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Chemoselective N-tert-butoxycarbonylation and N-formylation of Amines by $B(OSO_3H)_3/SiO_2$ as an Efficient Heterogeneous and Recyclable Catalyst

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A simple, efficient, and cost-effective procedure for N-tert-butoxycarbonylation and N-formylation of amines (primary, secondary), respectively, with di-tert-butyl dicarbonate and 85% aqueous formic acid under solvent-free condition using $B(OSO_3H)_3/SiO_2$ (SBSA) as a heterogeneous and recyclable catalyst has been developed. We demonstrated that the resulting catalyst is applicable to various aromatic and aliphatic amines giving excellent yields of the desired products in short reaction time (<20 min) at room temperature. The recoverability of the catalyst was achieved by a simple decantation and reused at least five times without significant degradation in catalytic activity. Furthermore, the leaching test showed no detectable homogeneous catalysis from active spices in the solution. SBSA act as a dual Brønsted/Lewis acid that is an air-stable and cost-effective solid acid. This protocol has shown excellent chemoselectivity.

Keywords: Protection, Boc, Formylation, Catalyst, $B(OSO_3H)_3$

INTRODUCTION

Choosing an appropriate chemoselective protection and deprotection strategy is one of the key steps in the synthetic sequence in the presence of various functional groups [1]. The protection of amines plays significant role in peptide synthesis, and so, various methods and protecting groups have been developed for amine protection such as carbamates (Cbz, Fmoc and Alloc), amides, formamides, imides, *ect.* Tert-butoxycarbonyl protecting group (Boc) is used extensively as amine protecting group, because the N-Boc moiety is stable toward catalytic hydrogenation and extremely resistant toward basic and nucleophilic reactions and also has resistant to racemization during synthesis and can be easily converted into the free amine [2]. A variety of methods are available for N-tert-butoxycarbonylation of amines using various catalysts and commercially available di-tert-butyl dicarbonate, $(Boc)_2O$, such as, DMAP [3], I_2 [4], TiO_2-Pr-SO_3H [5], IL [6], $Cu(BF_4)_2.xH_2O$ [7], β-cyclodextrin [8], $[H\text{-}Suc]HSO_4$ [9], $Zn(ClO_4)_2.6H_2O$ [10], imidazolium trifluoroacetate [11], montmorillonite [12], amberlyst-15 [13], nano-Fe_3O_4 [14] and $Br_3CCOCBr_3$ [15]. However, some of these methods suffer from different drawbacks such as application of expensive and toxic agents and catalysts, long reaction times, high temperatures and formation of by-products (biscarbamoylation, isocyanate and urea).

N-formylation is an important reaction in organic synthesis and medicinal chemistry having been widely used in preparation of pharmaceutically important compounds (fluoroquinolones [16], substituted aryl imidazoles [17], 1,2-dihydroquinolines [18], nitrogen bridged heterocycles [19], *etc.*), synthesis of formamidines [20] and isocyanides and as a reagent in Vilsmeier formylation reactions [21].

To overcome these problems, there is further need for new, facile, and effective methods that can be applied to a number of substrates in a catalytic process. In view of developing environmentally friendly procedure, using of recyclable catalyst and elimination of harmful organic solvents are promising approaches. Therefore, in continue

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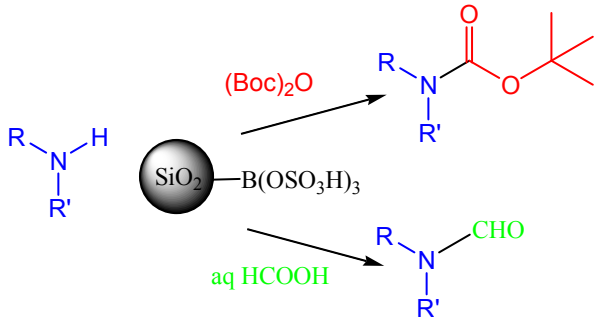
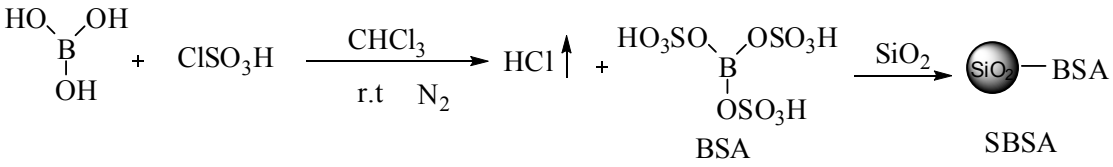


Scheme 1. N-tert-butyloxycarbonylation and N-formylation of amines catalyzed by SBSA under solvent-free condition



Scheme 2. Preparation of $B(OSO_3H)_3/SiO_2$

of our efforts to develop new synthetic routes [22], herein, we describe the use of silica boron sulfonic acid (SBSA) as the recoverable solid catalyst in the N-tert-butyloxy-carbonylation and N-formylation of amines under mild and solvent-free conditions (Scheme 1).

