RSC Advances

Volume 1 | Number 1 | Jan 2013 | Pages 1–100

RSC Advances

www.rsc.org/advances

ROYAL SOCIETY OF CHEMISTRY

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

ROYAL SOCIETY OF CHEMISTRY

Journal Name

ARTICLE

Catalytic asymmetric synthesis of enantioenriched β-nitronitrile bearing a C-CF$_3$ stereogenic center

Ajay Jakhar,[a,b] Prathibha Kumari,[a,b] Mohd Nazish,[a,b] Noor-ul H. Khan,*[a,b] Rukhsana I. Kureshy,[a,b] Sayed H. R. Abdi [a,b] and E. Suresh [b,c]

The CF$_3$ substituted β-nitronitriles having an all-carbon quaternary stereogenic center have been synthesized via asymmetric cyanation reaction. In situ generated chiral Ti^{IV} salen complexes were used as catalyst for asymmetric addition of TMSCN to nitroolefins containing trifluoromethylated prochiral center in the β- position to afford the corresponding β-nitronitriles in excellent yield (up to 93%) with good enantioselectivity (up to 99%). This newly developed catalytic protocol led to the efficient synthesis of useful but challenging chiral α,α'-disubstituted β-amino acids.

Introduction

The Catalytic enantioselective construction of all-carbon stereocenter containing CF$_3$ group is important from the perspective of producing novel bio-active motifs for their commercial exploitation. However, assembling these structural motifs in an enantioselective manner is particularly challenging and a current research of intense investigation. Despite the challenges, the necessity of producing such CF$_3$ group containing compound is driven by the fact that incorporation of trifluoromethyl group to organic molecules improve their lipophilicity, bioavailability, and metabolic stability thereby bioactivity.[1] Consequently, these facts clearly manifest its importance in pharmaceuticals, agrochemicals, and material science.[2] Though, great progress has been made to incorporate CF$_3$ group to organic scaffolds but surprisingly the synthesis of CF$_3$ substituted quaternary carbon stereocenter have received scant attention.[3] Shibata and coworkers for the first time reported an asymmetric synthesis of an all-carbon stereocenter bearing a CF$_3$ group through cyanation of β-aryl-β-CF$_3$-disubstituted enones.[4] Although different strategies were followed to construct CF$_3$-containing[5a-l] and fluorinated[5m] quaternary compounds however, to the best of our knowledge a direct route for the synthesis of tetrasubstituted carbon quaternary stereocenters via cyanation of CF$_3$-bearing simple disubstituted olefins, is not reported nevertheless there are

only few reports available in literature for the synthesis of chiral β-nitro nitrile by using simple nitroalkenes.[6] The asymmetric addition of cyanide to activated olefins like α,β-unsaturated ketones,[7] α,β -unsaturated imides,[8] α,β-unsaturated N-acylpyrroles,[9] α,β - unsaturated esters,[10] and nitroalkenes are scarcely studied when compared to the asymmetric cyanation of C=O[11] and C=N[12] double bonds. More specifically, in our continus interest in the development of enantioselective cyanation reactions, herein we are disclosing the cyanation reaction which is synthetically different from the other existing reports. In this report, we wish to describe an efficient catalytic protocol for the enantioselective conjugate Michael addition of TMSCN to β-CF$_3$-β-disubstituted nitroalkenes to give CF$_3$-substituted β-nitro nitrile (Scheme 1).
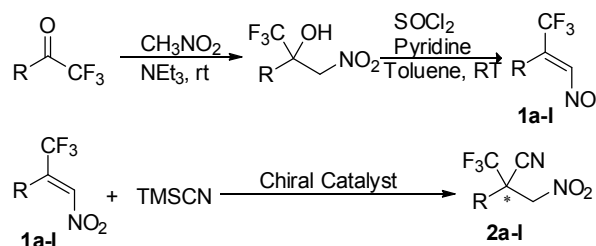
Scheme 1 Construction of CF$_3$ substituted quaternary stereocentres via asymmetric cyanation reaction

Recently, we reported asymmetric addition of cyanide to nitro olefins,[6f] however in the present report, in order to incorporate CF$_3$ group, we prepared desired nitroolefins 1a-l[5a] for their asymmetric cyanation. Thus obtained CF$_3$ substituted nitro nitrile products can be readily transformed into important compound like α-CF$_3$ substituted β-amino acid, CF$_3$ substituted amino alcohol and trifluromethylated diammine.

