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ARTICLE TYPE

Synthesis of Phthalic Acid Derivatives via Pd-Catalyzed Alkoxycarbonylation of Aromatic C–H Bonds with Alkyl Chloroformates

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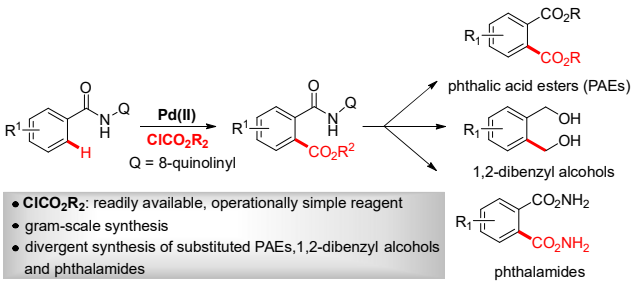
A Pd(II)-catalyzed alkoxycarbonylation of aromatic C-H bonds with alkyl chloroformates has been developed. A broad range of benzamides and alkyl chloroformates are compatible with this protocol. The reaction is operationally simple and scalable. The direct group could be readily removed to access substituted phthalic acid esters (PAEs), 1,2-dibenzyl alcohols and phthalamides. Besides alkoxycarbonylation of benzamide *β*-C–H bonds, γ-alkoxycarbonylation of 2-phenylacetamide is also feasible.

Aromatic esters are a privileged scaffold in natural products, agrochemicals, pharmaceuticals, and materials science. They are also widely used as versatile building blocks for various organic transformations.[1] Traditional methods, such as the condensation of activated acid derivatives with alcohols, the reaction of organometallic compounds with di-*tert*-butyl dicarbonate, and transition metal-catalyzed coupling of aryl halides with carbon monoxide or its precursors, have been widely used for the preparation of these scaffolds.[2] Recently, the direct introduction of a carbonyl group into organic molecules through transition metal-catalyzed C−H activation have attracted tremendous attentions.[3,4] In particular, direct carbonylation of inert C–H bonds with carbon monoxide (CO) has been extensively studied and found great applications in the synthesis of amides/lactams,[5] carboxylic acids,[6] and esters.[7-9] Although carbon monoxide is one of the most inexpensive and abundant C1 building block, there are several major limitations hurdle its use in laboratory-scale, such as the toxicity, gaseous form and flammability. Thus, the development of C–H alkoxycarbonylation reactions with esterification reagents other than carbon monoxide is highly desirable.

In 2008, Yu and co-workers reported the first palladium-catalyzed oxidative ethoxycarbonylation of aromatic C–H bonds with diethyl azodicarboxylate (DEAD).[10] Later on, the You group achieved the Pd(II)-catalyzed *ortho*-C–H ethoxycarbonylation of anilides with DEAD at ambient temperature.[11] Wang and co-workers demonstrated a Pd-catalyzed *ortho*-C−H ethoxycarboxylation of azobenzenes and azoxybenzenes with DEAD.[12] Besides DEAD, other regents, such as glyoxylate,[13] *α*-keto esters,[14] di-*tert*-butyl decarbonate (Boc_2O),[15] potassium oxalate[16], diaziridinone,[17] and formates[18] have also been used in the direct alkoxycarboxylation of inert C−H bonds to access esters. Although these elegant work have significantly extend the scope and synthetic applications of C−H carbonylation reactions, the discovery of new type of surrogates that can be easily applied to the divergent and expeditious synthesis of various carboxylic esters is still highly demanded. In this context, alkyl chloroformates are especially promising alkoxycarbonyl surrogates since they are readily available and operationally simple. In 2009, Kakiuchi and co-workers reported the first Ru-catalyzed alkoxycarbonylation of 2-arylpyridines with alkyl chloroformates.[19] However, the pyridyl directing group can't be removed or modified. Inspired by this elegant work, we have recently achieved the Pd(II)-catalyzed stereoselective alkoxycarbonylation of $C(sp^3)$–H bonds with alkyl chloroformates.[20] In consideration of the importance of aromatic esters and our continuous interests on C−H carbonylation, we wonder whether alkyl chloroformates could be used as esterification reagents for the divergent synthesis of aromatic esters. Herein, we report the Pd-catalyzed alkoxycarbonylation of aromatic C−H bonds with chloroformates. A variety of benzamides and alkyl chloroformates are compatible with this protocol, providing the access of diverse aromatic esters. The 8-aminoquinoline (AQ) directing group[21] can be readily removed to afford substituted phthalic acid esters (PAEs), 1,2-dibenzyl alcohols and phthalamides (Scheme 1). Furthermore, besides alkoxycarbonylation of the *β*-$C(sp^2)$−H bonds, *γ*-$C(sp^2)$−H alkoxycarbonylation via a six-membered palladacycle could also be achieved.

