Synthetic Communications®, 39: 2549–2559, 2009
Copyright © Taylor & Francis Group, LLC
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802657925

Taylor & Francis
Taylor & Francis Group

Green Protocol for Synthesis of 1,5-Benzodiazepines and 1,5-Benzothiazepines in the Presence of Nanocrystalline Aluminum Oxide

Rahim Hekmatshoar, Sodeh Sadjadi, Soudeh Shiri, Majid M. Heravi, and Yahya S. Beheshtiha
Department of Chemistry, School of Science, Alzahra University, Vanak, Tehran, Iran

Abstract: An efficient protocol associated with readily available starting materials, mild conditions, excellent yields, and a broad range of the products in synthetic chemistry was established for synthesis of 1,5-benzodiazepine and 1,5-benzothiazepine derivatives in the presence of a catalytic amount of nanocrystalline aluminum oxide in water.

Keywords: *o*-Aminothiophenol, 1,5-benzodiazepine, 1,5-benzothiazepine, nanocrystalline aluminum oxide, *o*-phenylenediamines, reusable catalyst

INTRODUCTION

Both 1,5-benzothiazepine and 1,5-benzothiazine ring systems have derivatives of biological importance. Many functionalized benzodiazepines have been used as analgesic, sedative, anticonvulsant, antianxiety, antidepressive, and hypnotic agents.[1] Because of its well-known bioactivities, 1,5-benzothiazepine is especially important in nitrogen- and sulfur-containing heterocyclic compounds in drug research. Thiazesim and diltiazem are well-known drugs that have 1,5-benzothiazepine skeletons.[2]

Received November 5, 2008.
Address correspondence to Rahim Hekmatshoar, Department of Chemistry, School of Science, Alzahra University, Vanak, Tehran, Iran. E-mail: rhekmatus@yahoo.com

A general way to construct the ring skeletons of 1,5-benzodiazepine and 1,5-benzothiazepine is via reactions of o-phenylenediamines (o-PDA) or o-aminothiophenol (o-ATP) with ketones, α,β-unsaturated carbonyl compounds, or β-haloketones. Catalysts such as $BF_3 \cdot Et_2O$, $NaBH_4$, polyphosphoric acid (PPA)/SiO_2, MgO/$POCl_3$, amberlyst-15, $Yb(OTf)_3$, Al_2O_3/P_2O_5, AcOH/MW, sulfated zirconia, N-bromosuccinimide (NBS), $Ga(OTf)_3$,[3] sodium dodecyl sulfate (SDS),[4] and ionic liquids[5–9] have been used to improve reaction efficiency.

There remains the necessity of developing a more effective and convenient synthetic procedure because the reported methods have one or more disadvantages such as the use of a high-boiling solvent (e.g., dimethylformamide, DMF) that is difficult to recover, excess amounts of acid or base, special apparatus, corrosive (e.g., HCl gas; trifluoroacetic acid TFA) and hazardous (e.g., pyridine, piperidine, halogenated hydrocarbon) reagents/solvents, and special efforts to prepare the catalysts and adsorb the reactants onto a solid support.

In continuation of our interest in exploring catalytic methodology in organic transformations,[10–12] we report herein recyclable Al_2O_3 nanoparticles as the catalyst for an efficient synthesis of 1,5-benzodiazepine and 1,5-benzothiazepine diaryl ethers.

Nanocrystalline metal oxides find excellent applications as active adsorbents for gases and destruction of hazardous chemicals.[13] They

