Organocatalysis

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Asymmetric Synthesis of Bioactive Hydrodibenzofuran Alkaloids: (−)-Lycoramine, (−)-Galanthamine, and (+)-Lunarine**

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Dedicated to Professor Henri B. Kagan

The hydrodibenzofuran alkaloids constitute a structurally diverse group of natural products, and include some of the *Amaryllidaceae*, *Lunaria*, and *Opium* alkaloids (Figure 1).[1] These compounds contain a functionalized *cis*-hydrodibenzofuran nucleus with a crucial all-carbon quaternary stereogenic center, which is a unique characteristic of their core molecular architecture. Importantly, the asymmetric construction, especially in a catalytic fashion, of chiral all-carbon quaternary centers, which are present in biologically important natural products, is one of the most challenging and dynamic research areas in modern organic synthesis.[2] From a synthetic point of view, the stereoselective establishment of the sterically congested quaternary carbon atom in **A** (Figure 1) would be the critical element in the diversity-oriented asymmetric synthesis of these alkaloids. Two *Amaryllidaceae* alkaloids (lycoramine and galanthamine) and one *Lunaria* alkaloid (lunarine) were selected as our present targets for the exploration of new synthetic methods and strategies in the total synthesis of related bioactive natural products. Owing to their intriguing structures as well as their biological and pharmacological potential, these alkaloids have attracted considerable attention from organic chemists. In regard to these three natural alkaloids, there are several synthetic routes for the asymmetric synthesis of galanthamine and lycoramine,[3–7] but no reports on the chiral synthesis of lunarine.[8] Over the past five decades since the first pioneering studies on the synthesis of (−)-galanthamine and (−)-lycoramine by Barton and Kirby in 1962,[4a] the stereoselective installation of such key quaternary stereogenic centers in the asymmetric total synthesis of these compounds has been strategically approached in the following two ways: 1) the indirect approach, which accesses such stereogenic centers from the prochiral quaternary carbon atom through the enantioselective desymmetrization[4] of racemic substrates by retro-oxa-Michael addition/oxa-Michael addition/spontaneous resolution or through the diastereoselective desymmetrization[5] of chiral substrates by intramolecular oxa-Michael addition, and 2) the direct approach for the formation of a C–C bond centered on the chiral quaternary carbon atom through diastereoselective intramolecular Heck reactions[6] and diastereoselective [3,3]-sigmatropic rearrangements,[7] with stoichiometric amounts of chiral precursors. To our knowledge, however, no direct C–C bond-forming, catalytic, enantioselective approach to the key quaternary stereogenic centers in galanthamine, lycoramine, and lunarine (Figure 1) has been reported.[3–8]

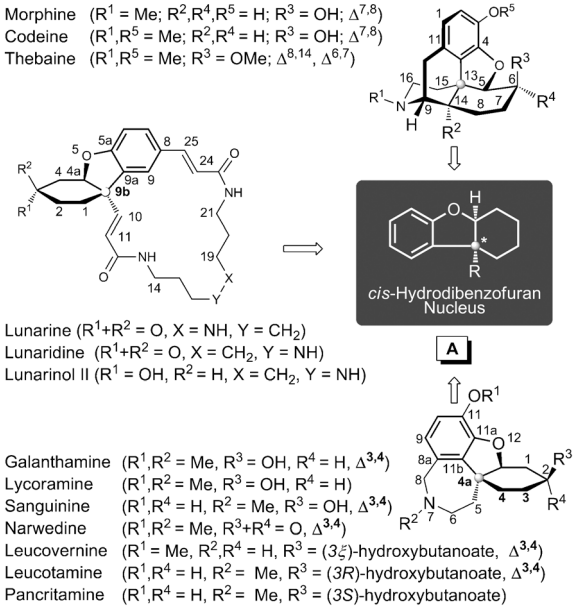

Figure 1. Representative members of hydrodibenzofuran alkaloids.

