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# Glucose-containing imidazolium salt-catalyzed cross-aldol reaction of isatins and unactivated ketones

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**Abstract** Ketone–ketone cross-aldol reaction of isatins and unactivated ketones was catalyzed by glucose-containing imidazolium salt β-1-imidazole-2,3,4,6-tetra-O-hydroxy-D-glucopyranosyl bromide in neutral condition to generate 3-alkyl-3-hydroxyindolin-2-ones in excellent yield.

**Keywords** Glucose-containing imidazolium salt · Noncovalent catalyst · Unactivated ketone–ketone cross-aldol reaction

## Introduction

The aldol reaction has drawn much attention for several decades because it is a very important protocol to form carbon–carbon bonds [1–5]. Moreover, it affords β-hydroxyl carbonyl compounds as versatile synthetic motifs of many biologically and pharmaceutically important intermediates [6–9].

Compared with normal ketones, isatins are relatively stronger H-bond acceptors [10–12], which makes them good substrates for various organic, e.g., condensation,

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reactions. The products generally contain a quaternary carbon at $C_3$-position, and this skeleton is widely found in natural products that show interesting biological activities [13–15].

Recently, cross-aldol reaction of isatins with unactivated ketones has gradually aroused our interest. Various catalysts have been used to improve the reaction. Application of amino acids or peptides in the reaction was reported successively. Tomasini's [16] and Bunge's group [17] used dipeptide and pseudopeptide as catalyst, respectively. Corrêa [18] reported the enantioselective aldol reaction of isatin with acetone catalyzed by L-proline, and Xie [19] reported the reaction of α,β-unsaturated ketones with isatin catalyzed by arginine. Although amino acids and peptides gave good yield and stereoselectivity, the reaction was very slow (2–6 days). Instead, many studies used amino acid derivatives, such as leucinol [9, 20], 2-(diphenylhydroxymethyl)pyrrolidine [21], amino amides [22–27], and amino acid sulfonamide [28], as catalyst, but this could not shorten the reaction time significantly. Quinidine thiourea [29, 30] and quinidine urea [31] performed well when used to catalyze the reaction of activated ketones such as acetylphosphonate, 3-acetyl-2*H*-chromen-2-ones or 2,2-difluoro-1,3-diketones with isatins, but the direct aldol reactions of unactivated ketones with isatins were very slow (3–7 days) when catalyzed by quinidine thiourea, binaphthyl-modified catalyst, or carbohydrate-derived thiourea [32–34]. The reaction of cycloketones and isatin was also studied; when using cyclohexanediamine as catalyst, the reaction could not proceed smoothly without cocatalyst [35], and when using biaryl-based bifunctional catalysts, the substrate scope was narrow [36]. 1,4-Diazabicyclo[2.2.2]octane (DABCO) showed good catalytic activity, but unfortunately the substrates were limited to acetophenones [37].

