ARTICLE IN PRESS

Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile synthesis of libraries of functionalized cyclopropanes and oxiranes using ionic liquids – A new approach to the classical Corey-Chaykovsky reaction

Shruti S. Malunavar [a], Suraj M. Sutar [a], Pavankumar Prabhala [a], Hemantkumar M. Savanur [b], Rajesh G. Kalkhambkar [a,*], Gopalakrishnan Aridoss [c], Kenneth K. Laali [d,*]

[a] Department of Chemistry, Karnatak University's Karnatak Science College, Dharwad, Karnatak 580001, India
[b] Department of Studies and Research in Chemistry, P. C. Jabin Science College, Hubli, Karnatak 580021, India
[c] Anygen Co., Ltd., Gwangju Technopark, Cheomdan Gwagi-ro, Buk-gu, Gwangju 61008, South Korea
[d] Department of Chemistry, University of North Florida, 1, UNF Drive, Jacksonville, FL 32224, USA

ARTICLE INFO

Article history:
Received 22 July 2021
Revised 9 August 2021
Accepted 15 August 2021
Available online xxxx

Keywords:
Cyclopropanation
Epoxidation
Ionic liquids as base and solvent
Application in quinoline synthesis

ABSTRACT

The potential of [PAIM][NTf_2]/BMIM-ILs as a base/solvent in the Corey-Chaykovsky reaction is demonstrated by the facile synthesis of libraries of functionalized cyclopropanes from enones and oxiranes from aldehydes and ketones, at room temperature in respectable isolated yields. To demonstrate their application, the synthesized epoxides were employed as substrates for the synthesis of a library of 2,3-disubstituted quinolines, using [BMIM(SO_3H)][OTf]/[BMIM][PF_6] as a catalyst/solvent. The potential for recycling/reuse of the IL solvents was also explored.

Introduction

In the classical Corey-Chaykovsky (CC) reaction, ylides derived from the deprotonation of sulfonium and sulfoxonium halides using a strong base react with aldehydes and ketones to give oxiranes and with enones to furnish cyclopropyl-ketones as *cis/trans* mixtures [1a]. A phase transfer catalysis (PTC) version of this reaction also gave *cis/trans* mixtures [1b]. Typical bases employed include NaH, BuLi, and *t*-BuOK, with DMF, THF, or dioxane as solvent [1a–3].

Due to the prominence of cyclopropane and oxirane motifs in a wide range of bioactive natural and synthetic compounds which are important in drug development [4], numerous studies aiming to improve on these transformations have been reported. Although cyclopropanation using milder bases such as DABCO and Et_3N in MeCN proved unsuccessful, guanidine bases (TMG, and MTBD) were effective, especially when used in excess, forming > 98% *trans* isomer [5].

The asymmetric version of the Corey-Chaykovsky cyclopropanation has also been studied [6]. Epoxidation of aryl-aldehydes using an *in-situ* generated benzyl-sulfonium salt (from tetrahydrothiophene (THT)/benzyl alcohol/HBF_4-Et_2O) with NaH as base, and *in-situ* generated sulfonium triflate (from THT/MeOTf), as well as its asymmetric version using chiral analogs of THT and phosphazene bases, have also been reported [7].

Zinc-derived sulfur ylides generated *via* the Simmons-Smith reaction offer an alternative for the epoxidation of aldehydes, and the cyclopropanation of α,β-unsaturated ketones and esters using $NiCl_2$ as a catalyst [8,9].

Despite considerable progress in this area, the development of alternative methods that utilize mild bases, avoid the use of metals and high boiling hazardous solvents, and offer the possibility for recycling/reuse of the solvent is still highly desirable.

In continuation of our studies focusing on the development of alternative synthetic methods employing ILs as catalysts and solvents [10], and in relation to our long standing interest in onium salts and their synthetic applications [11], we report herein the facile synthesis of libraries of functionalized cyclopropanes and oxiranes at room temperature, employing the piperidine-appended-IL [PAIM][NTf_2] [10f,10i] as base and BMIM-ILs as solvent (Fig. 1), without metals or additives, and with potential for recycling/reuse of the IL solvent. These studies underscore the potential of [PAIM][NTf_2]/[BMIM][X] for the *in-situ* generation of sulfur ylides from sulfoxonium and sulfonium salts at room

---

* Corresponding authors.
E-mail address: kenneth.laali@unf.edu (K.K. Laali).

https://doi.org/10.1016/j.tetlet.2021.153339
0040-4039/© 2021 Elsevier Ltd. All rights reserved.