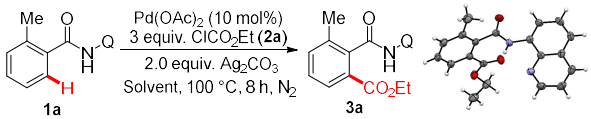


Scheme 1. Pd-catalyzed C–H alkoxycarboxylation of benzamides with alkyl chloroformates

We initiated our study by investigating the reaction of benamide **1a** with $ClCO_2Et$ **2a**. To our delight, the desired ethoxycarbonylation product **3a** was obtained in 72% yield in the presence of 10% mol $Pd(OAc)_2$, 2.0 equiv Ag_2CO_3 in DCE at

100 °C for 8 h (Table 1, entry 1). The structure of **3a** was unambiguously determined by X-ray crystallography.[23] The efficiency of the reaction was significantly affected by different solvents. Further screening of various solvents disclosed that toluene was the optimal for this reaction (entry 12). Other solvents totally inhibited the reaction (entries 2-7). It should be noted that the alkoxycarbonylation reaction was quite sensitive to the amount of Ag_2CO_3. Attempts to lower the loading of Ag_2CO_3 led to reduced yield (entry 13, 42% yield) and no desired product was observed in the absence of Ag_2CO_3 (entry 14). Other organic and inorganic oxidants didn't give satisfactory yields (see Table S2 for details). The reaction could also be conducted under air, albeit with lower yield (entry 15, 76% yield). We further tested other commonly used bidentate directing groups (DGs) (see Table S3 for details). No reaction occurred when 2-pyridinylisopropyl (PIP)[22a] and 4-amino-2,1,3-benzothiadiazole (ABTD)[22b] were used as DG. 2-Aminomethylpyridine[22c] led exclusively to the alkoxycarbonylation of amide, whereas the use of 2-methylthioaniline[22d] gave moderate yield (31%) together with the alkoxycarbonylation of amide (33%).

Table 1 Optimization of the Reaction conditions[a]



