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Cascade annulation reaction (CAR): highly diastereoselective synthesis of pyranopyrazole scaffolds†

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An unprecedented domino protocol for the novel synthesis of highly diverse and functionalized tetrahydro pyranopyrazole scaffolds using chalcone epoxide has been reported for the first time. This synthetic protocol generates three consecutive stereogenic centres in a highly diastereoselective manner with the formation of vicinal diol and a quaternary carbon centre. A wide range of substrates were utilized for the scope of this methodology and provided very good yields of pyranopyrazoles. The pyranopyrazoles were also transformed into densely functionalized tetrasubstituted olefins.

Introduction

Pyrazole and its derivatives are a versatile class of organic molecules, widely distributed in pharmaceuticals and agrochemicals, exhibiting a wide range of biological activities.¹ In leading drugs, such as Viagra^{2a} and Celebrex,^{2b} they are present as the integral part, and therefore the synthesis of pyrazole motifs is considered important in the pharmaceutical industry.^{2c} The design of cyclic ethers³ and its substructures is an important synthetic target material in organic chemistry since they form the structural nuclei of numerous natural products.⁴ Moreover, several types of bioactive molecules having wide medical and agrochemical applications contain a pyranopyrazole ring. The fused pyrazole⁵ molecular entities, display numerous biological activities such as anti-HIV,⁶ antimicrobial,⁷ antibacterial and antifungal,⁸ anticancer,⁹ and anti-inflammatory activity.¹⁰ Some of the representative examples of bioactive tetrahydropyranopyrazoles are shown in Fig. 1.

On the other hand, epoxides have attracted considerable attention as they play a very important role in organic synthetic chemistry,¹¹ as well as in the pharmaceutical industry.¹² Particularly, the relative ease of preparation of chalcone epoxides makes them a promising starting material for the preparation of various heterocyclic compounds.¹³ Due to the importance of pyranopyrazole framework in pharmacological and biological studies, particularly in the designing of new drug candidates, several groups have focused their efforts in the synthesis of pyranopyrazole scaffolds. For example, pyranopyrazoles have been synthesized *via* one-pot, Michael/Wittig/oxa-

Michael reaction sequence,¹⁴ solvent free multicomponent cascade reaction,¹⁵ NHC catalyzed annulation reaction,¹⁶ and through the reaction of isatylidene β , γ -unsaturated α -ketoester and enynones with pyrazolones¹⁷ (Scheme 1). Even though various methods are present in the literature to synthesize pyranopyrazoles, a new and practical alternative protocol for the synthesis of pyranopyrazoles is remarkably essential. To the best of our knowledge, the construction of the pyranopyrazole

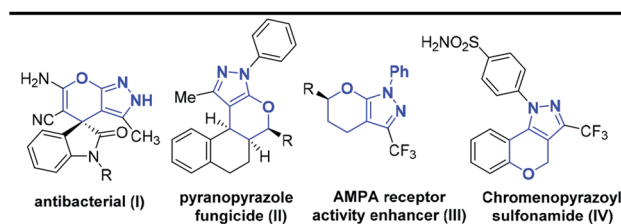
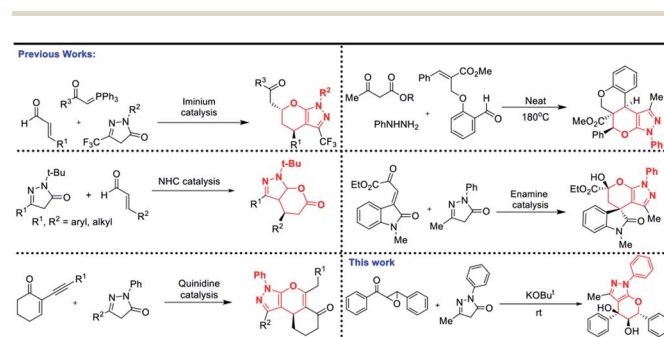


Fig. 1 Some representative examples of bioactive pyranopyrazole scaffolds.



Scheme 1 Reported methods and present approach for the synthesis of pyranopyrazole scaffolds.

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derivatives using chalcone epoxide and pyrazolone has not been reported so far in the literature. Hence, we design the first methodology to synthesize pyranopyrazoles *via* a cascade annulation reaction (CAR) using chalcone epoxide **1** and pyrazolone **2**.

