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An improved synthesis of telmisartan *via* the copper-catalyzed cyclization of *o*-haloarylamidines†

 Junchi Zhang,^{ab} Rui Li,^{ab} Fuqiang Zhu,^c Changliang Sun^{*c} and Jingshan Shen^{ID *ab}

A concise synthetic route was designed for making telmisartan. The key bis-benzimidazole structure was constructed *via* the copper-catalyzed cyclization of *o*-haloarylamidines. By adopting this approach, telmisartan was obtained in a 7-step overall yield of 54% starting from commercially available 3-methyl-4-nitrobenzoic acid, and the use of HNO₃/H₂SO₄ for nitration and polyphosphoric acid (PPA) for cyclization in the reported literatures were avoided.

1. Introduction

Telmisartan **1**, a potent and selective angiotensin II type 1 (AT₁) receptor antagonist, is one of the top-selling drugs for the treatment of essential hypertension.^{1,2} This drug is marketed under the brand name of Micardis®, and is characterized by excellent AT₁ receptor binding affinity, long half-life, and good tolerability.^{1–3}

Take a brief look at the structure of telmisartan, it is assembled from two different benzimidazole subunits and a biphenyl-2-carboxylic acid fragment. The original approach was reported by Ries *et al.* in 1993 (Scheme 1),⁴ in which, the central benzimidazole ring was initially constructed stepwise from 4-amino-3-methylbenzoic acid methyl ester **2**. Subsequently, after the saponification of **3**, the bis-benzimidazole intermediate **5** was formed *via* the condensation between the free carboxyl group of the central benzimidazole moiety and *N*-methyl-1,2-benzenediamine **4**. Finally, alkylation of **5** with the substituted biphenyl fragment **6** was followed by hydrolysis, and afforded the final product **1** in an eight-step overall yield of 21%.

However, excess amount of nitration reagent HNO₃/H₂SO₄ was utilized among the formation of the central benzimidazole moiety, which might bring concerns to safety and wastewater disposal.^{5–8} In addition, the crucial intermediate **5** was built using the viscous PPA as the solvent, increased the difficulty of production operation and sewage treatment.⁹ Moreover, regioisomer impurity was inevitable in the alkylation of **5** with **6**,

which might cause enhanced difficulty with purification and lose on yield.

Several routes with different synthetic strategies have been reported.^{2,10–13} Wang *et al.* adopted a PPA-free method to constructed the methylbenzimidazole ring by employing the cyclocondensation between aromatic aldehyde and *o*-phenylenediamine.² In addition, Goossen *et al.* developed a reductive amination–condensation sequence to build the central benzimidazole moiety,¹⁰ completely avoided the regioisomer impurity. However, the problem of the excess use of nitration reagent still remains in the above two routes. Martin *et al.* reported a convergent approach to the synthesis of telmisartan *via* a Suzuki cross-coupling, which is direct and efficient.¹³ However, considering the fact that palladium catalysts were utilized in two steps of the route, the price element might be taken into account.

Transition-metal-catalyzed cross-coupling reactions belong to the frontier areas in modern organic chemistry, among which, the copper-catalyzed Ullmann-type reaction are widely utilized in C–N bond formation due to the high efficiency, low cost, and low toxicity of copper catalysts.^{14–17} Considerable efforts have been devoted to the copper-catalyzed synthesis of benzimidazole derivatives,^{18–22} in which the cyclization of *o*-haloarylamidines has drawn much attention.^{23–29} Herein, we explored the idea to build the key bis-benzimidazole structure of telmisartan *via* the copper-catalyzed cyclization of *o*-haloarylamidines,^{30,31} which were accessible to be obtained from *o*-haloarylamines (Scheme 2). This approach was suitable to produce telmisartan with good overall yield while avoiding the shortcomings associated with the reported routes.

