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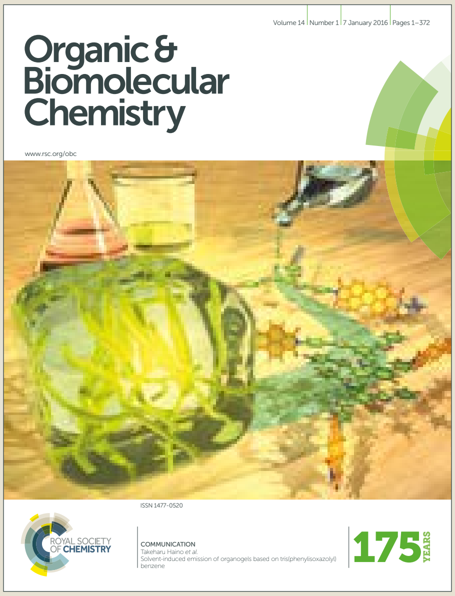

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ARTICLE

Copper(II)-mediated, carbon degradation-based amidation of phenylacetic acids toward *N*-substituted benzamides

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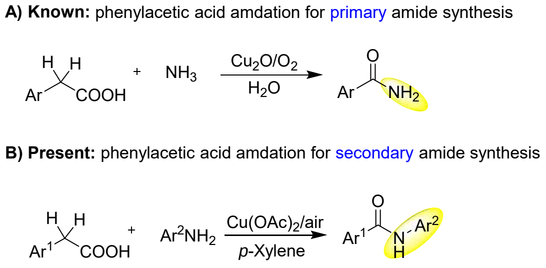
Leiling Deng,[a] Bin Huang[a] and Yunyun Liu[a,*]

Abstract. The unprecedented synthesis of *N*-aryl substituted benzamides via the assemblies of primary amines and phenylacetic acids has been developed in the presence of copper (II) acetate. This tandem transformation involving the carbon-carbon bond cleavage provides a complementary tool with particular application in the synthesis of secondary benzamides.

Introduction

The amide fragment is a fundamental and featured substructure in numerous biologically macromolecules and small organic compounds such as peptides and amino acids. In addition, amide structure is also found as the key functional group in many clinical drugs and valuable natural products.[1] The synthesis of amide constitutes one central issue throughout the development of the synthetic organic chemistry, which correspondingly gives birth to the occurrence of many different synthetic protocols towards the amides.[2] Despite the enriched availability on synthetic methods, the research work on developing new synthetic accesses to amides still attracts extensive interest of scientific communities not only for the requirement of complementary methods featuring enhanced sustainability and product diversity, but also the desire in and acquiring and making use of new routes of amide formation to understand related living processes.[3]

The C-C bond cleavage represents one of the most attractive models of bond transformation in modern organic chemistry, and the activation of C-C bond as well as its application in the designation of fascinating synthetic methods is concurrently receiving tremendous concerns.[4-5] Among the various known models of carbon-carbon bond transformation models, the cleavage of the carbon-carbon bonds in carboxylic acids via decarboxylation and/or other related bond transformation have been recognized as a reliable tactic enabling the synthesis of diversified organic products.[6-7] In 2014, Lei and Lan et al reported the efficient decarboxylative amidation of α-keto acids with the mediation of visible light under oxygen atomsphere.[8] Synthesis of similar products has later on been realized by Xu and co-workers via singlet oxygen promotion,[9a] and silver promotion,[9b] respectively. Notably, by means of direct transformation on phenylacetic acid, Song and co-workers developed a facile carbon-carbon bond cleavage-based amidation method via the reactions of phenylacetic acid and ammonium, which features advantages on the easily available and stable acyl source and the specifically applicability in the synthesis of primary amides (A, Scheme 1).[10a] However, a practical method on the synthesis of corresponding secondary amides by such carbon-carbon bond transformation is not yet available. During the process of our research in developing applicable amidation and their application in the directed C-H activation reaction of enhanced step efficiency,[11-12] we have recently identified that the phenylacetic acids can react with primary aryl amines to provide secondary benzamides via carbon-carbon bond cleavage in the presence of cooper (II) salt. Herein, we wish to report this amidation reaction to provide the first example on the synthesis of secondary amides by the carbon degradation of phenylacetic acids with primary amines without relying on any additional oxidant besides air (B, Scheme 1).



