RSC Advances

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Copper-catalyzed tandem oxidative cyclization of arylacetamides: efficient access to *N*-functionalized isatins†

Cite this: *RSC Advances*, 2013, **3**, 5824

Received 6th February 2013,
Accepted 1st March 2013

DOI: 10.1039/c3ra40657a

www.rsc.org/advances

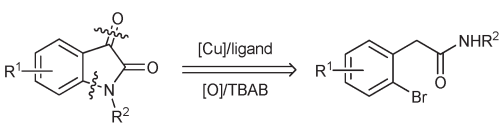
Jie Sun,[a] Bingxin Liu[a] and Bin Xu*[ab]

An efficient copper-catalyzed synthesis of *N*-substituted isatins has been developed in good yields from easily accessible arylacetamides. A wide range of electronically and structurally varied nitrogen fragments could be assembled through this tandem C–O/C–N bond-forming process by tuning the reaction conditions.

1*H*-Indole-2,3-dione (isatin) derivatives are of great pharmaceutical interest with a wide range of biological and pharmacological activities,[1] which play an increasingly important role in drug discovery. These compounds are structural units found in a vast array of natural products,[1d] synthetic materials,[1a,1d,2] and bioactive molecules as anticancer,[1c,3] anticonvulsant,[4] anti-HIV,[5] anti-inflammatory and analgesic,[6] antimicrobial,[7] antioxidant,[8] and antiviral agents.[9] Besides, isatins are synthetically versatile substrates, which could be used as intermediates for the synthesis of various heterocyclic compounds, such as isatoic anhydrides, indoles, quinolines, and as precursors for the synthesis of spirofused cyclic frameworks.[1d] Recently, the isatin derivative sunitinib malate (SU11248) was approved by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST). Such characteristics have made the molecules significant synthetic targets and, therefore, have resulted in sustained interest in developing general and direct methods for the preparation of this valuable structural unit.[1a,1d,2] Isatin was first obtained by Erdmann and Laurent in 1840 as a product from the oxidation of indigo dye by nitric and chromic acids.[10] Other improved synthetic methods to build this useful scaffold include the *N*-alkylation or arylation of isatins with alkyl halides,[11] aryl boronic acids[12] or triarylbismuth,[13] microwave-assisted modified Sandmeyer reactions of oximinoacetanilides,[14] reaction of arynes with methyl 2-oxo-2-(arylamino)acetates,[15] utilization of *N*,*N*-diarylamines with oxalyl chlorides,[16] and by ruthenium-catalyzed[17] or indium(III) chloride–2-iodoxybenzoic acid[18] promoted oxidation of indoles. Recently, Li and co-workers reported an efficient synthetic route to indoline-2,3-diones by copper-catalyzed intramolecular C–H oxidation–acylation of formyl-*N*-arylformamides.[19] However, some of these reactions suffer from relatively harsh reaction conditions, poor yields and limited diversification.

Metal-catalyzed intramolecular amidation reactions of arylacetamides usually lead to oxindoles in good to excellent yields (Scheme 1), however, no generation of the corresponding 1*H*-indole-2,3-diones has been reported among these reactions.[20] To continue our program aiming at the efficient construction of heterocycles through a tandem reaction strategy,[21] we herein describe a copper-catalyzed tandem oxidative cyclization reaction, whereby sequential C–O and C–N bonds are formed from easily accessible *ortho*-bromo substituted arylacetamides to give *N*-functionalized isatins in the presence of tetra-*n*-butylammonium bromide (Scheme 1). To our knowledge, this reaction represents the first efficient example of a one-pot synthesis of *N*-substituted isatins through a tandem C–O/C–N bond-forming process.

An initial study was performed by examining the reaction of **1a** in the presence of CuI, 1,10-Phen and TBAB in toluene using pyridine as a base. However, this reaction gave only a trace amount of *N*-benzylisatin (Table 1, entry 1). When using NaOH as the base, a 39% yield of **3a** could be isolated (entry 2). Amongst all the other bases tested, K_2CO_3 proved to be the most efficient one (entry 5), while K_3PO_4 and KOAc gave diminished yields (entries 3 and 4). Switching the solvent from toluene to dioxane, DMF, acetonitrile or mesitylene gave decreased yields or trace amounts of product (entries 6–9). An extensive screening concerning the

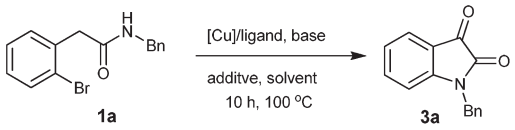


Scheme 1 Tandem strategy on isatin ring synthesis.

