Cascade Reactions

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Stereoselective Intermolecular Formal [3+3] Cycloaddition Reaction of Cyclic Enamines and Enones**

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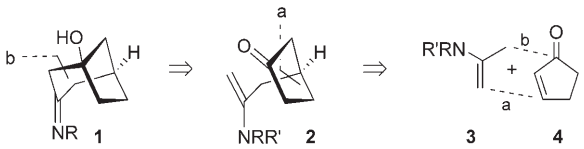
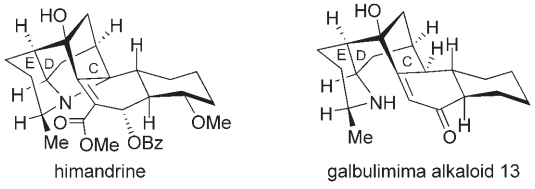
The development of new tandem C–C bond-forming reactions with control of stereochemistry is of fundamental interest in organic synthesis.[1] Important discoveries in conjugate-addition chemistry have resulted in a variety of valuable catalytic and asymmetric methodologies for fine-chemical synthesis.[2] Herein we report a new highly diastereoselective reaction involving cyclic enamines and enones that provides rapid access to tricyclic imino alcohols and derivatives thereof (Scheme 1). Additionally, we discuss our findings in the development of catalytic and asymmetric variants of this formal [3+3] cycloaddition reaction.



Scheme 1. Formal [3+3] cycloaddition reaction.

Enamines and metalloenamines have served as powerful nucleophiles in a wide range of bond-forming reactions,[3,4] including many cycloaddition reactions.[5] Motivated by the efficiency of the transient-δ-imino ketone strategy that we employed[6] for the introduction of the CDE ring system of class II and class III galbulimima alkaloids[7] (Scheme 2), we sought to develop a new formal [3+3] cycloaddition reaction.



Scheme 2. Representative galbulimima alkaloids. Bz = benzoyl.

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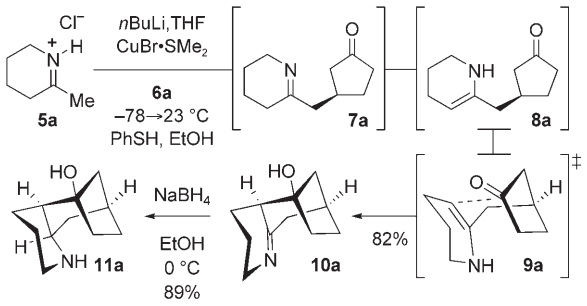
We postulated that the conjugate addition of the organocuprate reagent[8] derived from the readily available iminium chloride **5a** to cyclopent-2-enone (**6a**) would afford the imino ketone **7a**, which might spontaneously undergo tautomerization and addition to the carbonyl group to give the tricyclic imino alcohol **10a** (Scheme 3).[9,10] Gratifyingly, the addition

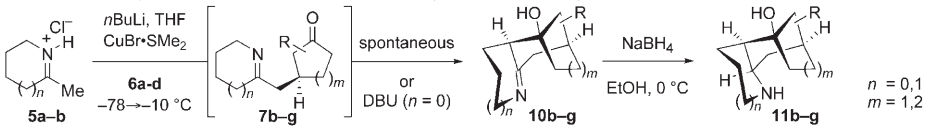


Scheme 3. Rapid synthesis of the CDE ring system of class II and III galbulimima alkaloids.

of enone **6a** to a cold solution of the homocuprate (1.5 equiv),[9,11] followed by warming of the mixture, gave the corresponding tricyclic imino alcohol **10a** as a single diastereomer in 82% yield. The addition of thiophenol (1.5 equiv) and strict exclusion of dioxygen during workup were critical in the isolation of this sensitive product.[9] Reduction of the imine with sodium borohydride gave the tricyclic amino alcohol **11a**, which constitutes the CDE tricyclic substructure of class II and III galbulimima alkaloids (Scheme 2).[12] The relative configuration of the four stereocenters in amino alcohol **11a** was confirmed by X-ray crystallographic analysis[9] and is consistent with the chairlike transition-state structure **9a** for the intramolecular addition to the carbonyl group.[13]

The reaction of iminium chloride **5a** with enones **6b–d** under the optimal reaction conditions described above afforded the corresponding tricyclic imino alcohols in a single step (Table 1, entries 1–3). As the imino alcohols **10c** and **10d** proved highly sensitive toward oxidation by air, they were converted into tricycles **11c** and **11d**, respectively, for ease of isolation (Table 1, entries 2–3). The configuration at C12[9] of amino alcohol **11c**, which has five contiguous stereocenters, is consistent with transient formation of imino ketone **7c**, followed by intramolecular addition of the enamine to the carbonyl group. The stereoselective formation of tricycles **11a–c** via the corresponding imino ketones **7a–c** is consistent with our proposed biogenesis of this substructure in the galbulimima alkaloids.[6] The use of iminium chloride **5b**[9]

Table 1: Highly diastereoselective sequential 1,4- and 1,2-addition of cyclic imines to cyclic enones.[a]



