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DMAP and PivOH-Promoted Amination/Allenization Reaction

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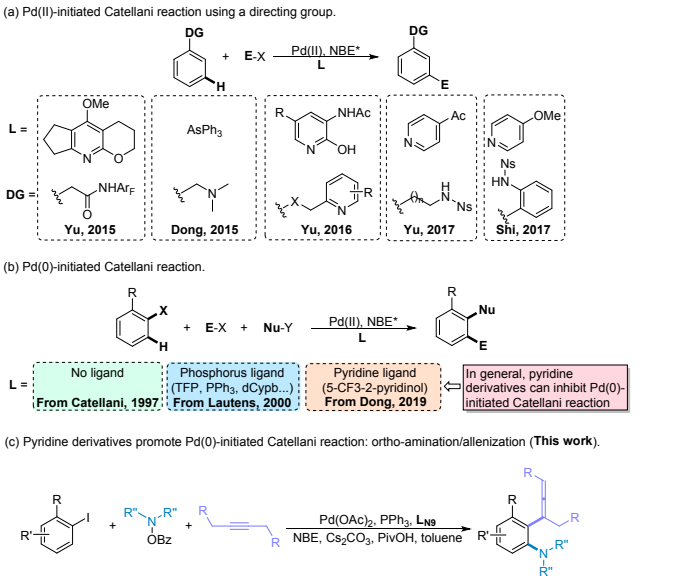
This report described the first DMAP and PivOH-Promoted *ortho*-C-H amination and ipso-allenization reaction of iodobenzenes realized by Pd/norbornene cooperative catalysis. Based on control experiments and DFT calculations, we speculated that the three ligands have different functions and mechanism paths in the reaction.

Palladium-catalyzed site-selective C-H activation has been the focus of organic synthesis chemistry.[1] The study of this catalytic system has become the key to realizing the unknown reaction smoothly or to improving the efficiency of a known reaction. When a newly screened material effectively promotes the reaction in the catalytic system, the progress of such reactions is likely to move forward as a whole. In recent years, Dong,[2] Yu,[3] Zhou[4] et al.[5] screened norbornene derivatives that had never been noticed before. Through this strategy, they effectively controlled the efficiency and chemoselectivity of the Catellani reaction. The Yu group used 2-carbomethoxy-substituted NBE to systematically realize the *m*-C-H functionalization reaction with a directing group (DG).[3] The Dong group used norbornene with large steric hindrance to simulate the "ortho effect" of the Catellani reaction, which changed people's understanding.[2d] Recently, they also used N-methylamine-substituted NBE to realize the Catellani reaction of olefins[6] and large steric aromatic rings[7]. In addition, Zhou used 5-NBE-2-carbonitrile to achieve the oxidation version of the Catellani reaction, and arylboric acid was used as the substrate.[4a] In 2015, the Yu group first used pyridine derivatives as ligands to realize the Pd(II)-initiated Catellani reaction using a directing group, which is also the first time that nitrogen ligands entered the field of Pd/NBE chemistry.[3d] At the same time, Dong group used triphenylarsenic as ligand and dimethylamine as directing group to realize the Pd/NBE reaction.[8] In recent years, this method has been proven to be generally applicable. From amide to pyridine and sulfonamide DG, the DG became easier to remove and easier to obtain. The substituents of ligands can adjust the electrical properties and steric resistance of palladium, which plays a key role in adapting to various DGs (Scheme 1a).[3a-c, 3e-h, 9] Therefore, finding a new material to improve the efficiency of the Catellani reaction may be the key to progress.

The field of the Pd(0)-initiated Catellani reaction was founded in 1997.[10] In 2000, Lautens used phosphorus ligands to broaden its compatibility and established the Catellani–Lautens reaction system.[11] Phosphorus ligands can not only reduce the Pd(II) to Pd(0) but also effectively inhibit the formation of by-products and improve the yield of the



