Tetrahedron Letters 65 (2021) 152794

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Copper-catalyzed aerobic oxidative cross-coupling reactions of vinylarenes with sulfinate salts: A direct approach to β-ketosulfones

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ARTICLE INFO

Article history:
Received 19 October 2020
Revised 14 December 2020
Accepted 17 December 2020
Available online 7 January 2021

Keywords:
Copper-catalyzed
Aerobic oxidative
Cross-coupling
β-ketosulfones
C—S bond

ABSTRACT

A copper-catalyzed aerobic oxidative cross-coupling reactions for the synthesis of β-ketosulfones via formation of a C—S bond has been demonstrated. Promoted by the crucial copper catalyst, perfect selectivity and good to excellent yields could be achieved. This method, including inexpensive copper catalyst, wide functional group tolerance, and open air conditions, make it very attractive and practical. More importantly, it also provides a versatile tool for the construction of β-ketosulfones from basic starting materials under mild conditions.

Introduction

With growing awareness of severe global energy and environmental constraints, thus, the past decades have witnessed the emergence of transition-metal-catalyzed carbon-heteroatom bonds formation reaction as an increasingly powerful tool in organic synthesis, ranging from pharmaceutical to large-scale commodities [1]. In particular, the C—S bond formation via an oxidative coupling process is considered as one of the most promising environmentally friendly and sustainable approach for the transformation of organic processes owing to not only its high atom-economy and step-economy but also readily available starting materials [2]. Thus far, a lot of efforts have been made to improve the approach for constructing new C—S bonds[3].

In the past reports, copper-catalyzed oxidative coupling reactions have been arguably considered as a reliable method to construct complex molecules [4]. Among these, recent achievements have highlighted the ability of copper as a versatile reagent in oxidative coupling reactions [5]. Compared to other transition-metal catalysts, copper is inexpensive, abundant, insensitive to air and water, and can be easily utilized [6]. Additionally, in view of green and sustainable chemistry, molecular oxygen is recognized as an ideal oxidant due to its inexpensive, abundant, and environmental friendly characteristics[7].

As a class of basic scaffold with high biological value, β-ketosulfones have found wide applications in natural products, biologically active compounds, agrochemicals including pesticides, fungicides, and herbicides [8]. Herein, we describe our efforts toward the development of copper-catalyzed oxidative coupling reaction for constructing new C—S bond: the direct approach to β-ketosulfones via the reaction of sulfinate salts and vinylarenes (Scheme 1). In contrast to the Pd-catalyzed [9], except for the diffident product, more importantly, this method, including inexpensive copper catalyst, wide functional group tolerance, and open air conditions, make it very attractive and practical.

Materials and methods

Reagent Information

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. All the olefins were bought from Aldrich and Alfa Aesar. Some olefins were synthesized from commercially available compounds by Wittig reaction following literature procedures. Thin layer chromatography

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https://doi.org/10.1016/j.tetlet.2020.152794
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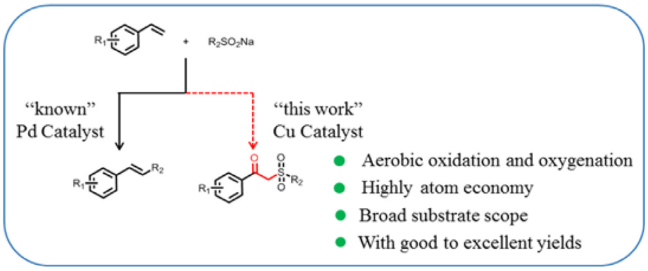


Scheme 1. Copper-catalyzed oxidative coupling route to β-ketosulfones under air condition.

(TLC) employed glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 200–300 mesh silica gel in petroleum ether (bp. 60–90 °C). A gradient elution using ethyl acetate and petroleum ether was performed, based on Merck aluminum TLC sheets (silica gel $60F_{254}$).

Analytical Information

All isolated compounds were characterized by ^1H, ^{13}C NMR spectroscopy, Copies of the ^1H NMR,^{13}C NMR can be found in the supporting information. Unless otherwise stated, all Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane (0 ppm for ^1H) and $CDCl_3$ (77.16 ppm for ^{13}C), respectively.

