Tetrahedron Letters 80 (2021) 153316

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Iron-catalyzed oxidative amidation of acylhydrazines with amines

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ARTICLE INFO

Article history:
Received 26 March 2021
Revised 3 August 2021
Accepted 4 August 2021
Available online 11 August 2021

Keywords:
Amide
Acylhydrazine
Iron-catalyst
Radical reaction
Cross-coupling reaction

ABSTRACT

A new approach for amide bond formation *via* a mild and efficient Iron-catalyzed cross-coupling reaction of acylhydrazines and amines using TBHP as oxidant is described. This protocol is compatible with a wide range of amines and acylhydrazines. In addition, the synthetic application of the reaction is presented.

Introduction

Amide bond formation is a fundamentally important process in organic synthesis. These kinds of bonds are not only present in biological systems (e.g. proteins), but are also key compositions of many valuable pharmaceuticals, agrochemicals and natural/synthetic polymers [1–9]. Indeed, according to a survey, the amide bond was one of the most abundant functional groups encountered in known drug databases [10]. The most frequently employed method for amide bond formation involves the direct coupling of pre- or "in situ" activated carboxylic acids with amines in the presence of a stoichiometric "coupling" reagent. Although this strategy has proven to be useful as evidenced by the incredible success with peptide synthesis [11–16], drawbacks include the large amounts of generated waste. Afterwards, the efforts were focused on the improvement of reaction, and many progresses had been made, particularly in the area of catalytic [17–27] and dehydrogenative coupling reactions [28–31].

Oxidative radical cross-coupling reaction has proven to be one of the most powerful strategies for forging various chemical bonds [32–38]. Within the context of amide bond formation, this strategy has been succesfully applied using a variety of reagents. For instance, Lei's group disclosed the formation of amide bonds *via* the coupling of acyl radicals generated from α-keto acids with amines (Scheme 1a) [39]. Furthermore, Wan and co-workers employed acyl radical precursors (generated from aldehyde) as coupling partners with formamides to construct new amide bonds (Scheme 1b) [40]. Meanwhile, the groups of Luca and Singh independently reported the successful cross-coupling of acyl radicals with *N*-chloroamines (Scheme 1c) [41–43]. Furthermore, Dyson described a Pd-catalyzed carbonylation protocol involving the oxidative coupling of C(sp^3)–H bonds with CO and amines (Scheme 1d) [44]. In spite of these advances, there is still need to develop efficient methods that does not involve 1) the use of pre-activated amines, 2) the use of aggressive/hazardous reagents and/or expensive photocatalysts, 3) the generation of toxic or irremovable byproducts.

Acylhydrazines are stable compounds that are easily prepared from acids or esters. They have been widely used as synthons for the preparation of pharmaceuticals, agrochemicals, polymers [45] and peptide synthesis etc [46–49]. Nevertheless, the use of acylhydrazines as acyl radical precursors for synthetic purposes have been less explored [50–53]. In continuation of our efforts on the development of cross-coupling processes towards efficient carbon-heteroatom bond formation [54–57], herein, we report an Fe-catalyzed cross-coupling of acyl radicals generated from acylhydrazines with amines to construct amide bonds (Scheme 1e).

Results and discussion

We began by investigating the feasibility of an oxidative coupling reaction between benzoylhydrazine **1a** and 4-toluidine **2a** in CH_3CN at 80 °C (Table 1). Initially, the reaction was conducted in the presence of $K_2S_2O_8$ oxidant (Table 1, entry 1). Fortunately, the expected N-(*p*-tolyl)benzamide **3a** was formed when the amount of **2a** was doubled, albeit in low yield (Table 1, entry 2). No product was detected when TBHP was used *in lieu* of $K_2S_2O_8$ (Table 1, entry 3). Although the same reaction afforded **3a** in 35%

