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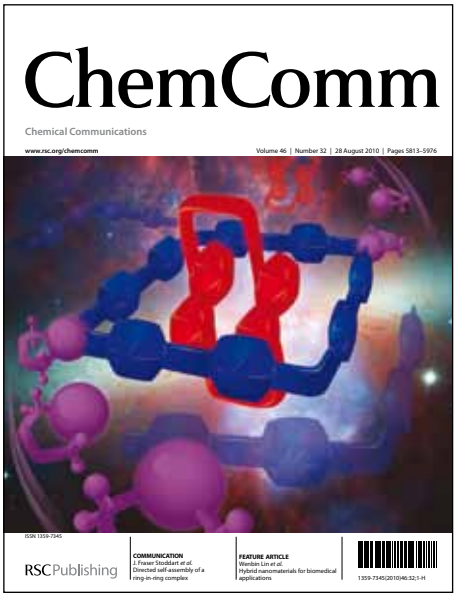

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ARTICLE TYPE

Synthesis of biaryl imino/keto carboxylic acid *via* aryl amide directed C-H activation reaction

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A novel Pd-catalysed C-H activation reaction for the synthesis of biaryl imino/keto carboxylic acid is developed. These reactions underwent aryl amide directed C-H activation *ortho*-acylation followed by ring closing and ring opening processes to give a range of biaryl imino/keto carboxylic acids. Our methodology features the utilization of cheap and green oxidant (TBHP) as well as readily available aldehydes.

Transition metal-mediated *ortho*-directed C–H activation has become one of the most important methods for the atom economical modification of aromatic systems.[1] As one of the weak directing groups, carboxylic acid directed C-H activation reactions have been less exploited.[2] Gooßen has recently developed an approach for the *ortho*-acylation of aryl carboxylic acids under Rh-catalysed C-H activation conditions (**Figure 1, eq. 1**).[3] Slightly later, Ge has demonstrated that under Pd-catalysed conditions, keto carboxylic acids could also be achieved using α-oxocarboxylic acids as the acyl source (**Figure 1, eq. 2**).[4] We have recently developed an efficient synthesis of aryl iminocarboxylic acid *via* directed *ortho*-acylation of benzamides. A range of biaryl imino/keto carboxylic acids were successfully prepared by the reactions of aryl amides and readily available aryl aldehydes (**Figure 1, eq. 3**).

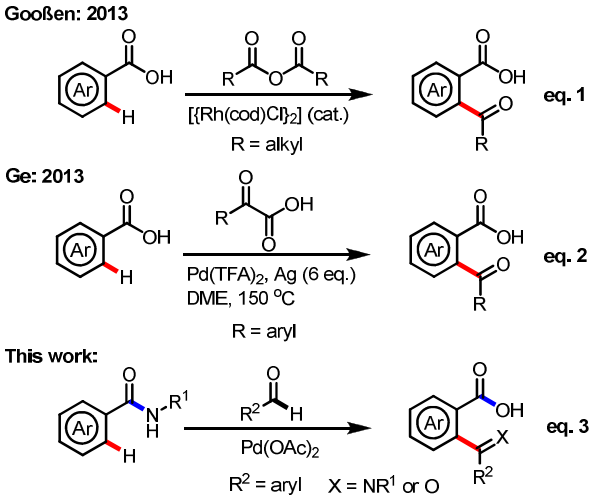
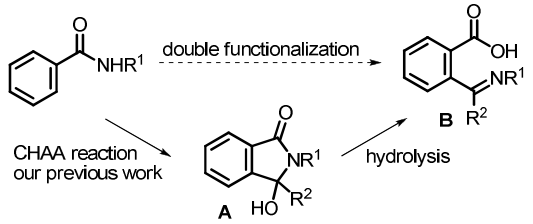


