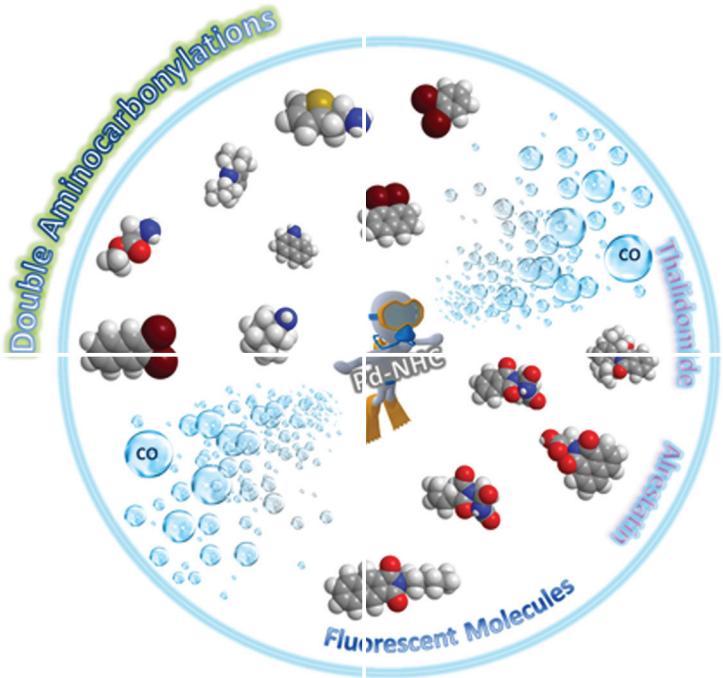
Volume 1 | Number 11 | 14 December 2014



ORGANIC CHEMISTRY

FRONTIERS

Chinese Chemical Society
SIOC 1950
ROYAL SOCIETY OF CHEMISTRY
http://rsc.li/frontiers-organic

ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2014, **1**, 1261

Efficient and scalable Pd-catalyzed double aminocarbonylations under atmospheric pressure at low catalyst loadings†‡

Shuangliang Liu,[a,b] Qinyue Deng,[a] Weiwei Fang,[a] Jun-Fang Gong,*[b] Mao-Ping Song,*[b] Mizhi Xu[a] and Tao Tu*[a]

Received 23rd September 2014,
Accepted 21st October 2014

DOI: 10.1039/c4qo00253a

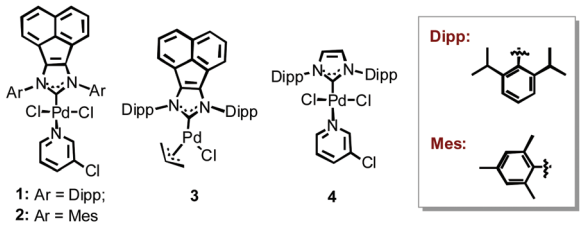
rsc.li/frontiers-organic

By using a robust acenaphthoimidazolylidene palladium complex (Pd-NHC **1**), a scalable approach to access a variety of chiral, pharmaceutical and structurally intriguing *N*-substituted phthalimides *via* double aminocarbonylations has been established under atmospheric carbon monoxide pressure at catalyst loadings as low as 0.05 mol%. In addition, the fluorescent properties of the selected *N*-substituted phthalimide products were also characterized. In comparison with 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 the useful motifs, imides widely exist 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 exhibit 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 of Heck in 1974, Ban and co-workers realized a nice example of Pd-catalyzed mono-aminocarbonylations.[8] A decade 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 catalyst containing air sensitive phosphine ligands is usually required to achieve satisfactory outcomes.[10] Besides high CO pressure (up to 39 atm), sterically demanding and heterocyclic substrates are still not well tolerated in the known protocols.[10]

As 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 of 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 substrate 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



Scheme 1 Representative Pd-NHCs complexes.

