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Amide-assisted intramolecular [3+2] annulation of cyclopropane ring-opening: a facile and diastereoselective access to the tricyclic core of (±)-scandine†

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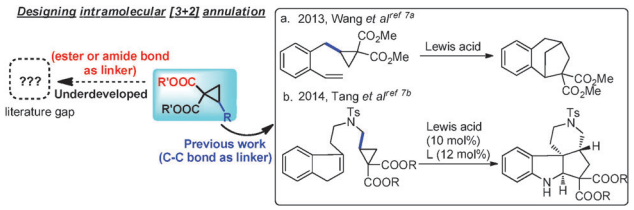
The highly diastereoselective intramolecular [3+2] annulation *via* the ring-opening of a cyclopropane diester derivative has been developed to construct a dihydroquinolinone scaffold. A series of tricyclic dihydroquinolinones bearing one or two all-carbon quaternary stereogenic centers were obtained in good yields and excellent diastereoselectivities (up to 20 : 1 dr). Moreover, the amide-linking mode shows obviously beneficial effects on the ring-opening of cyclopropane.

Ring-opening of donor–acceptor cyclopropane 1,1-diester has attracted increasing synthetic attention in the last decade, due to its superior efficiency in the construction of five-membered ring systems.[1,2] Generally, cyclopropane 1,1-diesters act as dipoles *via* the ring-opening promoted by strong Lewis acids, such as scandium(III) triflate, ytterbium(III) triflate, stannic chloride and so on, effectively furnishing five-membered carbocycles in one step.[3,4] To date, intermolecular [3+2] annulation of donor–acceptor cyclopropanes has evolved to become a versatile annulation pathway.[5,6] In contrast, as an efficient pathway for forming multicyclic ring systems, the intramolecular [3+2] annulation of donor–acceptor cyclopropane diester was sparsely studied (Scheme 1).[7] In 2013, Wang and coworkers reported the first LA-catalyzed intramolecular cycloaddition of cyclopropane diester with a linked alkene to construct bridged [n.2.1] carbocyclic rings.[7a] Very recently, Tang *et al.* developed an intramolecular cycloaddition of cyclopropane with indole to form tetracyclic spiroindolines with three continuous stereocenters.[7b] Commonly, the dipolarophiles were connected with cyclopropane diester through the formation of the C–C bond on the cyclopropane ring.[7c,d] Surprisingly, the linker installed on the diester moiety has never been reported. Despite these encouraging achievements in exploiting the intramolecular [3+2] annulation of cyclopropane diester, further development of a novel linking mode is still highly desirable to fill in the literature gap and deal with the structural complexity in the construction of polycyclic ring systems. In this context, given the facile formation of the amide bond, the conversion of ester to amide as the linker would be a straightforward and concise choice.



Scheme 1 Linking patterns for intramolecular [3+2] annulation based on the ring-opening of cyclopropane 1,1-diester.

Melodinus alkaloids are an important class of natural products belonging to the family of dihydroquinolinone.[8] Due to the intriguing structural features of the polycyclic dihydroquinolinone containing highly functionalized pentacarbocycles, these alkaloids, especially scandine and meloscine, have attracted considerable synthetic attention.[9,10] To date, a few synthetic strategies have been developed to assemble the polycyclic dihydroquinolinone core of (±)-scandine, though its total synthesis has not been completely achieved.[11] Noticeably, Stoltz *et al.* reported their elegant work on the installation of the C ring through a palladium-catalyzed intermolecular [3+2] annulation between cyclopropane 1,1-diester and substituted β-nitrostyrene in an unsatisfactory dr (1 : 2).[11a] The following reduction and lactamization afforded the B ring. Thus, the stereoselective and efficient assembly of the polycyclic core bearing four contiguous stereocenters and three all-carbon quaternary centers still remains challenging. We envisioned that the strategy of the intramolecular [3+2] annulation of cyclopropane 1,1-diester might allow the rapid and stereoselective construction