$B(OSO_3H)_3/SiO_2$ (SBSA) is a strong dual Brønsted/Lewis acid, which was simply prepared by addition of chlorosulfonic acid to boric acid under N_2 atmosphere at room temperature following by addition SiO_2 (1:5 ratio) under 50 °C (Scheme 2). According to FT-IR spectra (SI, Fig. 1), the band at 1107 cm^{-1} is attributed to O-Si vibration. The broad intense band of O-H stretching absorption appears in the area of 3350 cm^{-1}. The band at ~ 1160 cm^{-1} are assigned to stretching vibration of O=S=O, and the band centered at 650 cm^{-1} is related to stretching vibration of S-O.

EXPERIMENTAL

General Remarks

Chemicals were purchased from Merck and Fluka Companies and used as received. FT-IR spectra were obtained using BOMEM MB-Series 1998 FT-IR spectrometer. ^1H NMR was run on Bruker Avence (DRX 500 MHz). The progress of the reaction was followed by TLC, using silica gel SILG/UV 254 plates. All the products are known and were characterized by comparison of their spectra (FT-IR, ^1H NMR) and TLC with those reported in the literature.

General Procedure for N-formylation of Amines

SBSA (0.08 g) was added to a mixture of amine (1 mmol) and aqueous formic acid (3 mmol), and the mixture was stirred at 60 ºC for 20-30 min under solvent-free condition. After completion of the reaction monitored by TLC (EtOAc/n-hexane, 1:3), ethyl acetate (5 ml) was added to the reaction mixture and the solid catalyst was easily filtered. The crude product washed with H_2O (2-10 ml) and a saturated solution of $NaHCO_3$, and then, dried over anhydrous Na_2SO_4. The solvent was evaporated and the desired product was obtained. This was further purified by recrystallization with suitable solvent (n-pentane or n-hexane).

General Procedure for N-tert-butoxycarbonylation of Amines

SBSA (0.06 g) was added to a mixture of amine (1 mmol) and di-tert-butyl dicarbonate (1 mmol), and the mixture was stirred at room temperature (25 ºC) under solvent free condition for an appropriate time (Table 4). After completion of the reaction, monitored by TLC (EtOAc/n-hexane, 1:3), ethyl acetate (5 ml) was added to the reaction mixture and the solid catalyst was easily filtered. The crude product washed with H_2O (2-10 ml) and a saturated solution of $NaHCO_3$, and then, dried over anhydrous Na_2SO_4. The solvent was evaporated and the desired product was obtained. This was further purified by recrystallization with suitable solvent (n-pentane or n-hexane).

Spectral Data

N-(4-Methylphenyl) formamide (Table 2, Entry 4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, $2CH_3$), 7.02-7.47 (m, 8H, Ar-H),8.03 (brs, 1H cis), 8.34 (s, 1H, cis), 8.68 (d, 1H, J = 11.39 Hz, trans), 8.86 (brs, 1H, trans); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.22 (CH_3), 21.31 (CH_3), 119.5 (CH, Ar), 120.6 (CH, Ar), 129.96 (CH Ar), 130.64 (CH, Ar), 134.67-134.90 (3CH, Ar), 135.5 (CH, Ar), 159.8 (CHO), 163.57 (CHO)

N-(4-Nitrophenyl) formamide (Table 2, Entry 8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (brs, 1H), 8.10 (s, 1H), 7.87 (d, 2H, *J* = 9.1 Hz, Ar-H), 7.53 (d, 2H, *J* = 9.1 Hz, Ar-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.9, 119.5, 125.0, 125.6, 143.3, 144.3, 160.1

N-(4-Acetylphenyl) formamide (Table 2, Entry 10). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.48 (s, 1H), 8.02 (s, 1H), 7.99 (d, 2H, Ar-H), 7.69 (d, 2H, Ar-H), 2.62 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 117.6, 119.6, 130.2, 130.8, 133.6, 134.0, 141.8, 159.8, 162.5, 197.5

4-Morpholine carbaldehyde (Table 2, Entry 16). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 3.33-3.63 (m, 8H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.9, 46.1, 66.7, 67.5, 161.2.

