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Synthesis of quinolines *via* sequential addition and I₂-mediated desulfurative cyclization†

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An efficient one-pot approach for the synthesis of quinolines from *o*-aminothiophenol and 1,3-ynone under mild conditions is disclosed. With the aid of ESI-MS analysis and parallel experiments, a three-step mechanism is proposed—a two-step Michael addition–cyclization condensation step leading to intermediate 1,5-benzothiazepine catalyzed by zirconocene amino acid complex Cp₂Zr(η¹-C₉H₁₀NO₂)₂, followed by I₂-mediated desulfurative step.

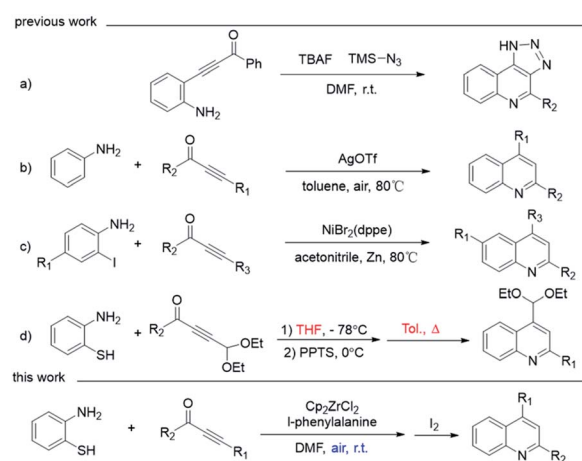
Introduction

Quinoline is a nitrogen containing heterocyclic aromatic compound^{1–5} which was first extracted from coal tar by Friedlieb Ferdinand Runge in 1834.⁶ Since that, extensive attention has been paid to the synthesis of quinolines and their derivatives for their broad range of pharmaceutical activity, such as anti-viral, anti-cancer and anti-HIV.^{7–9} Various synthetic transformations have been developed to obtain quinolines, including Combes synthesis,^{10–12} Skraup reaction,¹³ Conrad–Limpach synthesis,^{14–16} Povarov reaction,^{17,18} Doebner reaction,^{19,20} Doebner–Miller reaction,^{21–23} Gould–Jacobs reaction,^{24,25} Friedländer reaction,^{26–29} and so on. However, considering the extreme significance of quinoline derivatives, the development of mild and economic approaches is still attractive.

Recently, the ynones and amine synthons' combination toward the synthesis of quinolines have been verified as effective strategies,^{30,31} started by using preconnected starting materials containing both amine and ynone parts. For example, β-(2-aminophenyl)-α,β-ynones^{32–36} can undergo intramolecular cyclization to generate quinoline at room temperature (Scheme 1, entry a).³⁷ In contrast, the reaction between anilines and ynones *via* 3 + 3 cycloaddition is more direct and step-economical, thus became more popular. Although C–H activation of aniline has less demanding for starting material, the reaction usually needs to be driven by noble metal catalysts, such as AgOTf, under high temperature (entry b).³⁸ Therefore, using α-position preactivated aniline is more practical as cheap

metal catalyst could be adopted. For example, 2-iodoanilines and ynones can be catalyzed by a nickel-catalyzed cyclization to generate quinolines (entry c).³⁹ *o*-Sulfhydryl-aniline also proven to effective as preactivated 3-atom synthons,^{40,41} due to both the soft basic nature of sulfur atom for the ease to carry out 1,4-Michael addition reactions, and the viability to go through desulfurization *via* 7-membered ring's^{42–44} contraction from 1,5-benzothiazoles (entry d). However, such one-pot procedures are still suffering from negligible drawbacks, like incompatible solvent system for the thiol Michael addition and desulfurization processes, and high temperatures for desulfurization step. Therefore, it is still challenging to synthesize quinoline in one solvent under mild temperature.

In our previous work, by using titanocene complex as catalyst, 7-membered ring contained 1,5-benzodiazepines were successfully synthesized from *o*-phenylenediamine and 1,3-ynones through the [4 + 3] cyclization reaction under mild conditions, indicating such organometallic Lewis acid catalyst



Scheme 1 The synthesis of quinolines.

