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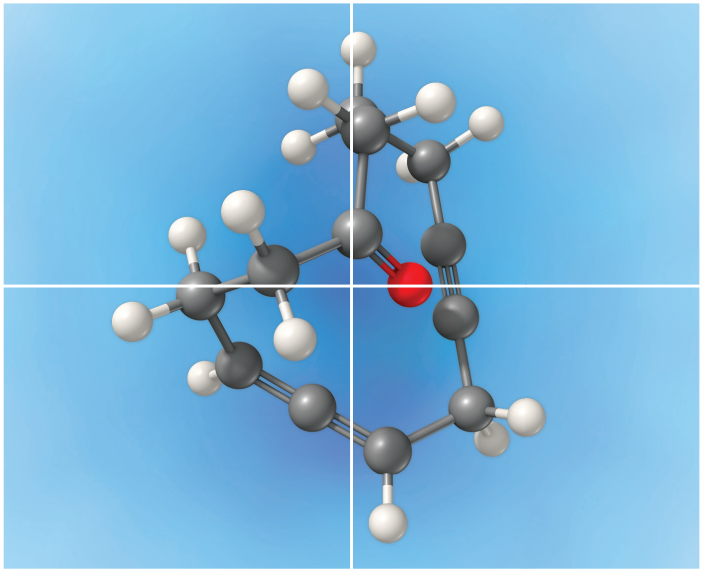

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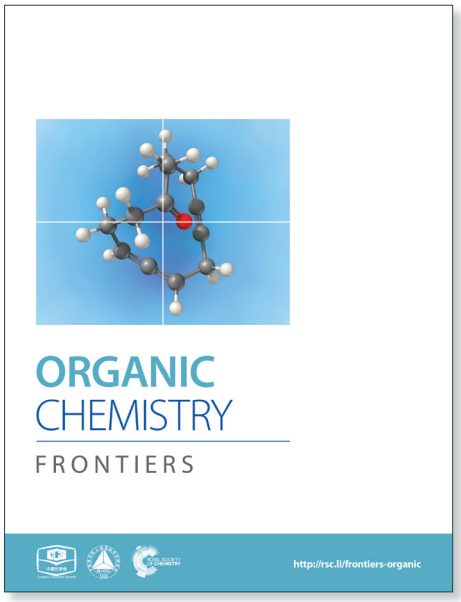

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ARTICLE

Efficient and Scalable Pd-Catalyzed Double Aminocarbonylations under Atmospheric Pressure at Low Catalyst Loadings†‡

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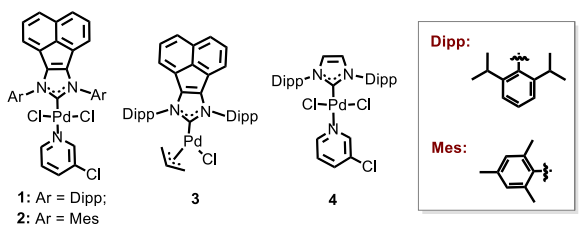
By using a robust acenaphthoimidazolyidene palladium complex (Pd-NHC 1), a scalable approach to access a variety of chiral, pharmaceutical and structure intriguing *N*-substituted phthalimides via double aminocarbonylations has been established under atmospheric carbon monoxide pressure at the catalyst loading as low as 0.05 mol %. In addition, the fluorescent properties of the selected *N*-substituted phthalimide products were also characterized. In comparison with the well-known fluorescent molecules, some of them exhibited enhanced violet emission, especially for the ester analogue of Alrestatin, which further confirmed the applicability of the protocol.

