ORGANIC LETTERS

2012
Vol. 14, No. 12
2932–2935

Highly Enantioselective Synthesis of Chiral Allenes by Sequential Creation of Stereogenic Center and Chirality Transfer in a Single Pot Operation

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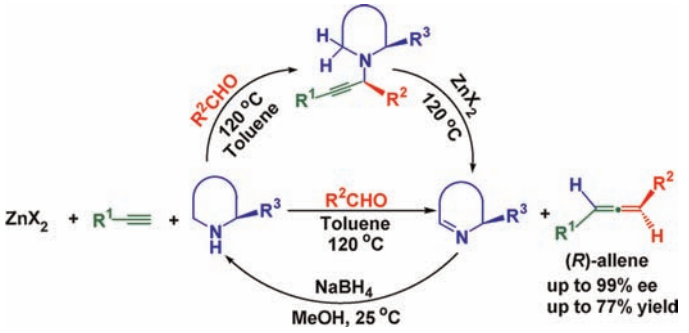
Received January 13, 2012

ABSTRACT



Chiral allenes are readily accessed in a single pot operation in the reaction of terminal alkynes, aldehydes, chiral secondary amines, and zinc halides in good yields (up to 77% yield) and excellent enantioselectivities (up to 99% ee) in toluene at 120 °C. The reaction proceeds through initial formation of chiral propargylamine intermediates with creation of a new stereogenic center and subsequent chirality transfer via an intramolecular hydride shift to produce chiral allenes with high enantiomeric purities.

Chiral allenes are versatile synthons with the potential to provide excellent axis-to-center chirality transfer in organic synthesis.[1] The chiral allene structural motifs are also present in several biologically active natural products and pharmaceuticals.[2] Many synthetic methods were reported for the preparation of racemic[3] and optically active allenes,[4] but generally the methods available to access enantiomerically enriched allenes require multistep synthetic operations. Recently, reports have appeared on enantioselective synthesis of chiral allenes from chiral propargylamines using silver(I) and gold catalysts involving a two-step synthetic protocol.[5] More recently, synthesis of racemic disubstituted allenes via a ZnI_2 promoted reaction of morpholine with aldehydes and terminal alkynes has been reported.[6a] Very recently, a two-step method for the synthesis of chiral allenes involving prior preparation of chiral propargylamine intermediates has been reported.[6b] We wish to report here a zinc halide promoted one-pot method for the enantioselective synthesis of chiral allenes (*R*)-**8** with up to 99% ee, using 1-alkynes, aldehydes, and readily accessible chiral secondary amines **1**–**5**.[7,8]

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(2) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196.

(3) (a) Rona, P.; Crabbe, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289. (b) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1979**, 859. (c) Nakamura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc.* **2004**, *126*, 5958. (d) Karunakar, G. V.; Periasamy, M. *J. Org. Chem.* **2006**, *71*, 7463. (e) Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763.

(4) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. (b) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470. (c) Li, C.-Y.; Sun, X.-L.; Jing, Q.; Tang, Y. *Chem. Commun.* **2006**, 2980. (d) Pu, X.; Ready, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 10874. (e) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212. (f) Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 6941. (g) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384.

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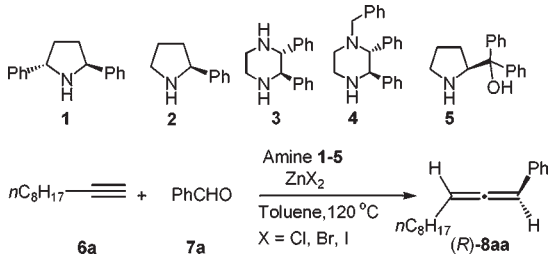
10.1021/ol300717e
Published on Web 05/15/2012

Table 1. Reaction of 1-Decyne **6a** and Benzaldehyde **7a** with Chiral Amines **1**–**5** Promoted by Zinc Halides[a]



entry	amine	ZnX_2 (equiv)	time (h)	yield (%)[b]	ee (%)[c]
1	**1**	ZnI_2 (0.5)	2	57	18
2	**2**	ZnI_2 (0.5)	2	72	66
3	**3**	ZnI_2 (0.6)	8	55	76
4	**4**	ZnI_2 (0.6)	4	65	95
5	**5**	$ZnBr_2$ (0.7)	10	65	98

