

Published in final edited form as:

Angew Chem Int Ed Engl. 2007 ; 46(4): 565–568. doi:10.1002/anie.200603302.

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

Prof. Dr. Mohammad Movassaghi* and Dr. Bin Chen

Department of Chemistry Massachusetts Institute of Technology Cambridge, Massachusetts 02139 (USA)

The development of new tandem C-C bond forming reactions with control of stereochemistry is of fundamental interest in organic synthesis.^[i] Important discoveries in conjugate addition chemistry have resulted in a variety of valuable catalytic and asymmetric methodologies for fine chemical synthesis.^[iii] 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.

Enamines and metalloenamines have served as powerful nucleophiles in a wide range of bond forming reactions,^[iii,iv] including many cycloaddition reactions.^[v] Motivated by the efficiency of the transient δ -iminoketone strategy that we employed^[vi] for the introduction of the CDE-ring system of Class II and Class III galbulimima alkaloids^[vii] (Figure 1) we sought to develop a new formal [3+3]-cycloaddition reaction. We postulated that the conjugate addition of the readily available iminium chloride **5a**-derived organocuprate reagent^[viii] to cyclopent-2-enone (**6a**) would afford the imino ketone **7a** (Scheme 2) which could spontaneously undergo tautomerization and carbonyl addition to give the tricyclic imino alcohol **10a**.^[ix,x] Gratifyingly, introduction of enone **6a** to a cold solution of the homocuprate (1.5 equiv)^[9,xi] followed by warming gave the corresponding tricyclic imino alcohol **10a** as a *single diastereomer* in 82% isolated yield. The introduction of thiophenol (1.5 equiv) and strict exclusion of dioxygen during workup were critical in isolation of this sensitive product.^[9] Reduction of the imine with sodium borohydride gave the tricyclic aminoalcohol **11a** which constitutes the CDE-tricyclic substructure of Class II and III galbulimima alkaloids (Figure 1).^[xii] The relative stereochemistry of the four stereocenters in amino alcohol **11a**, secured by X-ray analysis,^[9] is consistent with the chair-like transition state structure **9a** for the intramolecular carbonyl addition step.^[xiii]

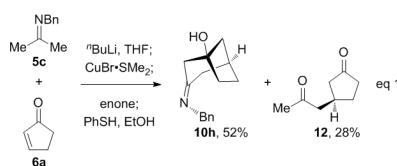
The iminium chloride **5a** was used along with enones **6b-d** (Table 1, entries 1-3) under the optimum reaction conditions described above to afford the corresponding tricyclic imino alcohols in a single-step. The imino alcohols **10c** and **10d** proved highly sensitive toward air-oxidation, prompting their derivatization to tricycles **11c** and **11d** (Table 1, entries 2-3), respectively, for ease of isolation. Interestingly, the C12-stereochemistry^[9] of amino alcohol **11c** is consistent with transient formation of the imino ketone **7c**, followed by intramolecular carbonyl addition of the enamine. The rapid introduction of five contiguous stereocenters in amino alcohol **11c** is noteworthy. The stereoselective formation of tricycles **11a-c** via the corresponding iminoketones **7a-c** is consistent with our proposed biogenesis of this substructure in the galbulimima alkaloids.^[6] The use of iminium chloride **5b**^[9] under the

[*]movassag@mit.edu Homepage: <http://web.mit.edu/movassag/www/index.html>.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

same reaction conditions resulted in stable imino ketones **7e-g** (Table 1, entries 4-6). The isolation and greater stability of these imino ketones is likely due to slower imine/enamine tautomerization (*vide infra*). 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** (Table 1, entries 4-6) as a single diastereomer. Imine reduction proceeded with complete diastereoselection to give the corresponding amino alcohols (Table 1, entries 4-6). Similarly, 1,2-addition of allyl magnesium chloride to imine **10e** gave the corresponding tertiary amine as a single diastereomer.^[xiv]

The resistance of cyclic imines toward hydrolysis renders them more effective substrates than acyclic imines for this chemistry. The use of acyclic imine **5c** and enone **6a** under the optimal reaction conditions described above provided the desired imino alcohol **10h** (52%), along with the competitive hydrolysis product **12** (28%, eq 1).^[xv] Use of acyclic enones (e.g., PhCH=CHCOPh or PhCH=CHCOMe) under the standard reaction conditions did not provide any tandem addition products.