[a]*Department of Chemistry, Fudan University, 220 Handan Road, 200433 Shanghai, China. E-mail: taotu@fudan.edu.cn; Fax: (+) 86-21-65102412*
[b]*College of Chemistry and Molecular Engineering, Zhengzhou University, 100 Science Avenue, 450001 Zhengzhou, China. E-mail: mpsong@zzu.edu.cn*
† Dedicated to Prof. Li-Xin Dai on the occasion of his 90th birthday.
‡ Electronic supplementary information (ESI) available: Experimental details and mechanism study. See DOI: 10.1039/c4qo00253a

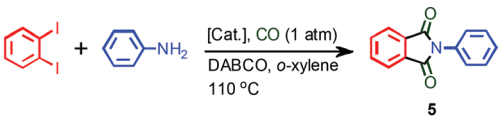
would like to extend the feasibility of these bulky Pd-NHCs (**1–3**) to fabricate a variety of structurally intriguing functional *N*-substituted phthalimides under mild reaction conditions, especially, at low catalyst loadings.

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 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 ligands than that from their imidazolium analogues.[14] In addition, no desired product was found in the blank test (entry 11, Table 1).

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 sterically 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 an α-tumor necrosis factor (TNF) inhibitor, was also synthesized in a good yield.[17]

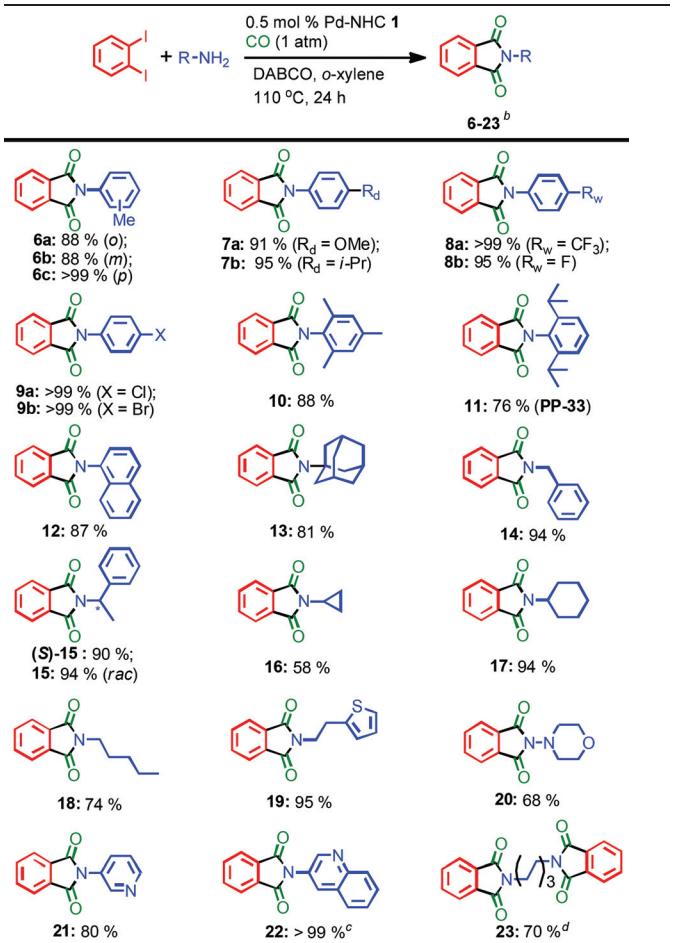
Table 1 Reaction conditions optimization[a]



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.

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



[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**.

In consideration of the satisfactory results obtained so far, we turned our attention to primary alkylamines. Besides benzyl amine, a 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 (**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 an alkyl diamine and produced di-*N*-phenylphthalimide **23** in a good yield (70%).

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 was 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 has 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 strongly fluorescent compound **29** having potential applications in molecular sensors,[19] several analogues produced by our protocol (**27**, **28**, **30**, and **31**) were selected to study their fluorescent properties (Fig. 1). In comparison with compound **29**, a slight 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 another potential functionality of Alrestatin.