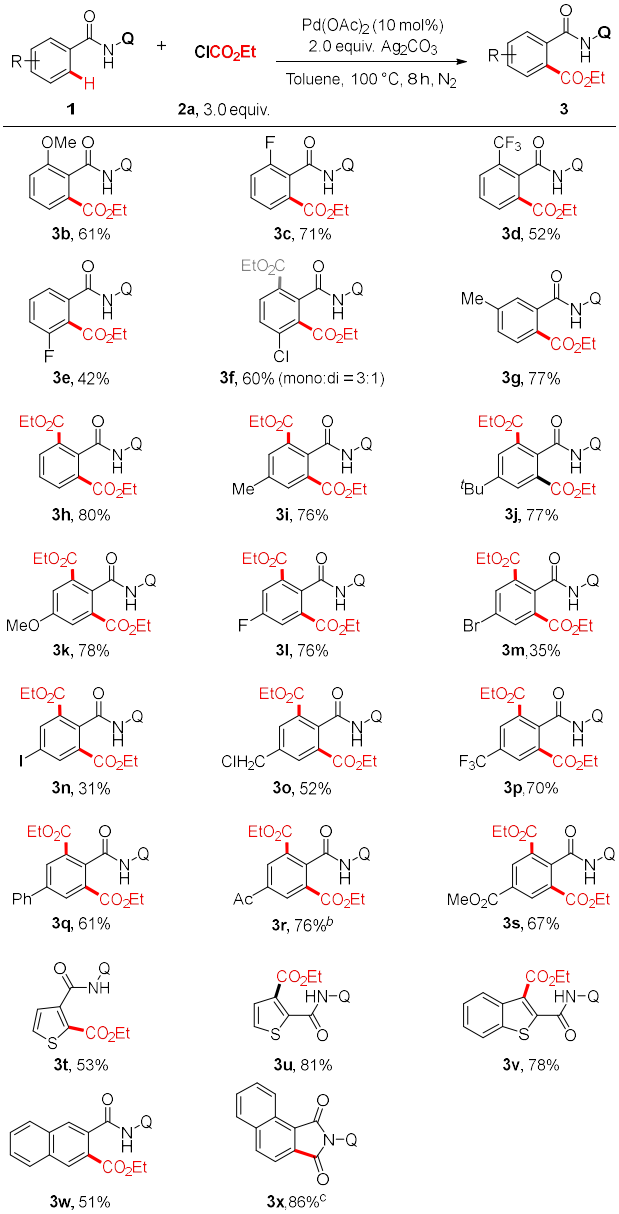
1a 3a

Entry	Solvent	Yield of **3a** (%)	**1a** (%)
1	DCE	72	4
2	CH_3CN	n.d.	72
3	DMF	n.d.	76
4	DMSO	n.d	81
5	HFIP	n.d	64
6	CH_3OH	n.d.	62
7	*t*BuOH	38	37
8	*t*-AmylOH	55	20
9	HOAc	n.d	69
10	1, 4-dioxane	73	26
11	THF	39	21
12	**Toluene**	**83 (81)[b]**	**--**
13[c]	Toluene	42	28
14[d]	Toluene	trace	76%
15[e]	Toluene	76	--

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (3.0 equiv), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.3 mmol) in 2.0 mL solvent at 100 °C under N_2 for 8 h. Yields were determined by ^1H NMR using CH_2Br_2 as the internal standard. [b]Isolated yield. [c]1.0 equiv. Ag_2CO_3 was used. [d]Without Ag_2CO_3. Under air. n.d. = no detected.

With the optimal reaction conditions in hand, the scope of the reaction of benzamides with $ClCO_2Et$ **2a** was explored. As shown in Table 2, benzamides bearing both electron-withdrawing and electron-donating groups on the aromatic ring were well tolerated, giving the desired products **3** in moderate to good yields. *ortho*-Substituted benzamides gave mono-ethoxycarbonylation product smoothly in good yields (**3a-3d**). The site selectivity was controled by both electronic and steric effect, when *meta*-substituted benzamides were used. For example, *meta*-fluoro and chloro benzamides (**1e** and **1f**) gave predominantly led to ethoxycarbonylation adjacent to fluoride or chloride, due to enhanced kinetic acidity of the corresponding C—H bonds; while *meta*-methyl benzamide **1g** exclusively gave **3g** in 77% yield, likely due to the steric interactions. When unsubstituted benzamide **1h** and *para*-substituted benzamides (**1i-1s**) were applied as substrates, the diethoxycarbonylated products were obtained (**3h-3s**). It it worth noting that a broad range of synthetically useful functional groups, such as fluoro, trifluoromethyl, chloro, methoxy, bromo, iodo, acetyl, and methoxycarbonyl, were all tolerated. Furthermore, thiophene-3-carboxamide (**1t**), thiophene-2-carboxamide (**1u**), and benzothiophene-2-carboxamide (**1v**), also reacted efficeintly with **2a** to give the derired ethoxycarbonylation products. 2-Naphthamide **1w** was also viable, albeit with moderate yield (**3w**, 51%). When 1-naphthamide **1x** was used, the desired ethoxycarbonylation product could slowly convert to the corresponding *N*-quinolinylpthalimide **3x** during the column purification. Therefore, a two-step sequence with alkoxycarbonyaltion/acidification was carried out and **3x** was obtained in 86% yield.