Interestingly, incomplete double deprotonation of iminium ion **5a** prior to cuprate formation led to equilibration between the isomeric metalloenamines. Monitoring a solution of the 6-membered ring imine **13a** in DMSO- d_6 - D_2O (3:2, [0.5mM]) revealed >90% deuterium incorporation at C3 and C2-Me within 10 min and 9 h, respectively (Scheme 3).^[9] However, the 5-membered ring imine **13b** required 96 h before 90% deuterium incorporation at C2-Me was observed at which time less than 25% C3-deuterium incorporation was detected.

The observed preferences of these enamine tautomers prompted us to explore the direct utilization of the enamines in place of the corresponding metalloenamine derivatives as nucleophiles in this formal [3+3]-cycloaddition chemistry. Inspired by the recent advances in organocatalytic transformations,^[xvi] we envisioned the activation of the enone in the form of an unsaturated iminium ion to facilitate the conjugate addition of the enamines. After screening various catalysts and solvents, proline^[xvii] proved particularly effective as the catalyst in a trifluoroethanol (TFE)–water mixture.^[9] Heating a solution of imine **13a** and enone **6a** in TFE–water (10:1) gave the desired tricyclic imino alcohol **10i** in 91% isolated yield as a single diastereomer (Table 2, entry 1).^[xviii] The relative stereochemistry of imino alcohol **10i** was secured by X-ray crystallography.^[9] It should be noted that the tricyclic iminoalcohol **10i** (Table 2, entry 1) is isomeric with the product obtained using the cuprate chemistry (**10a**, Scheme 1), consistent with the intermediacy of the preferred endocyclic 6-membered ring enamine (Scheme 3). Introduction of water as co-solvent increased the overall 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 be optimal. In only one case (Table 2, entry 3) was the intermediate 1,4-addition product isolated along with the desired tricyclic iminoalcohol. The use of the protic solvent system and higher temperatures allowed direct conversion of recalcitrant intermediates to the corresponding tricyclic iminoalcohols (i.e., imino ketones **7e** and **7g**).

Intrigued by the above results, we explored the extension of this chemistry to catalytic asymmetric synthesis. The use of chloroform as solvent in place of TFE–water provided a modest level of enantioselection in the conjugate addition of imine **13b** to enone **6a** (Scheme

4).^[9] Warming a solution of imine **13b** and enone **6a** in chloroform provided the initial 1,4-conjugate addition product, which upon treatment with DBU gave the desired tricyclic imino alcohol (–)-**10e** with 52% enantiomeric excess (ee). The optical activity was increased to 90% ee after a single recrystallization from *n*-pentane–diethyl ether (1:1).^[9] The absolute stereochemistry of the imino alcohol (–)-**10e** was secured by X-ray analysis of the corresponding amino alcohol co-crystallized with L-tartaric acid (1 equiv).^[9] This transformation, provides the first example of a catalytic asymmetric variant of the herein described intermolecular formal [3+3] cycloaddition reaction.

The chemistry described here relies on the sequential C- α - and C- α' -alkylation of unsymmetrical ketoimines, allowing rapid generation of molecular complexity with excellent stereochemical control. This new formal [3+3] cycloaddition reaction provides a practical solution for the synthesis of fused tricyclic iminoalcohol derivatives.^[xix] We envision further development and application of this chemistry to target oriented synthesis based on advances in catalyst and substrate controlled conjugate addition chemistry.^[2,16,xx] The complementary copper promoted and proline-catalyzed variants of this chemistry enable a highly selective and rapid introduction of at least three stereocenters in a convergent assembly of these tricyclic products, offering a valuable addendum to methodologies for complex molecule synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

[**] M.M. is a Dale F. and Betty Ann Frey Damon Runyon Scholar supported by the Damon Runyon Cancer Research Foundation (DRS-39-04). M.M. is a Firmenich Assistant Professor of Chemistry. We acknowledge financial support by NIH-NIGMS (GM074825), Amgen Inc., and Boehringer Ingelheim Pharmaceutical Inc.