Please cite this article as: S.S. Malunavar, S.M. Sutar, P. Prabhala et al., Facile synthesis of libraries of functionalized cyclopropanes and oxiranes using ionic liquids – A new approach to the classical Corey-Chaykovsky reaction, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2021.153339

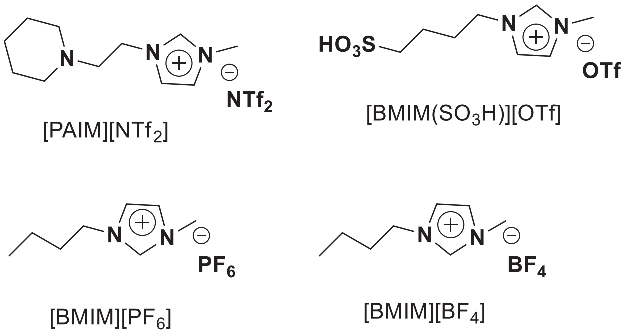


Fig. 1. Structures of the key ILs.

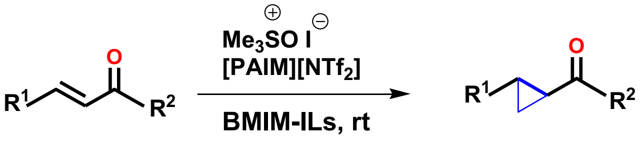
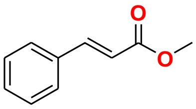
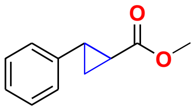
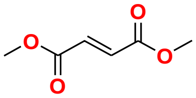
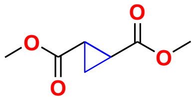
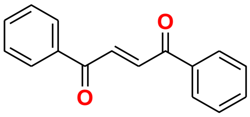
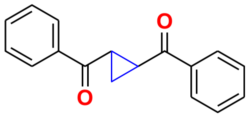
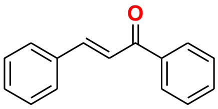
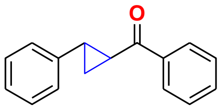
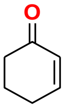
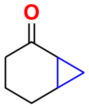
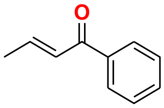
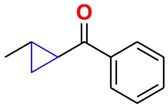
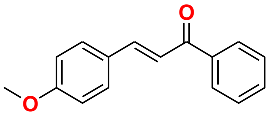
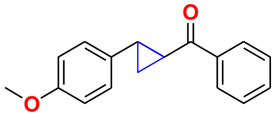
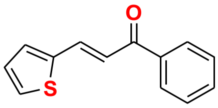
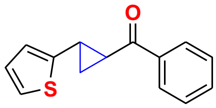
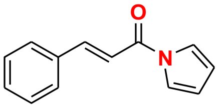
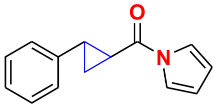
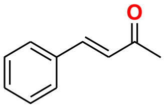
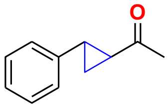
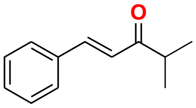
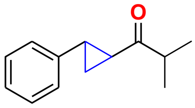


Fig. 2. Cyclopropanation of enones.

temperature. To the best of our knowledge there has only been one previous report of the CC reaction employing an IL as solvent with KOH as base [12]. In connection with recent reports regarding the synthesis of 2,3-disubstituted quinolones [13], application of the synthesized epoxides for the synthesis of a library of 2,3-disubsti-

Table 1
Cyclopropanation of enones employing ILs as base and solvent.[a]

Entry	Substrate	Product	IL Solvent	Time (min)	Yield (%)[b]
1.			[BMIM][PF$_6$]	90	90[c]
2.			[BMIM][BF$_4$]	90	92[c]
3.			[BMIM][PF$_6$]	100	85[e]
4.			[BMIM][BF$_4$]	90	91[c]
5.			[BMIM][PF$_6$]	60	87[d]
6.			[BMIM][PF$_6$]	80	82[e]
7.			[BMIM][BF$_4$]	80	85[d]
8.			[BMIM][PF$_6$]	120	81[e]
9.			[BMIM][PF$_6$]	120	83[d]
10.			[BMIM][BF$_4$]	60	90[c]
11.			[BMIM][BF$_4$]	80	87[d]

---

[a] Reagents and conditions: enone (1 mmol), trimethylsulfoxonium iodide (1.1 mmol), [BMIM][BF$_4$] or [BMIM][PF$_6$] (5–6 mL), [PAIM][NTf$_2$] (20 mol%), r.t.

