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A versatile way for the synthesis of monomethylamines by reduction of *N*-substituted carbonylimidazolides with $NaBH_4/I_2$ system

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Abstract

An economical and versatile protocol for the one-pot synthesis of monomethylamines by reduction of the *N*-substituted carbonylimidazolides with $NaBH_4/I_2$ in THF at reflux was described. By this method, no special catalyst is used and various monomethylamines can be easily obtained in a moderate to good yield from a wide range of raw materials including amines (primary amines and secondary amines), carboxylic acids and isocyanates. Besides, interesting reduction selectivity was demostrated. Exploration of the reaction process shows that it undergoes a two-step pathway via the formamide intermediate and the reduction of the formamide intermediate to monomethylamine is the rate-determining step. This work can contribute significantly to better expanding the application of the N-substituted carbonylimidazolides.

Keywords

Monomethylamines; N-Substituted carbonylimidazolides; Reduction; Amines; Carboxylic acids; Isocyanates

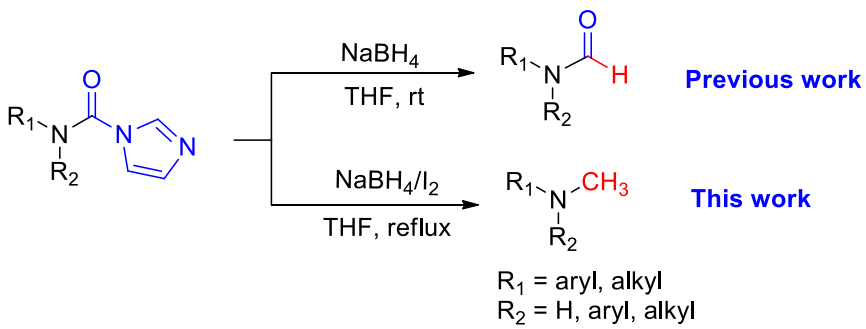
Introduction

N-Methyl amines are widely found in natural products, fine chemicals, agrochemicals, pharmaceuticals and dyes[1]. Traditional methods for the preparation of *N*-methyl amines involve the direct methylation of amines by using methyl halides[2], dimethyl sulphate[3], diazomethane[4], methyl triflate[5] or dimethyl carbonate[6] as the methylation reagents and the reductive amination reactions by using formaldehyde or paraformaldehyde as the “indirect” alkylation reagent[7]. Recently, a variety of promising methylating agents or C1 sources such as formic acid[8], methanol[9] and carbon dioxide (CO_2)[10] have been developed for the *N*-methylation of amines. However, these N-alkylation methods often require the employment of expensive catalysts, and the *N*-alkylation of primary amines generally does not stop with monomethylation as expected and inevitably provides a mixture of multiple methylated products because of the competing overalkylation reactions[6c,7,8,9,10,11].

In order to obtain pure monomethylation product, the conventional method is to introduce alkyl formate, formacyl, methylene or their equivalents to amines, followed by reduction to give methyl[12]. The protection/methylation/deprotection strategies have also been developed for the preparation of monomethylation objects, which are particularly suitable for peptide chemistry since the protecting groups are

often required in peptide synthesis[13]. These multi-step reaction methods are conducive to avoid overmethylation products.

Although procedures for the synthesis of monomethylamines have been developed over the past years, the starting materials are mainly restricted regarding amines, in addition, expensive reagents or catalysts are usually required, which limit their applications to some extent. *N*-substituted carbonylimidazolides are highly attractive intermediates with suitable stability for isolation or storage, and various good methods for preparing them have been developed by employing different starting materials such as amines[14], isocyanates[15] and carboxylic acids[16]. Because the carbonyl carbon atom on carbonylimidazolide moiety is easily attacked by nucleophile and the imidazole group is readily dissociated, the *N*-substituted carbonylimidazolides have favourable reactivity and can be widely used in the synthesis of various valuable products such as ureas[17], carbamates[17d,18], thiocarbamates[17d], cyanoformamides[19]. However, all of these works are primarily focused on the substitution reaction of *N*-substituted carbonylimidazolides. In our previous work, we conveniently prepared formamides by reducing N-substituted carbonylimidazolides with $NaBH_4$[16] (Scheme 1). The reaction mechanism shows that H^- ion acted as a nucleophile to attack the carbonyl carbon to cause the imidazolium ion to leave without reducing the carbonyl group. Although this work expands the application of N-substituted carbonylimidazolides, the reaction can still be regarded as a substitution reaction, which is attributed to the weak reducibility of $NaBH_4$.