[a]*Department of Chemistry, Shanghai University, Shanghai 200444, China. E-mail: xubin@shu.edu.cn; Fax: +86-21-66132830; Tel: +86-21-66132830*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P R China*

† Electronic supplementary information (ESI) available: General experimental procedures, characterization data and copies of the ^1H and ^{13}C NMR spectra for all compounds. See DOI: 10.1039/c3ra40657a

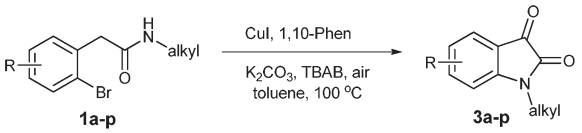
Table 1 Condition optimizations of isatin synthesis[a]



Entry	Cu source	Base	Solvent	Additive	Ligand	Yield[b] (%)
1	CuI	Pyridine	toluene	TBAB	1,10-Phen	<5
2	CuI	NaOH	toluene	TBAB	1,10-Phen	39
3	CuI	K_3PO_4	toluene	TBAB	1,10-Phen	59
4	CuI	KOAc	toluene	TBAB	1,10-Phen	65
5	**CuI**	**K_2CO_3**	**toluene**	**TBAB**	**1,10-Phen**	**74**
6	CuI	K_2CO_3	dioxane	TBAB	1,10-Phen	52
7	CuI	K_2CO_3	DMF	TBAB	1,10-Phen	<5
8	CuI	K_2CO_3	CH_3CN	TBAB	1,10-Phen	<5
9	CuI	K_2CO_3	mesitylene	TBAB	1,10-Phen	51
10	$CuCl_2$	K_2CO_3	toluene	TBAB	1,10-Phen	56
11	CuBr	K_2CO_3	toluene	TBAB	1,10-Phen	30
12	CuI	K_2CO_3	toluene	TBAB	TM-Phen	26
13	CuI	K_2CO_3	toluene	TBAB	Bipyridine	39
14	CuI	K_2CO_3	toluene	TBAB	DACH	<5
15	CuI	K_2CO_3	toluene	Bu_4NOAc	1,10-Phen	<5
16	CuI	K_2CO_3	toluene	Et_4NBr	1,10-Phen	61
17	CuI	K_2CO_3	toluene	TBAB	1,10-Phen	52[c]
18	/	K_2CO_3	toluene	TBAB	1,10-Phen	<5
19	CuI	K_2CO_3	toluene	/	1,10-Phen	50
20	CuI	K_2CO_3	toluene	TBAB	/	30
21	CuI	K_2CO_3	toluene	TBAB	1,10-Phen	25[d]

[a] Reaction conditions: **1a** (0.25 mmol), [Cu] (10 mol%), ligand (20 mol%), base (3.0 equiv.) and additive (1.4 equiv.) in solvent (1 mL), for 10 h, at 100 °C, open to air, dried through a calcium chloride tube. DACH = diaminocyclohexane, 1,10-Phen = 1,10-phenanthroline, TBAB = tetra-*n*-butylammonium bromide, TM-Phen = 3,4,7,8-tetramethyl-1,10-phenanthroline. [b] Isolated yields. [c] At 90 °C. [d] Under nitrogen.

Table 2 Substrate scope for the synthesis of *N*-alkyl substituted isatins[a]



Entry	R	Alkyl	Time (h)	Product	Yield[b] (%)
1	H	Bn	8	**3a**	74
2		Me	8	**3b**	67
3		*n*-C_3H_7	12	**3c**	64
4		*n*-C_4H_9	12	**3d**	61
5		$Me(CH_2)_{11}$	16	**3e**	58
6		*i*-Pr	12	**3f**	75
7		*c*-Pr	6	**3g**	69
8[c]		*c*-Hex	12	**3h**	68
9		Allyl	8	**3i**	72
10		$BnCH_2$	8	**3j**	50
11		Furan-2-ylmethyl	4	**3k**	69
12		$HOCH_2CH_2$	4	**3l**	60
13	5-OMe	Bn	6	**3m**	61
14	4,5-diOMe	Bn	6	**3n**	65
15	4,5-diOMe	*n*-C_4H_9	16	**3o**	46
16	5-OTs	Bn	2	**3p**	57
17	H	Ph	10	**4a**	27