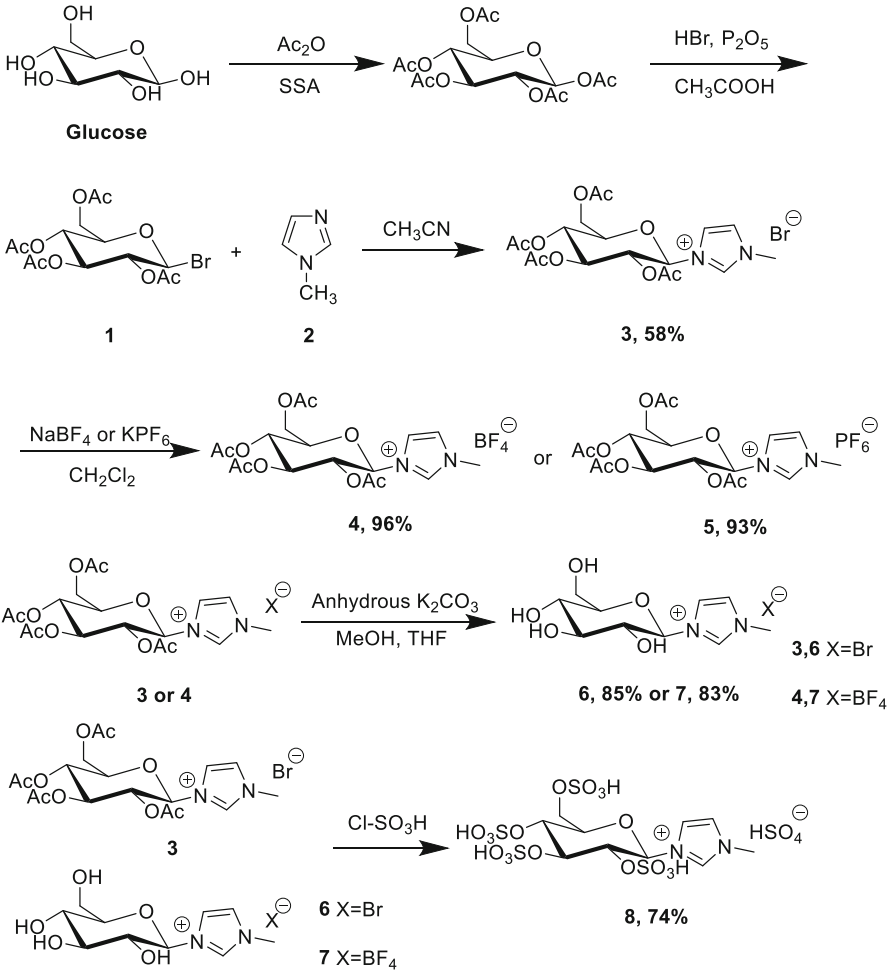
Recently, we found that glucose-containing imidazolium salts and glucose-containing pyridine salts showed high catalytic activity [38–40]. Herein, based on earlier research, we investigated the catalytic capability of glucose-containing imidazolium salts (Scheme 1) in ketone–ketone cross-aldol reactions of isatins and unactivated ketones. The results indicated that some of them could act as efficient catalysts for this reaction in neutral condition without any cocatalyst.

## Results and discussion

General procedures and apparatus are shown in the Electronic Supporting Information.

The structure of glucose-containing imidazolium salts **3**–**8** was determined by infrared (IR), and $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectroscopy. The $^1$H NMR spectrum of compound **3** exhibited a double peak at $\delta = 6.05$ ppm ($J = 8.4$ Hz) for the $C^1$–H. Comparing with the literature value [41], it is clear that the imidazole ring was seated in the equatorial bond of $C_1$ (Fig. 1) and compounds **3** and **6** ($J = 8.8$ Hz) had β-configuration.

The pH value of compounds **3**–**8** was then measured to evaluate their catalytic potential (Table 1). According to Table 1, the pH value varied considerably (1.44–10.09), influenced by the groups on the glucose ring. At the same




**Scheme 1** Synthesis of glucose-incorporated imidazoliums ($[Bmim\text{-}G']^+[X]^-$)

concentration ($10^{-2}$ mol $L^{-1}$), compounds **3–5** (with acetyl on sugar ring) displayed faint acidity while compounds **6**, **7** displayed alkalescency. Compared with them, compound **8** possessed strong acidity caused by four sulfonic acid groups. These results show that some of them could be used as acid catalysts, while others may be used as basic or neutral ones, indicating their wide potential for future use in organic synthesis.

Subsequently, their catalytic effect was investigated in direct condensation of isatin and acetophenone (Table 2, entries 1–6). It is interesting that only catalyst **6** (pH 10.09) could promote this reaction (Table 2, entry 4) with high yield (88 %). Weak acid L-proline (Table 2, entry 7) and strong acids *p*-toluenesulfonic acid (TsOH, Table 2, entry 8), Cl–$SO_3H$ (Table 2, entry 9), and trifluoroacetic acid (TFA, Table 2, entry 10) proved useless. Strong base 1,8-diazabicyclo[5.4.0]undec-