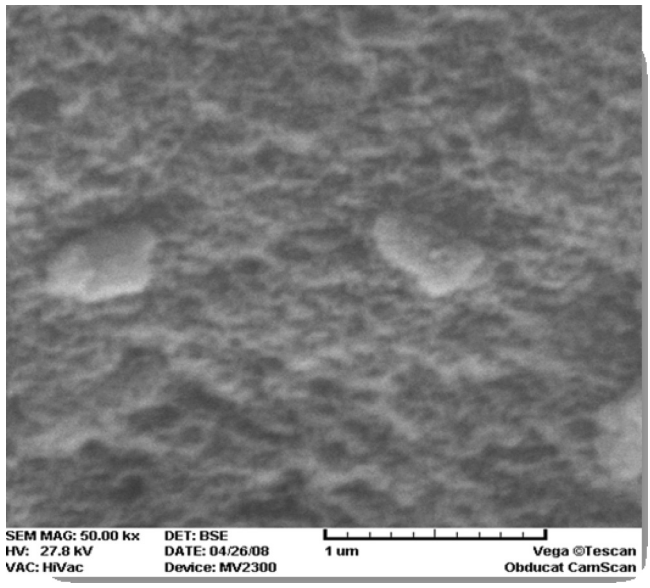
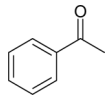
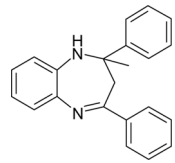
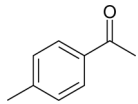
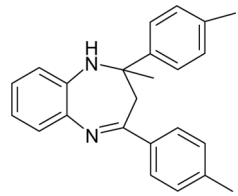
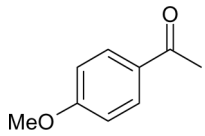
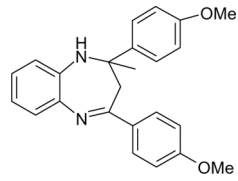
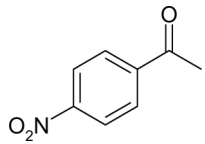
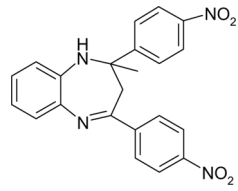
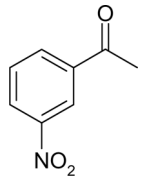
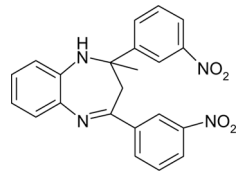
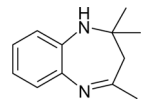
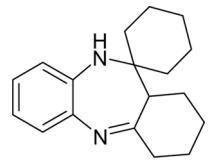


Figure 1. Scanning electron micrograph of nanosized Al_2O_3 particles.

Table 1. 1,5-Benzodiazepines from o-phenylenediamine and ketones

Entry	Ketone	Product	Yield (%)
1			95
2			90
3			93
4			87
5			91
6			93
7			71

are also gaining tremendous importance because of their distinct catalytic activities for various organic transformations. Recently, researchers have reported various[14] organic transformations using different nanocrystalline metal oxides. These high reactivities are due to the large surface areas combined with unusually reactive morphologies.

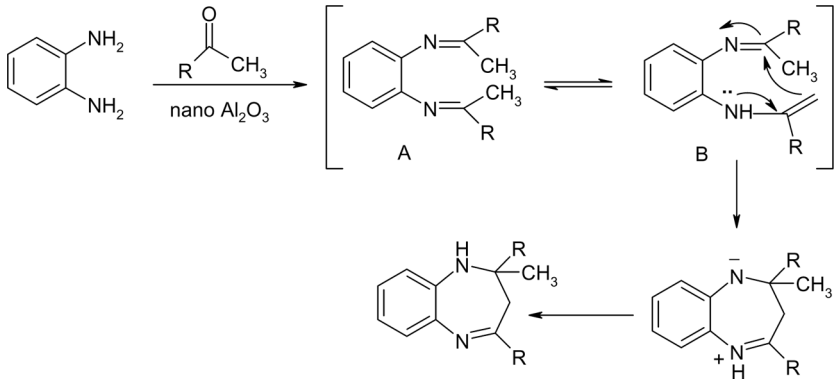
Al_2O_3 nanosized particles were synthesized by a wet chemical procedure. The morphology and size distribution of Al_2O_3 nanoparticles were determined by scanning electron micrography (SEM) (Fig. 1).

Tandem reactions involve one-pot, multistep transformations and avoid the isolation and purification of intermediates, thereby minimizing cost, time, labor, and waste. Hence, they are convergent, elegant, and ecofriendly procedures for the rapid construction of complex molecules and are attractive from the viewpoint of green chemistry.[15]

o-Phenylenediamine and acetophenone were chosen as the substrates for method development reactions. The reactions were carried out by taking a 1:2.5 molar ratio mixture of *o*-phenylenediamine and the ketone along with a catalytic amount of nano-Al_2O_3 with stirring at room temperature for the appropriate time. Cyclic ketones such as cyclohexanone also reacted effectively to produce the corresponding fused ring benzodiazepines. The results are summarized in Table 1.