Scheme 1. DMAP and PivOH-Promoted Amination/Alleni-zation Reaction

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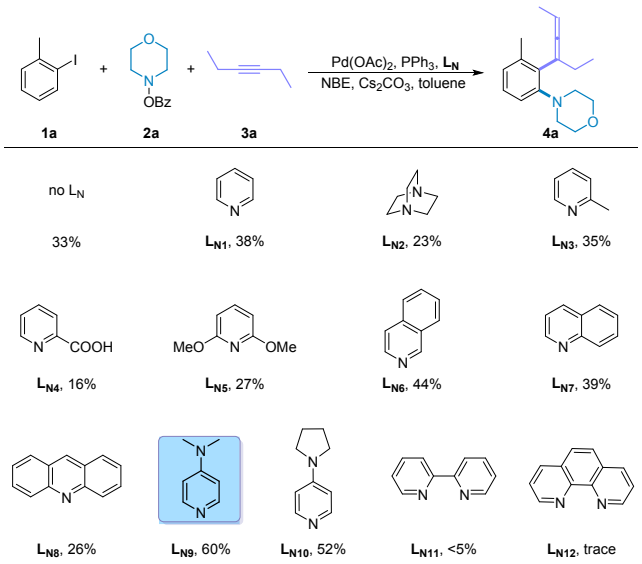
Table 1. Ligand Discovery for the Amination/Allenization Reaction[a]



[a] Reaction conditions: substrate **1** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), **3** (0.6 mmol, 3.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), norbornene (0.4 mmol, 2.0 equiv.), $\mathbf{L_N}$ (0.4 mmol, 2.0 equiv.), Cs_2CO_3 (0.8 mmol, 4.0 equiv.), toluene (3.0 mL), 140 °C, 24 h. Isolated yields.

reaction. Pyridine derivatives, as common palladium ligands, tend to inhibit the Pd(0)-initiated Catellani reaction.[12] Notably, Dong group reported the first case of Pd(II)-initiated Catellani reaction in 2019 (Scheme 1b).[6]

In 2001, Catellani accidentally discovered the individual case of the allenization reaction in a report regarding the formation of a phenanthrene skeleton via the Pd/NBE strategy.[13] Because the end step of the allenization reaction is the C(sp^3)-H activation, the reaction conditions are relatively harsh.[14] For example, DMF is the common solvent for palladium catalyzed allenization reaction, and the solvents of Catellani reactions (except for ortho-alkylation and arylation) are limited to the solvents with relatively weak polarity. Up to now, the allenization reaction is no longer compatible with other electrophilic reagents in Catellani reactions. The *ortho*-C-H amination of iodobenzene was first discovered by Dong in 2013,[15] and the substrate applicability was extended to bromobenzene in 2018.[16] This reaction has become an important tool for the site-selective amination of aromatics.[17] Therefore, it is a challenge to make the allenization reaction compatible with *ortho*-C-H amination.

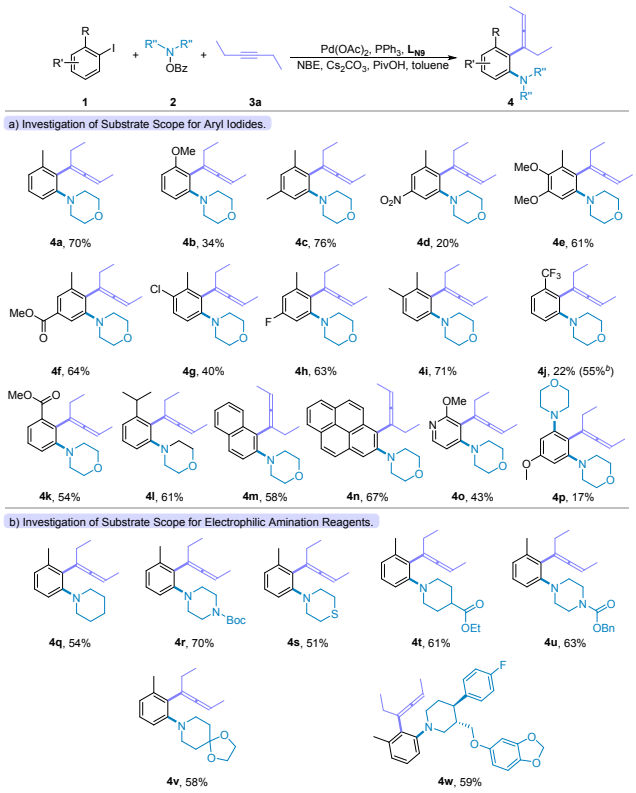
Initially, we used *o*-iodotoluene as the substrate, N-benzoylomorpholine as the electrophilic amination reagent, and 3-hexyne as the allenization reagent to screen the reaction conditions. After the systematic screening of palladium catalysts, phosphorus ligands, bases and solvents, the desired product was successfully obtained in 33% yield. At this time, the optimal reaction conditions were $Pd(OAc)_2$ as the palladium catalyst, triphenylphosphine as the phosphine ligand, Cs_2CO_3 as the base and toluene as the solvent. Because there is no other way to improve the yield, we began to try to add nitrogen ligands to the reaction system. Unexpectedly, when equivalent pyridine was added, the isolated yield slightly improved. Subsequently, DABCO, which is often used as a nucleophilic nitrogen ligand, was added, and the reaction was inhibited. Then, we added a variety of pyridine derivatives. *Ortho*-substituted pyridine inhibited the reaction, in particular, 2-picolinic acid reduced the yield of product **4a** by half. Quinoline derivatives promoted the reaction. Among them, isoquinoline was the best, and the target product was isolated to 44%. However, acridine inhibited the reaction, which may be due to its high steric hindrance. Fortunately, when dimethylaminopyridine (DMAP, $\mathbf{L_{N9}}$) was added to the reaction system, the yield of the target product increased to 60% (Table 1, $\mathbf{L_{N9}}$). Therefore, we further screened 4-pyrrolidinopyridine, and found that the reaction was also smooth, but it was not as good as that with DMAP. Finally, we tried bidentate pyridine ligands and found that the reaction was completely inhibited.