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can facilitate the Michael addition process and cyclization reaction at room temperature.⁴⁵ Additionally, the Lewis acidic catalytic activity^{46,47} and selectivity⁴⁸ of such metallocene could be conveniently adjusted by changing carboxylic acid ligand bearing different electronic characteristic,⁴⁹ based on our group's investigation accumulation of IVB metal based complex. In particular, the $-NH_2$ group as a Brønsted base is potential to activate *o*-aminothiophenol through hydrogen bonding. In this work, we disclosed a one-pot approach for the synthesis of quinolines from *o*-aminothiophenol and 1,3-ynone, catalyzed and mediated by Cp_2ZrCl_2 and I_2 at room temperature, *via* sequential thio-Michael addition, cyclization and desulfurization by ESI-MS and control experiments.

Results and discussion

It was proven in our previous study that solvents play important role for the synthesis of nitrogen containing cyclic products, so the solvent effect for the reaction were investigated initially. From the screening results shown in Table 1, we can see that aprotic polar solvent are helpful for the proceeding of the reaction, for example, 83% yield product could be produced when DMF was chosen (entry 6). What need to mention is that protic solvent, like EtOH, is extremely harmful for the reaction, as only 17% yield quinolines was afforded accompanied with a lot other byproducts, which might be attributed to the inhibition effect from the possible complexation between EtOH with zirconocene catalyst (entry 7). Next, we examined the ligand effect systematically by using various Brønsted acid ligand. In general, compared to aryl(heteroaryl) carboxylic acids (entries 13–15) and sulfonic acids (entry 16), amino acids ligands (entries 9–12) are more beneficial for the reaction. We tentatively speculate that the amino group on the ligand might be involved in the catalysis. At last, some other representative oxidant besides TBHP was evaluated, including H_2O_2 , DMP, and I_2 . It turns out that I_2 is the best option, as 92% yield product was obtained (entries 17–19). The yield of desired product declined to 60% without an oxidant (entry 20). Base on this optimized catalytic condition, a new one-pot method for the synthesis of quinolines have been developed.

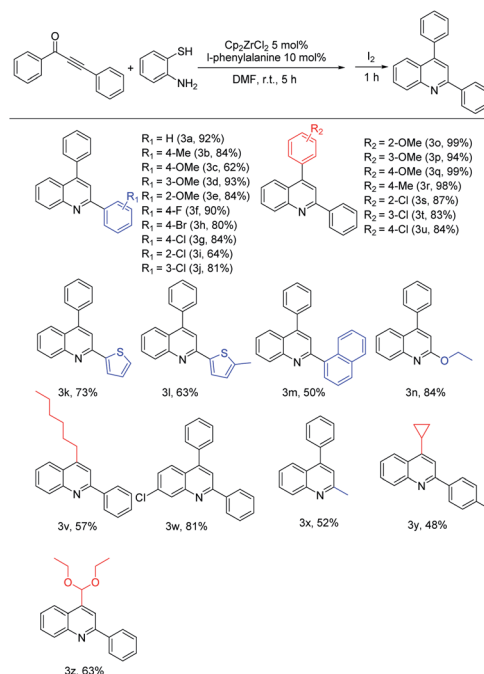
To further expand the substrate scope of this one-pot method, the utilization of 1,3-ynone derivatives was then explored (Table 2). The scope of this one-pot method concerning the substituents of the substrates was proven to be very wide. 1,3-Ynone bearing electron-donating and electron-withdrawing groups on the phenyl ring at the carbonyl group side were applied to the reaction. The introduction of electron-donating groups such as $-Me$ and $-OMe$ in different positions of the ring, affording quinolines in the yield range of 62–93% (**3b**, **3c**, **3d** and **3e**). Electron-withdrawing halogen groups like *p*-fluoro, *p*-chloro and *p*-bromo led to the desired products in good yields of 90%, 84% and 80% respectively (**3f–3h**). The reaction of *o*-chloro and *m*-chloro substituted 1,3-ynones proceeded to afford quinolines in good yields of 64% (**3i**) and 81% (**3j**), respectively. Fortunately, heterocyclic thiophene- methylthiophen- and naphthyl-substituted 1,3-ynone were also compatible with this reaction, giving products in yield of 73%,