Introduction

As one of useful motifs, imides widely existed in various bioactive, fluorescent and pharmaceutical molecules.[1] Besides pyromellitic diimides applied as high-performance polymeric materials for aerospacecrafts,[2] phthalimides and their derivatives also exhibited extensive applicability in drugs, pesticides and dyes.[3-5] Therefore, various efforts have been devoted to the syntheses of cyclic imides.[6] In contrast with conventional methodologies including condensation of a phthalic acid anhydride and a primary amine, which show rather limited substrate applicability even at high temperature, transition-metal catalyzed aminocarbonylations of haloarenes with inexpensive carbon monoxide (CO gas) represent an atom-economic, efficient and straightforward protocol.[7] Inspired by the seminal work by Heck in 1974, Ban and co-workers realized a nice example of Pd-catalyzed mono-aminocarbonylations.[8] A decennium later, Perry and co-workers extended it to the double aminocarbonylations under very high CO pressure.[9] After developing for decades, there are still various limitations in this less-studied topic. In general, a high amount of catalysts comprising of air sensitive phosphine ligands is usually required to achieve satisfactory outcomes.[10] Besides high CO pressure (up to 39 atm), the steric demanding and heterocyclic substrates are still not well tolerant by the known protocols.[10]

As one kind of robust ligands, *N*-heterocyclic carbenes (NHCs) have been successfully applied in numerous Pd-catalyzed cross-coupling reactions.[11] Furthermore, unlike phosphine ligands, NHCs behave as strong σ-donors almost without metal-to-ligand π-back-bonding ability, which can significantly increase the electron density on the metal center and constitute optional ligands for the carbonylation reactions.[12] However, to the best of our knowledge, there is still no example on the synthesis of *N*-substituted phthalimides by using Pd-NHC catalysts. Moreover, in comparison with imidazole analogues, we found that the less-explored ylidenes derived from acenaphthoimidazolium salts exhibited stronger σ-donor and weaker π-acceptor properties, and the corresponding Pd-NHCs (**1**-**3**, Scheme 1) revealed extremely high catalytic activity and broad substrates scope in several Pd-catalyzed cross-coupling reactions as well as aminocarbonylative reactions at extremely low catalyst loadings.[13] Encouraged by these promising results and our recent achievements in exploring a series of metal-complexes in the soft materials and catalysis,[13-15] herein, we would like to extend the feasibility of these bulky Pd-NHCs (**1**-**3**) to fabricate a variety of structural intriguing functional *N*-substituted phthalimides under mild reaction conditions, especially, at low catalyst loadings.



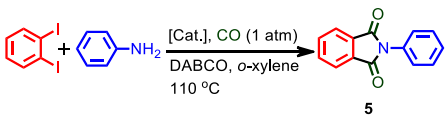
1: Ar = Dipp; **2**: Ar = Mes **3** **4**

Scheme 1. Represented Pd-NHCs complexes.

Results and Discussion

Initially, *o*-diiodobenzene and aniline were selected to explore the catalytic activity of Pd-NHCs **1**-**4** in the double aminocarbonylative reactions under atmospheric CO pressure. After detailed optimization of the reaction conditions (see ESI‡), a quantitative yield of *N*-phenylphthalimide **5** was obtained when the reaction was carried out with 1 mol % Pd-NHC **1** and 1.5 equiv. 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base in *o*-xylene at 110 °C for 30 hours (entry 1, Table 1). To our delight, a full conversion was still observed within 24 hours when the catalyst loading was reduced to 0.5 mol % (entries 2-3, Table 1). When other Pd-NHCs (**2**-**4**) were involved, all resulted in good to excellent outcomes (91->99%, entries 4-6, Table 1). Under the optimal reaction conditions, $Pd(OAc)_2$ and PPh_3, however, only gave out a 47% isolated yield (entry 7, Table 1), which indicated ligands with strong π-acceptor properties were unfavourable for the transformation. When the catalyst loading of Pd-NHC **1** was reduced to 0.05 mol %, a moderate yield was still observed within 30 hours, which can be further increased to a quantitative yield by extending the reaction time to 48 hours (entry 8, Table 1). Further decreasing the catalyst loading to 0.01 mol %, a 50% yield was still observed (TON: 5000, entry 10, Table 1), which was obviously superior to the result of Pd-NHC **4** (entry 9, Table 1) and further confirmed that ylidenes derived from the π-extended imidazolium salts are better ligand than that from their imidazolium analogue.[14] In addition, no desired product was found in the blank test (entry 11, Table 1).

