# An Enantioselective Approach to Functionalized Amino Acids: Total Synthesis of Antiepileptic Drug (*R*)-Lacosamide

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Ⓢ *Supporting Information*

ABSTRACT: A short and highly efficient synthetic approach to enantiopure functionalized amino acids (FAAs) **1** skeleton from racemic butadiene monoepoxide as a starting material and its application to the total synthesis of an antiepileptic drug (*R*)-lacosamide **2** are described. The synthesis utilizes the palladium catalyzed Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT) as key step.
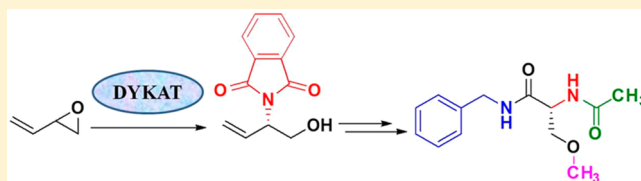
Functionalized amino acids (FAAs) **1** are advanced novel class of anticonvulsant agents, from which (*R*)-lacosamide **2** emerged as a best antiepileptic drug (AED) and has been suggested for the treatment of partial-onset seizures in patients with epilepsy and as add-on treatment in brain tumor patients (Figure 1).[1] Currently, (*R*)-Lacosamide **2** (Vimpat) is marketed in U.S. and Europe, and its worldwide expected sale in 2015–2020 is € 1.2 billion (UCB pharma). Epilepsy is a chronic neurological disorder that arises from dysregulations and hypersynchronous neuronal firing, which affects almost over 10 million people in India and 50 million people worldwide.[2] The precise mechanism of action of (*R*)-lacosamide **2** in humans has not yet been fully elucidated, but it enhances the slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.[3] Additionally, (*R*)-lacosamide **2** is also under clinical trials for the treatment of neuropathic pains.[4]
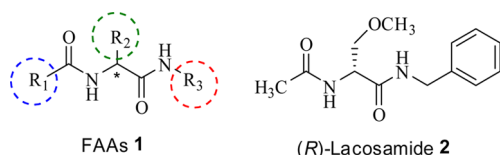

Figure 1. Structures of FAAs **1** and (*R*)-lacosamide **2**.

(*R*)-Lacosamide **2** has been a synthetic target of considerable interest due to its anticonvulsant activity with an array of functionalities. Various methods for the synthesis of (*R*)-lacosamide **2** have been documented in the literature from pharmaceutical industries and academia.[5,6] Most of the synthesis described employed chiral pool approach and started from unnatural amino acid D-serine and derivatives. The synthetic approaches of (*R*)-lacosamide **2** from D-serine mainly involve acylation, amidation, Kuhn's methylation, protection and deprotection strategies. The Kuhn *O*-methylation occurs in the presence of Ag₂O and MeI, which is commercially not viable due

to its high cost, nonregenerability of catalyst and longer reaction time (3−5 days).[7] Very recently, Sebastian Stecko reported the total synthesis of **2** employing stereospecific allylcyanate-to-isocyanate rearrangement, which proceeds with chirality transfer starting from ethyl L-lactate.[5h] Herein, we wish to report a new, general and highly efficient synthetic approach for FAAs **1** and its application to the total synthesis of (*R*)-lacosamide **2** employing Trost's DYKAT as a key step.[8]

Our synthetic approach for the synthesis of (*R*)-lacosamide **2** was envisioned via the retrosynthetic route as shown in Scheme 1. The phthalimide derivative **3** was visualized as a synthetic intermediate from which FAAs **1** and (*R*)-lacosamide **2** could be synthesized via phthalimide cleavage and acylation. The phthalimide derivative **3** in turn could be obtained from the phthaloyl alcohol derivative **4** through base catalyzed alkylation. The terminal double bond of derivative **4** could be available for the functional group manipulation via standard organic transformations. Enantiopure phthaloyl alcohol derivative **4** could be easily prepared from the racemic butadiene monoepoxide **5** by means of Trost's DYKAT. The (*S*)- and (*R*)- configuration of the derivative **4** could be manipulated by simply changing chiral ligands (*R,R*)-DACH and (*S,S*)-DACH (Figure 2), respectively, in the Trost's DYKAT step.