Scheme 1 Amidation of phenylacetic acids by carbon degradation

Results and discussion

Originally, when the 2-aminopyridine **1a** was subjected to react with phenylacetic acid **2a** in the presence of CuCl, the *N*-pyridinyl secondary amide **3a** was produced by heating in p-xylene at 120 °C (entry 1, Table 1). Considering the novelty of this amidation and the importance of the *N*-pyridinyl

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[a] *College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P.R. China.* Email: chemliuyunyun@jxnu.edu.cn

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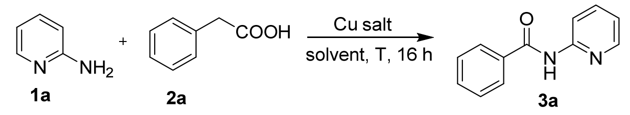
benzamide synthesis,[13] we then conducted systematic experiment to optimize the reaction parameters. The employment of several different copper (II) and copper(I) salts proved that $Cu(OAc)_2$ possesses the best activity for this amidation process (entries 2-6, Table 1). The subsequent experiments at lower copper (II) loading indicated the less $Cu(OAc)_2$ led to the decrease in product yield (entries 7-8, Table 1). Subsequently, the reaction was performed in different media, including toluene, DMF, DMSO, dioxane and ethyl lactate (EL), but no further improved yield was observed (entries 9-13, Table 1). In addition, the parallel reaction conducted at 110 °C gave lower yield of **3a**, and heightening the reaction temperature could not enhance the result, either (entries 14-15, Table 1). A control entry performed under N_2 showed the formation of product **3a** with trace amount, suggesting the indispensable role of oxygen (air) in the reaction (entry 16, Table 1). Further examination on the reaction using catalytic loading of $Cu(OAc)_2$ under O_2 was not practical, demonstrating the crucial role of the stoichiometric Cu(II) salt (entry 17, Table 1). In addition, the presence of TEMPO in the reaction showed no evident inhibition to the reaction, suggesting against the possible free radical pathway in this reaction (entry 18, Table 1).

Table 1 Optimization on reaction conditions[a]

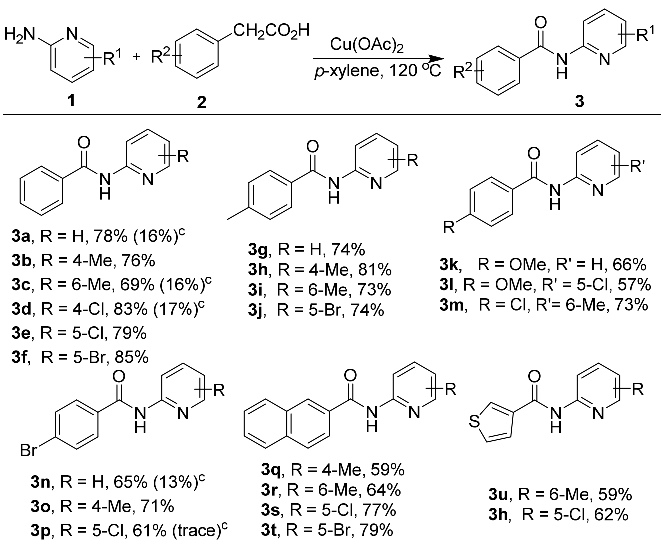


Entry	Copper	Solvent	T (°C)	Yield (%)[b]
1	CuCl	*p*-xylene	120	72
2	CuBr	*p*-xylene	120	25
3	CuI	*p*-xylene	120	31
4[c]	$Cu(OAc)_2$	*p*-xylene	120	78
5	$CuSO_4$	*p*-xylene	120	trace
6	CuO	*p*-xylene	120	trace
7[d]	$Cu(OAc)_2$	*p*-xylene	120	63
8[e]	$Cu(OAc)_2$	*p*-xylene	120	74
9	$Cu(OAc)_2$	toluene	120	68
10	$Cu(OAc)_2$	DMF	120	72
11	$Cu(OAc)_2$	DMSO	120	64
12	$Cu(OAc)_2$	1,4-dioxane	120	trace
13	$Cu(OAc)_2$	EL	120	trace
14	$Cu(OAc)_2$	*p*-xylene	110	61
15	$Cu(OAc)_2$	*p*-xylene	130	77
16[f]	$Cu(OAc)_2$	*p*-xylene	120	trace
17[g]	$Cu(OAc)_2$	*p*-xylene	120	15
18[h]	$Cu(OAc)_2$	*p*-xylene	120	51

