yields. Replacement of 2-thiophenylacetonitriles with 2-(benzo[*b*]-thiophen-3-yl)acetonitriles smoothly led to the corresponding tetracyclic products **3an–3ao**. In addition, the furan analogue was also productive and led to 57% yield of the furano-indolizinone **3ap**. The product **3aq** derived from 2-(1*H*-indol-3-yl)acetonitrile was detected using GC-MS in 40% yield, however, no product could be obtained after flash column chromatography even with basic alumina, which was probably due to the instability of this compound. Gratifyingly, 2-(3,4-dimethoxyphenyl)acetonitrile (**2r**) could be used to deliver the benzo-indolizinone **3ar** in 66% yield.

The ready access to the fused indolizinone derivatives through this chemistry offers a new strategy for many biologically interesting compounds. For example, the skeleton of crispine A[3g] is highly consistent with the product **3ar**. Considering that the phenyl group was not an ideal leaving group, we first subjected cyclopropyl carbaldehyde **1m** to this transformation, however, no desired product was detected. The employment of cyclopropyl amide and benzyl 2-cyclopropyl-2-oxoacetate was also unfruitful. After much experimentation, we finally found that aldimine, with the carbonyl group of **1m** protected by benzylamine, when treated with nitrile **2r** under the standard reaction conditions, could successfully afford 3,4-dimethoxyphenyl indolizinone, which was efficiently reduced to the target crispine A by lithium aluminum hydride [eqn (2)].



(2)

To shed light on the reaction mechanism, several control experiments were conducted (Scheme 1). Treatment of **1c** and **2j** with $BF_3{\cdot}Et_2O$, CuBr, and PBu_3 led to acyclic product **7** within 3 h (Scheme 1b), which could be further transformed to **3cj** in 93% yield in the presence of $BF_3{\cdot}Et_2O$ at 90 °C for 18 h *via* *N*-acyliminium ion cyclization (Scheme 1c). Moreover, when cyclopropyl ketone **1a** and benzonitrile were subjected to the standard reaction conditions, the Ritter product **8** was obtained (Scheme 1d), whereas a simple combination of **1a**, benzonitrile and $BF_3{\cdot}Et_2O$, with no addition of copper(I) and phosphine, exclusively afforded the [3 + 2] cycloaddition product **9** in 86% yield[16] (Scheme 1e). Thus, these results clarified the Lewis acid–copper(I) relay catalytic sequence of the cascade reaction and indicated that the copper(I) catalyst played an important role in the Ritter process rather than in the ring-opening of cyclopropanes or the *N*-acyliminium ion cyclization.[17]



Scheme 1 Control experiments.

In summary, we have developed a novel, efficient synthesis of fused indolizinones from cyclopropyl ketones and nitriles using a Lewis acid–copper(I) binary catalytic system, which involves the Lewis acid-triggered ring-opening reaction of cyclopropyl ketones with nitriles, copper(I)-catalyzed Ritter process, and acid-promoted *N*-acyliminium ion cyclization sequence. This protocol features a broad substrate scope and excellent functional-group tolerance and shows potential capabilities to construct complex molecules in synthetic and pharmaceutical chemistry, as notably bioactive crispine A was successfully synthesized in two steps with comparable overall yield by the key transformation. Further studies on the asymmetric version of this methodology are currently in progress and will be reported in due course.

This work was supported by the National Natural Science Foundation of China (20932002 and 21172076), the National Basic Research Program of China (973 Program) (2011CB808600), the Guangdong Natural Science Foundation (10351064101000000) and the Fundamental Research Funds for the Central Universities (2010ZP0003).

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15 See ESI† for details.

16 GC yield is given as the cycloaddition product **9** is sensitive to air. **1a** was completely recovered in the absence of $BF_3{\cdot}Et_2O$, suggesting ring-opening of cyclopropane would be trigged by $BF_3{\cdot}Et_2O$.

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