The synthesis of (*R*)-lacosamide **2** started from the commercially available racemic butadiene monoepoxide **5**, which can easily be synthesized from silver-catalyzed oxidation of 1,3-butadiene (Scheme 2).[9] Deracemisation of butadiene monoepoxide **5** with palladium catalyzed Trost's DYKAT in the presence of 1.2 mol % (*R,R*)-DACH and 0.4 mol % [η³-C₃H₅PdCl]₂, phthalimide and base Na₂CO₃ afforded asymmetric allylic alkylation (AAA) product phthaloyl alcohol **6** as a single enantiomer in 98% yield with ≥99% ee {[α]²⁵_D −72.2 (*c* 2.02, CH₂Cl₂) [Lit.⁸ −72.2 (*c* 2.02, CH₂Cl₂)]}.

With enantiomerically pure alcohol **6** in hand, we then subjected it to *O*-methylation with MeI in the presence of NaH

Scheme 1. Retrosynthetic Approach to Asymmetric Synthesis of FAAs 1
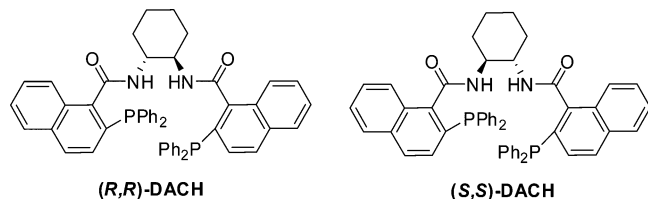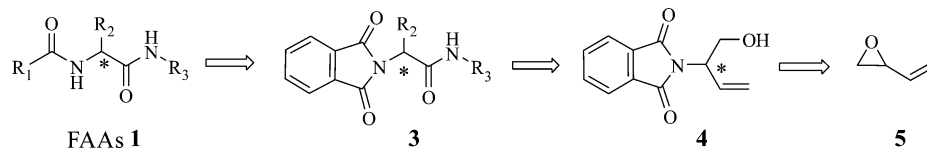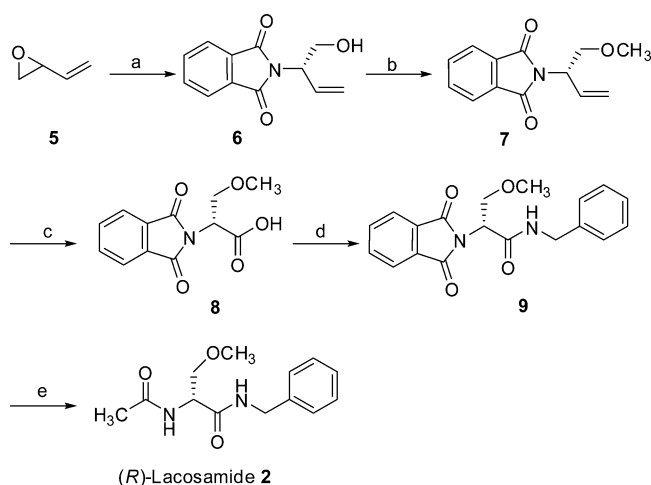

Figure 2. (R,R)- and (S,S)-N,N'-1,2-cyclohexanediylbis[2-(diphenyl-phosphino)-1-naphth-amide].

Scheme 2[a]

[a]Reagents and conditions: (a) Phthalimide, Na$_2$CO$_3$, 1.2 mol % (R,R)-DACH, 0.4 mol % [η^3-C$_3$H$_5$PdCl]$_2$, dry CH$_2$Cl$_2$, rt, 14 h, 98%; (b) MeI, NaH, DMF, 0 °C to rt, 3 h, 86%; (c) (i) OsO$_4$, NaIO$_4$, 2,6-lutidene, dioxane:water 3:1 v/v, 0 °C to rt, 2 h; (ii) Oxone, DMF, rt, 12 h (78% over two steps); (d) C$_6$H$_5$CH$_2$NH$_2$, N-methyl morpholine, isobutyl chloroformate, THF, −78 °C to rt, 1 h, 88%; (e) (i) NH$_2$NH$_2$.H$_2$O, isopropyl alcohol, 0 °C to rt, 2 h; (ii) CH$_3$COCl, Na$_2$CO$_3$, dry toluene, 0 to 5 °C, 1 h, (91% over two steps).

