Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective synthesis of *para*-quinone monoketals through tri-bromide (TBr) mediated oxidative dearomatization of phenols

Sushree Ranjan Sahoo, Debayan Sarkar *

Organic Synthesis and Molecular Engineering Laboratory, Department of Chemistry, National Institute of Technology, Rourkela, Odisha 769008, India

ARTICLE INFO

Article history:
Received 11 December 2019
Revised 14 January 2020
Accepted 16 January 2020
Available online xxxx

Keywords:
Stereoselective
Spiroquinone monoketal
Oxidative dearomatization
Tribromides

ABSTRACT

A metal free one-pot stereoselective synthesis of *para*-quinone monoketals and their derivatives has been reported in this present work. Tri-bromides (TBrs) have been employed as an effective reagent for intramolecular spirocyclizations leading to excellent yields of the monoketals. The TBrs are slowly turning out to be an important reagent for oxidative dearomatization which is further attested in the presented work. In addition, the obtained substituted *para*-quinone monoketals and their derivatives were readily transformed into more complex products by reaction with Pd/C under hydrogen atmosphere leading to saturated *para*-monoacetal, which are important building blocks in organic synthesis.

Introduction

Monoacetal i.e. masked *para* benzoquinones (MPBs) are efficient building blocks of various biologically and pharmaceutically active natural products. Some of these natural products are shown Fig. 1, which were synthesized from masked *para* benzoquinones as starting materials [1–3].

Recentll, Pansare and co-workers reported the total synthesis of (+)-fistulopsine B from 1,4-dioxaspiro[4.5]decan-8-one [1]. Previously, the same group also reported the formal synthesis of (+)-lasubine II and (−)-subcosine II *via* organocatalytic Michael addition of a ketone to α-nitrostyrene from 1,4-dioxaspiro[4.5] decan-8-one [2]. Danishefsky accomplished total synthesis of Jiadifenin molecule from 7-methyl-1,4-dioxaspiro[4.5]decan-8-one [3].

Masked benzoquinones (MBs), cyclohexa-2,4- and 2,5-dienones are thus attractive synthons. Transformations such as 1,2- and 1,4-additions, Diels–Alder reactions, sigmatropic rearrangement etc [4] are carried out on this benzoquinones. By far, oxidative dearomatization with *ortho*- and *para*-alkoxyphenols employing hypervalent iodine reagents have been the best possible strategies towards development of these MBs [4]. (Scheme 1a) Recently, Ishihara reported a chiral hypervalent iodine (III) catalyst in the presence of co-catalyst *meta*-chloroperbenzoic acid (*m*-CPBA) to generate Masked benzoquinones (MBs) [5]. The last decade has noted a rigorous application of hypervalent iodine reagents into dearomative spirooxacyclisation of phenols and naphthols towards generation of the spirocycles [6]. The problem retains with the development of a generalized arene-iodine catalyst which can be applied to a wide variety of substrate was mentioned by Harned [7]. Some marked reports in this direction comes from the groups of Ciufolini [8], Kita [9], Ishihara [10], Ibrahim [11] where hypervalent iodine reagents have been suitably employed to achieve varied spirooxacycles [10]. Preparation of hypervalent iodine reagents require presence of oxidative additives and are synthesized in multiple steps. There have been less successful attempts to develop metal free protocols towards such transformations. Previously, our group first recognized PTAB as an effective reagent for dearomatization of phenols [12]. (Scheme 1b) Based on our previous findings, we