Scheme 1. The synthesis of formamides and monomethylamines

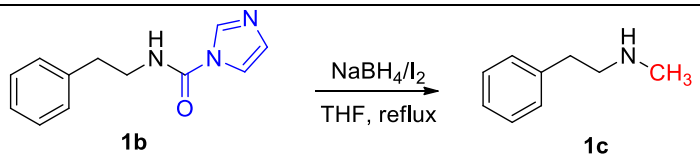
In this work, our goal is to reduce the carbonyl on N-substituted carbonylimidazolides. The inexpensive $NaBH_4/I_2$ system has great attraction because it is more reductive due to the generation of highly reactive BH_3-THF by adding iodine to $NaBH_4$ in THF [20] and the reaction conditions are not significantly changed compared to our previous preparation of formamide. With this reduction system, we achieved a one-step conversion from N-substituted carbonylimidazoliides to methylamine. This interesting work will help to synthesize pure monomethylamines from a wide range of raw materials including amines, carboxylic acids and isocyanates in a mild and safe reaction condition.

Results and Discussion

Initially, *N*-phenethyl carbonylimidazolide (**1b**) was chosen as a model substrate to react with 3.0 equiv. of $NaBH_4$ and 1.0 equiv. of I_2 in THF at reflux, as expected, the carbonylimidazolide moiety was successfully converted into methyl group and the target monomethylamine (**1c**) was obtained in 70% yield after 6 h (Table 1, entry 1). When the amount of $NaBH_4$ was increased from 3.0 equiv. to 4.0 equiv. and 5.0 equiv., the reaction time was shortened from 6 h to 4 h and 1 h, respectively. Further increasing the amount of $NaBH_4$ to 6.0 equiv., only a slight decrease of the reaction time was observed. In addition, the yield of **1c** showed few changes with the increase of the amount of $NaBH_4$ from 3.0 equiv. to 6.0 equiv. Obviously, 5.0 equiv. of $NaBH_4$ was optimal to perform the reaction. Since I_2 was used to improve the reducibility of $NaBH_4$, we next investigated the effect of the amounts of I_2 on the reaction. The use of 0.5 equiv. of I_2 in the presence of 5.0 equiv. of $NaBH_4$ afforded traces of methylamine but most of the *N*-phenethyl formamide in 6

h (Table 1, entry 5). Increasing the amount of I_2 from 1.0 equiv. to 1.5 equiv. (Table 1, entry 6), the reaction was not significantly accelerated. All the above results might indicate that an assembly of 1.0 equiv. of I_2 and 5.0 equiv. of $NaBH_4$ was sufficient to complete the reaction in one hour.

Table 1. Optimization of the reaction conditions.[a]



Entry	Starting material	$NaBH_4$ (equiv.)	I_2 (equiv.)	Time(h)[b]	Yield(%)[c]
1	**1b**	3.0	1.0	6	70
2	**1b**	4.0	1.0	4	72
3	**1b**	5.0	1.0	1	74
4	**1b**	6.0	1.0	0.9	75
5	**1b**	5.0	0.5	6	trace
6	**1b**	5.0	1.5	1	73

[a]The reactions were carried out with **1b** (1.0 equiv., 2 mmol), $NaBH_4$, I_2, THF (25 ml) under reflux.

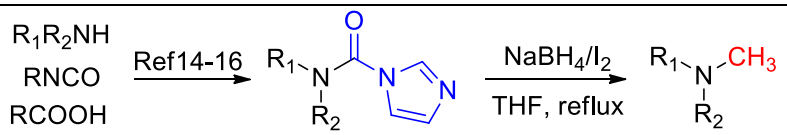
[b] The reaction was monitored by TLC.

[c] Isolated yield was based on **1c**.

With the optimized reaction conditions in hand, we investigated the synthesis of other *N*-methylamines from various *N*-substituted carbonylimidazolides (Table 2). As a proof of the versatility and applicability of the proposed method, *N*-substituted carbonylimidazolides were prepared from amines (**1b-14b**)[14,16,17b], isocyanates(**15b-17b**) [15], and carboxylic acids (**18b-20b**) [16], respectively (For detailed experimental procedures, see ESI). All types of these N-substituted carbonylimidazolides reacted smoothly with $NaBH_4/I_2$ to provide the corresponding N-methylamines in satisfactory yields.