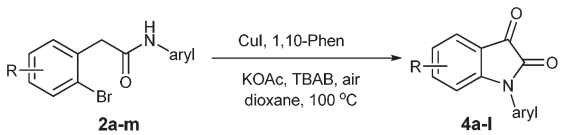
[a] Reagents and conditions: **1** (0.25 mmol), CuI (10 mol%), 1,10-Phen (20 mol%), K_2CO_3 (3.0 equiv.) and TBAB (1.4 equiv.) in toluene (2 mL), under air, at 100 °C, dried through a calcium chloride tube. [b] Isolated yields. [c] At 120 °C in *o*-xylene (2 mL).

copper resources (entries 10 and 11), ligands (entries 12–14), additive (entries 15 and 16) and temperature (entry 17) revealed that the use of TBAB as an additive in toluene at 100 °C under air is the best choice, and afforded **3a** in 74% yield (entry 5). Trace amounts of isatin product were detected in the absence of CuI (entry 18), and a decreased yield could be afforded without using an additive (entry 19) or a ligand (entry 20), which indicated that both the catalyst and ammonium salt were crucial for this oxidative cyclization reaction.[21e,22] The reaction became sluggish under nitrogen and a low yield was obtained (entry 21).

With the optimized reaction conditions in hand, we then extended the reaction to the synthesis of a range of *N*-alkyl substituted isatins. As illustrated in Table 2, a wide variety of substitution patterns and functionalities are tolerated. Substrates bearing *N*-alkyl or cycloalkyl substituents reacted smoothly, and afforded the corresponding isatins in moderate to good yields (**3a–3p**). A slight decrease in the yield of the isatins was observed when the aliphatic chain length on the *N*-substituent was varied (**3b–3e**). Employment of the *N*-isopropyl substrate performed well and gave **3f** in 75% yield. The *N*-cycloalkyl group containing substrates with various ring sizes participated smoothly in the reaction with comparable efficiency (**3g** and **3h**), although elevated temperature was needed for the substrate with a cyclohexyl group (**3h**); the reason may be due to its steric factor and resulted in a lower reactivity in this reaction. Substrates bearing benzyl (**3a**), allyl (**3i**), phenethyl (**3j**) or furfuryl (**3k**) groups illustrated better reactivities in this reaction, and produced isatins efficiently. Substrate **1l** with hydroxy functionality was readily incorporated and produced **3l** selectively in good yield, without observing any by-products *via* the intra- or inter-molecular nucleophilic attack of oxygen. Remarkably clean reactions were observed with the functionalized molecules bearing methoxyl (**3m** and **3n**) or tosyl (**3p**) substitutions on the aryl ring, whereas in the case of the *N*-butyl group the attached substrate gave a slightly complicated reaction (**3o**). However, when 2-(2-bromophenyl)-*N*-phenylacetamide (**2a**) was used under the optimized reaction, only 27% yield of the desired isatin product (**4a**) could be generated (entry 17).

To address this limitation and further explore the generality and scope of this approach, an extensive screening of copper catalysts and ligands together with solvents, bases and additives was carried out next, and we found that *N*-phenyl substituted isatin product **4a** could be achieved in the presence of CuI, 1,10-Phen and TBAB using 3.0 equivalents of KOAc as the base in dioxane (see Table S1 in the ESI† for details). Under the optimized conditions, the reaction proceeded smoothly and a series of *N*-aryl containing substrates could be tolerated as shown in Table 3. Substrates containing electron-donating (**4b–4g**), or bearing *ortho*- (**4b** and **4c**), *meta*- (**4d**), and *para*- groups (**4e–4g**) proceeded efficiently with moderate to good yields. However, substrates with electron-withdrawing groups showed relatively low reactivity (**4h–4j**). The reaction was not limited to simple benzene-containing