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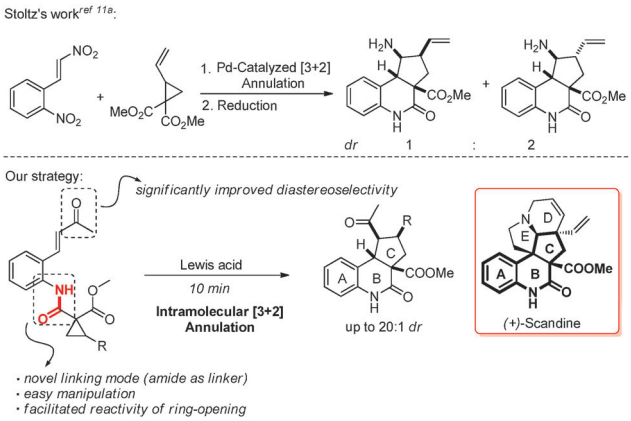
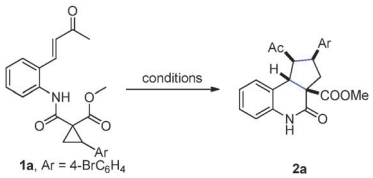


Scheme 2 Strategies for the construction of the tricyclic core of scandine.

of ABC rings. Herein, we report an amide-linked intramolecular [3+2] annulation promoted by titanium tetrachloride (Scheme 2). Moreover, α,β-unsaturated enones as the dipolarophile were found to significantly improve the diastereoselectivity. Interestingly, the amide linker plays a vital role in the ring-opening process. Using this optimal linking strategy, the tricyclic core of scandine with four contiguous stereogenic centers and one/two all-carbon quaternary centers was stereoselectively built in one step.

Based on our design employing the amide as the linker, we started our investigation by using enone **1a** as the substrate to evaluate this reaction and various Lewis acids were tested as the promoter. Unfortunately, the addition of 20 mol% of commonly used Lewis acid, such as $Cu(OTf)_2$, $Y(OTf)_3$, $Yb(OTf)_3$, and $Sc(OTf)_3$, did not yield the desired product at both room temperature and high temperature. And only the decomposition of the starting material was observed (Table 1, entries 1–4). The reaction proceeded with 100% conversion by using $SnCl_4$. However, only a trace amount of cycloadduct was observed even with the stoichiometric usage of $SnCl_4$ (entries 5 and 6). To our delight, when 20 mol% loading of titanium(IV) tetrachloride was used, 11% yield of cycloadduct **2a** was achieved. Further increase in the loading of the promoter led to a remarkable improvement of the yield. And 56% yield of **2a** was obtained with the loading of 1.2 equiv. of $TiCl_4$ in anhydrous 1,2-dichloroethane at room temperature (entries 7–9). Subsequently, various solvents were also screened. Interestingly, only a trace amount of **2a** was observed in the regular DCE. The yield of **2a** was increased to 53% by adding freshly dried 4 Å MS in the regular DCE, suggesting that water impeded the reaction and an anhydrous solvent would be demanding (entries 9–11). Moreover, no desired product was formed at low temperature (entry 12). Satisfyingly, the employment of anhydrous dichloromethane gave 67% yield and excellent dr (>20:1) within 10 minutes (entry 13). Unfortunately, other solvents including Et_2O, MeCN, and $CHCl_3$ provided unsatisfactory results. Severe decomposition was observed in anhydrous ether or methanol as the solvent. Similarly, no desired product was observed when anhydrous toluene was used (entries 14–17). Ultimately, the optimized reaction conditions were finalized as the addition of $TiCl_4$ (1.2 equiv.) in dry DCM.