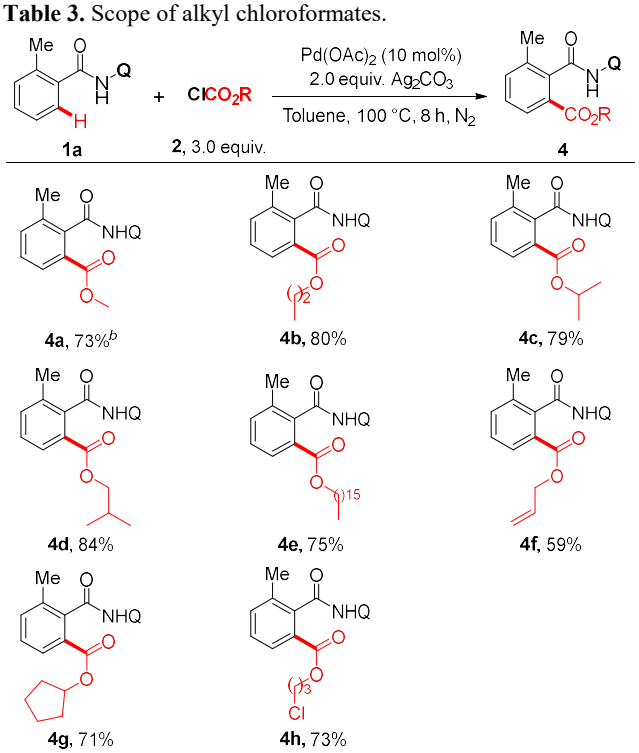
Table 2. Scope of benzamides[a]



[a] Reaction conditions: **1** (0.15 mmol), **2a** (0.45 mmol, 3.0 equiv), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.3 mmol) in 2.0 mL toluene at 100 °C under N_2 for 8 h. isolated yield. [b]120 °C, 12 h. [c]Two-step procedue (see Supporting Information for details).

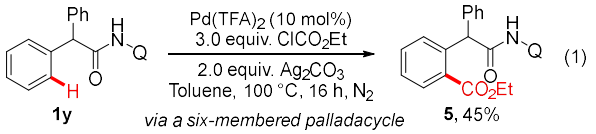
Next, the scope of alkyl chloroformates was investigated (Table 3). Generally, the reaction was compatible with a variety of cloroformates. Methoxycarbonylation of benzamide **1a** proceeded smoothly to give product **4a** in 73% yield under slightly modified conditions. A number of linear alkyl chloroformates reacted with **1a** to give the corresponding products in good yields. Interestingly, the introduction of more sterically hindered branched-alkyl chloroformates were also viable, affording the products in moderate to good yields. Allyl chloroformate could also furnish the product, albeit with a slightly lower yield (**4f**, 59%).

Table 3. Scope of alkyl chloroformates.



[a]Reaction conditions: **1** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2.0 equiv.), $ClCO_2R$ (3.0 equiv.), toluene (2 mL), 100 °C, N_2, 8 h. Isolated yield. [b]120 °C,12 h.