which afforded methyl ether **7** in 86% yield. Our next aim was to carry out the amide formation at terminal double bond site. To this end, compound (S)-**7** on oxidative cleavage in the presence of OsO$_4$ and sodium periodate followed by oxidation with oxone at room temperature furnished the phthaloyl acid **8**.[10,11] The treatment of acid (R)-**8** with benzylamine in the presence of isobutyl chloroformate and N-methyl morpholine in THF at −78 °C afforded the phthaloyl amide **9** in 88% yield. An alternative method for the amide formation with benzylamine is using HOBt and EDCI-HCl furnished phthaloyl amide **9** in 61% yield. Finally, the cleavage of phthalimide group of amide (R)-**9** with hydrazine monohydrate in the presence of isopropyl alcohol followed by N-acetylation using acetyl chloride under basic conditions furnished the target compound (R)-lacosamide **2** in 91% yield {[α]^{25}$_D$ +16.1 (c 1, MeOH) [Lit. +16.2 (c 1, MeOH),[5g] +16.1 (c 1.2, MeOH)[5h]]}. The physical and spectroscopic data of (R)-lacosamide **2** were in full agreement with literature data.[5,6]

In conclusion, a simple, flexible and highly efficient synthetic approach for FAAs **1** and its application to the total synthesis of (R)-lacosamide **2** has been developed. The overall yield for (R)-lacosamide **2** was 52% in five steps. The merits of this synthesis are high enantioselectivity with high yielding reaction steps, protection free synthesis, catalyst regenerability and cost-effective strategy. Moreover, the synthetic strategy has significant potential for variation of substituents at the amide site, 2-aza and 3-oxy sites to synthesize various FAAs **1** with expected increase in anticonvulsant activities.

■ EXPERIMENTAL SECTION

(S)-2-(Isoindolin-2-yl)but-3-en-1-ol (6). A mixture of π-allylpalladium chloride dimer 0.4 mol % (20 mg, 53 μmol), 1.2 mol % (R,R)-DACH ligand (125 mg, 158 μmol), Na$_2$CO$_3$ (70 mg, 0.66 mmol) and phthalimide (1.94 g, 13.2 mmol) in 100 mL of dry CH$_2$Cl$_2$ was purged with nitrogen for 1 h. The resulting mixture was stirred for 10 min at room temperature to which butadiene monoepoxide **5** (920 mg, 13.2 mmol) was added. The resulting mixture was stirred at room temperature under nitrogen for 14 h, concentrated in vacuo and purified by silica gel column chromatography using EtOAc/hexane (3:7) as eluent furnishing 2.8 g (98%) yield of (S)-**6** as a crystalline white solid. Mp 61−63 °C; [R$_f$ = 0.21, EtOAc/hexane 3:7 v/v]; [α]^{25}$_D$ −72.2 (c 2.02, CH$_2$Cl$_2$) [Lit.[8] −72.2 (c 2.02, CH$_2$Cl$_2$)]; IR (CH$_2$Cl$_2$) ν: 3467, 1773, 1698, 1467, 1383 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.8 (m, 2H), 7.7 (m, 2H), 6.1 (ddd, J = 17.4, 10.56, 6.88 Hz, 1H), 5.27−5.30 (m, 2H), 4.9 (m, 1H), 4.1 (m, 1H), 3.9 (m, 1H), 2.7 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 168.5, 134.2, 131.9, 131.7, 123.4, 118.8, 62.8, 55.9.