[a] General conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), copper catalyst (0.5 mmol), in 2 mL solvent, stirred for 16 h under the open air atmosphere. [b] Yield of isolated product based on **1a**. [c] The $Cu(OAc)_2$ in the experiment refers to the commercial $Cu(OAc)_2{\cdot}H_2O$ reagent. [d] 0.4 mmol $Cu(OAc)_2$ was used; [e] 0.6 mmol $Cu(OAc)_2$ was used. [f] Reaction under N_2. [g] Reaction under O_2 with 0.1 mmol $Cu(OAc)_2$. [h] In the presence of TEMPO (2 eq).

To examine the application scope, the reactions employing different 2-aminopyridines and phenylacetic acids were first carried out. As showing in Table 2, the expected synthesis of N-pyridinyl amides **3** was found with satisfactory tolerance to substituents in both components. Functional groups such as alkyl, alkoxyl, halogen and (hetero)aryl etc were found all with compatibility to this amidation process. The yields were fair to excellent and the electronic property of the substituent displayed no defined effect to the formation of the amides. Notably, to further examine the effect of Cu(II) loading to the reaction, some entries in this section were also carried out in the presence of 40 mol% $Cu(OAc)_2$, and all these entries gave very low yield of corresponding products, confirming the fact that stoichiometric copper(II) salt was necessary for the reaction (**3a**, **3c**, **3d**, **3n**, **3p**).

Table 2 Scope for the synthesis of N-pyridinyl benzamides[a,b,c]



[a] General conditions: **1** (0.5 mmol), **2** (0.75 mmol), $Cu(OAc)_2$ (0.5 mmol) in p-xylene (2 mL), stirred at 120 °C for 16 h under air atmosphere. The yield on the parenthesis were acquired in the presence of 40 mol% $Cu(OAc)_2$. [b] Yield of isolated product based on **1**. [c] The yields in the parenthesis were acquired in the presence of 40 mol% $Cu(OAc)_2$.

On the basis of these results, efforts were then further made in employing analogous heteroaryl amine, the 2-aminoquinoline as the reaction partner to react with different phenylacetic acids. Delightfully, equally fine substrate tolerance and yields of corresponding products **5** were achieved in this section of experiments. As shown in Table 3, the *N*-quinolinyl benzamides **5** were provided with moderate to excellent yields under the standard reactions, indicating the general application scope of the present method toward the synthesis of *N*-electron deficient heteroaryl benzamides. The reaction using *N*-methyl 2-aminopyridine was found inapplicable for such reaction as no tertiary amide was given, which could be attributed to the steric hindrance of the *N*-methyl group to the intramolecular addition step (see Scheme 3). In addition, when subjected with **1a**, the aliphatic propionic acid didn’t take part this degradation amidation, either.

The good results from *N*-heteroaryl amines encouraged us to further explore the possible application of such transformation in the synthesis of benzamides with full carbon aryl *N*-substitution by accordingly employing anilines **6** to react with