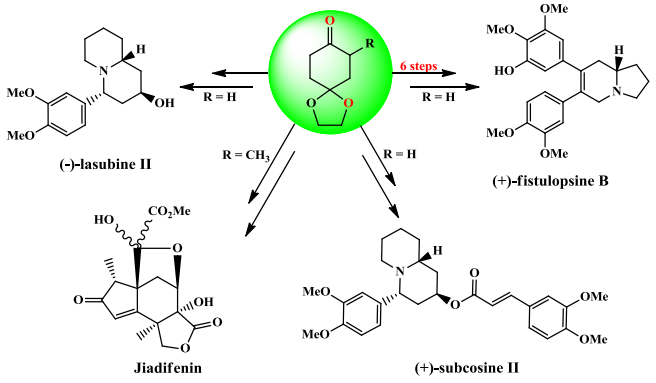
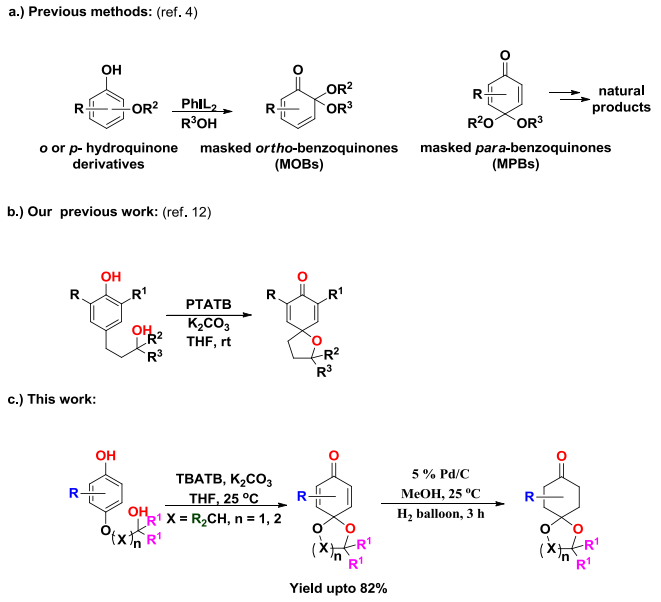


Fig. 1. Biologically important natural product synthesized from *para*-monoketals.

* Corresponding author.
E-mail address: sarkard@nitrkl.ac.in (D. Sarkar).

https://doi.org/10.1016/j.tetlet.2020.151646
0040-4039/



Scheme 1. Reaction design for the synthesis of MBs.

envisioned that our tri-bromide salts could be applied to the oxidative dearomatization of 4-alkoxy phenols at *para*-position for the generation of masked *para*-benzoquinones (MPBs). (Scheme 1c)

Results and discussion

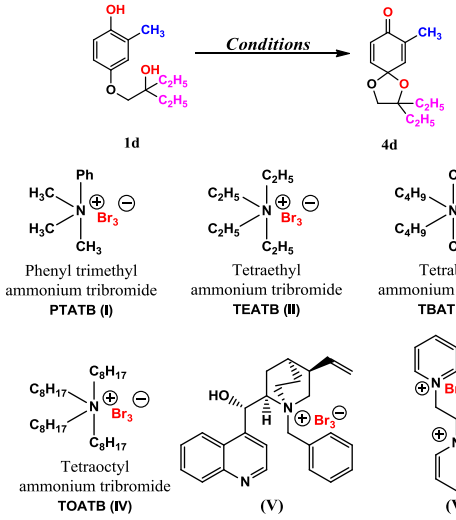
To start with, 4-(2-ethyl-2-hydroxybutoxy)-2-methylphenol 1d was chosen as a model substrate for the planned reaction. On exposure, the reaction mixture in the presence of PTATB (1 equiv), K_2CO_3 (1 equiv) as a base and CH_3CN as a solvent, delivered the desired 2,2-diethyl-7-methyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one 4d at 25 °C with 66% yield (Table 1, entry 1). On screening of different solvents, bases and TBrs towards the standardization of the experiments, it was observed that a combination of the TBATB, K_2CO_3 and THF as the solvent conveyed the best combination (Table 1, entry 12).

With the optimized reaction conditions in hand, a variety of substituted phenols underwent the same transformation which illustrated a wider substrate scope for the formation of *para*-1,4-quinone monoketals. The reaction has been quite general and delivered for a wide substrate scope of 2-hydroxyphenol. Different alkyl substituents on branch chain as well as substituents with electron-donating and withdrawing groups in different substituents of the aromatic ring smoothly afforded the desired products in high to excellent yields. Substituent like phenyl and benzyl on branch chain (R^1) did not deliver the desired compound due to enhanced steric hindrance. For *para*-1,4-quinone monoketals, the substrate scopes are illustrated in Table 2.

In order to further increase the substrate scope, the synthesis was further extended to *para*-1,5-quinone monoketals with optimized reaction conditions and in all cases we were able to found good yields. Different alkyl substituents on branch chain as well as alkyl substituents on aromatic ring were afforded good yields. For *para*-1,5-quinone monoketals, the substrate scope are illustrated in Table 3.