To address this topic, a strategic diversity-oriented retrosynthetic analysis is shown in Scheme 1; the key feature of this analysis is a new catalytic asymmetric intermolecular Michael addition of α-cyanoketones with acrylates for the stereocontrolled construction of highly functionalized building blocks **3**, which contain the key sterically congested aryl-substituted quaternary carbon atom.[9–11] Notably, the catalytic enantioselective assembly of all-carbon quaternary stereocenters by a Michael addition has still not yet been fully explored in

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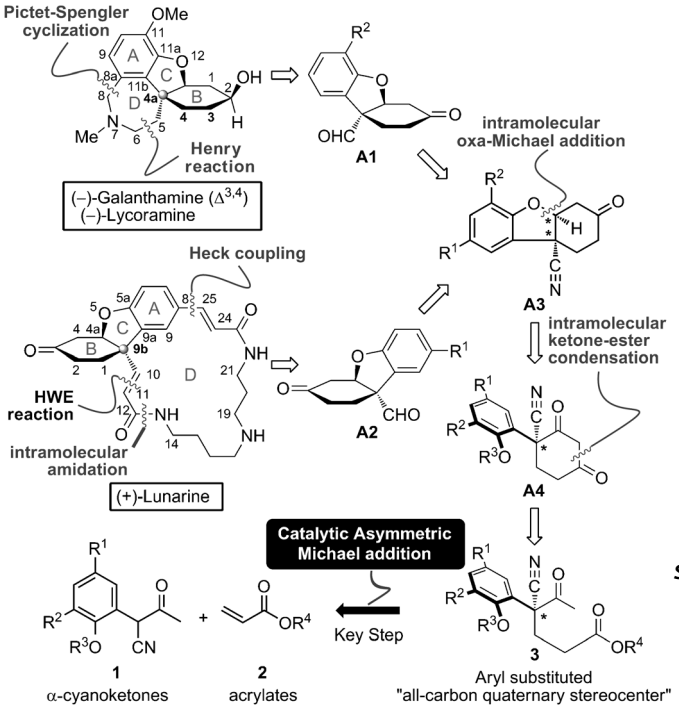
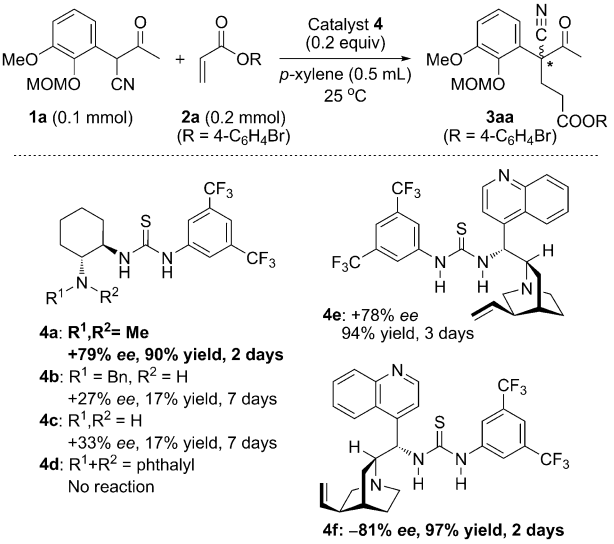


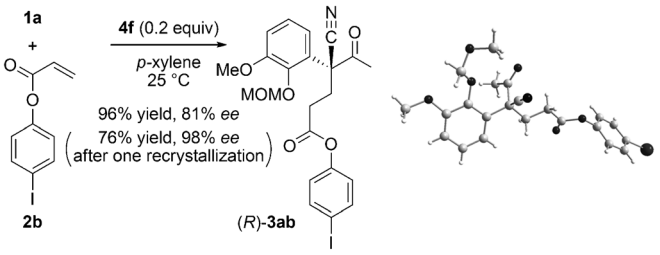
Scheme 1. Strategically diversity-oriented retrosynthetic analysis.



Scheme 2. Optimization of the designed key Michael addition.

