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Palladium on Carbon-Catalyzed Chemoselective Oxygen Oxidation of Aromatic Acetals

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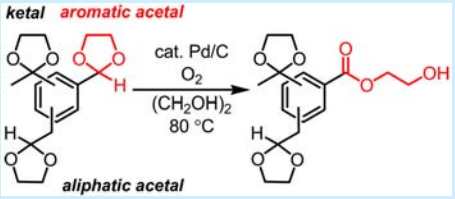
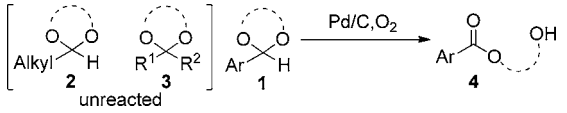
Supporting Information

ABSTRACT: The development of an unprecedented chemoselective transformation has contributed to forming a novel synthetic process for target molecules. Chemoselective oxidation of aromatic acetals has been accomplished using a reusable palladium on carbon catalyst under atmospheric oxygen conditions to form ester derivatives with tolerance of aliphatic acetals and ketals.



Direct transformation methods that display novel chemoselectivity are crucially important to synthesize target molecules in fewer steps. Acetals and ketals are widely utilized as protected carbonyl compounds and generally transformed into various functionalities via the acid-mediated formation of oxonium ion intermediates.[1] Nevertheless ketals preferentially undergo various transformations such as deprotection in the presence of acetals because of the added stability of their oxonium ion intermediates.[1] Fujioka and Kita have also pioneered the chemoselective transformation of acetals via the specific formation of pyridinium-type salts mediated by stoichiometic silyl triflates and an adequate pyridine derivative.[2] Significantly, this method tolerates ketals, permitting the efficient synthesis of target molecules in fewer steps. Nevertheless, a catalytic method with the ability to distinguish between acetals and ketals has not been accomplished, and the development of an unprecedented chemoselective transformation of aromatic versus aliphatic acetals is still challenging. On the other hand, various oxidative cleavages of cyclic acetals into hydroxyalkyl esters have been widely developed using stoichiometric oxidants [*tert*-butyl hydroperoxide (TBHP) with transition metals,[3] TBHP/pyridinium dichromate,[4] TBHP/iodine(III) compound,[5] *o*-iodoxybenzoic acid/Et_4NBr,[6] PhI(OAc)$_2$/LiBr,[7] $KMnO_4$,[8] ozone,[9] oxone,[10] *N*-hydroxyphthalimide,[11] NaOCl,[12] electrophilic halogens,[13] *m*-chloroperoxybenzoic acid,[14] dimethyldioxirane,[15] and hydrogen peroxide[16]] because of the utility of the generated hydroxyalkyl esters as synthetic precursors, such as in cross-linking of polyesters[17] and the site-selecitve Diels–Alder reaction.[18] Additionally, the hydroxyalkyl ester moiety is known to be a useful structural unit of an active hypolipidemic agent.[19] The clean oxidation of cyclic acetals under atmospheric molecular oxygen conditions is particularly attractive from the viewpoint of environmental and economic considerations.[20] However, these reaction conditions never control the chemoselectivity between aromatic and aliphatic cyclic acetals, which are equally oxidized to the corresponding hydroxyalkyl esters. Furthermore, the heterogeneously catalyzed method and the chemoselective oxidation of an acetal function in the presence of acid-labile ketals have not been reported. We now report a novel chemoselective oxygen oxidation of aromatic cyclic acetals **1** bearing benzylic C–H bonds into hydroxyalkyl ester derivatives **4** in the presence of aliphatic acetals **2** or ketals **3** using reusable Pd/C as a catalyst (Scheme 1).

