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A stereoselective $C^{7n}C^{5x}$ free-radical cascade route to optically pure and potentially useful tetracyclic amines

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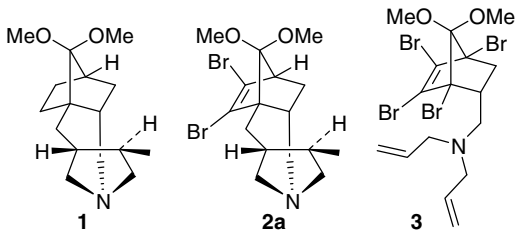
ABSTRACT

Nucleophilic racemic amines have been synthesized utilizing a $C^{7n}C^{5x}$ free-radical cascade reaction from a bis-allyl amine starting material. Being potentially useful organocatalytic bases as is evident from their screening in the Baylis–Hillman reaction, optically pure amines were also synthesized from optically pure aldehydes (−) or (+)-**4**. Bis-allyl amides under similar radical reaction condition resulted in C^{7n} cyclized products.

Syntheses of useful organic molecules besides naturally occurring ones have gained a lot of impetus not only for the investigation of biological properties but also because of their versatile uses in materials[1] and organocatalysis.[2] Naturally occurring small molecules such as proline,[3] cinchona alkaloids[4] and their derivatives[5] obtained through judicious manipulations in their functional groups have proven to be excellent catalysts for organocatalytic enantioselective reactions. Optically active DABCO {2,3-bis(benzyloxymethyl)-1,4-diazabicyclo(2.2.2)octane},[6] pyrrolizidine[7] and bicyclic azetidine[8] derivatives are some of the very few synthetic chiral catalysts for the asymmetric Baylis–Hillman[9] reaction. Noting the presence of the bridged nitrogen in all three cases, it was evident that the nucleophilicity of the amine increases with the increased pyramidalization.[8]

In view of the aforementioned literature reports, we wanted to design a molecule bearing a tertiary nitrogen whose lone pair would be more accessible due to increased pyramidalization by locking the nitrogen at the bridge making it more nucleophilic and a useful molecule for organocatalysis. Impressive examples of complex asymmetric structures obtained through radical cascade reactions have been reported in the last two decades.[10] A well-designed precursor often leads to high stereoselectivity, and is a very desirable characteristic in synthetic organic chemistry through radical cascade processes.[11] We envisioned that the norbornyl-based tetracyclic amines **1** and **2a** could be expeditiously obtained through radical cascade cyclization from bis-allyl amine precursor **3**. Herein we report a practical synthesis of racemic as well as both the optical antipodes of highly nucleophilic tetracyclic amines through a stereoselective 7-*endo-trig* followed by 5-*exo-trig* radical cascade.



The aldehyde[12] **4** was condensed with allylamine and the resulting imine was reduced with sodium borohydride in the same pot. The mono allyl amine **5** was further allylated to give the bis-allyl amine **3** in excellent yield (Scheme 1). Bis-allyl amine **3** was then subjected to intramolecular radical cascade cyclization to yield **2a** and **2b**[13] or only **2a** depending on the reaction conditions employed (Table 1). Hydrodebromination of **2a** in sodium-liquid NH_3 followed by reduction of the double bond under catalytic hydrogenation conditions afforded **1** in 91% yield from **2a**.

Initially, the radical cascade cyclization reaction was carried out with a slow addition of 2.4 equiv of tributyltin hydride (TBTH) through syringe pump to a dilute (0.004 M), refluxing solution of substrate **3** in benzene over 10 h. The reaction was further refluxed for another 2 h. Purification of the crude reaction mixture afforded **2a** and **2b** in 14% and 12% yields, respectively (Table 1, entry a). The tribromo derivative **2b** was transformed into **2a** by bridgehead hydrodebromination using 1.2 equiv of TBTH. The yield of **2a** could be improved to 52% by adding freshly distilled tributyltin hydride (2.4 equiv) through syringe pump over a period of 5 h. Monitoring the reaction (TLC) at this stage revealed the presence of a substantial amount of **2b** along with **2a** and traces of unreacted starting material. Addition of a further portion of 1.2 equiv TBTH and refluxing the reaction mixture for another 2 h converted **2b** into **2a**. Amines are prone to decompose at higher temperature.