[a] The reactions were carried out by taking amines **1**, **2**, **4**, **5** (1.0 mmol) or **3** (0.5 mmol), ZnX_2 and 1-decyne **6a** (1.1 or 1.0 mmol with amine **3** and **4**) in toluene (3 mL) at 25 °C, heating for 10 min at 120 °C, followed by addition of the aldehyde (1 mmol) at 25 °C and heating to 120 °C in 45 min and further stirring at 120 °C for the required time. Heating all components together at 120 °C gives the (*R*)-allene **8aa** in lower ee (by about 10%). The reaction was stopped as soon as tlc analysis indicated the absence of benzaldehyde . [b] Isolated yield. [c] The % ee was determined by HPLC analysis on a chiralcel OD-H or OJ-H column.

Initially, we have examined this $ZnCl_2$, $ZnBr_2$, and ZnI_2 promoted chiral allene synthesis using chiral secondary amines **1**–**5**, 1-decyne **6a**, and benzaldehyde **7a** at 120 °C. Optimum results obtained are summarized in Table 1, and the results obtained using different amounts of zinc halides are given in Table S1 in the Supporting Information.[8] Whereas the C_2 symmetrical chiral amine **1**–ZnI_2 reagent system gave the allene (*R*)-**8aa**[9] in 57% yield with only 18% ee, the C_1 symmetrical amine **2** afforded the allene (*R*)-**8aa** in higher yield (72%) and selectivity (66% ee) (Table 1, entries 1 and 2).[8] The chiral 2,3-diphenyl-piperazine **3** and ZnI_2 combination gave the allene (*R*)-**8aa** in 55% yield with 76% ee, and the chiral *N*-benzyl-2,3-diphenyl-piperazine **4**–ZnI_2 (0.6 equiv) combination gave the allene (*R*)-**8aa** in higher yield (65%) and selectivity (95% ee) (Table 1, entries 3 and 4). The chiral (*S*)-diphenyl-prolinol (DPP) **5**–$ZnBr_2$ (0.7 equiv) combination also gave the allene (*R*)-**8aa** in comparable yields and selectivity (65% yield and 98% ee, Table 1, entry 5).

The chiral amines **4** and **5** gave better results in this transformation compared to the amine **2** (Table 1 and Table S2 in Supporting Information). Surprisingly, in the case of phenylacetylene **6g**, the chiral amines **2** and **4** gave the allene (*R*)-**8ga** in 48% yield, 46% ee and 48% yield, 94% ee, respectively (Table S2)[8] but (*S*)-DPP **5** gave only a mixture of unidentifiable products. Since the chiral (*S*)-DPP **5** can be readily accessed from (*S*)-proline[7a] and both enantiomers of the DPP **5** are commercially available, we have examined the scope of this transformation with various substrates using (*S*)-DPP **5** (Table 2).

(*S*)-DPP **5**, $ZnBr_2$, and substituted benzaldehydes **7** react with 1-decyne **6a** to give the corresponding (*R*)-allenes **8** in 50–70% yields and 82–98% ee (Table 2, entries 1–7). The chloro and cyano substituted alkynes **6c** and **6d** react with benzaldehyde **7a** to give the allenes (*R*)-**8ca** and (*R*)-**8da** in 62% and 69% yields, 93% and 99% ee, respectively (Table 2, entries 10 and 11). Whereas the unprotected propargyl alcohol reacts with benzaldehyde **7a** to give only a complex mixture of products under these conditions, the corresponding benzoyl ester leads to the formation of the *N*-benzoyl derivative of the (*S*)-DPP and the corresponding allene was not formed. Fortunately, the *p*-nitrobenzyl ether derivative **6e** gave the allene (*R*)-**8ea** in 64% yield and 99% ee (entry 12, Table 2). Also, the enyne **6f** gave the allene (*R*)-**8fa** in 51% yield and 99% ee (entry 13, Table 2).

