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Nickel-catalyzed Reductive Amidation of Aryl-triazine Ethers

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The reaction of activated phenolic compounds, 2,4,6-triaryloxy-1,3,5-triazine (aryl-triazine ethers) with various isocyanates or carbodiimides in the presence of a nickel pre-catalyst resulted in the synthesis of aryl amides in good to excellent yields.

Since an amidic bond as an ubiquitous functionality is extensively found in great number of pharmaceuticals, natural products, biologically active compounds and advanced materials, it has attracted much interest of synthetic organic chemists, worldwide.[1] To express the invaluably of this bond, it is enough to point out the chemical structure of peptides and proteins, as well as number of privileged and prescribed drugs containing amidic bond.[2] Benzamide subunits are among the most important building block in the structure of many biological important compounds. The chemical structures of some biologically important compounds containing benzamide group are illustrated in Figure 1.[3]

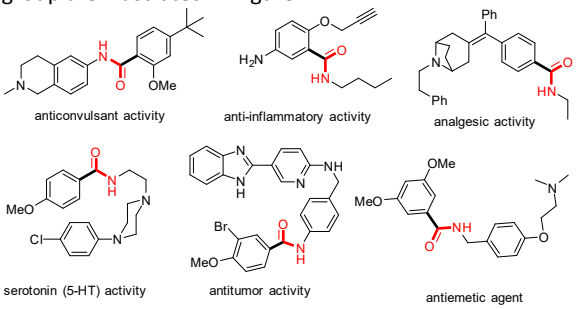
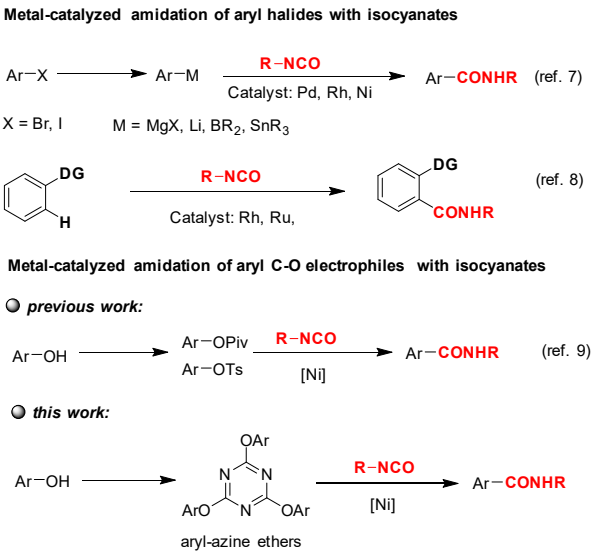


Figure 1. The chemical structure of some biologically active molecules containing benzamide moiety

To synthesize benzamide derivatives especially those which are known as prescribed drugs, the facile traditional methods are commonly used. They are based on the condensation of benzoic acid derivatives with amines. These methods often suffer from main drawbacks mainly, the use of harsh reaction conditions, tedious workup procedures as well as showing limited scope.[4] Furthermore, these classical methods are unfavourable in viewpoint of environmental because of low atom efficiency and production of huge amounts of waste products.[5] To overcome these problems, opening the new and efficient gate ways of new and efficient synthetic approaches are still in much demands.[6]

One of the most practical, atom economic and efficient synthetic methods to obtain benzamides is based on the use of isocyanates through transition metal catalysis.[7-9] In such approaches, aryl halides are used as starting materials for the synthesis of benzamides *via* the reaction of appropriate organometallic reagents (such as Li, MgX, BR_2, SnR_3) with isocyanate in the presence of a transition metal catalyst (Scheme 1, a).[7]



Scheme 1. Metal-catalyzed amidation reaction for synthesis of amides using isocyanates

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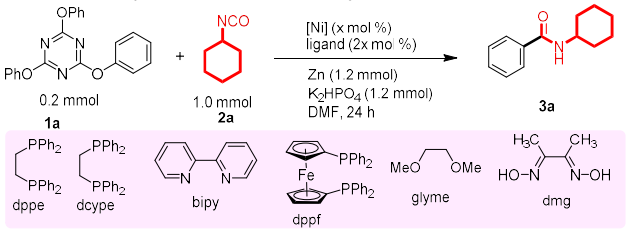
Carbon–hydrogen functionalization of aryl rings containing *ortho*-directing groups with isocyanates in the presence of a Rh or Ru catalyst system can also give raise to benzamides.[8] Another substance which can be used instead of aryl halides in reaction with isocyanates is activated phenolic compounds as the reactive aryl C-O electrophiles. In spite of such importance, literature survey showed only a single report dealing with the direct conversion of aryl C-O electrophiles to benzamides (Scheme 1, b).[9] However, C–O electrophiles have emerged as prevailing and environmentally friendly alternatives for being used instead of aryl halides.[10]

Herein, we wish to report that the reaction of activated phenolic compounds with cyanuric chloride (aryl-triazine ethers)[11] and isocyanates in the presence of a nickel catalyst system could afford a wide range of benzamide derivatives (Scheme 1). Noticeably, literature survey showed no report on the Ni-catalyzed reductive amidation[12] of aryl-triazine ethers with isocyanates. This new synthetic method is highlighted by its broad scope and good chemoselectivity profile for phenolic compounds, as well as challenging substrate. The use of readily available and air-stable aryl electrophiles in this coupling reaction also makes the practicality of this method more smoothly.