[b] Isolated yield.

[c] Yield employing fresh IL.

[d] Yield using recycled IL (2nd cycle).

[e] Yield using recycled IL (3rd cycle).

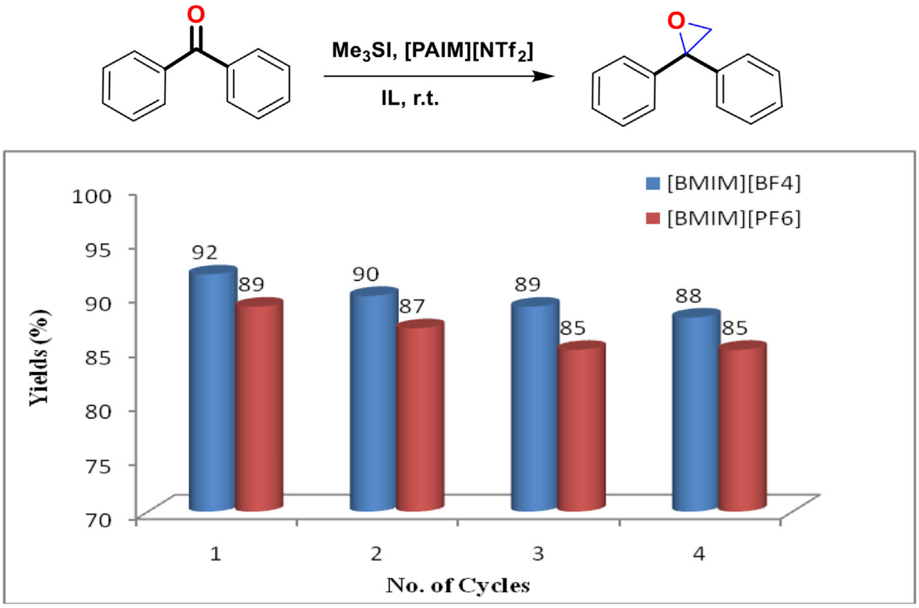


Fig. 3. Graphical representation for recycling/reuse of the ILs in the cyclopropanation reaction.

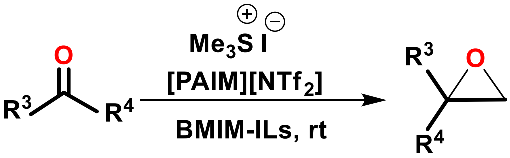
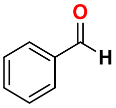
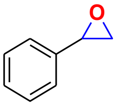
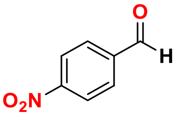
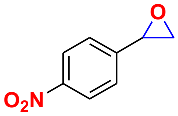
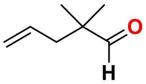
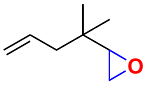
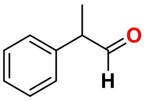
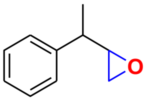
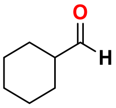
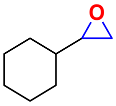
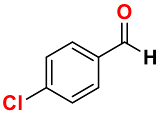
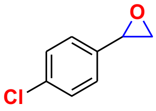


Fig. 4. Synthesis of oxiranes.

tuted quinolines using [BMIM(SO_3H)][OTf]/[BMIM][PF_6] as a catalyst/solvent is also demonstrated.