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https://doi.org/10.1016/j.tetlet.2021.153316
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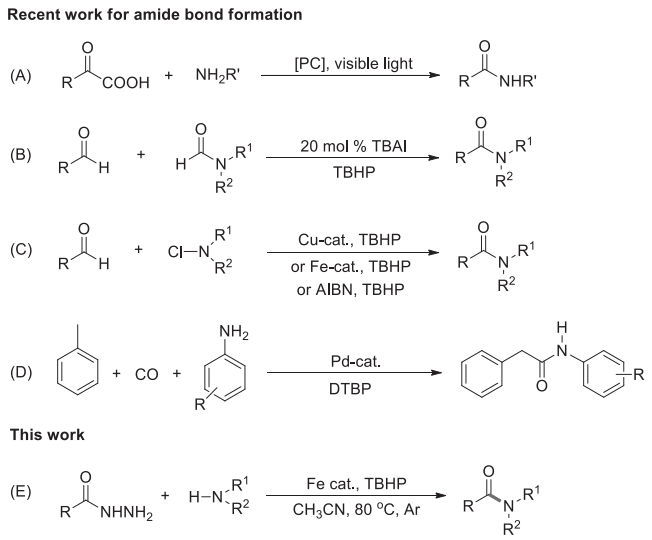


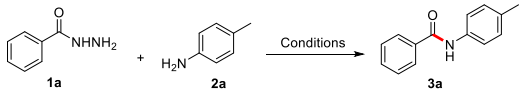
Scheme 1. Amide bond formation.

yield when carried out at 120 °C, the efficiency was still not satisfactory (Table 1, entry 4). Pleasingly, the use of $FeCl_3$ as oxidant resulted in a remarkable 84% yield of **3a** (Table 1, entry 6). However, the requisite use of 4 equiv of $FeCl_3$ is not desirable from an economic standpoint. To this end, further optimizations were carried out towards rendering the reaction catalytic. Fortunately, the use of a catalytic amount of $FeCl_3$ and 6 equiv of TBHP afforded **3a** in 82% yield (Table 1, entry 7). Notably, the reaction efficiency was still relatively maintained when conducted at room temperature (Table 1, entry 8), which might be beneficial in the case of amino acids. Further attempts to improve reaction efficiency by increasing the amount of amine were unsuccessful (Table 1, entries 9–10). Moreover, the catalytic behavior of other metal salts (such as Ag and Cu) was investigated; while $AgNO_3$ was ineffective, $CuCl_2$ displayed good catalytic behavior, albeit in comparably lower yields (Table 1, entries 11–13).

With the optimized reaction conditions in hand, the scope of the reaction with respect to amines was explored. As shown in Table 2, a variety of amines, including aromatic/aliphatic and primary/secondary substrates were suitable to the reaction. In the case of anilines bearing *para*- or *meta*-electron-donating groups such as methyl or methoxy, the reaction furnished the corresponding products in good yields (**3a**, **3c** and **3f**). However, the yields of anilines bearing *ortho*-substituents were noticeably affected by steric hindrance as exemplified by products **3d** and **3 g**. Moreover, this effect was more pronounced with the bulky 2-*tert*-butyl group (**3e**). In addition, the reactions of anilines bearing electron-withdrawing halogen groups afforded the desired products (**3h**-**3j**) in moderate yields (55 ~ 61%), however, 4-nitroaniline could only afford the corresponding product **3l** in trace amount, probably due to the greater electron-pulling effect of the $-NO_2$ group. It is noteworthy that the steric effect was more pronounced for *ortho*-brominated aniline (**3k**, 28%). Furthermore, aliphatic amines were found to be viable substrates. For instance, benzylamine and *n*-hexylamine afforded the corresponding products **3m** and **3n** in 75% and 92% yields, respectively. Notably, the reaction of the secondary alkylated arylamine, *N*-methylaniline occurred smoothly to give the desired amide **3o** in 85% yield; meanwhile the secondary dialkylamines such as piperidine and diethylamine furnished the desired products **3p**, **3q** in lower 38% and 35% yields, respectively, it may attribute to the steric hindrance of amines; but the reaction of the secondary diarylamine such as diphenylamine did not give the desired product **3r**. Unfortunately, amines both in which the amine nitrogen atom is electron-deficient such as benzamide, 4-methylbenzenesulfonamide, phthalimide and heteroaromatic amines like 2-aminopyridine, pyrrole were largely unreactive under standard conditions (**3s** ~ **3w**).