Experimental section

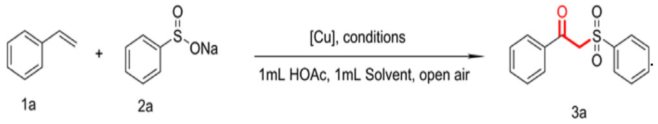
General Procedure for the Synthesis of β-ketosulfones

Typical procedure: The reaction mixture of styrene 1a (0.5 mmol), sodium benzenesulfinate 2a (1.0 mmol), $CuCl_2$ (0.05 mmol) and 1 mL HOAc in 1 mL PEG400 in a 25 mL tube was stirred at 60 °C for 6 h under air atmosphere and monitored periodically by TLC. Upon completion, the crude product was cooled to room temperature and then quenched by the addition of 5 mL water. The aqueous solution was extracted with ethyl acetate (3 × 5 mL) and the combined extracts were dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure by an aspirator, and the crude product was purified by silica gel column chromatography with petroleum ether and ethyl acetate as eluent to afford the desired product 3a.

Results and discussion

Our initial efforts focused on styrene 1a and sodium benzenesulfinate 2a as the model reaction (Table 1). The reaction parameters (i.e., catalyst, solvent, temperature, acid) were varied to achieve this goal. To our delight, when 1a was treated with 2a, 0.5 equiv of $CuCl_2$, and 1.0 equiv of HOAc in PEG400 under open air at 40 °C and 6 h, the desired product 3a was obtained in 75% yield (Table 1, Entry 9). The test reaction was carried out at different temperatures in order to check the effect of temperature on the reaction. It was noted that the maximum conversion occurred at 60 °C, providing the desired product 3a in 94% yield after 6 h (Table 1, Entry 6). However, by further increasing the reaction temperature (80 °C), the yield did not improve (Table 1, Entry 8). Using other Copper(Ⅱ), such as $CuBr_2$, $Cu(SO_4)_2$, $Cu(NO_3)_2$ and $Cu(OAc)_2$, also gave slightly lower yields (Table 1, Entry 4, Entry 5, Entry 14–16). Compared with Copper(Ⅱ), Copper(Ⅰ) showed ineffective ability in this transformation (Table 1, Entry 1–3, Table S1, Entry 15–26). Unfortunately, other metal catalysts (Table S1, Entry 1–4) and copper catalyst-free conditions (Table S1, Entry 5) proved to be ineffective. A solvent screen showed PEG400 as most effective, other solvent loadings led to reduced yields (Table 1, Entry 7, Entry 10–13 and Table S1, Entry 6–9). Notably, 1.0 equiv of added HOAc was important to obtain good yields (Table S1, Entry 10–12), the reaction without HOAc gave only 5% of the desired

Table 1
Optimization of the Reaction Conditions



Entry	[Cu](equiv.)	Solvent1 mL	t[h]	T[°C]	Yield of 3a[%]
1	CuI	PEG400	10	60	10
2	CuCl	PEG400	10	60	12
3	CuBr	PEG400	10	60	14
4	$CuBr_2$	PEG400	6	60	90
5	$CuBr_2$	PEG600	6	60	85
6	**$CuCl_2$**	**PEG400**	**6**	**60**	**94**
7	$CuCl_2$	PEG600	6	60	86
8	$CuCl_2$	PEG400	6	80	88
9	$CuCl_2$	PEG400	6	40	75
10	$CuCl_2$	PEG400	8	60	92
11	$CuCl_2$	PEG400	4	60	85
10	$CuCl_2$	DMF	12	60	78
11	$CuCl_2$	DMA	9	60	74
12	$CuCl_2$	NMP	6	60	61
13	$CuCl_2$	MeOH	12	60	40
14	$Cu(OAc)_2$	PEG400	6	60	90
15	$Cu(NO_3)_2$	PEG400	6	60	86
16	$Cu(SO_4)_2$	PEG400	6	60	85
17	$CuCl_2$	PEG400	6	60	95[a]
18	$CuCl_2$	PEG400	6	60	0[b]
19	$CuCl_2$	PEG400	6	60	5[c]

Reaction conditions: 1a (0.5 mmol), 2a (1.0 mmol), Cu catalyst (5.0 mol%), HOAc (0.5 mmol), PEG400 (1 mL) under air. Yields of isolated products based on 1a. [a] under O_2, [b] under N_2, [c] No HOAc.