Tert-butyl phenyl carbamate (Table 4, Entry 1). M. p.: 132 ºC; IR (KBr) ν = 3316, 2979, 1688, 1596, 1526, 1439, 1314, 1152, 745 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (9H, $3CH_3$), 6.52 (brs, 1H, NH), 7.04-7.39 (5H, Ar) ppm.

RESULTS AND DISCUSSION

Initially we started with the *N*-formylation of aniline using 85% formic acid catalyzed by SBSA as a model compound in order to examine the optimum conditions and catalytic activity of the catalyst (Table 1).

According to Table 1, the best result was obtained by performing the model reaction using 0.08 g of boronsulfonic acid/SiO_2 (SBSA) under solvent-free condition at 60 ºC (Table 1, Entry 5). Using different solvents indicates that increasing the polarity of solvent leads to better yields. This can be in accordance with a polar intermediate mechanism through which the system is stabilized by polar solvent.

Accordingly, SBSA could be an excellent catalyst for the formylation of various amines through which the best results are obtained with 3 eq. formic acid and 0.08 g of SBSA at 60 ºC. The products obtained are summarized in Table 2. Primary and secondary amines, cyclic amines and various aromatic amines bearing both electron-donating and -withdrawing groups were studied under similar reaction conditions (see Table 2). All amines give readily the corresponding formamides. The optimized condition can be applied for conversion of hindered amines (Table 2, Entry 11), as well as the less reactive 4-nitroaniline (Table 2, Entry 8).

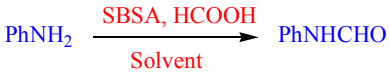
As shown in Table 2, primary aliphatic amines such as benzylamine, cyclohexylamine and n-propyl amine were easily formylated to provide alkyl diformamide in good yields (Table 2, Entries 12-14). Also, secondary amines (diphenylamine) readily reacted to afford the corresponding formamide in 81% yield (Table 2, Entry 11). Cyclic amines (Table 2, Entries 16, 17) are easily formylated to provide formamide in good yields.

It was found that this protocol is chemoselective, and then only *N*-formylated product was formed by molecules containing both the hydroxyl and the amino group (Table 2, Entries 18, 19).

Furthermore, in optimum condition, the catalyst was applied for the formylation of aliphatic alcohols with formic acid and the corresponding O-formylated products were obtained in high yields (Table 3). It is found that these reactions give the products in longer reaction times than formylation of amines.

With the optimum conditions established for N-tert-

Table 1. Screening Condition for the Model Reaction of N-formylation



Entry	HCOOH (equiv.)	SBSA (g)	Solvent	Temp. (ºC)	Time (min)	Yield (%)[a]
1	5	None	-	25	240	10
2	5	None	-	60	240	40
3	3	0.04	-	60	30	45
4	3	0.06	-	60	30	60
5	3	0.08	-	60	20	94
6	3	0.08	-	80	20	96
7	3	0.08	-	25	60	85
8	2	0.08	-	60	20	80
9	3	0.10	-	60	20	94
10	3	0.08	$CHCl_3$	60	120	54
11	3	0.08	EtOAc	60	120	73
12	3	0.08	DMF	60	120	85
13	3	0.08	CH_3CN	60	120	90

[a]Isolated yields.

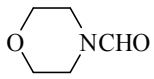
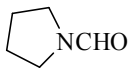
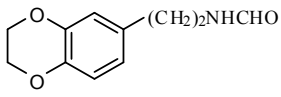
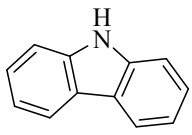
butyloxycarbonylation,various aromatic, heteroaromatic and aliphatic (cyclic and acyclic) amines were treated with $(Boc)_2O$ (1:1) under solvent-free conditions at 25 ºC in the presence of 0.06 g SBSA, as indicate by the results summarized in Table 4. All the amines reacted efficiently giving the corresponding protected amines in good to excellent yields.

The obtained result in Table 4 indicates that N-tert-butyloxycarbonylation of aniline and aromatic amines bearing electron donating group (Table 4, Entries 1, 2, 6, 7) proceed quickly with excellent yields while aromatic amines bearing electron-withdrawing groups react in the longer time and lower yields (Table 4, Entries 3, 4, 5, 8, 9, 10). The reaction of primary and secondary aliphatic amines (Table 4, Entries 14-21) with $(Boc)_2O$ required shorter reaction time and proceeded quickly to yield the corresponding N-Boc amines. Notably, chemoselectivity was observed in the reactions of 4-hydroxy aniline, yielding just the corresponding N-Boc products in excellent yields (Table 4, Entry 11). Chemoselectivity was also examined using different amine groups to show the electronic effects in this catalytic system.