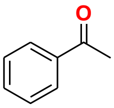
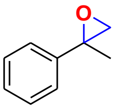
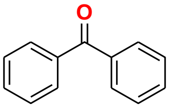
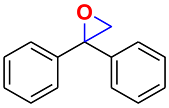
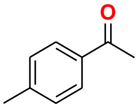
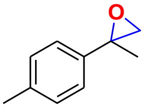
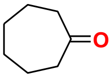
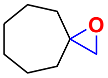
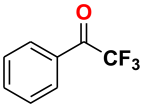
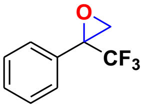
The cyclopropanation of a variety of electron-deficient alkenes was effected by the *in-situ* generated sulfur ylide derived from trimethylsulfoxonium iodide at r.t., employing [PAIM][NTf_2] as a basic-IL in readily available BMIM-ILs as solvent (Fig. 2 and Table 1).

Table 2
Epoxidation of aldehydes and ketones employing ILs as base and solvent.[a]

Entry	Substrate	Product	IL Solvent	Time (min)	Yield[b] (%)
1.			[BMIM][BF_4]	60	89[e]
2.			[BMIM][PF_6]	120	83[e]
3.			[BMIM][PF_6]	90	88[d]
4.			[BMIM][BF_4]	100	81[e]
5.			[BMIM][BF_4]	150	85[d]
6.			[BMIM][BF_4]	80	91[c]

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product	IL Solvent	Time (min)	Yield[b] (%)
7.			[BMIM][PF$_6$]	90	90[c]
8.			[BMIM][BF$_4$]	90	92[c]
9.			[BMIM][PF$_6$]	80	89[c]
10.			[BMIM][BF$_4$]	120	84[e]
11.			[BMIM][BF$_4$]	120	82[d]

[a] Reagents and conditions: carbonyl compound (1 mmol), trimethylsulfonium iodide (1.1 mmol), [BMIM][BF$_4$] or [BMIM][PF$_6$] (5–6 mL), [PAIM][NTf$_2$] (20 mol%), r.t.

[b] Isolated yield.

[c] Yield employing fresh IL.

[d] Yield using recycled IL (2nd cycle).

[e] Yield using recycled IL (3rd cycle).

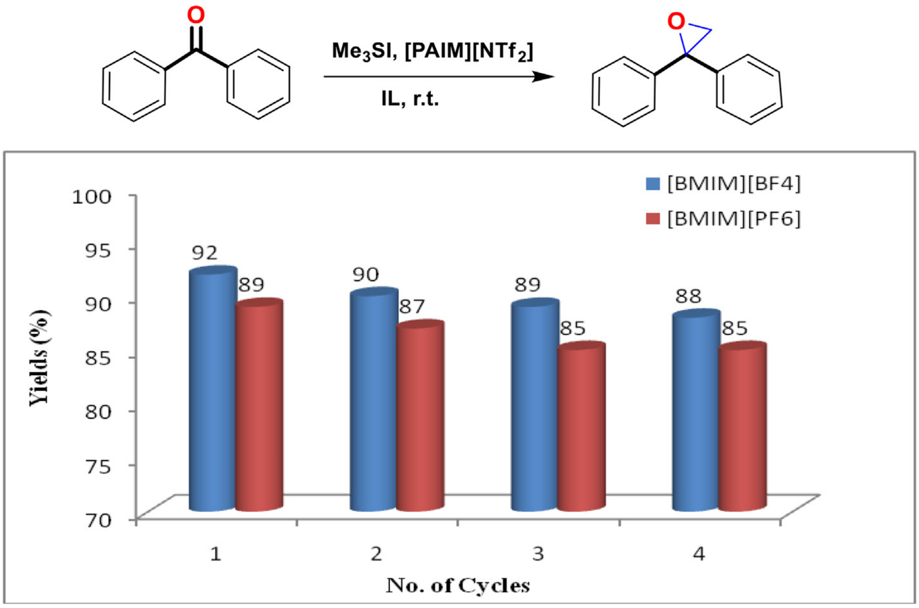


Fig. 5. Graphical representation for recycling/reuse of the ILs in the epoxidation reaction.

