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Construction of an isoquinolinone framework from carboxylic-ester-directed umpolung ring opening of methylenecyclopropanes†

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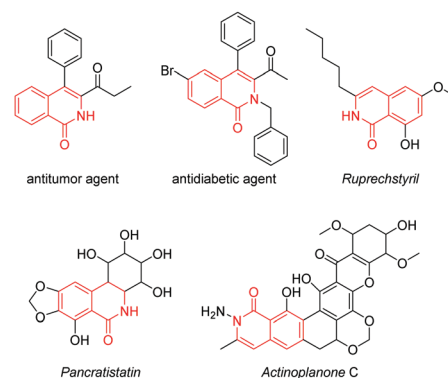
An interesting type of reaction involving functionalized methylenecyclopropanes (MCPs) has been revealed. Here, a nucleophilic attack of an anionic species onto a partially polarity-reversed MCP was realized by treating a neighbouring carboxylic ester tethered to the MCP and amine with KHMDS to realize an umpolung ring opening of the MCP. This work established an operationally convenient protocol for the rapid construction of isoquinolinone frameworks.

Isoquinolin-1(2*H*)-one derivatives have attracted extensive interest for being a class of essential alkaloids and were documented early on to exhibit excellent biological and clinical activities, such as various antitumor and antidiabetic activities (Scheme 1).¹ Moreover, the skeletons of some naturally and biologically valuable compounds such as ruprechstyryl, pancratistatin and actinoplanone C consist of the significant isoquinolinone units (Scheme 1). To date, the efforts at constructing this key structural motif have been reported to mainly depend on using transition-metal-catalyzed transformations under harsh conditions, limiting their practical applications, especially in drug discovery.²

Methylenecyclopropanes (MCPs) are highly strained molecules that provide a sufficient thermodynamic driving force in organic reactions for generating carbocycles.³ Traditional types of reactions involving MCPs include (A) thermally induced or thermally promoted cyclizations,⁴ (B) reactions catalyzed by Lewis or Brønsted acids,⁵ (C) transition-metal-catalyzed reactions,⁶ (D) radical-promoted reactions,⁷ and other reactions

similar to those involving alkenes (Scheme 2). However, to the best of our knowledge, the type of reaction in which an MCP is the direct target of a nucleophilic attack made by an electron-rich anionic species has not yet been reported, presumably due to the MCP unit itself being an electron-rich moiety. Hence, we envisaged that an electron-withdrawing carboxylic ester group introduced next to the MCP unit as a directing group⁸ might attract a nearby nucleophilic species, leading to an interesting umpolung ring opening of the cyclopropane (Scheme 2, this work).

Our working hypothesis is shown in Scheme 3. Amides could be converted to amide anions upon being treated with a strong base having electron-withdrawing carbonyl groups and stabilized nucleophilic species. Therefore, considering that aromatic acid esters have been shown to react with anilines to provide amides in the presence of strong bases,⁹ we assumed that methyl-ester-tethered MCP **1a** could be first transformed to amide **III** in the presence of *p*-methoxyaniline **2a** and the base through a nucleophilic addition-elimination mechanism, and amide **III** could be next transformed to anion **IV**. Subsequently, the nucleophilic attack of nitrogen anion onto the partially polarity-reversed MCP unit owing to the neighbouring carbonyl



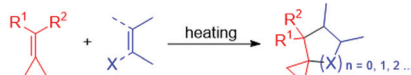
Scheme 1 Bioactive and natural compounds each containing an isoquinolin-1(2*H*)-one framework.

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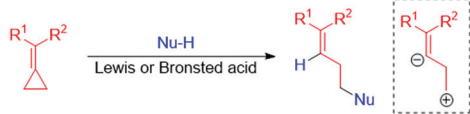
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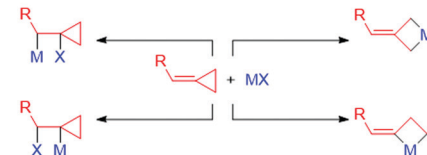
A) Thermally induced or promoted cyclizations of MCPs



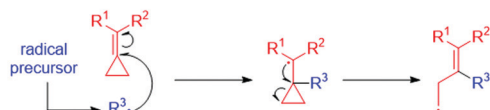
B) Lewis or Bronsted acid-catalyzed reactions of MCPs



C) Transition metal-catalyzed ring-opening reaction pattern of MCPs



D) Radical-promoted reactions of MCPs

E) Ester-directed umpolung ring opening of MCPs (*this work*)

Scheme 2 Reactions of MCPs.