Reaction condition: Amine (1 mmol), Boc_2O (1 mmol), SBSA (0.06 g) and 25 ºC, Solvent free

The reaction of aniline (1 mmol) and benzylamine (1 mmol) with $(Boc)_2O$ (1 mmol) afforded tert-butyl N-phenylcarbamate. The reaction of aniline (1 mmol) and cyclohexylamine (1 mmol) with $(Boc)_2O$ (1 mmol) afforded

Table 2. SBSA Catalyzed Green N-formylation

Entry	Product	Yield (%)	M. p./reported M. p. (ºC) [23-30]
1	C_6H_5NHCHO	94	44-48/44-45
2	4-$MeOC_6H_4NHCHO$	94	79-80/78-92
3	2,5-$DiMeC_6H_3NHCHO$	90	115/ 114-118
4	4-MeC_6H_4NHCHO	92	53-57/52-54
5	4-BrC_6H_4NHCHO	88	116-118/117-121
6	3-BrC_6H_4NHCHO	86	61-63/60-64
7	2-BrC_6H_4NHCHO	82	87-89/88-92
8	4-$NO_2C_6H_4NHCHO$	74	193-196/196-200
9	4-CNC_6H_4NHCHO	76	186
10	4-$CH_3COC_6H_4NHCHO$	80	100-102
11	Di-Phenyl-NCHO	81	65-70/69-73
12	$PhCH_2N(CHO)_2$	93	98-100
13	Cyclohexyl-$N(CHO)_2$	90	77-80
14	n-Propyl-$N(CHO)_2$	91	107-109
15	Et_2NCHO	87	175-176/176-177
16		90	Oil
17		90	117-119
18	4-HOC_6H_4NHCHO	90	135-136/135-137
19	2-HO 4-$CH_3C_6H_4NHCHO$	88	Oil
20		83	Oil
21		-	-

Reaction condition: Amine (1 mmol), HCOOH (3 mmol), SBSA (0.08 g) and 60 ºC, Solvent free.

Table 3. SBSA Catalyzed Green O-formylation of Alcohols

Entry	Product	Yield (%)
1	$PhCH_2OCHO$	86
2	$4\text{-}CH_3PhCH_2OCHO$	93
3	$4\text{-}ClPhCH_2OCHO$	80
4	$4\text{-}NO_2PhCH_2OCHO$	72
5	Cyclohexyl-OCHO	91

Reaction condition: Alcohol (1 mmol), HCOOH (3 mmol), SBSA (0.08 g) and 60 ºC, Solvent free.