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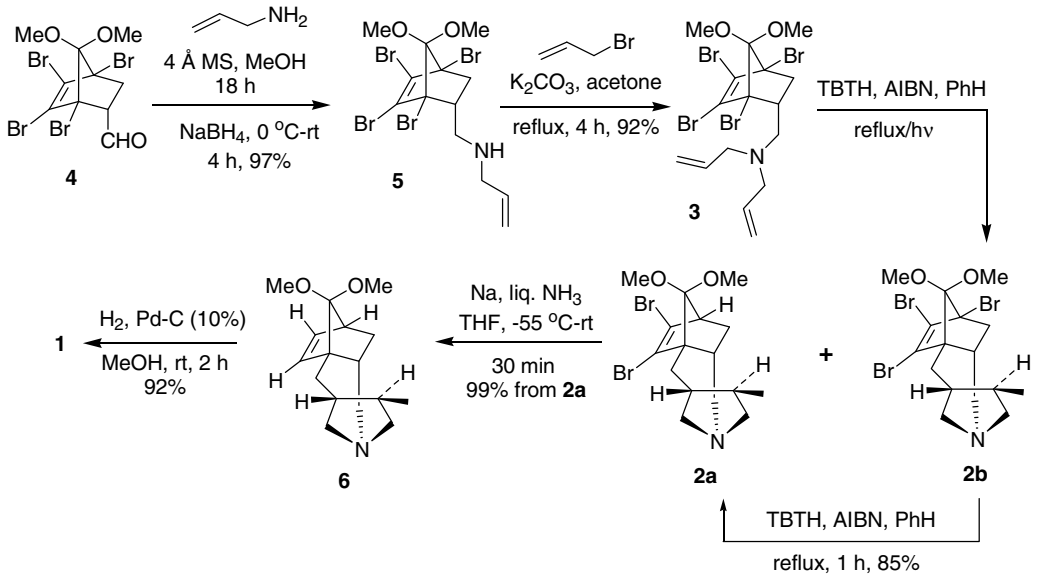


Scheme 1.

Table 1
Radical cascade cyclization of **3**[13]

Entry	Reaction condition	TBTH (equiv)	Time (h)	Yield (%)	
				2a	**2b**
a	Reflux	2.4	12	14	12
b	Reflux	3.6	7	52	—
c	Reflux	3.6	3	33	—
d	*hν*	2.4	3	14	—

Attempts to circumvent the decomposition of amine by reducing the time of addition of TBTH to 3 h afforded **2a** in 33% yield (Table 1, entry c). The radical reaction, when carried out under photochemical conditions using a 450 W UV lamp at the same dilution, resulted in 14% of **2a** (Table 1, entry d).

The radical cascade cyclization reaction was highly stereoselective leading to only one product in which the methyl group on the cyclopentane ring has a β-stereochemistry. If the methyl group was to be disposed on the α-face, it would face strong steric crowding as shown in Figure 1. Unambiguous structural proof was obtained by single crystal X-ray analysis of **2a**.[14]

To check the effect of an amide moiety on the radical cyclization, bis-allyl amide **8** was prepared from the acid derivative **7**.[15] Employing the radical cyclization on amide **8** resulted in a mono-cyclized product **9** in 66% yield without any detectable amount of the cascade cyclized product (Scheme 2). The pyramidal orientation of the substituents on nitrogen is essential for the cascade cyclization to occur. While such a pyramidal orientation is feasible for the bis-allyl amine **3**, the same is not feasible for the bis-allyl amide **8**. This is because of the partial delocalization of the nitrogen lone pair to the amide oxygen. Attempted radical cyclizations of the mono-allyl amine **5** and mono-allyl amide **10** led to an intractable reaction mixture. The ease of bridgehead cyclization in bis-allyl derivatives **3** and **8** vis-a-vis the mono-allyl derivatives **5** and **10** could be because of the more probable availability of the double bond to the bridgehead radical.

