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Copper(I)/Lewis Acid Triggered Ring-Opening Coupling Reaction of Cyclopropenes with Nitriles

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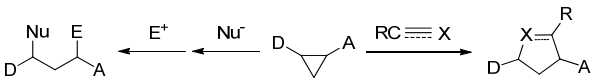
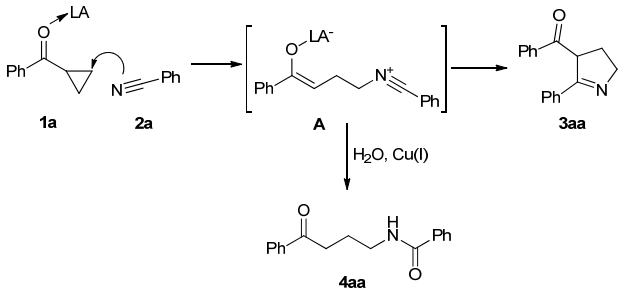
A ring-opening coupling reaction of D–A cyclopropenes and nitriles is described for the facile synthesis of γ-amino ketones. The copper(I)/Lewis acid co-catalytic system would be inspiring since it disfavors [3+2] cycloaddition to turn the selectivity over Ritter process.

In last decade, two popular ways of crucial transformations of donor–acceptor (D–A) cyclopropanes en route to more sophisticated molecules were cycloaddition with unsaturated compounds such as alkynes, alkenes, aldehydes, and imines, and ring-opening coupling process with other active partners (Scheme 1).[1] Lewis acid-catalyzed [3+2][2] and [3+3][3] cycloaddition of cyclopropanes bearing a malonyl diester acceptor group with unsaturated compounds has been intensively studied for use in the preparation of useful five- and six-membered-ring compounds, although some cycloaddition reactions of other type of cyclopropanes, such as cyclopropyl ketones,[4] amides,[5] amines,[6] and vinylcyclopropanes[7] etc., were known. However, of them ring-opening reactions of cyclopropyl ketones generally proceeded under strong acidic conditions probably because of the relative low-energy HOMO of this species.



Scheme 1 Cycloaddition and ring-opening coupling reaction of D–A cyclopropanes.

Ring-opening coupling reaction of cyclopropane plays important role in synthetic chemistry to provide chain products which are hardly obtained by traditional route.[8] Herein, we report Lewis acid and copper(I)-promoted ring-opening coupling reaction of cyclopropyl ketones with nitriles for the facile Ritter synthesis of γ-amino ketones,which usually used to be linker groups in preparation of active pharmaceuticals and agrochemicals.[9]



Scheme 2 Cycloadditon and ring-opening coupling of cyclopropyl ketone with nitrile.

Cyclopropyl ketone (**1a**) and benzonitrile (**2a**) were chosen as the model substrates (Scheme 2). On the assumption that intermediate A is generated by intermolecular nucleophilic attack of **2a** to the Lewis acid-activated **1a**, the subsequent intramolecular 1–5 nucleophilic cyclization gives [3+2] cycloaddition product **3aa**,[10] otherwise the intermediate A reacts with water to give the ring-opened Ritter product **4aa**.[10c] Further investigation, however, indicates that water is not the crucial fact for the selectivity and interestingly the reaction is enhanced with copper(I) catalyst exclusively giving the ring-opened Ritter reaction product. Mechanistically, we envisioned that the coordination interaction that may arise between the transition metal and intermediate **A** has disfavored intramolecular 1–5 nucleophilic cyclization of **A** to turn the selectivity over Ritter process.

To optimize the reaction conditions, several Lewis acids, such as $AlClMe_2$, $Sn(OTf)_2$, and $SnCl_4$, were firstly subjected to this ring-opening reaction, and it was found that neither **3aa** nor **4aa** was detected when the reaction was performed at room temperature (Table 1, entries 1–2). Higher reaction temperature gave low yield of **3aa**, with over 50% of **1a** recovered (Table 1, entries 3–4), suggesting that this reaction requires increased Lewis acidity to active the cyclopropane. $BF_3{\cdot}Et_2O$-mediated reaction gave