Thiophene-2-aldehyde **7i** also reacts with alkynes **6a**, **6c**, and **6d** to give the corresponding allenes (*R*)-**8ai**, (*R*)-**8ci**, and (*R*)-**8di** in reasonable yields and selectivity (entries 14–16, Table 2). The allene (*R*)-**8aj** is obtained in 35% yield and 86% ee (entry 17, Table 2) after 2 h in the reaction of furfural **7j** and 1-decyne **6a** with $ZnBr_2$ at 120 °C, but only a complex mixture of unidentifiable products remained after a 4 h reaction.

The aliphatic aldehydes **7k**, **7l**, and **7m** react with the 4-phenyl-1-butyne **6b**, cyano substituted alkyne **6d**, and *p*-nitrobenzyl propargyl ether **6e** to give the allenes (*R*)-**8bk**, (*R*)-**8dl**, and (*R*)-**8em** in 48%–59% yield and 92%–99% ee (Table 2, entries 18, 19, and 21). Simple alkynes like 1-decyne **6a** react with the aliphatic aldehydes, but chromatographic separation of the mixtures containing the allenic products was somewhat difficult in the absence of chromophoric groups in these cases. The use of ethyl propiolate lead to a complex mixture of products in the reaction with benzaldehyde **6a** with the chiral amine **5**. Also, substrates like cinnamaldehyde, *N*-methyl-2-formylindole, and acetophenone gave only complex mixtures of unidentifiable products in the reaction with 1-decyne under the reaction conditions.

We have also carried out a series of experiments to isolate the propargylamine intermediates that are expected to form in this transformation (Schemes 1 and S1).[6,8] We have observed that the propargylamine intermediates are also readily converted to the allene (*R*)-**8aa** upon reaction with zinc halides (Schemes 1 and S1).[8] Also, the imine byproducts could be easily converted to the starting chiral amines by simple borohydride reduction without any change in enantiomeric purity.[8]

A tentative mechanism outlined in Scheme 2 could be considered for this transformation based on previous reports[5,6,10] and the relative configuration of chiral propargylamine intermediates.[11] The initially formed alkynylzinc species **12** would attack the *Re*-face of iminium ion

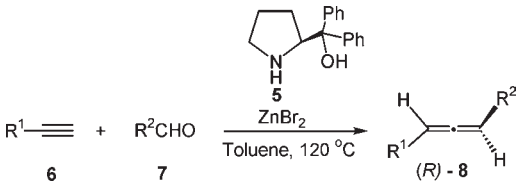
(6) (a) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786. (b) Ye, J.; Li, S.; Chen, B.; Fan, W.; Kuang, J.; Liu, J.; Liu, Y.; Miao, B.; Wan, B.; Wang, Y.; Xie, X.; Yu, Q.; Yuan, W.; Ma, S. *Org. Lett.* **2012**, *14*, 1346.

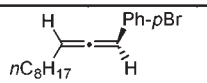
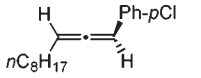
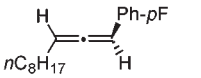
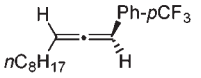
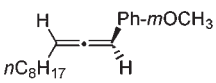
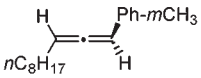
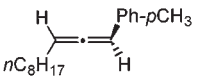
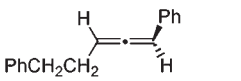
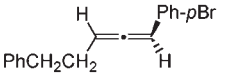
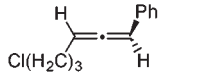
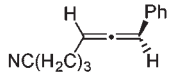
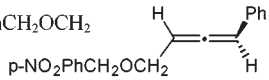
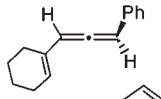
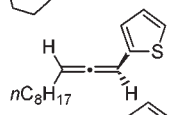
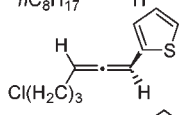
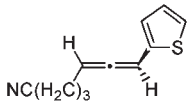
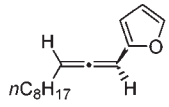
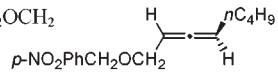
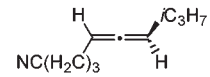
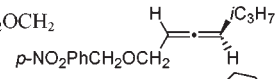
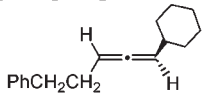
(7) (a) Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127. (b) Periasamy, M.; Gurubrahamam, R.; Muthukumaragopal, G. P. *Synthesis* **2009**, 1739. (c) Vairaprakash, P.; Periasamy, M. *J. Org. Chem.* **2006**, *71*, 3636.