Next, we turned attention to investigating the scope of the reaction with respect to a variety of acylhydrazines (Table 3). In contrast to the amine coupling partners, the reactions of acylhydrazines were not noticeably influenced by either steric or electronic factors. Both electron-rich and electron-deficient substrates afforded good yields of the corresponding coupling products (**4a**-**4g**), it is noteworthy that the reaction of 4-nitrobenzoylhydrazine gave the desired product **4h** in 66% yield. Notably, aliphatic acylhydrazines are also compatible under standard conditions to give the corresponding products (**4i-4n**) in good yields.

Table 1
Optimization of the reaction[a].



Entry	1a:2a	Catalyst (10 mol%)	Oxidant (equiv)	Time (h)	Yield (%)[b]
1	1:1	–	$K_2S_2O_8$ (4)	24	trace
2	1:2	–	$K_2S_2O_8$ (4)	24	15
3	1:1	–	TBHP (6)	24	N.D.[c]
4	1:1	–	TBHP (6)	2	35[d]
5	1:1	–	$FeCl_3$ (4)	24	85
6	1:1	–	$FeCl_3$ (4)	2	84
7	1:1	$FeCl_3$	TBHP (6)	2	82
8	1:1	$FeCl_3$	TBHP (6)	12	70[e]
9	1:1.5	$FeCl_3$	TBHP (6)	2	79
10	1:2	$FeCl_3$	TBHP (6)	2	68
11	1:1	$CuCl_2$	TBHP (6)	24	80
12	1:1	$CuCl_2$	$K_2S_2O_8$ (4)	24	70
13	1:1	$AgNO_3$	$K_2S_2O_8$ (4)	24	trace

[a] Reactions conditions: **1a** (1 mmol%) and **2a** (1 mmol) in CH_3CN (5 mL) at 80° C under argon atmosphere. [b] Isolated yield. [c] N.D. means not detected. [d] at 120 °C. [e] at 25 °C.

Table 2
Scope of amines[a]

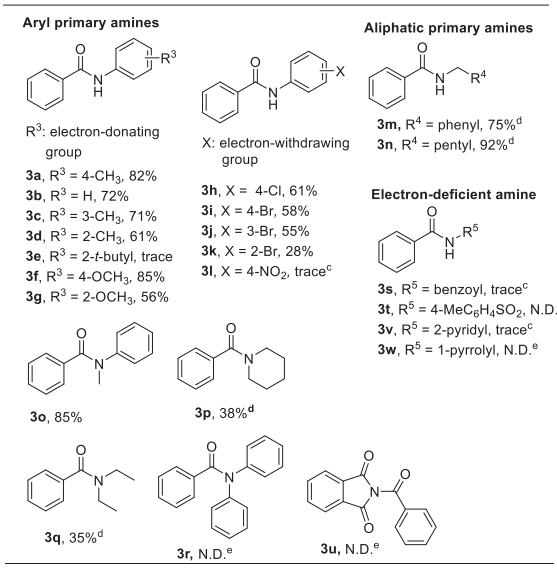
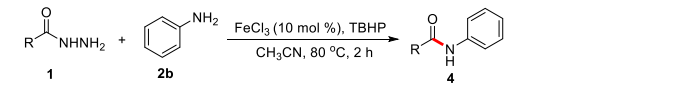


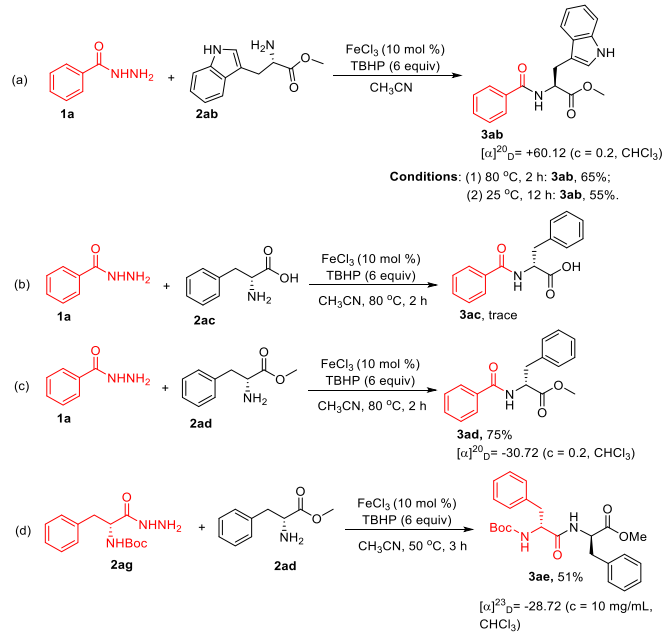
Table 3
Scope of acylhydrazines[a]