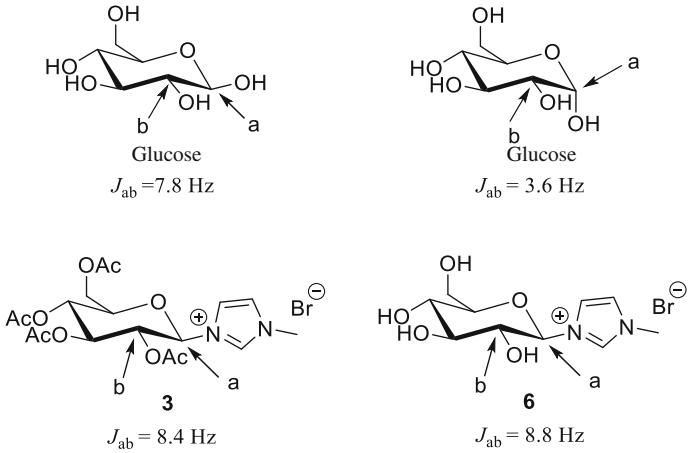



**Fig. 1** Coupling constant of $C_1$–H in glucose [11] and compound **3**

**Table 1** pH of imidazolium salts and other catalysts

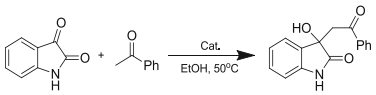
| Entry | Compound | pH[a] |
|---|---|---|
| 1 | **3** | 4.63 |
| 2 | **4** | 3.67 |
| 3 | **5** | 4.10 |
| 4 | **6** | 10.09 |
| 5 | **7** | 9.12 |
| 6 | **8** | 1.44 |
| 7 | L-Proline | 6.40 |
| 8 | TsOH | 1.84 |
| 9 | Cl–$SO_3H$ | 1.44 |
| 10 | TFA | 1.62 |
| 11 | *N*-Methylimidazole | 8.54 |
| 12 | DBU | 12.15 |

Measured by pH meter; working solution ($10^{-2}$ mol $L^{-1}$) was prepared by dissolving $10^{-3}$ mol catalyst in 5 mL deionized water and diluting to 100.0 mL with deionized water

7-ene (DBU) could also promote the reaction, but with lower yield compared with **6**. A possible reason is decomposition of isatin in strong alkali environment. These results confirm the importance of proper acidity in this reaction. Moreover, *N*-methylimidazole could not catalyze the reaction, highlighting the key role of the glucose ring of catalyst **6** for the reaction. The effective amount of catalyst **6** was 20 mol%, and increasing the catalyst loading could not further enhance the product yield (Entry **14**).

The reaction conditions were then optimized based on the yield of **11a** (Table 3). According to Table 3, ethanol was the best solvent (entry 2), and the most economical reaction time was 12 h (entry 14). The optimal temperature was 50 °C. Therefore, 20 mol% **6** as catalyst in EtOH at 50 °C for 12 h was the optimum reaction condition.

**Table 2** Screening of catalysts




| Entry | Catalyst | *X* (mol%) | Yield (%)[a] |
|---|---|---|---|
| 1 | **3** | 20 | Nr[b] |
| 2 | **4** | 20 | Nr[b] |
| 3 | **5** | 20 | Nr[b] |
| 4 | **6** | 20 | 88 |
| 5 | **7** | 20 | Nr[b] |
| 6 | **8** | 20 | Nr[b] |
| 7 | TFA | 20 | Nr[b] |
| 8 | 6 + TFA (1:1) | 20 | Nr[b] |
| 9 | L-Proline | 20 | Nr[b] |
| 10 | **6** + L-proline (1:1) | 20 | 40 |
| 11 | DBU | 20 | 75 |
| 12 | *N*-Methylimidazole | 20 | Nr[b] |
| 13 | **6** | 10 | 79 |
| 14 | **6** | 30 | 87 |

All reactions carried out at scale of 0.1 mmol isatin (**9a**) and 3.0 mmol acetophenone (**10a**) in 2 mL ethanol at r.t. for 12 h

[a]Isolated yield

[b]No reaction

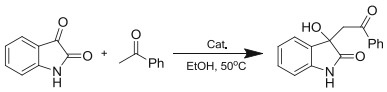
To explore the application of this method, the scope of the substrate was evaluated using a variety of isatins at the optimal condition (Table 4). Both acetophenone and acetone could afford moderate to high yield, while acetone bearing more active α-H atoms gave higher yield, indicating that the reaction was cross-aldol condensation from α-H of ketone carbonyl to isatin. Higher yield and faster reaction rate were obtained using isatins bearing electron-withdrawing groups (Table 4, entries 2–4, 11, 12). A possible reason is that electron-withdrawing groups increased the reactivity of the β-carbonyl, facilitating the reaction.

To further confirm the structure of the product **11**, we cultivated the crystal of **11m** and carried out X-ray diffraction analysis (Figs. 2, 3).

Catalyst recyclability was also investigated using synthesis of **11j** (Table 5). After completion, the solvent was evaporated and water was added. The aqueous phase was extracted using $CH_2Cl_2$ (3 × 15 mL) to separate the catalyst and product. The catalyst was recovered by concentration and drying the aqueous phase. It was observed that the catalyst could be used for three times with minimal loss of catalytic activity.