Scheme 1. Palladium on Carbon-Catalyzed Chemoselective Oxygen Oxidation of Aromatic Acetals 1 to Hydroxylalkyl Esters 4



We initially investigated the catalyst and solvent efficiencies of the oxidation of five-membered cyclic acetal **1a** derived from benzaldehyde and ethylene glycol as an aromatic acetal using 5 mol % catalyst under atmospheric oxygen at 80 °C for 6 h (Table 1). The desired benzoic acid hydroxyethyl ester (**4a**) was obtained using either 10% Pd/C or 10% Pt/C in MeOH in high yield (entries 1 and 2), while Rh/C, Ru/C, and Au/C were inefficient (entries 3–5). Ethylene glycol was also an efficient solvent, giving **4a** in 85% yield (entry 6). Because some reactions in MeOH using other substrates (as shown in Table 2) gave the corresponding aromatic aldehyde dimethyl acetals as byproducts by transacetalization, ethylene glycol proved to be a better solvent. *i*-PrOH and THF were inadequate solvents (entries 7 and 8), and the reaction in H_2O gave benzoic acid via hydrolysis of **4a** (entry 9). The 20-fold scale-up reaction of **1a** (5 mmol) under the optimized reaction conditions using 10% Pd/C in ethylene glycol (entry 6) could also be successfully performed to give **4a** in 84% yield (entry 10). Reuse of the catalyst is important from the viewpoint of green sustainable chemistry and cost performance. The 10% Pd/C can be reused several times after simple filtration, a wash with H_2O and

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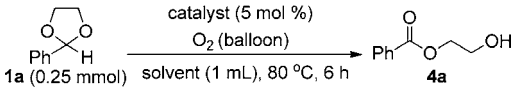
Table 1. Catalyst and Solvent Effects



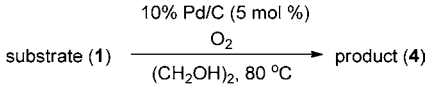
entry	catalyst	solvent	yield (%) SM (1a)	4a
1	10% Pd/C	MeOH	0	88
2	10% Pt/C	MeOH	0	70
3	10% Rh/C	MeOH	16	0
4	10% Ru/C	MeOH	2	0
5	10% Au/C	MeOH	3	4
6	10% Pd/C	$(CH_2OH)_2$	0	85
7	10% Pd/C	*i*-PrOH	53	37
8	10% Pd/C	THF	45	43
9	10% Pd/C	H_2O	0	0
10[a]	10% Pd/C	$(CH_2OH)_2$	0	84
11[b,c]	10% Pd/C	$(CH_2OH)_2$	0	82
12[b,d]	10% Pd/C	$(CH_2OH)_2$	0	84
13[e]	10% Pd/C	$(CH_2OH)_2$	17	69
14[f]	10% Pd/C	$(CH_2OH)_2$	0	86
15[g]	10% Pd/C	$(CH_2OH)_2$	51	31
16[h]	10% Pd/C	$(CH_2OH)_2$	0	84
17[i]	10% Pd/C	$(CH_2OH)_2$	4	82
18[j]	10% Pd/C	$(CH_2OH)_2$	0	86

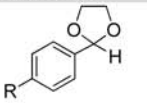
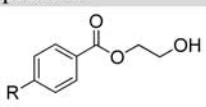
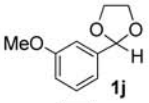
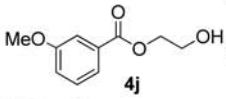
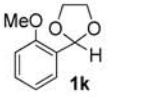
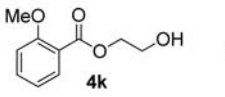
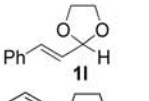
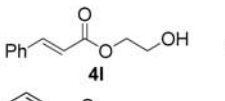
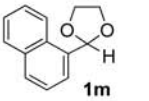
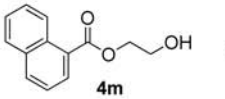
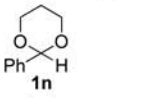
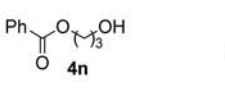
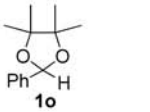
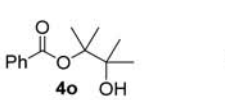
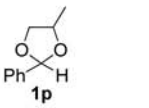
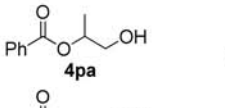
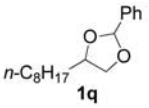
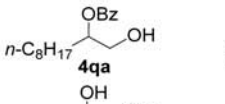
[a]5 mmol of **1a** was used. [b]10% Pd/C was reused after simple filtration, washing with H_2O and MeOH, and drying in vacuo. In each run, 95–99% of the Pd/C could be recovered. [c]Second use of 10% Pd/C after the reaction in entry 6. [d]Third use of 10% Pd/C after the reaction in entry 11. [e]For 1 h. [f]For 3 h. [g]At room temperature. [h]At 60 °C. [i]Under air. [j]1 mol % of 10% Pd/C was used.