Scheme 3 Proposed process achieving an umpolung ring opening of an MCP.

group would provide the cyclized intermediate V, which would undergo aromatization and concerted protonation upon release of ring strain as the driving force to afford the ring-opened product **3a** bearing an isoquinolinone motif.

We initially used **1a** as the model substrate to verify the reaction outcome in the presence of *p*-methoxyaniline **2a** and LiHMDS (2.0 equiv.) in toluene at room temperature. To our delight, the desired cyclized product **3a** was obtained in 54% yield after 24 h (Table 1, entry 1). When LiHMDS was added into the reaction mixture at 0 °C, **3a** was obtained in 98% yield after 10 h (Table 1, entry 2). Considering that the nucleophilic attack of an anionic species onto the MCP unit is unusual and may be sensitive to the reaction temperature, we next carried

Table 1 Optimization of reaction conditions

Entry	Base	Solvent ^a	T [°C]	Time (h)	Yield/ 3a ^b [%]
1	LiHMDS	Toluene	r.t.	24	54
2	LiHMDS	Toluene	0–r.t.	10	98
3	LiHMDS	Toluene	0–50	1.5	86
4	KHMDS	Toluene	0–50	1.5	96
5	<i>t</i> BuOK	Toluene	0–50	1.5	0
6	DBU	Toluene	0–50	1.5	0
7	K ₂ CO ₃	Toluene	0–50	1.5	0
8	KHMDS	MeCN	0–50	1.5	0
9	KHMDS	DCE	0–50	1.5	0
10	KHMDS	THF	0–50	1.5	94
11	KHMDS	Toluene	0–50	1.5	95 ^c

Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.24 mmol, 1.2 equiv.), base (0.4 mmol, 2.0 equiv.), solvent, T °C, time, quenched by water. ^a Except DBU and K₂CO₃, bases were dissolved in THF, thus solvents are mixed solvents in these entries in fact. ^b ¹H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. ^c Isolated yield.

out the reaction at 50 °C after adding LiHMDS into the reaction mixture at 0 °C. As we expected, the required reaction duration was reduced to 1.5 h, affording **3a** in 86% yield (Table 1, entry 3). Subsequently, several other bases such as KHMDS, *t*-BuOK, DBU, and K₂CO₃ were examined, and we found KHMDS to be the best choice, furnishing **3a** in 96% yield after 1.5 h (Table 1, entries 4–7). Some other solvents were also tested for the reaction, but no improved results were obtained (Table 1, entries 8–10), and hence toluene was considered to be the solvent of choice in this transformation, and gave **3a** in 95% isolated yield (Table 1, entry 11). It should be noted that LiHMDS and KHMDS, but not DBU and K₂CO₃, were dissolved in THF, and thus the solvents in these cases were actually mixed solvents (for more details, see Table S1 in the ESI†).

