Chinese Chemical Letters 31 (2020) 1293–1296

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

Diastereoselective synthesis of functionalized tetrahydro-γ-carbolines *via* a [3 + 3] cycloaddition of 2,2′-diester aziridines with β-(indol-2-yl)-α,β-unsaturated ketones

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ARTICLE INFO

Article history:
Received 30 July 2019
Received in revised form 24 August 2019
Accepted 2 September 2019
Available online 4 September 2019

Keywords:
Aziridine
Tetrahydro-γ-carboline
[3 + 3] cycloaddition
$Sc(OTf)_3$
Diastereoselectivity

ABSTRACT

A $Sc(OTf)_3$-catalyzed [3 + 3] cycloaddition of 2,2′-diester aziridines with β-(indol-2-yl)-α,β-unsaturated ketones was developed, affording polysubstituted tetrahydro-γ-carbolines in single diastereoisomers in good to excellent yields.

Tetrahydro-γ-carboline derivatives featuring various biological properties have received an intense focus among medical chemists [1]. Efficient synthetic routes to this scaffold are still intensively pursued. Intramolecular cyclizations of functionalized indole derivatives for the synthesis of tetrahydro-γ-carbolines have received great attentions, including *iso*-Pictet-Spengler reaction [2] and Pd-catalyzed intramolecular alkylation [3]. In contrast, direct access to highly-substituted tetrahydro-γ-carbolines *via* the intermolecular cycloadditions of indolyl synthons still remained in highly desirable [4,5]. Considering the unique advantage of [3 + 3] cycloadditions in the rapid construction of diverse six-member ring structures [6–11], we recently reported copper-catalyzed asymmetric [3 + 3] cycloaddition of 2-indolylnitroethylenes with azomethine ylides [12], generated from aldimino esters, to construct highly substituted tetrahydro-γ-carbolines in moderate to high yields and an excellent level of stereoselectivity (Scheme 1, Eq. (1)). However, the transformation is companied with an inevitable competition between [3 + 2] cycloaddition and [3 + 3] cycloaddition, which displays an unsatisfying regioselectivity in some cases. Subsequently, the ketones derived azomethine ylides were employed in the reaction to prevent the competitive [3 + 2] cycloaddition and delivered the tetrahydro-γ-carbolines in excellent regioselectivities, however, a stronger Lewis acid $BF_3{\cdot}Et_2O$ was essential for the cyclization (Scheme 1, Eq. (2)) [13,14].

Donor-acceptor (D-A) aziridines, as potent precursors of azomethine ylides, prefer the C—C bond cleavage in the presence of Lewis acids, which can further undergo cycloadditions with various dipolarphiles [15–30]. Compared to the well-developed [3 +2] cycloadditions with two-atom dipolarphiles, [3 + 3] cycloadditions with three-atom moieties were still merely reported by Banerjee [31] and Kim [32,33]. In the context, we envisage selecting the 2,2′-diester aziridines as the precursors of azomethine ylides, which are attacked by the nucleophilic C3 position of the indole ring followed by an intermolecular Michael addition, to construct the biologically important tetrahydro-γ-carboline skeletons in one-step process (Scheme 1, Eq. (3)).

We initiated the present investigation of β-(indol-2-yl)-α,β-unsaturated ketone **1a** (1.0 equiv.) with 2,2′-diester aziridine **2a** (1.5 equiv.) in the presence of a catalytic amount of $Sc(OTf)_3$ (10 mol%) as the Lewis acid catalyst in DCM at room temperature. Since **2a** was the moisture sensitive compound, activated 4 Å molecular sieves (MS) were added. To our delight, the target product tetrahydro-γ-carboline **3aa** was generated in 96% yield with a single diastereoisomer (Table 1, entry 1). Subsequently, various Lewis acids were examined to optimize the reaction conditions (Table 1, entries 1–6), and $Sc(OTf)_3$ was selected as the optimal Lewis acid. Then, the effect of MS was evaluated (Table 1, entries 7 and 8). The absence of MS caused a diminished yield (71% yield), while switching to 5 Å MS led to the reaction time extending from 0.5 h to 2 h. Thus, 4 Å MS was chosen as an optimal additive.