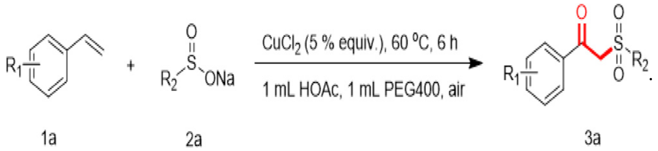
product (Table 1, Entry 19). Alternatively, no product was formed under nitrogen atmosphere (Table 1, Entry 18). Using pure oxygen as the terminal oxidant provided a comparable result to that of the reaction with air (Table 1, Entry 17). After further screening of temperature, reaction time, the reaction of sodium benzenesulfinate 1a and styrene 2a to give 3a in 94% yield using the conditions: $CuCl_2$ (0.05 mmol), HOAc (1.0 mL), in PEG400 (1 mL) with stirring at 60 °C open to air for 6 h (Table 1, Entry 6 and Table S1, Entry 13–14). The mild reaction conditions, including shorter reaction times (6 h), operational simplicity (open air), cost-effectiveness and excellent yields (94%), make this protocol an alternative method for the facile construction of numerous β-ketosulfones.

Furthermore, having identified the optimized conditions, we investigated the scope of the reaction with respect to 2a and different styrenes. As shown in Table 2, a range of vinylarenes, with either electron-donating groups (R_1 = Me, OMe, N, *N*-dimethy) or electron-withdrawing groups (R_1 = F, Cl, Br) on aromatic ring, were viable in this transformation (Table 2, 3b-g). Electron-donating vinylarenes (Table 2, 3b-d) displayed higher reactivity than those bearing electron-with-drawing groups (Table 2, 3e-g). Significantly, several functional groups (nitro, 3,4-dichloro) were well tolerated (Table 2, 3 h-k), affording the corresponding β-ketosulfones in good to excellent yield. Interestingly, a nitro substituent, which is usually unfavorable in the transformation with aerobic oxidative cross-coupling reaction, was also well tolerated, affording the corresponding 3 h-3j in good yields. It was observed that the electronic variation at the *ortho*-, *meta*-, *para*-substituents of the aryl ring vinylarenes did not affect the transformation, gave the corresponding 3 h, 3i and 3j in 88%, 86% and 84% yield, respectively. It should be noted that 2-vinylnaphthalene was also found to be compatible with this transformation, albeit in slightly lower yield (Table 2, 3 l, 3u).

Additionally, to highlight the wide functional group tolerance of this process, sulfinate salts with aliphatic and alkyl groups were investigated under standard conditions. To our satisfaction, a variety of aryl sulfinate salts, bearing either electron-donating groups (Table 2, 3 m-t) or electron-withdrawing groups (Table 2, 3u, 3v) on the aryl ring, reacted smoothly with vinylarenes, affording the corresponding β-ketosulfones in good to excellent yield. As can be seen in Table 2, sodium *p*-toluenesulfinate displayed higher reactivity than sodium 4-chlorobenzene sulfinate, although affording the corresponding β-ketosulfones in good to excellent yield. It was interesting to note that sodium methane sulfinate, an aliphatic sodium sulfinate, was also suitable substrate for this transformation (Table 2, 3w-z and 3Ⅰ-Ⅴ). The reaction proceeded efficiently to afford their corresponding β-ketosulfones products in moderate to good yields even for the substrates vinylarenes bearing functional groups such as halide, Me, OMe, and nitro, especially, F, Cl and Br group, thus further enhancing the scope of our reaction. Because of the steric hindrance effect of *ortho*-position substitution, 80% of 3Ⅴwas formed, which is in contrast with the case for 3Ⅱ, where the chloro group is located on the *para* position of the phenyl ring. This similar effect was then confirmed when *meta*-nitro substituted vinylarene afforded 81% yield (Table 2, 3IV).