MeOH, and drying (entries 11 and 12). During the present oxidation, no Pd leaching into the reaction solution was observed by inductively coupled plasma–optical emission spectrometry (ICP-OES) analysis (see the Supporting Information). Further experiments revealed that the oxidation using 10% Pd/C (5 mol %) in ethylene glycol was complete within 3 h (entry 6 vs entries 13 and 14) and could effectively proceed even at 60 °C (entry 6 vs entries 15 and 16). The desired oxidation could be performed under air (entry 17), and a decrease in the catalyst loading to 1 mol % did not influence the reaction efficiency, giving **4a** in good yield (entry 18).[21]

The scope of substrates bearing a benzylic C–H bond was next investigated (Table 2). Various aromatic five-membered cyclic acetals **1b–h** bearing electron-donating or electron-withdrawing groups at the *para* position of each aromatic nucleus efficiently underwent oxygen oxidation to give the corresponding esters **4b–h** in good to excellent yields (entries 1–7). Substrate **1i** bearing an aromatic bromide moiety could also be oxidized into the corresponding ester product **4i** in good yield, but a small amount of debrominated product **4a** was obtained (entry 8). Moreover, **1j** and **1k** bearing a methoxy group at the *meta* and *ortho* positions, respectively, were converted into the desired ester products in efficient yields (entries 9 and 10). The oxidation of **1l** derived from cinnamaldehyde also proceeded effectively to provide α,β-unsaturated ester **4l** (entry 11). Naphthalene derivative **1m** could also be transformed into the corresponding ester **4m** (entry 12). Furthermore, the present oxidation method was applicable to other types of aromatic cyclic acetals bearing 1,3-dioxane (**1n**), 4,4,5,5-tetramethyldioxolane (**1o**), and unsymmetrical dioxolanes derived from benzaldehyde (**1p** and **1q**) to

Table 2. Scope of Substrates



entry	substrate	product	yield[d] (time)
			
1	R = OMe (**1b**)	**4b**	quant (6 h)
2	R = CF_3 (**1c**)	**4c**	85% (9 h)
3	R = CO_2Me (**1d**)	**4d**	92% (6 h)
4	R = NO_2 (**1e**)	**4e**	54% (24 h) [42%][a]
5	R = CH_2OH (**1f**)	**4f**	53% (6 h)
6	R = CH_2OTBS (**1g**)	**4g**	58% (3 h)
7	R = CH_2OAc (**1h**)	**4h**	61% (6 h)
8[b]	R = Br (**1i**)	**4i** / **4a**	51% / 6% (6 h) [24%][a]
9			91% (9 h)
10			77% (12 h)
11			82% (12 h)[c]
12			79% (12 h)
13			60% (6 h)
14			79% (6 h)
15			41% / 49% (6 h)
16			60% / 28% (6 h)

[a]Recovered yield of the starting material. [b]At 120 °C (the reaction hardly proceeded at 80 °C). [c]The formation of an inseparable reduced product of the olefin moiety was observed. See the Supporting Information. [d]Substrates were completely consumed except for entries 4 and 8. Bz: benzoyl.

give the corresponding esters in good yields (entries 13–16). However, regiocontrolled cleavage of the unsymmetrical dioxolanes **1p** and **1q** was extremely difficult, and mixtures of regioisomers (**4pa**/**4pb** and **4qa**/**4qb**) were obtained (entries 15 and 16).

