Scandium triflate catalyzed cycloaddition of imines with 1,1-cyclopropanediesters: efficient and diastereoselective synthesis of multisubstituted pyrrolidines†

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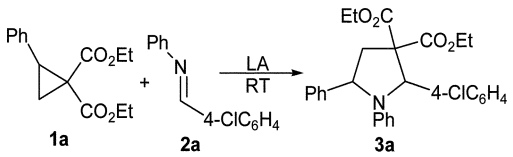
A tandem ring-opening–cyclization reaction of cyclopropanes with imines in the presence of 5 mol% of scandium triflate was developed for the highly diastereoselective synthesis of multisubstituted pyrrolidines.

Introduction

Pyrrolidines are very important five-membered heterocycles because of their frequent occurrence in biologically active compounds,[1] as well as their utilities as valuable synthetic intermediates[2] or organocatalysts.[3] Of the synthetic methods developed, [3 + 2] dipolar cycloaddition of azomethine ylides with activated alkenes is one of the most convenient and efficient ways.[4] The reaction of monoactivated cyclopropanes[5,6] with imines is also developed.[7–8] Nakamura *et al.* described the thermal [3 + 2] cycloaddition reactions of highly activated methylenecyclopropanes with imines to produce pyrrolidine derivatives.[7] Recently, Carreira *et al.*[8a,8d] pioneered a reaction of cyclopropanes with imines promoted by MgI_2, providing easy access to spiro[pyrrolidin-3,3′-oxindoles]. Using stoichiometric MgI_2, Lautens and coworkers extended successfully the cyclopropanes to methylenecyclopropyl amides and developed a good method for the synthesis of five- and six-membered heterocyclic compounds.[8b] Olsson described an iodide-promoted three-component synthesis of disubstituted pyrrolidines.[8c] In our study on the synthesis and applications of cyclopropanes,[9] we found that the imines could directly attack the 1,1-cyclopropane carboxylic esters to form tetrasubstituted pyrrolidines stereoselectively in the presence of Lewis acid. In this paper, we wish to report the results in details.[10]

Results and discussion

Initially, an attempt to use stoichiometric magnesium iodide to promote the cycloaddition of electron-deficient cyclopropane **1a** and imine **2a** failed (Scheme 1). Although the cyclopropane disappeared in *ca.* 6 hours in THF, only a trace amount of the annulation adduct with poor stereoselectivity was observed. Replacing the solvent with CH_2Cl_2 did not give the desired product. Fortunately, we found that this reaction could be catalyzed very well by using 5 mol% of $Sc(OTf)_3$ instead of MgI_2. In this case, the annulation reaction of diethyl 2-phenyl-1,1-cyclopropane dicarboxylates with **2a** gave pyrrolidine **3a** in 60% yield in CH_2Cl_2 at room temperature.



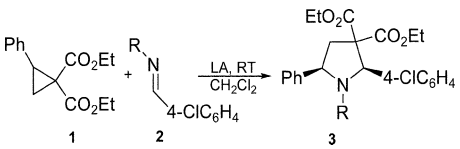
Conditions[a]	yield (%)	cis/trans
MgI_2 (1 eq.), THF	trace	2.5/1
MgI_2 (1 eq.), CH_2Cl_2	0	/

[a] **1a** disappeared.

Scheme 1

To further improve the yield and the diastereoselectivity, several Lewis acids were optimized. As shown in Table 1, $Yb(OTf)_3$,

Table 1 Effects of Lewis acids on the annulation reaction[a]