To gain preliminary mechanistic information about this protocol, a series of experiments were carried out to provide insight

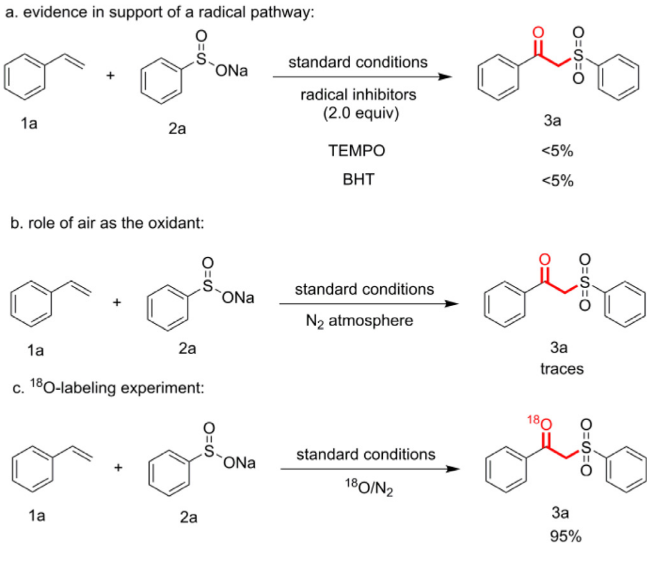
Table 2
Substrate Scope for the Synthesis of Various β-ketosulfones under air condition



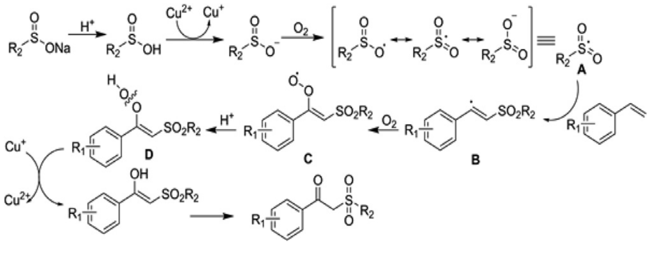
Entry	R_1	R_2	3	Yield of **3** [%]
1	H	Phenyl	3a	94
2	4-CH_3	Phenyl	3b	95
3	4-OCH_3	Phenyl	3c	96
4	4-N,*N*-dimethy	Phenyl	3d	96
5	4-F	Phenyl	3e	90
6	4-Cl	Phenyl	3f	92
7	4-Br	Phenyl	3 g	92
8	4-NO_2	Phenyl	3 h	88
9	3-NO_2	Phenyl	3i	86
10	2-NO_2	Phenyl	3j	84
11	3,4-dichloro	Phenyl	3 k	91
12	Phenyl	Phenyl	3 l	85
13	H	4-CH_3-Phenyl	3 *m*	95
14	4-CH_3	4-CH_3-Phenyl	3*n*	96
15	4-OCH_3	4-CH_3-phenyl	3o	97
16	4-N,N-dimethy	4-CH_3-phenyl	3p	97
17	4-F	4-CH_3-Phenyl	3q	91
18	4-Cl	4-CH_3-Phenyl	3r	93
19	4-Br	4-CH_3-Phenyl	3s	90
20	4-NO_2	4-CH_3-Phenyl	3t	89
21	Phenyl	4-Cl-Phenyl	3u	86
22	H	4-Cl-Phenyl	3v	84
23	4-CH_3-phenyl	CH_3	3w	85
24	H	CH_3	3x	86
25	4-CH_3	CH_3	3y	86
26	4-OCH_3	CH_3	3z	87
27	4-F	CH_3	3Ⅰ	84
28	4-Cl	CH_3	3Ⅱ	84
29	4-Br	CH_3	3III	84
30	3-NO_2	CH_3	3 IV	81
31	2-Cl	CH_3	3Ⅴ	80