Since we observed that the addition of $\mathbf{L_{N9}}$ can significantly promote the reaction, we carried out the control experiment on the reaction system (Supporting Information, SI). The yield of the target product **4a** was less than 5%, when neither triphenylphosphine nor $\mathbf{L_{N9}}$ were added to the reaction system. When only $\mathbf{L_{N9}}$ was added into the reaction system instead of triphenylphosphine, the desired product was obtained in 48% yield. This showed that $\mathbf{L_{N9}}$ is better than triphenylphosphine in a single ligand system. It should be noted that $\mathbf{L_{N9}}$ was present in a stoichiometric amount, with a catalytic amount of triphenylphosphine under the optimal conditions. When we decreased $\mathbf{L_{N9}}$ to the catalytic amount, the yield was reduced to 49%. Cesium carbonate is necessary, which may be due to the CMD process of the Catellani reaction. According to our previous study on C(sp^3)-H activation of the Catellani reaction, we added 40 mol% pivalic acid to the reaction system, and the yield increased to 70%. Further control experiments showed that when only pivalic acid was used to replace triphenylphosphine and $\mathbf{L_{N9}}$, the reaction also went well.

After the control experiment of the reaction system, we found that the best reaction conditions needed the addition of triphenylphosphine, $\mathbf{L_{N9}}$ and pivalic acid to the reaction system. In the best reaction condition, we investigated the scope of iodobenzene as the substrate (Table 2). The desired products can be obtained with good yield when using electron- donating and electron-withdrawing iodobenzene as substrates. In particular, the reaction is also compatible with other *ortho*-substituted iodobenzene; the *ortho*-groups were methoxy (-OMe), trifluoromethyl (-CF_3), ester (-CO_2Me), and the isopropyl group with large steric hindrance, which can synthesize the target product smoothly. In addition, fused ring compounds (**1n**, **1m)** and 3-iodo-2-methoxypyridine **1o**, can obtain the corresponding products in medium yield, which showed that the reaction had good practical value. Finally, we used *p*-methoxyiodobenzene as the substrate to obtain the diaminogenated product **4p**. Next, we continued to expand the substrate scope for N-benzoyloxyamines **2**. Many varieties of six-membered ring amines were suitable for this reaction, in which the Boc and ketal groups which were sensitive to acid were compatible. It is worth mentioning that paroxetine can be derived by this method (**4w**).

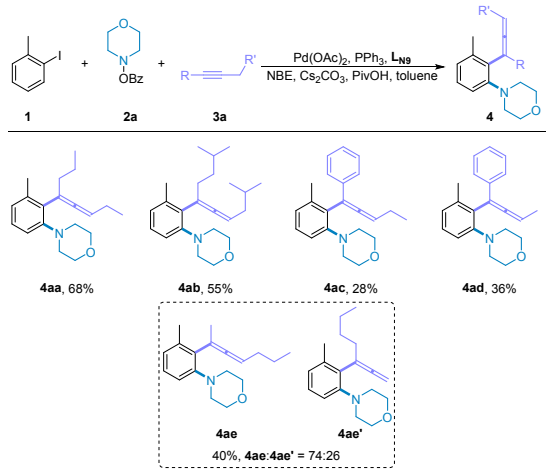
Later, we investigated the allenization reagents, and found that the length of alkyl chain on both sides of the alkynes had little

Table 2. Investigation of the Substrate Scope[a]



[a] Reaction conditions: substrate **1** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), **3** (0.6 mmol, 3.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), norbornene (0.4 mmol, 2.0 equiv.), $\mathbf{L_{N9}}$ (0.4 mmol, 2.0 equiv.), PivOH (40 mol%), Cs_2CO_3 (0.8 mmol, 4.0 equiv.), toluene (3.0 mL), 140 °C, 24 h. Isolated yields. [b] Without $\mathbf{L_{N9}}$.