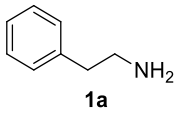
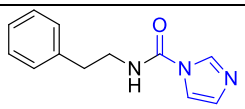
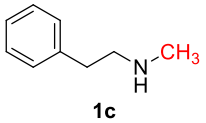
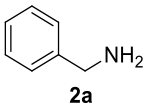
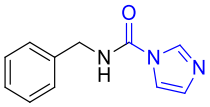
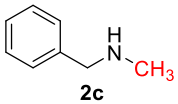
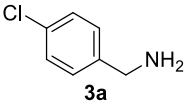
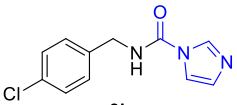
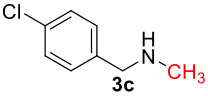
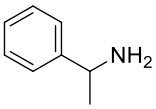
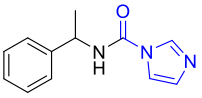
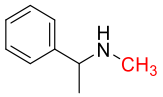
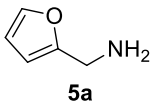
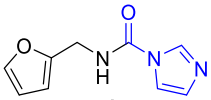
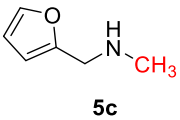
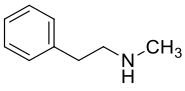
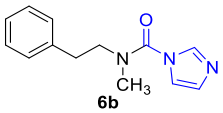
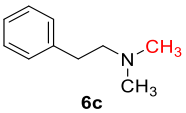
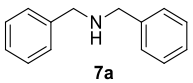
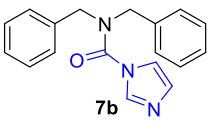
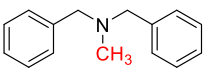
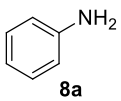
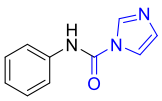
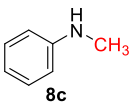
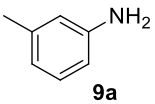
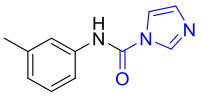
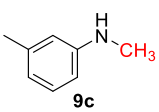
The impacts of different substituents on the reaction were well investigated. As shown in Table 2, the alkyl substituents (R) in the *N*-alkyl carbonylimidazolides had weak influence on the reaction (Table 2, entries 1-7, 18, 19). Whether bearing one substituent (e.g. **1b-5b**, **15b**, **18b**, **19b**) or two substituents (e.g. **6b** and **7b**) in the *N*-alkyl carbonylimidazolides, the reaction proceeded well, affording the desired product in 60-83% yields. Noted that the reaction time of **7b** (2 h) was obviously longer than that of **1b-6b** (1 h), **18b** (1 h) and **19b** (1 h), possibly because the steric hindrance of two benzyl groups on **7b** slowed the reaction. Encouraged by the above mentioned results, we then tested *N*-aryl carbonylimidazolides in the reaction. To our delight, *N*-aryl carbonylimidazolides with either electron-donating (**9b** and **10b**) or electron-withdrawing groups (**11b**, **16b** and **17b**) on the aryl rings were all transformed, affording the expected products in 70-85% yields. Bearing two substituents in the *N*-aryl carbonylimidazolides, such as **12b** (R^1= methyl, R^2= phenyl) and **13b** (R^1= phenyl, R^2= phenyl), they were also amenable to this protocol, giving the corresponding product **12c** and **13c** in 71% and 67% yield respectively. Furthermore, by using 2.0 equiv. of I_2 and 10.0 equiv. of $NaBH_4$, the substrate **14b** with double *N*-substituted carbonylimidazolide moieties could also undergo this reaction and provide the desired product **14c** in moderate yield (70%). Additionally, our protocol was applicable to prepare *N, N*-dimethylamines by step-by-step methylation way. Employing the mono-methylated product **1c** (**6a**) and **8c** (**12a**), *N, N*-dimethylamine **6c** and **12c** can be obtained respectively via repeating our synthesis procedure.