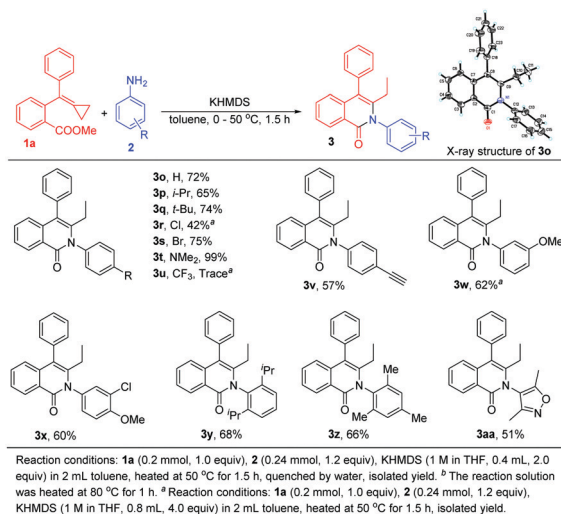
With the optimal reaction conditions in hand, we next evaluated various aromatic acid esters each tethered to the MCP unit for this reaction (Scheme 4). A methyl group, tertiary butyl group, methoxy group and halogen atoms were each tested as the R¹ group at the *para*-position of the benzene ring and provided the corresponding products **3b–3g** in 65%–98% yields. However, when MCP **1h** bearing a trifluoromethyl group was applied to the reaction, only a trace amount of **3h** was obtained, and the reaction system became messy even at low temperature, presumably due to the high reactivity of the substituted trifluoromethyl group and ester moiety tethered to the MCP in this base-promoted transformation. When methyl or methoxy as the R¹ group was introduced at the other positions, the desired products **3i–3k** were also attained in high yields. Then, we examined a methyl group or halogen atom as the R² position substituent, and found that the cyclization reactions proceeded smoothly, affording **3l** and **3m** in 87% and 98% yields, respectively. It should be pointed out that for substrate **1l**, a higher temperature (80 °C) was required for the



Scheme 4 Scope of aromatic acid esters tethered to the MCP group for the cyclization.

reaction to proceed to this yield, perhaps due to the induction effect of the carbonyl group having been impaired by the methyl substituent. Interestingly, using **1n** as a substrate, **3n'** was obtained in 95% yield, and was derived from the substitution of *in situ*-generated methoxyl anion at the fluorine atom position.¹⁰

Various aromatic amines were also examined (Scheme 5). An H atom, an isopropyl group, a tertiary butyl group, halogen atoms, an *N,N*-dimethyl group, and an acetenyl group were each tested as an R group at the *para*-position, and resulted in the formation of **3o–3t** and **3v** in moderate to excellent yields ranging from 42% to 99%. The structure of **3o** was unambiguously determined in the current work using X-ray diffraction and its ORTEP drawing is shown in Scheme 5. (For details of **3o**'s X-ray crystallographic data, see the ESI[†]). Nevertheless, for the 4-trifluoromethylaniline **2u**, only a trace amount of product was obtained, perhaps owing to its weak nucleophilicity. The



Scheme 5 Scope of aromatic amines for the cyclization.



Scheme 6 Migrations of the pyridine rings.

use of other anilines, in particular 3-methoxyaniline and 3-chloro-4-methoxyaniline, delivered the corresponding products **3w** and **3x** in good yields as well. When using sterically hindered anilines in this reaction, the reaction also proceeded smoothly, providing **3y** and **3z** in 68% and 66% yields, respectively. Heterocyclic aromatic amine **2aa** was also compatible with this reaction, giving **3aa** in 51% yield.

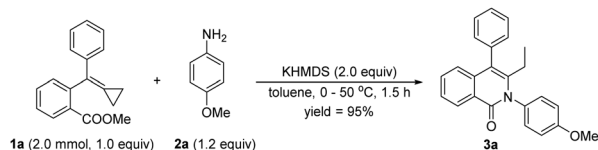
When 2-aminopyridine **2ab** was applied to this cyclization, we found an interesting migration of the pyridine ring, affording **4a** in 85% yield (Scheme 6). Its structure was determined using X-ray diffraction and the corresponding products **4b** and **4c** were obtained in moderate yields when R was a halogen atom.

To clarify the reaction mechanism, we carried out the reaction of **1a** with **2a** at room temperature and quenched the reaction with saturated aqueous NH_4Cl in 10 minutes. We found that the amide **5a** was isolated in 80% yield along with 5% of **3a**, and that **5a** was subsequently transformed to **3a** in 56% yield upon adding KHMDS (for more details, see section S4 in ESI[†]), supporting the mechanism proposed in Scheme 3 (Scheme 7a). Therefore, the pyridine ring migration may have proceeded through a Meisenheimer complex as shown in Scheme 7b.