Table 3. Investigation of the Substrate Scope for Allenization Reagents [a]



[a] Reaction conditions: substrate **1** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), **3** (0.6 mmol, 3.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), norbornene (0.4 mmol, 2.0 equiv.), $\mathbf{L_{N9}}$ (0.4 mmol, 2.0 equiv.), PivOH (40 mol%), Cs_2CO_3 (0.8 mmol, 4.0 equiv.), toluene (3.0 mL), 140 °C, 24 h. Isolated yields.

effect on the reaction (Table 3, **4aa**, **4ab**). When the two sides of the alkynes had different substituent groups, that is, when one side was aromatics and the other side was alkanes, the C-H bonds of alkanes will be selectively activated to form

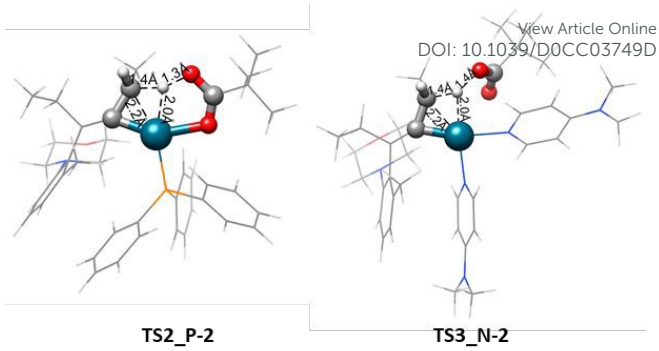


Figure 1. The transition states in the process of the allenization, the bond lengths are given in Å.

dienes (**4ac**, **4ad**). In addition, the reaction rate of the secondary carbon **4ae**, is faster than that of the primary carbon **4ae'**.

The results of the control experiment shows that all three ligands can independently complete the key ANP process of the Catellani reaction. According to previous reports,[12] the specific mechanism of C-H amination in the ANP process is more controversial in the field of the Catellani reaction, so we hope to speculate on the actual action ligand of the ANP process by studying the specific mechanism of the subsequent diene formation process.

Based on density functional theory (DFT) calculations, we first studied the dienenylation process when the ligand was triphenylphosphine. The results show that the energy barrier of the migration and insertion process between palladium and alkyne is very low (15.2 kcal/mol). The energy barrier of *β*-hydrogen elimination is 2.0 kcal/mol, which is lower than that of the CMD process, but the coordination of the carboxylic carbonyl and palladium will first release a Gibbs free energy of 5.6 kcal/mol before the CMD process (Scheme S1). Therefore, the reaction mechanism should favor the CMD process (SI, Scheme S1). When 4-dimethylamino-pyridine ($\mathbf{L_{N9}}$) was used as the ligand, the energy barrier of migration and insertion reaction between palladium and alkyne was lower, only 11.8 kcal/mol. we speculate that DMAP and palladium may form a double coordination intermediate **VIII_N-2** in this process. Then, the intermediate **VIII_N-2** undergoes the *β*-hydrogen elimination process (**TS3_N-2**, Figure 1). The energy barrier of this process is only 24.6 kcal/mol, so it can be carried out very quickly at 140 ℃ (Scheme S1). Therefore, we have verified that the allenization can be successfully completed when triphenylphosphine and $\mathbf{L_{N9}}$ are used as ligands. Moreover, when triphenylphosphine is used as the ligand, the reaction rate of diene formation is faster. The results of control experiments (SI, entries 6 and 9) show that the yields of triphenylphosphine and $\mathbf{L_{N9}}$ were 57% and 56%, respectively in the presence of PivOH, indicating that the process of allenization was not the rate-determining step of the reaction. DFT calculation results are consistent with the experimental results. In addition, the experimental results (SI, entries 1, 4 and 7) also show that the ANP process of the Catellani reaction can be completed by triphenylphosphine, $\mathbf{L_{N9}}$ and PivOH separately, which is unprecedented. These results greatly enrich the understanding of the Catellani reaction system.