about the reaction. First, radical trapping experiment was performed, inspired by the previous reports that dioxygen activation based processes mostly involve radical species [10]. Under the standard reaction conditions, β-ketosulfone 3a was extremely inhibited in the presence of TEMPO or BHT, which were well-known radical scavengers, elucidating a radical pathway (Scheme 2a). Furthermore, demonstrating the role of air in the reaction was very vital to unfold the intricacies of the mechanism. The reaction was not at all formed under nitrogen (Scheme 2b). Finally, an isotope labeling experiment was also conducted to elucidate the origination of the carbonyl oxygen atom of the β-ketosulfone. The reaction of 1a with 2a under an $^{18}O_2/N_2$ (1:4) atmosphere under the standard conditions generated the ^{18}O-labeled product 3a in 95% yield (Scheme 2c, Figure S1, Figure S2). It is proved that O_2 took part in this reaction and the oxygen atom in the product came from O_2.

Based on the above results and previous reports [10] (Lu et al., 2013; Handa et al., 2014; Huang et al., 2014; Maji et al., 2014), a plausible mechanism is proposed and illustrated in Scheme 3. The overall sequence starts from in situ generation of free sulfinic acid from its sodium salt and HOAc. Afterward, $CuCl_2/O_2$ catalyst system triggers the sulfonyl radical A formation from sulfinate salt. Then, this sulfonyl radical attacks the double bond to give vinyl radical B, which is ultimately captured by oxygen to form peroxy radical intermediate C. This active species C abstracted one hydrogen atom from HOAc generating hydroperoxo species D. Finally, the intermediate D interacted with Cu (I) species by single-electron transfer (SET) and generates an enol that tautomerizes to the desired product 3a, meanwhile regenerated Cu (II) catalyst, thus completing the catalytic cycle. Further studies to clearly understand the reaction mechanism are ongoing in our laboratory.



Scheme 2. Relevant Experiments for the Mechanistic Studies.



Scheme 3. Plausible Mechanistic Pathway.

Conclusions

In summary, we have developed a copper-catalyzed aerobic oxidative cross-coupling reactions for the synthesis of β-ketosulfones via formation of a new C—S bond. Notably, the method exhibits wide functional group tolerance and can be operated in open air conditions, which make it very attractive and practical. Pleasingly, the success of unique transformation provides a new route for the synthesis of β-ketosulfones under mild conditions. Application of this methodology to ongoing research including further mechanistic details are currently underway.

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.

Acknowledgements

This study was financially supported by the research fund of Anhui Agricultural University (Grant No. wd2018-03), the Natural Science Foundation of Anhui Province (Grant No. 2008085 MB41), the Anhui Province Key Laboratory of Chemistry for Inorganic/Organic Hybrid Functionalized Materials, Anhui University and finance support from Soil and Fertilizer Institute of Anhui Academy of Agricultural Science.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152794.

References

[1] (a) F. Zhou, J. Liu, Q. Cai, Synlett. 27 (2016) 664–675;
(b) P. Gandeepan, T. Muller, D. Zell, G. Cera, S. Warratz, L. Ackermann, Chem Rev. 119 (2019) 2192–2452;
(c) L.F. Peng, Z.F. Hu, Z.L. Tang, Y.C. Jiao, X.H. Xu, Chin. Chem. Lett. 30 (2019) 1481–1487;
(d) M. Zhang, Q.H. Wang, Y.Y. Peng, Z.Y. Chen, C.F. Wan, J.M. Chen, Y.L. Zhao, R. L. Zhang, A.Q. Zhang, Chem. Commun. 55 (2019) 13048–13065.

[2] (a) F. Pan, Z.J. Shi, ACS Catal. 4 (2014) 280–288;
(b) X. Liang, M.T. Xiong, H.P. Zhu, K.X. Shen, Y.J. Pan, J. Org. Chem. 84 (2019) 11210–11218;
(c) P.M. Matos, W. Lewis, S.P. Argent, J.C. Moore, R.A. Stockman, Org. Lett. 22 (2020) 2776–2780.