Figure 1. Modular syntheses of imino/keto aryl carboxylic acids

During our previous studies, we have shown that the five-membered hydroxyl isoindolone **A** could be formed under Pd-catalysed C-H activation/annulation (CHAA) reaction conditions.[5] We then envisaged that the hydroxyl isoindolone **A** could be an intermediate for the double functionalization of benzamide for the synthesis of imino carboxylic acid **B** as shown in **Scheme 1**. The proposed synthesis would be the conversion of aryl amide to the corresponding imino carboxylic acid *via* C-H activation, ring closing and ring opening processes. Iminocarboxylic acid is a class of useful organic building block which can be converted into a series of hetercycles.[6] The current available syntheses are normally tedious with multi-step processes.[7]



Scheme 1. Proposed double functionization of aryl amide for the synthesis of imino carboxylic acid

To test the hypothesis, the reaction of benzamide **1a** and benzaldehyde **2a** was studied. Preliminary results suggested that polar aprotic solvent DMSO is a good solvent which provided the desired product **3a** in a good yield of 67% (SI, table 1, entry 1). TBHP prior to other oxidants has shown the best reactivity towards the imino carboxylic acid synthesis, whereas other oxidants such as $K_2S_2O_8$, H_2O_2, *m*-CPBA, BQ and Ag_2O all failed to give our desired product (SI, Table 1, entries 2-6). Mixed solvents of DMSO with diglyme, MeCN and dioxane gave the desired product in 53%, 40% and 73% yields respectively (SI Table 1, entries 7-9). Further screening on the additives is fruitful. Reactions in the presence of molecular iodine or halogen salts as the additive failed to give the corresponding imino carboxylic acid, interestingly, however, when Lewis acid such as catalytic amount of BF_3•Et_2O was utilized the reaction yield has been improved to 84% yield (SI, Table 1, entries 10-17). Other Pd source, for example $PdCl_2$ only gave trace amount of the desired product while $Pd(TFA)_2$ is an efficient catalyst for this transformation which leading to imino carboxylic acid **3a** in a comparable good 76% yield. Similar to our early studies on CHAA reactions, Pd(0) source, Pd_2dba_3, is also a potential catalyst although our desired product was isolated only in 29%

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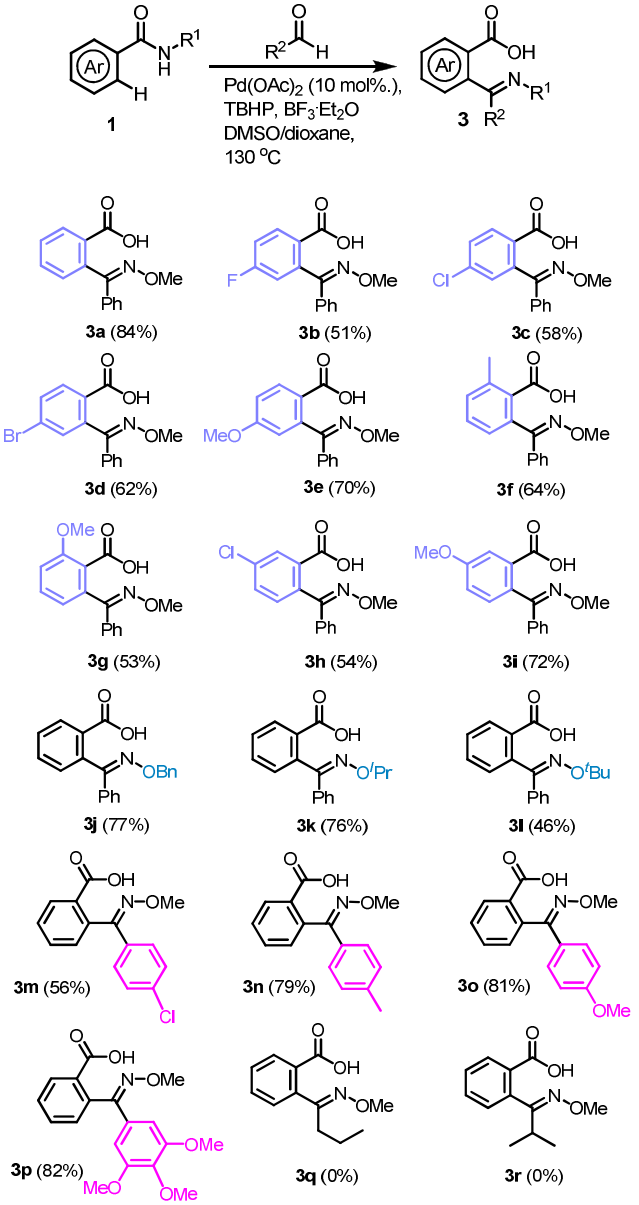
yield (SI Table 1, entry 20).