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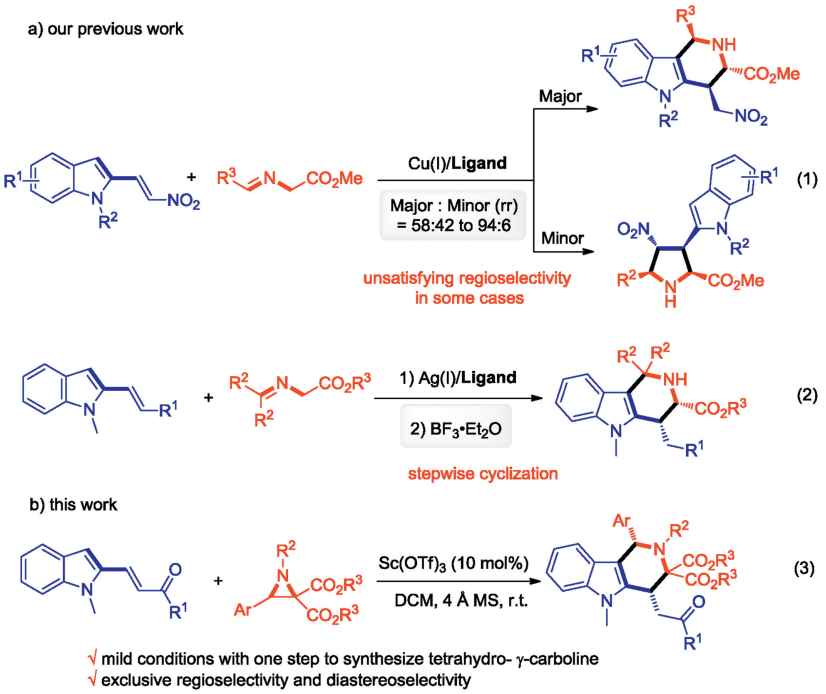
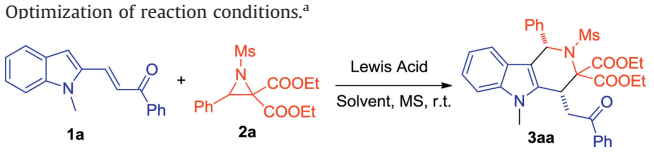
https://doi.org/10.1016/j.cclet.2019.09.002



Scheme 1. [3 + 3] cycloadditions to synthesize tetrahydro-γ-carbolines.

Table 1
Optimization of reaction conditions.[a]



Entry	Metal	MS	Solvent	Yield (%)[b]	Time (h)
1	$Sc(OTf)_3$	4 Å	DCM	96	0.5
2	$Cu(OTf)_2$	4 Å	DCM	95	0.5
3	$Cu(CH_3CN)_4BF_4$	4 Å	DCM	NR	48
4	$Ni(ClO_4)_2{\cdot}6H_2O$	4 Å	DCM	90	2
5	$NiCl_2{\cdot}6H_2O$	4 Å	DCM	NR	48
6	$Mg(OTf)_2$	4 Å	DCM	NR	48
7	$Sc(OTf)_3$	–	DCM	71	0.5
8	$Sc(OTf)_3$	54 Å	DCM	95	2
9	$Sc(OTf)_3$	44 Å	DCE	95	1
10	$Sc(OTf)_3$	44 Å	THF	80	72
11	$Sc(OTf)_3$	44 Å	Toluene	95	1
12[c]	$Sc(OTf)_3$	44 Å	DCM	84	2
13[d]	$Sc(OTf)_3$	44 Å	DCM	67	24

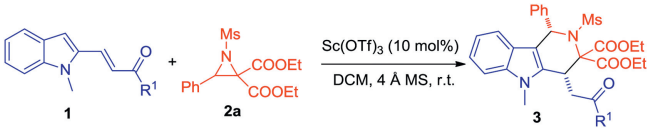
[a] **1a** (0.10 mmol), **2a** (0.15 mmol), Lewis acid (10 mol%), activated MS (100 mg) in anhydrous solvent (1.0 mL) at room temperature.
[b] Isolated yields, and only a diastereomer was observed in all cases.
[c] $Sc(OTf)_3$ (5 mol%) was used.
[d] $Sc(OTf)_3$ (2 mol%) was used.

Examination of solvent effect indicated that the reaction proceeds better in a chlorinated solvent considering yield and reaction time (Table 1, entries 9–11), with DCM as the best choice. Finally, by reducing the amount of the catalyst, the product was obtained with a decreased rate and a lowered yield (Table 1, entries 12 and 13). Therefore, we chose 10 mol% $Sc(OTf)_3$/4 Å MS/DCM as the optimal reaction conditions.