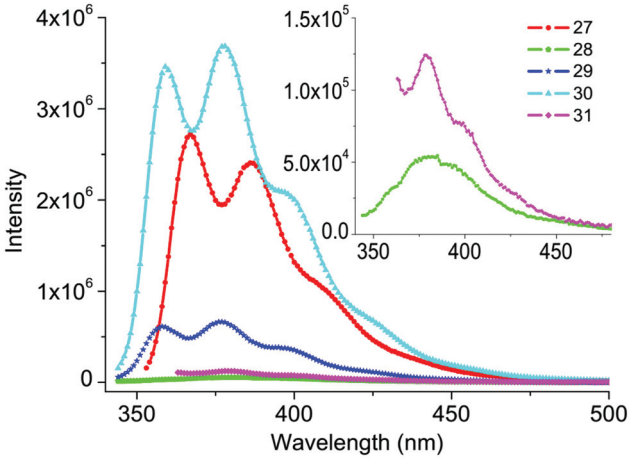
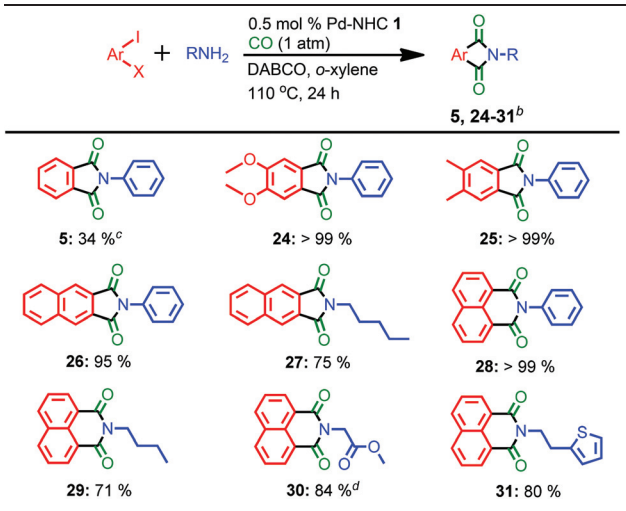


Fig. 1 The fluorescence spectra of compounds **27–31** (measured in CH_2Cl_2 at 1×10^{-5} mol L^{-1} at room temperature, excitation wavelength at 334 nm for compounds **27–30** and 346 nm for compound **31**).

Scheme 2 Synthesis of thalidomide.

Table 3 Pd-Catalyzed double aminocarbonylation 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.

In light of the high efficiency of our protocol to access a variety of pharmaceutical and fluorescent molecules, which are hard to access by the conventional protocol, we paid attention to the synthesis of well-known thalidomide. Currently, thalidomide has exhibited therapeutic value in the treatment of myeloma and leprosy.[20] By using 3-amino-piperidine-2,6-dione hydrochloride instead of the 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.

Conclusion

In summary, by using a robust acenaphthoimidazolylidene palladium complex (Pd-NHC **1**), we have successfully developed a mild, practical and scalable protocol to access a variety of functional and structurally intriguing *N*-substituted phthalimides

via palladium-catalyzed double aminocarbonylation of *o*-dihaloarenes with diverse primary amines under atmospheric carbon monoxide pressure at catalyst loadings 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 loadings. Meanwhile, sterically hindered (heterocyclic) amines are also applicable under the optimized reaction conditions, which constitute a challenging task for aminocarbonylative reactions and also are hard to access by using the conventional approaches. Notably, several important chiral, pharmaceutical and fluorescent molecules such as thalidomide and Alrestatin are also accessible by our newly 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** which also demonstrated another application of Alrestatin besides pharmaceutical utilization.

Acknowledgements

Financial support from the National Natural Science Foundation of China (no. 21172045 and 91127041), the Changjiang Scholars and Innovative Research Team in University (IRT1117), the doctoral fund of Ministry of Education of China (20130071110032), Shanghai Shuguang and Pujiang Programs and Department of Chemistry, Fudan University is gratefully acknowledged.