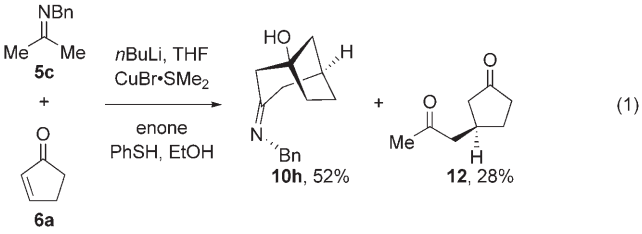
Entry	Iminium chloride	Enone	1,4-Adduct	Yield [%][b]	Imino alcohol	Yield [%][b]	Amino alcohol	Yield [%][b]
1	**5a**	**6b**	**7b**	–	**10b**	72	**11b**	91
2	**5a**	**6c**	**7c**	–	**10c**	–	**11c**	55[c]
3	**5a**	**6d**	**7d**	–	**10d**	–	**11d**	50
4	**5b**	**6a**	**7e**	88	**10e**	85	**11e**	93
5	**5b**	**6b**	**7f**	67	**10f**	91	**11f**	87
6	**5b**	**6d**	**7g**	70	**10g**	82	**11g**	88

[a] The optimized reaction conditions were used uniformly.[9] [b] Yield of the isolated product as a single diastereomer. [c] Yield of the isolated product as a mixture of diastereomers at C12 (8:1); major isomer shown.[9] Cbz = benzyloxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

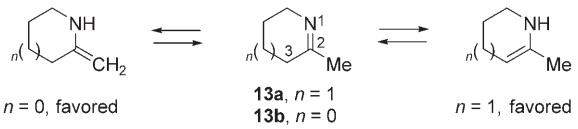
under the same reaction conditions resulted in the stable imino ketones **7e–g** (Table 1, entries 4–6). The isolation and greater stability of these imino ketones is probably a result of slower imine/enamine tautomerization (see below). Treatment of the isolated imino ketones **7e–g** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ethanol provided the desired tricyclic imino alcohols **10e–g** as single diastereomers. Reduction of the imine proceeded with complete diastereoselectivity to give the corresponding amino alcohols (Table 1, entries 4–6). Similarly, 1,2-addition of allylmagnesium chloride to a derivative of imine **10e** gave the corresponding tertiary amine as a single diastereomer.[14]

The resistance of cyclic imines toward hydrolysis makes them more effective substrates than acyclic imines for this chemistry. The use of the acyclic imine **5c** and enone **6a** under the optimal reaction conditions described above provided the desired imino alcohol **10h** (52%), along with the product of competitive hydrolysis **12** [28%, Eq. (1); Bn = benzyl].[15] No products of sequential addition were observed when acyclic enones (e.g., PhCH=CHCOPh or PhCH=CHCOMe) were used under the standard reaction conditions.

Interestingly, incomplete double deprotonation of iminium ion **5a** prior to cuprate formation led to equilibration between the isomeric metalloenamines. Monitoring of a solution of the six-membered-ring imine **13a** in [D_6]DMSO–D_2O (3:2, 0.5 mM) revealed greater than 90% deuterium incorporation at C3 and C2–Me within 10 min and 9 h, respectively (Scheme 4).[9] However, the five-membered-ring imine **13b** required 96 h before 90% deuterium incorporation at C2–Me was observed, at which time less than 25% deuterium incorporation at C3 was detected.



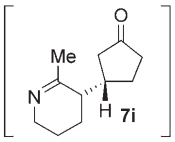
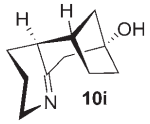
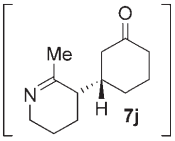
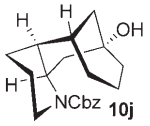
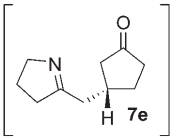
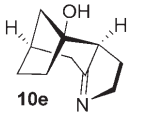
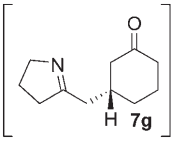
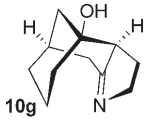
These observations revealed the favored enamine tautomers and prompted us to explore the direct utilization of the



Scheme 4. Equilibration of enamine tautomers.[9]