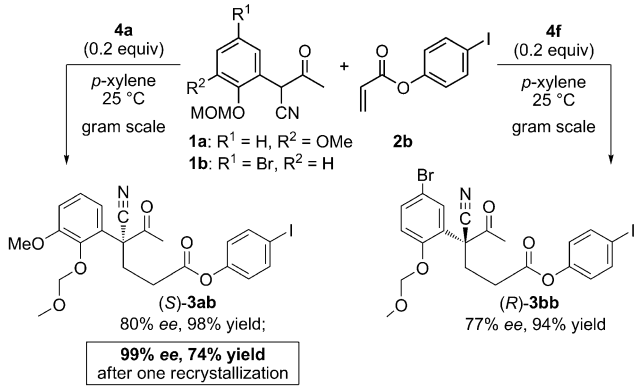
natural product total synthesis.[2] As conceived above, once the Michael adduct **3**, the enantioselectivity of which is tunable, is formed, the stereochemically defined synthon **A3** having a *cis*-hydrodibenzofuran core structure can be envisaged to arise through transformations that mainly involve a intramolecular ketone-ester condensation and a intramolecular oxa-Michael addition. Divergently, the two key advanced building blocks **A1** and **A2**, a pair of pseudoenantiomers, can be designed for the enantioselective approach to these three alkaloids. In the synthesis of (−)-lycoramine and (−)-galanthamine, the C5–C6 and C8–C8a bonds will be formed by a Henry reaction and a Pictet–Spengler cyclization, respectively. For the synthesis of (+)-lunarine, the formation of the bonds C8–C25, C10–C11, and C12–N will be considered sequentially by a Heck coupling, a Horner–Wadsworth–Emmons reaction (HWE reaction), and an intramolecular amidation.

To explore the unprecedented asymmetric Michael addition that was proposed in the retrosynthetic strategy, α-aryl-α-cyanoketone **1a** and 4-bromophenyl acrylate (**2a**) were initially used as a model for our total synthesis (Scheme 2). Among the various solvents examined, *p*-xylene was the more suitable reaction medium in terms of the enantioselectivity as well as the reactivity of the current catalyst. Based on the bifunctional catalysis mode involving Brønsted acid and base, a series of readily available amine-thiourea catalysts **4a**–**4f** in *p*-xylene were then investigated, of which the Takemoto catalyst **4a**[12] and cinchonidine-derived bifunctional catalyst **4f**[13] gave the optimum results and allowed for tuning of the enantioselectivity. As shown in the retrosynthetic analysis (Scheme 1), the configuration of all the requisite stereocenters in the target alkaloids would originate from the key quaternary carbon center, and so the unambiguous assignment of the configuration in the related Michael adduct **3** is necessary for our natural product synthesis. Because of the failed attempts to crystallize **3aa** (Scheme 2), an alternative Michael acceptor **2b** containing the heavy iodine atom was subjected to the current optimized reaction conditions (Scheme 3), and the desired Michael product **3ab** (96% yield, 81% *ee*) was obtained in the presence of the catalyst **4f**. The absolute configuration of the chiral all-carbon quaternary stereocenter in **3ab** (98% *ee*, after one recrystallization) was then successfully confirmed as *R* by X-ray crystallography.[14]



Scheme 3. Determination of the absolute configuration.

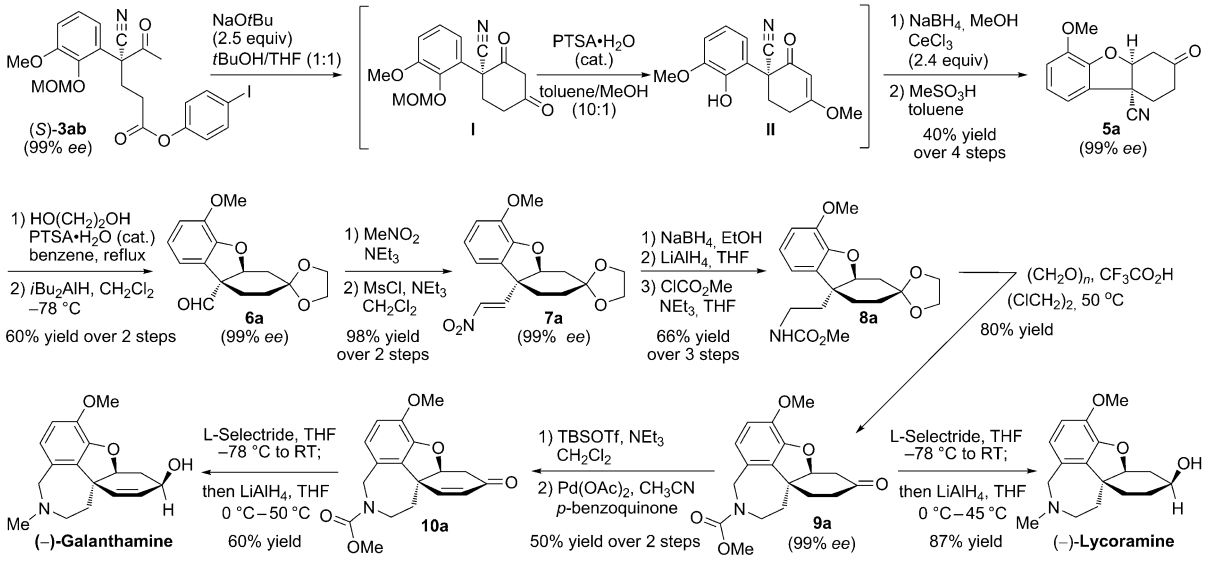
Having developed this organocatalytic Michael reaction, we could focus our attention on the synthesis of key intermediates **3**, which possess the requisite stereochemistry for the synthesis of natural alkaloids (Scheme 1). As shown in Scheme 4, the functionalized δ-keto ester (*S*)-**3ab** featuring an aryl-substituted all-carbon quaternary center[15] was readily obtained as a white solid by the Michael addition of **1a** and **2b** on a gram scale under the catalysis of **4a**, and an optical purity of 99% *ee* with 74% yield could be achieved after one recrystallization, thus providing a basis for the enantioselective synthesis of galanthamine-type alkaloids. The use of catalyst **4f** led to the reversed enantioselectivity in the asymmetric Michael addition of **1b** and **2b** on a gram scale, and the multifunctionalized δ-keto ester (*R*)-**3bb** was