References

- [i]a). Tietze LF. Chem. Rev. 1996; 96:115. [PubMed: 11848746] b) Nicolaou KC, Montagnon T, Snyder SA. Chem. Commun. 2003:551.c) Overman LE, Pennington LD. J. Org. Chem. 2003; 68:7143. [PubMed: 12968864]
- [ii]a). Alexakis A, Benhaim C. Eur. J. Org. Chem. 2002:3221.b) Berner OM, Tedeschi L, Enders D. Eur. J. Org. Chem. 2002:1877.c) Feringa, BL.; Naasz, R.; Imbos, R.; Arnold, LA. Modern Organocopper Chemistry. Krause, N., editor. Wiley-VCH; Weinheim, Germany: 2002. p. 224-258.d) Krause N, Hoffmann-Röder A. Synthesis. 2001:171.e) Sibi MP, Manyem S. Tetrahedron. 2000; 56:8033.f) Jacobsen, EN.; Pfaltz, A.; Yamamoto, H., editors. Comprehensive Asymmetric Catalysis I-III. Springer-Verlag; Berlin, Germany: 1999.
- [iii]a). Stork G, Terrell R, Szmuszkovicz J. J. Am. Chem. Soc. 1954; 76:2029.; Wittig G, Frommelt HD, Suchanek P. Angew. Chem. 1963; 75:978.; Angew. Chem. Int. Ed. 1963; 2:683.; Stork G, Dowd SR. J. Am. Chem. Soc. 1963; 85:2178.; Corey EJ, Enders D. Tetrahedron Lett. 1976:3.; Seebach D, Golinski J, Helv J. Chim. Acta. 1981; 64:1413.; f) Also see Hickmott PW. Rappoport Z. The Chemistry of Enamines. 1994WileyChichester and Job A, Janecek CF, Bettray W, Peters R, Enders D. Tetrahedron. 2002; 58:2253. and references therein.
- [iv]. For representative reports, see: Stork G, Brizzolara A, Landesman H, Szmuszkovicz J, Terrell R. J. Am. Chem. Soc. 1963; 85:207.; Hendrickson JB, Boeckman RK Jr. J. Am. Chem. Soc. 1971; 93:1307.; Pfau M, Revial G, Guingant A, d'Angelo J. J. Am. Chem. Soc. 1985; 107:273.; Pfau M, Tomas A, Lim S, Revial G. J. Org. Chem. 1995; 60:1143.; Gunawardena GU, Arif AM, West FG. J. Am. Chem. Soc. 1997; 119:2066.; Benovsky P, Stephenson GA, Stille JR. J. Am. Chem. Soc. 1998; 120:2493.; Jabin I, Revial G, Monnier-Benoit N, Netchitailo P. J. Org. Chem. 2001; 66:256. [PubMed: 11429908] ; Nakamura M, Hatakeyama T, Hara K, Nakamura E. J. Am.