Table 3 Substrate scope for the synthesis of *N*-aryl substituted isatins[a]



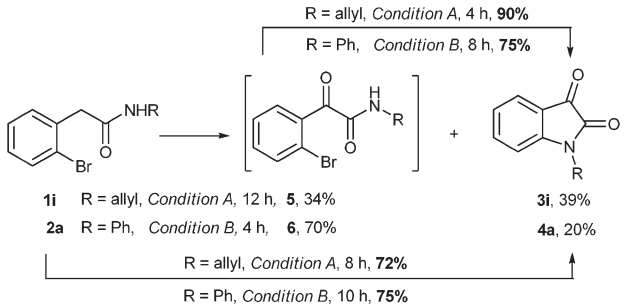
Entry	R	Aryl	Time (h)	Product	Yield[b] (%)
1	H	Ph	10	**4a**	75
2	H	2-MeC_6H_4	10	**4b**	47
3	H	2-$OMeC_6H_4$	10	**4c**	47
4	H	3-MeC_6H_4	10	**4d**	61
5	H	4-MeC_6H_4	10	**4e**	64
6	H	4-$OMeC_6H_4$	10	**4f**	64
7	H	4-$OEtC_6H_4$	10	**4g**	62
8	H	4-BrPh	12	**4h**	33
9	H	4-ClPh	12	**4i**	34
10	H	4-$CO_2EtC_6H_4$	12	**4j**	23
11	H	Naphthalen-1-yl	6	**4k**	61
12	5-OMe	Ph	6	**4l**	51
13[c]	H	Ph	12	**4a**	14

[a] Reagents and conditions: acetamide (0.25 mmol), CuI (10 mol%), 1,10-Phen (20 mol%), KOAc (3.0 equiv.) and TBAB (1.4 equiv.) in 1,4-dioxane (2 mL), under air, at 100 °C, dried through a calcium chloride tube. [b] Isolated yields. [c] 2-(2-Chlorophenyl)-*N*-phenylacetamide (**2m**) was used.

aromatics, but the naphthyl substrate also gave the desired product in 61% yield (**4k**) and substitution on the aryl ring was also tolerated during the reaction (**4l**). It should be noted that the less reactive chloro-substituted substrate, 2-(2-chlorophenyl)-*N*-phenylacetamide (**2m**), gave product **4a** in only 14% yield (entry 13). Furthermore, when we used **1a** as the substrate under these conditions, a 52% yield of **3a** was isolated.

To clarify the mechanism, the reaction intermediate **5** was isolated in 34% yield after reacting for 12 h from *N*-allyl substituted amide **1i** under Conditions A, together with 39% isolated yield of isatin product **3i** (Scheme 2). Furthermore, the isolated intermediate **5** could be further transformed to **3i** in 90% yield under the same conditions. The two-step reaction could afford isatin **3i** in about 70% overall yield from **1i**, which is comparable with the result of the one-step reaction in 72% yield (Table 2, entry 9). Similarly, for the formation of *N*-phenyl substituted isatins, compound **6** could be the key intermediate during the reaction under Conditions B (Scheme 2). Based on these results, we envisioned that the benzylic oxidation followed by the cyclic amidation process is the major pathway to afford the target isatins.

In conclusion, we have developed an efficient method for the straightforward synthesis of *N*-substituted isatins from easily accessible arylacetamides. A wide range of electronically and structurally varied nitrogen fragments could be introduced through this tandem C–O/C–N bond-forming process. Compared with other reported methods, the current approach provides a very simple and convenient route. The produced *N*-substituted isatins and their derivatives are present as the key structural motif in many marketed drugs, and will find their application in medicinal chemistry. Further studies on the substrate scope and synthetic



[a] Conditions A: CuI (10 mol%), 1,10-Phen (20 mol%), K_2CO_3 (3.0 equiv) and TBAB (1.4 equiv) in toluene (2 mL), at 100 °C, under air. Conditions B: CuI (10 mol%), 1,10-Phen (20 mol%), KOAc (3.0 equiv), and TBAB (1.4 equiv) in dioxane (2 mL), at 100 °C, under air.

Scheme 2 Formation of *N*-substituted isatins.[a]

applications for bioactive compounds are currently under investigation in our laboratory and will be reported in due course.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 21272149) for financial support of this work. The authors thank Prof. Hongmei Deng (Laboratory for Microstructures, SHU) for NMR support.