(8) See Supporting Information for details.

(9) (a) Lowe, G. *Chem. Commun.* **1965**, 411. (b) Brewster, J. H. *Top. Stereochem.* **1967**, *2*, 1.

Table 2. Synthesis of Chiral Allenes **8** by $ZnBr_2$ Promoted Reaction of Chiral Amine **5** with Substituted 1-Alkynes **6** and Aldehydes **7**[a]



entry	alkyne **6**, aldehyde **7**, time (h)	(*R*)-allene	**8**	yield (%)[b]	ee (%)[c]
1	**6a,7b,** 14 $R^1 = nC_8H_{17}$ $R^2 = p$BrPh		**8ab**	68	90
2	**6a, 7c,** 14 $R^1 = nC_8H_{17}$ $R^2 =$ Ph-*p*Cl		**8ac**	65	90
3	**6a,7d,** 9 $R^1 = nC_8H_{17}$ $R^2 =$ Ph-*p*F		**8ad**	70	90
4	**6a,7e,** 13 $R^1 = nC_8H_{17}$ $R^2 =$ Ph-*p*CF_3		**8ae**	60	82
5	**6a,7f,** 13 $R^1 = nC_8H_{17}$ $R^2 =$ Ph-*m*OCH_3		**8af**	58	94
6	**6a,7i,** 12 $R^1 = nC_8H_{17}$ $R^2 =$ Ph-*m*CH_3		**8ag**	60	90
7	**6a,7j,** 17 $R^1 = nC_8H_{17}$, $R^2 =$ Ph-*p*CH_3		**8ah**	50	90
8	**6b,7a,** 14 $R^1 = PhCH_2CH_2$, $R^2 =$ Ph		**8ba**	61	93
9	**6b,7b,** 14 $R^1 = PhCH_2CH_2$, $R^2 =$ Ph-*p*Br		**8bb**	55	88
10	**6c,7a**, 8 $R^1 = Cl(CH_2)_3$ $R^2 =$ Ph		**8ca**	62	93
11	**6d,7a,** 6 $R^1 = NC(CH_2)_3$ $R^2 =$ Ph		**8da**	69	99
12	**6e,7a,** 13 $R^1 = p$$NO_2PhCH_2OCH_2$ $R^2 =$ Ph		**8ea**	64	99
13	**6f,7a,** 8 $R^1 =$ 1-Cyclohexenyl $R^2 =$ Ph		**8fa**	51	99
14	**6a,7i,** 16 $R^1 = nC_8H_{17}$ $R^2 =$ 2-Thiophenyl		**8ai**	62	92
15	**6c,7i,** 14, $R^1 = Cl(CH_2)_3$ $R^2 =$ 2-Thiophenyl		**8ci**	52	88
16	**6d,7i,** 14 $R^1 = NC(CH_2)_3$ $R^2 =$ 2-Thiophenyl		**8di**	52[d]	--
17	**6a,7j,** 2 $R^1 = nC_8H_{17}$ $R^2 =$ 2-Furanyl		**8aj**	35	86
18	**6e,7k,** 22 $R^1 = p$$NO_2PhCH_2OCH_2$ $R^2 = nC_4H_9$		**8ek**	59	98
19	**6d,7l,** 20 $R^1 = NC(CH_2)_3$, $R^2 = iC_3H_7$		**8dl**	59[d]	--
20	**6e,7l,** 20 $R^1 = p$$NO_2PhCH_2OCH_2$ $R^2 = iC_3H_7$		**8el**	48	99
21	**6b,7m,** 12 $R^1 = PhCH_2CH_2$ $R^2 =$ Cyclohexyl		**8bm**	51	84