Table 1 Solvent effect and ligand effect in the reaction of 1,3-ynones with *o*-aminothiophenol^a

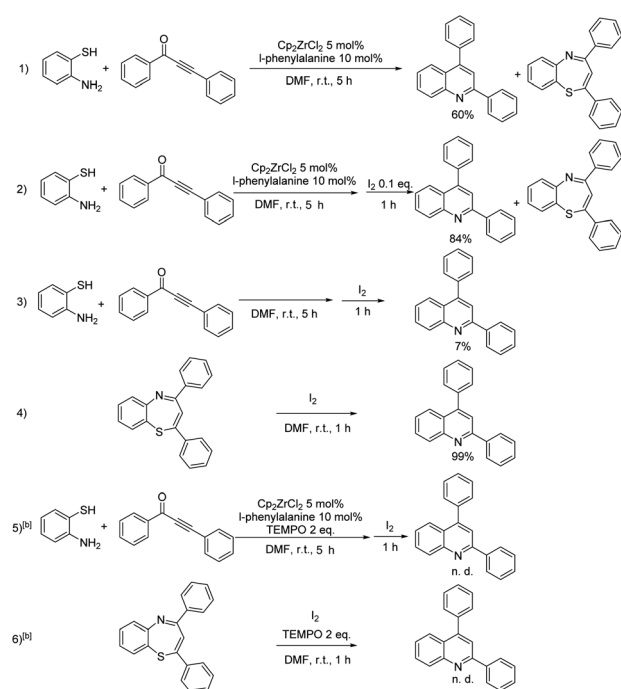
Run	Solvent	Ligand	Oxidant	Yield ^b (%)
1	Toluene	L-Phenylalanine	TBHP	56
2	CH ₂ Cl ₂	L-Phenylalanine	TBHP	56
3	THF	L-Phenylalanine	TBHP	43
4	1,4-Dioxane	L-Phenylalanine	TBHP	65
5	CH ₃ CN	L-Phenylalanine	TBHP	48
6	DMF	L-Phenylalanine	TBHP	83
7	DMSO	L-Phenylalanine	TBHP	67
7	EtOH	L-Phenylalanine	TBHP	17
9	DMF	Alanine	TBHP	78
10	DMF	Tyrosine	TBHP	80
11	DMF	Serine	TBHP	77
12	DMF	L-Proline	TBHP	77
13	DMF	Salicylic acid	TBHP	62
14	DMF	Benzoic acid	TBHP	60
15	DMF	2-Hydroxynicotinic acid	TBHP	52
16	DMF	Camphorsulfonic acid	TBHP	24
17	DMF	L-Phenylalanine	H ₂ O ₂	80
18	DMF	L-Phenylalanine	DMP	83
19	DMF	L-Phenylalanine	I ₂	92
20	DMF	L-Phenylalanine	—	60

^a Reaction conditions: 0.5 mmol of 1,3-ynone, 0.6 mmol of *o*-aminothiophenol, 5 mol% of Cp_2ZrCl_2 and 10 mol% of ligand in 1 mL DMF at room temperature for 5 h, then 0.6 mmol oxidant was added for 1 h. ^b Yield of the GC.

Table 2 Cyclization of 1,3-ynones and *o*-aminothiophenol^a



^a Reaction conditions: 0.5 mmol of 1,3-ynone, 0.6 mmol of *o*-aminothiophenol in the presence of 5 mol% Cp_2ZrCl_2 , 10 mol% of *l*-phenylalanine and 1 mL DMF at room temperature for 5 h, then 0.6 mmol I_2 was added for 1 h. Isolated yields were obtained after purification by column chromatography.