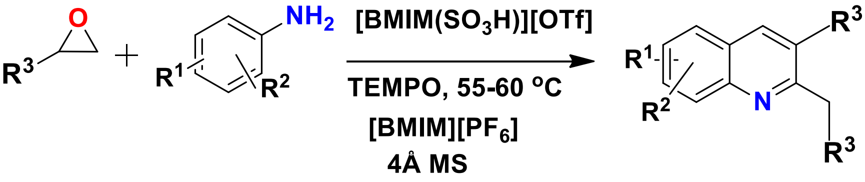
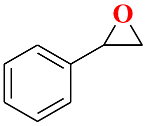
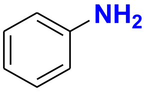
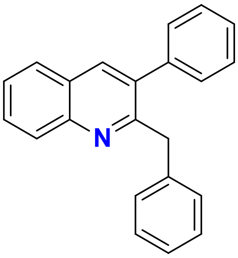
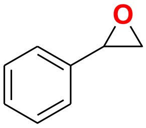
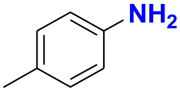
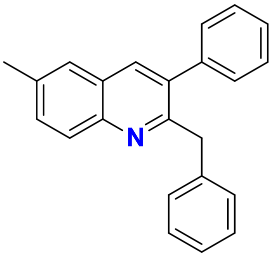
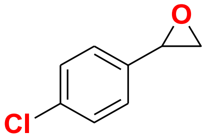
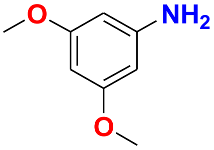
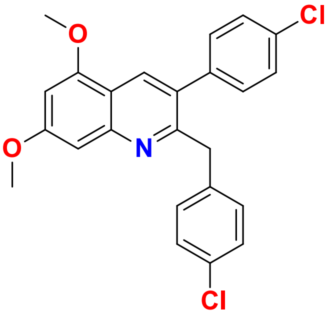
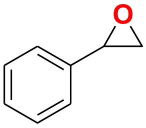
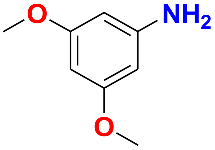
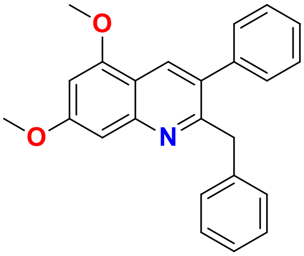
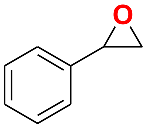
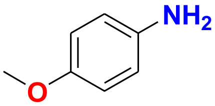
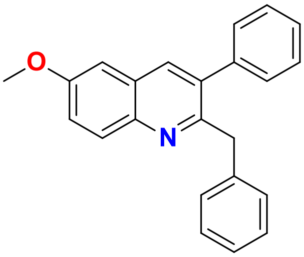
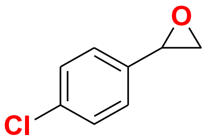
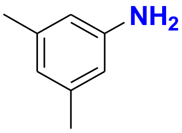
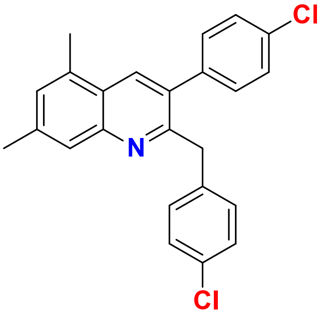


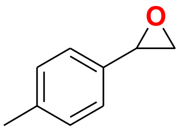
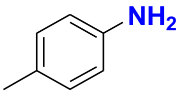
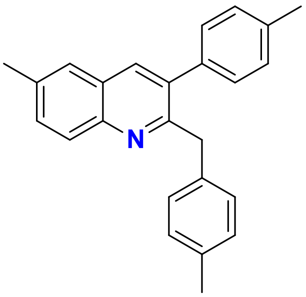
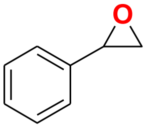
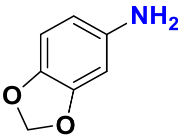
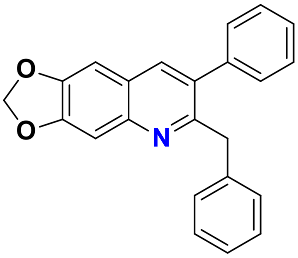
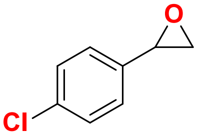
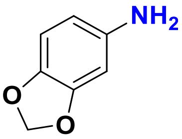
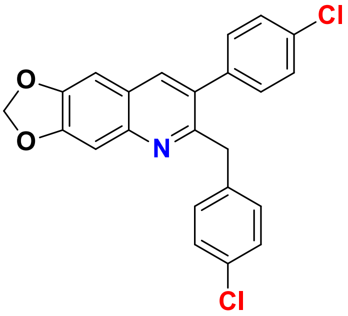
Fig. 6. Synthesis of 2,3-disubstituted quinolines.