- Chem. Soc. 2003; 125:6362. [PubMed: 12785764] ; Peltier HM, Ellman JA. J. Org. Chem. 2005; 70:7342. [PubMed: 16122257]
- [v]a). Seebach D, Missback M, Calderari G, Eberle M. J. Am. Chem. Soc. 1990; 112:7625. b) For related reviews, see: Harrity JPA, Provoost O. Org. Biomol. Chem. 2005; 3:1349. [PubMed: 15827625] and Hsung RP, Kurdyumov AV, Sydorenko N. Eur. J. Org. Chem. 2005:23.
- [vi]. Movassaghi M, Hunt DK, Tjandra M. J. Am. Chem. Soc. 2006; 128:8126. [PubMed: 16787063]
- [vii]. For isolation reports, see: Binns SV, Dustan PJ, Guise GB, Holder GM, Hollis AF, McCredie RS, Pinhey JT, Prager RH, Rasmussen M, Ritchie E, Taylor WC. Aust. J. Chem. 1965; 18:569.; Mander LN, Prager RH, Rasmussen M, Ritchie E, Taylor WC. Aust. J. Chem. 1967; 20:1473.
- [viii]. Krause, N. Modern Organocopper Chemistry. Wiley-VCH; Weinheim, Germany: 2002.
- [ix]. See Supporting Information for details.
- [x]. Imine **13a** was readily prepared via a procedure based on Van TN, De Kimpe N. Tetrahedron. 2000; 56:7969. and Davis BG, Maughan MAT, Chapman TM, Villard R, Courtney S. Org. Lett. 2002; 4:103. [PubMed: 11772101] For optimum results **13a** is stored as the corresponding HCl salt **5a**, minimizing air oxidation.
- [xi]. The use of heterocuprates or fewer than 1.5 equiv of the homocuprate were found to be non-optimal.
- [xii]. Isolation and purification of **10a** prior to reduction is not required, but is recommended for optimum results.
- [xiii]. The product of a boat-like transition state has not been observed.
- [xiv]. The use of the corresponding O-TMS derivative of **10e** was optimal. For a review, see: Enders D, Reinhold U. Tetrahedron: Asymmetry. 1997; 8:1895.
- [xv]. Competitive hydrolysis of the initial 1,4-addition product occurs during workup.
- [xvi]a). List B. Tetrahedron. 2002; 58:5573.b) Dalko PI, Moisan L. Angew. Chem. 2004; 116:5248. Angew. Chem. Int. Ed. 2004; 43:5138.c) Berkessel, A.; Groger, H. Asymmetric Organocatalysis. Wiley-VCH; Weinheim, Germany: 2005. d) Lelais G, MacMillan DWC. Aldrichimica Acta. 2006; 39:79.e) Taylor MS, Jacobsen EN. Angew. Chem. 2006; 118:1550. Angew. Chem. Int. Ed. 2006; 45:1520.f) Enders D, Hüttl MRM, Grondal C, Raabe G. Nature. 2006; 441:861. [PubMed: 16778886]
- [xvii]. The suggested mode of catalysis is based on prior reports in related transformation (see reference xvi).
- [xviii]. The use of TFE–water provided products (Table 2) with 5–10% enantiomeric excess.
- [xix]. A variety of cholinergic activity modulators contain cyclic amines/amino alcohols as rigid acetylcholine analogs; see: Clader JW, Wang Y. Curr., Pharm. Design. 2005; 11:3353.; Buffat MGP. Tetrahedron. 2004; 60:1701.; Broadley KJ, Kelly DR. Molecules. 2001; 6:142.
- [xx]. For substrate controlled diastereoselective conjugate addition, see: Breit B, Demel P. Krause N. Modern Organocopper Chemistry. 2002:188–223. Wiley-VCH Weinheim, Germany; Leonard J, Díez-Barra E, Merino S. Eur. J. Org. Chem. 1998:2051.

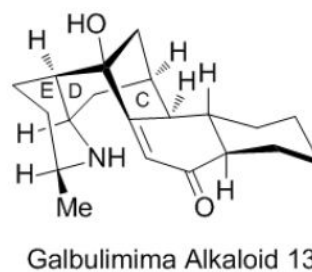
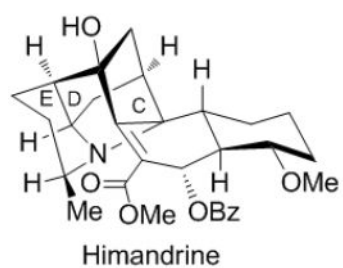
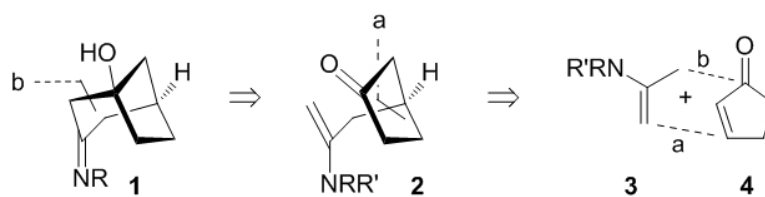
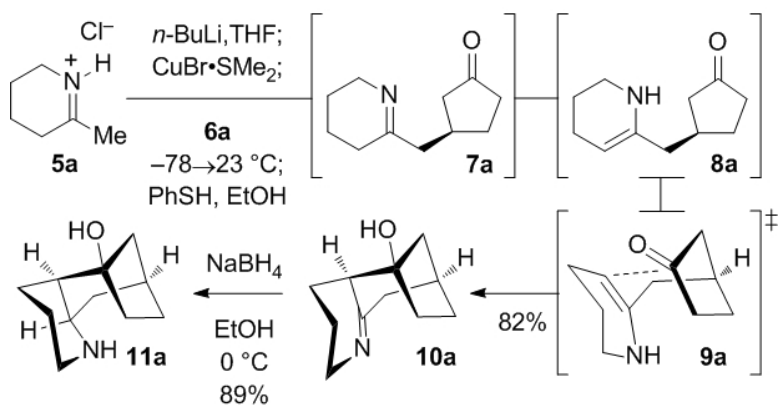