Table 1 Optimization of the intramolecular [3+2] annulation reaction[a]

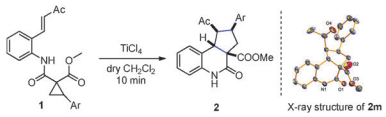


Entry	LA (mol%)	Solvent	T (°C)	Time	Yield (%)	dr
1	$Cu(OTf)_2$ (20)	Dry DCE	RT	72 h	nd	—
2	$Yb(OTf)_3$ (20)	Dry DCE	RT	72 h	nd	—
3	$Y(OTf)_3$ (20)	Dry DCE	RT	72 h	nd	—
4	$Sc(OTf)_3$ (20)	Dry DCE	RT	72 h	nd	—
5	$SnCl_4$ (20)	Dry DCE	RT	72 h	nd	—
6	$SnCl_4$ (100)	Dry DCE	RT	8 h	Trace	—
7	$TiCl_4$ (20)	Dry DCE	RT	12 h	11	>20:1
8	$TiCl_4$ (50)	Dry DCE	RT	12 h	32	>20:1
9	$TiCl_4$ (120)	Dry DCE	RT	10 min	56	>20:1
10[b]	$TiCl_4$ (120)	DCE	RT	0.5 h	53	>20:1
11	$TiCl_4$ (120)	DCE	RT	0.5 h	Trace	—
12	$TiCl_4$ (120)	Dry DCE	0	0.5 h	nd	—
13	**$TiCl_4$ (120)**	**Dry DCM**	**RT**	**10 min**	**69**	**>20:1**
14	$TiCl_4$ (120)	Dry $CHCl_3$	RT	10 min	Trace	—
15	$TiCl_4$ (120)	Dry MeCN	RT	1 h	nd	—
16	$TiCl_4$ (120)	Dry toluene	RT	1 h	Trace	—
17	$TiCl_4$ (120)	Dry Et_2O	RT	1 h	nd	—

[a] Unless otherwise noted, the reaction was performed on a 0.2 mmol scale in a solvent (2 mL) at r.t. with the specified Lewis acid. [b] 100 mg of 4 Å MS was added.

Once the optimal conditions had been established, the substrate scope of this reaction was studied and various substituted cyclopropane derivatives were examined (Table 2). In general, high to modest yields with excellent diastereoselectivity (>20:1 dr) were obtained when the phenyl group on the cyclopropane ring was substituted on the C4 position. It was found that the introduction of an electron-donating group onto the phenyl group would slightly decrease the yield without affecting the diastereoselectivity (entries 1–6). 3-Substituted derivatives afforded comparable results including modest yields and excellent diastereoselectivities (entries 7 and 8). The presence of the methyl group on the C2 position led to a relatively low yield and comparable diastereoselectivity (>20:1 dr). The markedly dropped diastereoselective ratios and modest chemical yields were obtained when the C2 position possesses a chloro- or bromo group. Interestingly, the introduction of the methoxyl group severely affected the diastereoselectivity, but improved the chemical yield (entries 9–12). Presumably, this observance might be mainly attributed to the steric effect induced by the *ortho*-substituents on the phenyl moiety. Satisfactory results (75% yield, > 20:1 dr) were achieved for the unsubstituted substrate **1m**. Ultimately, the regio- and stereochemical outcomes of this reaction were unambiguously established by the single crystal X-ray analysis of cycloadduct **2m**.[12] Gratifyingly, the ring-opening of vinylogous analogue **1n** also delivered the corresponding cycloadduct in a good chemical yield (64%) with excellent dr (>20:1). It is worth mentioning that the existence of the carbon–carbon double bond in **2n** would facilitate the further modification of the tricycle to install the multicyclic core of scandine. An increase in the steric effect led to a markedly dropped diastereoselectivity (**2o**, 1:1 dr),

Table 2 Substrate scope of the intramolecular [3+2] annulation[a]