In order to investigate the stereoselectivity synthesis of *para*-1,4-quinone monoketals, we were explored racemic 4-((3-ethyl-3-hydroxypentan-2-yl)oxy)-2-methylphenol 3c, was use as a primary substrate to check the diastereoselectivity. On exploring the substrate 3c with PTATB, we were able to found that the diastereoselectivity of the product *para*-1,4-quinone monoketals

Table 1
Optimization of reaction conditions[a] for the formation of **4d**.



Entry No.	Solvent	TBr	Base	Yield (%)[b]
1	CH_3CN	I	K_2CO_3	66
2	DCM	I	K_2CO_3 / MeONa	< 55
3	DCE	I	K_2CO_3 / MeONa	> 55

Entry No.	Solvent	TBr	Base	Yield (%)[b]
1	CH_3CN	I	K_2CO_3	66
2	DCM	I	K_2CO_3/MeONa	<55
3	DCE	I	K_2CO_3/MeONa	>55
4	Dioxane	I	K_2CO_3/Cs_2CO_3	<72
5	MeOH	I	K_2CO_3	65
6	Et_2O	I	K_2CO_3/Na_2CO_3	>60
7	THF	I	MeONa/EtONa	<70
8	THF	I	Cs_2CO_3	65
9	THF	I	Pyridine	<55
10	THF	I	K_2CO_3	70
11	THF	II	K_2CO_3	62
12	THF	III	K_2CO_3	80
13	THF	IV	K_2CO_3	64
14	THF	V	K_2CO_3	68
15	THF	VI	K_2CO_3	62

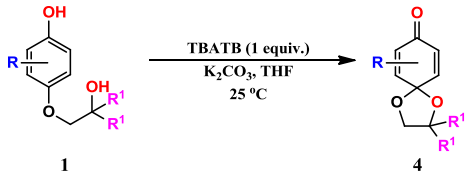
[a] Reaction conditions: 1d (0.2 mmol), Base (0.2 mmol), TBr (0.2 mmol), dry solvent (5 mL), for 12 h under a nitrogen atmosphere at 25 °C.
[b] Isolated yield after column chromatography.

(6c:6c'), with a ratio of 5:1 and overall yield of 70% (Table 4, entry-1). On screening of different tri-bromides, delivered TBATB (III) as the best choice and the overall yield of the product *para*-1,4-quinone monoketals (6c:6c') enhanced to 82% with good diastereoselectivity of ratio 8:1 (Table 4, entry 3).

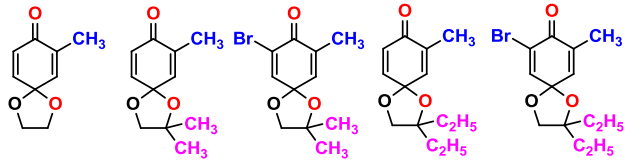
With the optimized reaction conditions in hand, different alkyl substituents on branch chain as well as substituents on aromatic ring were afforded good yields and good diastereoselectivity. Substituent like phenyl and benzyl on branch chain (R^2) did not deliver the desired compound due to enhanced steric hindrance but substituent like homo benzyl on branch chain (R^2), was delivered good diasterioselectivity 6e of ratio 20:1. If there is no substitution on branch chain (R^2), then there was a slight decrease in diasteriose-lectivity 6a of ratio 6:1. Interestingly, the seemingly stereoselective *para*-1,4-quinone monoketals could be easily separated in silica-gel chromatography. Here we report the major diastereomer as (3*R*,5*R*)/(3*S*,5*S*)-spiropara-quinone monoketal. The substrate scope for the stereoselective synthesis of *para*-1,4-quinone monoketals were illustrated in Table 5.

Please cite this article as: S. R. Sahoo and D. Sarkar, Stereoselective synthesis of *para*-quinone monoketals through tri-bromide (TBr) mediated oxidative dearomatization of phenols, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2020.151646

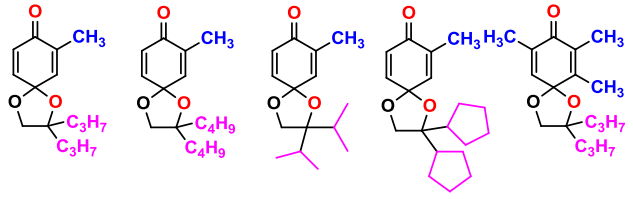
Table 2
Substrate scope for synthesis of *para*-1,4-quinone monoketals.