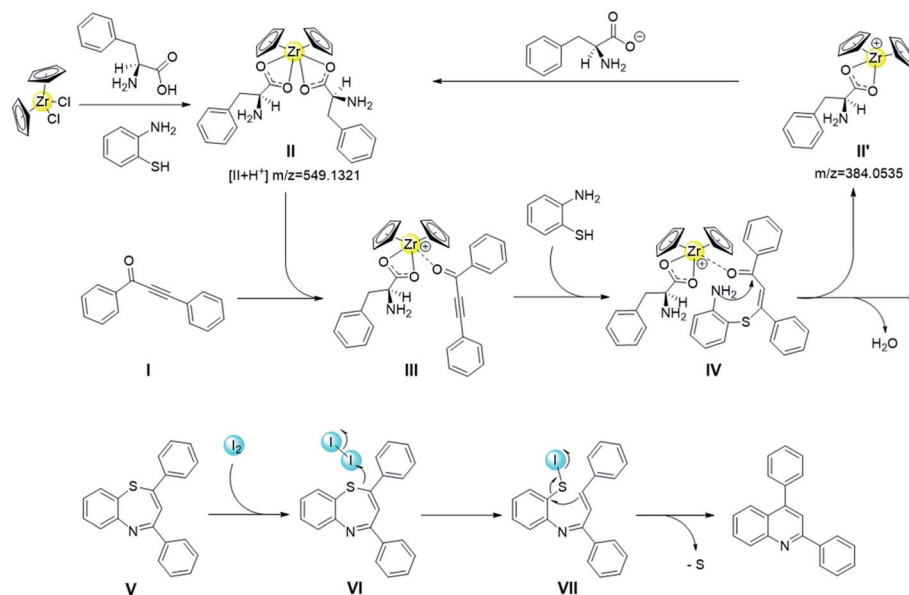
Table 3 Parallel experiments^a

^a Normal reaction conditions: 0.5 mmol of 1,3-ynone, 0.6 mmol of *o*-aminothiophenol in the presence of 5 mol% of Cp₂ZrCl₂, 10 mol% of *l*-phenylalanine and 1 mL DMF at room temperature for 5 h, then 0.6 mmol I₂ was added and reaction for 1 h, yields were obtained after separation and purification of the product by column chromatography. ^b Adding 2 equiv. of TEMPO.

63%, and 50%, respectively (**3k–3m**). Then we turned attention to test the toleration with aliphatic 1,3-ynones. Ethoxy-substituted 1,3-ynone afforded the product in 84% yield (**3n**). Methyl-substituted 1,3-ynone assured a yield in 52% (**3x**).

Secondly, we investigated the scope of this method concerning the impact of substitution of the alkyne side on 1,3-ynones. For *p*-methoxy, *m*-methoxy and *o*-methoxy substituents, the products were afforded in excellent yields of 99%, 94% and 99% (**3o–3q**), respectively. And *p*-methyl group also assured an excellent yield in 98% (**3r**). When electron-withdrawing substrates were subjected to this transformation, halogen groups like *o*-chloro, *m*-chloro and *p*-chloro also led to the product in good yields of 87%, 83% and 84% respectively (**3s–3u**). These results indicate that 1,3-ynones derivatives with whether electron-donating or electron-withdrawing groups can be used in this method to give excellent yields. Even for 1,3-ynone derivatives with aliphatic substituents, such as hexyl-, cyclopropyl- and diethoxymethyl-, were successfully applied to the reaction and gave the corresponding products in good yields (**3v**, **3y** and **3z**). Moreover, the *p*-chloro derivative of *o*-aminothiophenol provided the corresponding quinoline **3w** in an excellent yield of 81%.

The next task is to map the route for the reaction. To elucidate the action mode of this one-pot tandem reaction, some reactions were performed (Table 3). Under the oxidant-free condition, the conversion of 1,3-ynone was almost 100%, but the yield of the target product was only 60%, and 1,5-benzothiazepines in 40% yield was obtained (Table 3, entry 1). This result indicates that both 1,5-benzothiazepines containing 7-membered ring and quinolines containing 6-membered ring could be formed from 1,3-ynones and *o*-aminothiophenol without I₂. 0.1 equiv. of I₂ prompted the reaction to give the quinoline in yield of 84% (entry 2), which indicated that a small amount of oxidant benefits the conversion from 1,5-benzothiazepine to quinoline. Meanwhile, the reaction couldn't be catalyzed by the oxidant alone, for that only 7% yield of quinoline was detected in Cp₂ZrCl₂-free and ligand-free condition (entry 3). However, 1,5-benzothiazepine could be almost completely converted to quinoline by I₂, which further