Table 4. N-tert-Butyloxycarbonylation of Amines in the Presence of SBSA

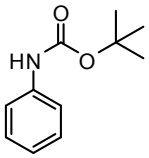
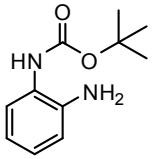
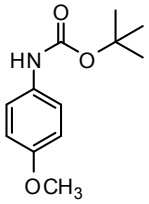
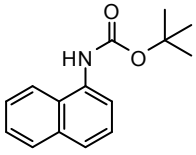
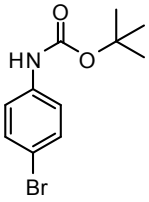
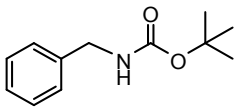
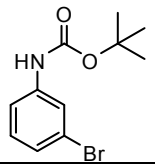
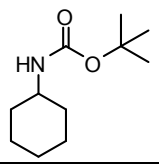
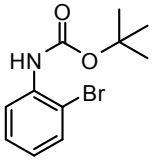
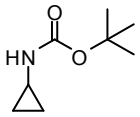
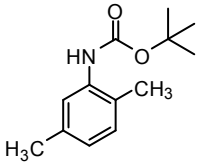
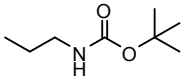
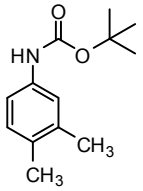
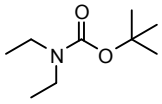
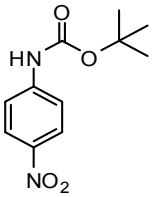
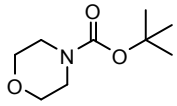
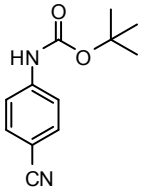
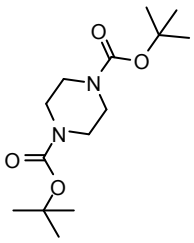
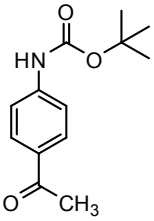
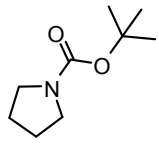
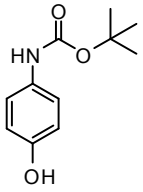
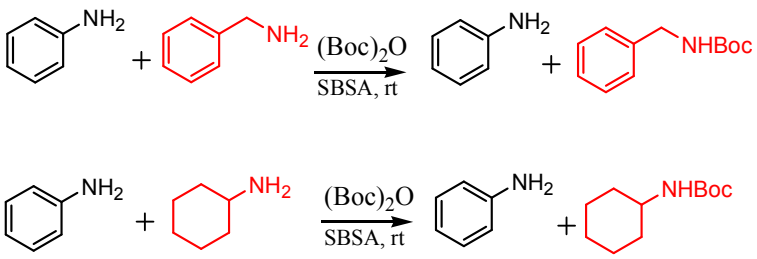
No.	Product	Time (min)	M. p. (ºC)	Yield (%)	Entry	Product	Time (min)	M. p. (ºC)	Yield (%)
1		30	132	97	12		40	112-114	93
2		10	91-93	98	13		240	97-99	96
3		180	100-102	96	14		10	55-57	97
4		270	Oil	90	15		10	66-67	97

Table 4. Continued

5		24 h	-	Trace	16		20	Oil	98
6		50	106-108	97	17		10	Oil	97
7		10	126-128	98	18		40	Oil	98
8		24 h	-	trace	19		10	56-58	98
9		24 h	119-121	58	20		10	157	98
10		24 h	109-110	70	21		10	Oil	97
11		8 h	145-146	98					

Reaction condition: Amine (1 mmol), Boc_2O (1 mmol), SBSA (0.06 g) and 25 ºC, Solvent free



Scheme 3. Competitive N-Boc protection of the different amine groups

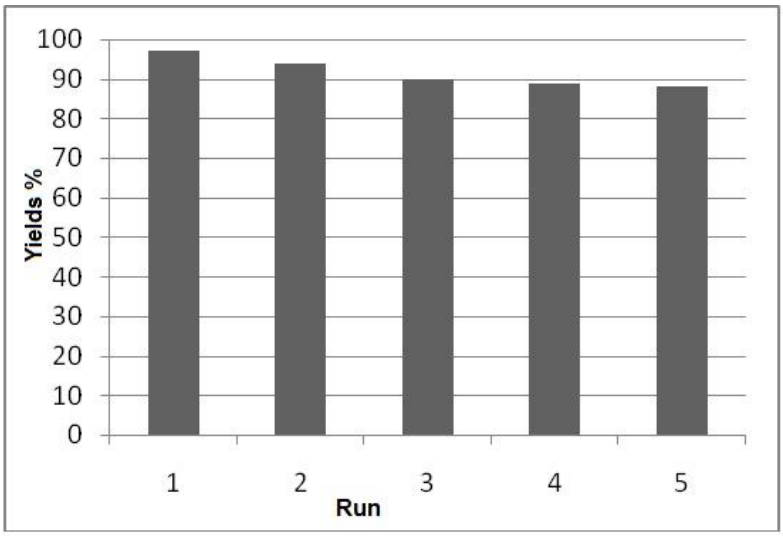


Fig. 1. Recyclability of the catalyst.

tert-butyl cyclohexyl carbamate, (Scheme 2).

Once the reaction was over, the catalyst was isolated by simple filtration, and washed with ether to remove any residue. pH analysis for measuring total H^+ in the initial SBSA (3.3 mmol g^{-1} H^+) and the recovered SBSA after five runs (3 mmol g^{-1} H^+) revealed the stability and the recoverability of the catalyst. The FT-IR spectroscopy also confirmed the same structure of the recovered catalyst. The recovered catalyst in subsequent reaction showed only slightly yields decreasing after five times. For example, N-tert-butyloxycarbonylation of aniline afforded the corresponding N-Boc aniline in 97%, 94%, 90%, 89% and 88% yields over five cycles.