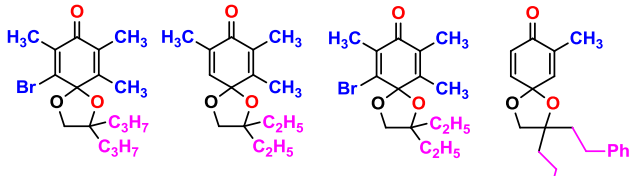
1 4



4a, 73% **4b**, 80% **4c**, 77% **4d**, 80% **4e**, 75%

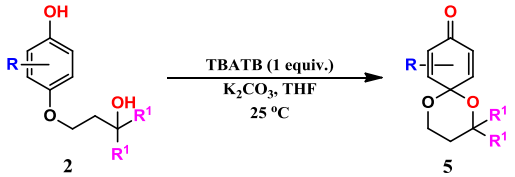


4f, 78% **4g**, 78% **4h**, 75% **4i**, 72% **4j**, 76%

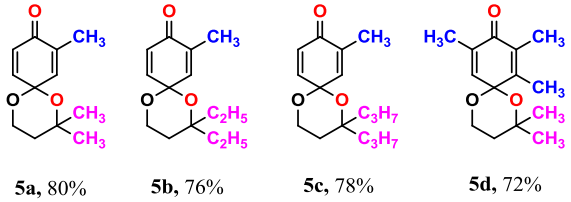


4k, 79% **4l**, 80% **4m**, 78% **4n**, 80%

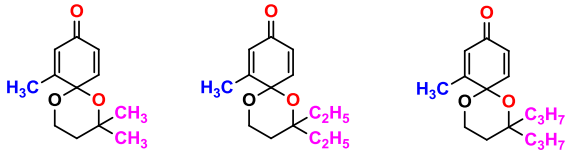
Table 3
Substrate scope for synthesis of *para*-1,5-quinone monoketals.



2 5

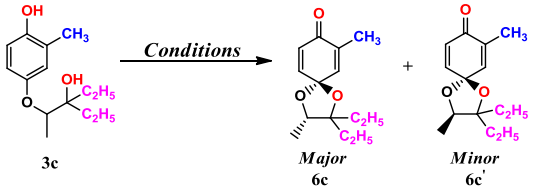


5a, 80% **5b**, 76% **5c**, 78% **5d**, 72%



5e, 77% **5f**, 79% **5g**, 78%

Table 4
Optimization of reaction conditions[a] for 6**c** and 6**c'**.

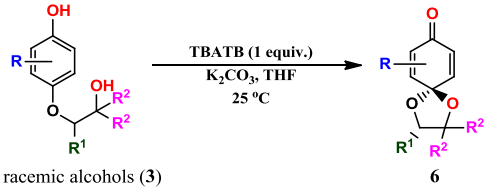


Entry No.	QATB	*dr* (6c:6c')[b]	Yield (%)[c]
1	I	5:1	70
2	II	1:1	62
3	**III**	**8:1**	**82**
4	IV	1:1	65
5	V	3:1	68
6	VI	1:1	60

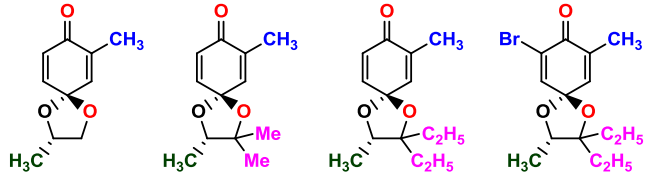
Entry No.	QATB	*dr* (6c:6c')[b]	Yield (%)[c]
1	I	5:1	70
2	II	1:1	62
3	III	8:1	82
4	IV	1:1	65
5	V	3:1	68
6	VI	1:1	60

[a] Reaction conditions: 3c (0.2 mmol), K_2CO_3 (0.2 mmol), TBr (0.2 mmol), dry THF (5 mL), for 12 h under a nitrogen atmosphere at 25 °C.
[b] *dr* is determined by ^{1}H NMR.
[c] Isolated yields after column chromatography for both diastereomers.