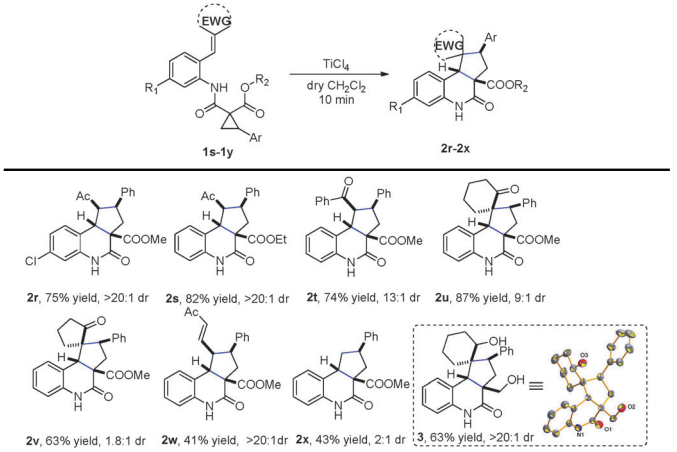
Entry	Ar	Yield (%)	Product	dr
1	4-BrC_6H_4 (**1a**)	69	**2a**	>20 : 1
2	4-FC_6H_4 (**1b**)	77	**2b**	>20 : 1
3	4-ClC_6H_4 (**1c**)	84	**2c**	>20 : 1
4	4-MeC_6H_4 (**1d**)	76	**2d**	>20 : 1
5	4-EtC_6H_4 (**1e**)	61	**2e**	>20 : 1
6	4-$OMeC_6H_4$ (**1f**)	55	**2f**	>20 : 1
7	3-MeC_6H_4 (**1g**)	71	**2g**	>20 : 1
8	3-BrC_6H_4 (**1h**)	62	**2h**	>20 : 1
9	2-MeC_6H_4 (**1i**)	53	**2i**	>20 : 1
10	2-ClC_6H_4 (**1j**)	66	**2j**	1.4 : 1
11	2-BrC_6H_4 (**1k**)	69	**2k**	1.5 : 1
12	2-$OMeC_6H_4$ (**1l**)	87	**2l**	1.5 : 1
13	Ph (**1m**)	75	**2m**	>20 : 1
14	(1*E*)-2-Phenylethenyl (**1n**)	64	**2n**	>20 : 1
15	(1*E*)-1-Methyl-2-phenylethenyl (**1o**)	77	**2o**	1 : 1
16	2-Naphthyl (**1p**)	79	**2p**	>20 : 1
17	2-Thienyl (**1q**)	64	**2q**	>20 : 1
18	2-Furyl (**1r**)	Trace	—	—

[a] Unless otherwise noted, the reaction was performed on the 0.2 mmol scale in anhydrous CH_2Cl_2 (2 mL) at r.t. with 1.2 equiv. of $TiCl_4$.

albeit with a relatively high chemical yield (entries 14 and 15). Other aromatic groups were also investigated in this reaction. The 2-naphthyl substrate **1p** afforded good chemical yield and excellent dr. As for the 2-thienyl derivative, the yield was slightly decreased despite the excellent dr (entries 16 and 17). Moreover, due to the instability of the furan ring under acidic conditions, severe decomposition occurred and only a trace amount of the desired product was observed for 2-furfural derived substrate **1p** (entry 18).

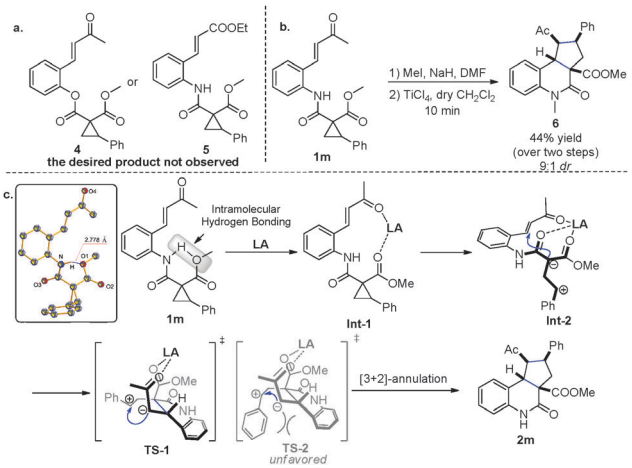
Next, the structural features on the other parts of the substrates were further modified to investigate the viability of the strategy (Table 3). The introduction of the chloro group onto the central phenyl ring has a negligible effect on yield and dr (**2r**, 75% yield, > 20 : 1 dr). Switching the methyl ester to an ethyl ester gave a slightly increased yield and excellent dr (**2s**). The high level of diastereoselectivity was unexpectedly lowered to 13 : 1 when the acetyl group was replaced with the benzoyl group (**2t**). Then, exocyclic enone substrates were tested in this reaction. While the six-membered derivatized substrate performed well with high yield and good dr (**2u**, 87%, 9 : 1 dr), degraded yield (63%) and dr (1.8 : 1) were observed for the five-membered derivative (**2v**). Moreover, the vinylogous analogue **1x** was also tested and the chemical yield of **2w** was remarkably dragged down (41% yield) with an unchanged dr (> 20 : 1). Surprisingly, the absence of the acetyl group was deleterious to the diastereoselectivity and chemical yield. And only 2 : 1 dr and 43% yield were obtained (**2x**). Obviously, the acetyl group played a crucial role in improving the dr and chemical yield of the annulation reaction. Moreover, spiropolycycle **2u** was further derivatized by LAH reduction. And the structure and relative configuration of the resulting alcohol **3** were confirmed through X-ray analysis of the single crystal.[12]