2. Results and discussion

2.1 Synthesis of *o*-haloarylamidines **12a–c** and **14**

Initially, the *o*-haloarylamines **10a–c** were formed in three steps starting from commercially available 3-methyl-4-nitrobenzoic

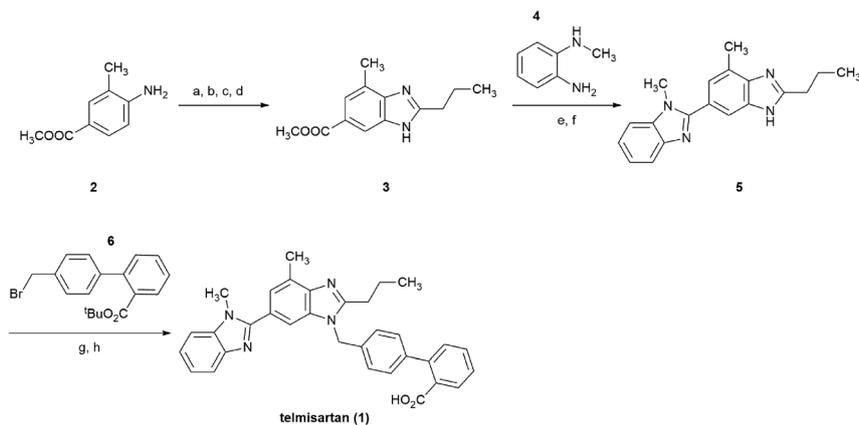
^aCAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences (CAS), 555 Zuchongzhi Road, Shanghai 201203, People's Republic of China. E-mail: shenjingshan@simm.ac.cn

^bUniversity of Chinese Academy of Sciences, No. 19A Yuquan Road, Beijing 100049, People's Republic of China

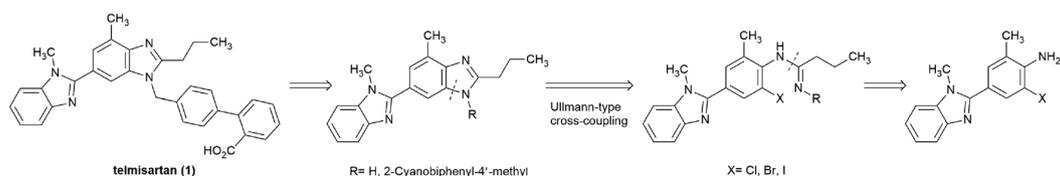
^cTopharman Shanghai Co., Ltd, Building 1, No. 388 Jialilue Road, Zhangjiang Hitech Park, Shanghai 201203, People's Republic of China. E-mail: changliang.sun@topharman.cn

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Scheme 1 Original approach for the synthesis of telmisartan. Reagents and conditions: (a) *n*-PrCOCl, C₆H₅Cl, 100 °C; (b) HNO₃/H₂SO₄, 0 °C; (c) Pd/C, 5 bar H₂, MeOH; (d) AcOH, reflux; (e) NaOH, MeOH/H₂O, reflux; (f) **4**, PPA, 150 °C; (g) **6**, *t*-BuOK, DMF, rt; (h) TFA, DCM, rt.



Scheme 2 Retrosynthetic analysis of telmisartan.

acid **7** (Scheme 3). An amidation–condensation sequence was conducted from compound **7** with **4**, afforded **8** in the yield of 85%. Afterwards, reduction of nitro group was easy to occur under Pd/C–H₂ condition, and the downstream selective halogenation of **9** was amenable to be carried out by *N*-halosuccinimides, gave the *o*-haloarylamines **10a–c** with satisfactory regioselectivity and yields, probably due to the higher reactivity on *ortho*-amino position of **9**. Furthermore, the isolated yields of both *o*-bromoarylamine **10b** (86%) and *o*-iodoarylamine **10c** (89%) were higher than *o*-chloroarylamine **10a** (70%).