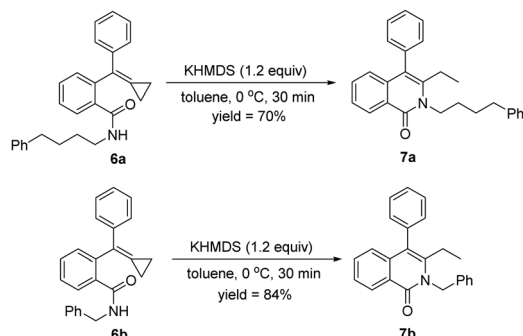
To further evaluate the practicability of this novel synthetic methodology, the scale of the reaction of **1a** with **2a** was increased, specifically to a gram scale, and afforded **3a** in



Scheme 7 Proposed mechanism for the pyridine ring migration.



Scheme 8 Cyclization reaction on a gram scale.



Scheme 9 Use of alkyl amines instead of aromatic amines for the cyclization.

95% yield, showing the synthesis to be potentially practical for constructing heterocyclic materials and bioactive molecules (Scheme 8).

When alkyl amines were used instead of aromatic amines for this cyclization reaction with **1a**, none of the cyclized products formed, and **1a** was not consumed at all, indicating that the amide intermediates were not generated. Therefore, we attempted to synthesize the alkyl-substituted amides from condensations between carboxylic-acid-tethered MCPs and alkyl amines to directly obtain **6a** and **6b**, which were applied for the cyclization in the presence of KHMDS (1.2 equiv.). To our delight, the desired products **7a** and **7b** were obtained in, respectively, 70% and 84% yields at 0 °C within 30 minutes, demonstrating a broad scope for this reaction (Scheme 9).

In addition, it should be emphasized here that when the MCP unit of **1a** was replaced by a methylene group, no cyclization took place, indicating the essential nature of the MCP unit for this protocol (for more details, see section S4 in ESI†).