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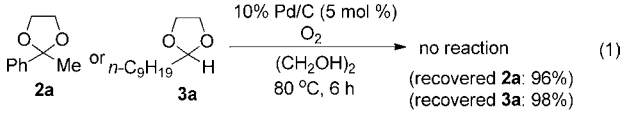
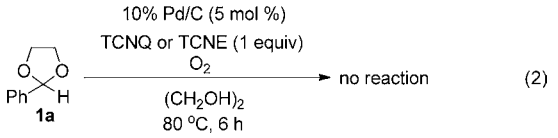
It is noteworthy that a ketal (**2a**) and an aliphatic acetal (**3a**) did not undergo the present oxidation and remained unchanged (eq 1). Since the reaction of **1a** was completely inhibited by the

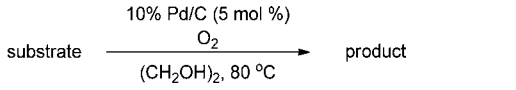


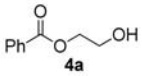
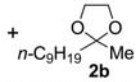
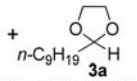
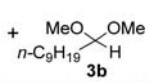
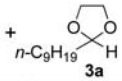
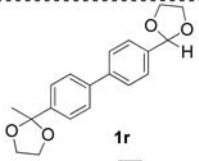
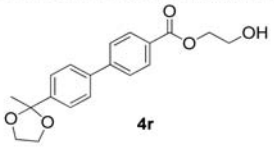
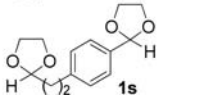
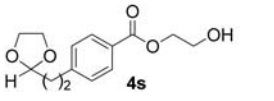


addition of 7,7,8,8-tetracyanoquinodimethane (TCNQ) or tetracyanoethylene (TCNE) as a radical scavenger (eq 2), the present oxidation of aromatic acetals probably proceeds via a benzylic radical intermediate, which is known to be comparatively stable, formed by C−H activation of the benzylic C−H bonds.[20b−e] The detailed elucidation of the reaction mechanism is under investigation.

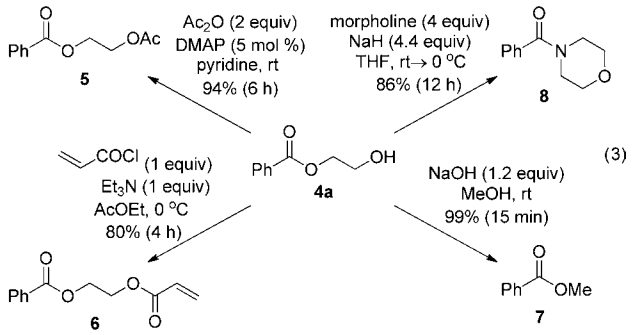
Encouraged by the unprecedented chemoselectivities shown in eq 1, we carried out the selective oxidation of aromatic acetals in the presence of aliphatic acetals or ketals (Table 3). The Pd/C-catalyzed oxygen oxidation of **1a** to give **4a** could be selectively performed without any transformation of the aromatic and aliphatic cyclic ketals **2a** and **2b** (entries 1 and 2). The aliphatic cyclic acetal **3a** was perfectly unchanged during the oxidation of **1a** to **4a** (entry 3). The aliphatic aldehyde dimethyl acetal **3b** was transformed into the five-membered cyclic acetal **3a** by transacetalization with ethylene glycol (entry 4). The present chemoselectivities could be realized by the use of substrates bearing an aromatic acetal and an aliphatic acetal or ketal in the same molecule, as the aromatic acetal moieties in **1r** and **1s** were selectively transformed into the corresponding ester products **4r** and **4s** in good yields with tolerance of the ketal and aliphatic acetal units (entries 5 and 6).