Results and Discussion

a. Inorganic Materials and Catalysis Division, CSIR-Central Salt and Marine Chemicals Research Institute, G. B. Marg, Bhavnagar- 364 002, Gujarat, India.
b. Academy of Scientific and Innovative Research, CSIR-Central Salt and Marine Chemicals Research Institute, G. B. Marg, Bhavnagar- 364 002, Gujarat, India
c. Analytical Division and Centralized Instrument Facility, CSIR-Central Salt and Marine Chemicals Research Institute, G. B. Marg, Bhavnagar- 364 002, Gujarat, India.
† E-mail: khan251293@yahoo.in†

RSC Advances Accepted Manuscript

In our quest to develop a simple catalytic system for asymmetric cyanation of β,β-disubstituted nitro alkenes our first choice was the use of chiral Ti(O^{i}Pr)$_4$:salen complexes as catalysts as these have proven record in the cyanation of carbonyls and activated olefins.[11,6d] Accordingly, various chiral ligands (**L1**-**L11**, 10 mol%) (Fig. 1) with Ti(O^{i}Pr)$_4$ (10 mol %) were used to *in situ* generate active catalyst for the cyanation of **1a** used as a model substrate and TMSCN as a cyanide source in toluene at room temperature (Table 1). We observed that the yield and enantioselectivity of product **2a** were greatly affected by the substituents on the salen ligands: as shown in Table 1 (entries 1-11), the best salen ligand was **L3**, bearing ^{t}Bu groups at the 3'- and the 5'-positions in the salicylidene phenyl rings (90% yield, 77% ee, entry 3). In addition, dimer (**L6** & **L7**; entries 6 & 7), polymer (**L8**; entry 8) and macrocyclic (**L9**-**L11**; entries 9-11) salen ligands were not so effective both in terms of reactivity and enantioselectivity. Therefore, taking **L3** as best among the screened ligand, and in order to further improve the results, we varied titanium metal sources viz., Ti(OEt)$_4$, Ti(OBu)$_4$, Ti(O^{t}Bu)$_4$ and TiCl$_4$ (entry 12-15). We observed that the chiral **L3** ligand in combination with Ti(O^{t}Bu) generates most effective catalyst to give the desired product in 95% yield and 80% ee (entry 14).
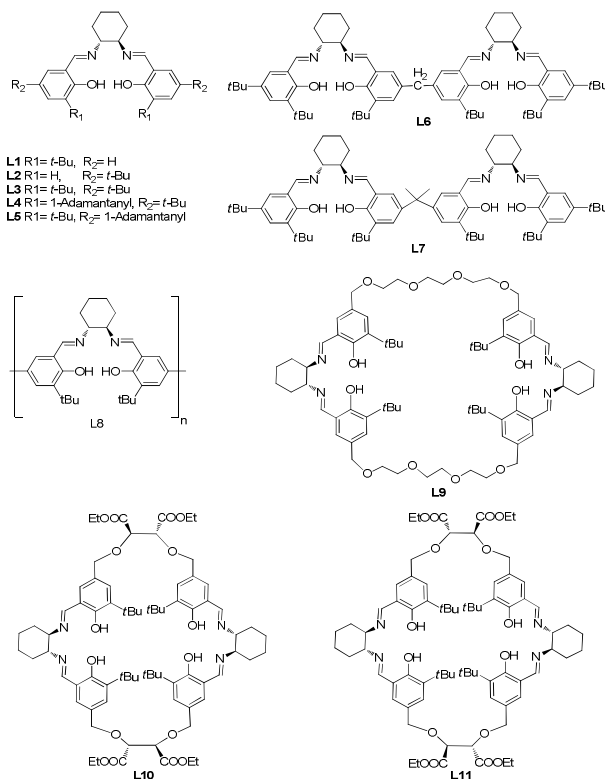

L1 R1= *t*-Bu, R2= H
L2 R1= H, R2= *t*-Bu
L3 R1= *t*-Bu, R2= *t*-Bu
L4 R1= 1-Adamantanyl, R2= *t*-Bu
L5 R1= *t*-Bu, R2= 1-Adamantanyl

Fig. 1 Ligands used in the model reaction

Having established, the combination of **L3**:Ti(O^{t}Bu)$_4$ as effective catalyst, we experimented on optimization of solvent, temperature and catalyst loading. First we screened solvents viz., toluene, benzene, CH$_2$Cl$_2$, CHCl$_3$, DCE, THF, and dioxane to carry out the asymmetric cyanation reaction under the above optimized condition (Table 2, entries 1-7), however toluene