Scheme 4. Synthesis of key pseudoenantiomeric synthons.

obtained as a viscous liquid in 77% *ee* and 94% yield, after which the enantiopurity could be further enriched to 99% *ee* by a late-stage recrystallization (see **6b** in Scheme 6) in the synthesis of (+)-lunarine.

As a member of the *Amaryllidaceae* alkaloids, (−)-galanthamine, which structurally could also be regarded as a hydrodibenzofuran alkaloid, was originally isolated from *Galanthus woronowill* in 1952,[16] and its absolute configuration was first established by X-ray crystallography in 1964.[17] Since the 1990s, (−)-galanthamine has been used clinically as a selective, reversible, and competitive acetylcholinesterase inhibitor for the treatment of Alzheimer's disease.[3] Another galanthamine-type alkaloid, (−)-lycoramine was isolated earlier from *Lycoris radiate* in 1932,[18] and its relative configuration was definitively assigned in 1962.[4a] Biologically, (−)-lycoramine has a similar acetylcholinesterase-inhibiting activity, and also has been claimed to significantly inhibit the formation of peptide bonds in protein synthesis.[19] Because of their biological significance and unique tetracyclic structure, several elegant asymmetric routes have been described.[3–7] In this context, our enantioselective synthesis is shown in Scheme 5. (*S*)-**3ab**, obtained above, underwent an intramolecular ketone-ester condensation in the presence of sodium *tert*-butoxide to give the 1,3-diketone **I**. Acid-catalyzed regioselective methyl etherification, followed by the in situ deprotection of the phenolic MOM ether, afforded the labile phenolic enol ether **II**, which was then sequentially subjected to a Luche reduction, acidic hydrolysis, and an in situ intramolecular oxa-Michael addition, to give the tricyclic intermediate **5a** with the key *cis*-hydrodibenzofuran skeleton in 40% yield over 4 steps. Then, an acid-catalyzed ketalization of the ketone group and a subsequent DIBAL-H reduction of the cyano group resulted in the formation of the enantiopure aldehyde **6a** in 60% yield over 2 steps. A Henry reaction and a subsequent elimination of the resultant methanesulfonate were used for the one-carbon homologation, which delivered the nitroolefin **7a** in 98% yield over 2 steps. The N protection of the primary amine, which was generated from the sequential reduction of the conjugated nitroalkene **7a**, afforded the carbamate **8a** in 66% yield over 3 steps. A Pictet–Spengler cyclization of **8a** using paraformaldehyde gave the tetracyclic intermediate **9a** with the seven-membered azepine ring in 80% yield. Notably, no loss of enantiomeric excess was observed in these chemical transformations, and all the isolated intermediates (**5a**–**9a**) were obtained with 99% *ee*. From the common intermediate **9a**, asymmetric access to (−)-lycoramine (8.1% overall yield from **1a**) was smoothly achieved by diastereoselective reduction of the ketone motif and a further one-pot reduction of the carbamate group. The NMR spectroscopic data are identical to those from previous syntheses,[7b,20] and the specific rotation of our synthetic (−)-lycoramine ($[\alpha]_D^{21} = -92.7\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 3.5 \times 10^{-3}\ \mathrm{g\,cm^{-3}}$, EtOH)) was consistent with the reported value.[7b,21] Divergently, the regioselective dehydrogenation of **9a** proceeded by a Saegusa oxidation of the silyl enol ether to furnish the desired enone