With optimized reaction conditions in hand, we embarked on the investigation of several β-(indol-2-yl)-α,β-unsaturated ketones with a variety of aryl and alkyl substituents. As summarized in Table 2, various tetrahydro-γ-carbolines were obtained in good to excellent yields. Introducing groups onto the *para*-situation of the phenyl ring, reactions gave the desired products in a yield of 61%–84% (**3ba**-**3fa**). Halogens such as Cl and Br, electron withdrawing groups such as CN, and electron donating groups such as CH_3 and CH_3O are tolerated in this transformation. The *ortho*-Bromo or *meta*-Bromo substituent does not affect the reaction result (**3ga**, **3ha**). Substrates with 2-thienyl and 2-naphthyl are also suitable for this reaction (**3ia**, **3ja**). When the phenyl ring on the indole derivatives was changed to *n*-butyl, the product **3ka** was obtained smoothly in a good yield.

Encouraged by these results, we further probed the reaction scope of the 2,2′-diester aziridines with different substituents. As illustrated in Table 3, aziridines were broadly tolerated with

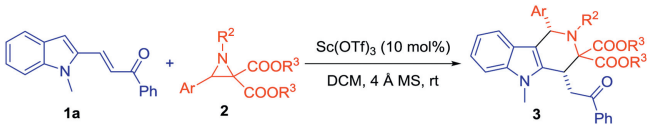
Table 2
Optimization of substrate scope of β-(indol-2-yl)-α,β-unsaturated ketones.[a]



Entry	R^1	3	Yield (%)[b]	Time (h)
1	*p*-ClC_6H_4 (**1b**)	**3ba**	71	1
2	*p*-BrC_6H_4 (**1c**)	**3ca**	74	1
3	*p*-CNC_6H_4 (**1d**)	**3da**	84	1
4	*p*-$CH_3C_6H_4$ (**1e**)	**3ea**	73	2
5	*p*-$MeOC_6H_4$ (**1f**)	**3fa**	61	1
6	*m*-BrC_6H_4 (**1 g**)	**3ga**	88	2
7	*o*-BrC_6H_4 (**1 h**)	**3ha**	80	2
8	2-thienyl (**1i**)	**3ia**	81	1
9	2-naphthyl (**1 j**)	**3ja**	78	3
10	*n*-butyl (**1k**)	**3ka**	82	2

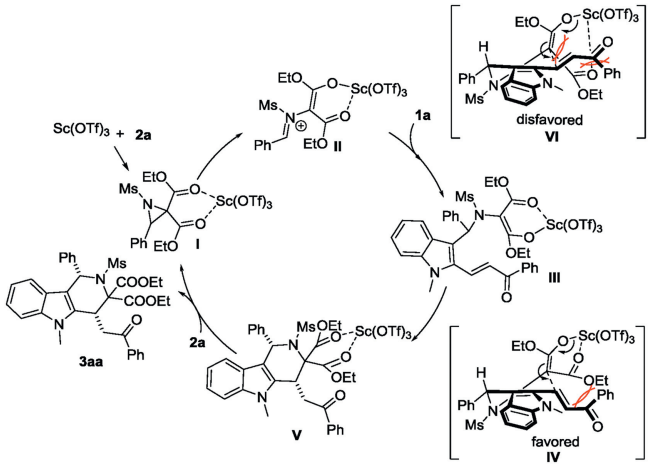
[a] **1** (0.10 mmol), **2a** (0.15 mmol), $Sc(OTf)_3$ (10 mol%), activated 4 Å MS (100 mg) in anhydrous DCM (1.0 mL) at room temperature.
[b] Isolated yields, and only a diastereomer was observed in all cases.

Table 3
Substrate scope of 2,2′-diester aziridines.[a]