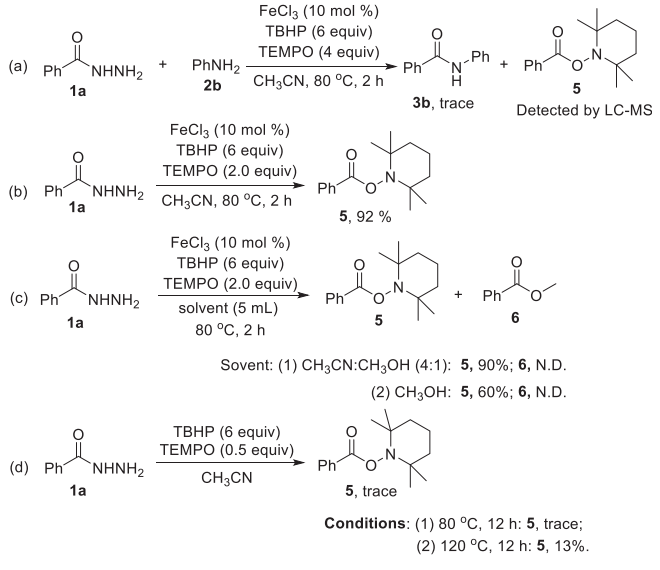
Furthermore, the synthetic applicability of this protocol was demonstrated by the reaction of optically pure aminoacid ester. Benzoylhydrazine **1a** underwent oxidative coupling with the L-tryptophan ester **2ab** under standard conditions to furnish product **3ab** in 65% yield. Notably, the same reaction when carried out at 25 °C produced **3ab** in 55% yield, **3ab** remained its optically pure ($[\alpha]_D^{20}$ = +60.12 (*c* = 0.2, $CHCl_3$ (lit. value: [58] $[\alpha]_D^{23}$ = +57.13 (*c* = 0.32, $CHCl_3$))) (Scheme 2a); then, the reaction was extended to D-phenylalanine **2ac**, but the expected product **3ac** was not detected, it may attribute to the presence of a free carboxylic acid group (Scheme 2b); therefore, the ester **2ad** derived from **2ac** was then applied to the reaction, the expected product **3ad** was obtained in 75% yield, it also remained its optically pure (methyl benzoyl-D-phenylalaninate $[a]_D^{20}$ = −30.72 (*c* = 0.2, $CHCl_3$ (lit. value: [58] methyl benzoyl-L-phenylalaninate $[\alpha]_D^{23}$ = +35.1 (*c* = 0.60, $CHCl_3$)) (Scheme 2c). Finally, the reaction of optically pure aminoacylhydrazine **2ag** and aminoacid ester **2ad** both of them derived from D-phenylalanine **2ac** was carried out, the expected product **3ae** was obtained in 51% yield, it also remained its optically pure (methyl (*tert*-butoxycarbonyl)- D-phenylalanyl-D-phenylalaninate $[\alpha]_D^{23}$ = −28.72 (*c* 10 mg/mL $CHCl_3$) (lit. value: methyl (*tert*-butoxycarbonyl)-L-phenyl- alanyl-L-phenylalaninate $[\alpha]_D^{25}$ = +26 (*c* 10 mg/mL, $CHCl_3$) (Scheme 2d) [59].

In order to gain an insight into the reaction mechanism, some control experiments were carried out (Scheme 3). Firstly, the addition of the radical trapping agent, 2,2,6,6-tetramethyl- 1-piperidinyloxy (TEMPO, 4.0 equiv) to the reaction of benzoylhydrazine **1a** with aniline **2b** significantly inhibited the formation of **3b**; instead the compound **5**, presumably formed from a benzoyl radical capture by TEMPO was detected by LC–MS (Scheme 3a). Meanwhile, in the absence of aniline **2b**, the reaction of benzoylhydrazine **1a** with TEMPO (2.0 equiv) under the standard conditions afforded compound **5** in 92% yield (Scheme 3b). In order to know whether benzoyl radical formed could be further oxidized to the corresponding benzoyl cation [52], the same reaction as Scheme 3b was performed in the solvent CH_3CN:CH_3OH (4:1) and CH_3OH. The results indicated that two cases afforded compound **5** in 90% and 60% yield, respectively; while benzoic methyl ester **6**, presumably formed from a benzoyl cation capture by CH_3OH, was not detected (Scheme 3c). In addition, compound **5** was still isolated in 13% yield in the absence of $FeCl_3$ catalyst (Scheme 3d). These results implicate the possible participation of benzoyl radical intermediate in the reaction, not including benzoyl cation one.