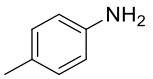
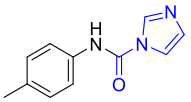
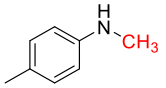
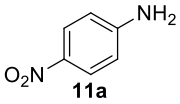
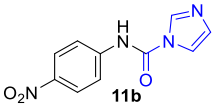
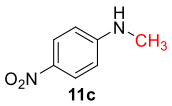
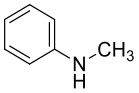
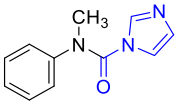
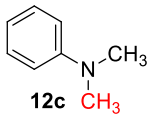
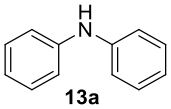
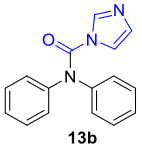
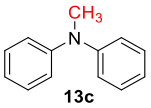
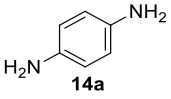
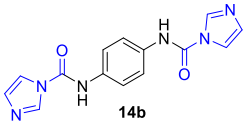
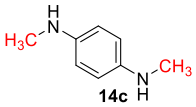
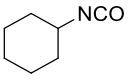
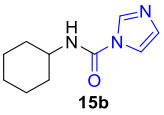
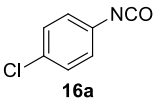
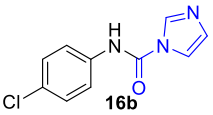
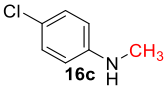
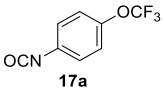
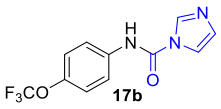
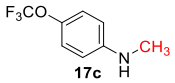
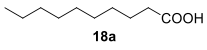
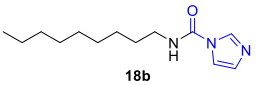
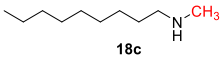
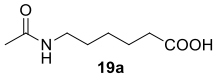
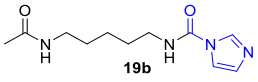
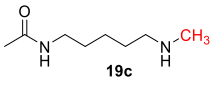
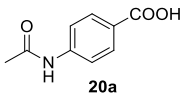
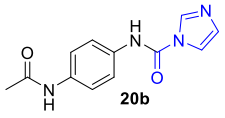
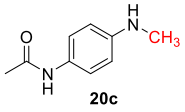
Table 2. Synthesis of monomethylamines from amines, carboxylic acids and isocyanates [a].



R^1 = aryl, alkyl

R^2 = H, aryl, alkyl

Entry	Substrate	Carbamoylimidazole	Time(h)[c]	Product	Yield(%)[d]
1	 1a	 1b	1	 1c	74
2	 2a	 2b	1	 2c	67
3	 3a	 3b	1	 3c	67
4	 4a	 4b	1	 4c	65
5	 5a	 5b	1	 5c	70
6	 6a(1c)	 6b	1	 6c	83
7	 7a	 7b	2	 7c	60
8	 8a	 8b	4	 8c	72
9	 9a	 9b	4	 9c	85

10	 **10a**	 **10b**	4	 **10c**	80
11	 **11a**	 **11b**	4	 **11c**	70
12	 **12a(8c)**	 **12b**	4	 **12c**	71
13	 **13a**	 **13b**	6	 **13c**	67
14[b]	 **14a**	 **14b**	10	 **14c**	70
15	 **15a**	 **15b**	1	 **15c**	74
16	 **16a**	 **16b**	4	 **16c**	74
17	 **17a**	 **17b**	4	 **17c**	72
18	 **18a**	 **18b**	1	 **18c**	75
19	 **19a**	 **19b**	1	 **19c**	65
20	 **20a**	 **20b**	4	 **20c**	68

[a]The reactions were carried out with **b** (1.0 equiv., 2 mmol), $NaBH_4$ (5.0 equiv., 10.0 mmol), I_2 (1.0 equiv., 2 mmol) and THF (25 ml) under reflux.

[b] 10.0 equiv. of $NaBH_4$ and 2 equiv. of I_2 was used.

[c] Monitored by TLC.

[d]Isolated yield was based on **b**.

In order to understand the reduction selectivity of the method, the substrates bearing acetamide groups (**19b** and **20b**) were tested in the reaction. To our pleasure, both aliphatic and aromatic amides reacted smoothly and provided the expected products in satisfactory yields, with the acetyl groups being unaffected. This suggested that the *N*-acetyl groups in *N*-substituted carbonylimidazolide were well tolerated during the reduction, and our method showed interesting reduction selectivity.