To determine the mechanism, catalyst **12** was synthesized from 1,2-dimethylimidazole instead of 1-methylimidazole. When the 2-position of imidazole ring was

**Table 3** Screening of solvent, temperature, and time



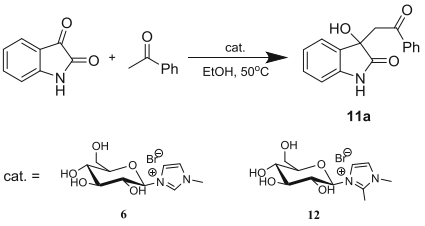

| Entry | Solvent | *T* (°C) | *t* (h) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | $H_2O$ | R.t. | 48 | 50 |
| 2 | $Et_2O$ | R.t. | 48 | 65 |
| 3 | THF | R.t. | 48 | 63 |
| 4 | EtOH | R.t. | 48 | 88 |
| 5 | $CH_2Cl_2$ | R.t. | 48 | 46 |
| 6 | $CH_3CN$ | R.t. | 48 | 75 |
| 7 | Toluene | R.t. | 48 | 43 |
| 8 | 1,4-Dioxane | R.t. | 48 | 80 |
| 9 | [BMIM][$BF_4$] | R.t. | 48 | Nr[b] |
| 10 | EtOH | 0 | 48 | 68 |
| 11 | EtOH | −25 | 48 | Nr[b] |
| 12 | EtOH | 50 | 48 | 96 |
| 13 | EtOH | 50 | 24 | 94 |
| 14 | EtOH | 50 | 12 | 94 |
| 15 | EtOH | 50 | 6 | 80 |

All reactions carried out at scale of 0.1 mmol isatin (**9a**) and 3.0 mmol acetophenone (**10a**) in 2 mL ethanol

[a]Isolated yield

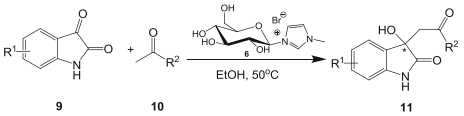
[b]No reaction

substituted by $CH_3$ (cat. **12**), the yield dropped remarkably (Table 6), indicating that the acidity of C–H in imidazole plays an important role.




The possible transition state in the formation of **11** is shown in Scheme 2. We supposed that the product was generated from the synergistic effect of the enolate anion **A** (blue) of ketone, isatin (green), and catalyst **6**. We believe that the imidazolium ion made the H at 2-position a better proton donor, and catalyst **6** may play a dual role: acting as a proton donor to promote ketone to form enolate ion and as a hydrogen-bond donor to bind with isatin.

**Table 4** Synthesis of **11** under optimum conditions




| Product | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| **11a** | H | $C_6H_5$ | 90 |
| **11b** | 5-F | $C_6H_5$ | 88 |
| **11c** | 5-Cl | $C_6H_5$ | 96 |
| **11d** | 5-Br | $C_6H_5$ | 95 |
| **11e** | 5-$CH_3$ | $C_6H_5$ | 87 |
| **11f** | 5-$CH_3O$ | $C_6H_5$ | 85 |
| **11g** | 5,7-$(CH_3)_2$ | $C_6H_5$ | 80 |
| **11h** | H | $CH_3$ | 76 |
| **11i** | 5-F | $CH_3$ | 70 |
| **11j** | 5-Cl | $CH_3$ | 99 |
| **11k** | 5-Br | $CH_3$ | 97 |
| **11l** | 5-$NO_2$ | $CH_3$ | 97 |
| **11m** | 5-$CH_3$ | $CH_3$ | 85 |
| **11n** | 5-$CH_3O$ | $CH_3$ | 87 |
| **11o** | 5,7-$(CH_3)_2$ | $CH_3$ | 73 |