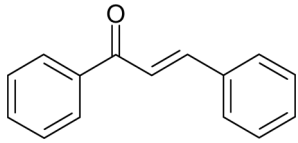
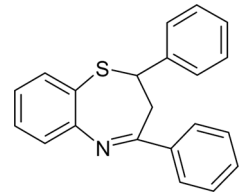
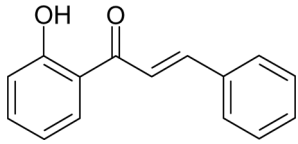
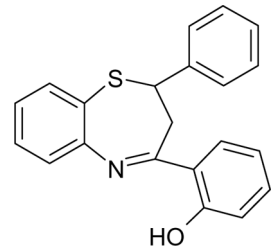
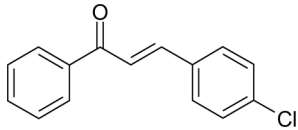
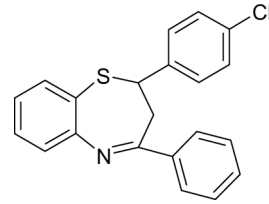
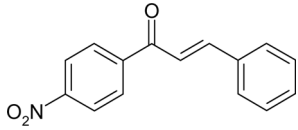
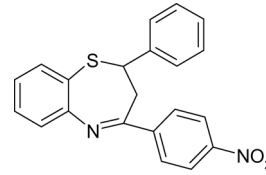
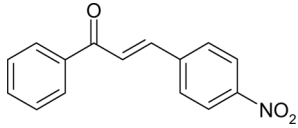
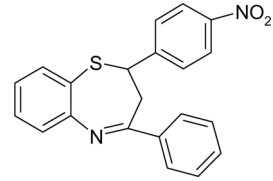
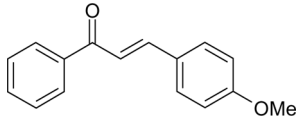
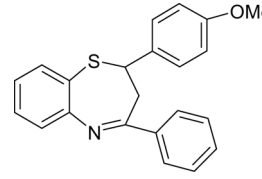
No reaction was observed when o-PDA was reacted with acetone under similar conditions in the absence of the catalyst, thus highlighting the role of nano-Al_2O_3 as a promoter.

Reactions of *o*-PDA with acetophenones bearing electron-donating and electron-withdrawing substitution groups gave products in good to excellent yields (71–95%) (Table 1, entries 1–7). Reactions of alkylketones such as acetone and cyclohexanone also gave benzodiazapines (Table 1, entries 6 and 7).



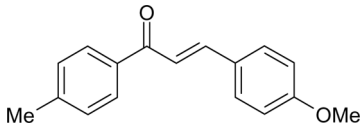
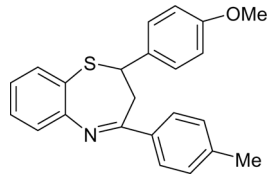
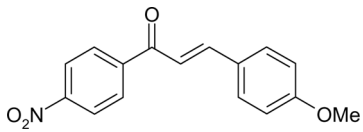
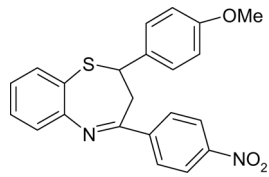
Scheme 1. A plausible mechanism for 1,5-benzodiazepines.

Table 2. Synthesis of 1,5-benzothiazepines from o-aminothiophenol and chalcones

Entry	Ketone	Product	Yield (%)
1			71
2			79
3			85
4			81
5			86
6			90

(*Continued*)

Table 2. Continued

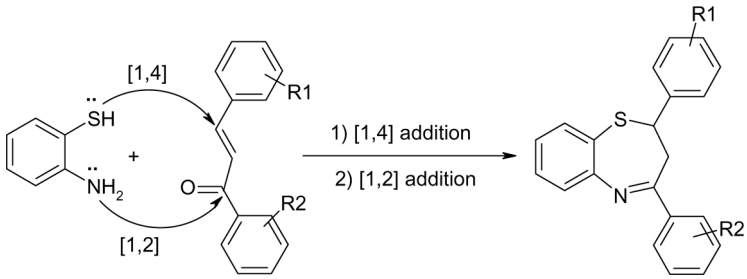
Entry	Ketone	Product	Yield (%)
7			84
8			75

The mechanism of the reactions 1–7 probably involves an intramolecular imine–enamine cyclization promoted by nano-Al_2O_3 as shown in Scheme 1. The amine of *o*-PDA attacks the carbonyl group of ketone, giving the intermediate diimine A. A 1,3-shift of the hydrogen-attached methyl group then occurs to form isomeric enamine B, which cyclizes to afford a seven-membered ring.[16]

To analyze the scope of the reaction, we tested chalcones as carbonylic sources to afford the 1,5-benzodiazepines. Our initial efforts to react chalcones with *o*-aminothiophenol under reflux (oil-bath temperature 110°C) for 12 h did not produce any significant amount of 1,5-benzodiazepines in the presence of nanosized Al_2O_3. Thus, *o*-aminothiophenol was used to replace *o*-PDA for the reaction. When the reaction was carried out in water under the same condition, 1,3-diphenyl-2,3-dihydro-1,5-benzothiazepine was formed in 71% yield (Table 2, entry 1).