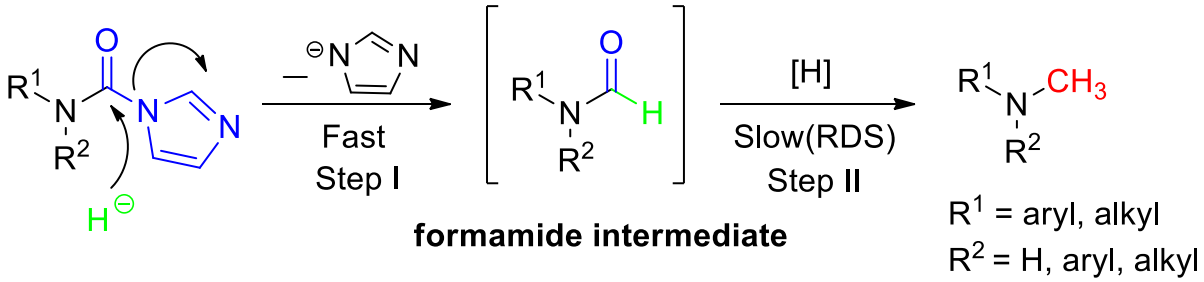
To gain some preliminary insight into the reaction process, two representative intermediates for the synthesis of aliphatic methylamine (**1c**) and aromatic methylamine (**8c**) had been isolated and identified as corresponding formamide (see ESI). Furthermore, by detecting the reaction with TLC, we found that the reaction time (hours) from the formamide intermediate to the corresponding methylamine product was much longer than the time (minutes) from the *N*-substituted carbonylimidazolide to the formamide. These indicated the reaction might undergo a two-step pathway via the formamide intermediate (**Scheme 2**).

In the first step (Step I), *N*-substituted carbonylimidazolides were rapidly converted into formamide intermediates at the attack of hydrogen anion as we had reported before[16]. Subsequently, the carbonyl group of formamide intermediates were reduced to furnish the desired *N*-methylamines in the second step (Step II) [21]. Step II proceeded much slower than Step I, so it could be treated as rate-determining step (RDS). The required longer reaction time for *N*-aryl carbonylimidazolides (over 4 h) than that for *N*-alkyl carbonylimidazolides (about 1 h) can be well explained by the two-step mechanism. In step I, the *N*-aryl carbonylimidazolides might react much faster than *N*-alkyl carbonylimidazolides, because the stronger conjugation system of

the resulting *N*-aromatic formamides made them more stable and easier to generate. However, these more stable *N*-aryl formamide intermediates were less reactive and directly slowed the reaction in step II, which resulted in longer reaction time of the *N*-arylcarbonylimidazolides in the whole reaction.

The substrate **13b**, bearing two phenyl, which not only had a large steric hindrance like **7b**, but also had a strong conjugation system, took much longer time (6 h) to complete the reaction.

As shown by the reaction mechanism, the methyl group was converted from the carbonylimidazolide moiety by full reduction and therefore no competing overalkylation reactions occured.



Scheme 2. The possible reaction mechanism.

Although the *N*-methyl amine could be prepared from carboxylic acid or amine by our method, the methyl source was remarkably different. For amine, the carbon source of CH_3 was from carbonyl of CDI; while for carboxylic acid, the carbon source came from the carboxyl group. When carboxylic acid was used, the carboxyl moiety was first converted to isocyanate via Curtius rearrangement[22], then reacted with imidazole to form carbonylimidazolide, and eventually reduced to the methyl moiety. In the whole process, no extra carbon was introduced.

Conclusion

In conclusion, we have developed an economical and versatile protocol for the one-pot synthesis of monomethylamines by reduction of the N-substituted carbonylimidazolides with $NaBH_4/I_2$ system. This work further extends the application of N-substituted carbonylimidazoles. By employing inexpensive and commercial available reagents, a variety of aliphatic and aromatic monomethylamines were obtained in moderate to good yields from a broad substrate scope including not only amines (both primary amines and secondary amines) but also carboxylic acids or isocyanates. The acetamide group was well tolerated in our reduction, implying our method showed interesting reduction selectivity.

Supporting Information

Supporting Information File 1:

File Name: BJOC-Supporting Information

File Format: word

Title: A versatile way for the synthesis of monomethylamines by reduction of N-substituted carbonylimidazolides with $NaBH_4/I_2$ system

Acknowledgements

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References

1. (a) Paul, B.; Shee, S.; Chakrabarti, K.; Kundu. K. *ChemSusChem* **2017,** *10,* 2370–2374. (b) Davis, D. A.; Hamilton, A.; Yang, J.; Cremar, L. D.; Gough, D. V.; Potisek,

S. L.; Ong, M. T.; Braun, P. V.; Martinez, T. J.; White, S. R.; Moore, J. S.; Sottos, N. R. *Nature* **2009,** *459,* 68–72. (c) Seayad, A.; Ahmed, M.; Klein, H.; Jackstell, R.; Gross, T.; Beller. M. *Science* **2002,** *297,* 1676–1678. (d) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001,** *57,* 7785–7811.

2. (a) Olsen, R. *J. Org. Chem.* **1970,** *36,* 1913–1915. (b) Schreiber, S. L.; Anthony, N. J.; Dorsey, B. D.; Hawley, R. C. *Tetrahedron Lett.* **1988,** *29,* 6577–6580. (c) Vedejs, E.; Kongkittingam, C. *J. Org. Chem.* **2001,** *66,* 7355–7364.