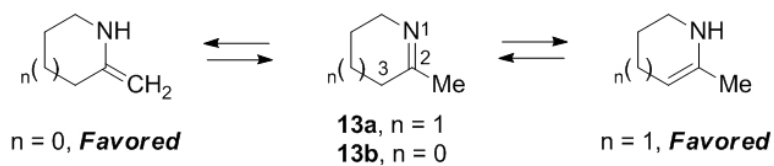
Figure 1.
Representative galbulimima alkaloids.



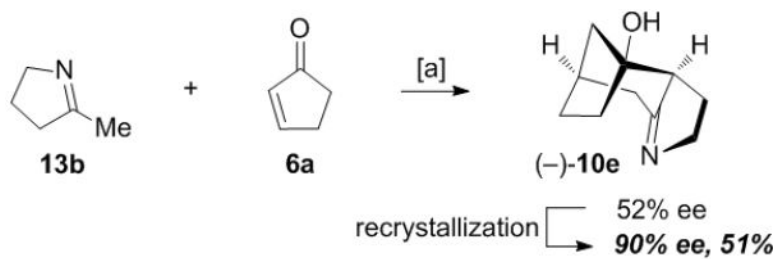
Scheme 1.
Formal [3+3] cycloaddition reaction.

**Scheme 2.**

Rapid synthesis of the CDE-ring system of Class II and III galbulimima alkaloids.



Scheme 3.
Equilibration of Enamine Tautomers.^[9]

**Scheme 4.**

Catalytic Asymmetric Synthesis of (-)-**10e**. Conditions: [a] L-Proline (20 mol%), CHCl_3 , 45 °C, 48 h (50%); 1,8-Diazabicyclo-[5.4.0]undec-7-ene, EtOH, 78 °C, (80%).

Table 1

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

entry	imminium chloride	enone	1,4-adduct	yield [%] ^[b]	imino alcohol	yield [%] ^[b]	amino alcohol	yield [%] ^[b]
1				-		72		91
2				-		-		55 ^[d]
3				-		-		50
4				88		85		93
5				67		91		87
6				70		82		88

^[a]Optimum reaction conditions used uniformly.^[9]^[b]Isolated yields as a single diastereomer.^[c]Isolated yield of C12-diastereomeric mixture (8:1); major isomer shown.^[9]

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

Table 2

Single-step Catalytic Diastereoselective Intermolecular Formal [3+3] Cycloaddition Reaction.^[a]

entry	imine	enone	1,4-adduct	product	yield [%] ^[b]
1 ^[c]	13a	6a			91 90 ^[d]
2 ^[c]	13a	6d			78 ^[e]
3 ^[f]	13b	6a			40 21 ^[g]
4 ^[f]	13b	6d			56

^[a] Reaction conditions: L-Proline (10 mol%), trifluoroethanol-water (10:1), 16 h.^[9]^[b] Isolated yields as a single diastereomer.^[c] 50 °C.^[d] Isolated yield of the corresponding amino alcohol.^[e] Isolated yield after imine reduction and *N*-protection.^[f] 80 °C.^[g] Isolated yield of **7e**.