Table 1 Ligand Screening in the Model Reaction^a

Entry	Ligand (10 mol%)	Metal source (10 mol%)	Time (h)	Yield^b (%)	ee^c (%)
1	**L1**	Ti(O^{i}Pr)$_4$	08	91	54
2	**L2**	Ti(O^{i}Pr)$_4$	08	92	40
3	**L3**	Ti(O^{i}Pr)$_4$	08	90	77
4	**L4**	Ti(O^{i}Pr)$_4$	24	Trace	-
5	**L5**	Ti(O^{i}Pr)$_4$	12	82	67
6	**L6**	Ti(O^{i}Pr)$_4$	10	88	59
7	**L7**	Ti(O^{i}Pr)$_4$	10	88	74
8	**L8**	Ti(O^{i}Pr)$_4$	12	85	42
9	**L9**	Ti(O^{i}Pr)$_4$	12	82	40
10	**L10**	Ti(O^{i}Pr)$_4$	12	80	15
11	**L11**	Ti(O^{i}Pr)$_4$	12	80	25
12	**L3**	Ti(OEt)$_4$	08	90	74
13	**L3**	Ti(OBu)$_4$	08	92	77
14	**L3**	Ti(O^{t}Bu)$_4$	08	95	80
15	**L3**	TiCl$_4$	14	80	75

^{a} Enantioselective hydrocyanation reaction of **1a** (0.1 mmol) was carried out with Ti:salen catalyst in toluene (1 mL) using TMSCN (0.20 mmol) as a source of cyanide. ^{b} Isolated yield. ^{c} ee were determined by chiral HPLC using OD-H column

remained the solvent of choice (entry 1). Temperature had significant effect on enanatioselectivity of product (entries 1, 8-10). Lowering the temperature from room temperature to 0 ^{o}C

Table 2 Optimization of the reaction conditions^a

Journal Name

ARTICLE
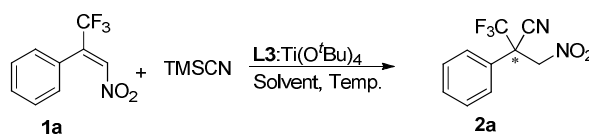
Entry	Catalyst loading (mol%)	Solvent	Temp. (^{o}C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	10	Toluene	RT	08	95	80
2	10	Benzene	RT	08	91	78
3	10	CH$_2$Cl$_2$	RT	08	92	52
4	10	CHCl$_3$	RT	10	86	54
5	10	THF	RT	16	73	58
6	10	1,4-Dioxane	RT	20	70	59
7	10	DCE	RT	20	76	48
8	10	Toluene	10	16	93	85
9	10	Toluene	0	24	92	89
10	10	Toluene	-10	48	76	89
11	2	Toluene	0	48	trace	-
12	5	Toluene	0	48	54	89
13	7	Toluene	0	36	70	89
14	15	Toluene	0	16	93	86

[a] Enantioselective hydrocyanation reaction of **1a** (0.1 mmol) was carried out with **L3**: Ti(O^{t}Bu)$_4$ catalyst using TMSCN (0.20 mmol) as a source of cyanide. [b] Isolated yield. [c] ee were determined by chiral HPLC using OD-H column

showed beneficial effect on the product ee (from rt 80% to 89%) though the reaction took longer time (24 h, entry 9) to reach completion. A further lowering of the temperature (-10 ^{o}C) did not have any positive impact on the product ee at the same time reaction became very sluggish (48 h, entry 10). Therefore, 0 ^{o}C (entry 9) was taken as optimum for further studies on catalyst loading varied through 2, 5, 7, 10 and 15 mol% (entries 11-13, 9 and 14 respectively). However, 10 mol% catalyst loading (entry 9) was found to be optimum.

To further improve the results we considered using different like *N*-oxides, phenols, molecular sieve (4Å) but the results (Table S1) were rather not very encouraging (see ESI).