Entry	R	LA	Dr[b]	Conversion (%)[b]
1	Ph	$Sc(OTf)_3$	1 : 1	60[c]
2	Ph	$Yb(OTf)_3$	—	Trace
3	Ph	$Ga(OTf)_3$	—	Trace
4	Ph	$In(OTf)_3$	—	36
5	Ph	$Mg(ClO_4)_2$	—	Trace
6	Ph	$Ni(ClO_4)_2$	—	45
7	Ph	$Cu(ClO_4)_2$	—	Trace
8	Ph	$Zn(ClO_4)_2$	—	Trace
9	Ph	$AlCl_3$	—	Trace
10[d]	Ph	$Sc(OTf)_3$	1.5 : 1	100
11[d]	Ph	$Yb(OTf)_3$	1.8 : 1	29
12[d]	Ph	$Ga(OTf)_3$	1.8 : 1	30
13[d]	Ph	$In(OTf)_3$	1.7 : 1	87
14[d]	Ph	$Ni(ClO_4)_2$	—	0
15[d]	Ph	$Mg(ClO_4)_2$	—	0
16[d]	Ph	$Cu(ClO_4)_2$	1.7 : 1	25
17[d]	Ph	$Zn(ClO_4)_2$	1.2 : 1	10
18[d]	Ph	$FeCl_3$	2.1 : 1	49
19[d,e]	Ph	$Sc(OTf)_3$	1 : 1	77
20[d,f]	Ph	$Sc(OTf)_3$	1.3 : 1	54
21[d]	Ts	$Sc(OTf)_3$	—	0
22[d]	Bn	$Sc(OTf)_3$	24 : 1	85

[a] 10 mol% of Lewis acid. [b] Determined by ^1H NMR. [c] Isolated yield. [d] 4 Å molecular sieves were added. [e] In toluene. [f] In diethyl ether.

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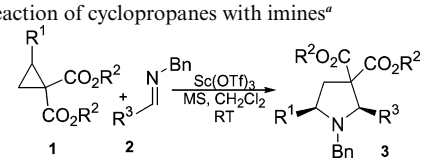
$Ga(OTf)_3$, $Mg(ClO_4)_2$, $Cu(ClO_4)_2$, $Zn(ClO_4)_2$ and $AlCl_3$ could not catalyze this reaction well and only a trace amount of the desired product was observed (Entries 2, 3, 5 and 7–9). $In(OTf)_3$ and $Ni(ClO_4)_2$ gave moderate yields in CH_2Cl_2 (Entries 4 and 6). Noticeably, the conversion of this reaction could be improved to 100% using $Sc(OTf)_3$ as a catalyst in the presence of 4 Å molecular sieves (Entry 10). Under these conditions, $In(OTf)_3$ also promoted this reaction well to give pyrrolidine in 87% conversion (Entry 13). Solvent effects were also examined and we found that THF, EtOAc, EtOH and CH_3CN did not work. Diethyl ether and toluene gave good yields (Entries 19–20) and CH_2Cl_2 proved to be the optimal solvent. The substituents on nitrogen of imine **2** influenced the reaction strongly (Entries 10, 21–22). *N*-Tosyl imine was not a good substrate. Compared with the *N*-phenyl imine, *N*-benzyl gave the optimal results in both yield and diastereoselectivity in our screened conditions.

Having established the feasibility and optimal conditions for the cycloaddition reaction, we surveyed the scope of the imines and cyclopropanes. The imines were synthesized *via* a condensation between amines and aldehydes with a ratio of 1 : 1 in the presence of 4 Å MS, followed by filtering off the molecular sieves and concentration. They were used directly without further purification. As shown in Table 2, the reaction of cyclopropane dicarboxylates with imines gave good to high yields with high diastereoselectivities. The ratio of *cis*-isomer to *trans*-isomer ranged from 8 : 1 to 30 : 1. It is noteworthy that both electron-rich and electron-deficient imines proceeded well. For instance, 3,4-methylenedioxybenzylaldimine gave the desired product in 94% yield and 4-methoxycarbonyl benzylaldimine afforded the corresponding pyrrolidine in 52% yield, both with high diastereoselectivities. Compared with *para*-substituted benzylaldimine, the *ortho*-substituted one was less active (Entries 7–8) probably due to the steric hindrance. *N*-benzyl isobutyraldimine didn't work in this condition.