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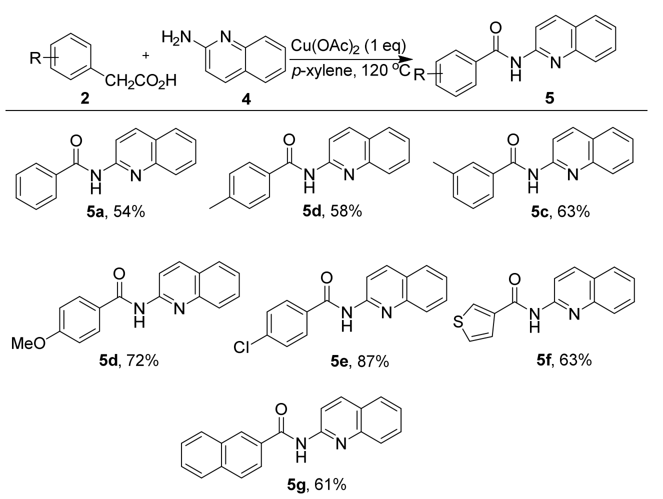
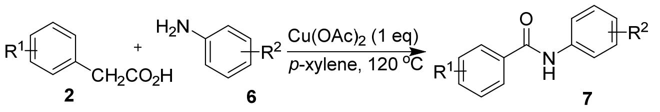
Table 3 Scope on the synthesis of *N*-quinolinyl benzamides[a,b]



[a]Generation reaction conditions as Table 2. [b]Yield of isolated product based on **4**.

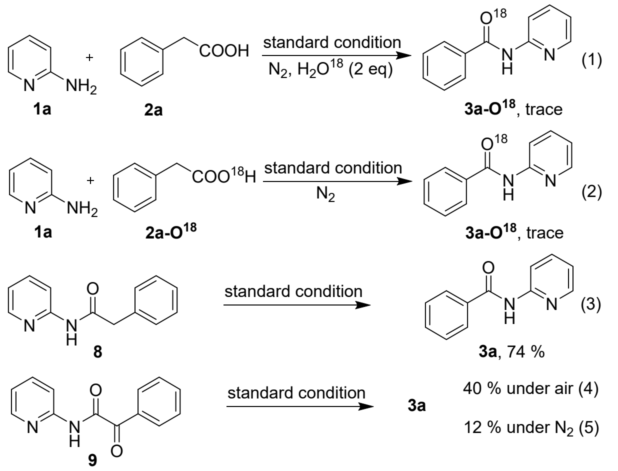
phenylacetic acids. As expected, the corresponding *N*-phenyl benzamides **7** could be acquired with different functional groups in both aniline and benzoyl fragments, albeit with much lower yield than corresponding products **3** and **5** (Scheme 2), suggesting that the electron deficient aryl amines were much favourable in this kind of C-C bond degradation amidation. Actually, no similar reaction happened when aliphatic amine such as *i*-propylamine was utilized with **2a**, supporting that electron deficient amines were more proper for the reaction. The product yields from this section were much lower than the reactions employing 2-aminopyridines, probably because the chelation of 2-aminopyridines with the Cu(II) salt promoted this amidation reaction.



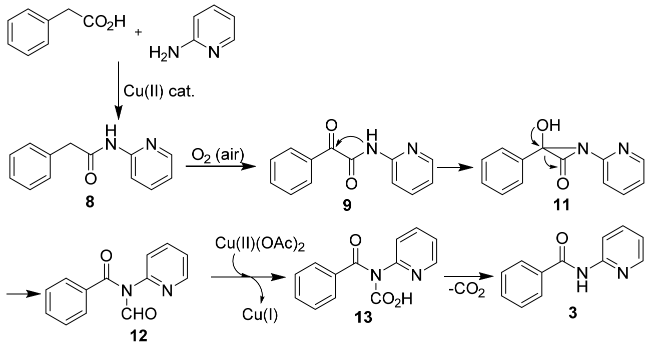
7a, R^1 = 4-Me, R^2 = H, 40%; **7b**, R^1 = 3-Me, R^2 = H, 41%
7c, R^1 = 4-Me, R^2 = 3-Me, 31%; **7d**, R^1 = 4-Br, R^2 = 3-Me, 30%
7e, R^1 = 4-Br, R^2 = H, 35%