To establish the generality of this method, we investigated the cyclocondensation of various substituted 1,3-diarylpropenones. The reaction of various 1,3-diarylpropenones with 2-aminothiophenol afforded the corresponding 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines in 71–90% yields (Table 2). The reaction was compatible with various electron-donating (Me and OMe) and electron-withdrawing (Cl and NO_2) substituents.

The reaction of *o*-aminothiophenol (o-ATP) with an α,β-unsaturated carbonyl functionality leads to benzodiazepines and benzothiazepines, respectively, via [4 + 3]-annulation. Although in all reactions between a dinucleophile (hydrazines, hydroxylamine, *o*-phenylenediamine, etc.) with a dielectrophile of the type mentioned, two compounds can be



Scheme 2. A plausible mechanism for 1,5-benzothiazepines.

formed; because only benzothiazepines were isolated, it was assumed that the reaction starts by 1,4-Michael addition of the SH on the CC double bond followed by the condensation of the NH_2 on the carbonyl group (Scheme 2).[17]

The efficiency of bulk Al_2O_3 and basic Al_2O_3 as catalysts was also studied for this reaction, but the model reaction (of 1,3-diphenylpropenone and 2-aminothiophenol) did not complete in the presence of these catalysts, even after long reaction times (48 h) and with more catalyst (Table 3).

The increased catalytic activity of nano-Al_2O_3 over commercially available bulk Al_2O_3 and basic Al_2O_3 may be attributed to the larger surface area of nano-Al_2O_3 than bulk Al_2O_3 as well as the greater surface concentration of the reactive sites. As seen with other metal oxides, once they are made into nanoparticles, their reactivity is greatly enhanced. This is thought to be due to the morphological differences: whereas larger crystallites have only a small percentage of the reactive sites on the surface, smaller crystallites possess a much greater surface concentration of such sites.[18]

The nano-Al_2O_3 catalyst could be reused for four cycles without loss of activity and selectivity. Infrared (IR) spectra of fresh and used nano-Al_2O_3 catalyst confirmed the fact that the structure and morphology of the catalyst remained the same during the course of the reaction (Figure 2).

Table 3. Comparison between nano-Al_2O_3 and commercially available bulk Al_2O_3 and basic Al_2O_3 catalysts in the reaction of 1,3-diphenylpropenone and 2-aminothiophenol

Entry	Catalyst	Time (h)	Amount of catalyst (mmol)	Yield (%)
1	Nano-Al_2O_3	12	0.03 mmol	71
2	Bulk Al_2O_3	48	0.1 mmol	27
3	Basic Al_2O_3	48	0.1 mmol	34

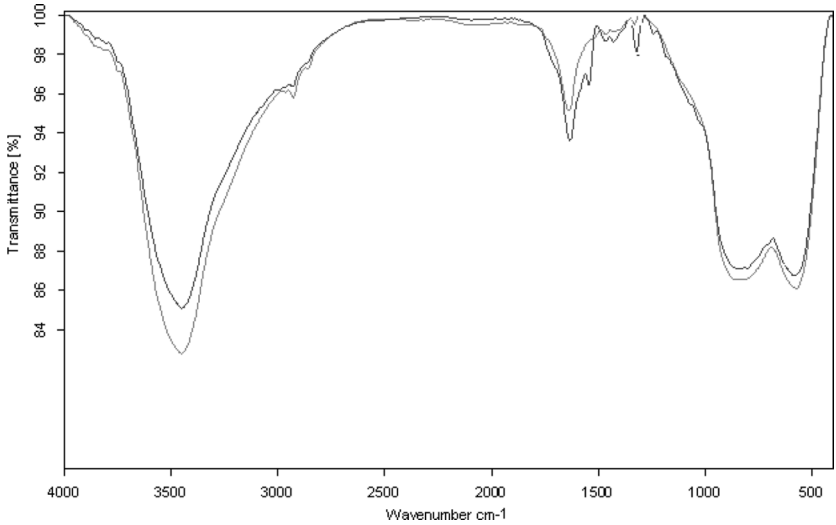


Figure 2. IR spectrum of nanosized Al_2O_3 before (a) and after (b) use.