There are only a few reports of 7-*endo* selectivity during radical cascade processes. The molecule is organized in such a way that it follows a $\mathbf{C^{7n}C^{5x}}$ free radical cascade[16] route to a constrained amine **2a**, whose lone pair is well exposed, making it a good candidate for organocatalytic reactions. The mechanism for the radical cascade cyclization of **3** to **2b** involves the formation of a bridgehead radi-

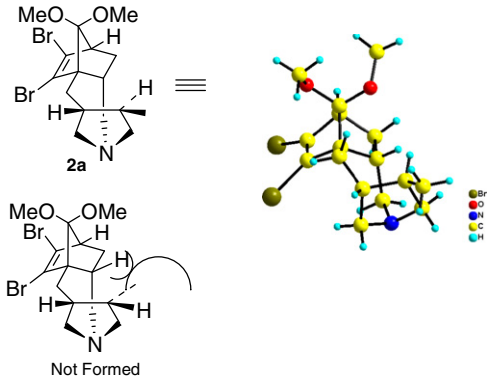
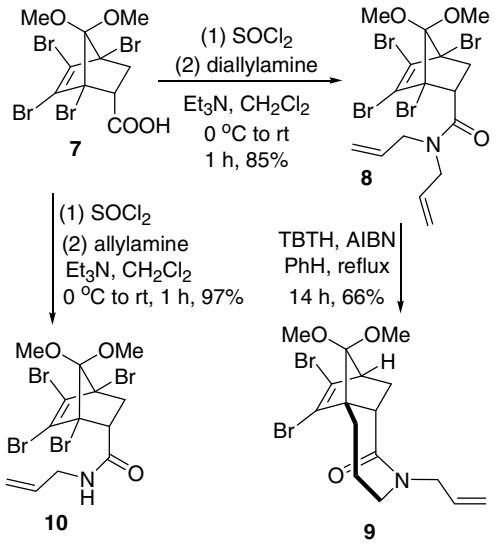
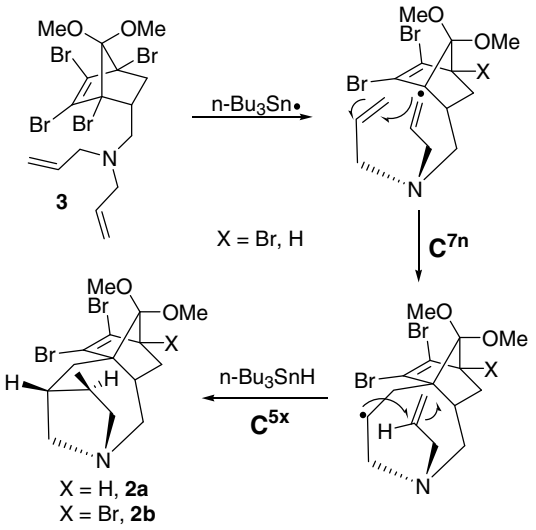


Figure 1. Stereoselective ring formation.



Scheme 2.

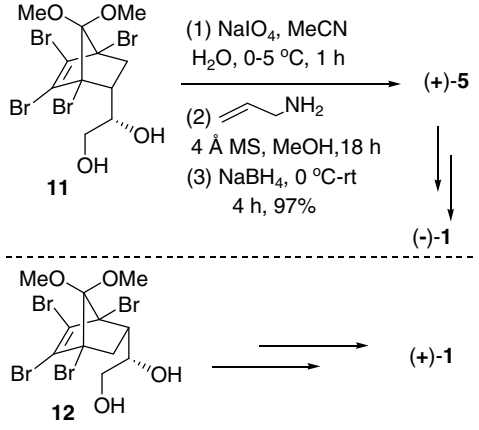


Scheme 3.

cal by abstraction of a bridgehead bromine from **3**. This is followed by preferential cyclization with the double bond in a 7-*endo-trig* fashion instead of the alternative 6-*exo-trig* mode, resulting in a more stabilized secondary radical. This radical then undergoes addition to the other double bond in a 5-*exo-trig* fashion to afford the tetracyclic amines **2a** or **2b** (Scheme 3).