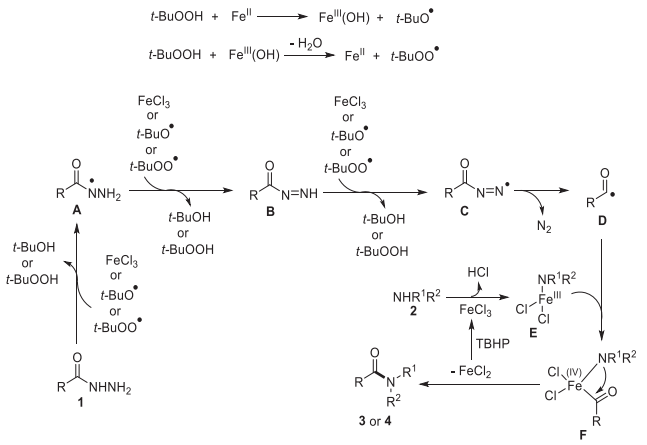
On the basis of results obtained and related literature [60–66], a plausible mechanism for this reaction is depicted in Scheme 4. As illustrated in Table 1, since Fe^{III} salt is critical for the cross-coupling of acyl radical and amine, then it is reasonable that the iron catalyst is largely responsible for mediating this process. Initially, $FeCl_3$



Scheme 2. Synthetic application.



Scheme 3. Control experiments.



Scheme 4. Proposed mechanism.

or *tert*-butoxy radical or *tert*-butylperoxy radical abstracts proton from acylhydrazine **1** to afford radical **A** first, then diazene intermediate **B**. Further proton abstraction step generates the diazenyl radical **C**, from which acyl radical **D** is formed, subsequently, **D** can be trapped by complex **E** formed in situ from Fe^{III} species and amine **2** to produce complex **F**, followed by reductive elimination to afford products **3** or **4**. [62–63,65–66]

Conclusion

In summary, a new approach for amide bond formation *via* an efficient Fe^{III}-catalyzed cross-coupling reaction of acylhydrazines and amines using TBHP as oxidant is developed. The system is shown to be compatible with a wide range of amines (aromatic/aliphatic) and acylhydrazines (aromatic/aliphatic). In addition, the synthetic utility of the reaction was demonstrated by the oxidative coupling of the derivative of the amino acid, tryptophan. This mild method represents an attractive alternative to existing amide-bond forming protocols, thus expanding the toolbox of the synthetic organic chemist.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

J.-P. Zou appreciates the generous financial support by National Natural Science Foundation of China (No. 21472133), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) and Key Laboratory of Organic Synthesis of Jiangsu Province (KJS1749).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153316.