Scheme 2 Plausible mechanism for the synthesis of quinolines.

suggested the positive effect of I₂ on the desulfurization of 1,5-benzothiazepine (entry 4). Regardless of the starting material, quinoline was not detectable after adding the radical scavenger TEMPO in the experiment (entries 5, 6). These results suggested that the iodine-mediated desulfurization is most likely a radical process. We also carried out ESI-MS experiment for the real reaction system, with important intermediates detected (proposed structures shown in Scheme 2), including zirconocene catalytic species Cp₂Zr(η¹-C₉H₁₀NO₂)₂ (II), and intermediate II'.

Taking all the aforementioned control experiment results and ESI-MS analysis together, a plausible reaction mechanism is proposed in Scheme 2. Initially, the zirconocene catalyst Cp₂Zr(η¹-C₉H₁₀NO₂)₂ is very likely to be formed *in situ* by the pre-catalyst and ligand in the presence of *o*-aminothiophenol.^{50,51} As one amino acid ligand is labile, the 1,3-ynone readily coordinated to the generated Cp₂Zr(η¹-C₉H₁₀NO₂)₂ to form the catalyst-substrate intermediate III, which facilitates a Michael addition with *o*-phenylenediamine to form an intermediate IV.⁴⁵ Then the intermediate IV experiences an intramolecular cyclization condensation, followed by the removal of one molecule of H₂O to form a seven-membered ring 1,5-benzothiazepine V, thus a catalytic cycle furnished. Finally, intermediate V experiences a desulfurization process mediated by I₂.⁵²⁻⁵⁴ An intermediate VI is formed from the V and iodine molecular *via* I-S coordination, followed by a cleavage of I-I bond that generates an intermediate VII. Finally, the subsequent intramolecular cycloaddition followed by cleavage of the C-S bond affords the quinoline framework.

Conclusions

In summary, a one-pot, tandem process has been developed for the synthesis of quinolines. The procedure for the synthesis of quinolines is composed of the Michael addition-cyclization condensation catalyzed by a Lewis acid catalyst, Cp₂Zr(η¹-C₉H₁₀NO₂)₂, generated *in situ*, and the desulfuration process promoted by I₂. ESI-MS analysis verified the tandem formation of quinolines underwent the less stable 1,5-benzothiazepine intermediates and designed control experiments clarified how the desulfurization conducted. This one-pot method is illuminated efficient for broad substrate scope that provides a new approach for the synthesis of quinolines.

Experimental

General procedure for the synthesis of the product 3a

A representative example for preparation of 2,4-diphenylquinoline (3a) is as following: a reactor was charged with 1,3-ynone (103 mg, 0.5 mmol), *o*-phenylenediamine (64.8 mg, 0.6 mmol), Cp₂ZrCl₂ (7.31 mg, 0.025 mmol), L-phenylalanine (8.26 mg, 0.05 mmol) and DMF (1 mL) to form a reaction system. The reaction was then carried out under magnetic stirring at room temperature for 5 hours, followed by adding I₂ (152.28 mg, 0.6 mmol) and continuing for another 1 hour. TLC analysis indicated the completion of the reaction. Finally, 4 mL of ethyl acetate was added to the reagent to form a mixture, in which the DMF and

iodine were washed away for three times with saturated sodium thiosulfate solution by extraction and separation. The organic phase was carried out *via* silica gel flash column chromatography (eluent: petroleum ether: EtOAc = 10:1) to obtain 129 mg of the target product, 3a (white solid, yield: 92%).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