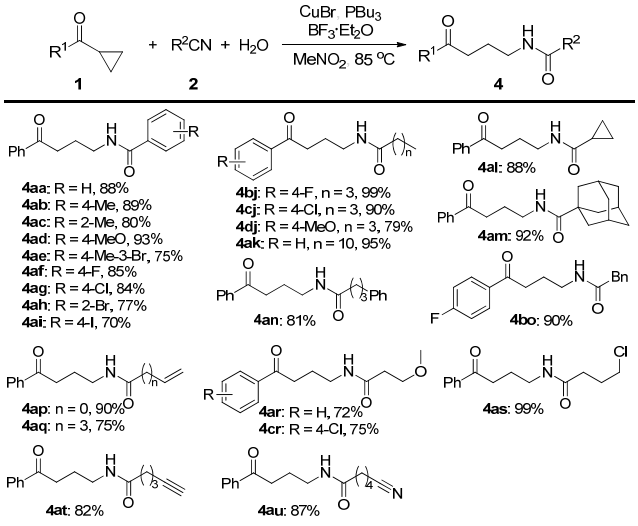
significant yield enhancement for cycloaddition product (Table 1, entry 5). Medium testing showed that nitromethane was greater than others although a little yield of chain product was obtained, and this reaction was found to be optimal at 85 °C (Table 1, entries 6-8).

Table 1 Optimization of reaction conditions.[a]

Entry	Lewis acid	Cat.	H_2O (equiv)	Solvent	Temp (°C)	Yield (%)[b] 3aa	4aa
1	$AlClMe_2$	-	-	THF	rt	n.d.	n.d.
2	$Sn(OTf)_2$	-	-	CH_2Cl_2	rt	n.d.	n.d.
3	$Sn(OTf)_2$	-	-	$(CH_2)_2Cl_2$	80	22	n.d.
4	$SnCl_4$	-	-	$(CH_2)_2Cl_2$	80	19	n.d.
5	$BF_3{\cdot}Et_2O$	-	-	$(CH_2)_2Cl_2$	80	68	n.d.
6	$BF_3{\cdot}Et_2O$	-	-	$MeNO_2$	80	80	<5
7	$BF_3{\cdot}Et_2O$	-	-	$MeNO_2$	85	82	<5
8	$BF_3{\cdot}Et_2O$	-	-	$MeNO_2$	90	82	<5
9	$BF_3{\cdot}Et_2O$	-	1	$MeNO_2$	85	80	<5
10	$BF_3{\cdot}Et_2O$	-	4	$MeNO_2$	85	79	8
11	$BF_3{\cdot}Et_2O$	CuI	1	$MeNO_2$	85	15	42
12	$BF_3{\cdot}Et_2O$	CuBr	1	$MeNO_2$	85	8	56
13	$BF_3{\cdot}Et_2O$	CuCl	1	$MeNO_2$	85	6	50
14	$BF_3{\cdot}Et_2O$	$CuCl_2$	1	$MeNO_2$	85	54	n.d.
15[c]	$BF_3{\cdot}Et_2O$	CuBr	1	$MeNO_2$	85	9	61
16[d]	$BF_3{\cdot}Et_2O$	CuBr	1	$MeNO_2$	85	8	85
17[e]	$BF_3{\cdot}Et_2O$	CuBr	1	$MeNO_2$	85	5	92

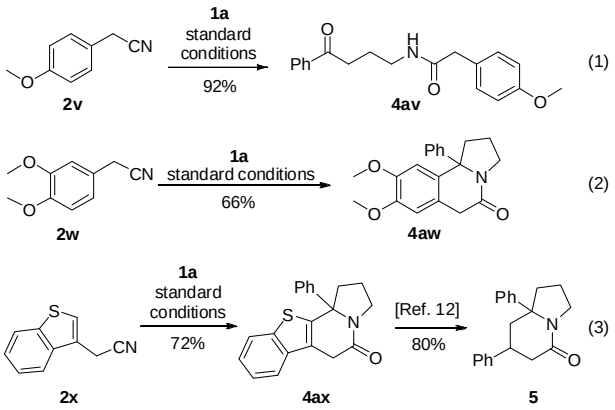
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (3.0 equiv), Lewis acid (1 equiv), catalyst (5 mol%), water in solvent (1.5 mL) for 18 h. [b] GC yield based on **1a** was given. n.d. means no product was detected. [c] With addition of PPh_3 (10 mol%). [d] With addition of P(*p*-Me-C_6H_4)$_3$ (10 mol%). [e] With addition of PBu_3 (10 mol%).