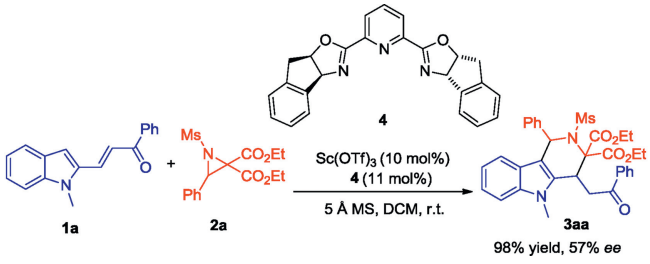
Entry	Ar/R^2/R^3	3	Yield (%)[b]	Time (h)
1	*p*-MeC_6H_4/Ms/Et (**2b**)	**3ab**	73	1
2	*p*-FC_6H_4/Ms/Et (**2c**)	**3ac**	91	0.5
3	*p*-ClC_6H_4/Ms/Et (**2d**)	**3ad**	59	1
4	*p*-$NO_2C_6H_4$/Ms/Et (**2e**)	**3ae**	73	1
5	*p*-PhC_6H_4/Ms/Et (**2f**)	**3af**	75	2
6	*m*-ClC_6H_4/Ms/Et (**2g**)	**3ag**	92	1
7	*o*-ClC_6H_4/Ms/Et (**2h**)	**3ah**	67	1
8	2-naphthyl/Ms/Et (**2i**)	**3ai**	89	1
9	C_6H_5/Ts/Et (**2j**)	**3aj**	94	24
10	C_6H_5/Ms/Me (**2k**)	**3ak**	88	0.5
11	C_6H_5/Ms/*i*-Pr (**2l**)	**3al**	98	4

[a] **1** (0.10 mmol), **2a** (0.15 mmol), $Sc(OTf)_3$ (10 mol%), activated 4 Å MS (100 mg) in anhydrous DCM (1.0 mL) at room temperature.
[b] Isolated yields, and only a diastereomer was observed in all cases.



Scheme 2. Mechanism of the reaction and origin of diastereoselectivity.

reasonable scope, irrespective of the electronic nature of the substituents on the phenyl ring (**3ab**-**3ai**). The structure and the relative stereochemistry of **3ag** were determined unambiguously by single crystal X-ray crystallographic analysis where phenyl and benzoylmethylene groups were found in the *cis* configuration (Supporting information for details). Crystallographic data of **3ag** (CCDC 1943454) can be obtained free of charge from the Cambridge Crystallographic Data Centre. *N*-Methylsulfonyl, 2,2-dimethyl ester and 2,2-diisopropyl ester substituted aziridines are also amenable to this transformation, providing corresponding products in good to excellent yields (**3aj**-**3al**).



Scheme 3. Catalytic enantioselective reaction to tetrahydro-γ-carbolines.

In the view of X-ray crystal results and literature reports [34], we outlined the plausible mechanism for this [3 + 3] cycloaddition in Scheme 2. To take the reaction between *β*-(indol-2-yl)-*α*,*β*-unsaturated ketone **1a** and 2,2′-diester aziridine **2a** as an example, **2a** first coordinates to $Sc(OTf)_3$ to form intermediate **I**, which results in C—C bond cleavage to form azomethine ylide **II**. Subsequently, a stepwise [3 + 3] cycloaddition occurs. The C3 position of indole nucleophile attacks the *N*-Ms iminium carbon, delivering intermediate **III**. By attacking the tethered activated olefin of its malonate anion moiety in Michael fashion, the following ring closing process gives rise to a $Sc(OTf)_3$ coordinated polysubstituted tetrahydro-*γ*-carboline **V**. Compared with the Michael acceptor in pseudoequatorial position suffering a severe gauche interaction with two ester groups in conformer **VI**, Michael acceptor in pseudoaxial position only has an interaction with one ester moiety in conformer **IV**, which is the favored conformer, providing the tetrahydro-*γ*-carboline **3aa** with the phenyl and benzoylmethylene groups in *cis* configuration. The final ligand exchange with **2a** liberates the product **3aa** and furnishes the catalytic cycle.

In principle, stereochemically enriched tetrahydro-γ-carboline derivatives of optical purity can be obtained by introducing the suitable chiral ligand onto the Lewis acid $Sc(OTf)_3$. After screening of various chiral ligands (Supporting inforamtion for details), unfortunately, only moderate enantioselectivity (57% *ee*) was obtained by using the commercially available Pybox **4** as the ligand under reaction conditions depicted in Scheme 3. Although the enantioselectivity is not good enough as yet, it still manifests that an asymmetric reaction is feasible.

In conclusion, we have developed a mild and practical synthetic strategy to polysubstituted tetrahydro-*γ*-carbolines in one-step process. A wide range of tetrahydro-*γ*-carbolines were obtained in single diastereoisomers in good to excellent yields *via* $Sc(OTf)_3$ catalyzed [3 + 3] cycloaddition of 2,2′-diester aziridines with *β*-(indol-2-yl)-*α*,*β*-unsaturated ketones. In addition, the enantioselective version was also investigated, albeit with moderate *ee* value.

Acknowledgments

This work is supported by the National Natural Science Foundation of China (No. 21772038) and the China Postdoctoral Science Foundation (No. 2018M632037).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cclet.2019.09.002.

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