The racemic amine **2a** thus obtained through the radical cascade route was employed in a Baylis–Hillman reaction with *p*-nitrobenzaldehyde and methyl acrylate under sonication condition[17] to give the Baylis–Hillman adduct in excellent yield (81%). A similar result was obtained by employing tetracyclic amine **1** as the catalyst. While the tetracyclic amines **2a** and **1** were good catalysts, **3** failed to catalyze the Baylis–Hillman reaction.

Pleased by the efficiency of the racemic amines **2a** and **1** as catalysts for the Baylis–Hillman reaction, we wanted to obtain them in enantiomerically pure form. Attempts to resolve the amines **2a** and **1** by salt formation with various enantiomerically pure acids met with failure as the diastereomeric mixture of the salts formed could not be purified on repeated crystallization. Because of these difficulties, we relied on the chiron approach to obtain the optically active amines **2a** and **1**. The diastereomeric diols **11** and **12** obtained from D-mannitol as described recently[12] were employed for this task (Scheme 4).



Scheme 4.

After obtaining the optically pure amines in good yields, we employed them for the asymmetric Baylis–Hillman reaction. Using 20 mol % of the optically pure amine (−)-**1** or (+)-**1** along with *p*-nitrobenzaldehyde and methyl acrylate in MeOH under sonication conditions[17] afforded the Baylis–Hillman adduct. While the time required (22 h) for the formation of the adduct and the yields obtained are comparable to the best conditions reported,[18] the asymmetric induction was very low (8%).

In summary, we have reported a practical and expedient synthesis of racemic as well as optically pure antipodes of tetracyclic amines involving a stereoselective $\mathbf{C^{7n}C^{5x}}$ free radical cascade protocol. Bis-allyl amide when subjected to radical cascade conditions resulted in $\mathbf{C^{7n}}$ mono cyclized product. The optically pure and highly nucleophilic amines were synthesized and screened for the asymmetric Baylis–Hillman reactions.

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References and notes

1. (a) Kato, T.; Mizoshita, N.; Kishimoto, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 38; (b) Gokel, G. W.; Leevy, W. M.; Weber, M. E. *Chem. Rev.* **2004**, *104*, 2723; (c) Gokel, G. W.; Barbour, L. J.; Ferdani, R.; Hu, J. *Acc. Chem. Res.* **2002**, *35*, 878.
2. (a) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451; (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119; (c) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897; (d) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172; (e) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837.
3. Reviews of the use of proline and its derivatives as organocatalysts, see: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471; (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580; (c) List, B. *Acc. Chem. Res.* **2004**, *37*, 548.
4. For reviews, see: (a) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496; (b) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621; (c) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985; (d) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965; (e) Kacprzak, K.; Gawroński, J. *Synthesis* **2001**, 961.
5. For use of cinchona alkaloid derivatives as organocatalysts, see: (a) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929; (b) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105; (c) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481; (d) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948; (e) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167; (f) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.
6. (a) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241; (b) Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1992**, *33*, 639.
7. Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533.
8. Barrett, A. G. M.; Dozzo, P.; White, A. J. P.; Williams, D. J. *Tetrahedron* **2002**, *58*, 7303.
9. For reviews on the Baylis–Hillman reaction, see: (a) Basavaiah, D.; Rao, K. V.; Reddy, R. *J. Chem. Soc. Rev.* **2007**, *36*, 1581; (b) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614; (c) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
10. (a) Dhimane, A.-L.; A, C.; Malacria, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3284; (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237; (c) Curran, D. P. *Synthesis* **1988**, 417; (d) Zard, S. Z. *Radicals Reactions in Organic Synthesis*; Oxford University Press: New York, 2003.
11. For recent examples of tandem radical cyclizations, see: (a) Moman, E.; Nicoletti, D.; Mouriño, A. *Org. Lett.* **2006**, *8*, 1249; (b) Shen, L.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 775; (c) Lee, H.-Y.; Lee, S.; Kim, B. G.; Bahn, J. S. *Tetrahedron Lett.* **2004**, *45*, 7225; (d) Allan, G. M.; Parsons, A. F.; Pons, J.-F. *Synlett* **2002**, 1431.
12. Khan, F. A.; Sudheer, Ch. *Org. Lett.* **2008**. doi:10.1021/ol800990m.
13. *Procedure for radical cascade cyclization (Table 1, entry a)*: *Tetracyclic amine* (**2a**) *and tetracyclic amine* (**2b**). The radical reaction was carried out in a 500 mL round-bottomed flask equipped with a teflon coated stirring bar and a reflux condenser connected to a three way stopcock, one end of which was sealed with precision seal rubber septum to which was passed the needle of the syringe pump and other end was connected with an argon balloon. The flask was charged with bis-allyl amine **3** (400 mg, 0.69 mmol) along with AIBN (20 mg, 0.12 mmol). Dry, argon purged benzene (160 mL) was injected and the