In summary, nanosized Al_2O_3 was an effective catalyst for the synthesis of 2,2,4-trisubstituted-1,5-benzodiazepines under mild reaction conditions. We also report nanosized Al_2O_3 as a highly efficient heterogeneous reusable catalyst for chemoselective thia-Michael addition to α,β-unsaturated carbonyl compounds. The methodology finds application in a one-pot synthesis of 2,3-dihydro-1,5-benzothiazepines.

EXPERIMENTAL

Synthesis of Nanosized Al_2O_3

The Al_2O_3 nanoparticles were synthesized by precipitation of the aluminum hydroxide gels in aqueous solution using $Al(NO_3)_3$ as salt and aqueous ammonia as the precipitating agent. Initially, the pH of 200 ml of distilled water was adjusted to 5 by addition of aqueous ammonia. To this solution, 0.1 M aluminum nitrate solution was added dropwise with continuous stirring. The rate of addition of the salt solution was kept at 20 ml/h during the addition; the pH was maintained at 7 by controlled addition of aqueous ammonia solution. After completion of the precipitation procedure, the mixture was stirred at room temperature for 12 h, filtered, repeatedly washed with distilled water, dried at 120°C, and calcined at 500°C for 2 h. The temperature of the furnace

was linearly raised from room temperature to 500°C with an increment of 10°C/min. At 500°C, the temperature was maintained for 2 h to yield the final material.

General Procedure for Synthesis of 2,2,4-Trisubstituted-1,5-benzodiazepines (Table 1)

A mixture of *o*-PDA (0.21 g, 2 mmol), acetophenone (0.54 g, 4.5 mmol), and nano-Al_2O_3 (0.003 g, 0.03 mmol) in 10 mL of water was refluxed (oil-bath temp. 110°C) for 6 h. After completion of the reaction [thin-layer chromatographic (TLC) analysis], the catalyst was filtered, and the reaction mixture was extracted with dichloromethane (2×10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to dryness in vacuo, and the residue was purified by column chromatography (eluted with 2:8 EtOAc–petroleum ether) to afford pure diazepine.

Synthesis of 2,3-Dihydro-2,4-diphenyl-1,5-benzothiazepine (Table 2, Entry 1)

A mixture of 1,3-diphenylpropenone (0.21 g, 1 mmol) in water (5 mL) was heated under reflux (oil-bath temp 110°C) under magnetic stirring until it formed a melt and mixed with water as tiny droplets. 2-Aminothiophenol (0.13 g, 1.1 mmol, 1.1 equiv) was added, followed by nano-Al_2O_3 (0.003 g, 0.03 mmol), and the mixture was stirred at 110°C for 12 h. The cooled (rt) reaction mixture was extracted with EtOAc (3×5 mL), the catalyst was filtered, and the combined EtOAc extracts were washed with brine, dried (Na_2SO_4), and concentrated under rotary vacuum evaporation. The crude product was subjected to column chromatography using EtOAc/hexane (2:98) as eluent to afford 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine (71%) as a yellow solid, identical (spectral data and mp) with an authentic compound.[3–4] The remaining reactions were carried out following this general procedure. All the product structures were in full agreement with the spectral data (IR, NMR, and MS) and gave satisfactory elemental analyses.

Reusing the Catalyst

After completing the model reaction, the catalyst was filtered and washed three times with 10-ml portions of methanol, dried at 150°C overnight, and subjected to a second run of the reaction process with the same substrate.

ACKNOWLEDGMENT

The authors are thankful to the Alzahra Research Council for partial financial support.