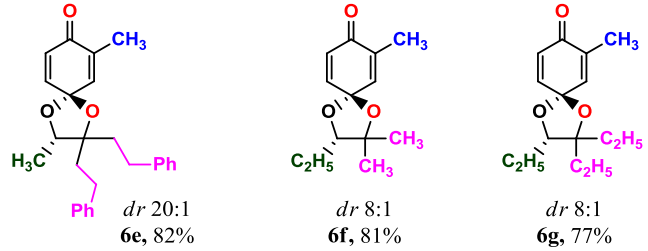
Table 5
Substrate scope for synthesis of stereoselective *para*-1,4-quinone monoketals.



racemic alcohols (**3**) **6**



dr 6:1 **6a**, 80% *dr* 8:1 **6b**, 79% *dr* 8:1 **6c**, 82% *dr* 8:1 **6d**, 80%



dr 20:1 **6e**, 82% *dr* 8:1 **6f**, 81% *dr* 8:1 **6g**, 77%

Please cite this article as: S. R. Sahoo and D. Sarkar, Stereoselective synthesis of *para*-quinone monoketals through tri-bromide (TBr) mediated oxidative dearomatization of phenols, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2020.151646

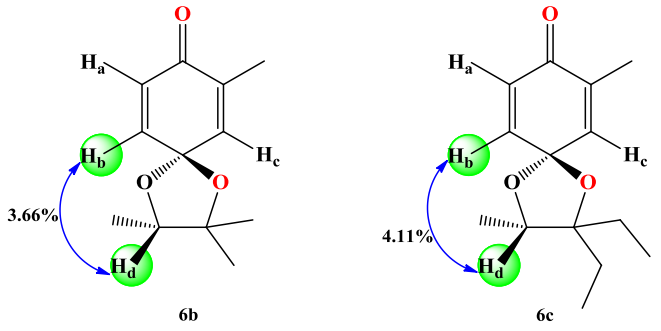
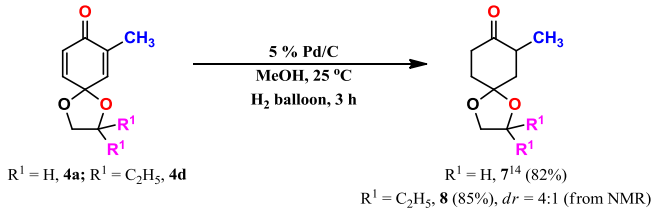
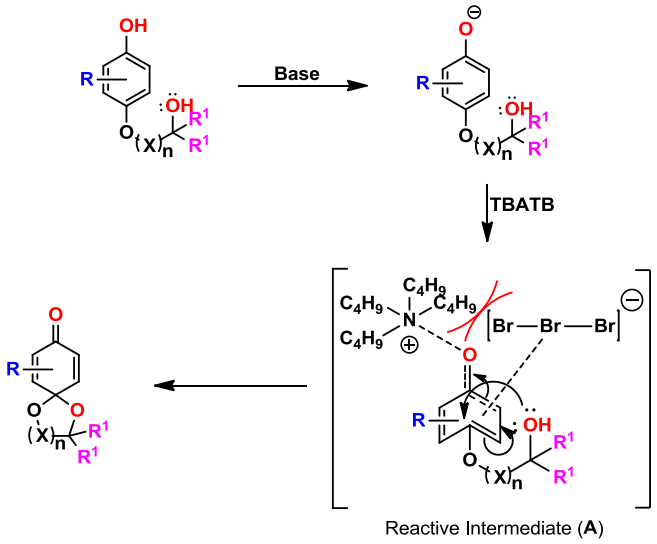


Fig. 2. NOE studies attesting the relative stereochemistry for compound 6b and 6c.



Scheme 2. Product diversification of the *para*-1,4-quinone monoketals product.



Scheme 3. Proposed reaction mechanism.

The monoketal generation has been stereoselective and the stereochemistry has been confirmed with extensive NOE studies and the stereo chemistry is *trans* to each other (Fig. 2).

The compound 4a and 4d was further functionalized by performing hydrogenation (5% Pd/C) to access saturated spirocyclic ketone 7 and 8 respectively in excellent yields (Scheme 2).

Based on our previous and our ongoing studies, a plausible reaction mechanism is proposed for our reaction route in Scheme 3 [12,13]. It is proposed that the electrophlic tri-bromide ion is the key reagent of intramolecular ketal generation. It is strongly precedent with our ongoing studies that the phenoxide get exposed to the dual activation, one by the ammonium ion and secondly by the electrophilic tri-bromide ion and proceed *via* partially planner reactive intermediate (A). The reactive intermediate (A), then under goes an intramolecular attack by the υ-alkoxide to deliver the *para* spiroquinone monoketals.