3. Prashad, M.; Har, D.; Hu, B.; Kim, H. Y.; Repic, O.; Blacklock, T. J. *Org. Lett.* **2003,** *5,* 125–128.

4. Leggio, A.; Alò, D.; Belsito, E. L.; Gioia, M. L. D.; Romio, E.; Siciliano, C.; Liguori, A. *J. Pept. Sci.* **2015,** *21,* 644–650.

5. (a) Lebleu, T.; Ma, X.; Maddaluno, J.; Legros, J. *Chem. Commun.* **2014,** *50,* 1836–1838. (b) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007,** *63,* 8658–8664.

6. (a) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2002**, *67,* 9238–9247. (b) Zheng, J. X.; Darcel, C.; Sortais, J. B. *Chem. Commun.* **2014,** *50*, 14229–14232. (c) Cabrero-Antonino, J. R.; Adam, R.; Junge, K.; Beller, M. *Catal. Sci. Technol.* **2016,** *6,* 7956–7966. (d) Seo, H.; Bedard, A.-C.; Chen, W. P.; Hicklin, R. W.; Alabugin, A.; Jamison, T. F. *Tetrahedron* **2018,** *74,* 3124–3128.

7. (a) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972,** *37,* 1673–1674. (b) Alinezhad, H.; Tajbakhsh, M.; Salehian, F.; Fazli, K. *Synth. Commun.* **2010,** *40,* 2415–2420. (c) Ge, X.; Luo, C.; Qian, C.; Yu, Z.; Chen, X. *RSC Adv.* **2014,** *4,* 43195–43203. (d) Petricci, E.; Santillo, N.; Castagnolo, D.; Cini, E.; Taddei, M. *Adv. Synth. Catal.* **2018,** *360,* 2560–2565.

8. (a) Savourey, S.; Lefe`vre, G.; Berthet, J. C.; Cantat, T. *Chem. Commun.* **2014,** *50,* 14033–14036. (b) Sorribes, I.; Junge, K.; Beller, M. *Chem. Eur. J.* **2014,** *20,* 7878–7883.

9. (a) Zhang, L. N.; Zhang, Y.; Deng, Y. Q.; Shi, F. *RSC Adv.* **2015,** *5,* 14514–14521. (b) Bruneau-Voisine, A.; Wang, D.; Dorcet, V.; Roisnel, T.; Darcel, C.; Sortais, J. B. *J. Catal.* **2017,** *347,* 57–62. (c) Neumann, J.; Elangovan, S.; Spannenberg, A.; Junge, K.; Beller, M. *Chem. Eur. J.* **2017,** *23,* 5410–5413. (d) Dang, T. T.; Ramalingam, B.; Seayad, A. M. *ACS Catal.* **2015,** *5,* 4082–4088. (e) Liang, R.; Li, S.; Wang, R.; Lu, L.; Li, F. *Org. Lett.* **2017,** *19,* 5790–5793. (f) Choi, G.; Hong, S. H. *Angew. Chem. Int. Ed.* **2018,** *57,* 6166–6170. (g) Maji, M.; Chakrabarti, K.; Paul, B.; Roy, B. C.; Kundu, S. *Adv. Synth. Catal.* **2018,** *360,* 722–729. (h) Jiang L.; Zhang X.; Wang Y.; Guo F.; Hou Z. *Asian J. Org. Chem.* **2021,** *10,* 1–6. (i) Wang, J.; Qiang, W.; Ye, S.; Zhu, L.; Liu, X.; Loh, T. *Catal. Sci. Technol.* **2021,** *11,* 3364–3375. (j) Paul, B.; Maji, M.; Panja, D.; Kundu, S. *Asian J. Org. Chem.* **2021,** DOI: 10.1002/ajoc.202100678.