Table 1. Reaction conditions optimization.[a]

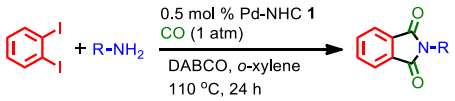


Entry	[Cat.]	mol %	Time (h.)	Yield (%)[b]
1	**1**	1	30	>99
2	**1**	0.5	30	>99
3	**1**	0.5	24	>99
4	**2**	0.5	24	91
5	**3**	0.5	24	>99
6	**4**	0.5	24	96
7	$Pd(OAc)_2/PPh_3$	0.5	24	47
8	**1**	0.05	30/48	71/>99
9	**4**	0.05	48	6
10	**1**	0.01	48	50
11	/	/	24	N.D.

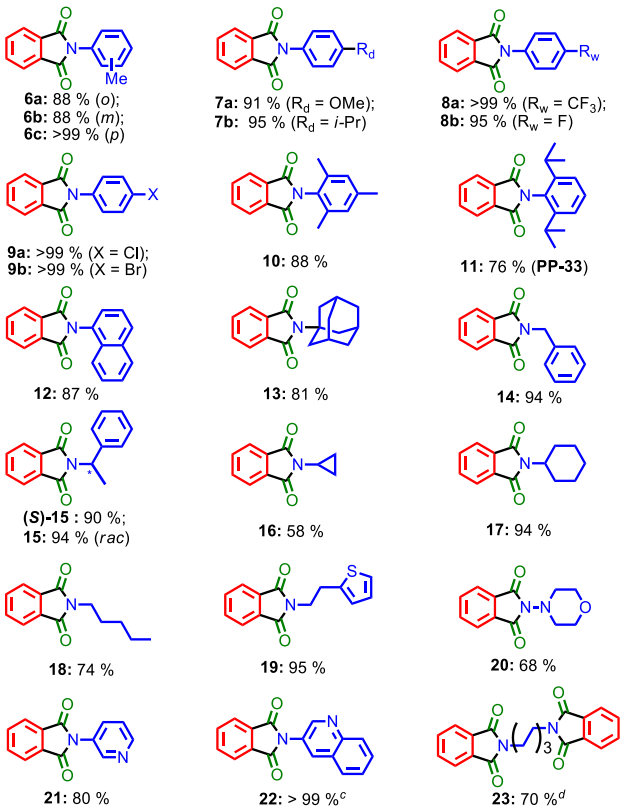
[a] 0.5 mmol scale. [b] Isolated yield.

With the optimal reaction conditions in hand, 0.5 mol % catalyst and 24 hours were selected to further evaluate the substrate scope. As shown in Table 2, our protocol well tolerated various primary amines with diverse electronic and steric properties. The relative position of substituents on anilines slightly influenced the process: *p*-toluidine resulted in a higher yield than its *o*-and *m*- analogues (**6c** *vs.* **6a** and **6b**). Anilines with electron-donating groups were well tolerated (**7a**-**b**, up to 95%). As an efficient anticonvulsant drug without neurotoxicity and mortality,[16] to our delight, compound **7a** was readily prepared in gram scale at such low catalyst loading (1.14 g, 90%). Anilines containing electron-withdrawing groups (-CF_3 and -F) also resulted in up to quantitative yields (**8a**-**b**). The halogen atoms such as Cl and Br were well accommodated (**9a**-**b**), which provided possibility for further functionalization. Although the previous reports were all inefficient for steric demanding anilines,[10] satisfactory isolated yields (**10**-**13**, 76-88%) were achieved by our protocol in all selected cases, which further confirmed our protocol efficiency. Among them, compound **11** (PP-33), approved as a *α*-tumor necrosis factor (TNF) inhibitor, was also synthesized in a good yield.[17] In consideration of the satisfactory results obtained so far, we turned our attention on primary alkylamines. Besides benzyl amine, chiral amine also resulted in an excellent yield without affecting the chiral center (**15**, 90%). Other aliphatic amines were also suitable substrates, up to 95% yields were obtained with linear, cyclic, and heterocyclic substituted amines (**16**-**19**), and slightly inferior outcomes were observed with low-boiling aliphatic amines

Table 2. Pd-Catalyzed double aminocarbonylation of *o*-diiodobenzene with various primary amines.[a]