Subsequently, with the *o*-haloarylamines **10a–c** in hand, efforts were focused on the construction of the *o*-haloarylamidines **12a–c** and **14** (Scheme 3). Firstly, **12a–c** were directly prepared from **10a–c** with *n*-butyronitrile in the presence of Lewis acids or Brønsted acids,³² however, yields of **12a–c** in this method were low (<50%), probably due to the steric hindrance and electronic effect of the *ortho*-halogen in primary arylamines **10a–c**. Hence, we adopted the approach to construct **12a–c** and **14** from the arylamides **11a–c**, which could be easily prepared from **10a–c** through a base-free acylation reaction. The classic method for preparing arylamidines from arylamides usually requires oxalyl chloride/thionyl chloride/phosphorus chloride and so on, however, we attempted herein to introduce triphosgene (also named bis(trichloromethyl)carbonate), regarded broadly as a cleaner alternative, in our synthetic route. Direct reaction of compound **11a–c** as free bases with triphosgene resulted in a rapid decomposition of triphosgene, while the monohydrochloride salts of **11a–c** facilitated the chlorination step greatly, and the following quenching with

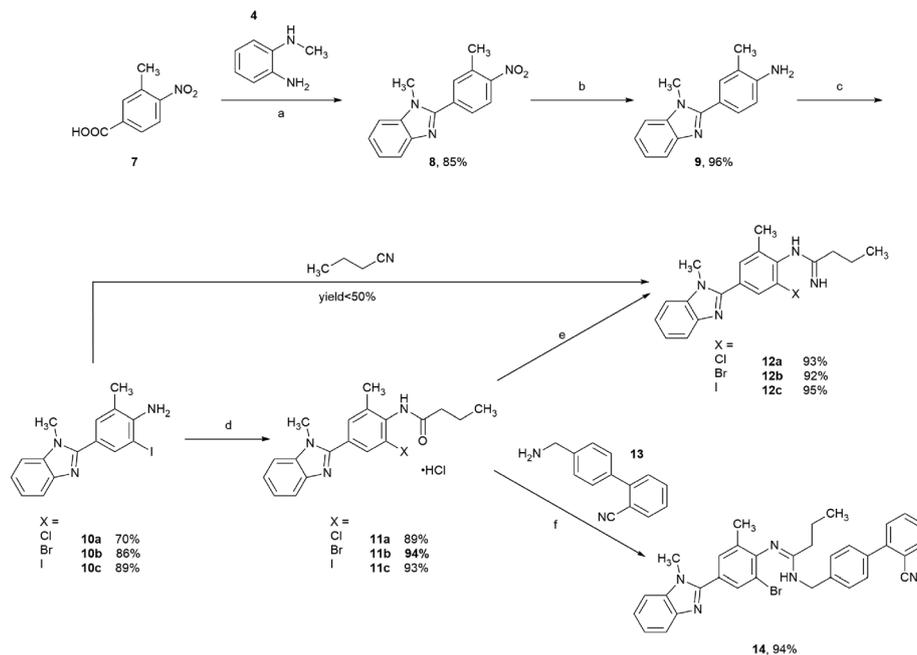
NH₃ solution in methanol or 4'-(aminomethyl)-[1,1'-biphenyl]-2-carbonitrile **13** (commercially available and is easy to obtain *via* reported methods^{33,34}), afforded *N*-monosubstituted *o*-haloarylamidines **12a–c** and *N,N'*-disubstituted *o*-haloarylamidine **14** with high yields. Furthermore, based on the construction of the *N,N'*-disubstituted *o*-haloarylamidine **14**, the biphenyl moiety was introduced prior to the cyclization of the central benzimidazole ring, circumvented the generation of undesirable regioisomer caused by the *N*-alkylation of the benzimidazole ring in the previously reported method.¹⁰

2.2 Optimization of the reaction conditions for the cyclization of *o*-haloarylamidines

The final cyclization of **12a–c** and **14** was conducted *via* the Ullmann-type cross-coupling reaction. Since the copper-catalyzed cyclization of *o*-haloarylamidines were the key steps in our research, efforts were devoted to the optimization of reaction conditions for the *o*-bromoarylamidine **12b** (Table 1).