Finally, according to the above conclusion, we propose the possible mechanism (Scheme S2): The oxidation addition of iodobenzene and Pd (0) produces palladium intermediate **I**. PPh_3 or $\mathbf{L_{N9}}$ can catalyze the reaction alone, so the palladium ligand can be any either of them. The reaction mechanism of only adding pivalic acid should be special, requiring further study in the future. Subsequently, the migration and insertion reaction of intermediate **I** with norbornene and the *ortho*-C(sp^2)-H activation occurs to form ANP intermediate **II**. This process is a kind of CMD process promoted by cesium carbonate. The coordination between iodine and cesium may occur, so the cation of carbonate has an important influence on the reaction.[18] Next, ANP intermediate **II** and electrophilic amination reagent **2** undergo an oxidation addition or concerted addition process to generate the *ortho*-C-H amination intermediate **IV**, and then the *β*-carbon elimination process occurs to produce intermediate **V**. According to our previous work, intermediate **V** and Cesium valerate undergo a carboxylic acid exchange process to generate intermediate **VI**.[19] Finally, intermediate **VII** is formed by migration and insertion with alkyne **3**, and the intermediate **VII** then undergoes two different processes to produce target product **4**.

In summary, this report described the first DMAP and PivOH-promoted *ortho*-C-H amination and ipso-allenization reaction of iodobenzenes realized by Pd/norbornene cooperative catalysis. Non-terminal alkynes were used as the allenization reagents, and allenization was completed through the concerted metalation deprotonation (CMD) and *β*-hydrogen elimination process. Through control experiments and DFT calculations, we discussed the mechanism of the three ligands in the reaction process in detail.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315-1345; (b) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107-1295; (c) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, *Chem. Rev.*, 2017, **117**, 9333-9403; (d) Y.-F. Yang, X. Hong, J.-Q. Yu and K. N. Houk, *Acc. Chem. Res.*, 2017, **50**, 2853-2860; (e) J. Xu, C. Chen, H. Zhao, C. Xu, Y. Pan, X. Xu, H. Li, L. Xu and B. Fan, *Org. Chem. Front.*, 2018, **5**, 734-740.

2

3 (a) Z. Dong, J. Wang, Z. Ren and G. Dong, *Angew. Chem. Int. Ed.*, 2015, **54**, 12664-12668; (b) R. Li and G. Dong, *Angew. Chem. Int. Ed.*, 2018, **57**, 1697-1701; (c) F. Liu, Z. Dong, J. Wang and G. Dong, *Angew. Chem. Int. Ed.*, 2019, **58**, 2144-2148; (d) J. Wang, R. Li, Z. Dong, P. Liu and G. Dong, *Nat. Chem.*, 2018, **10**, 866-872.

4 (a) G. Cheng, P. Wang and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2017, **56**, 8183-8186; (b) M. E. Farmer, P. Wang, H. Shi and J.-Q. Yu, *ACS Catal.*, 2018, **8**, 7362-7367; (c) G.-C. Li, P. Wang, M. E. Farmer and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2017, **56**, 6874-6877; (d) P.-X. Shen, X.-C. Wang, P. Wang, R.-Y. Zhu and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 11574-11577; (e) H. Shi, A. N. Herron, Y. Shao, Q. Shao and J.-Q. Yu, *Nature*, 2018, **558**, 581-585; (f) H. Shi, P. Wang, S. Suzuki, M. E. Farmer and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 14876-14879; (g) P. Wang, M. E. Farmer and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2017, **56**, 5125-5129; (h) P. Wang, G.-C. Li, P. Jain, M. E. Farmer, J. He, P.-X. Shen and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 14092-14099.

5 (a) S. Chen, Z.-S. Liu, T. Yang, Y. Hua, Z. Zhou, H.-G. Cheng and Q. Zhou, *Angew. Chem. Int. Ed.*, 2018, **57**, 7161-7165; (b) H.-G. Cheng, C. Wu, H. Chen, R. Chen, G. Qian, Z. Geng, Q. Wei, Y. Xia, J. Zhang, Y. Zhang and Q. Zhou, *Angew. Chem. Int. Ed.*, 2018, **57**, 3444-3448; (c) Z.-S. Liu, G. Qian, Q. Gao, P. Wang, H.-G. Cheng, Q. Wei, Q. Liu and Q. Zhou, *ACS Catal.*, 2018, **8**, 4783-4788; (d) G. Qian, M. Bai, S. Gao, H. Chen, S. Zhou, H.-G. Cheng, W. Yan and Q. Zhou, *Angew. Chem. Int. Ed.*, 2018, **57**, 10980-10984.