CONCLUSIONS

In summary, we prepared Boronsulfonic acid/SiO_2 (SBSA) and utilized it for N-Boc and N-formylation under mild conditions with excellent yields. This simple heterogeneous solid catalyst has many advantages such as chemoselectivity, short reaction time, excellent yields, and facilely recycled, which provides an effective and green methodology for these reactions.

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Supplementary Information (SI)

All additional information pertaining to characterization of the products and catalyst using NMR technique and IR spectra are given in the supporting information.

REFERENCES

[1] P.J. Kocienski, Protecting Groups, Georg ThiemeVerlag: NewYork, 2000.

[2] B. Deb, S. Debnath, A. Deb, D.K. Maiti, S. Majumdar, Tetrahedron Lett. 58 (2017) 629

[3] Y. Basel, A. Hassner, J. Org. Chem. 65 (2000) 6368.

[4] R. Varala, S. Navula, S.R. Adapa, J. Org. Chem. 71 (2006) 8283.

[5] S.V. Atghia, S.S. Beigbaghlou, J. Organomet. Chem. 745 (2013) 42.

[6] F. Shirini, N.G. Khaligh, J. Mol. Liq. 177 (2013) 386.

[7] A.K. Chakraborti, S.V. Chankeshwara, Tetrahedron Lett. 47 (2006) 1087.

[8] M.S. Reddy, M. Narender, Y.V.D. Nageswar, K.R. Rao, Synlett (2006) 1110.

[9] F. Shirini, O.G. Jolodar, M. Seddigh, H.T. Borujeni, RSC Adv. 5 (2015) 19790.

[10] G.B.M. Bartoli, M. Locatelli, E. Marcantoni, M. Massaccesi, P. Melchiorre, L.A. Sambri, Synlett (2004) 1794.

[11] S. Majumdar, A.De J. Chakraborty, D.K. Maiti, RSC Adv. 4 (2014) 24544.

[12] S. Chankeshwara, A.K. Chakraborti, J. Mol. Catal. A: Chem. 253 (2006) 198.

[13] K.S. Kumar, J. Iqbal, M. Pal, Tetrahedron Lett. 50 (2009) 6244.

[14] M.A. Zolfigol, A.R. Moosavi-Zare, P. Moosavi, V. Khakyzadeh, A. Zare, C.R. Chim. 16 (2013) 962.

[15] O. Chantarasriwong, B. Jiangchareon, C.K. Putra, W. Suwankrua, W. Chavasiri, Tetrahedron Lett. 57 (2016) 4807.

[16] A. Jackson, O. Meth-Cohn, J. Chem. Soc., Chem. Commun. 0 (1995) 1319.

[17] B.C. Chen, M.S. Bednarz, R. Zhao, J.E. Sundeen, P. Chen, Z. Shen, A.P. Skoumbourdis, J.C. Barrish, Tetrahedron Lett. 41 (2000) 5453.

[18] K. Kobayashi, S. Nagato, M. Kawakita, O. Morikawa, H. Konishi, Chem. Lett. (1995) 575.

[19] A. Kakehi, S. Ito, S. Hayashi, T. Fujii, Bull. Chem. Soc. Jpn. 68 (1995) 3573.

[20] Y. Han, L. Cai, Tetrahedron Lett. 38 (1997) 5423.

[21] I.M. Downie, M.J. Earle, H. Heaney, K.F. Shuhaibar, Tetrahedron 49 (1993) 4015.

[22] H. Hamadi, S. Javadi, J. Chem. Sci. 129 (2017) 75.

[23] D. Habibi, M. Nasrollahzadeh, C.R. Chimie 16 (2013) 1008.

[24] D. Habibi, H. Sahebekhtiari, M. Nasrollahzadeh, A. Taghipour, Lett. Org. Chem. 10 (2013) 209.

[25] S. Bahari, Lett. Org. Chem. 10 (2013) 532.

[26] Z. Wang, M. Lu, RSC Adv. 4 (2014) 1234.

[27] G. Brahmachari, S. Laskar, Tetrahedron Lett. 51 (2010) 2319

[28] N. Ortega, C. Richter, F. Glorius, Org. Lett. 15 (2013) 1776

[29] H.J. Park, J.C. Lee, Bull. Korean Chem. Soc. 29 (2008) 856.

[30] A. Rostami, A. Khazaei, H.A. Alavi-Nik, Z. Toodeh-Roosta, Chin. J. Catal. 32 (2011) 60.