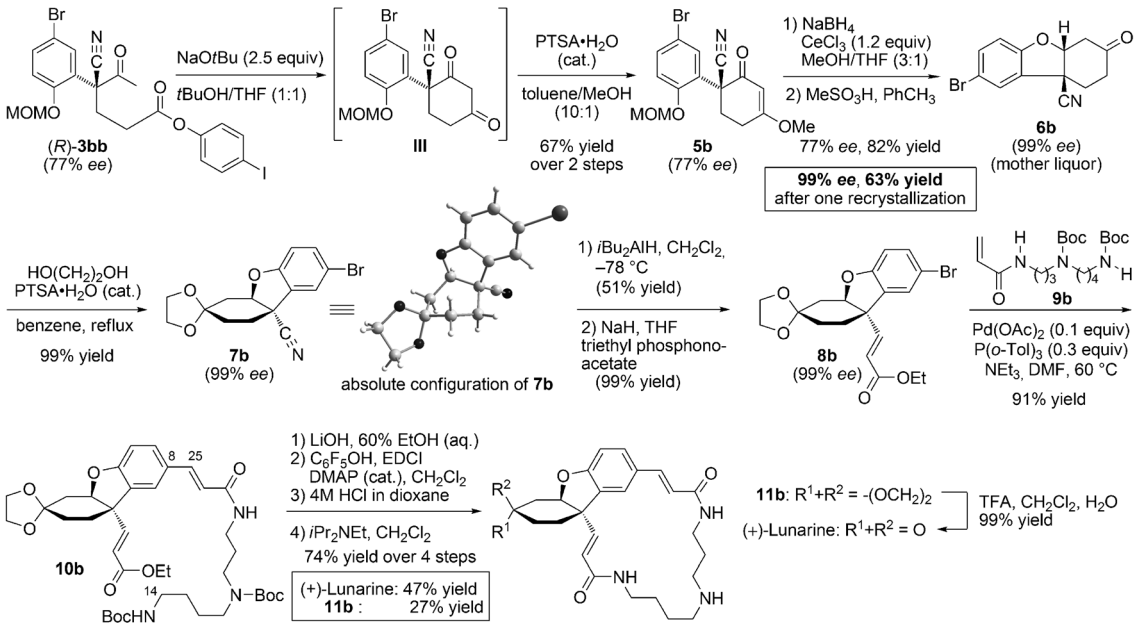


Scheme 5. Enantioselective synthesis of (−)-lycoramine and (−)-galanthamine. MOM = methoxymethyl, Ms = methanesulfonyl, PTSA = *p*-toluenesulfonic acid, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

10a. This enone might be a potentially useful synthetic intermediate for the late-stage synthesis of more potent galanthamine analogues, which bear various nitrogen substituents,[6b,22] through a procedure involving enone reduction, carbamate hydrolysis, and N alkylation. A one-pot reduction protocol with L-Selectride and $LiAlH_4$ was then applied to **10a**, which led successfully to the enantioselective synthesis of (−)-galanthamine (2.8% overall yield from **1a**; $[\alpha]_D^{21} = -91.3\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.0\times10^{-2}\ g\,cm^{-3}$, $CHCl_3$); natural galanthamine $[\alpha]_D^{25} = -91.0\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.0\times10^{-2}\ g\,cm^{-3}$, $CHCl_3$);[4b] $[\alpha]_D^{25} = -93.4\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.0\times10^{-2}\ g\,cm^{-3}$, $CHCl_3$))[4b] with spectroscopic characteristics identical to those reported in the literature.[5,6,23]