As shown in entries 1–10, the impact of solvents was enormous according to the results of HPLC. DMSO exhibited a better result than DMF, dioxane, or toluene, indicating a favored solvent circumstance with higher polarity (Table 1, entries 1–2, entries 4–5), and also a favored condition of higher temperature (Table 1, entries 3). But pure water as solvent worked not effectively due to the low solubility of organic compounds (entry 6). Therefore, biphasic system of water and hydrosoluble solvents instead of DMSO provided a potential solution for the contradiction of polarity and solubility as described above (entries 7–10). The level of **5** reached 91.8% in 1,4-dioxane/H₂O





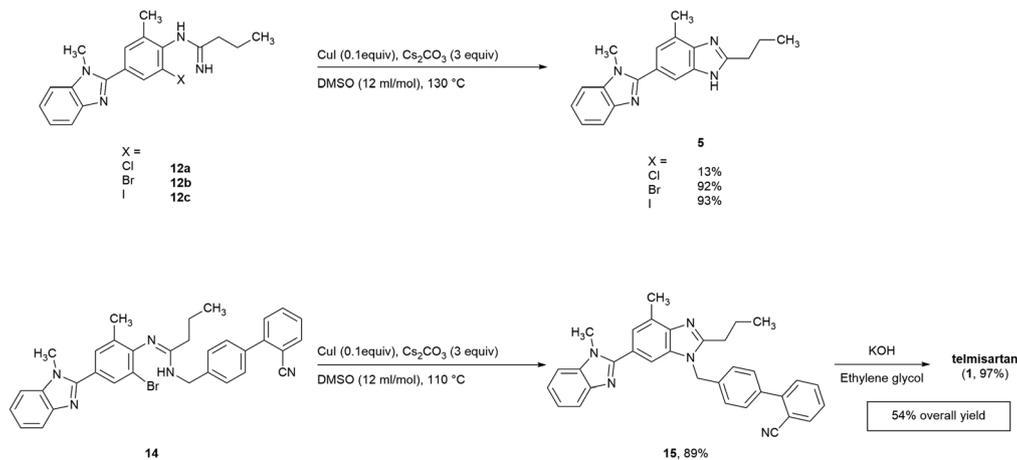
Scheme 3 Synthesis of *o*-haloarylamidines **12a–c** and **14**. Reagents and conditions: (a) (i) oxalyl chloride, DMF, DCM, 0 °C, rt; (ii) **4**, DIPEA, DCM, 0 °C, rt; (iii) TsOH·H₂O, toluene, reflux; (b) Pd/C, 5 bar, MeOH, THF, 50 °C; (c) *N*-halosuccinimide; (d) *n*-PrCOCl, MeCN, reflux; (e) (i) triphosgene, DMF, MeCN, reflux; (ii) NH₃ (7.0 M solution in MeOH); (f) (i) triphosgene, DMF, MeCN, reflux; (ii) **13**, Et₃N, DCM.