Table 3
Synthesis of 2,3-disubstituted quinolines in ILs.[a]

Entry	Epoxide	Ar-amine	Product	Time (h)	Yield (%)[b]
1.				17	43[c]
2.				18	45[e]
3.				15	78[c]
4.				16	72[c]
5.				18	56[d]
6.				16	68[d]

(*continued on next page*)

Table 3 (*continued*)

Entry	Epoxide	Ar-amine	Product	Time (h)	Yield (%)[b]
7.				16	66[c]
8.				18	59[d]
9.				18	65[c]

---

[a] Reagents and conditions: epoxide (5 mmol), arylamine (1 mmol), [BMIM][PF₆] (5–6 mL), [BMIM(SO₃H)][OTf] (1 mmol), TEMPO (1 mmol), 4 Å MS (1 g), oil bath (55–60 °C).

[b] Isolated yield.

[c] Yield employing fresh IL.

[d] Yield using recycled IL (2nd cycle).

[e] Yield using recycled IL (3rd cycle).

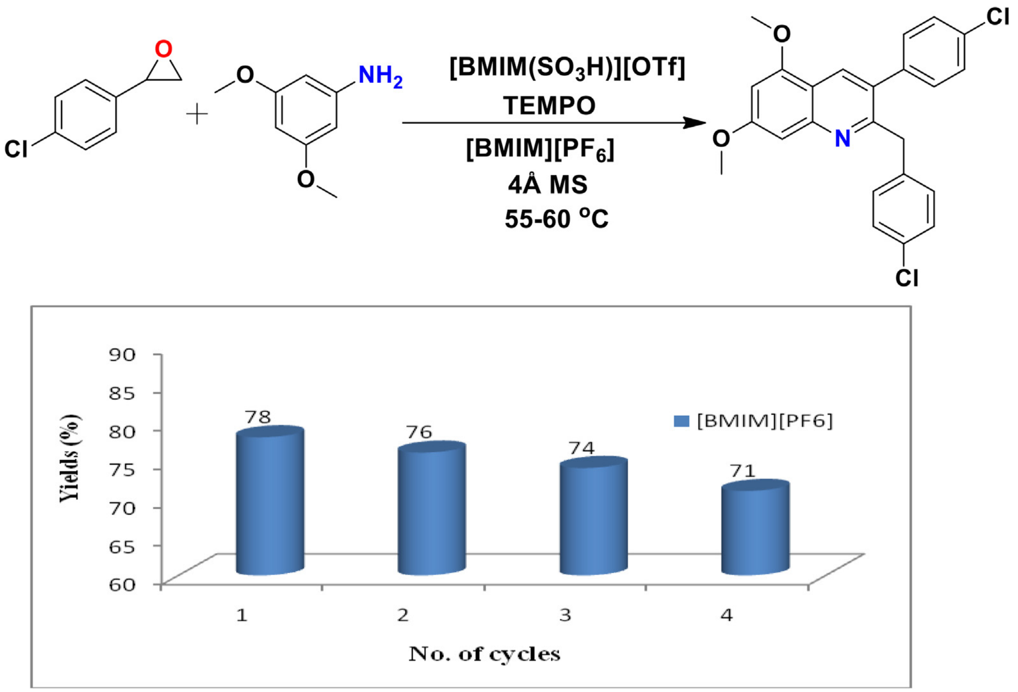


Fig. 7. Graphical representation of recycling/reuse of the IL solvent in quinoline synthesis.

The isolated yields were in the 89–90% range when using fresh ILs, decreasing only slightly in reused/recycled ILs. Fig. 3 is a graphical representation of the cyclopropanation reaction using recovered/reused ILs up to 4 cycles, with entry 10 in Table 1 as a model reaction.

The predominant *trans* stereochemistry (>97%) of the cyclopropanation products in the present study was determined based on ^{1}H NMR spectroscopy along with GC–MS and by comparison with the reported NMR data (see ESI).