References

[1] J.E. Taylor, S.D. Bull, *N*-Acylation Reactions of Amines, in: P. Knochel, G.A. Molander (Eds.), Comprehensive Organic Synthesis, 2nd Ed., Elsevier, New York, 2014, pp. 427–478.
[2] A. Greenberg, C.M. Breneman, J.F. Liebman, The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science, Wiley-Interscience, New York, 2000.
[3] J. Magano, J.R. Dunetz, Chem. Rev. 111 (2011) 2177–2250.
[4] E. Valeur, M. Bradley, Chem. Soc. Rev. 38 (2009) 606–631.
[5] J.R. Dunetz, J. Magano, G.A. Weisenburger, Org. Process Res. Dev. 20 (2016) 140–177.
[6] C.A.G.N. Montalbetti, V. Falque, Tetrahedron 61 (2005) 10827–10852.
[7] J.M. Humphrey, A.R. Chamberlin, Chem. Rev. 97 (1997) 2243–2266.
[8] A. El-Faham, F. Albericio, Chem. Rev. 111 (2011) 6557.
[9] K. Scheidt, Nature 465 (2010) 1020.
[10] A.K. Ghose, V.N. Viswanadhan, J.J. Wendoloski, J. Comb. Chem. 1 (1999) 55–68.
[11] G. Windridge, E.C. Jorgensen, J. Am. Chem. Soc. 93 (1971) 6318–6319.
[12] L. Kisfaludy, I. Schön, T. Szirtes, O. Nyéki, M. Löw, Tetrahedron Lett. 15 (1974) 1785–1786.
[13] M. Mikozlajczyk, P. Kiezlbasiński, Tetrahedron 37 (1981) 233–284.
[14] L.A. Carpino, A. El-Faham, Tetrahedron 55 (1999) 6813–6830.
[15] J. Coste, E. Frérot, P. Jouin, B. Castro, Tetrahedron Lett. 32 (1991) 1967–1970.
[16] S.Y. Han, Y.A. Kim, Tetrahedron 60 (2004) 2447–2467.
[17] A. Ojeda-Porras, D. Gamba-Sánchez, J. Org. Chem. 81 (2016) 11548–11555.
[18] H. Lundberg, F. Tinnis, N. Selander, H. Adolfsson, Chem. Soc. Rev. 43 (2014) 2714–2742.
[19] C.L. Allen, J.M.J. Williams, Chem. Soc. Rev. 40 (2011) 3405–3415.
[20] V.R. Pattabiraman, J.W. Bode, Nature 480 (2011) 471–479.
[21] T. Krause, S. Baader, B. Erb, L.J. Gooßen, Nat. Commun. 7 (2016) 11732.
[22] K. Ishihara, Y. Lu, Chem. Sci. 7 (2016) 1276–1280.
[23] E.L. Baker, M.M. Yamano, Y.J. Zhou, S.M. Anthony, N.K. Garg, Nat. Commun. 7 (2016) 11554.
[24] Z.G. Ke, Y. Zhang, X.J. Cui, F. Shi, Green Chem. 18 (2016) 808–816.
[25] S.L. Zultanski, J.Y. Zhao, S.S. Stahl, J. Am. Chem. Soc. 138 (2016) 6416–6419.
[26] S. Xie, Y. Zhang, O. Ramstrom, M.D. Yan, Chem. Sci. 7 (2016) 713–718.
[27] P.E. Piszel, A. Vasilopoulos, S.S. Stahl, Angew. Chem. Int. Ed. 58 (2019) 12211–12215.
[28] C. Chen, F. Verpoort, O. Wu, RSC Adv. 6 (2016) 55599–55607.
[29] C. Gunanathan, D. Milstein, Science 341 (2013) 249.
[30] C. Chen, S.H. Hong, Org. Biomol. Chem. 9 (2011) 20–26.
[31] S. Selvamurugan, R. Ramachandran, G. Prakash, M. Nirmala, P. Viswanathamurthi, S. Fujiwara, A. Endo, Inorg. Chim. Acta 454 (2017) 46–53.
[32] D. Staveness, I. Bosque, C.R. Stephenson, Acc. Chem. Res. 49 (2016) 2295–2306.
[33] A. Studer, D.P. Curran, Angew. Chem. Int. Ed. 55 (2016) 58–102.
[34] M. Yan, J.C. Lo, J.T. Edwards, P.S. Baran, J. Am. Chem. Soc. 138 (2016) 12692–12714.
[35] C. Liu, D. Liu, A. Lei, Acc. Chem. Res. 47 (2014) 3459–3470.
[36] Q. Liu, R. Jackstell, M. Beller, Angew. Chem. Int. Ed. 52 (2013) 13871–13873.