6-23 [b]



6a: 88 % (*o*); **6b:** 88 % (*m*); **6c:** >99 % (*p*)

7a: 91 % (R_d = OMe); **7b:** 95 % (R_d = *i*-Pr)

8a: >99 % (R_w = CF_3); **8b:** 95 % (R_w = F)

9a: >99 % (X = Cl); **9b:** >99 % (X = Br)

10: 88 %

11: 76 % (**PP-33**)

12: 87 %

13: 81 %

14: 94 %

(*S*)-15 : 90 %; **15:** 94 % (*rac*)

16: 58 %

17: 94 %

18: 74 %

19: 95 %

20: 68 %

21: 80 %

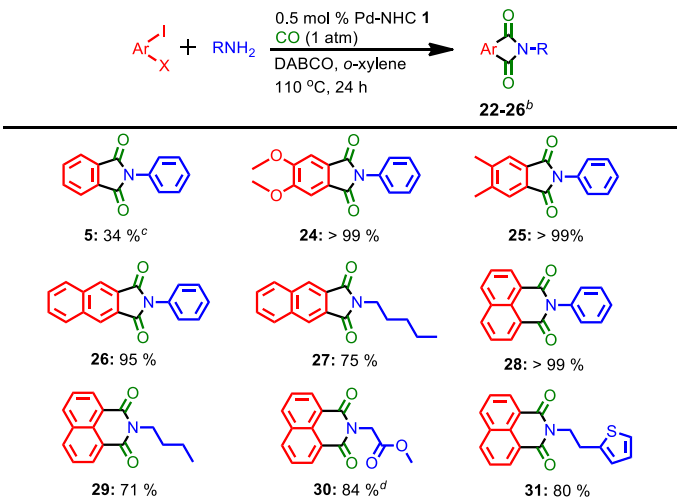
22: > 99 %[c]

23: 70 %[d]

[a] 0.5 mmol scale for 24 h. [b] Isolated yield. [c] With 0.05 mol % Pd-NHC **1**. [d] With 0.5 mmol 1,6-diaminohexane, 1.25 mmol diiodobenzene, 3.0 mmol DABCO and 1 mol % Pd-NHC **1**.

(**16** and **18**), When morpholin-4-amine was involved, a moderate yield was obtained (**20**, 68%). *N*-heterocyclic anilines were usually regarded as worse partners in the transition-metal catalyzed coupling reactions due to their strong coordination ability,[10c] however, our protocol well tolerated pyridin-3-amine and bulky quinolin-3-amine (**21**-**22**), and even up to quantitative yields were observed at 0.5 mol % catalyst loading. In addition, our approach was also suitable for alkyl diamine and produced di-*N*-phenylphthalimide **23** in a good yield (70 %).

Table 3. Pd-Catalyzed double aminocarbonlation of *o*-dihaloarenes.[a]



[a] 0.5 mmol scale for 24 h. [b] Isolated yield. [c] In case of *o*-bromoiodobenzene. [d] Glycine methyl ester hydrochloride was used as amine source.

Subsequently, our attention was focused on the feasibility of other *o*-dihaloarenes. As expected, in the presence of 0.5 mol % Pd-NHC **1**, the aminocarbonylation of selected *o*-diiodoarenes with aniline and aliphatic amines all produced corresponding products in good to quantitative yields under the optimized conditions (**24**-**31**, Table 3), whereas, a lower yield encountered with *o*-bromoiodobenzene (**5**, Table 3). When bulkier 1,8-diiodonaphthalene was applied, diverse 1,8-naphthalimides were easily accessible in good to quantitative yields (**28**-**31**). It had to be noted that compound **30** was readily completely hydrolyzed in aqueous sodium hydroxide to give a well-known aldose reductase inhibitor (Alrestatin, **32**, see ESI‡) in a quantitative yield.[18] Moreover, in consideration of strong florescent compound **29** having potential application in molecular sensor,[19] several analogues produced by our protocol (**27**, **28**, **30**, and **31**) were selected to study their fluorescent properties (Figure 1). In comparison with compound **29**, slightly red shift was observed with all tested samples (1×10^{-5} mol•L^{-1}, in CH_2Cl_2). Compounds **27** and **30** exhibited significant enhanced violet emission. However, the intensity of compounds **28** and **31** at the same concentration were slightly low, which may be caused by (hetero)-aryl substituent groups partially quenching the emission. These results not only indicated our protocol was practical to access various fluorescent molecules, but also highlighted the other potential functionality of Alrestatin.