Turning our attention to epoxidation, structurally diverse aldehydes and ketones were conveniently transformed into oxiranes *via* the *in-situ* generated sulfur ylide derived from trimethylsulfonium iodide at r.t., employing [PAIM][NTf_2] as a basic-IL in readily available BMIM-ILs as solvent (Fig. 4 and Table 2). The isolated yields were in the 89–92% range when using fresh ILs, decreasing only slightly when employing reused/recycled ILs.

Fig. 5 is a graphical representation of the epoxidation using recovered/reused ILs up to 4 cycles, with entry 8 in Table 2 as a model reaction, showing only a minor decrease in the isolated yields.

There has been renewed interest in the synthesis of 2,3-disubstituted quinolones [13], in particular *via* the condensation of epoxides with anilines using $Sc(OTf)_3$ in THF [13a]. To demonstrate application, in the context of the present study, and for comparison with the literature data, we prepared a library of 2-benzyl-3-aryl-quinolines employing [BMIM(SO_3H)][OTf]/[BMIM][PF_6] (Fig. 6 and Table 3). In line with the earlier reported study, TEMPO was used as an additive to avoid the formation of side products [13a]. Isolated yields were in the 43–78% range, depending on the choice of epoxide and aniline, which is similar to the previously reported outcomes (10–96%) [13a].

Fig. 7 is a graphical representation of the quinoline synthesis using recovered/reused [BMIM][PF_6] up to 4 cycles, with entry 3 in Table 3 as a model reaction, showing only a small decrease in the isolated yields.

In summary, we have shown that [PAIM][NTf_2]/BMIM-ILs represents a suitable medium for the *in-situ* generation of sulfur ylides from sulfoxonium and sulfonium salts, thus enabling access to libraries of functionalized cyclopropanes from enones, and oxiranes from aldehydes and ketones, at room temperature in respectable isolated yields, with reasonable prospects for the reuse/recycling of the IL solvent. The synthesized oxiranes were employed as starting materials for the synthesis of a small library of 2-benzyl-3-aryl-quinolines using [BMIM(SO_3H)][OTf]/[BMIM][PF_6] as catalyst/solvent. The reported cyclopropanation and epoxidation methods avoid the use of strong bases and high boiling solvents typically employed in the CC reaction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

K. L. thanks University of North Florida for the Outstanding Faculty Scholarship and Presidential Professorship awards, UNF Foundation Board grant, and the Dean's Leadership Council award. The authors at Karnatak Science College, Dharwad thank the University Sophisticated Instrument Center and DST-SAIF KUD for IR, NMR and GC-MS. They also thank ALR Labs, Hyderabad for ^{1}H NMR and ^{13}C NMR spectroscopy. S. S. Malunavar is grateful to Government of Karnataka for Vidyasiri fellowship. Thanks are also given to Planning, Monitoring and Evaluation Board KUD Project No. KU/PMEB/2020-21/69 for financial assistance.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2021.153339.