flask was placed in an oil bath on magnetic stirrer preheated to 90 °C. A solution of TBTH (482 mg, 1.66 mmol) and AIBN (40 mg, 0.24 mmol) in dry, argon purged benzene (15 mL) was injected into the reaction mixture by syringe pump over 10 h. After being refluxed for another 2 h the reaction mixture was cooled and the solvent was evaporated under reduced pressure. Column chromatography using silica gel (300 mL of hexane to remove tin impurities and then by 2 → 4 → 6% methanol in ethyl acetate) afforded **2a** (41 mg, 14%) as a yellowish crystalline solid and **2b** (41 mg, 12%) as a viscous liquid. **2a:** mp 132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.46 (dd, 1H, J = 13.2, 2.2 Hz), 3.27 (s, 3H), 3.24 (s, 3H), 3.10 (ddd, 1H, J = 12.9, 8.0, 2.2 Hz), 2.87 (d, 1H, J = 4.1 Hz), 2.84–2.79 (m, 1H), 2.63 (dd, 2H, J = 14.4, 2.9 Hz), 2.40 (dd, 1H, J = 12.9, 7.3 Hz), 2.28 (dd, 1H, J = 14.4, 12.4 Hz), 2.19 (dd, 1H, J = 15.3, 6.4 Hz), 2.07–1.98 (m, 3H), 1.91 (ddd, 1H, J = 12.0, 8.8, 4.2 Hz), 1.02 (d, 3H, J = 6.8 Hz), 0.65 (dd, 1H, J = 11.9, 4.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 127.0, 124.0, 117.0, 66.9, 60.9, 58.0, 55.8, 54.5, 52.4, 50.2, 47.5, 44.0, 39.2, 30.8, 28.2, 21.7; IR (KBr) 2850, 2800, 1580, 1440, 1420, 1310, 1250 cm^{-1}. Anal. Calcd for $C_{16}H_{23}Br_2NO_2$: C, 45.63; H, 5.50; N, 3.33. Found: C, 45.59; H, 5.48; N, 3.30. Compound **2b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.50 (s, 3H), 3.42 (d, 1H, J = 13.1 Hz), 3.25 (s, 3H), 3.04–2.81 (m, 3H), 2.57 (d, 1H, J = 14.4 Hz), 2.39 (dd, 1H, J = 16.5, 7.1 Hz), 2.29–2.16 (m, 3H), 2.04–2.01 (m, 3H), 1.12 (dd, 1H, J = 11.8, 4.9 Hz), 0.98 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 128.5, 126.4, 114.6, 70.9, 65.4, 60.7, 57.0, 55.6, 52.7, 51.4, 47.5, 43.7, 40.1, 38.9, 31.7, 21.8; IR (neat) 2900, 1560, 1430, 1250 cm^{-1}. Anal. Calcd for $C_{16}H_{22}Br_3NO_2$: C, 38.43; H, 4.43; N, 2.80. Found: C, 38.47; H, 4.40; N, 2.78.

14. Crystallographic data (excluding structure factors) for **2a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 693416. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.
15. Mustafaev, A. M.; Imamaliev, A. B.; Guseinov, N. M. *Zh. Org. Khim.* **1989**, *25*, 1908.
16. (a) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224; (b) McCarroll, A. J.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215.
17. Ultrasonic cleaner ELMA model T490 DH (350 W, 40 kHz) was used.
18. Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Lopes, E. C. S.; Rossi, R. C.; Silveira, G. P. C.; Pavam, C. H. *Tetrahedron* **2002**, *58*, 7437.