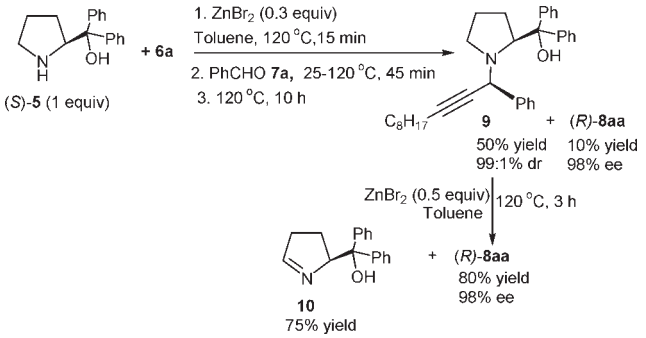
[a] The reactions were carried out by taking amine **5** (1.0 mmol), $ZnBr_2$ (0.7 mmol), and 1-alkyne (1.1 mmol) in toluene (3 mL) at 25 °C following the sequence of addition of reagents as outlined under Table 1. [b] Isolated yield. [c] The % ee was determined by HPLC analysis on a chiralcel OD-H, OJ-H or OB-H column . [d] Optically active (*R*)-allenes were obtained in these cases, but the ee's could not be determined as the corresponding racemic allenes could not be resolved using the available OD-H, OJ-H, OB-H, AD-H, or AS-H chiral HPLC column.

14a formed *in situ* to yield the propargylamine **16**. Subsequent 1,5-hydride transfer[5,6] and elimination of $ZnBr_2$ could afford the allene (*R*)-**8** and the imine **10** (Scheme 2). The chiral amines **4** and **5** give better enantioselectivity in this transformation compared to the amine **2** (Tables 1, 2, and Table S2) which may be due to coordination of the additional amino or hydroxyl moieties present in the amines **4** and **5** with the zinc halide in the transition states. Such hydroxyl moiety coordinations with $ZnBr_2$ in the transitions states **15** and **17** for the transformation using (*S*)-DPP **5** are shown in Scheme 2.

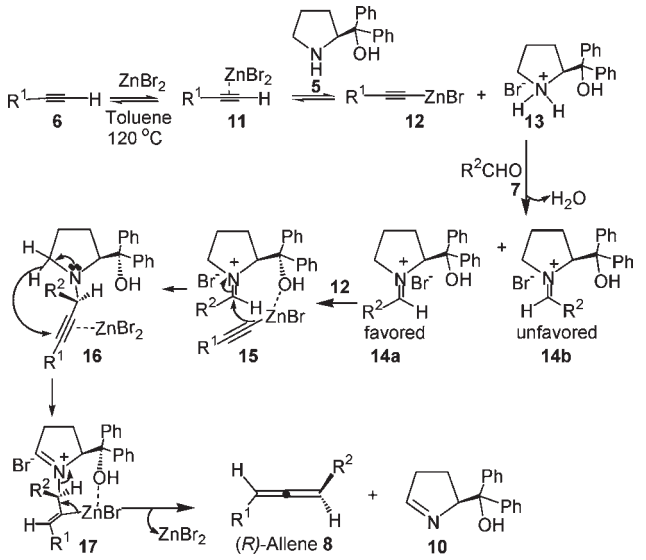
(10) (a) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497. (b) Tomooka, C, S.; Fässler, R.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843.

(11) (a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (b) Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Org. Chem.* **1972**, *37*, 3052.