Table 1 Optimization of the reaction conditions for the cyclization of **12b**^a

Entry	Solvent	Temp. (°C)	Catalyst	Ligand (0.1 equiv.)	Base	HPLC results in reaction mixture ^b (%)			
						5	12b	11b	10b
1	DMF	110	CuI	DMEDA	CS ₂ CO ₃	79.4	16.9	1.2	2.5
2	DMSO	110	CuI	DMEDA	CS ₂ CO ₃	91.0	6.2	0.9	1.9
3	DMSO	130	CuI	DMEDA	CS ₂ CO ₃	98.5	<0.1	0.2	1.3
4	Toluene	Reflux	CuI	DMEDA	CS ₂ CO ₃	12.6	86.6	0.8	— ^c
5	1,4-Dioxane	Reflux	CuI	DMEDA	CS ₂ CO ₃	32.0	66.0	<0.1	2.0
6	H ₂ O	Reflux	CuI	DMEDA	CS ₂ CO ₃	4.1	94.4	1.5	0
7	1,4-Dioxane/H ₂ O ^d	Reflux	CuI	DMEDA	CS ₂ CO ₃	91.8	7.6	<0.1	0.5
8	MeCN/H ₂ O ^d	Reflux	CuI	DMEDA	CS ₂ CO ₃	63.6	34.5	1.3	0.6
9	2-Me-THF/H ₂ O ^d	Reflux	CuI	DMEDA	CS ₂ CO ₃	71.9	26.1	1.9	<0.1
10	DME/H ₂ O ^d	Reflux	CuI	DMEDA	CS ₂ CO ₃	87.9	10.8	0.4	0.9
11	DMSO	130	— ^e	— ^e	CS ₂ CO ₃	1.4	44.0	1.2	53.4
12	DMSO	130	CuI	— ^e	CS ₂ CO ₃	97.8	0.3	0.3	1.5
13	DMSO	130	CuBr	— ^e	CS ₂ CO ₃	97.6	0	0.6	1.9
14	DMSO	130	CuCl	— ^e	CS ₂ CO ₃	96.7	0.5	1.0	1.8
15	DMSO	130	Cu ₂ O	— ^e	CS ₂ CO ₃	96.4	0	0.8	2.8
16	DMSO	130	CuBr ₂	— ^e	CS ₂ CO ₃	82.0	10.7	1.2	6.0
17	DMSO	130	CuCl ₂	— ^e	CS ₂ CO ₃	83.1	10.5	1.2	5.2
18	DMSO	130	CuO	— ^e	CS ₂ CO ₃	61.3	17.7	1.1	19.9
19	DMSO	130	Cu(OAc) ₂	— ^e	CS ₂ CO ₃	71.4	21.7	1.3	5.6
20	DMSO	130	CuI	— ^e	K ₂ CO ₃	83.3	12.8	1.5	2.4
21	DMSO	130	CuI	— ^e	KOH	97.0	0	0.5	2.5

^a The reactions were performed on the scale of 0.5 mmol of **12b** under the conditions: 0.1 equiv. of copper catalyst, 3.0 equiv. of base, 12 ml mmol⁻¹ of solvent, heat for 8 h. ^b Calculated for the reaction mixture from the HPLC area percentage at 220 nm. ^c Not detected. ^d The ratio of mixed solvents was 2 : 1 by volume. ^e Not added.





Scheme 4 Synthesis of bis-benzimidazole intermediates and telmisartan.

(entry 7), and the slightly lower efficiency might be derived from the relative lower boiling point of biphasic solvent systems. Taken all together, DMSO was regarded as the optimal solvent system for further research.

Since several metal-free,^{35–37} and ligand-free^{23,26} conditions were reported for the cyclization of *o*-haloarylamidines, the necessity of copper catalyst and ligand in our route was subsequently investigated (entries 11 and 12). The copper catalyst was proved to be essential, since a significant decline of **5**, along with an obvious augment of impurity **10b** were observed in the absence of copper (entry 11). Moreover, in a ligand-free condition (entry 12), there was almost no change in the levels of **5** and impurities **10b**, **11b**, and **12b** in comparison with the result in entry 3, suggesting additional ligand could be dispensable in our method, and the coordination effect between copper catalyst and the benzimidazole subunit from substance might play a very similar role in the reaction system.^{38,39}

Afterwards, a series of commonly utilized copper catalysts were investigated in DMSO under a ligand-free condition, using three equivalents of Cs₂CO₃ as the base (entries 12–19). Copper(i) salts displayed distinct advantages over copper(ii) catalysts, and CuI (entry 12) was selected as the optimal choice. In addition, the evaluation of bases was also carried out (entries 12, 20 and 21). Three commonly used bases were employed, and the results showed that both Cs₂CO₃ and KOH displayed higher yields than K₂CO₃.

As a consequence, the utilization of CuI (0.1 equiv.) and Cs₂CO₃ (3.0 equiv.) in DMSO (entry 12) was chosen as the optimal condition for the cyclization of **12b**, and the key bis-benzimidazole intermediate **5** was obtained in an isolated yield of 92% in such manner (Scheme 4).

2.3 Synthesis of bis-benzimidazole intermediates and telmisartan

Based on the screening results of **12b**, the cyclization of other *o*-haloarylamidines **12a**, **12c**, and **14** were subsequently conducted in DMSO under the similar conditions (Scheme 4). The isolated yield of **5** obtained from the iodo precursor **12c** (93%) was

similar with that from **12b**. However, such yield of the cyclization of **12a** was merely 13%, which may be caused by the poor leaving group ability of chlorine, while the yield of the impurity **10a** could reach the level of 82%, suggesting the competitive relationship between cyclization and hydrolysis reactions in this step.