10. (a) Jacquet, O.; Frogneux, X.; Gomes, C. D. N.; Cantat, T. *Chem. Sci.* **2013,** *4,* 2127–2131. (b) Li, Y. H.; Fang, X. J.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2013,** *52,* 9568–9571. (c) Yang, Z. Z.; Yu, B.; Zhang, H. Y.; Zhao, Y. F.; Ji, G. P.; Ma, Z. S.; Gao, X.; Liu, Z. M. *Green Chem.* **2015,** *17,* 4189–4193. (d) Niu, H. Y.; Lu, L. J.; Shi, R. Y.; Chiang, C. W.; Lei, A. W. *Chem. Commun.* **2017,** *53,* 1148–1151. (e) Cui, X.; Dai, X.; Zhang, Y.; Deng, Y.; Shi, F. *Chem. Sci.* **2014,** *5,* 649–655. (f) Tamura, M.; Miura, A.; Gu, Y.; Nakagawa, Y.; Tomishige, K. *Chem. Lett.* **2017,** *46,* 1243–1246. (g) Toyao, T.; Siddiki, S. M. A. H.; Morita, Y.; Kamachi, T.; Touchy, A. S.; Onodera, W.; Kon, K.; Furukawa, S.; Ariga, H.; Asakura, K.; Yoshizawa, K.; Shimizu, K.-i. *Chem. Eur. J.* **2017,** *23,* 14848–14859. (h)Lin, S.; Liu, J.; Ma L. *J. CO_2 Util.* **2021,** DOI: 10.1016/j.jcou.2021.101759.

11. (a) Du, X. L.; Tang, G.; Bao, H. L.; Jiang, Z.; Zhong, X. H.; Su, D. S.; Wang, J. Q. *ChemSusChem* **2015,** *8,* 3489–3496. (b) Santoro, O.; Lazreg, F.; Minenkov, Y.; Cavallob, L.; Cazin, C. S. J. *Dalton Trans.* **2015,** *44,* 18138-18144. (c) Jiang, X.; Wang, C.; Wei, Y.; Xue, D.; Liu, Z.; Xiao, J. *Chem. Eur. J.* **2014,** *20,* 58–63. (d) Goyal

V.; Naik, G.; Narani, A.; Natte, K.; Jagadeesh, R. V. *Tetrahedron* **2021,** DOI: 10.1016/j.tet.2021.132414.

12. (a) Paquette, L. A.; Tae, J. *J. Org. Chem.* **1988,** *63,* 2022–2030. (b) Benoit, W. L.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **2009,** *20,* 69–77. (c) Fuentes de Arriba, A. L.; Seisdedos, D. G.; Simon, L.; Alcazar, V.; Raposo, C.; Moran, J. R. *J. Org. Chem.* **2010,** *75,* 8303–8306. (d) Sun, N.; Wang, S.; Mo, W. M.; Hu, B. X.; Shen, Z. L.; Hu, X. Q. *Tetrahedron* **2010,** *66,* 7142–7148. (e) Barluenga, J.; Bayon, A. M.; Campos, P. J*. Chem. Soc., Perkin Trans. 1* **1988,** 1631–1636. (f) Crochet, R. A.; Blanton, C. B. *Synthesis* **1974,** 55–56. (g) Zhang, J.; Chang, H. M.; Kane, R. R. *Synlett* **2001,** 643–645. (h) Blackburn, C.; LaMarche, M. J.; Brown, J.; Che, J. L.; Cullis, C. A.; Lai, S.; Maguire, M.; Marsilje, T.; Geddes, B.; Govek, E.; Kadambi, V.; Doherty, C.; Dayton, B.; Brodjian, S.; Marsh, K. C.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2006,** *16,* 2621–2627.

13. (a) Das, D.; Khan, H. P. A.; Shivahare, R.; Gupta, S.; Sarkar, J.; Siddiqui, M. I.; Ampapathi, R. S.; Chakraborty, T. K. *Org. Biomol. Chem.* **2017,** *15*, 3337–3352. (b) Avula, K.; Mohapatra, D. K. *Tetrahedron Lett.* **2016,** *57*, 1715–1717.

14. (a) Rawling, T.; McDonagh, A. M.; Tattam, B.; Murray, M. *Tetrahedron* **2012,** *68,* 6065–6070. (b) Velavan, A.; Sumathi, S.; Balasubramanian, K. K. *Org. Biomol. Chem.* **2012,** *10*, 6420–6431. (c) McBurney, R. T.; Walton, J. C. *J. Am. Chem. Soc.* **2013,** *135*, 7349–7354.

15. (a) Jöst, C.; Nitsche, C.; Scholz, T.; Roux, L.; Klein, C. D. *J. Med. Chem.* **2014,** *57*, 7590–7599. (b) Ren, Y.; Rousseaux, S. A. L. *J. Org. Chem.* **2018,** *83,* 913−920. (c) Meng, H.; Sun, K.; Xu, Z.; Tian, L.; Wang, Y. *Eur. J. Org. Chem.* **2021,** 1768–1772.