The scope of the Pd-catalysed reaction with various benzamides and aldehydes is summarised in **Table 1**. Reactions with benzamides poccessing electron-withdrawing and electron-donating substitutes all gave the corresponding products in moderate to good yields. Under the optimal conditions, a range of aryl amides as well as aldehydes were examined. The reactions of *para*-halide (F-, Cl- or Br-) substituted benzamides went smoothly providing the corresponding *para*-halo imino carboxylic acids **3b-3d** in 51%-62% yields.

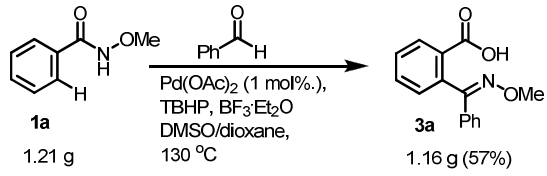
Table 1. imino carboxylic acid synthesis



Reaction conditions: benzamide **1** (0.3 mmol), aldehyde **2** (1.2 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (70% in H_2O) (5.0 equiv), BF_3•Et_2O (0.4 equiv) at 130 °C in DMSO:dioxane 4:1 (1.5 mL, 0.2 M), 1.5-3 h.

Comparing to the benzamides bearing electron withdrawing groups, *para*-OMe imino carboxylic acid **3e** was isolated in a higher 70% yield. *Ortho*-substituents did not affect the reaction reactivity as *ortho*-Me and *ortho*-OMe substituted imino carboxylic acids were isolated in good 64% and 53% yields respectively. Meta-substituted benzamides are also tolerated in the reactions, only one of regioisomers was isolated for both electron rich and electron deficient benzamides. The excellent regioselectivity is agreed with the one we previously studied during the isoindolone synthesis. Primary, secondary and tertiary alkoxyl iminos **3j-3l** have also been successfully synthesised when the corresponding benzamides were employed. The evaluations of a number of aryl aldehydes bearing both electron withdrawing as well as electron donating groups were also carried out. The treatment of benzamide **1a** with *para*-Cl benzaldehyde under our standard conditions provided the corresponding imino carboxylic acid **3m** in 56% yield. Aldehydes such as *para*-OMe and 3,4,5-tri-OMe substituted benzaldehydes afforded our desired products **3o** and **3p** in good 81% and 82% respectively. Unfortunately, under the optimal conditions the attempts on aliphatic aldehydes failed to give the corresponding imino carboxylic acid. Reactions of benzamide **1a** with both butyraldehyde and isobutyraldehyde gave rise to benzoic acid without the observation of C-H activation products. Interestingly, due to the hydrogen bonding of carboxylic acid proton to the oxime nitrogen, the E-oximes were obtained exclusively.

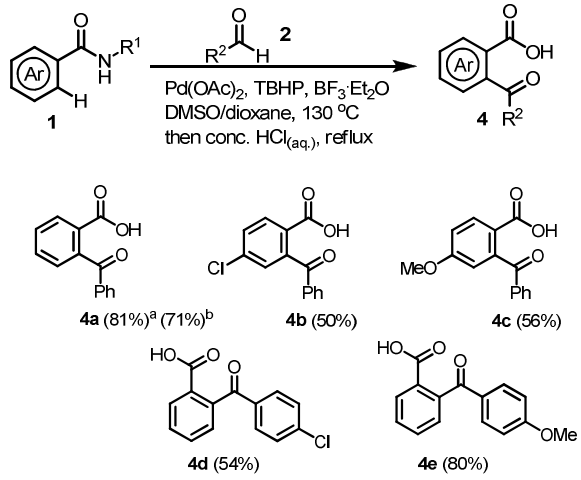
To test the reaction reliability, a gram-scale synthesis has also been examined, we successfully isolated our desired product in 57% yield even under the conditions with reduced catalyst loading (1 mol% of $Pd(OAc)_2$) as shown in **Scheme 2**.