In continuation of our ongoing research program in the field of heterocyclic chemistry and domino reactions,¹⁸ we herein report an unprecedented method for the construction of highly functionalized pyranopyrazole scaffolds using chalcone epoxides and pyrazolone in a highly diastereoselective manner *via* CAR.

Results and discussions

To execute our idea, we initially investigated the reaction of chalcone epoxide **1a** (1 eq.) and pyrazolone **2a** (1 eq.) with 1 equivalent of base (K_2CO_3) in CH_3CN as a solvent at room temperature which provided the desired product tetrahydropyranopyrazole **3a** as a white solid in 35% yield as shown in Table 1 and entry 1. Next, different types of bases such as L-Proline, $KOBu^t$, piperidine, DABCO, NaH, DBU, CS_2CO_3 , NaOH, and $KHCO_3$ were screened in presence of solvents like MeOH, EtOH, acetone, $tBuOH$, DCM and $iPrOH$. The yield of the final product got increased from 35 to 62% (Table 1, entries 2–16). Interestingly, the yield of the final product was improved to 78%, when $KOBu^t$ is used as a base and EtOH as a solvent (Table

1 and entry 17). The yield of the reaction did not improve significantly when the base loading is increased from 1 to 1.2 equivalents. The combination of $KOBu^t$ (1 eq.) in ethanol is found to be the optimal condition for the cascade annulation reaction (CAR) as given in Table 1.

To the best of our knowledge, this is the first report for the synthesis of pyranopyrazoles utilizing chalcone epoxide and pyrazolone under ambient temperature. The highlight of this reaction is that it is highly diastereoselective in nature, affording predominantly only one pair of diastereomer. Prompted by this result, we have examined different types of chalcone epoxides with pyrazolone under the optimal condition which successfully provided the wide variety of tetrahydropyrano pyrazoles **3** in very good yields (60–81%) and the results are summarized in Table 2.

To further investigate the enantioselectivity of this new annulative domino protocol, optically pure epoxide **1aa** was chosen as the reactant.¹⁹ The reaction of this chiral epoxide **1aa** with pyrazolone **2a** provided the corresponding diol **3aa** in 75% yield with enantiomeric ratio 78 : 22 (refer ESI†). The enantioselective nature of the reaction is confirmed by the HPLC analysis of the final product using chiral column where only two peaks are obtained in the chromatogram thereby unambiguously confirming the presence of enantiomer as shown in Scheme 2 (**3aa**).

The stereochemical (relative stereochemistry) outcome of the trans conformation (5th and 6th position) of the compounds **3a-w** was confirmed by the coupling constant of proton value at 5th and 6th positions in the 1H -NMR spectrum. In compound **3a**, the 1H NMR spectrum has peaks at δ 4.12 ppm (d, 1H, J = 9.9 Hz, H6) and 5.28 ppm (d, 1H, J = 9.9 Hz, H5), in which the

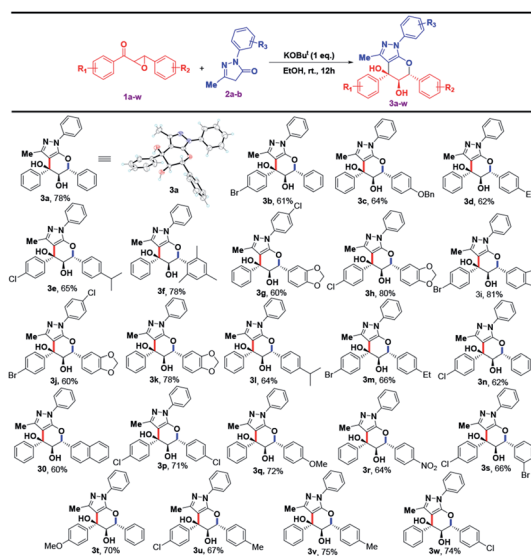
Table 1 Optimization conditions for the synthesis of tetrahydropyranopyrazole **3a** under various conditions^{a,b}