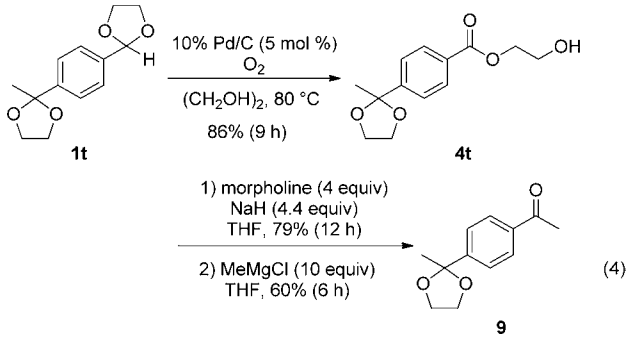
Table 3. Chemoselective Reaction of Aromatic Acetals



entry	substrate	product	yield (time)
1			86%
	+ 	recovered **2a**	86% (6 h)
2	**1a**	**4a**	77%
	+ 	recovered **2b**	93% (6 h)
3	**1a**	**4a**	78%
	+ 	recovered **3a**	quant (6 h)
4	**1a**	**4a**	71%
	+ 	+ 	97% (6 h)
5			88% (24 h)
6			65% (36 h)

The obtained hydroxyalkyl ester **4a** effectively underwent esterification (acetylation or acryloylation) to give **5** or **6** as unsymmetrical compounds bearing an ethylene glycol as the basic framework structure (eq 3). The acrylated product can be





a useful backbone for constructing valuable functional materials, such as the dendritic polyethylene−cationic poly(*p*-phenylene ethynylene) polyvalent nanocarrier[22] and a biorenewable alternative for the glassy end blocks of the triblock copolymer.[23] Furthermore, transesterification using methanol and amidation using morpholine under basic conditions provided the corresponding methyl ester **7** and morpholine amide **8**,[24] respectively (eq 3). These reactions could be performed under basic conditions, which are inactive toward ketals.[1] Namely, the aromatic acetal moiety of **1t** could be chemoselectively transformed into a ketone (**9**) by consecutive Pd/C-catalyzed oxygen oxidation, amidation using morpholine, and methylation[24] using a Grignard reagent without the chemical conversion of the coexisting ketal moiety in the same molecule (eq 4). This type of transformation has never been accomplished as a general synthetic procedure via the acid-mediated transformation of acetals because ketals are preferentially deprotected into ketones under acidic conditions.[1]

We have developed an unprecedented catalytic and chemoselective transformation of aromatic cyclic acetals into the corresponding hydroxyalkyl ester derivatives in the presence of aliphatic cyclic acetals or ketals. The present mild and neutral oxidation method using oxygen as a clean oxidant and a

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reusable heterogeneous Pd/C catalyst is valuable from the viewpoint of green sustainable chemistry and provides a novel synthetic process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02833.

Typical procedures and spectroscopic data for the products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Wuts, P. G. M.; Greene, T. W. In *Greene's Protective Groups in Organic Synthesis*, 5th ed.; Wiley: Hoboken, NJ, 2014.

(2) For examples where acetals are deprotected or transformed selectively in the presence of ketals, see: (a) Fujioka, H.; Sawama, Y.; Murata, N.; Okitsu, T.; Kubo, O.; Matsuda, S.; Kita, Y. *J. Am. Chem. Soc.* **2004**, *126*, 11800−11801. (b) Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930−5938. (c) Fujioka, H.; Yahata, K.; Hamada, T.; Kubo, O.; Okitsu, T.; Sawama, Y.; Ohnaka, T.; Maegawa, T.; Kita, Y. *Chem. - Asian J.* **2012**, *7*, 367−373. (d) Fujioka, H.; Okitsu, T.; Ohnaka, T.; Li, R.; Kubo, O.; Okamoto, K.; Sawama, Y.; Kita, Y. *J. Org. Chem.* **2007**, *72*, 7898−7902. (e) Fujioka, H.; Okitsu, T.; Sawama, Y.; Ohnaka, T.; Kita, Y. *Synlett* **2006**, 3077−3080.

(3) (a) Hosokawa, T.; Imada, Y.; Murahashi, S. *J. Chem. Soc., Chem. Commun.* **1983**, *21*, 1245−1246. (b) Murahashi, S.; Oda, Y.; Naota, T. *Chem. Lett.* **1992**, *21*, 2237−2240. (c) Choudary, B. M.; Reddy, P. N. *Synlett* **1995**, 959−960.

(4) Chidambaram, N.; Bhat, S.; Chandrasekaran, S. *J. Org. Chem.* **1992**, *57*, 5013−5015.