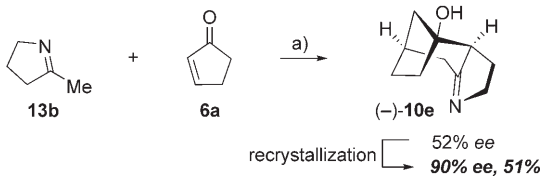
enamines in place of the corresponding metalloenamine derivatives as nucleophiles in this formal [3+3] cycloaddition. Inspired by the recent advances in organocatalytic transformations,[16] we envisaged the activation of the enone in the form of an unsaturated iminium ion to facilitate the conjugate addition of the enamines. Various catalysts and solvents were screened, and proline[17] proved particularly effective as the catalyst in a mixture of trifluoroethanol (TFE) and water.[9] When a solution of imine **13a** and enone **6a** in TFE–water (10:1) was heated at 50 °C, the desired tricyclic imino alcohol **10i** was isolated in 91% yield as a single diastereomer (Table 2, entry 1).[18] The relative stereochemistry of imino alcohol **10i** was established by X-ray crystallography.[9] The tricyclic imino alcohol **10i** is isomeric with the product obtained with the cuprate chemistry (imino alcohol **10a**, Scheme 3), and its formation is consistent with the intermediacy of the preferred six-membered-ring enamine with an endocyclic double bond (Scheme 4). The exclusion of water as a cosolvent led to a decrease in the yield of the desired tricyclic imino alcohol products. The use of the free-base imines **13a–b** in place of the corresponding iminium chloride derivatives **5a–b** was found to give generally better results. In only one case was the intermediate 1,4-addition product isolated along with the desired tricyclic imino alcohol (Table 2, entry 3). The use of the protic solvent system and higher temperatures allowed direct conversion of recalcitrant intermediates (that is, imino ketones **7e** and **7g**) into the corresponding tricyclic imino alcohols.

Table 2: Single-step catalytic diastereoselective intermolecular formal [3+3] cycloaddition reaction.[a]

Entry	13	6	1,4-adduct	Product	Yield [%][b]
1[c]	**13a**	**6a**	 **7i**	 **10i**	91, 90[d]
2[c]	**13a**	**6d**	 **7j**	 **10j**	78[e]
3[f]	**13b**	**6a**	 **7e**	 **10e**	40, 21[g]
4[f]	**13b**	**6d**	 **7g**	 **10g**	56

[a] Reaction conditions: L-proline (10 mol%), TFE–water (10:1), 16 h.[9] [b] Yield of the isolated product as a single diastereomer. [c] $T = 50$ °C. [d] Yield of the corresponding amino alcohol upon the treatment of **10i** with $NaBH_4$ and EtOH at 0 °C. [e] Yield after reduction of the imine and N protection. [f] $T = 80$ °C. [g] Yield of **7e**.

Intrigued by the above results, we explored the extension of this chemistry to catalytic asymmetric synthesis. The use of chloroform as the solvent in place of TFE–water led to a modest level of enantioselectivity in the conjugate addition of imine **13b** to enone **6a** (Scheme 5).[9] Warming of a solution of imine **13b** and enone **6a** in chloroform provided the initial 1,4-conjugate-addition product, which was converted upon treatment with DBU into the desired tricyclic imino alcohol (−)-**10e** with 52% *ee*. The optical purity was increased to 90% *ee* through a single recrystallization from *n*-pentane–diethyl ether (1:1).[9] The absolute stereochemistry of the imino alcohol (−)-**10e** was determined by X-ray crystallographic analysis of the corresponding amino alcohol cocrystallized with L-tartaric acid (1 equiv).[9]



Scheme 5. Catalytic asymmetric synthesis of (−)-**10e**: a) L-proline (20 mol%), $CHCl_3$, 45 °C, 48 h (50%); DBU, EtOH, 78 °C (80%).

The chemistry described herein relies on the sequential Cα and Cα′ alkylation of unsymmetrical ketoimines and allows rapid generation of molecular complexity with excellent stereochemical control. This new formal [3+3] cycloaddition reaction provides a practical solution to the synthesis of fused tricyclic imino alcohol derivatives.[19] We envisage the further development of this methodology and its application to target-oriented synthesis by building on advances in catalyst- and substrate-controlled conjugate-addition chemistry.[2,16,20] The complementary copper-promoted and proline-catalyzed variants of this reaction enable the highly selective and rapid introduction of at least three stereocenters in a convergent assembly of these tricyclic products and offer a valuable addendum to methodologies for the synthesis of complex molecules.

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[9] See Supporting Information for details.

[10] Imine **13a** was readily prepared by a procedure based on those described by: T. N. Van, N. De Kimpe, *Tetrahedron* **2000**, *56*, 7969; B. G. Davis, M. A. T. Maughan, T. M. Chapman, R. Villard, S. Courtney, *Org. Lett.* **2002**, *4*, 103; for optimum results, **13a** is stored as the corresponding HCl salt **5a** to minimize oxidation by air.

[11] The use of heterocuprates or fewer than 1.5 equivalents of the homocuprate gave inferior results.

[12] The isolation and purification of **10a** prior to its reduction is not required, but is recommended for optimum results.

[13] The product of a boatlike transition state has not been observed.

[14] The use of the corresponding *O*-TMS derivative of **10e** was found to be optimal; for a review, see: D. Enders, U. Reinhold, *Tetrahedron: Asymmetry* **1997**, *8*, 1895.

[15] Competitive hydrolysis of the initial 1,4-addition product occurs during workup.

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[19] A variety of modulators of cholinergic activity contain cyclic amines or amino alcohols as rigid acetylcholine analogues; see: a) J. W. Clader, Y. Wang, *Curr. Pharm. Design* **2005**, *11*, 3353; b) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701; c) K. J. Broadley, D. R. Kelly, *Molecules* **2001**, *6*, 142.

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