Entry	Base	Equiv.	Solvent	Time	Yield ^b (%)
1	K_2CO_3	1.0	CH_3CN	12 h	35
2	L-Proline	0.2	MeOH	10 h	21
3	$KOBu^t$	1.0	CH_3CN	10 h	45
4	Piperidine	1.0	CH_3CN	10 h	46
5	DABCO	1.0	CH_3CN	10 h	21
6	NaH	1.0	CH_3CN	12 h	53
7	DBU	0.5	CH_3CN	10 h	50
8	CS_2CO_3	0.5	CH_3CN	10 h	46
9	NaOH	0.5	MeOH	10 h	37
10	$KHCO_3$	1.0	EtOH	10 h	55
11	NaH	1.0	MeOH	12 h	60
12	$KOBu^t$	1.0	Acetone	12 h	40
13	$KOBu^t$	1.0	$tBuOH$	12 h	35
14	$KOBu^t$	1.0	DCM	12 h	38
15	$KOBu^t$	1.0	MeOH	12 h	58
16	$KOBu^t$	1.0	$iPrOH$	12 h	62
17	$KOBu^t$	1.0	EtOH	12 h	78
18	$KOBu^t$	1.2	EtOH	12 h	78

^a All reactions were carried out with 1 mmol scale of chalcone epoxide.

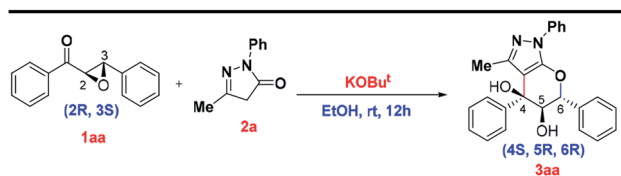
^b Isolated yield of the pure product obtained after column chromatography purification.

Table 2 Substrate scope of tetrahydropyranopyrazole derivatives^{a,b}



^a All the reactions were carried out using 1 mmol of chalcone epoxide and 1 mmol of pyrazolone with 1 equiv. of $KOBu^t$ in the presence of ethanol solvent (5 ml). ^b Isolated yields of the pure products.





Scheme 2 Synthesis of optically active pyranopyrazole scaffold from chiral chalcone epoxide.

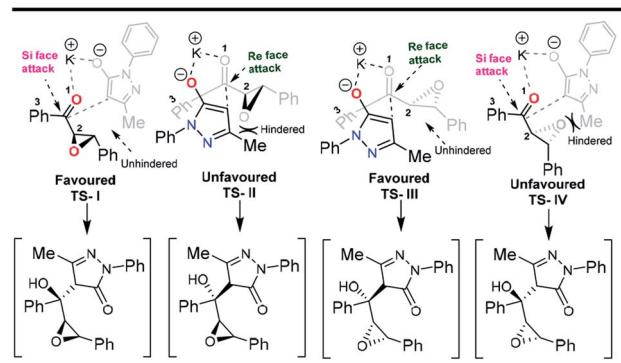


Fig. 2 Possible transition state models for the racemic chalcone epoxide with C-nucleophile.

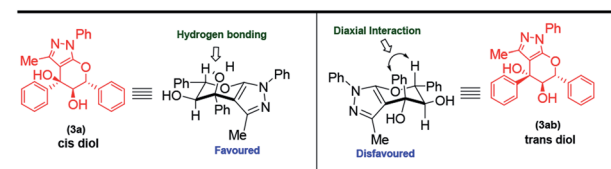
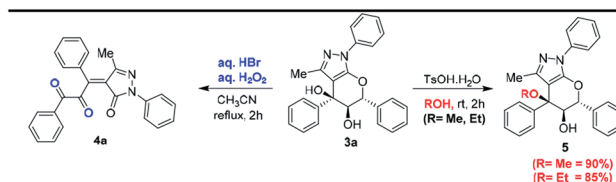


Fig. 3 Favoured (3a) and disfavoured (3b) conformations.

coupling constants ($J = 9.9$ Hz) clearly indicated an anti-geometry.

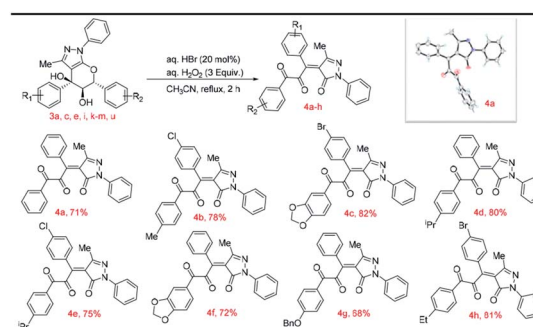
Stereochemistry of the nucleophilic addition of the enolate to the ketone can be explained by the transition state models given in Fig. 2. The attack of the enolate on the ketone takes place from Si face leading to the formation of C–C bond in TS-I. The alternative Re face attack of the enolate to the ketone is unfavored due to steric hindrance between the oxirane ring and methyl group in the TS-II. Similarly, the above mentioned concept is applicable to the transition states TS-III and TS-IV respectively for the other isomer.