Scheme 2. Gram-scale synthesis of imino benzoic acid **3a**

The synthesis of aryl ketocarboxylic acids was also straightforward as shown in **Table 2**. Both electron rich and deficient benzamides as well as electron rich and poor benzaldehydes have shown good reactivity during the reactions.

Table 2. ketobenzoic acid synthesis



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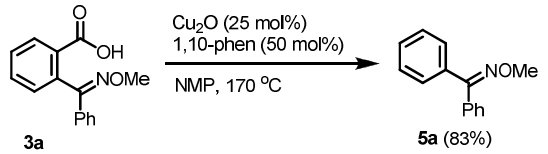
Reaction conditions: benzamide **1** (0.3 mmol), aldehyde **2** (1.2 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (70% in H_2O) (5.0 equiv), BF_3•Et_2O (0.4 equiv) at 130 °C in DMSO:dioxane 4:1 (1.5 mL, 0.2 M), 5 h. Then conc. $HCl_{(aq)}$ (10.0 equiv) was added, reflux for 6 h. [a]N-OMe benzamide was used; [b]N-O^{i}Pr benzamide was used.

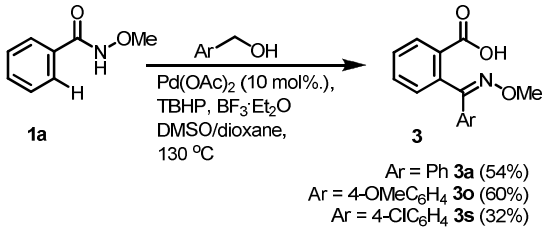
The treatment of benzamides **1** with aryl aldehydes under our standard reaction conditions followed by the introduction of concentrated HCl solution, the corresponding aryl keto carboxylic acids **4a**-**4e** were successfully obtained in good yields. Both electron rich and poor benzamides as well as aryl aldehydes bearing electron donating group and electron withdrawing group are tolerated under these reaction conditions.

Attempts on the decarboxylication of **3a** were also carried out. Under Gooβen's decarboxylation conditions,[8] carboxylic acid **3a** was treated with 25 mol% of Cu_2O in the presence of 1,2-phenanthroline resulted in the corresponding aryl imine **5a** in 83% yield without the detection of the hydrolysis product.



Scheme 3. Cu-mediated decaboxylation for the synthesis of biaryl imine **5a**

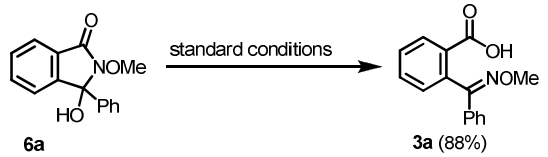
In addition, a one-pot procedure using benzyl alcohols was also developed.[9] The corresponding iminocarboxylic acids **3a**, **3o** and **3s** were isolated in useful to good yields. (**Scheme 4**)



Reaction conditions: benzamide **1a** (0.3 mmol), alcohol (1.8 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (70% in H_2O) (8.0 equiv), BF_3•Et_2O (0.4 equiv) at 130 °C in DMSO:dioxane 4:1 (1.5 mL, 0.2 M), 2-8 h.

Scheme 4. One-pot procedure for the synthesis of iminocarboxylic acid from alcohol.

To further prove our initial proposal, the subjection of hydroxyl isoindolone **6a** into the reaction system under our standard iminocarboxylic acid forming conditions resulted in our desired imino caroxylic acid **3a** in a good yield of 88%. It is also worth noting that we have observed the formation of hydroxyl isoindolone **6a** during our reaction both by TLC and NMR analyses.