Having established the reaction parameters for the use of the **L3**:Ti(O^{t}Bu)4 catalyst in the asymmetric cyanation reaction with the substrate **1a** and TMSCN at 0 ^{o}C, we next extended this protocol to a range of trifluoromethylated nitroalkenes (**1a-l**) to check the general applicability of our system and the results are summarized in Table 3. Both electron donating and withdrawing substituents at different positions on the aryl ring of the trifluoromethylated nitroalkenes (entries 2-11) afforded the products in high yields and enanatioselectivities. The results of these studies do not indicate any pronounced effect of electronic properties of the substrates used herein.

Table 3 Substrate scope in the synthesis of β-nitro nitrile using **L3**: Ti(O^{t}Bu)$_4$ catalyst[a]
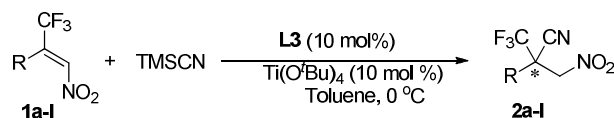
Entry	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	C$_6$H$_5$ (**1a**)	24	91	89 (99)[d] (*S*)[e]
2	3-MeC$_6$H$_4$ (**1b**)	24	87	83
3	4-MeC$_6$H$_4$ (**1c**)	24	92	88
4[f]	2-MeOC$_6$H$_4$ (**1d**)	60	52	75
5	4-MeOC$_6$H$_4$ (**1e**)	24	93	88
6	4-ClC$_6$H$_4$ (**1f**)	24	86	82
7	4-FC$_6$H$_4$ (**1g**)	24	88	83
8	3-FC$_6$H$_4$ (**1h**)	24	87	79
9	2-FC$_6$H$_4$ (**1i**)	24	80	99
10	3,4-FC$_6$H$_3$ (**1j**)	24	88	74
11	3-CF$_3$C$_6$H$_4$ (**1k**)	24	85	80
12	C$_6$H$_5$CH$_2$ (**1l**)	36	82	53
13[g]	C$_6$H$_5$ (**1a**)	24	91	89

[a] Enantioselective hydrocyanation reaction of **1a**-**l** (0.1 mmol) was carried out with L3: Ti(O^{t}Bu)4 catalyst (10 mol%) in toluene (1 mL) using TMSCN (0.20 mmol) as a source of cyanide. [b] Isolated yield. [c] ee were determined by chiral HPLC using OD-H column. [d] ee were determined after crystallization by chiral HPLC using OD-H column. [e] The absolute configuration was determined by single-crystal X-ray structure. [f] The reaction of **1d** was carried out at room tempreture for 60 h. [g] Reaction of **1a** carried out in 10 mmol scale.

Moreover, benzyl susbstituted nitroalkene (**1l**) gave product with 53% ee though in good yield (82%; entry 12). Since these products are new we have characterized them with fully, however for determining absolute configuration single-crystal X-ray structure of product **2a** was determined, which was found to be *S* with (+) rotation. For rest of the compounds the rotation was found to be (+) but in the absence of single crystals of these compounds absolute conference was not determined. However, based on the absolute configuration of **2a**, a working model for asymmetric induction is proposed (Fig. 2) where the
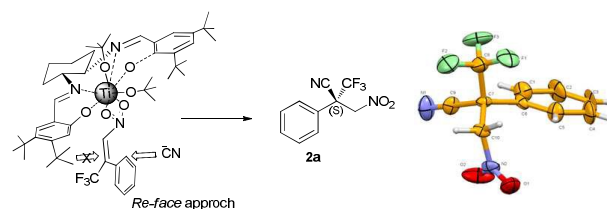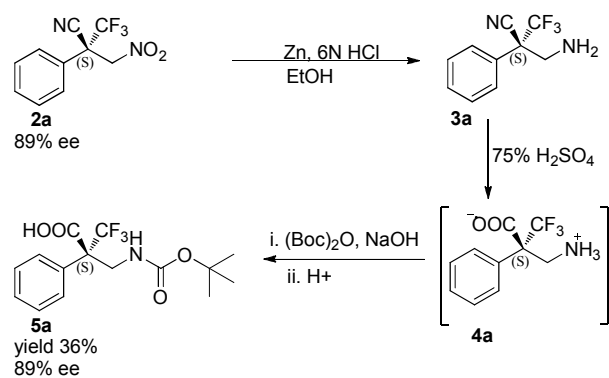

Fig. 2 Proposed model for asymmetric induction

nitro group of alkene weakly coordinates to Ti(IV) and due to the presence of ^{t}Bu-groups in the catalyst only *Re-face* is open to attack of cyanide at the β-position of the nitroalkene.