6 (a) L. Ding, X. Sui and Z. Gu, *ACS Catal.*, 2018, **8**, 5630-5635; (b) G. Shi, C. Shao, X. Ma, Y. Gu and Y. Zhang, *ACS Catal.*, 2018, **8**, 3775-3779.

7 J. Wang, Z. Dong, C. Yang and G. Dong, *Nat. Chem.*, 2019, **11**, 1106-1112.

8 J. Wang, Y. Zhou, X. Xu, P. Liu and G. Dong, *J. Am. Chem. Soc.*, 2020, **142**, 3050-3059.

9 Z. Dong, J. Wang and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 5887-5890.

10 P. Wang, M. E. Farmer, X. Huo, P. Jain, P.-X. Shen, M. Ishoey, J. E. Bradner, S. R. Wisniewski, M. D. Eastgate and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 9269-9276.

11 M. Catellani, F. Frignani and A. Rangoni, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 119-122.

12 M. Lautens and S. Piguel, *Angew. Chem. Int. Ed.*, 2000, **39**, 1045-1046.

13 (a) J. Ye and M. Lautens, *Nat. Chem.*, 2015, **7**, 863-870; (b) J. Ye and M. Lautens, *Nat. Chem.*, 2015, **7**, 863; (c) N. Della Ca', M. Fontana, E. Motti and M. Catellani, *Acc. Chem. Res.*, 2016, **49**, 1389-1400; (d) H.-G. Cheng, S. Chen, R. Chen and Q. Zhou, *Angew. Chem. Int. Ed.*, 2019, **58**, 5832-5844; (e) J. Wang and G. Dong, *Chem. Rev.*, 2019, **119**, 7478−7528; (f) K. Zhao, L. Ding and Z. Gu, *Synlett*, 2019, **30**, 129-140.

14 M. Catellani, E. Motti and S. Baratta, *Org. Lett.*, 2001, **3**, 3611-3614.

15 (a) N. Nella, E. Parker, J. Hitce, P. Larini, R. Jazzar and O. Baudoin, *Chem.– Eur. J.*, 2014, **20**, 13272-13278; (b) W. Lv, Y. Chen, Z. Zhao, S. Wen and G. Cheng, *Org. Lett.*, 2019, **21**, 7795-7798.

16 Z. Dong and G. Dong, *J. Am. Chem. Soc.*, 2013, **135**, 18350-18353.

17 Z. Dong, G. Lu, J. Wang, P. Liu and G. Dong, *J. Am. Chem. Soc.*, 2018, **140**, 8551-8562.

18 (a) Z.-Y. Chen, C.-Q. Ye, H. Zhu, X.-P. Zeng and J.-J. Yuan, *Chem.–Eur. J.*, 2014, **20**, 4237-4241; (b) S. Pan, X. Ma, D. Zhong, W. Chen, M. Liu and H. Wu, *Adv. Synth. Catal.*, 2015, **357**, 3052-3056; (c) H. Shi, D. J. Babinski and T. Ritter, *J. Am. Chem. Soc.*, 2015, **137**, 3775-3778; (d) F. Sun and Z. Gu, *Org. Lett.*, 2015, **17**, 2222-2225; (e) C. Ye, H. Zhu and Z. Chen, *J. Org. Chem.*, 2014, **79**, 8900-8905; (f) P.-X. Zhou, Y.-Y. Ye, J.-W. Ma, L. Zheng, Q. Tang, Y.-F. Qiu, B. Song, Z.-H. Qiu, P.-F. Xu and Y.-M. Liang, *J. Org. Chem.*, 2014, **79**, 6627-6633.

19 Y. Liang, Y.-Y. Jiang, Y. Liu and S. Bi, *Org. Biomol. Chem.*, 2017, **15**, 6147-6156.

20 B.-S. Zhang, Y. Li, Y. An, Z. Zhang, C. Liu, X.-G. Wang and Y.-M. Liang, *ACS Catal.*, 2018, **8**, 11827-11833.