Further, the *syn* diol conformation of the product arises due to the favored chair conformation of the six membered pyran ring where the hydrogen bonding²⁰ takes place between the axial H and OH. The other conformation for the pyran ring in the chair form is disfavored due to 1,3-diaxial interactions between the phenyl group and hydrogen atom and therefore the trans diol is not formed (Fig. 3). Furthermore, we have confirmed the *syn* conformation of the vicinal diol groups in structure 3a by NOESY NMR spectrum. Finally, the relative

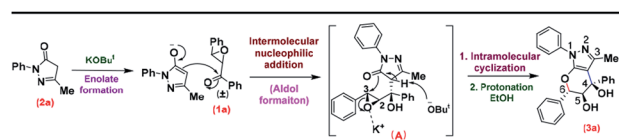


Scheme 3 Functional group transformation of 3a.

Table 3 Substrate scope of densely functionalized tetrasubstituted olefins^{a,b}



^a Reaction conditions: tetrahydropyranopyrazole 3a (1 equiv.), aq. HBr (0.2 equiv.), aq. H₂O₂ (3.0 equiv.) and CH₃CN (5 ml) at reflux temperature. ^b Isolated yields of the pure products.



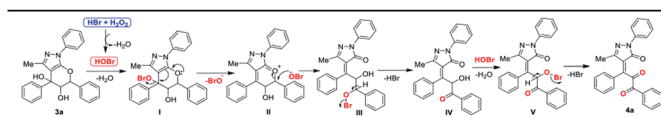
Scheme 4 The proposed reaction pathway for the preparation of racemic tetrahydropyranopyrazoles.

stereochemistry of the compound 3a was confirmed by single crystal XRD analysis.

To demonstrate the synthetic transformation of the product 3a, couple of reactions were performed as shown in Scheme 3. A very interesting chemoselective etherification has been carried out where selectively the tertiary alcohol has been converted into corresponding ethers which might be proceeding *via* S_N1 reaction mechanism as shown in Scheme 3. The reaction of tetrahydro pyranopyrazole 3a with aq. HBr in the presence of aq. H₂O₂ leads to the formation of novel and highly diversified tetrasubstituted olefins with dicarbonyl functionality (4a) in very good yields *via* cleavage of six membered cyclic ether (pyran) ring as shown in Scheme 3 and the results are summarized in Table 3.

The plausible mechanism for the synthesis of tetrahydropyranopyrazole 3a using racemic chalcone epoxide 1a and pyrazolone 2a is shown in Scheme 4. Pyrazolone 2a can serve as a nucleophilic component to react with the electrophilic racemic chalcone epoxide 1a, which was mediated by KOBu^t.





Scheme 5 Proposed mechanism for the formation of densely functionalized tetrasubstituted olefins.

First, the C-nucleophile of the enolate **2a** reacts with the carbonyl group of the chalcone epoxide **1a** giving rise to intermediate **A**. Subsequently, the intermediate **A** undergoes abstraction of the proton by a base that lead to enolate and the enolate oxygen attack on the β -position of the epoxide to give the cyclic product which undergoes protonation to provide the desired product **3a** as shown in Scheme 4.

The proposed mechanism for the formation of densely functionalized tetrasubstituted olefins is given in Scheme 5. The reaction of hydrobromic acid with aqueous hydrogen peroxide generates the hypobromous acid.²¹ Hypobromous acid reacts with the tertiary alcohol in pyranopyrazole **3a** to give intermediate **I**. The intermediate **I** is then transformed into intermediate **II** by the removal of hypobromite ion. Pyran ring opening takes place by the attack of hypobromite ion which gives intermediate **III**. The intermediate **III** loses a molecule of HBr to give the intermediate **IV**. Reaction of hypobromous acid with the secondary alcohol in intermediate **IV** provided intermediate **V** through the loss of the water molecule. The intermediate **V** loses a molecule of HBr to give the tetrasubstituted olefin **4a** as given in Scheme 3.