(5) Sueda, T.; Fukuda, S.; Ochiai, M. *Org. Lett.* **2001**, *3*, 2387−2390.

(6) Kuhakarn, C.; Panchan, W.; Chiampanichayakul, S.; Samakkanad, N.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T. *Synthesis* **2009**, 929−934.

(7) Panchan, W.; Chiampanichayakul, S.; Snyder, D. L.; Yodbuntung, S.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Kuhakarn, C. *Tetrahedron* **2010**, *66*, 2732−2735.

(8) Nai-ju, H.; Liang-heng, X. *Synth. Commun.* **1990**, *20*, 1563−1567.

(9) Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651−3664.

(10) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Synlett* **1999**, 777−779.

(11) Masui, M.; Kawaguchi, T.; Yoshida, S.; Ozaki, S. *Chem. Pharm. Bull.* **1986**, *34*, 1837−1839.

(12) (a) Sugai, S.; Kodama, T.; Akaboshi, S.; Ikegami, S. *Chem. Pharm. Bull.* **1984**, *32*, 99−105. (b) Gonsalvi, L.; Arends, I. W. C. E.; Moilanen, P.; Sheldon, R. A. *Adv. Synth. Catal.* **2003**, *345*, 1321−1328.

(13) Mingotaud, A.-F.; Florentin, D.; Marquet, A. *Synth. Commun.* **1992**, *22*, 2401−2404.

(14) (a) Luzzio, F. A.; Bobb, R. A. *Tetrahedron Lett.* **1997**, *38*, 1733−1736. (b) Kim, J. Y.; Rhee, H.; Kim, M. *J. Korean Chem. Soc.* **2002**, *46*, 479−483.

(15) (a) Meng, S.-S.; Liang, Y.; Cao, K.-S.; Zou, L.; Lin, X.-B.; Yang, H.; Houk, K. N.; Zheng, W.-H. *J. Am. Chem. Soc.* **2014**, *136*, 12249−12252. (b) Mycock, D. K.; Sherlock, A. E.; Glossop, P. A.; Hayes, C. J. *Tetrahedron Lett.* **2008**, *49*, 6390−6392.

(16) Espenson, J. H.; Zhu, Z.; Zauche, T. H. *J. Org. Chem.* **1999**, *64*, 1191−1196.

(17) Babler, J. H.; Coghlan, M. J. *Tetrahedron Lett.* **1979**, *20*, 1971−1974.

(18) Clapham, G.; Shipman, M. *Tetrahedron Lett.* **1999**, *40*, 5639−5642.

(19) (a) Takashima, K.; Ohyama, K.; Mori, T.; Takeyama, S. *Biochem. Pharmacol.* **1978**, *27*, 2631−2635. (b) Takashima, K.; Takeyama, S. *Biochem. Pharmacol.* **1978**, *27*, 2637−2639.

(20) (a) Yamaguchi, T.; Kudo, Y.; Hirashima, S.; Yamaguchi, E.; Tada, N.; Miura, T.; Itoh, A. *Tetrahedron Lett.* **2015**, *56*, 1973−1975. (b) Karimi, B.; Rajabi, J. *Synthesis* **2003**, 2373−2377. (c) Karimi, B.; Rajabi, J. *J. Mol. Catal. A: Chem.* **2005**, *226*, 165−169. (d) Chen, Y.; Wang, P. G. *Tetrahedron Lett.* **2001**, *42*, 4955−4958. (e) Li, P.; Alper, H. *Can. J. Chem.* **1993**, *71*, 84−89.

(21) Other side products were not isolated.

(22) Zhang, L.; Huang, H.; Xu, N.; Yin, Q. *J. Mater. Chem. B* **2014**, *2*, 4935−4942.

(23) Wang, S.; Ding, W.; Yang, G.; Robertson, M. L. *Macromol. Chem. Phys.* **2016**, *217*, 292−303.

(24) Martin, R.; Romea, P.; Tey, C.; Urpi, F.; Vilarrasa, J. *Synlett* **1997**, 1414−1416.

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