Table 3 Construction of various polycyclic dihydroquinolinones through intramolecular [3+2] annulation[a]



[a] Unless otherwise noted, the reaction was performed on a 0.2 mmol scale in anhydrous CH_2Cl_2 (2 mL) at r.t. with 1.2 equiv. of $TiCl_4$.

In order to better understand the details of this reaction, control experiments were carried out (Scheme 3). The variation of the linker from amide to ester would allow us to look into the effect of the linker on the annulation process. Surprisingly, the subjection of cyclopropane 1,1-diester derivative **4** to the standard conditions did not afford the desired product although various Lewis acids and reaction temperatures were tried (Scheme 3a). Presumably, the amide might be involved with the ring-opening to enhance the formation of the corresponding intermediate at the early stage of the reaction sequence. Moreover, no desired product was observed upon switching the acetyl group to the ethyl carboxylate group. On the other hand, the N–H moiety was intentionally shielded *via* methylation and the following ring-opening successfully furnished the corresponding annulation product with a slightly eroded dr (9 : 1) (Scheme 3b). According to the single crystal structure of **1m**, a hydrogen bond (2.778 Å) is formed between the N–H of amide and the oxygen atom in the neighboring ester group. Although the detailed mechanism of



Scheme 3 Control experiments and the proposed pathway of the intramolecular [3+2] annulation.

this reaction cannot be fully clarified at this stage, a plausible reaction pathway is illustrated in Scheme 3c. Presumably, two carbonyl groups belonging to enone and carboxylate respectively coordinate with titanium(IV) (**Int-1**), which would remarkably facilitate the ring-opening of cyclopropane to instantaneously form the corresponding intermediate **Int-2**. At this stage, the intramolecular H-bond was destroyed due to the strong coordination between titanium(IV) and carbonyl groups. Subsequently, the dicarbonyl anion would attack the enone moiety to furnish the six-membered lactam ring. With the aid of the coordination of carbonyl groups with Lewis acid, the following ring-closure proceeds as shown in **TS-1**. Presumably, the other possible transition state **TS-2** with different orientations of the phenyl ring would be unfavorable due to the introduction of the steric repulsion between two phenyl moieties. In this way, tricyclic product **2m** can be formed in high diastereoselectivity.

In summary, we have developed a novel amide-linked intramolecular [3+2] annulation based on the ring-opening of donor–acceptor cyclopropane 1,1-diester motif. Consequently, a series of tricyclic dihydroquinolinones, as the tricyclic core of scandine, were rapidly constructed in good to modest yields with excellent diastereoselectivities ($>20:1$). Interestingly, the introduction of amide as the linker significantly facilitated the annulation. This developed linking mode would broaden the utilization of cyclopropane ring-opening in the assembly of polycyclic scaffolds with diverse structural features.

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12 CCDC 1420711 for (**1m**), 1420712 for (**2m**) and 1420822 for (**3**), see the ESI† for details.