In conclusion, we have developed an interesting type of reaction involving carrying out a nucleophilic attack of an anionic species onto a partially polarity-reversed MCP unit upon treating a neighbouring carboxylic ester tethered to the MCP and an amine with KHMDS for the rapid construction of an isoquinolinone framework through an umpolung ring opening of the MCP under mild conditions. The ester moiety served as a directing group in this transformation. This newly developed protocol represents a straightforward and environmentally friendly manipulation without using transition metal catalyst, and has provided a valuable tool for the applications of functionalized MCPs in organic synthesis.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) Q. Long, K. Zou, W. Dong, D. Xie and D. An, *Synth. Commun.*, 2021, 1–12, DOI: 10.1080/00397911.2021.1952433; (b) K. Hemalatha and G. Madhumitha, *Appl. Microbiol. Biotechnol.*, 2016, **100**, 7799–7814; (c) S. F. Hussain, S. Nakkady, L. Khan and M. Shamma, *Phytochemistry*, 1983, **22**, 319–320; (d) V. U. Ahmad, R. Atta ur, T. Rasheed, R. Habib ur and A. Q. Khan, *Tetrahedron*, 1987, **43**, 5865–5872; (e) Y. Aly, A. Galal, L. K. Wong, E. W. Fu, F.-T. Lin, F. K. Duah and P. L. Schiff, *Phytochemistry*, 1989, **28**, 1967–1971; (f) B. D. Krane and M. Shamma, *J. Nat. Prod.*, 1982, **45**, 377–384.
- (a) S. Allu and K. C. K. Swamy, *J. Org. Chem.*, 2014, **79**, 3963–3972; (b) K. Takamatsu, K. Hirano and M. Miura, *Angew. Chem., Int. Ed.*, 2017, **56**, 5353–5357; (c) T. Li, C. Zhang, Y. Tan, W. Pan and Y. Rao, *Org. Chem. Front.*, 2017, **4**, 204–209; (d) D.-G. Yu, F. de Azambuja, T. Gensch, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 9650–9654; (e) L. Grigorjeva and O. Daugulis, *Angew. Chem., Int. Ed.*, 2014, **53**, 10209–10212; (f) N. Thrimurtulu, A. Dey, D. Maiti and C. M. R. Volla, *Angew. Chem., Int. Ed.*, 2016, **55**, 12361–12365.
- (a) J. Liu, R. Liu, Y. Wei and M. Shi, *Trends Chem.*, 2019, **1**, 779–793; (b) H. Cao, F. Chen, C. Su and L. Yu, *Adv. Synth. Catal.*, 2019, **362**, 438–461; (c) L. Yu, M. Liu, F. Chen and Q. Xu, *Org. Biomol. Chem.*, 2015, **13**, 8379–8392; (d) A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, *Chem. Rev.*, 2014, **114**, 7317–7420; (e) G. Fumagalli, S. Stanton and J. F. Bower, *Chem. Rev.*, 2017, **117**, 9404–9432.
- (a) L.-Z. Yu, X.-B. Hu, Q. Xu and M. Shi, *Chem. Commun.*, 2016, **52**, 2701–2704; (b) H.-Z. Wei, Q.-Z. Li, Y. Wei and M. Shi, *Org. Biomol. Chem.*, 2020, **18**, 7396–7400; (c) H.-Z. Wei, L.-Z. Yu and M. Shi, *Org. Biomol. Chem.*, 2020, **18**, 135–139.
- (a) L.-P. Liu and M. Shi, *J. Org. Chem.*, 2004, **69**, 2805–2808; (b) L. Ackermann, S. Kozhushkov, D. Yufit and I. Marek, *Synlett*, 2011, 1515–1518; (c) M. Shi, M. Jiang and L.-P. Liu, *Org. Biomol. Chem.*, 2007, **5**, 438–440; (d) B. Xu and M. Shi, *Org. Lett.*, 2003, **5**, 1415–1418.
- (a) D. Li, W. Zang, M. J. Bird, C. J. T. Hyland and M. Shi, *Chem. Rev.*, 2020, **121**, 8685–8755; (b) N. Kimura, S. Katta, Y. Kitazawa, T. Kochi and F. Kakiuchi, *J. Am. Chem. Soc.*, 2021, **143**, 4543–4549; (c) J. Yao, Z. Chen, L. Yu, L. Lv, D. Cao and C.-J. Li, *Chem. Sci.*, 2020, **11**, 10759–10763; (d) Y. Liu, A. A. Ogunlana and X. Bao, *Dalton Trans.*, 2018, **47**, 5660–5669; (e) Y. Liu, S. Feng and X. Bao, *ChemCatChem*, 2018, **10**, 2817–2825.
- (a) H.-Z. Wei, Y. Wei and M. Shi, *Org. Chem. Front.*, 2021, **8**, 4527–4532; (b) Y. Liu, Q.-L. Wang, Z. Chen, H. Li, B.-Q. Xiong, P.-L. Zhang and K.-W. Tang, *Chem. Commun.*, 2020, **56**, 3011–3014; (c) M. Chen, Y. Wei and M. Shi, *Org. Chem. Front.*, 2020, **7**, 374–379; (d) Z.-Z. Zhu, K. Chen, L.-Z. Yu, X.-Y. Tang and M. Shi, *Org. Lett.*, 2015, **17**, 5994–5997.
- (a) X. He, Y. Tang, Y. Wang, J. Chen, S. Xu, J. Dou and Y. Li, *Angew. Chem., Int. Ed.*, 2019, **58**, 10698–10702; (b) J. Wu, Y. Tang, W. Wei, Y. Wu, Y. Li, J. Zhang, Y. Zheng and S. Xu, *Angew. Chem., Int. Ed.*, 2018, **57**, 6284–6288.
- G. Li, C.-L. Ji, X. Hong and M. Szostak, *J. Am. Chem. Soc.*, 2019, **141**, 11161–11172.
- J. Su, Q. Chen, L. Lu, Y. Ma, G. H. L. Auyoung and R. Hua, *Tetrahedron*, 2018, **74**, 303–307.