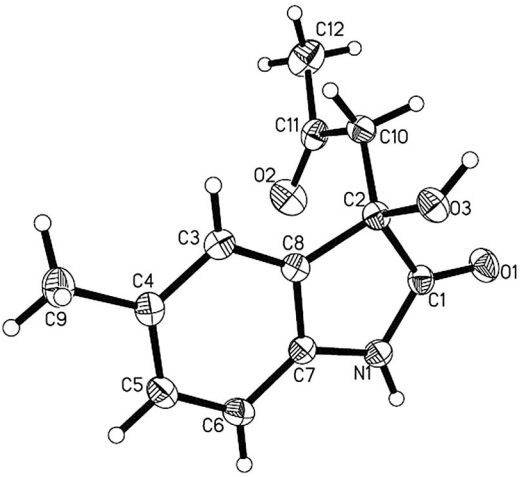



**Fig. 2** Crystal structure of **11m**

**Fig. 3** Crystal packing diagram of **11m**

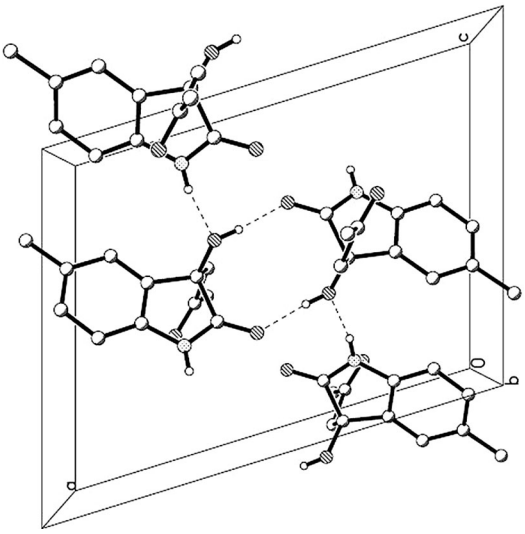
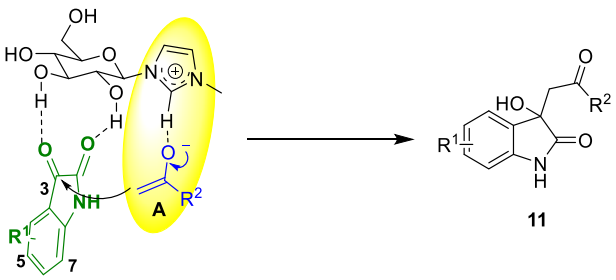


**Table 5** Recyclability of catalyst in synthesis of **11j**

| Cycle no. | Isolated yield (%) |
|---|---|
| 1 | 99 |
| 2 | 90 |
| 3 | 78 |
| 4 | 56 |

**Table 6** Control experiment for synthesis of **11a**

| Catalyst | Isolated yield (%) |
|---|---|
| **6** | 90 |
| **12** | 24.7 |




**Scheme 2** Possible transition state

## Conclusions

We synthesized and used β-1-imidazole-2,3,4,6-tetrahydroxy-D-glucopyranosyl bromide as catalyst in the cross-aldol reaction between unactivated ketones and isatins. The reaction proceeded smoothly in neutral condition without any cocatalyst. The substrate scope was broad, and the product could be obtained in high yield. These results indicate that the catalyst can remarkably promote the cross-aldol reaction and may be utilized for synthesis of biologically significant 3-alkyl-3-hydroxyindolin-2-ones in industry.