- 1 V. Sridharan, P. A. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157–7259.
- 2 Y. Wang, C. Chen, J. Peng and M. Li, *Angew. Chem., Int. Ed.*, 2013, **52**, 5323–5327.
- 3 M. A. Gouda, A. A. Abu-Hashem and A. A. M. Abdelgawad, *J. Heterocycl. Chem.*, 2021, **58**, 908–927.
- 4 K. Ilina and M. Henary, *Chem.–Eur. J.*, 2021, **27**, 4230–4248.
- 5 A. Weyesa and E. Mulugeta, *RSC Adv.*, 2020, **10**, 20784–20793.
- 6 M. Akhil and C. Tejpal Singh, *Mini-Rev. Org. Chem.*, 2019, **16**, 631–652.
- 7 J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 166–187.
- 8 R. Kaur and K. Kumar, *Eur. J. Med. Chem.*, 2021, **215**, 113220.
- 9 F. A. Saddique, M. Farhad, S. Aslam and M. Ahmad, *Synth. Commun.*, 2021, **51**, 13–36.
- 10 S. Yuan, K. Zhang and J. Xia, *Asian J. Chem.*, 2013, **25**, 5535–5538.
- 11 S. E. Kharrat, P. Laurent and H. Blancou, *Tetrahedron*, 2014, **70**, 1252–1266.
- 12 S. Banerjee and R. N. Zare, *J. Phys. Chem. A*, 2019, **123**, 7704–7709.
- 13 J. Jin, S. Guidi, Z. Abada, Z. Amara, M. Selva, M. W. George and M. Poliakoff, *Green Chem.*, 2017, **19**, 2439–2447.
- 14 A. Monastyrskiy, N. K. Namelikonda and R. Manetsch, *J. Org. Chem.*, 2015, **80**, 2513–2520.
- 15 B. Lórincki, A. Csámpai, F. Fülöp and I. Szatmári, *RSC Adv.*, 2021, **11**, 543–554.
- 16 C. Tan, H. Xiang, Q. He and C. Yang, *Eur. J. Org. Chem.*, 2015, **2015**, 3656–3660.
- 17 S. Yamamoto, Z. Y. Zhou, G. Hiruta, K. Takeuchi, J.-C. Choi, T. Yasuda, T. Kanbara and J. Kuwabara, *J. Org. Chem.*, 2021, **86**, 7920–7927.
- 18 X.-X. Yu, P. Zhao, Y. Zhou, C. Huang, L.-S. Wang, Y.-D. Wu and A.-X. Wu, *J. Org. Chem.*, 2021, **86**, 8381–8388.
- 19 T. T. H. Hajalsiddig and A. E. M. Saeed, *Eur. J. Chem.*, 2019, **10**, 57–63.