16. Chen, Z.; Cao, Y; Tian, Z; Zhou, X.; Xu, W; Yang, J.; Teng, H. *Tetrahedron Lett.* **2017,** *58*, 2166–2170.

17. (a) Peng, Z. H.; Wong, J. W.; Hansen, E. C.; Puchlopek-Dermenci, A. L. A.; Clarke, H. J. *Org. Lett.* **2014,** *16*, 860–863. (b) Padiya, K. J.; Gavade, S.; Kardile, B.; Tiwari, M.; Bajare, S.; Mane, M.; Gaware, V.; Varghese, S.; Harel, D.; Kurhade, S. *Org. Lett.* **2012,** *14*, 2814–2817. (c) de. Greef, T. F. A.; Nieuwenhuizen, M. M. L.; Sijbesma, R. P.; Meijer, E. W. *J. Org. Chem.* **2010,** *75*, 598–610. (d) Duspara, P. A.; Islam, M. S.; Lough, A. J.; Batey, R. A. *J. Org. Chem.* **2012,** *77*, 10362–10368. (e) Wong, E. C. N.; Reekie, T. A.; Werry, E. L.; O'Brien-Brown, J.; Bowyer, S. L.; Kassiou, M. *Bioorg. Med. Chem. Lett.* **2017,** *27(11),* 2439-2442. (f) Venter, J.; Perez, C.; van Otterlo, W. A. L.; Martinez, A.; Blackie, M. A. L. *Bioorg. Med. Chem. Lett.* **2019,** *29(13),* 1597-1600. (g) Jones, C. D.; Simmons, H. T. D.; Horner, K.E.; Liu, K.; Thompson, R. L.; Steed, J. W. *Nat. Chem.* **2019,** *11(4),* 375-381. (h) Kondoh, A.; Ishikawa, S.; Terada, M. *J. Am. Chem. Soc.* **2020,** *142(8),* 3724-3728.

18. (a) Steve, P. R.; Nicola, J. D.; Ian, H. *Macromolecules* **2004,** *37*, 9418–9430. (b) Griffin, R. J.; Evers, E.; Davison, R.; Gibson, A. E.; Layton, D.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1996,** 1205–1211. (c) Alsarraf, J.; Petitpoisson, L.; Pichette, A. *Org. Lett*. ***2021****, 23(15),* 6052-6056. (d) Zhao, C.; Ye, Z.; Ma, Z.; Wildman, S. A.; Blaszczyk, S. A.; Hu, L.; Guizei, I. A.; Tang, W. *Nat. Commun.* **2019,** *10(1)*, 1-10.

19. Nugent, J.; Campbell, S. G.; Vo, Y.; Schwartz, B. D. *Eur. J. Org. Chem.* **2017,** *34,* 5110–5118.

20. (a) Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1992,** *48*, 4623–4628. (b) Rodrigues, A.; Olivato, P. R.; Rittner, R. *Synthesis* **2005,** *15*, 2578–2582; (c) Vagala, H.; Mariappan, P. *Tetrahedron: Asymmetry* **2017,** *28*, 175–180.

21. (a) Abinet, E.; Martin, D.; Standfuss, S.; Kulinna, H.; Spaniol, T. P.; Okuda, J. *Chem. Eur. J.* **2011,** *17*, 15014–15026. (b) Garnier-Amblard, E. C.; Mays, S. G.; Arrendale, R. F.; Baillie, M. T.; Bushnev, A. S.; Culver, D. G.; Evers, T. J.; Holt, J. J.; Howard, R. B.; Liebeskind, L. S.; Menaldino, D. S.; Natchus, M. G.; Petros, J. A.;

Ramaraju, H.; Reddy, G. P.; Liotta, D. C. *ACS Med. Chem. Lett.* **2011,** *2*, 438–443. (c) Nakagawa, Y.; Irie, K.; Yanagita, R. C.; Ohigashi, H.; Tsuda, K.; Kashiwagi, K.; Saito, N. *J. Med. Chem.* **2006,** *49*, 2683–2688.

22. (a) Teng, H. B.; He, Y. J.; Wu, L. M.; Su, J. T.; Feng, X. C.; Qiu, G. F.; Liang, S. C.; Hu, X. M. *Synlett* **2006,** *6*, 877–880. (b) Teng, H. B.; Zhang, Z. W.; Zhou, Y. F.; Chen, Z. Y.; Chen, Q.; Liu, Y.; Xu. W. J.; *RSC Adv.* **2015,** *5,* 71868–71872. (c) Balci, M. *Synthesis* **2018,** *50*, 1373–1401. (d) Wang, L.; Qin, R.; Yan, H.; Ding, M. *Synthesis* **2015,** *47,* 3522–3528.