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## References

1. H. Pellissier, Tetrahedron **63** (2007)
2. B. List, Acc. Chem. Res. **37** (2004)
3. W. Notz, F. Tanaka, C.F. Barbas III, Acc. Chem. Res. **37** (2004)
4. B. List, Tetrahedron **58** (2002)
5. B. List, R.A. Lerner, C.F. Barbas III, J. Am. Chem. Soc. **122** (2000)
6. T. Kano, R. Sakamoto, K. Maruoka, Org. Lett. **16** (2014)
7. F. Sladojevich, A. Trabocchi, A. Guarna, D.J. Dixon, J. Am. Chem. Soc. **133** (2011)
8. J.Y. Li, N.K. Fu, X. Li, S.Z. Luo, J.P. Cheng, J. Org. Chem. **75** (2010)
9. V. Malkov, A. Kabeshov, M. Bella, O. Kysilka, A. Malyshev, K. Pluháêkova, P. Koêvsky, Org. Lett. **9** (2007)
10. W.B. Chen, X.L. Du, L.F. Cun, X.M. Zhang, W.C. Yuan, Tetrahedron **66** (2010)
11. W.B. Chen, Y.H. Liao, X.L. Du, X.M. Zhang, W.C. Yuan, Green Chem. **11** (2009)
12. F. Xue, S. Zhang, L. Liu, W. Duan, W. Wang, Chem. Asian J. **4** (2009)
13. B. Zhu, W. Zhang, R. Lee, Z.Q. Han, W.G. Yang, D. Tan, K.W. Huang, Z.Y. Jiang, Angew. Chem. Int. Ed. **125** (2013)
14. P. Satyamaheshwar, Curr. Bioact. Compd. **5** (2009)
15. M. Kitajima, I. Mori, K. Arai, N. Kogure, H. Takayama, Tetrahedron Lett. **47** (2006)
16. G. Luppi, P.G. Cozzi, M. Monari, B. Kaptein, Q.B. Broxterman, C. Tomasini, J. Org. Chem. **70** (2005)
17. A.J. Pearson, S. Panda, S.D. Bunge, J. Org. Chem. **78** (2013)
18. R.J. Corrêa, S.J. Garden, G. Angelici, C. Tomasini, Eur. J. Org. Chem. **4** (2008)
19. T.T. Yan, X.Y. Wang, H.B. Sun, J. Liu, Y.M. Xie, Molecules **18** (2013)
20. M.A. Kabeshov, O. Kysilka, L. Rulíšek, Y.V. Suleimanov, M. Bella, A.V. Malkov, P. Kočovský, Chem. Eur. J. **21** (2015)
21. T. Itoh, H. Ishikawa, Y. Hayashi, Org. Lett. **11** (2009)
22. N. Hara, S. Nakamura, N. Shibata, T. Toru, Adv. Synth. Catal. **352** (2010)
23. A. Bañón-Caballero, J. Flores-Ferrándiz, G. Guillena, C. Nájera, Molecules **20** (2015)
24. T.P. Kumar, N. Manjula, K. Katragunta, Tetrahedron Asymmetr. **26** (2015)
25. J. Kimura, U.V.S. Reddy, Y. Kohari, C. Seki, Y. Mawatari, K. Uwai, Y. Okuyama, E. Kwon, M. Tokiwa, M. Takeshita, T. Iwasa, H. Nakano, Eur. J. Org. Chem. **22** (2016)
26. P.H. Mohite, P. Drabina, F. Bureš, Synthesis **49** (2016)
27. G.D. Yadav, S. Singh, Tetrahedron Asymmetr. **27** (2016)
28. J. Wang, Q. Liu, Q. Hao, Y.H. Sun, Y.M. Luo, H. Yang, Chirality **27** (2015)
29. J. Guang, Q.S. Guo, J.C.G. Zhao, Org. Lett. **14** (2012)
30. J.L. Qian, W.B. Yi, X. Huang, J.P. Jasinski, W. Zhang, Adv. Synth. Catal. **358** (2016)
31. S. Abbarajua, J.C.G. Zhao, Adv. Synth. Catal. **356** (2014)

32. Q.S. Guo, M. Bhanushali, C.G. Zhao, Angew. Chem. Int. Ed. **49** (2010)
33. C. Shen, F.Y. Shen, H.J. Xia, P.F. Zhang, X.Z. Chen, Tetrahedron Asymmetr. **22** (2011)
34. C.W. Suh, C.W. Chang, K.W. Choi, Y.J. Lim, D.Y. Kim, Tetrahedron Lett. **54** (2013)
35. Y. Liu, P.C. Gao, J.F. Wang, Q. Sun, Z.M. Ge, R.T. Li, Synlett **23** (2012)
36. H.W. Zhao, W. Meng, Z. Yang, T. Tian, Z.H. Sheng, H.L. Li, X.Q. Song, Y.T. Zhang, S. Yang, B. Li, Chin. J. Chem. **32** (2014)
37. K.N. Tiwari, D. Bora, G. Chauhan, D. Yadav, K. Sharma, A. Thakur, L. Singh, V. Tripathi, Synth. Commun. **46** (2016)
38. Q.J. Zhou, Y. Wan, X.X. Zhang, L.Z. Zhang, H. Zou, H. Cui, S.L. Zhou, H.Y. Wang, H. Wu, Tetrahedron **71** (2015)
39. L.Z. Zhang, Y. Wan, X.X. Zhang, H. Cui, H. Zou, Q.J. Zhou, H. Wu, Tetrahedron Lett. **56** (2015)
40. R. Yuan, Y.J. Wang, Y. Fang, W.H. Ge, W. Lin, M.Q. Li, J.B. Xu, Y. Wan, Y. Liu, H. Wu, Chem. Eng. J. **316** (2017)
41. E. Pretsch, P. Buhlmann, C. Affolter, *Structure Determination of Organic Compounds Tables of Spectral Data* (Springer, Berlin, 2000)