Table 2 Reaction of cyclopropanes with imines[a]



Entry	R^1	R^2	R^3	**3**	Dr[b]	Yield (%)[c]
1	Styryl	Me	Ph	**b**	9 : 1	91
2	Styryl	Me	$4\text{-}FC_6H_4$	**c**	10 : 1	94
3	Styryl	Me	$4\text{-}ClC_6H_4$	**d**	11 : 1	92
4	Styryl	Me	$4\text{-}BrC_6H_4$	**e**	10 : 1	71
5[d]	Styryl	Me	$4\text{-}MeO_2CC_6H_4$	**f**	12 : 1	52[e]
6[d]	Styryl	Me	$4\text{-}MeC_6H_4$	**g**	8 : 1	86
7	Styryl	Me	$4\text{-}MeOC_6H_4$	**h**	9 : 1	86
8	Styryl	Me	$2\text{-}MeOC_6H_4$	**i**	10 : 1	59
9	Styryl	Me	$2,4\text{-}Cl_2C_6H_4$	**j**	30 : 1	59
10	Styryl	Me	3,4-Methylenedioxylphenyl	**k**	10 : 1	94
11[f]	Vinyl	Me	$4\text{-}ClC_6H_4$	**l**	6 : 1	92
12[d]	Phenyl	Et	$4\text{-}ClC_6H_4$	**m**	24 : 1	85
13[f]	H	Et	$4\text{-}ClC_6H_4$	**n**	>99 : 1	42
14[d]	Phenyl	Me	$4\text{-}ClC_6H_4$	**o**	30 : 1	98[e]

[a] Reaction conditions: 0.25 mmol scale, 5 mol% of scandium triflate, **2** : **1** = 0.3 : 0.25 (mmol : mmol), rt. [b] dr = *cis* : *trans*, determined by ^1H NMR. [c] Isolated yield. [d] 10 mol% of $Sc(OTf)_3$ used. [e] At 40 °C. [f] 20 mol% of $Sc(OTf)_3$ used.

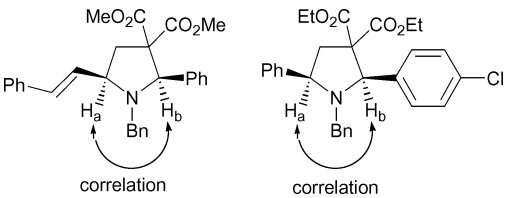
Various 2-substituted 1,1-cyclopropane carboxylates proved to be good substrates for the present cycloaddition. For example, the reaction of both 2-vinyl- and 2-phenyl-1,1-cyclopropanes with 4-chlorobenzylaldimne proceeded well to provide the pyrrolidines in 92% and 85% yields, respectively (Entries 11 and 12). The cyclopropane with substituent at 3-position, such as diethyl 2-ethyl-3-styrylcyclopropane-1,1-dicarboxylate, was inactive in this reaction.

Considering that the imine is readily available from aldehyde and amine, we tried a three-component reaction and found that the one-pot reaction by combination of the aldehyde (1.2 equivalent) and the benzyl amine (1.2 equiv.) in CH_2Cl_2 in the presence of 4 Å molecular sieves and 5 mol% of $Sc(OTf)_3$, followed by addition of cyclopropane **1b** (1.0 equiv.) in 0.5 mL of CH_2Cl_2 worked well to give the pyrrolidine in good yields with low to high diastereoselectivities, providing an efficient access to pyrrolidines (Scheme 2).

R^1/ R^2	cis/trans	Yield(%)	**3**
$4\text{-}ClC_6H_4$ / styryl	91/9	82	**d**
$4\text{-}MeOC_6H_4$ / styryl	89/11	79	**h**

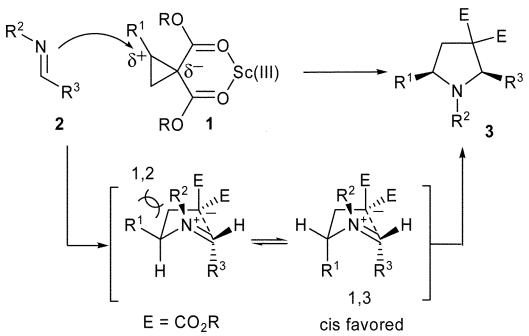
Scheme 2

The relative configurations of the adducts were assigned by ^1H–^1H NOESY as shown in Scheme 3.