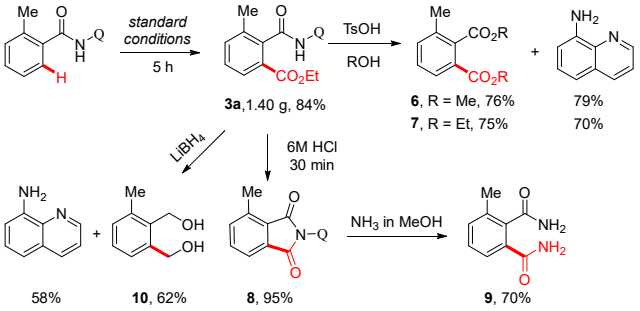
Alkoxycarbonylation of γ-C(sp^2)—H of 2-phenylacetamides is also possible, affording the desired product **5** in 45% yield under slightly modified reaction conditions (eq 1, $Pd(TFA)_2$ as catalyst). However, satifactory conversions could only be afforded with α-substituted 2-phenylacetamides. It is noteworthy that this reaction proceeds via a six-membered palladacycle.



(1)

Finally, a gram-scale synthesis was carried out as shown in Scheme 2, which showcases the robust nature of this alkoxycarbonylation protocol. The ability to easily remove the directing group from the final product is crucial for synthetic applications of this reaction. Treatment of **3a** with TsOH in methanol or ethanol afforded the corresponding PAEs in good yields (MeOH: **6**, 76%; EtOH: **7**, 75%). Notably, the 8-aminoquinoline could be easily recovered by simple extraction. When **3a** was treated with HCl (6M), *N*-quinolinylpthalimide **8** was produced in 95% yield. Subsequent aminolysis gave the phthalamide **9** in 70% yield. 1,2-Dibenzyl alcohol **3ae** was obtained in 62% yield with 8-aminoquinoline recovered in 58% yield when **10** was reduced with $LiBH_4$.

Scheme 2. Gram-scale synthesis and the removal of directing group



In summary, we have developed a new protocol for direct alkoxycarbonylation of β-C(sp^2)—H bonds of benamides and γ-C(sp^2)—H bonds of 2-phenylacetamides. This esterification reaction employs readily available and easily handled alkyl chloroformates as etherification reagent. A variety functional groups are tolerated. The reaction is scalable and the direct group could be readily removed to access substituted phthalic acid esters (PAEs), 1,2-dibenzyl alcohols and phthalamides.

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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 R. C. Larock, Comprehensive Organic Transformations: A Guide to Functional Group Preparations, John Wiley & Sons, New York, **1999**.
2 J. Otera, Esterification: Methods, Reactions, and Applications, Wiley-VCH, Weinheim, **2003**.
3 For selected recent reviews on C–H activation, see: (a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. - Eur. J.* 2010, **16**, 2654; (b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* 2010,

110, 1147; (c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* 2010, **110**, 624; (d) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* 2010, **110**, 890; (e) C. S. Yeung, V. M. Dong, *Chem. Rev.* 2011, **111**, 1215; (f) M. Zhou, R. H. Crabtree, *Chem. Soc. Rev.* 2011, **40**, 1875; (g) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* 2011, **40**, 5068; (h) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* 2012, **51**, 10236; (i) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (j) L. Ackermann, *Acc. Chem. Res*. 2014, **47**, 281; (k) Z. Huang, H. N. Lim, F. Mo, M. C. Young, G. Dong, *Chem. Soc. Rev.* 2015, **44**, 7764; (l) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* 2015**, 48**, 1053; (m) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* 2015, **2**, 1107; (n) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu *Chem. Rev.*, 2017, **117**, 8754.

4 For selected recent reviews on C–H carbonylation, see: (a) Q. Liu, H. Zhang, A. Lei, *Angew. Chem. Int. Ed.* 2011, **50**, 10788; (b) X.-F. Wu, H. Neumann, *ChemCatChem* 2012, **4**, 447; (c) X. F. Wu, H. Neumann, M. Beller, *Chem. Rev.* 2013, **113**, 1; (d) B. Liu, F. Hu, and B.-F. Shi, *ACS Catal.*, 2015, **5** , 1863. (e) J.-B. Peng, F.-P. Wu, X.-F. Wu, *Chem. Rev.* 2018, DOI: 10.1021/acs.chemrev.8b00068.