- 20 N. Omidkhah and R. Ghodsi, *Synth. Commun.*, 2021, **51**, 1947–1955.
- 21 G. A. Ramann and B. J. Cowen, *Tetrahedron Lett.*, 2015, **56**, 6436–6439.
- 22 S. K. Ghosh and R. Nagarajan, *Tetrahedron Lett.*, 2016, **57**, 4009–4011.
- 23 M. N. Shahi, N. Perveen, M. N. Khan, S. Khakwani and M. A. Khan, *Asian J. Chem.*, 2016, **28**, 2665–2669.
- 24 N. M. Shah, V. C. Ramani and R. D. Shah, *Asian J. Chem.*, 2017, **29**, 2750–2754.
- 25 M. Wernik, P. E. Hartmann, G. Sipos, F. Darvas, A. D. Boese, D. Dallinger and C. O. Kappe, *Eur. J. Org. Chem.*, 2020, **2020**, 7051–7061.
- 26 N. Anand, S. Koley, B. J. Ramulu and M. S. Singh, *Org. Biomol. Chem.*, 2015, **13**, 9570–9574.
- 27 L. Guy, M. Mosser, D. Pitrat, J.-C. Mulatier, M. Kukułka, M. Srebro-Hooper, E. Jeanneau, A. Bensalah-Ledoux, B. Baguenard and S. Guy, *J. Org. Chem.*, 2019, **84**, 10870–10876.
- 28 J. Xu, Q. Chen, Z. Luo, X. Tang and J. Zhao, *RSC Adv.*, 2019, **9**, 28764–28767.
- 29 S. S. Choudhury, S. Jena, D. K. Sahoo, S. Shekh, R. K. Kar, A. Dhakad, K. H. Gowd and H. S. Biswal, *ACS Omega*, 2021, **6**, 19304–19313.
- 30 Y. Zhang, Y. Sun, Y. Wei and M. Shi, *Adv. Synth. Catal.*, 2019, **361**, 2129–2135.
- 31 B. Ganesan, K. Govindan, G. C. Senadi, M. Kandasamy and W.-Y. Lin, *Chem. Commun.*, 2020, **56**, 6488–6491.
- 32 G. Abbiati, A. Arcadi, F. Marinelli and E. Rossi, *Synthesis*, 2014, **46**, 0687–0721.
- 33 A. Arcadi, F. Marinelli and E. Rossi, *Tetrahedron*, 1999, **55**, 13233–13250.
- 34 G. Abbiati, A. Arcadi, F. Marinelli and E. Rossi, *Eur. J. Org. Chem.*, 2003, 1423–1427.
- 35 E. Rossi, G. Abbiati, V. Canevari, D. Nava and A. Arcadi, *Tetrahedron*, 2004, **60**, 11391–11398.
- 36 G. Abbiati, A. Arcadi, F. Marinelli, E. Rossi and M. Verdecchia, *Eur. J. Org. Chem.*, 2009, 1027–1031.
- 37 N. Sun, H. Yang, K. Zheng, L. Jin, B. Hu, Z. Shen and X. Hu, *Eur. J. Org. Chem.*, 2020, **2020**, 6805–6812.
- 38 X. Zhang and X. Xu, *Chem.-Asian J.*, 2014, **9**, 3089–3093.
- 39 R. P. Korivi and C.-H. Cheng, *J. Org. Chem.*, 2006, **71**, 7079–7082.
- 40 T. Masquelin and D. Obrecht, *Tetrahedron*, 1997, **53**, 641–646.
- 41 G. Cabarrocas, M. Ventura, M. Maestro, J. Mahía and J. M. Villalgordo, *Tetrahedron: Asymmetry*, 2001, **12**, 1851–1863.
- 42 G. Cabarrocas, S. Rafel, M. Ventura and J. M. Villalgordo, *Synlett*, 2000, 595–598.
- 43 T. Blitzke, D. Sicker and H. Wilde, *Synthesis*, 1995, 236–238.
- 44 L. Nagarapu, N. Ravirala and D. Akkewar, *Heterocycl. Commun.*, 2001, **7**, 237–242.
- 45 M. Yang, Y. Wang, Y. Jian, D. Leng, W. Zhang, G. Zhang, H. Sun and Z. Gao, *Mol. Catal.*, 2020, **498**, 111247.
- 46 Y. Luo, H. Sun, W. Zhang, X. Wang, S. Xu, G. Zhang, Y. Jian and Z. Gao, *RSC Adv.*, 2017, **7**, 28616–28625.
- 47 Y. Wu, C. Chen, G. Jia, X. Zhu, H. Sun, G. Zhang, W. Zhang and Z. Gao, *Chem.-Eur. J.*, 2014, **20**, 8530–8535.
- 48 X. Wang, Z. Wang, G. Zhang, W. Zhang, Y. Wu and Z. Gao, *Eur. J. Org. Chem.*, 2016, **2016**, 502–507.
- 49 Y. Wang, Y. Jian, Y. Wu, H. Sun, G. Zhang, W. Zhang and Z. Gao, *Appl. Organomet. Chem.*, 2019, **33**, e4925.
- 50 R. L. Webster, *RSC Adv.*, 2014, **4**, 5254–5260.
- 51 T. M. Klapötke, H. Köpf, I. C. Tornieporth-Oetting and P. S. White, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1518–1519.
- 52 J. Nath, B. K. Patel, L. Jamir, U. B. Sinha and K. V. V. Satyanarayana, *Green Chem.*, 2009, **11**, 1503–1506.
- 53 M. S. Chernov'yants, I. V. Burykin, Z. A. Starikova, A. Y. Tereznikov and T. S. Kolesnikova, *J. Mol. Struct.*, 2013, **1047**, 204–208.
- 54 S. Zhang, Q. Zhao, Y. Zhao, W. Yu and J. Chang, *Adv. Synth. Catal.*, 2020, **362**, 1993–1997.