(S)-2-(1-Methoxybut-3-en-2-yl)isoindoline (7). To a solution of (S)-**6** (2.0 g, 9.2 mmol) in 40 mL DMF was successively added NaH (442 mg, 18.4 mmol) at 0 °C, stirred for 10 min followed by addition of MeI (1.73 mL, 27.6 mmol), and then the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched by addition of ice cold water, extracted with diethyl ether, washed with brine and dried over anhydrous MgSO$_4$. The organic layer was then concentrated in vacuo and purified by silica gel column chromatography using EtOAc/hexane (1:9) as eluent to furnish 1.83 g (86%) yield of (S)-**7** as a crystalline white solid. [R$_f$ = 0.56, EtOAc/hexane 3:7 v/v]; [α]^{25}$_D$ −75.1 (c 1.0, CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$) ν: 1773, 1708, 1468, and 1384 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.80 (m, 2H), 7.68 (m, 2H), 6.1 (ddd, J = 17.44, 10.56, 7.36 Hz, 1H), 5.25−5.34 (m, 2H), 5.0 (m, 1H), 4.0 (m, 1H), 3.6 (m, 1H), 3.3 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 168.0, 133.9, 132.1, 131.9, 123.2, 119.0, 71.3, 58.7, 52.8; HRMS (ESI-TOF) m/z calcd for C$_{13}$H$_{13}$NO$_3$Na [M + Na$^+$] 254.080; found 254.079.

(R)-2-(Isoindolin-2-yl)-3-methoxypropanoic Acid (8). To a solution of compound (S)-**7** (1.5 g, 6.5 mmol) in dioxane−water (3:1, 40 mL) was added 2,6-lutidine (1.5 mL, 13 mmol), OsO$_4$ (0.1 M solution in toluene, 1.3 mL, 0.13 mmol) and NaIO$_4$ (2.78 g, 13 mmol). The reaction was stirred at 25 °C for 2 h. After completion of reaction, water (10 mL) and CH$_2$Cl$_2$ (30 mL) were added. The organic layer was separated, and the water layer extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous MgSO$_4$, and concentrated in vacuo to give crude aldehyde, which was used as such for the next step without further purification.

The above aldehyde was dissolved in DMF and oxone (2 g, 6.5 mmol) added in one portion, and stirred at room temperature for 12 h. The resulting solution was diluted with water, filtered through a Celite pad, and washed and extracted with diethyl ether (3 × 20 mL). The organic extract was washed with brine, dried over anhydrous MgSO$_4$, and the solvent was removed in vacuo to obtain the crude product (R)-**8** which

was used as such for the next step without further purification due to more polar nature of acid compound (*R*)-**8** (1.26 g, 78% yield determined by ^{1}H NMR). The analytical sample was obtained by preparative chromatography on silica gel (CH$_2$Cl$_2$/MeOH, 9:1 v/v) as yellow oil. $[\alpha]^{25}_{D}$ +66.5 (*c* 0.1, MeOH); IR (CH$_2$Cl$_2$) ν: 2896, 1775, 1699, 1604, and 1392 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.36 (s, 3H), 4.0 (m, 1H), 4.17 (t, *J* = 10.08 Hz, 1H), 5.17–5.19 (m, 1H), 7.7 (dd, 2H), 7.8 (dd, 2H), 8.05 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 58.6, 60.5, 70.1, 119.0, 123.3, 128.6, 131.9, 133.8, 168.1, 171.2; HRMS (ESI-TOF) *m/z* calcd for C$_{12}$H$_{11}$NO$_5$Na [M + Na$^+$] 272.050; found 272.053.

(*R*)-*N*-Benzyl-2-(isoindolin-2-yl)-3-methoxypropanamide (9). To a crude acid (*R*)-**8** (1.25 g, 5 mmol) in dry THF was added *N*-methyl morpholine (0.66 mL, 6.0 mmol) at −78 °C under an argon atmosphere. After 5 min, isobutyl chloroformate (0.78 mL, 6.0 mmol) was added and the mixture stirred for another 5 min. To this reaction mixture was added benzylamine (0.65 mL, 6.0 mmol) at −78 °C after which the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was filtered through a Celite pad, washed with ethyl acetate, and dried over anhydrous MgSO$_4$. The solvent was removed *in vacuo* and the crude product was subjected to silica gel column chromatography (EtOAc/Hexane 4:6 v/v) to yield 1.48 g (88%) of (*R*)-**9** as a crystalline solid. [R_f = 0.26, EtOAc/hexane 4:6 v/v]; $[\alpha]^{25}_{D}$ +81.8 (*c* 1, CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$) ν: 1718, 1685, 1535, and 1387 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.8 (m, 2H), 7.7 (m, 2H), 7.27–7.3 (m, 5H), 7.2 (bs, 1H), 5.0 (m, 1H), 4.4 (m, 2H), 4.3 (t, *J* = 9.64 Hz, 1H), 3.7 (m, 1H), 3.4 (bs, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 167.9, 167.3, 137.9, 134.1, 131.8, 128.6, 128.4, 127.4, 127.4, 127.3, 123.5, 70.1, 58.9, 51.7, 43.5; HRMS (ESI-TOF) *m/z* calcd for C$_{19}$H$_{18}$N$_2$O$_4$Na [M + Na$^+$] 361.120; found 361.116.