The traditional method for the preparation of compound **15**, an industrially widely utilized precursor of telmisartan,^{40–42} requires the *N*-alkylation compound of **5** with the 2-cyano-4'-(bromomethyl)biphenyl, resulting in regioisomer impurities. Herein, the cyclization of *N,N'*-disubstituted *o*-haloarylamidine **14** was utilized, offering **15** in an isolated yield of 89%. Afterwards, the downstream cyano-group hydrolysis was able to achieve through reported method,⁴¹ leading to the formation of the final product with 97% yield after simple purification.

3. Conclusions

In conclusion, an improved synthesis was developed for the preparation of telmisartan, featuring a ligand-free copper-catalyzed cyclization of benzimidazolyl-substituted *o*-haloarylamidines to form the core bis-benzimidazole fragment, while the use of HNO₃/H₂SO₄ and PPA in the original route was averted. Furthermore, our approach provided a new manner for introducing the biphenyl-4-methyl subunit, which avoided the generation of regioisomer impurities in the traditional *N*-alkylation method. By adopting this route, telmisartan was obtained in a 7-step overall yield of 54%, while achieving an all-around improvement in safety, waste disposal, and operability. In the long run, such copper-catalyzed cyclization strategy brings a new avenue to the preparation of drugs and their derivatives containing benzimidazole pharmacophores.

Conflicts of interest

There are no conflicts of interest to declare.