Scheme 5. Ring opening of hydoxyl isoindolone **6a**

In conclusion, we have reported the first Pd-catalysed synthesis of imino/ketocarboxylic acids *via* aryl amide directed C-H activation reaction. A range of representative biaryl imino carboxylic acids were successfully prepared. In addition, this methodology has also provided an alternative approach for the preparation of keto carboxylic acids *via* cheap readily available aldehydes.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 For transition metal-mediated *ortho*-directed C-H activations, see: a) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev*., 2010, **110**, 624; b) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; c) B.-J. Li and Z.-J. Shi, *Chem. Soc. Rev.*, 2012, **41**, 5588; d) D.-G. Yu, M. Suri and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 8802; e) X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 1236; f) K. D. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 11430; g) H. Wang, N. Schrçder and F. Glorius, *Angew. Chem., Int. Ed*., 2013, **52**, 5386; h) A. S. Tsai, M. E. Tauchert, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 1248; i) O. Basl, J. Bidange, Q. Shuai and C.-J. Li, *Adv. Synth. Catal.*, 2010, **352**, 1145; j) Y. Yang, B. Zhou and Y. Li, *Adv. Synth. Catal.*, 2012, **354**, 2916; k) C. Li, L. Wang, P. Li and W. Zhou, *Chem. Eur. J*., 2011, **17**, 10208; l) J. Park, E. Park, A. Kim, Y. Lee, K.-W. Chi, J. H. Kwak, Y. H. Jung and I. S. Kim, *Org. Lett.*, 2011, **13**, 4390; m) M. Li and H. Ge, *Org. Lett.*, 2010, **12**, 3464; n) M. Kim, J. Park, S. Sharma, A. Kim, E. Park, J. H. Kwak, Y. H. Jung and I. S. Kim, *Chem. Commun.*, 2013, **49**, 925; o) H. Wang, L.-N. Guo and X.-H. Duan, *Org. Lett*., 2012, **14**, 4358; p) J. Park, M. Kim, S. Sharma, E. Park, A. Kim, S. H. Lee, J. H. Kwak, Y. H. Jung and I. S. Kim, *Chem. Commun.*, 2013, **49**, 1654; q) S. Guin, S. K. Rout, A. Banerjee, S. Nandi and B. K. Patel, *Org. Lett*., 2012, **14**, 5294.

2 For carboxylic acid directed C-H activations, see: a) Y.-H. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 14654; b) T.-S. Mei, R. Giri, N. Maugel and J.-Q. Yu, *Angew. Chem., Int. Ed*., 2008, **47**, 5215.

3 P. Mamone, G. Danoun and L. J. Gooßen, *Angew. Chem., Int. Ed.*, 2013, **52**, 6704.

4 J. Miao and H. Ge, *Org. Lett.*, 2013, **15**, 2930.

5 Q. Yu, N. Zhang, J. Huang, S. Lu, Y. Zhu, X. Yu and K. Zhao, *Chem. Eur. J*., 2013, doi: 10.1002/chem.201302031.

6 N. N. Smolyar and Y. M. Yutilov, *Russian J. Org. Chem*., 2008, **44**, 274.

7 C. B. Aakeröy, A. S. Sinha, K. N. Epa, C. L. Spartz and J. Desper, *Chem. Commun*., 2012, **48**, 11289.

8 a) L. J. Gooßen, F. Manjolinho, B. A. Khan, N. Rodríguez, *J. Org. Chem.*, 2009, **74**, 2620; b) M. Rudzki, A. Alcalde-Aragonés, W. I. Dzik, N. Rodríguez, L. J. Gooßen, *Synthesis*, 2012, **44**, 184; c) L. J. Gooßen, W. R. Thiel , N. Rodríguez, C. Linder and B. Melzer, *Adv. Synth. Catal.*, 2007, **349**, 2241.

9 F. Xiao, Q. Shuai, F. Zhao, O. Baslé, G. Deng and C-J. Li, *Org. Lett.*, 2011, **13**, 1614.