Scheme 2 Synthesis of benzamides employing phenylacetic acids and anilines

In order to probe the possible pathway of this amidation reaction, a series of control experiments were then conducted. Firstly, the optimized model reaction in additional presence of 2 equiv. of O^{18} labelled water from which the corresponding product **3a-O^{18}** was observed in HRMS with only trace amount (Eq. 1), suggesting that the oxygen in the product did come from moisture. Furthermore, the entry utilizing hydroxyl O^{18} labeled phenylacetic acid as substrate afforded also trace amount of **3a-O^{18}**, indicating that the hydroxyl in the phenylacetic acid was not the source of the carbonyl group in product **3**, either (Eq 2). Notably, when the N-pyridinyl phenylacetamide was subjected to the standard reaction condition, the product **3a** was isolated with good yield (Eq 3), supporting that this phenylacetamide was a possible key intermediate in the reaction. In addition, α-ketoamide **9** underwent transformations to give **3a** under the atmosphere of both air and N_2, indicating that the subsequent C-C bond cleavage might mediated by both air and Cu(II) salt (Eqs 4, 5).



Following the information from these experiments, the entry under N_2 and related literature knowledge,[10b,14] we proposed the general mechanism of this C-C bond cleavage based amidation reaction. As outlined in Scheme 3, the reaction may start from the amidation of the phenylacetic acid forming phenylacetamide **8**. The benzyl methylene C-H bonds therein are known to be capable of getting oxidized by oxygen to generate carbonyl and provide α-ketoamide **9**. The intramolecular nucleophilic addition of the nitrogen atom to the newly formed carbonyl enables the formation of intermediate **11**. The bond reorganization initiated by the ring opening provides N-formyl intermediate **12**, which may be converted to corresponding carboxyl species **13** via the oxidation of $Cu(OAc)_2$. The decarboxylation of **13** then yields the amide products **3**.



Scheme 3 The proposed reaction mechanism

Conclusions

In conclusion, we have disclosed the carbon degradation-based amidation reaction via the assembly of phenylacetic acids and (hetero)aryl primary amines, which provides a series of N-(hetero)aryl benzamides. On the basis of known literature reporting similar phenylacetic acid amidation for the synthesis of N-unsubstituted benzamides, the present work partially fills in the virgin of the C-C bond cleavage amidation of

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phenylacetic acid by providing the complementary access to the N-substituted benzamides.

Experimental section

General procedure for the synthesis of benzamides 3, 5 and 7. To a 25 mL round-bottom flask equipped with stirring bar and air condenser was charged with aryl amine **1** (**4** or **6**) (0.5 mmol), phenylacetic acid **2** (0.75 mmol), $Cu(OAc)_2$ (0.5 mmol) and *p*-xylene (2 mL). The resulting mixture was stirred at 120 ^{o}C for 16 h. Upon completion, the reaction mixture was allowed to cool down to rt, and H_2O (5 mL) was added to the vessel. The resulting suspension was extracted with ethyl acetate (3 × 8 mL). The organic phases were combined and dried over Na_2SO_4. After filtration, the solvent was removed from the solution under reduced pressure. The acquired residue was subjected to silica gel column chromatography to provide pure product by using mixed petroleum ether/ethyl acetate 10:1 (v/v) as the eluent.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (a) J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, *97*, 2243; (c) A. Greenberg, C. M. Breneman and J. F. Liebman, The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science, John Wiley & Sons, 2000; (c) S. Son and B. A. Lewis, J. Agric. Food Chem., 2002, 50, 468. (d) A. Mishra, N. K. Kaushik, A. K. Verma and R. Gupta, *Eur. J. Med. Chem.*, 2008, **43**, 2189.

2 (a) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606. (b) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471. (c) A. Ojeda-Porras and D. Gamba-Sánchez, *J. Org. Chem.*, 2016, **81**, 11548. (d) J.-P. Wan and Y. Jing, *Beilstein J. Org. Chem.*, 2015, **11**, 2209. (e) R. M. Lanigan and T. D. Sheppard, *Eur. J. Org. Chem.*, 2013, 7453.