[37] Z.J. Liu, X. Lu, G. Wang, L. Li, W.T. Jiang, Y.D. Wang, B. Xiao, Y. Fu, J. Am. Chem. Soc. 138 (2016) 9714–9719.
[38] C.C. Nawrat, C.R. Jamison, Y. Slutskyy, D.W.C. MacMillan, L.E. Overman, J. Am. Chem. Soc. 137 (2015) 11270–11273.
[39] J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan, A. Lei, Angew. Chem. Int. Ed. 53 (2014) 502–506.
[40] Z. Liu, J. Zhang, S. Chen, E. Shi, Y. Xu, X. Wan, Angew. Chem. Int. Ed. 51 (2012) 3231–3235.
[41] R. Cadoni, A. Porcheddu, G. Giacomelli, L. De Luca, Org. Lett. 14 (2012) 5014–5017.
[42] A. Porcheddu, L. De Luca, Adv. Synth. Catal. 354 (2012) 2949–2953.
[43] R. Vanjari, T. Guntreddi, K.N. Singh, Green Chem. 16 (2014) 351–356.
[44] H. Liu, G. Laurenczy, N. Yan, P.J. Dyson, Chem. Commun. 50 (2014) 341–343.
[45] P. Majumdar, A. Pati, M. Patra, R.K. Behera, A.K. Behera, Chem. Rev. 114 (2014) 2942–2977.
[46] P. Wang, R. Layfield, M. Landon, R.J. Mayer, R. Ramage, J. Peptide Res. 53 (1999) 673–677.
[47] P. Wang, K.T. Shaw, B. Whigham, R. Ramage, Tetrahedron Lett. 39 (1998) 8719–8720.
[48] P. Wang, R. Layfield, M. Landon, R.J. Mayer, R. Ramage, Tetrahedron Lett. 39 (1998) 8711–8714.
[49] G.M. Fang, Y.M. Li, H.K. Cui, L. Liu, Angew. Chem. Int. Ed. 50 (2011) 7645–7649.
[50] R. Braslau, M.O. Anderson, F. Rivera, A. Jimenez, T. Haddad, J.R. Axon, Tetrahedron 58 (2002) 5513–5523.
[51] S. Bath, N.M. Laso, H. Lopez-Ruiz, B. Quiclet-Sire, S.Z. Zard, Chem. Commun. 39 (2003) 204–205.
[52] R.I.J. Amos, B.S. Gourlay, C.H. Schiesser, J.A. Smith, B.F.A. Yates, Chem. Commun. 44 (2008) 1695–1697.
[53] S.M. Xie, L.B. Su, M. Mo, W. Zhou, Y.B. Zhou, J.Y. Dong, J. Org. Chem. 86 (2021) 739–749.
[54] G.Y. Zhang, S.S. Lv, A. Shoberu, J.P. Zou, J. Org. Chem. 82 (2017) 9801–9807.
[55] H.F. Qian, C.K. Li, Z.H. Zhou, Z.K. Tao, A. Shoberu, J.P. Zou, Org. Lett. 20 (2018) 5947–5951.
[56] A. Shoberu, C.K. Li, Z.K. Tao, G.Y. Zhang, J.P. Zou, Adv. Synth. Catal. 361 (2019) 2255–2261.
[57] G.-Y. Zhang, L. Fu, P.H. Chen, J.P. Zou, G.S. Liu, Org. Lett. 21 (2019) 5015–5020.
[58] D.N. Sawant, D.B. Bagal, S. Ogawa, K. Selvam, S. Saito, Org. Lett. 20 (2018) 4397–4400.
[59] C. Hollanders, E. Renders, C. Gadais, D. Masullo, L.V. Raemdonck, C.C.D. Wybon, C. Martin, W.A. Herrebout, B.U.W. Maes, S. Ballet, ACS Catal. 10 (2020) 4280–4289.
[60] T. Taniguchi, Y. Sugiura, H. Zaimoku, H. Ishibashi, Angew. Chem. Int. Ed. 49 (2010) 10154–10157.
[61] T. Taniguchi, A. Idota, H. Ishibashi, Org. Biomol. Chem. 9 (2011) 3151–3153.

[62] X. Li, X. Shi, M. Fang, X. Xu, J. Org. Chem. 78 (2013) 9499–9504.
[63] L. Ge, Y. Li, H. Bao, Org. Lett. 21 (2019) 256–260.
[64] X. Xu, Y. Tang, X. Li, G. Hong, M. Fang, X.I. Du, J. Org. Chem. 79 (2014) 446–451.
[65] C.H. Tang, N. Jiao, J. Am. Chem. Soc. 134 (2012) 18924–18927.
[66] Y. Ding, S.-Y. Zhang, Y.-C. Chen, S.-X. Fan, J.-S. Tian, T.-P. Loh, Org. Lett. 21 (2019) 2736–2739.