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Notes and references

- 1 M. Sharpe, B. Jarvis and K. L. Goa, *Drugs*, 2001, **61**, 1501–1529.
- 2 P. Wang, G.-j. Zheng, Y.-p. Wang, X.-j. Wang, H.-g. Wei and W.-s. Xiang, *Tetrahedron*, 2012, **68**, 2509–2512.
- 3 A. J. Battershill and L. J. Scott, *Drugs*, 2006, **66**, 51–83.
- 4 U. J. Ries, G. Mihm, B. Narr, K. M. Hasselbach, H. Wittneben, M. Entzeroth, M. J. C. van, W. Wienen and N. H. Huel, *J. Med. Chem.*, 1993, **36**, 4040–4051.
- 5 M.-X. Zhang, A. J. DeHope and P. F. Pagoria, *Org. Process Res. Dev.*, 2019, **23**, 2527–2531.
- 6 K. Qiao and C. Yokoyama, *Chem. Lett.*, 2004, **33**, 808–809.
- 7 K. K. Laali and V. J. Gettwert, *J. Org. Chem.*, 2001, **66**, 35–40.
- 8 L. Lu, J. Xin, C.-S. Woo, T. Cai and H.-I. Lee, *Stud. Surf. Sci. Catal.*, 2006, **159**, 353–356.
- 9 J. T. Vicenzi, T. Y. Zhang, R. L. Robey and C. A. Alt, *Org. Process Res. Dev.*, 1999, **3**, 56–59.
- 10 L. J. Goossen and T. Knauber, *J. Org. Chem.*, 2008, **73**, 8631–8634.
- 11 A. S. Kumar, S. Ghosh, G. N. Mehta, R. Soundararajan, P. S. R. Sarma and K. Bhima, *Synth. Commun.*, 2009, **39**, 4149–4157.
- 12 A. Sanjeev Kumar, S. Ghosh and G. N. Mehta, *Beilstein J. Org. Chem.*, 2010, **6**, 25.
- 13 A. D. Martin, A. R. Siamaki, K. Belecki and B. F. Gupton, *J. Org. Chem.*, 2015, **80**, 1915–1919.
- 14 S. Bhunia, G. G. Pawar, S. V. Kumar, Y. W. Jiang and D. W. Ma, *Angew. Chem., Int. Ed.*, 2017, **56**, 16136–16179.
- 15 S. H. Cho, J. Yoon and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 5996–6005.
- 16 K. Sun, S. Q. Mu, Z. H. Liu, R. R. Feng, Y. L. Li, K. Pang and B. Zhang, *Org. Biomol. Chem.*, 2018, **16**, 6655–6658.
- 17 F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954–6971.
- 18 T. Liu and H. Fu, *Synthesis*, 2012, **44**, 2805–2824.
- 19 M. Langeron and K. M. H. Nguyen, *Synthesis*, 2018, **50**, 241–253.
- 20 Y. Y. Qu, L. Pan, Z. Q. Wu and X. G. Zhou, *Tetrahedron*, 2013, **69**, 1717–1719.
- 21 J. H. Li, S. Benard, L. Neuville and J. P. Zhu, *Org. Lett.*, 2012, **14**, 5980–5983.
- 22 D. Yu, Q. You, X. M. Zhang, G. D. Tao and W. Zhang, *Appl. Organomet. Chem.*, 2016, **30**, 695–698.
- 23 P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul and T. Punniyamurthy, *J. Org. Chem.*, 2009, **74**, 8719–8725.
- 24 J. S. Peng, M. Ye, C. J. Zong, F. Y. Hu, L. T. Feng, X. Y. Wang, Y. F. Wang and C. X. Chen, *J. Org. Chem.*, 2011, **76**, 716–719.
- 25 J. T. Zhu, H. B. Xie, Z. X. Chen, S. Li and Y. M. Wu, *Chem. Commun.*, 2009, 2338–2340, DOI: 10.1039/b900984a.
- 26 B. G. Szczepankiewicz, J. J. Rohde and R. Kurukulasuriya, *Org. Lett.*, 2005, **7**, 1833–1835.
- 27 N. Mishra, A. S. Singh, A. K. Agrahari, S. K. Singh, M. Singh and V. K. Tiwari, *ACS Comb. Sci.*, 2019, **21**, 389–399.
- 28 J. Yu, Y. Xia and M. Lu, *Appl. Organomet. Chem.*, 2014, **28**, 764–767.
- 29 K. Liubchak, K. Nazarenko and A. Tolmachev, *Tetrahedron*, 2012, **68**, 2993–3000.
- 30 M. De Greef, B. Peter and R. Stumpf, WO2017017096A1, 2017.
- 31 T. Schaefer, M. Kawamura and H. Nagashima, WO2017056052A1, 2017.
- 32 G. T. Lee, K. Prasad and O. Repic, *Tetrahedron Lett.*, 2002, **43**, 3255–3257.
- 33 C. Lamanna, A. Catalano, A. Carocci, A. Di Mola, C. Franchini, V. Tortorella, P. M. L. Vanderheyden, M. S. Sinicropi, K. A. Watson and S. Sciabola, *ChemMedChem*, 2007, **2**, 1298–1310.
- 34 CN107325092A, 2017.
- 35 H. Baars, A. Beyer, S. V. Kohlhepp and C. Bolm, *Org. Lett.*, 2014, **16**, 536–539.
- 36 C. Chen, C. Chen, B. Li, J. Tao and J. Peng, *Molecules*, 2012, **17**, 12506–12520.
- 37 S.-K. Xiang, W. Tan, D.-X. Zhang, X.-L. Tian, C. Feng, B.-Q. Wang, K.-Q. Zhao, P. Hu and H. Yang, *Org. Biomol. Chem.*, 2013, **11**, 7271–7275.
- 38 J. C. Geng, L. Qin, C. H. He and G. H. Cui, *Transition Met. Chem.*, 2012, **37**, 579–585.
- 39 X. Xu, Z. Xi, W. Chen and D. Wang, *J. Coord. Chem.*, 2007, **60**, 2297–2308.
- 40 U. A. Amarnath and U. S. Suryakiran, WO2014027280A1, 2014.
- 41 P. C. Ray, S. Nigam, A. K. Pandey, P. Patil, J. M. Reddy and N. Oruganti, WO2011077444A1, 2011.
- 42 M. Wu, J. Li, W. Chen, G. Tian, F. Zhu, J. Suo and J. Shen, WO2014067237A1, 2014.