ARTICLE   **Journal Name**

Scheme 2 Synthetic transformations of product **2a**

As a showcase we have subjected the nitrile product **2a** to reduction, hydrolysis and Boc-protection[6a,6d] to produce enantioenriched *N*-Boc protected trifluoromethylated β-amino acid **5a** where no racemization of the intermediates was noticed under the reaction conditions used for this conversion. (Scheme 2) Analogous β-amino acids are very important molecules in pharmaceuticals.[13]

Experimental Section

Different aldehydes and reagents were used as received. All the solvents used in the present study were dried by known purification technique.[14] NMR spectra were obtained with a Bruker F113V spectrometer (500 MHz / 200 MHz) and are referenced internally with TMS. Splitting patterns were reported as s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. Enantiomeric excess (ee) were determined by HPLC using Daicel Chiralcel OD-H chiral columns with 2-propanol/hexane as eluent. Optical rotations were determined by automatic polarimeter. For the product purification flash chromatography was performed using silica gel 100-200 mesh. Differrent ligands **L1**-**L4**,[15a-d] **L6**-**L8**,[15e-g] and **L9**-**L11**[15h] were synthesized according to the previously reported methods. Trifluoromethylated nitroalkenes **(1a-l)** were prepared according to the reported literature.[5a]

Synthesis of Ligand **L5**

(i) Synthesis of 4-(Adamantan-1-yl)-2-(*tert*-butyl)phenol (A1):
To a solution of 2-*tert*-Butylphenol (10 mmol) and 1-admantanol (10 mmol) were dissolved in DCM (20 mL). Con. H₂SO₄ (0.6 mL) was added dropwise slowly to reaction mixture at 0 °C over 10 minutes. The reaction mixture was stirred two hours at room temperature and neutralized by adding 5% aqueous sodium hydroxide solution. The resulting mixture was extracted with DCM (40 mL x 3) and organic phase washed with brine and dried over anhydrous sodium sulphate. After removing solvent, crude product was purified by silica gel chromatography using EtOAc/hexane to afford the desired product (yield 42%).

(ii) Synthesis of 5-(Adamantan-1-yl)-3-(*tert*-butyl)-2-hydroxybenzaldehyde (A2):
A mixture of 2,6-lutidine (2.0 mmol), SnCl₄ (1.0 mmol) and 4-(adamantan-1-yl)-2-(*tert*-butyl)phenol (3.5 mmol) in 15 mL of dry toluene was stirred at room temperature under inert atmosphere. After 1 h paraformaldehyde (1.3 mmol) was added to reaction mixture and heated under reflux for 8 h and the reaction progress was checked on TLC. Once the reaction was completed, the reaction mixture was allowed to cool to 25 °C and mixture of water and diethyl ether (40 mL) each was added to it. The resulting emulsion was filtered through a pad of celite and the layers were separated. The organic phase was washed with water, brine, and dried over anhydrous Na₂SO₄, and then concentrated on rota-evaporater. The crude product was purified by silica gel chromatography using EtOAc/hexane as eluent to afford the desired product (yield 88%).

(iii) (*R, R*)-(-)*N,N*-Bis(5-Adamantyl-3-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (L5):
5-(Adamantan-1-yl)-3-(*tert*-butyl)-2-hydroxybenzaldehyde (1mmol) was dissolved in 3 mL of ethanol/DCM (9:1). The solution of (1*R*, 2*R*)-(-)-cyclohexanediamine (0.5 mmol) in ethanol (0.5 mL) was added slowly to reaction mixture, and stirred at room temperature for 6-8 h. After completion of reaction, the resulting solution was concentrated on rota-evaporater and yellow solid washed with cold ethanol to give desired compound (yield 87%).

Typical procedure for asymmetric cyanation of trifluoromethylated nitro olefins:

Ti(OᵗBu)₄ (10 mol%, 0.01mmol) was added to stirring solution of ligand **L3** (10 mol%, 0.01 mmol) in freshly dry toluene (1 mL) under inert atmosphere at room temperature. After stirring for 45 min, substrate (0.1 mmol) was added and resulting solution was cooled to 0 °C. To cooled solution TMSCN (0.2 mmol) was added slowly drop wise over 20 min. The reaction was monitored by TLC, after the completion of the reaction, aqueous NaHCO₃ was added to quench the reaction and extracted with DCM (15 mL x 3). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and solvent was removed on rotavapor. The residue was purified by silica gel column chromatography using EtOAc/hexane (10:90) to afford the desired product. The purified new products are characterized by ¹H NMR, ¹³C NMR and ¹⁹F NMR and LCMS, HRMS.