Notes and references

1 For selective reviews on bioactivity of isatins, see: (*a*) J. F. M. Da Silva, S. J. Garden and A. C. Pinto, *J. Braz. Chem. Soc.*, 2001, **12**, 273; (*b*) S. N. Pandeya, S. Smitha, M. Jyoti and S. K. Sridhar, *Acta Pharm.*, 2005, **55**, 27; (*c*) K. L. Vine, L. Matesic, J. M. Locke, M. Ranson and D. Skropeta, *Anti-Cancer Agents Med. Chem.*, 2009, **9**, 397; (*d*) G. S. Singh and Z. Y. Desta, *Chem. Rev.*, 2012, **112**, 6104.

2 (*a*) W. C. Sumpter, *Chem. Rev.*, 1944, **34**, 393; (*b*) F. D. Popp, *Adv. Heterocycl. Chem.*, 1975, **18**, 1; (*c*) M. G. A. Shvekhgeimer, *Chem. Heterocycl. Compd.*, 1996, **32**, 249.

3 (*a*) X. K. Wee, W. K. Yeo, B. Zhang, V. B. C. Tan, K. M. Lim, T. E. Tay and M.-L. Go, *Bioorg. Med. Chem.*, 2009, **17**, 7562; (*b*) V. R. Solomon, C. Hu and H. Lee, *Bioorg. Med. Chem.*, 2009, **17**, 7585.

4 F. Palluotto, A. Carotti, G. Casini, F. Campagna, G. Genchi, M. Rizzo and S. G. B. De, *Bioorg. Med. Chem.*, 1996, **4**, 2091.

5 V. S. Pawar, D. K. Lokwani, S. V. Bhandari, K. G. Bothara, T. S. Chitre, T. L. Devale, N. S. Modhave and J. K. Parikh, *Med. Chem. Res.*, 2011, **20**, 370.

6 M. E. Matheus, F. d. A. Violante, S. J. Garden, A. C. Pinto and P. D. Fernandes, *Eur. J. Pharmacol.*, 2007, **556**, 200.

7 (*a*) A. H. Abdel-Rahman, E. M. Keshk, M. A. Hanna and S. M. El-Bady, *Bioorg. Med. Chem.*, 2004, **12**, 2483; (*b*) A. Patel, S. Bari, G. Talele, J. Patel and M. Sarangapani, *Iran. J. Pharm. Res.*, 2006, **5**, 249.

8 A. Andreani, S. Burnelli, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, L. Varoli, M. A. Cremonini, G. Placucci, R. Cervellati and E. Greco, *Eur. J. Med. Chem.*, 2010, **45**, 1374.