All the newly synthesized compounds were characterized by ¹H-NMR, ¹³C-NMR and HRMS techniques. The structure of the compounds **3a** and **4a** were further confirmed by single crystal X-ray diffraction (XRD) method and the ORTEP diagram²² of the compounds **3a** and **4a** are shown in Table 2 and 3

Conclusions

In conclusion, we have successfully developed an efficient cascade annulation reaction (CAR) for the construction of highly functionalized pyranopyrazole scaffolds with wide variety of substrate scope using chalcone epoxides for the first time. This unprecedented domino protocol is highly diastereoselective in nature. Interestingly, this reaction creates a six membered pyran ring with three contiguous stereogenic centers which include one quaternary chiral center in a unique manner. Moreover, the pyranopyrazoles were successfully manipulated to access novel tetra substituted olefins having dicarbonyl functionality which may act as valuable synthetic building blocks.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) Y. Zheng, L. Cui, Y. Wang and Z. J. Zhou, *Org. Chem.*, 2016, **81**, 4340; (b) A. Ansari, A. Ali, M. Asif and Shamsuzzaman, *New J. Chem.*, 2017, **41**, 16; (c) W. Li, R. Ruzi and K. Ablajan, *Tetrahedron*, 2017, **73**, 164; (d) J. V. Faria, P. F. Vegi, A. G. C. Migueta, M. S. dos Santos, N. Boechat and A. M. R. Bernardino, *Bioorg. Med. Chem.*, 2017, **25**, 5891; (e) S. G. Küçüküzümlü and S. Şenkardes, *Eur. J. Med. Chem.*, 2015, **97**, 786.
- (a) T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang and P. C. J. Isakson, *Med. Chem.*, 1997, **40**, 1347; (b) N. K. Terrett, A. S. Bell, D. Brown and P. Ellis, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1819; (c) C. Despotopoulou, L. Klier and P. Knochel, *Org. Lett.*, 2009, **11**, 3326.
- (a) B. M. Trost, A. C. Gutierrez and R. C. Livingston, *Org. Lett.*, 2009, **11**, 2539; (b) D. P. Steinhuebel and J. D. Bois, *Org. Lett.*, 2002, **4**, 293.
- (a) E. Kurosawa, A. Fukuzawa and T. Irie, *Tetrahedron Lett.*, 1973, **14**, 4135; (b) M. Suzuki, K. Kurata and E. Kurosawa, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2953; (c) A. Fukuzawa and T. Masamune, *Tetrahedron Lett.*, 1981, **22**, 4081; (d) K. Audouze, E. O. Nielsen and D. J. Peters, *Med. Chem.*, 2004, **47**, 3089; (e) G. P. Penga, G. Tiana, X. F. Huang and F. C. Lou, *Phytochemistry*, 2003, **63**, 877; (f) A. D. Rodriguez, O. M. Cobar and O. L. Padilla, *J. Nat. Prod.*, 1997, **60**, 915.
- (a) A. Shaabani, A. Sarvary and S. Keshipour, *Tetrahedron*, 2009, **65**, 3492; (b) M. Aleem and A. Remaily, *Tetrahedron*, 2014, **70**, 2971; (c) S. Paul, K. Pradhan and A. R. Das, *Tetrahedron*, 2014, **70**, 6088; (d) J. Xie, F. Sha and X. Wu, *Tetrahedron*, 2016, **72**, 4047; (e) M. Seydimemet, K. Ablajan and M. Obul, *Tetrahedron*, 2016, **72**, 7599.
- J. Kim, D. Lee, C. Park, W. So, M. Jo, T. Ok, J. Kwon, S. Kong, S. Jo, Y. Kim, J. Choi, H. C. Kim, Y. Ko, I. Choi, Y. Park, J. Yoon, M. K. Ju, J. Kim, J. Lee and Z. No, *ACS Med. Chem. Lett.*, 2012, **3**, 678.
- (a) P. T. Mistry, N. R. Kamdar, D. D. Haveliwala and K. S. J. Patel, *Heterocycl. Chem.*, 2012, **49**, 349; (b) A. H. Mandour, E. R. El-Sawy, M. S. Ebaid and S. M. Hassan, *Acta Pharm.*, 2012, **62**, 15; (c) P. Cherry, D. I. Starkey and N. K. Cobley, *J. Med. Chem.*, 1998, **41**, 787.
- R. Nagamallu and A. K. Kariyappa, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 6406.
- (a) J. L. Wang, D. Liu, Z. J. Zheng, S. Shan, X. Han, S. M. Srinivasula, C. M. Croce, E. S. Alnemri and Z. Huang, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **97**, 7124; (b) J. Li, Y. F. Zhao, X. Y. Yuan and P. Gong, *Molecules*, 2006, **11**, 574.
- (a) S. Prekupec, D. Makuc, J. Plavec, L. Suman, M. Kralj, K. Pavelic, J. Balzarini, E. D. Clercq, M. Mintas and