(+)-Lunarine, one of the *Lunaria* alkaloids, was first isolated from *Lunaria biennis* Moench (Cruciferae) in 1908,[24] and its absolute configuration was determined by X-ray diffraction analysis in 1970.[25] The related biological study demonstrated that this macrocyclic polyamine alkaloid could be a potential lead inhibitor of trypanothione reductase (TryR), which plays an important role in the parasites' defence against reactive oxygen species generated by host cells.[8b,c] A recent biological study interestingly revealed that the unnatural (−)-lunarine could be a more potent inhibitor of TryR.[8c] Over the past 40 years since the establishment of its absolute configuration, there has been no report on its asymmetric synthesis to date.[8] One route for the enantioselective synthesis of (+)-lunarine was developed as shown in Scheme 6. With the key functionalized intermediate (*R*)-**3bb** in hand, the corresponding intramolecular ketone-ester condensation in the presence of sodium *tert*-butoxide was carried out to give the 1,3-diketone **III**, which was then directly transformed through an acid-catalyzed regioselective etherification into the stable enol ether **5b** in 67% yield over 2 steps. The sequential procedure that includes the Luche reduction of the enone group and an acid-promoted hydrolysis delivered the key tricyclic intermediate **6b**. Gratifyingly, a recrystallization of **6b** could be readily performed, thus achieving the enantiomeric enrichment of the mother liquor to obtain **6b** in 63% yield and 99% *ee* after the separation of the racemate crystals. Following the acid-catalyzed ketalization using ethylene glycol, 1,3-dioxolane **7b** was obtained in a crystalline form in 99% yield and 99% *ee*, and its absolute configuration was further confirmed by X-ray crystallography.[14] Upon reduction of the cyano group in **7b**, and a subsequent Horner–Wadsworth–Emmons reaction, the unsaturated ester **8b** was obtained in 50% yield and 99% *ee* over 2 steps. A Heck reaction with the known spermidine derivative **9b**[8b,26] was performed to attach the nitrogen-containing side chain (C14–C25) at the C8-position in **10b**.[8b] By subsequently employing the four-step procedure described by Eggleston and co-workers,[8b] the asymmetric synthesis of (+)-lunarine was finally accomplished through a basic aqueous hydrolysis of the ester, a carboxylic acid activation using a pentafluorophenyl ester, a non-aqueous acidic N-Boc deprotection with the partial removal of the 1,3-dioxolane group, and a regioselective intramolecular macrocyclization of the less sterically hindered primary amine. In addition to the isolation of (+)-lunarine in 47% yield over 4 steps ($[\alpha]_D^{21} = +262.3\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.0\times10^{-2}\ g\,cm^{-3}$, $CHCl_3$); Lit. $[\alpha]_D^{20} = +291\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.03\times10^{-2}\ g\,cm^{-3}$, $CHCl_3$)[27]), the macrocyclic product **11b**, in which the carbonyl group was protected as a dioxolane, was also obtained in 27% yield; this compound could be completely transformed in the presence of aqueous trifluoroacetic acid to (+)-lunarine in almost quantitative yield. All spectroscopic data (^1H NMR, ^{13}C NMR, and HRMS) of our synthetic (+)-lunarine (13.4% overall yield from cyanoketone **1b**) were in accord with the structure in the literature.[8b,28]

In conclusion, by using an unprecedented Michael addition of α-cyanoketones and acrylates under the bifunctional



Scheme 6. First asymmetric synthesis of (+)-lunarine. Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*′-dimethylformamide, EDCI = 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride, TFA = trifluoroacetic acid, Tol = tolyl.

catalysis of a tertiary amine-thiourea catalyst, our current study, which focused on the asymmetric synthesis of *Amaryllidaceae* and *Lunaria* alkaloids, presents the first synthetic strategy for the catalytic enantioselective creation of the key aryl-substituted quaternary carbon center by a direct C–C bond-forming tactic. Based on the preliminary exploration of this method, as well as a recrystallization process, a novel enantioselective synthesis of (−)-lycoramine and (−)-galanthamine was accomplished, and also the first asymmetric synthesis of (+)-lunarine was achieved. Synthetically, this divergent nonbiomimetic strategy should allow for a stereocontrolled entry into a variety of biologically important natural and unnatural galanthamine-type *Amaryllidaceae* and lunarine-type *Lunaria* alkaloids.

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