References

[1] (a) E.J. Corey, M. Chaykovsky, J. Am. Chem. Soc. 87 (1965) 1353–1364;
(b) A. Merz, G. Märkl, Angew. Chem., Int. Ed. Engl. 12 (1973) 845–846.
[2] (a) J.A. Ciaccio, A.L. Drahus, R.M. Meis, C.T. Tingle, M. Smrtka, R. Geneste, Synth. Commun. 33 (12) (2003) 2135–2143;
(b) J.A. Ciaccio, C.E. Aman, Synth. Commun. 36 (10) (2006) 1333–1341.
[3] (a) L. Liu, R. Tian, S. Liu, X. Chen, L. Guo, Y. Che, Bioorg&Med. Chem. 16 (2008) 6021–6026;
(b) M. Watanabe, T. Hirokawa, T. Kobayashi, A. Yoshida, Y. Ito, S. Yamada, N. Orimoto, Y. Yamasaki, M. Arisawa, S. Shuto, J. Med. Chem. 53 (2010) 3585–3593;
(c) H.-K. Zhang, L.-F. Yu, J.B. Eaton, P. Whiteaker, O.K. Onajole, T. Hanania, D. Brunner, R.J. Lukas, A.P. Kozikowski, J. Med. Chem. 56 (2013) 5495–5504;
(d) J.X. Qiao, D.L. Cheney, R.S. Alexander, A.M. Smallwood, S.R. King, K. He, A.R. Rendina, J.M. Luettgen, R.M. Knabb, R.R. Wexler, P.Y.S. Lam, Bioorg. Med. Chem. Lett. 18 (2008) 4118–4123;
(e) J. Salaun, M.S. Baird, Cur. Med. Chem. 2 (1995) 511–542.
[4] (a) M.D. Delost, D.T. Smith, B.J. Anderson, J.T. Njardarson, J. Med. Chem. 61 (2018) 10996–11020;
(b) M.M. Heravi, S. Asadi, N. Nazari, B.M. Lashkariani, Cur. Org. Syn. 13 (2016) 308–333;
(c) F. Moschona, I. Savvopoulou, M. Tsitopoulou, D. Tataraki, G. Rassias, Catalysts 10 (2020) 1117;
(d) D.G. Brown, H.J. Wobst, J. Med. Chem. 64 (5) (2021) 2321–2338;
(e) P. Bhutani, G. Joshi, N. Raja, N. Bachhav, P.K. Rajanna, H. Bhutani, A.T. Paul, R. Kumar, J. Med. Chem. 64 (2021) 2339.
[5] R.J. Paxton, R.J.K. Taylor, Synlett (No. 4) (2007) 633–637.
[6] (a) H. Kakei, T. Sone, Y. Sohtome, S. Matsunaga, M. Shibasaki, J. Am. Chem. Soc. 129 (2007) 13410–13411;
(b) A.B. Charette, M.K. Janes, H. LeBel, Tetrahedron: Asymm. 14 (2003) 867–872.
[7] a) E. Alfonso, J.W.L. Mendoza, A.B. Beeler, Beilstein. J. Org. Chem. 14 (2018) 2308–2312;
b) A. Piccinini, S.A. Kavanagh, P.B. Connon, S.J. Connon, Org. Lett. 12 (3) (2010) 608–611.
[8] V.K. Aggarwal, A. Ali, M.P. Coogan, J. Org. Chem. 62 (1997) 8628–8629.
[9] J. Xu, N.B. Samsuri, H.A. Duong, Chem. Commun. 52 (2016) 3372–3375.
[10] (a) S.M. Sutar, P. Prabhala, H.M. Savanur, R.G. Kalkhambkar, G. Aridoss, K.K. Laali, ChemistrySelect 6 (2021) 1–10;
(b) S.S. Malunavar, S.M. Sutar, H.M. Savanur, R.G. Kalkhambkar, K.K. Laali, Tetrahedron Lett. 61 (2020) 151509;
(c) P. Prabhala, H.M. Savanur, S.M. Sutar, S.S. Malunavar, R.G. Kalkhambkar, K. K. Laali, Tetrahedron Lett. 61 (2020);
(d) S.S. Malunavar, S.M. Sutar, P. Prabhala, R.G. Kalkhambkar, K.K. Laali, Tetrahedron Lett. 61 (2020);
(e) P. Prabhala, H.M. Savanur, R.G. Kalkhambkar, K.K. Laali, Eur. J. Org. Chem. (2019) 2061–2064;
(f) H.M. Savanur, R.G. Kalkhambkar, K.K. Laali, Eur. J. Org. Chem. (2018) 5285–5288;
(g) S.M. Sutar, H.M. Savanur, S.S. Malunavar, P. Prabhala, R.G. Kalkhambkar, K. K. Laali, Eur. J. Org. Chem. (2019) 6088–6093;
(h) S.M. Sutar, H.M. Savanur, C. Patil, P. Prabhala, G. Aridoss, R.G. Kalkhambkar, ChemistrySelect 5 (2020) 12324–12327;
(i) H.M. Savanur, R.G. Kalkhambkar, K.K. Laali, App. Cat. A, Gen. 543 (2017) 150–161;
(j) K.K. Laali, Arkivoc (2016) 150–171.
[11] G.A. Olah, K.K. Laali, Q. Wang, G.K.S. Prakash, Onium Ions, Wiley, New York, 1998.
[12] S. Chandrasekhar, C. Narasihmulu, V. Jagadeshwar, K.V. Reddy, Tetrahedron Lett. 44 (2003) 3629–3630.
[13] (a) M.-S. Al Mehedi, J.J. Tepe, J. Org. Chem. 85 (2020) 6741–6746;
(b) J.T. Zhang, L.X. Wang, J.F. Xiang, J. Cui, B.Q. Hu, L. Yang, Y.L. Tang, ChemistrySelect 4 (2019) 9392–9395.