[3] (a) G.T. Zhang, C. Liu, H. Yi, Q.Y. Meng, C.L. Bian, H. Chen, J.X. Jian, L.Z. Wu, A.W. Lei, J. Am. Chem. Soc. 137 (2015) 9273–9280;
(b) F.L. Sun, X.M. Liu, X.Z. Chen, C. Qian, X. Ge, Chin. J. Org. Chem. 37 (2017) 2211–2220;
(c) W. Guo, K. Tao, W. Tan, M. Zhao, L. Zheng, X. Fan, Org. Chem. Front. 6 (2019) 2048–2066;
(d) A. Hosseinian, P.D.K. Nezhad, S. Ahmadi, Z. Rahmani, A. Monfared, J. Sulfur Chem. 40 (2019) 88–112.

[4] (a) A.E. Wendlandt, A.M. Suess, S.S. Stahl, Angew., Chem. Int.l Ed. 50 (2011) 11062–11087;
(b) S.E. Allen, R.R. Walvoord, R. Padilla-Salinas, M.C. Kozlowski, Chem Rev. 113 (2013) 6234–6458;
(c) C. Sambiagio, S.P. Marsden, A.J. Blacker, P.C. McGowan, Chem. Soc. Rev. 43 (2014) 3525–3550;
(d) X.X. Guo, D.W. Gu, Z.X. Wu, W.B. Zhang, Chem Rev. 115 (2015) 1622–1651.

[5] (a) J. Ranjith, P.R. Krishna, Tetrahedron Lett. 60 (2019) 1437–1440;
(b) M.C. Ryan, Y.J. Kim, J.B. Gerken, F. Wang, M.M. Aristov, J.R. Martinelli, S.S. Stahl, Chem. Sci. 11 (2010) 1170–1175.

[6] (a) S. Bhunia, G.G. Pawar, S.V. Kumar, Y.W. Jiang, D.W. Ma, Angew. Chem. Int. Ed. 56 (2017) 16136–16179;
(b) X.D. Tang, W.Q. Wu, W. Zeng, H.F. Jiang, Accounts Chem. Res. 51 (2018) 1092–1105;
(c) K. Wang, Z. Ding, Z. Zhou, W. Kong, J. Am. Chem. Soc. 140 (2018) 12364–12368;
(d) J. Zhu, W. Zhu, P. Xie, C.U. Pittman, A. Zhou, Tetrahedron. 74 (2018) 6569–6576.

[7] (a) Z.Z. Shi, C. Zhang, C.H. Tang, N. Jiao, Chem. Soc. Rev. 41 (2012) 3381–3430;
(b) Y.F. Liang, N. Jiao, Accounts Chem. Res. 50 (2017) 1640–1653.

[8] (a) N.S. Simpkins, Sulfones in Organic Synthesis, in: J.E. Baldwin (Ed.), Tetrahedron Organic Chemistry Series No. 10, Pergamon Press: Oxford, 1993;
(b) J.L. Marco, J. Org. Chem. 62 (1997) 6575–6581;
(c) S. Sengupta, D. Sen Sarma, S. Mondal, Tetrahedron. 54 (1998) 9791–9798;
(d) A. El-Awa, M.N. Noshi, X.M. du Jourdin, P.L. Fuchs, Chem Rev. 109 (2009) 2315–2349;
(e) H. Yang, R.G. Carter, L.N.Z. Kharov, J. Am. Chem. Soc. 130 (2008) 9238–9239.

[9] (a) M. Ueda, J.F. Hartwig, Org. Lett. 12 (2010) 92–94;
(b) G.W. Wang, T. Miao, Chemistry. 17 (2011) 5787–5790;
(c) F. Zhou, J. Liu, Q. Cai, Synlett. 27 (2016) 664–675.

[10] (a) Q.Q. Lu, J. Zhang, G.L. Zhao, Y. Qi, H.M. Wang, A.W. Lei, J. Am. Chem. Soc. 135 (2013) 11481–11484;
(b) S. Handa, J.C. Fennewald, B.H. Lipshutz, Angew. Chem. Int. Ed. 53 (2014) 3432–3435;
(c) X.Q. Huang, X.Y. Li, M.C. Zou, S. Song, C.H. Tang, Y.Z. Yuan, N. Jiao, J. Am. Chem. Soc. 136 (2014) 14858–14865;
(d) A. Maji, A. Hazra, D. Maiti, Org. Lett. 16 (2014) 4524–4527.