After establishing the capability of $BF_3{\cdot}Et_2O$ for ring-opening of cyclopropyl ketones, we presumed that addition of water was competent for the Ritter reaction product, but that was not the case even with four equivalents of water (Table 1, entries 9 and 10). Our first success in reversing the selectivity was found with copper(I) catalysts that favored the ring-opened Ritter reaction product (Table 1, entries 11–13). By way of contrast copper(II) did not work for **4aa** (Table 1, entry 14), indeed indicating that the reaction forming amide was not conventional Ritter process. Finally, we tried different ligands and found electron-rich tributylphosphine was optimal for the reaction affording **4aa** in 92% yield (Table 1, entries 15–17), which may be complained by the increased stability of copper complex intermediate.



Scheme 3 The scope of the substrates for the synthesis of γ-amino ketones. Reaction conditions: the mixture of cyclopropyl ketone (0.2 mmol, 1.0 equiv) and nitrile (aryl-carbonitrile: 3 equiv; alkyl-carbonitrile: 1.5 equiv), CuBr (5 mol%), PBu_3 (10 mol%), $BF_3{\cdot}Et_2O$ (1.0 equiv), H_2O (1.0 equiv), and $MeNO_2$ (1.5 mL) was stirred under 85 °C for 18 h, isolated yields were given.

Having identified selective reaction conditions set, the novel copper-catalyzed Ritter-type process triggered us to screen the generality and scale of the substrates for the ring-opening coupling reaction. Various aryl-substituted carbonitriles reacted smoothly to access the respective product (**4aa**–**4ai**). Generally, electron-donating groups on the aryl ring enhanced the reaction (**4ab** and **4ad**), consistent with the nucleophilic attack in the first step of Lewis acid-activated ring-opening process. Halogens including F, Cl, Br, and I were all tolerated, furnishing the corresponding γ-amino ketones (**4af**–**4ai**) in 70-85% yield. In case of alkyl nitriles, pentanenitrile (**2j**), dodecanenitrile (**2k**), cyclopropanecarbonitrile (**2l**), adamantane-1-carbonitrile (**2m**), 4-phenyl-butyronitrile (**2n**), and phenyl-acetonitrile (**2o**) gave the final products in good to excellent yield. Moreover, alkyl nitriles with terminal vinyl, ether, halogen, or terminal alkynyl were successfully converted to final γ-amino ketone products in the ring-opening coupling reactions (**4ap**–**4at**). This result was particularly satisfying given that these functional groups are considered primary in synthetic chemistry. An interesting case was found with hexanedinitrile which only delivered the product with one nitrile group transformed (**4au**).



A surprising result was observed when methoxyl-substituted phenyl-acetonitriles **2v** and **2w** were subjected to the reaction conditions. While the reaction of **2v** and **1a** under the standard conditions even for 24 hours smoothly gave the γ-amino ketone **4av** in 92% yield [Eq. (1)], the only product observed was the indolizine derivative **4aw** (66% yield) when **2w** was transformed [Eq. (2)], which was postulated to be generated via Pictet–Spengler type reaction[11] from the corresponding γ-amino ketone prepared in situ. Interestingly **4aw** contains the key structure of the natural product Crispine A. According this reaction patern, 3-benzo[b]thiophen acetonitrile **2x** readily generated expected polycyclic product **4ax** in 72% yield, which could smoothly undergo desulfurization[12] to give corresponding hexahydro-indolizin-5-one (**5**) in 80% yield [Eq. (3)].

Conclusions

In summary, we have developed a novel copper(I)-catalyzed Ritter reaction for synthesis of γ-amino ketones by Lewis acid-assisted ring-opening reaction of cyclopropyl ketones. This method is efficient, highly applicable, and allows the facile formation of functionalized ketones. Thus it shows potential capabilities to construct complex molecules in synthetic and pharmaceutical chemistry. More importantly copper-mediated

selectivity over Ritter-type process will be inspired to other case with the fact that almost all conventional Ritter reactions proceed under acidic condition rather than with transition metal. Efforts to understand the actual role of copper in this transformation are currently underway.

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Notes and references

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Electronic Supplementary Information (ESI) available: experimental details and spectral data for all synthesized compounds. See DOI: 10.1039/c000000x/

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