Single-crystal X-ray structure determination

CCDC 1412289 contains the supplementary crystallographic data for this paper. For more detailed crystallographic information see ESI

Conclusions

We have developed an enantioselective hydrocyanation reaction of β-trifluoromethyl-β-disubstituted nitroalkenes

Journal Name ARTICLE

using TMSCN catalyzed by a Ti(IV) salen complex. In the present protocol we have disclosed the first and efficient enantioselective transformation to synthesis β-nitronitrile containing all-carbon quaternary stereogenic centers bearing a trifluoromethyl group with very good enantioselectivity (up to 99%). The product β-nitronitrile was conveniently transformed to the corresponding trifluoromethylated β-amino acids.

Acknowledgements

Notes and references

1 (*a*) H. Hasegawa, M. Muraoka, K. Matsui and A. Kojima, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3471; (*b*) P. R. Daga and R. J. Doerksen, *J. Comput. Chem.*, 2008, **29**, 1945; (*c*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (*d*) R. Filler and R. Saha, *Future Med. Chem.*, 2009, **1**, 777; (*e*) H. Xie, Y. Zhang, S. Zhang, X. Chen and W. Wang, *Angew. Chem. Int. Ed.*, 2011, **50**, 11773.
2 (*a*) J. T. Welch and S. Eswarakrishman, *Fluorine in Bioorganic Chemistry,* Wiley, New York 1991; (*b*) B. E. Smart, *J. Fluorine Chem.*, 2001, **109**, 3; (*c*) T. Mita, T. Kikuchi, T. Mizukoshi, M. Yaosaka and M. Komoda, WO2005085216, 2005; (*d*) K. Mìller, C. Faeh, and F. Diederich, *Science*, 2007, **317**, 1881; (*e*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (*f*) G. Chaume, N. Lensen, C. Caupéne and T. Brigaud, *Eur. J. Org. Chem.*, 2009, 5717; (*g*) S. Lectard, Y. Hamashima and M. Sodeoka, *Adv. Synth. Catal.*, 2010, **352**, 2708; (*h*) Y. Ozoe, M. Asahi, F. Ozoe, K. Nakahira and T. Mita, *Biochem. Biophys. Res. Commun.*, 2010, **391**, 744; (*i*) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455.
3 For selected reviews on trifluoromethylation of organic compounds, see: (*a*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, 37, 320; (*b*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475. (*c*) Y. Ye and M. S. Sanford, *Synlett*, 2012, **23**, 2005; (*d*) T. Furuya, A. S. Kamlet, and T. Ritter, *Nature*, 2011, **473**, 470; (*e*) X.-F. Wu, H. Neumann and M. Beller, *Chem.-Asian J.*, 2012, 7, 1744; (*f*) A. Studer, *Angew. Chem. Int. Ed.*, 2012, **51**, 8950; (*g*) Y.-Y. Huang, X. Yang, Z. Chen, F. Verpoort and N. Shibata, *Chem. Eur. J.*, 2015, **21**, 8664.
4 H. Kawai, S. Okusu, E. Tokunaga, H. Sato, M. Shiro and N. Shibata, *Angew.Chem. Int. Ed.*, 2012, **51**, 4959.
5 (*a*) J.-R. Gao, H. Wu, B. Xiang, W.-B. Yu, L. Han and Y.-X. Jia, *J. Am. Chem. Soc.*, 2013, **135**, 2983; (*b*) Q. Chen, G. Wang, X. Jiang, Z. Xu, L. Lin, and R. Wang, *Org. Lett.*, 2014, **16**, 1394; (*c*) P. Kwiatkowski, A. Cholewiak and A. Kasztelan, *Org. Lett*., 2014, **16**, 5930; (*d*) C.-H. Ma, T.-R. Kang, L. He and Q.-Z. Liu, *Eur. J. Org. Chem.*, 2014, 3981; (*e*) H. Wu, R.-R. Liu and Y.-X. Jia *Synlett*, 2014, **25**, 457; (*f*) W. Chen, Z. Jing, K. F. Chin, B. Qiao, Y. Zhao, L. Yan, C.-H. Tan and Z. Jiang, *Adv. Synth. Catal.*, 2014, **392**, 1256; (*g*) F.-L. Liu, J.-R. Chen, B. Feng, X.-Q. Hu, L.-H. Ye, L.-Q. Lu and W.-J. Xiao, *Org. Biomol. Chem.*, 2014, **12**, 105; (*h*) J. Chen, S. Meng, L. Wang, H. Tang and Y. Huang, *Chem. Sci.*, 2015, **6**, 4184; (*i*) L. Wang, J. Chen, Y. Huang, *Angew. Chem. Int. Ed.*, 2015, **54**, 15414; (*j*) D. Du, Y. Jiang, Q. Xu, X.-Y. Tang and M. Shi, *ChemCatChem*, 2015, **7**,