Notes and references

1 (*a*) R. Antunes, H. Batista, R. M. Srivastava, G. Thomas and C. C. Araujo, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3071; (*b*) L. M. Lima, P. Castro, A. L. Machado, C. A. M. Fraga, C. Lugnier, V. L. G. de Moraes and E. J. Barreiro, *Bioorg. Med. Chem.*, 2002, **10**, 3067; (*c*) U. Sharma, P. Kumar, N. Kumar and B. Singh, *Mini-Rev. Med. Chem.*, 2010, **10**, 678; (*d*) M. A. Bhat and M. A. Al-Omar, *Acta Pol. Pharm. Drug Res.*, 2011, **68**, 375.

2 (*a*) K. H. Chae and Y. H. Kim, *Adv. Funct. Mater.*, 2007, **17**, 3470; (*b*) G. Chen, X. Zhang, S. Zhang, T. Chen and Y. Wu, *J. Appl. Polym. Sci.*, 2007, **106**, 2808.

3 (*a*) E. de Almeida Neto, *Hansenol. Int.*, 1981, **6**, 114; (*b*) M. Walchner, M. Meurer, G. Plewig and G. Messer, *Int. J. Dermatol.*, 2000, **39**, 383.

4 W. D. Figg, S. Raje, K. S. Bauer, A. Tompkins, D. Venzon, R. Bergan, A. Chen, M. Hamilton, J. Pluda and E. Reed, *J. Pharm. Sci.*, 1999, **88**, 121.

5 (*a*) N. S. Pawar, U. R. Kapadi, D. G. Hundiwale and P. P. Kumbhar, *J. Sci. Ind. Res.*, 2002, **61**, 454; (*b*) S. P. Gromov, M. V. Fomina, A. S. Nikiforov, A. I. Vedernikov, L. G. Kuz'mina and J. A. K. Howard, *Tetrahedron*, 2013, **69**, 5898.

6 (*a*) J. C. Sheehan and V. S. Frank, *J. Am. Chem. Soc.*, 1949, **71**, 1856; (*b*) J. C. Sheehan, D. W. Chapman and R. W. Roth, *J. Am. Chem. Soc.*, 1952, **74**, 3822; (*c*) T. Han and C.-F. Chen, *J. Org. Chem.*, 2007, **72**, 7287; (*d*) M. Sani, G. Fossati, F. Huguenot and M. Zanda, *Angew. Chem., Int. Ed.*, 2007, **46**, 3526; (*e*) J. Zhang, M. Senthilkumar, S. C. Ghosh and S. H. Hong, *Angew. Chem., Int. Ed.*, 2010, **49**, 6391.

7 (*a*) R. Skoda-Foldes and L. Kollar, *Curr. Org. Chem.*, 2002, **6**, 1097; (*b*) A. Brennführer, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114; (*c*) W. Fang, H. Zhu, Q. Deng, S. Liu, X. Liu, Y. Shen and T. Tu, *Synthesis*, 2014, **46**, 1689; (*d*) S. T. Gadge and B. M. Bhanage, *RSC Adv.*, 2014, **4**, 10367 and references therein.

8 (*a*) A. Schoennberg and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3327; (*b*) M. Mori, K. Chiba, N. Ohta and Y. Ban, *Heterocycles*, 1979, **13**, 329.

9 R. J. Perry and S. R. Turner, *J. Org. Chem.*, 1991, **56**, 6573.

10 (*a*) A. Takács, P. Ács and L. Kollár, *Tetrahedron*, 2008, **64**, 983; (*b*) S. Inoue, H. Shiota, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2009, **131**, 6898; (*c*) H. Cao and H. Alper, *Org. Lett.*, 2010, **12**, 4126; (*d*) M. V. Khedkar, S. R. Khan, D. N. Sawant, D. B. Bagal and B. M. Bhanage, *Adv. Synth. Catal.*, 2011, **353**, 3415; (*e*) D. Marosvölgyi-Haskó, A. Petz, A. Takács and L. Kollár, *Tetrahedron*, 2011, **67**, 9122; (*f*) X.-F. Wu, S. Oschatz, M. Sharif, A. Flader, L. Krey, M. Beller and P. Langer, *Adv. Synth. Catal.*, 2013, **355**, 3581; (*g*) J. Chen, K. Natte, A. Spannenberg, H. Neumann, M. Beller and X.-F. Wu, *Org. Biomol. Chem.*, 2014, **12**, 5578.