Scheme 3

The mechanism[6] for this cycloaddition is proposed as in Scheme 4. A possible path is that the imine S_N2 attacks the cyclopropane directly in the assistance of $Sc(OTf)_3$ to form an iminium-enolate zwitterionic intermediate, which cyclizes immediately to afford the pyrrolidine. In this case, *cis*-isomer is produced preferably due to the steric hindrance between R^1 and R^2. This



Scheme 4

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is consistent with the stereochemistry produced. This mechanism can also explain that *N*-sulfonyl imine was inactive in this reaction.

In summary, we have developed an efficient method for the diastereoselective synthesis of multisubstituted pyrrolidines *via* a Lewis acid-catalyzed annulation reaction of cyclopropanes with imines. Noticeably, a corresponding three-component one-pot reaction, directly from aldehydes, amines and cyclopropanes, has proved to work well. The readily available starting material, high selectivity as well as high yield make this protocol potentially useful in organic synthesis. Efforts to develop its asymmetric version are in progress in our laboratory.

Experimental

All reactions were carried out under a nitrogen atmosphere. All of dialkyl 1,1-cyclopropanediesters[11] and their derivates[12] were synthesized according to the literature. The *N*-benzyl imines were synthesized *via* condensation of the corresponding aldehydes and benzyl amine.[13] MS 4 Å was powdered and vacuum activated at 250 °C before use.

General procedure

To an oven-dried reaction tube was sequentially added $Sc(OTf)_3$ (6.2 mg, 0.0125 mmol, 5 mol%), MS 4 Å (250 mg), cyclopropane (0.25 mmol in 1.5 mL of CH_2Cl_2) and imine (0.30 mmol in 1.0 mL of CH_2Cl_2). The resulting solution was further stirred at 25 °C. After the reaction was complete (monitored by TLC), the mixture was filtered rapidly through a glass funnel with a thin layer of silica gel, washed with CH_2Cl_2. The filtrate was concentrated and the residue was purified by flash column chromatography to afford the desired product.

General procedure for three-component reaction

To an oven-dried reaction tube was sequentially added MS 4 Å (250 mg), benzylamine and aldehyde in CH_2Cl_2 (2 mL) under stirring at 25 °C. The resulting suspension was stirred for 30 min and $Sc(OTf)_3$ (6.2 mg, 0.0125 mmol, 5 mol%) and cyclopropane (0.25 mmol in 0.5 mL of CH_2Cl_2) were added. The resulting mixture was further stirred at 25 °C for the desired time and filtered rapidly through a glass funnel with a thin layer of silica gel, washed with CH_2Cl_2. The filtrate was concentrated and the residue was purified by flash column chromatography to afford the desired product.

All compounds gave satisfactory spectral data (^{1}H NMR, ^{13}C NMR, IR, LRMS, HRMS, elemental analysis). Spectral data for representative compound **3b**: colorless oil (91% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, $J = 6.9$ Hz, 1H), 7.31–7.07 (m, 13H), 6.55 (d, $J = 16.2$ Hz, 1H), 6.16 (dd, $J = 11.4$, 15.9 Hz, 1H), 4.67 (s, 1H), 3.83 (d, $J = 14.1$ Hz, 1H), 3.70 (s, 3H), 3.64 (d, $J = 14.1$ Hz, 1H), 3.42–3.34 (m, 1H), 3.06 (s, 3H), 2.81 (dd, $J_{AB} = 13.5$ Hz, $J_{AX} = 10.8$ Hz, 1H), 2.25 (dd, $J_{AB} = 13.5$ Hz, $J_{BX} = 6.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.96, 169.55, 139.24, 136.87, 136.51, 131.98, 131.66, 129.82, 128.84, 128.41, 127.75, 127.70, 127.54, 127.44, 126.73, 126.34, 70.54, 63.95, 63.92, 54.07, 52.77, 51.96, 39.23; LRMS-ESI: 456.1 $(M + H)^+$; IR (thin film, cm^{-1}): 3027, 2951, 2830, 1733, 967, 755, 699; HRMS-ESI: Exact mass calcd for $C_{29}H_{30}NO_4$ $[M + H]^+$, 456.2169. Found 456.2167.

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