9 L.-R. Chen, Y.-C. Wang, Y. W. Lin, S.-Y. Chou, S.-F. Chen, L. T. Liu, Y.-T. Wu, C.-J. Kuo, T. S.-S. Chen and S.-H. Juang, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3058.
10 (*a*) O. L. Erdmann, *J. Prakt. Chem.*, 1840, **19**, 321; (*b*) A. Laurent, *Ann. Chim. Phys.*, 1840, **3**, 393.
11 D. D. Bhragual, N. Kumar and S. Drabu, *J. Chem. Pharm. Res.*, 2010, **2**, 345.
12 (*a*) P. Y. S. Lam, G. Vincent, C. G. Clark, S. Deudon and P. K. Jadhav, *Tetrahedron Lett.*, 2001, **42**, 3415; (*b*) M. J. Konkel, M. Packiarajan, H. Chen, U. P. Topiwala, H. Jimenez, I. J. Talisman, H. Coate and M. W. Walker, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3950; (*c*) M. G. Bursavich, A. M. Gilbert, S. Lombardi, K. E. Georgiadis, E. Reifenberg, C. R. Flannery and E. A. Morris, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5630; (*d*) R. Romagnoli, P. G. Baraldi, O. Cruz-Lopez, D. Preti, J. Bermejo and F. Estévez, *ChemMedChem*, 2009, **4**, 1668.
13 D. M. T. Chan, *Tetrahedron Lett.*, 1996, **37**, 9013.
14 M. M. Hossain, R. M. Islam, S. K. Saha and M. K. Islam, *Tetrahedron Lett.*, 2010, **51**, 1155.
15 D. C. Rogness and R. C. Larock, *J. Org. Chem.*, 2011, **76**, 4980.
16 (*a*) A. V. Shindikar, F. Khan and C. L. Viswanathan, *Eur. J. Med. Chem.*, 2006, **41**, 786; (*b*) P. Moser, A. Sallmann and I. Wiesenberg, *J. Med. Chem.*, 1990, **33**, 2358; (*c*) R. Sarges, H. R. Howard, B. K. Koe and A. Weissman, *J. Med. Chem.*, 1989, **32**, 437.
17 S. Chen, Z. Liu, E. Shi, L. Chen, W. Wei, H. Li, Y. Cheng and X. Wan, *Org. Lett.*, 2011, **13**, 2274.
18 J. S. Yadav, B. V. S. Reddy, C. S. Reddy and A. D. Krishna, *Synthesis*, 2007, 693.
19 B.-X. Tang, R.-J. Song, C.-Y. Wu, Y. Liu, M.-B. Zhou, W.-T. Wei, G.-B. Deng, D.-L. Yin and J.-H. Li, *J. Am. Chem. Soc.*, 2010, **132**, 8900.
20 For some examples using Pd: (*a*) J. P. Wolfe, R. A. Rennels and S. L. Buchwald, *Tetrahedron*, 1996, **52**, 7525; (*b*) B. H. Yang and S. L. Buchwald, *Org. Lett.*, 1999, **1**, 35; (*c*) A. van den Hoogenband, J. A. J. den Hartog, J. H. M. Lange and J. W. Terpstra, *Tetrahedron Lett.*, 2004, **45**, 8535; (*d*) R. R. Poondra and N. J. Turner, *Org. Lett.*, 2005, **7**, 863; (*e*) Y. Kitamura, A. Hashimoto, S. Yoshikawa, J.-I. Odaira, T. Furuta, T. Kan and K. Tanaka, *Synlett*, 2006, 115; (*f*) K. Flyrén, L. O. Bergquist, V. M. Castro, C. Fotsch, L. Johansson, D. J. St. Jean Jr, L. Sutin and M. Williams, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3421. For some examples using Cu: (*g*) T. Kukosha, N. Trufilkina and M. Katkevics, *Synlett*, 2011, 2525; (*h*) R. Harada, N. Nishida, S. Uchiito, Y. Onozaki, N. Kurono, H. Senboku, T. Masao, T. Ohkuma and K. Orito, *Eur. J. Org. Chem.*, 2012, 366; (*i*) T. Kukosha, N. Trufilkina, S. Belyakov and M. Katkevics, *Synthesis*, 2012, **44**, 2413. For an example using Ag: (*j*) M. Kawase, T. Kitamura and Y. Kikugawa, *J. Org. Chem.*, 1989, **54**, 3394.
21 (*a*) C. Sun and B. Xu, *J. Org. Chem.*, 2008, **73**, 7361; (*b*) W. Ye, J. Mo, T. Zhao and B. Xu, *Chem. Commun.*, 2009, 3246; (*c*) T.-K. Zhao and B. Xu, *Org. Lett.*, 2010, **12**, 212; (*d*) C. Wang, C. Sun, F. Weng, M. Gao, B. Liu and B. Xu, *Tetrahedron Lett.*, 2011, **52**, 2984; (*e*) J. Shao, X. Huang, S. Wang, B. Liu and B. Xu, *Tetrahedron*, 2012, **68**, 573; (*f*) J. Shao, X. Huang, X. Hong, B. Liu and B. Xu, *Synthesis*, 2012, **44**, 1798; (*g*) B. Liu, X. Hong, D. Yan, S. Xu, X. Huang and B. Xu, *Org. Lett.*, 2012, **14**, 4398; (*h*) S. Xu, X. Huang, X. Hong and B. Xu, *Org. Lett.*, 2012, **14**, 4614; (*i*) G. Li, Z. Ding and B. Xu, *Org. Lett.*, 2012, **14**, 5338.
22 B. Orlińska, J. Zawadiak and D. Gilner, *Appl. Catal., A*, 2005, **287**, 68.