5 For selected examples on C-H carbonyaltion, see: (a) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, M. Tokuda, *J. Am. Chem. Soc.* 2004, **126**, 14342; (b) B. Haffemayer, M. Gulias, M. J. Gaunt, *Chem. Sci.* 2011, **2**, 312; (c) Z.-H. Guan, M. Chen, Z.-H. Ren, *J. Am. Chem. Soc.* 2012, **134**, 17490; (d) H. Zhang, R. Shi, P. Gan, C. Liu, A. Ding, Q. Wang and A. Lei, *Angew. Chem., Int. Ed.*, 2012, **51**, 5204; (e) S. Luo, F.-X. Luo, X.-S. Zhang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2013, **52**, 10598; (f) R. Shi, L. Lu, H. Zhang, B. Chen, Y. Sha, C. Liu, A. Lei, *Angew. Chem. Int. Ed.* 2013, **52**, 10582; (g) L. Grigorjeva and O. Daugulis, *Org. Lett.*, 2014, **16**, 4688; (h) D. Liang, Y. He, Q. Zhu, *Org. Lett.* 2014, **16**, 2748; (i) X. Li, X. Li, N. Jiao, *J. Am. Chem. Soc.* 2015, **137**, 9246; (j) J. Chen, J.-B. Feng, K. Natte, and X.-F. Wu, *Chem. Eur. J.* 2015, **21**, 16370; (k) T. T. Nguyen, L. Grigorjeva, O. Daugulis, *Chem. Commun.,* 2017, **53**, 5136. (l) S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* 2009, **131**, 6898; ((m) E. J. Yoo, M. Masa, J.-Q. Yu, *J. Am. Chem. Soc.* 2010, **132**, 17378; (n) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* 2014, **510**, 129; (o) S. Li, G. Chen, C.-G. Feng, W. Gong, J.-Q. Yu, *J. Am. Chem. Soc.* 2014, **136**, 5267; (p) P.-L. Wang, Y. Li, Y. Wu, C. Li, Q. Lan, X.-S. Wang, *Org. Lett.* 2015, **17**, 3698; (q) C. Wang, L. Zhang, C. Chen, J. Han, Y. Yao and Y. Zhao, *Chem. Sci.* 2015, **6**, 4610; (r) J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer, M. J. Gaunt, *Nat. Chem.* 2015, **7**, 1009; (s) K. F. Hogg, A. Trowbridge, A. Alvarez-Perez ´and M. J. Gaunt, *Chem. Sci.*, 2017, **8**, 8198; (t) N. Barsu, S. K. Bolli and B. Sundararaju, *Chem. Sci.*, 2017, **8**, 2431; (u) L. Zeng, S. Tang, D. Wang, Y. Deng, J.-L. Chen, J.-F. Lee, and A. Lei, *Org. Lett.* 2017, **19**, 2170.

6 (a) R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* 2008, **130**, 14082; (b) R. Giri, J. K. Lam, J.-Q. Yu, *J. Am. Chem. Soc.* 2010, **132**, 686.

7 (a) H. Zhang, D. Liu, C. Chen, C. Liu, A. Lei, *Chem. Eur. J.* 2011, **17**, 9581; (b) H. Chen, C. Cai, X. Liu, X. Li, H. Jiang, *Chem. Commun.* 2011, **47**, 12224; (c) R. Lang, J. Wu, L. Shi, C. Xia, F. Li, *Chem. Commun.* 2011, **47**, 12553; (d) R. Lang, L. Shi, D. Li, C. Xia, F. Li, *Org. Lett.* 2012, **14**, 4130; (e) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia, H. Huang, *J. Am. Chem. Soc.* 2012, **134**, 9902.