3 For selected recent examples, see (a) D.-G. Yu, M. Suri and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 8802. (b) T. Hamada, X. Ye and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 833. (c) Q. Zhang, K. Chen, W. Rao, Y. Zhang, F.-J. Chen and B.-F. Shi, *Angew. Chem. Int. Ed.*, 2013, **52**, 13588. (d) Y. Li, F. Zhu, Z. Wang and X.-F. Wu, *ACS Catal.*, 2016, **6**, 5561. (e) S. Premaletha, A. Ghosh, S. Joseph, S. R. Yetra and A. T. Biju, *Chem. Commun.*, 2017, **53**, 1478. (f) F. Wang, L. Jin, L. Kong and X. Li, *Org. Lett.,* 2017, **19**, 1812. (g) Q. Qin, Y.-Y. Han, Y.-Y. Jiao, Y. He and S. Yu, *Org. Lett.*, 2017, **19**, 2909. (h) A. Kumar, N. A. Espinosa-Jalapa, G. Leitus, Y. Diskin-Posner, L. Avram and D. Milstein, *Angew. Chem. Int. Ed.*, 2017, **56**, 14992. (i) X.-F. Wang, S.-S. Yu, C. Wang, D. Xue and J. Xiao, *Org. Biomol. Chem.,* 2016, **14**, 7028. (j) W. Tong, P, Cao, Y. Liu and J. Chen, *J. Org. Chem.*, 2017, **82**, 11603. (k) J.-W. Wu, Y.-D. Wu, J.-J. Dai and H.-J. Xu *Adv. Synth. Catal.,* 2014, **356**, 2429.

4 (a) L. Souillart and N. Cramer, *Chem. Rev.*, 2015, **115**, 9410. (b) Y. J. Park, J.-W. Park and C.-H. Jun, *Acc. Chem. Res.*, 2008, **41**, 222. (c) K. Ruhland, *Eur. J. Org. Chem.*, 2012, 2683. (d) C. Nájera, and J. M. Sansano, *Angew. Chem. Int. Ed.*, 2009, **48**, 2452. (e) Y.-F. Liang and N. Jiao, *Acc. Chem. Res.*, 2017, **50**, 1640. (f) H. Yan and C. Zhu, *Sci. China Chem.*, 2017, **60**, 214.

5 For some recent examples, see (a) T. Xu and G. Dong, *Angew. Chem. Int. Ed.*, 2012, **51**, 7567. (f) J. Yu, H. Yan, C. Zhu, *Angew. Chem. Int. Ed.*, 2016, **55**, 1143. (c) H. Yue, L. Guo, H.-H. Liao, Y. Cai, C. Zhu and M. Rueping, *Angew. Chem. Int. Ed.*, 2017, **56**, 4282. (d) S. M. Banik, K. M. Mennie and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2017, **139**, 9152. (e) A. Vasseur and I. Marek, *Nat. Protoc.,* 2017, **12**, 74. (f) S. Feng, F. Mo, Y. Xia, Z. Liu, Z. Liu, Y. Zhang and J. Wang, *Angew. Chem. Int. Ed.,* 2016, **55**, 15401. (g) J.-P. Wan, Y. Lin, X. Cao, Y. Liu and L. Wei, *Chem. Commun.,* 2016, **52**, 1270. (h) C. R. Pitts, M. S. Bloom, D. D. Bume, Q. A. Zhang and T. Lectka, *Chem. Sci.,* 2015, **6**, 5225.

6 For reviews, see (a) N. Rodríguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030. (b) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. A. Hor and X. Liu, *Chem. Soc. Rev.*, 2015, **44**, 291. (c) L.-N. Guo, H. Wang and X. Duan, *Org. Biomol. Chem.*, 2016, **14**, 7380. (d) Z.-L. Wang, *Adv. Synth. Catal.*, 2013, **355**, 2745. (e) Y. Li, L. Ge, M. T. Muhammad and H. Bao, *Synthesis*, 2017, **49**, 5263. (f) H. Li, T. Miao, M. Wang, P. Li and L. Wang, *Synlett*, 2016, **27**, 1635. (g) G. J. P. Perry and I. Larrosa, *Eur. J. Org. Chem.*, 2017, 3517. (h) T. Patra and D. Maiti, *Chem. Eur. J.,* 2017, **23**, 7382. (i) P. Liu, G. Zhang and P. Sun, *Org. Biomol. Chem.*, 2016, **14**, 10763. (j) L. Shang and L. Liu, *Sci. China Chem.,* 2011, **54**, 1670.