Conclusion

In a nutshell, we feel enthusiastic to report the way out of tribromide (TBr) mediated dearomative intramolecular stereoselective spiropara-quinone monoketals of 2-alkoxy phenols and 3-alkoxy phenols, with overall fantastic yields and good diastereoselectivity under mild conditions along with the economy involved make this sustainable methodology. Additionally, this work has no side reactions like polymerization and bromination at *ortho*-position of phenol which is commonly observed in dearomatisation reactions, thus makes it an effective reaction. The study of asymmetric version is currently in progress in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We sincerely acknowledge the Department of Science and Technology (DST), Government of India (Grant No. EEQ/2016/000518), INSPIRE-DST, Government of India (Grant 04/2013/000751) and NIT Rourkela.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151646.

References

[1] N.V.G. Moorthy, S.V. Pansare, Tetrahedron 74 (2018) 1422–1429.
[2] N.V.G. Moorthy, R. Dyapa, S.V. Pansare, Org. Lett. 17 (2015) 5312–5315.
[3] D.A. Carcache, Y.S. Cho, Z. Hua, Y. Tian, Y.-M. Li, S.J. Danishefsky, J. Am. Chem. Soc. 128 (2006) 1016–1022.
[4] (a) C.-C. Liao, R.K. Peddinti, Acc. Chem. Res. 35 (2002) 856–866;
(b) D. Magdziak, S.J. Meek, T.R.R. Pettus, Chem. Rev. 104 (2004) 1383–1430;
(c) S. Quideau, D. Deffieux, L. Pouysegu, Tetrahedron 66 (2010) 2235–2261;
(d) S.P. Roche, J.A.P. Jr, Angew. Chem. Int. Ed. 50 (2011) 4068–4093;
(e) A. Bartoli, F. Rodier, L. Commeiras, J.-L. Parrain, G. Chouraqui, Nat. Prod. Rep. 28 (2011) 763–782;
(f) C.-X. Zhuo, W. Zhang, S.-L. You, Angew. Chem., Int. Ed. 51 (2012) 12662–12686;
(g) M. Uyanik, K. Ishihara, in: Asymmetric Dearomatisation Reactions, John Wiley & Sons, Weinheim, 2016, pp. 126–152.
[5] M. Uyanik, N. Sasakura, M. Mizuno, K. Ishihara, ACS Catal. 7 (2017) 872–876.
[6] (a) T.A. Wenderski, C. Hoarau, L. Mejorado, T.R. Pettus, Tetrahedron 66 (2010) 5873;
(b) F. Portalier, F. Bourdreux, J. Marrot, X. Moreau, V. Coeffard, C. Greck, Org. Lett. 15 (2013) 5642;
(c) D. Magdziak, A.A. Rodriguez, R.W. Van De Water, T.R. Pettus, Org. Lett. 4 (2002) 285;
(d) A. Ozanne, L. Pouységu, D. Depernet, B. Francois, S. Quideau, Org. Lett. 5 (2003) 2903.
[7] A.M. Harned, Org. Biomol. Chem. 16 (2018) 2324–2329.
[8] N. Jain, S. Xu, M.A. Ciufolini, Chem. Eur. J. 23 (2017) 4542–4546.
[9] (a) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, Y. Kita, Angew. Chem. Int. Ed. 47 (2008) 3787, Angew. Chem. 120 (2008) 3847;
(b) T. Dohi, N. Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama, Y. Kita, J. Am. Chem. Soc. 135 (2013) 4558.
[10] (a) M. Uyanik, N. Sasakura, E. Kaneko, K. Ohori, K. Ishihara, Chem. Lett. 44 (2015) 179;
(b) M. Uyanik, T. Yasui, K. Ishihara, Tetrahedron 66 (2010) 5841;
(c) M. Uyanik, T. Yasui, K. Ishihara, Angew. Chem. Int. Ed. 49 (2010) 2175, Angew. Chem. 2010, 122, 2221.
[11] S.J. Murray, H. Ibrahim, Chem. Commun. 51 (2015) 2376.
[12] D. Sarkar, M.K. Ghosh, N. Rout, Org. Biomol. Chem. 14 (2016) 7883–7898.
[13] D. Sarkar, P. Kuila, D. Sood, Eur. J. Org. Chem. 34 (2019) 5894–5904.