11 N. Marion and S. P. Nolan, *Acc. Chem. Res.*, 2008, **41**, 1440.

12 (*a*) S. Würtz and F. Glorius, *Acc. Chem. Res.*, 2008, **41**, 1523; (*b*) S. Díez-González, N. Marion and S. P. Nolan, *Chem. Rev.*, 2009, **109**, 3612.

13 W. Fang, Q. Deng, M. Xu and T. Tu, *Org. Lett.*, 2013, **15**, 3678.

14 (*a*) T. Tu, W. Assenmacher, H. Peterlik, R. Weisbarth, M. Nieger and K. H. Dötz, *Angew. Chem., Int. Ed.*, 2007, **46**, 6368; (*b*) T. Tu, W. Assenmacher, H. Peterlik, G. Schnakenburg and K. H. Dötz, *Angew. Chem., Int. Ed.*, 2008, **47**, 7127; (*c*) T. Tu, X. Bao, W. Assenmacher, H. Peterlik, J. Daniels and K. H. Dötz, *Chem. – Eur. J.*, 2009, **15**, 1853; (*d*) T. Tu, W. Fang, X. Bao, X. Li and K. H. Dötz, *Angew. Chem., Int. Ed.*, 2011, **50**, 6601; (*e*) W. Fang, Z. Sun and T. Tu, *J. Phys. Chem. C*, 2013, **117**, 25185; (*f*) W. Fang, X. Liu, Z. Lu and T. Tu, *Chem. Commun.*, 2014, **50**, 3313.

15 (*a*) T. Tu, H. Mao, C. Herbert, M. Xu and K. H. Dötz, *Chem. Commun.*, 2010, **46**, 7796; (*b*) T. Tu, X. Feng, Z. Wang and X. Liu, *Dalton Trans.*, 2010, **39**, 10598; (*c*) Z. Wang, X. Feng, W. Fang and T. Tu, *Synlett*, 2011, 951; (*d*) T. Tu, W. Fang and J. Jiang, *Chem. Commun.*, 2011, **47**, 12358; (*e*) T. Tu, Z. Sun, W. Fang, M. Xu and Y. Zhou, *Org. Lett.*, 2012, **14**, 4250; (*f*) W. Fang, J. Jiang, Y. Xu, J. Zhou and T. Tu, *Tetrahedron*, 2013, **69**, 673; (*g*) Z. Liu, N. Dong, M. Xu, Z. Sun

and T. Tu, *J. Org. Chem.*, 2013, **78**, 7436; (*h*) M. Xu, X. Li, Z. Sun and T. Tu, *Chem. Commun.*, 2013, **49**, 11539.
16 A. A.-M. AbdeI-Hafez, *Arch. Pharmacal Res.*, 2004, **27**, 495.
17 H. Miyachi, A. Azuma, E. Hioki, S. Iwasaki, Y. Kobayashi and Y. Hashimoto, *Biochem. Biophys. Res. Commun.*, 1996, **224**, 426.
18 A. DaSettimo, G. Primofiore, F. Da Settimo, F. Simorini, C. La Motta, A. Martinelli and E. Boldrini, *Eur. J. Med. Chem.*, 1996, **31**, 49.
19 S. Erten-Ela, S. Ozcelik and E. Eren, *J. Fluoresc.*, 2011, **21**, 1565.
20 S. M. Capitosti, T. P. Hansen and M. L. Brown, *Org. Lett.*, 2003, **5**, 2865.