(*R*)-Lacosamide (2). To a solution of compound (*R*)-**9** (1.4 g, 4.1 mmol) in 20 mL of isopropyl alcohol was added hydrazine monohydrate (0.22 mL, 4.5 mmol) at 0 °C under nitrogen atmosphere. The reaction was stirred at 25 °C for 2 h. The resulting solution was filtered, washed with diethyl ether, brine, dried over magnesium sulfate, and concentrated *in vacuo* to furnish the crude compound (R_f = 0.36, CH$_2$Cl$_2$/MeOH 9:1 v/v). The resulting crude was used as such for the next step without further purification.

The residue was then dissolved in dry toluene followed by addition of Na$_2$CO$_3$ (1.3 g, 12.3 mmol). The reaction mixture was cooled to 0 °C after which acetyl chloride (0.33 mL, 4.5 mmol) was slowly added and the solution stirred at 5 °C for 1 h. After completion of the reaction, the solid was filtered through a Celite pad and the solvent was evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (CH$_2$Cl$_2$/MeOH 19:1 v/v) to afford 935 mg (91%) yield of (*R*)-lacosamide **2** as white solid. [R_f = 0.47, CH$_2$Cl$_2$/MeOH 9:1 v/v]; mp 143–144 °C [Lit. 140–141 °C,^{5g} 142–143 °C^{5h}]; $[\alpha]^{25}_{D}$ +16.1 (*c* 1, MeOH) [Lit. +16.2 (*c* 1, MeOH),^{5g} +16.1 (*c* 1.2, MeOH)^{5h}]; IR (CH$_2$Cl$_2$) ν: 3054, 2928, 1650, 1529, 1372, 1264, and 1118 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.24–7.68 (m, 5H), 6.86 (s, 1H), 6.54 (s, 1H), 4.5 (m, 1H), 4.4 (m, 2H), 3.80 (dd, *J* = 9.2, 4.1 Hz, 1H), 3.4 (m, 1H), 3.37 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 170.3, 169.9, 137.8, 128.7, 127.5, 127.4, 71.6, 59.0, 52.3, 43.5, 23.2.