1366; (*k*) Y. Zhu, X. Li, Q. Chen, J. Su, F. Jia, S. Qiu, M. Ma, Q. Sun, W. Yan, K. Wang and R. Wang, *Org. Lett.,* 2015, **17**, 3826; (*l*) H. Wu, R.-R. Liu, C. Shen, M.-D. Zhang, J. Gao and Y.-X. Jia, *Org. Chem. Front.*, 2015, **2**, 124; (*m*) D. Yan, Q. Li. and C. Wang, *Chin. J. Chem.*, 2012, **30**, 2714.
6 (*a*) J. C. Anderson, A. J. Blake, M. Mills and P. D. Ratcliffe, *Org. Lett.*, 2008, **10**, 4141; (*b*) L. Bernardi, F. Fini, M. Fochi and A. Ricci, *Synlett*, 2008, **12**, 1857; (*c*) P. Bernal, R. Fernández and J. M. Lassaletta, *Chem. Eur. J.*, 2010, **16**, 7714; (*d*) L. Lin, W. Yin, X. Fu, J. Zhang, X. Ma and R. Wang, *Org. Biomol. Chem*., 2012, **10**, 83; (*e*) M. North and J. M. Watson, *ChemCatChem,* 2013, **5**, 2405; *(f)* A. Jakhar, A. Sadhukhan, N. H. Khan, S. Saravanan, R. I. Kureshy, S. H. R. Abdi and H. C. Bajaj, *ChemCatChem*, 2014, **6**, 2656.
7 (*a*) H. Iida, T. Moromizato, H. Hamana and K. Matsumoto, *Tetrahedron Lett.*, 2007, **48**, 2037; (*b*) Y. Tanaka, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.,* 2008, **130**, 6072; (*c*) J. Yang, Y. Wang, W. Shaoxiang and F.-X. Chen, *Synlett,* 2009, 3365; (*d*) Y. Tanaka, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 8862; (*e*) N. Kurono, N. Nii, Y. Sakaguchi, M. Uemura and T. Ohkuma, *Angew. Chem. Int. Ed.*, 2011, **50**, 5541; *(f)* B. A. Provencher, K. J. Bartelson, Y. Liu, B. M. Foxman and L. Deng, *Angew. Chem. Int. Ed.*, 2011, **50**, 10565; *(g)* H. Kawai, S. Okusu, E. Tokunaga, H. Sato, M. Shiro and N. Shibata, *Angew. Chem. Int. Ed.,* 2012, **51**, 4959; (*h*) S. Lin, Y. Wei and F. Liang, *Chem. Commun.*, 2012, **48**, 9879; (*i*) S. Ramesh and A. Lalitha, *Acta Chim. Slov.*, 2013, **60**, 689; (*j*) C. Dong, T. Song, X.-F. Bai, Y.-M. Cui, Z. Xu and L.-W. Xu, *Catal. Sci. Technol*., 2015, **5**, 4755; (*k*) X.-P. Zeng, Z.-Y. Cao, X. Wang, L. Chen, F. Zhou, F. Zhu, C.-H. Wang, and J. Zhou, *J. Am. Chem. Soc*., 2016, **138**, 416.
8 (*a*) G. M. Sammis and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2003, **125**, 4442; *J. Am. Chem. Soc.*, 2004, **126**, 9928; *(b)* C. Mazet and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2008, **47**, 1762; *(c)* N. Madhavana and M. Weck, *Adv. Synth. Catal.*, 2008, **350**, 419.
9 (*a*) T. Mita, K. Sasaki, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 514; (*b*) I. Fujimori, T. Mita, K. Maki, M. Shiro, A. Sato, S. Furusho, M. Kanaia and M. Shibasaki, *Tetrahedron*, 2007, **63**, 5820.
10 (*a*) Wang, W. Li, Y. Liu, Y. Chu, L. Lin, X. Liu and X. Feng, *Org. Lett.*, 2010, **12**, 1280; (*b*) H. Mukherjee and C. A. Martinez, *ACS Catal.*, 2011, **1**, 1010; (*c*) Y. Liu, S. Shirakawa and K. Maruoka, *Org. Lett.* 2013, **15**, 1230.
11 (*a*) N. H. Khan, R. I. Kureshy, S. H. R. Abdi, S. Agrawal and R. V. Jasra, *Coord. Chem. Rev.*, 2008, **252**, 593; (*b*) N. H. Khan, R. I. Kureshy, S. H. R. Abdi, H. C. Bajaj and A. Sadhukhan, "Asymmetric cyanation reactions" Elsevier Publication in Comprehensive Inorganic Chemistry II, Oxford Elsevier, 2013, vol. **6**, 413; **(c)** M. North, D. L. Usanov and C. Young, *Chem. Rev*., 2008, **108**, 5146; *(d)* W. Wang, X. Liu, L. Lin and X. Feng, *Eur. J. Org. Chem.,* 2010, 4751; (e) Z. Zhang, Z. Wang, R. Zhang, K. Ding, *Angew. Chem. Int. Ed.*, 2010, **49**, 6746; *(f)* H. Pellissier, *Adv. Synth. Catal.*, 2015, **357**, 857; *(g)* N. Kurono and T. Ohkuma, *ACS Catal.*, 2016, **6**, 989.
12 (*a*) S. J. Zuend, M. P. Coughlin, M. P. Lalonde and E. N. Jacobsen, *Nature*, 2009, **461**, 968; *(b)* J. Wang, X. Liu and X. Feng, *Chem. Rev.*, 2011, **111**, 6947; (c) X. H. Cai and B. Xie, *ARKIVOC*, 2014, **1**, 205; *(d)* S. Saravanan, N. H. Khan, A. Jakhar, A. Ansari, R. I. Kureshy, S. H. R. Abdi and G. Kumar, *RSC Adv.*, 2015, **5**, 99951.
13 (*a*) J. X. Qiu, E. J. Petersson, E. E. Matthews and A. Schepartz, *J. Am. Chem. Soc.*, 2006, **128**, 11338; (*b*) B. Weiner, W. Szymaǹski, D. B. Janssen, A. J. Minnaarda and B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 1656; (*c*) A. Ishii, M. Yasumoto, T. Yamazaki, K. Mogi and T. Masuda, US20110152536 A1, 23 Jun 2011.