8 (a) Z.-H. Guan, Z.-H. Ren, S. M. Spinella, S. Yu, Y.-M. Liang, X. Zhang, *J. Am. Chem. Soc.* 2009, **131**, 729; (b) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem., Int. Ed.* 2009, **48**, 1830; (c) H. Li, G.-X. Cai and Z.-J. Shi, *Dalton Trans.,* 2010, **39**, 10442; (d) Y. Lu, D. Leow, X. Wang, K. M. Engle and J.-Q. Yu, *Chem. Sci.*, 2011, **2**, 967; (e) B. Liu, H.-Z. Jiang, B.-F. Shi, *Org. Biomol. Chem.* 2014, **12**, 2538; (f) M. Chen, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *J. Org. Chem.* 2015, **80**, 1258; (g) Y. Wang and V. Gevorgyan, *Angew. Chem. Int. Ed.* 2017, **56**, 3191;

9 CO_2: (a) H. Mizuno, J. Takaya and N. Iwasawa, *J. Am. Chem. Soc.* 2011, **133**, 1251; (b) K. Sasano, J. Takaya and N. Iwasawa, *J. Am. Chem. Soc.* 2013, **135**, 10954.

10 W.-Y. Yu, W. N. Sit, K.-M. Lai, Z. Zhou, A. S. C. Chan, *J. Am. Chem. Soc.* 2008, **130**, 3304.

11 Y. Huang, G. Li, J. Huang, J. You, *Org. Chem. Front.* 2014, **1**, 347.

12 N. Xu, D. Li, Y. Zhang and L. Wang, *Org. Biomol. Chem.,* 2015, **13**, 9083.

13 S. Wang, Z. Yang, J. Liu, K. Xie, A. Wang, X. Chen and Z. Tan, *Chem. Commun.*, 2012, **48**, 9924.

14 W. Zhou, P. Li, Y. Zhang and L. Wang, *Adv. Synth. Catal.*, 2013, **355**, 2343.

15 X. Hong, H. Wang, B. Liu and B. Xu, *Chem. Commun.,* 2014, **50**, 14129

16 Z.-Y. Li and G.-W. Wang, *Org. Lett.*, 2015, **17**, 4866

17 X. Peng, Y. Zhu, T. A. Ramirez, B. Zhao and Y. Shi, *Org. Lett.,* 2011, **13**, 5244.

18 J. Wu, J. Lan, S. Guo, J. You, *Org. Lett.* 2014, **16**, 5862.

19 T. Kochi, S. Urano, H. Seki, E. Mizushima, M. Sato and F. Kakiuchi, *J. Am. Chem. Soc.,* 2009, **131**, 2792.

20 G. Liao, X.-S. Yin, K. Chen, Q. Zhang, S.-Q. Zhang, B.-F. Shi, *Nat. Comm.* 2016, **7**, 12901.

21 V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.* 2005, **127**, 13154.

22 (a) F.-J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.*, 2013, **4**, 4187; (b) C. Reddy, N. Bisht, R. Parella and S. A. Babu, *J. Org. Chem.*, 2016, **81**, 12143; (c) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.* 2011, **133**, 14952; (d) D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.* 2010, **132**, 3965.

23 CCDC 1497110 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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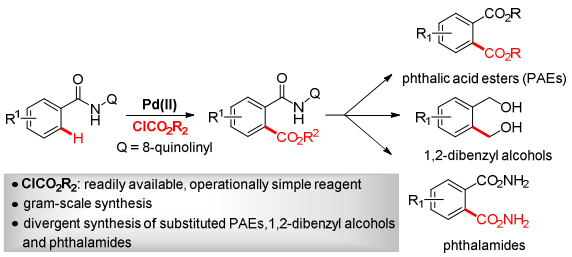

A Pd(II)-catalyzed alkoxycarbonylation of benzamide β-C-H bonds and 2-phenylacetamide γ-C-H bonds with alkyl chloroformates has been reported.·