7 For selected examples, see (a) L. J. Gooßen, G. Deng and L. M. Levy, *Science*, 2006, **31**3, 5787. (b) C. Wang, S. Rakshit and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 14006. (c) R. Shang, D.-S. Ji, L. Chu, Y. Fu and L. Liu, *Angew. Chem. Int. Ed.*, 2011, **50**, 4470. (d) J.-M. Becht and C. Le Drian, *Org. Lett.*, 2008, **10**, 3161. (e) L. Chu, J. M. Lipshultz and D. W. C. MacMillan, *Angew. Chem. Int. Ed.*, 2015, **54**, 7929. (f) P. Hu, Y. Shang and W. Su, *Angew. Chem. Int. Ed.,* 2012, **51**, 5945. (g) H.-N. Yuan, S. Wang, J. Nie, W. Meng, D. Yao and J.-A. Ma, *Angew. Chem. Int. Ed.*, 2013, **52**, 3869. (h) J. Lindh, P. J. R. Sjöberg and M. Larhed, *Angew. Chem. Int. Ed.,* 2010, **49**, 7733. (i) J. G. Knight, S. W. Ainge, A. M. Harm, S. J. Harwood, H. I. Maughan, D. R. Armour, D. M. Mollinshead and A. A. Jaxa-Chamie, *J. Am. Chem. Soc.,* 2000, **122**, 2944. (j) W. Jian, L. Ge, Y. Jiao, B. Qian and H. Bao, *Angew. Chem. Int. Ed.*, 2017, **129**, 3704.

8 J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan and A. Lei, *Angew. Chem. Int. Ed.*, **2014**, *53*, 502-506.

9 (a) W.-T. Xu, B. Huang, J.-J. Dai, J. Xu and H.-J. Xu, *Org. Lett.*, 2016, **18**, 3144. (b) X.-L. Xu, W.-T. Xu, J.-W. Wu, J.-B. He and H.-J. Xu, *Org. Biomol. Chem.*, 2016, **14**, 9970.

10 (a) Q. Song, Q. Feng and K. Yang, *Org. Lett.*, 2014, **16**, 624. (b) Q. Feng and Q. Song, *J. Org. Chem.*, 2014, **79**, 1867.

11 For the featured review on step efficient multicomponent C-H activation, see: J.-P. Wan, L. Gan and Y. Liu, *Org. Biomol. Chem.,* 2017, **15**, 9031.

12 (a) Y. Liu, Y. Zhang and J.-P. Wan, *J. Org. Chem.*, 2017, **82**, 8950. (b) Y. Liu, B. Huang, X. Cao and J.-P. Wan, *ChemCatChem*, 2016, **8**, 1470.

13 O. P. S. Patel, D. Anand, R. K. Maurya and P. P. Yadav, *Green Chem.*, 2015, **17**, 3728. (b) S. Yang, H. Yan, X. Ren, X. Shi, J. Li, Y. Wang and G. Huang, *Tetrahedron*, 2013, **69**, 6431. (c) A. Ragupathi, A. Sagadevan, C.-C. Lin, J.-R. Hwu and K. C. Hwang, *Chem. Commun.*, 2016, **52**, 11756.

14 (a) X. Wang, R.-X. Chen, Z.-F. Wei, C.-Y. Zhang, H.-Y. Tu and A.-D. Zhang, *J. Org. Chem.*, 2016, **81**, 238. (b) X.-F. Wu, C. B. Bheeter, H. Neumann, P. H. Dixneuf and M. Beller, *Chem. Commun.*, 2012, **48**, 12237.

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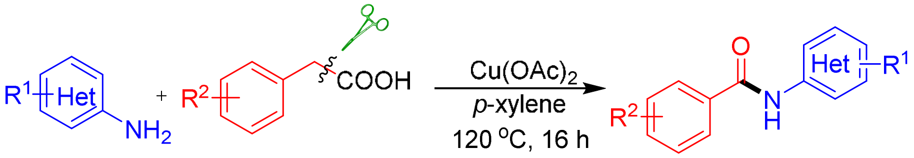

The carbon degradation-based amidation of phenylacetic acids with aryl amides has been realized in the presence of $Cu(OAc)_2$, which provides a practical route in the synthesis of *N*-aryl secondary benzamides.