RSC Advances Accepted Manuscript

Please do not adjust margins

ARTICLE

Journal Name

14 D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals;*Pergamon: New York, **1981**.

15 (*a*) C. M. Mascarenhas, S. P. Miller, P. S. White and J. P. Morken, *Angew. Chem. Int. Ed.,* 2001, **40**, 601; (*b*) X. Yao, M. Qiu, W. Lu, H.Chen and Z. Zheng, *Tetrahedron: Asymmetry*, 2001, **12**, 197; (*c*) J. F. Larrow and E. N. Jacobsen, *J. Org. Chem.*, 1994, **59**, 1939; (*d*) S.-K. Chen, D.Peng, H. Zhou, L.-W. Wang, F.-X. Chen and X.-M. Feng, *Eur. J. Org. Chem.*, 2007, 639; (*e*) R. I. Kureshy, N. H. Khan, S. H. R. Abdi, S. T. Patel and R. V. Jasra, *Tetrahedron Letters*, 2001, **42**, 2915; (*f*) R. I. Kureshy, N. H. Khan, S. H. R. Abdi, S. Singh, I. Ahmad, R. V. Jasra and A. P. Vyas., *Journal of Catalysis*, 2004, **224**, 229; (*g*) R. I. Kureshy, M. Kumar, S. Agrawal, N. H Khan, B. Dangi, S. H. R. Abdi and H. C. Bajaj, *Chirality*, 2011, **23**, 76; (*h*) S. Saravanan, N. H. Khan, P. K. Bera, R. I. Kureshy, S. H. R. Abdi, P. Kumari and H. C. Bajaj, *ChemCatChem*, 2013, **5**, 1374.

RSC Advances Accepted Manuscript

Please do not adjust margins

80-93% yield
53-99% ee