ASSOCIATED CONTENT

$\mathbf{S}$ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of compounds **2** and **6–9**,. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Simoens, S. *Curr. Med. Res. Opin.* **2011**, *27*, 1329–1338.
(2) (a) Sridharan, R.; Murthy, B. N. *Epilepsia* **1999**, *40*, 631–636. (b) Stafstrom, C. E. *J. Cereb. Blood Flow Metab.* **2006**, *26*, 983–1004. (c) Duncan, J. S.; Sander, J. W.; Sisodia, S. M.; Walker, M. C. *Lancet* **2006**, *367*, 1087–1100. (d) Costigan, M.; Scholz, J.; Woolf, C. J. *Annu. Rev. Neurosci.* **2009**, *32*, 1–32. (e) Miziak, B.; Błaszczyk, B.; Chrościńska, M. K.; Danilkiewicz, G.; Jagiełło, E. W.; Czuczwar, S. J. *Expert Opin. Drug Saf.* **2014**, *13*, 935–946.
(3) (a) Saussele, T. *Med. Monatsschr. Pharm.* **2008**, *31*, 374–377. (b) Beydaun, A.; D'Souza, J.; Hebert, D.; Doty, P. *Expert Rev. Neurother.* **2009**, *9*, 33–42.
(4) (a) Biton, V. *Expert Rev. Neurother.* **2008**, *8*, 1649–1660. (b) Mccleane, G. *Expert Opin. Invest. Drugs* **2010**, *19*, 1129–1134. (c) Hearn, L.; Derry, S.; Moore, R. A. *Cochrane Database Syst. Rev.* **2012**, *2*, CD009318.
(5) (a) Choi, D.; Stables, J. P.; Kohn, H. *J. Med. Chem.* **1996**, *39*, 1907–1916. (b) Andurkar, S. V.; Stables, J. P.; Kohn, H. *Tetrahedron: Asymmetry* **1998**, *9*, 3841–3854. (c) Morieux, P.; Stables, J. P.; Kohn, H. *Bioorg. Med. Chem.* **2008**, *16*, 8968–8975. (d) Park, K. D.; Stables, J. P.; Liu, R.; Kohn, H. *Org. Biomol. Chem.* **2010**, *8*, 2803–2813. (e) Etayo, P.; Núñez-Rico, J. L.; Vidal-Ferran, A. *Organometallics* **2011**, *30*, 6718–6725. (f) Muthukrishnan, M.; Mujahid, M.; Sasikumar, M.; Mujumdar, P. *Tetrahedron: Asymmetry* **2011**, *22*, 1353–1357. (g) Wadavrao, S. B.; Narikimalli, A.; Narsaiah, A. V. *Synthesis* **2013**, *45*, 3383–3386. (h) Stecko, S. *J. Org. Chem.* **2014**, *79*, 6342–6346.
(6) (a) Anumula, R. R.; Gilla, G.; Bolla, Y.; Macharla, P.; Akkireddy, T.; Charagondla, K.; Narayana, R. K. R.; Bhavanipurapu, J. D. P. Patent WO 2011130615, 2011. (b) Bosch, I. L. J.; Duran, L. E. Patent WO 2011158194, 2011. (c) Garimella, N. K.; Danda, S. R.; Budidet, S. R.; Katuroju, S.; Kaki, G. R.; Yatcherla, S. R.; Aminul, I.; Meenakshisunderam, S. Patent WO 2011144983, 2011. (d) Muddasani, P. R.; Madalapu, V.; Nannapaneni, V. C. Patent WO 2011095995, 2011. (e) Pandey, B.; Shah, K. Patent WO 2011039781 A1, 2011. (f) Bologna, A.; Castoldi, P.; Vergani, D.; Bertolini, G. Patent US 20130030216, 2013. (g) Branneby, C. K.; Eek, M. Patent US 20130317109, 2013. (h) Merschaert, A.; Bouvy, D.; Vasselin, D.; Carly, N. Patent US 20130190533, 2013. (i) Davuluri, R. R.; Batthini, G.; Mustyala, S.; Kallepalli, S.; Neela, P. K.; Ponnaiah, R. Patent WO 2013072936 A2, 2013. (j) Gharpure, M.; Srivastava, S.; Crasto, A.; Sharma, T.; Narayanan, S. B.; Bhirud, S. B.; Singh, S. K.; Mishra, S. K.; Yadav, P. R.; Patekar, D. S. Patent WO 2013072933 A2, 2013. (k) Wehlan, H.; Rossen, K.; Oehme, J.; Kral, V. Patent WO 2013072330 A1, 2013. (l) Bernaz-Vazquez, P. M.; Lazcano-Seres, J. M.; Contreras-Martinez, Y. M.; Juarez-Lagunas, J. A.; Sanchez-Mereles, D.; Vazquez-Miranda, J. R.; Zambrano-Huerta, A. Patent WO 2013030654 A1, 2013. (m) Biswas, S.; Bansal, V.; Gupta, N. K.; Vir, D.; Chakravarty, R. Patent WO 2014155264 A1, 2014. (n) Muthukrishnan, M.; Mujahid, M.; Mujumdar, P. P. Patent US 20140012044 A1, 2014.
(7) Kuhn, R. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 19.
(8) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976.
(9) Monnier, J. R.; Muehlbauer, P. J. Patent US 508096, 1992. *Chem. Abstr.* **1992**, *116*, 114395b; Patent US 5138077, 1992;. *Chem. Abstr.* **1992**, *117*, 212303k.
(10) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.
(11) Benjamin, R. T.; Meenakshi, S.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031–1034.