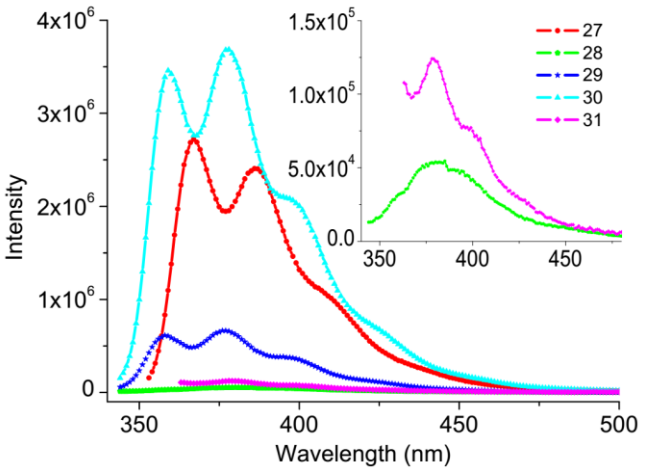
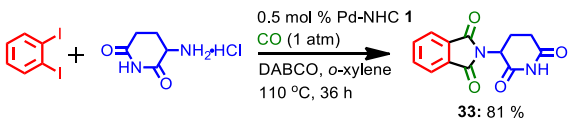


Fig. 1 The fluorescence spectra of compounds **27**-**31** (measured in CH_2Cl_2 at 1×10^{-5} mol•L^{-1} at room temperature, excitation wavelength at 334 nm for compounds **27**-**30** and 346 nm for compound **31**).

In light of the high efficiency of our protocol to access a variety of pharmaceutical and fluorescence molecules, which is hard to access by the conventional protocol, we paid our attention to the synthesis of well-known thalidomide. Currently, thalidomide have been exhibited therapeutic value in the treatment of myeloma and leprosy.[20] By using 3-amino-piperidine-2,6-dione hydrochloride to instead of sensitive amine, in the presence of 0.5 mol % Pd-NHC **1**, double aminocarbonylation of *o*-diiodobenzene also successfully produced the desired thalidomide in a good isolated yield (81%, Scheme 2), which further confirmed the broad and practical feasibility of the new developed methodology.



Scheme 2. Synthesis of thalidomide.

Conclusion

In summary, by using a robust acenaphthoimidazolyidene palladium complex (Pd-NHC **1**), we have successfully developed a mild, practical and scalable protocol to access a variety of functional and structural intriguing *N*-substituted phthalimides via palladium-catalyzed double amino-carbonylation of *o*-dihaloarenes with diverse primary amines under atmospheric carbon monoxide pressure at the catalyst loading as low as 0.05 mol %. In comparison with previous reports with phosphine ligands, diverse electron-rich, electron-poor and heterocyclic substrates are easily converted to

corresponding products even for di-phthalimides in good to excellent yields under the mild reaction conditions at such low catalyst loading. Meanwhile, the steric hindered (heterocyclic) amines are also applicable under the optimized reaction conditions, which constitute a challenging task for the aminocarbonylative reactions and also hard accessible by using the conventional approaches. Notably, several important chiral, pharmaceutical and fluorescent molecules such as thalidomide and Alrestatin are also accessible by our new developed approach even in gram scale. Additionally, the fluorescent properties of the selected *N*-substituted phthalimide products were also characterized; among them the enhanced fluorescence of compound **30** also demonstrated the other application of Alrestatin besides pharmaceutical utilization.

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Notes and references

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† Dedicated to Prof. Li-Xin Dai on the occasion of his 90th birthday.
‡Electronic Supplementary Information (ESI) available: Experiment detail and mechanism study. See DOI: 10.1039/c000000x/

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