REFERENCES

1. Randall, L. O.; Kappel, B. *Benzodiazepines*. S. Garattini, E. Mussini, L. O. Randall (Eds.); Raven Press: New York, 1973; p. 27.
2. Anshu Dandia, A.; Singh, R.; Khaturia, S. Efficient microwave-enhanced solvent-free synthesis of potent antifungal agents: Fluorinated benzothiazepine fused β-lactam derivatives. *J. Fluorine Chem.* **2007**, *128*, 524–529.
3. Pan, X.-Q.; Zou, J.-P.; Huang, Z.-H.; Zhang, W. $Ga(OTf)_3$-promoted condensation reactions for 1,5-benzodiazepines and 1,5-benzothiazepines. *Tetrahedron Lett.* **2008**, *49*, 5302–5308.
4. Sharma, G.; Kumar, R.; Chakraborti, A. K. "On water" synthesis of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines catalysed by sodium dodecyl sulfate (SDS). *Tetrahedron Lett.* **2008**, *49*, 4269–4271.
5. Yadav, J. S.; Reddy, B. V. S.; Eshwaraiah, B.; Anuradha, K. Amberlyst-15®: A novel and recyclable reagent for the synthesis of 1,5-benzodiazepines in ionic liquids. *Green Chem.* **2002**, *4*, 592–594.
6. Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. Ytterbium triflate promoted synthesis of 1,5-benzodiazepine derivatives. *Tetrahedron Lett.* **2001**, *42*, 3193–3195.
7. Pozarentzi, M.; Stephanidou-Stephanatou, J.; Tsoleridis, C. A. An efficient method for the synthesis of 1,5-benzodiazepine derivatives under microwave irradiation without solvent. *Tetrahedron Lett.* **2002**, *43*, 1755–1758.
8. Reddy, B. M.; Sreekanth, P. M. An efficient synthesis of 1,5-benzodiazepine derivatives catalyzed by a solid superacid sulfated zirconia. *Tetrahedron Lett.* **2003**, *44*, 4447–4449.
9. Kuo, C.-W.; More, S. V.; Yao, C.-F. NBS as an efficient catalyst for the synthesis of 1,5-benzodiazepine derivatives under mild conditions. *Tetrahedron Lett.* **2006**, *47*, 8523–8528.
10. Hekmatshoar, R.; Heravi, M. M.; Sadjadi, S.; Oskooie, H. A.; Bamoharram, F. F. Catalytic performance of Preyssler heteropolyacid $[NaP_5W_{30}O_{110}]^{14-}$ in liquid phase alkylation of phenol with 1-octene. *Catal. Commun.* **2008**, *9*, 837–841.
11. Heravi, M. M.; Sadjadi, S.; Oskooie, H. A.; Hekmat Shoar, R.; Bamoharram, F. F. Heteropolyacids as heterogeneous and recyclable catalysts for the synthesis of benzimidazoles. *Catal. Commun.* **2008**, *9*, 504–507.
12. Heravi, M. M.; Sadjadi, S.; Oskooie, H. A.; Hekmat Shoar, R.; Bamoharram, F. F. The synthesis of coumarin-3-carboxylic acids and 3-acetyl-coumarin derivatives using heteropolyacids as heterogeneous and recyclable catalysts. *Catal. Commun.* **2008**, *9*, 470–474.
13. Klabunde, K. J.; Mulukutla, R. *Nanoscale Materials in Chemistry*; Wiley Interscience: New York, 2001; chap. 7, p. 223.

14. Choudary, B. M.; Kantam, M. L.; Ranganath, K. V. S.; Mahendar, K.; Sreedhar, B. Bifunctional nanocrystalline MgO for chiral epoxy ketones via Claisen-Schmidt condensation–asymmetric epoxidation reactions. *J. Am. Chem. Soc.* **2004**, *126* (11), 3396–3397.
15. Karthikeyan, S. V.; Perumal, S. A facile tandem protocol for the regioselective synthesis of novel thienobenzothiazepines. *Tetrahedron Lett.* **2007**, *48*, 2261–2265.
16. De, S. K.; Gibbs, R. A. Scandium(III) triflate as an efficient and reusable catalyst for synthesis of 1,5-benzodiazepine derivatives. *Tetrahedron Lett.* **2005**, *46*, 1811–1813.
17. Prakash, O.; Kumar, A.; Sadana, A.; Prakash, R.; Singh, S. P.; Claramunt, R. M.; Sanz, D.; Alkorta, I.; Elguero, J. Study of the reaction of chalcone analogs of dehydroacetic acid and *o*-aminothiophenol: Synthesis and structure of 1,5-benzothiazepines and 1,4-benzothiazines. *Tetrahedron* **2005**, *61*, 6642–6651.
18. Kantam, M. L.; Laha, S.; Yadav, J.; Bhargava, S. An efficient synthesis of propargylamines via three-component coupling of aldehydes, amines, and alkynes catalyzed by nanocrystalline copper(II) oxide. *Tetrahedron Lett.* **2008**, *49*, 3083–3086.