Scheme 1. Propargylamine Intermediate and Imine Byproduct



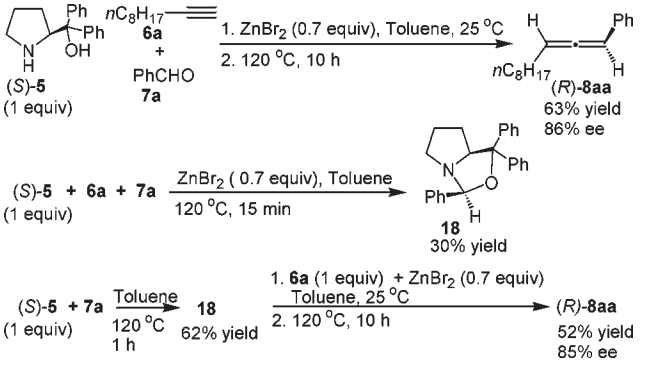
Scheme 2. Plausible Reaction Mechanism



We have observed that the enantioselectivity is also affected by the sequence of addition of reagents (Table 1, footnote *a*).[8] Whereas heating the chiral amine DPP **5**, $ZnBr_2$, and 1-decyne in toluene for 10 min at 120 °C, followed by addition of the aldehyde at 25 °C and further stirring at 120 °C for 10 h, gave the (*R*)-allene **8aa** in 65% yied and 98% ee (Table 1, entry 5), heating all the components together at 120 °C afforded the (*R*)-allene **8aa** only in 86% ee and 63% yield (Scheme 3). We have carried out experiments to account for this observation (Scheme 3). When the amine **5**, 1-decyne **6a**, and benzaldehyde **7a** were heated with $ZnBr_2$ in toluene at 120 °C only for 15 min, the oxazolidine **18**[12] was isolated in 30% yield (Scheme 3). The oxazolidine **18** was also obtained in 62% yield by heating the amine **5** and benzaldehyde **7a** in toluene at 120 °C for 1 h which further illustrates the ease of formation of this intermediate upon heating (Scheme 3).

(12) Zuo, G.; Zhang, Q.; Xu, J. *Heteroatom. Chem.* **2003**, *14*, 42.

Scheme 3. Oxazolidine Intermediate **18** and Its Reaction with $ZnBr_2$ and 1-Decyne **6a**



Interestingly, this oxazolidine intermediate **18** reacts with 1-decyne **6a** and $ZnBr_2$ at 120 °C to give the (*R*)-allene **8aa** only in 85% ee and 52% yield (Scheme 3).

Presumably, when all the components are heated together, the predominant reaction is between the amino alcohol DPP **5** and benzaldehyde **7a** to give the iminium ion species **14a** (Scheme 2) which could cyclize to give the oxazolidine **18** (Scheme 3) in the absence of the alkynylzinc bromide **12**. The oxazolidine **18** could then deprotonate the alkyne–$ZnBr_2$ complex **11**[10b] (Scheme 2), and the resulting alkynylzinc species **12** could directly attack the oxazolidine **18**, leading to a different enantioselectivity in the formation of the allene **8aa**. Further studies on the preparation and reactions of various intermediates expected to be involved in this transformation (Schemes 2 and 3) would help in understanding the mechanism and enantioselectivity.

In summary, since the chiral amines employed here are readily accessible[7,8] and both enantiomers of the DPP **5** are also commercially available, the methods described for the synthesis of chiral allenes have good synthetic potential. Moreover, the methods disclosed here for isolation of the propargylamine intermediates and subsequent zinc halide promoted conversion to chiral allenes **8aa** (Schemes 2 and S2) illustrate the scope of this synthetic protocol for further development.

Acknowledgment. We are thankful to the DST (New Delhi) for a J. C. Bose National Fellowship grant to M.P. and for the FIST and IRPHA programs. Support of the UGC under UPE and CAS programs is also gratefully acknowledged. N.S.K., M.D., R.G., and P.O.R. are thankful to the CSIR (New Delhi) for research fellowships.

Supporting Information Available. Tables S1 and S2, Scheme S1, experimental procedures, physical constant data, ^1H and ^{13}C NMR data, ORTEP diagram, and HPLC analysis profiles. This material is available for free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.