- S. J. RaicMalic, *Med. Chem.*, 2007, **50**, 3037; (b) M. E. A. Zaki, A. H. Saliman, O. A. Hickal and A. E. Z. Rashad, *Biosci*, 2006, **61**, 1.
- 11 (a) M. Pineschi, *Eur. J. Org. Chem.*, 2006, 4979; (b) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59**, 737; (c) I. Erden, A. R. Katritzky, C. W. Rees and E. F. V. Scriven, *Comprehensive Heterocyclic Chemistry II*, Pergamon, Oxford, 1996, vol. 1A, p. 97.
- 12 (a) C. Y. Huang and A. G. Doyle, *Chem. Rev.*, 2014, **114**, 8153; (b) S. Park, *Chem.-Asian J.*, 2019, **14**, 2048; (c) E. Thiery, J. Le Bras and J. Muzart, *Chem.-Eur. J.*, 2009, 961.
- 13 (a) C. Huo, X. Xu, J. An, X. Jia, X. Wang and C. J. Wang, *Org. Chem.*, 2012, **77**, 8310; (b) T. Patonay, A. L. Vai and C. J. Nemes, *Org. Chem.*, 1996, **61**, 5375; (c) D. Black, N. Kumar and P. S. R. Mitchell, *J. Org. Chem.*, 2002, **67**, 2464.
- 14 D. Enders, A. Grossmann, B. Gieraths, M. Dü zdemir and C. Merckens, *Org. Lett.*, 2012, **14**, 4254.
- 15 M. Bakthadoss, D. Kannan and R. Selvakumar, *Chem. Commun.*, 2013, **49**, 10947.
- 16 S. R. Yetra, S. Mondal, E. Suresh and A. T. Biju, *Org. Lett.*, 2015, **17**, 1417.
- 17 (a) R. N. Kumarswamy and V. Kesavan, *Org. Lett.*, 2016, **18**, 1354; (b) S. Liu, X. Bao and B. Wang, *Chem. Commun.*, 2018, **54**, 11515.
- 18 (a) M. Bakthadoss, G. Sivakumar and D. Kannan, *Org. Lett.*, 2009, **11**, 4466; (b) M. Bakthadoss and R. Selvakumar, *J. Org. Chem.*, 2016, **81**, 3391; (c) M. Bakthadoss, R. Selvakumar and M. Mushaf, *Org. Biomol. Chem.*, 2019, **17**, 4767; (d) D. Basavaiah, M. Bakthadoss and S. Pandiaraju, *Chem. Commun.*, 1998, 1639; (e) M. Bakthadoss and M. Mushaf, *RSC Adv.*, 2018, **8**, 12152; (f) M. Bakthadoss, A. Devaraj and D. Kannan, *Eur. J. Org. Chem.*, 2014, 1505; (g) M. Bakthadoss and G. Murugan, *Eur. J. Org. Chem.*, 2010, 5825.
- 19 E. J. Corey and F. Y. Zhang, *Org. Lett.*, 1999, **1**, 1287.
- 20 A. Kolocouris, *J. Org. Chem.*, 2009, **74**, 1842.
- 21 (a) R. B. Daniel, P. Samuel, S. Shaik and R. Neumann, *J. Am. Chem. Soc.*, 2003, **125**, 12116; (b) V. P. Sharma, S. L. Jain and B. Sain, *Synlett*, 2005, **1**, 173; (c) R. D. Patil, G. Joshi and S. Adimurthy, *Ind. Eng. Chem. Res.*, 2010, **49**, 8100.
- 22 Structures were confirmed by single-crystal X-ray data. CCDC number for **3a** and **4a** are 1943125 and 1977496† respectively.