We set out the optimization study using the reaction of 2,4,6-triphenoxy-1,3,5-triazine (**1a**) and cyclohexyl isocyanate (**2a**) in the presence of a nickel catalyst system (Table 1).

Table 1. Optimization study of the amidation of aryl-azine ethers in the presence of a Ni catalyst



entry	catalyst (mol %)	ligand (mol %)	temp (°C)	yield (%)[b]
1	$NiCl_2.6H_2O$ (10)	dppf (20)	80	55
2	$NiCl_2$(dppf) (10)	dppf (10)	80	67
3	$NiCl_2$(dppe) (10)	dppf (10)	80	35
4	$NiCl_2(PCy_3)_2$ (10)	dppf (10)	80	72
5	$NiCl_2$.dmg (10)	dppf (20)	80	90
6	$NiCl_2$.glyme (10)	dppf (20)	80	77
7	$NiCl_2$.dmg (10)	dcype (20)	80	90
8	$NiCl_2$.dmg (10)	dppe (20)	80	80
9	**$NiCl_2$.dmg (10)**	**dppf (20)**	**90**	**92**
10	$NiCl_2$.dmg (10)	dppf (20)	100	88
11	$NiCl_2$.dmg (10)	dppf (20)	rt	0
12	$NiCl_2$.dmg (8)	dppf (16)	90	88
13	$NiCl_2$.dmg (12)	dppf (24)	90	92
14	$NiCl_2$.dmg (10)	dppf (20)	90	85[c]
15	$NiCl_2$.dmg (10)	dppf (20)	90	51[d]
16	$NiCl_2$.dmg (10)	dppf (20)	90	83[e]
17	$NiCl_2$.dmg (10)	dppf (20)	90	92[f]
18	$NiCl_2$.dmg (10)	dppf (20)	90	11[g]
19	$NiCl_2$.dmg (10)	dppf (20)	90	56[h]
20	none	dppf (20)	90	0
21	$NiCl_2$.dmg (10)	none	90	27
22	$NiCl_2$.dmg (10)	bipy (20)	90	54

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mmol), catalyst (x mol%), ligand (x or 2x mol %), Zn (1.2 mmol), K_2HPO_4 (1.2 mmol), dry solvent (2 mL) and under inert gas conditions. [b] Isolated yields. [c] DMA was used as solvent. [d] Dioxane was used as solvent. [e] Mn was used as reducing agent. [f] 2.0 mmol of cyclohexyl isocyanate was used. [g] no reducing agent was used. [h] 0.6 mmol Zn was used.

The reaction between 2,4,6-triphenoxy-1,3,5-triazine (**1a**) and cyclohexyl isocyanate afforded to the *N*-cyclohexylbenzamide (**3a**) in 55% isolated yield in the presence of $NiCl_2.6H_2O$ as catalyst and dppf as ligand at 80 °C (Table 1, entry 1). The reaction yield was increased to 67% by use of $NiCl_2$(dppf) as nickel source (Table 1, entry 2). Then, we checked different Ni pre-catalysts and $NiCl_2$.dmg showed superior activity and 90% of the desired product was isolated from the reaction mixture (Table 1, entries 3-6). Beside of $NiCl_2$.dmg, other ligands were tested and dppf found being the ligand of choice (Table 1, entries 7 & 8).

We found out that by increasing the reaction temperature the yields were not changed remarkably and at room temperature no product was observed (Table 1, entries 9-11). The catalyst loading was optimized and 10 mol% of catalyst was recognized as optimum amount (Table 1, entries 12 & 13). By use of other solvents no improvement in the reaction yield and conditions was observed, thus, DMF was used as the solvent of choice (Table 1, entries 14&15). It was also found that zinc is the better reducing agent in this reaction and no increasing in the reaction yield was observed when 2 equivalents of cyclohexyl isocyanate was used (Table 1, entries 16 & 17). In the absence of reducing agent the reaction yield was decreased remarkably and also by decreasing of its amount, demonstrating key role of reducing agent in this process (Table 1, entries 18 & 19). It should be noted that in the absence of Ni catalyst source no product observed (Table 1, entry 20). Also the reaction yield was decreased to 27% without using ligand (Table 1, entry 20). The reaction yield for bipy as a nitrogen-based ligand was decreased to 54%, therefore this type of ligands are not effective than phosphin ligands in this reaction. In this way the entry 9 of Table 1 was selected as a model reaction to secure the optimized reaction conditions for this protocol.

With optimized reaction conditions in hand, the scope of substrates tolerated in the reaction was investigated. To explore the substrate scope and establishing the generality of the new method, differently substituted phenols were also successfully converted to their benzamides using isocyanates (Scheme 2).

As shown in Scheme 2, amide bond formation happens under optimized reaction conditions with a range of phenolic and isocyanate substrates. The reaction tolerates a wide variety of functional groups, including -Me (**3c-e, 3ab**), -NO_2 (**3l-n,v,w**), -Cl (**3i-k,x**), -F (**3o-r**), -CF_3 (**3s,t**), and –NMe_2 (**3u,ad**) (Scheme 2). Both electron-poor and electron-rich phenols are worked well with this procedure. A chemoselectivity was observed between C–O and C–Cl bond cleavage and

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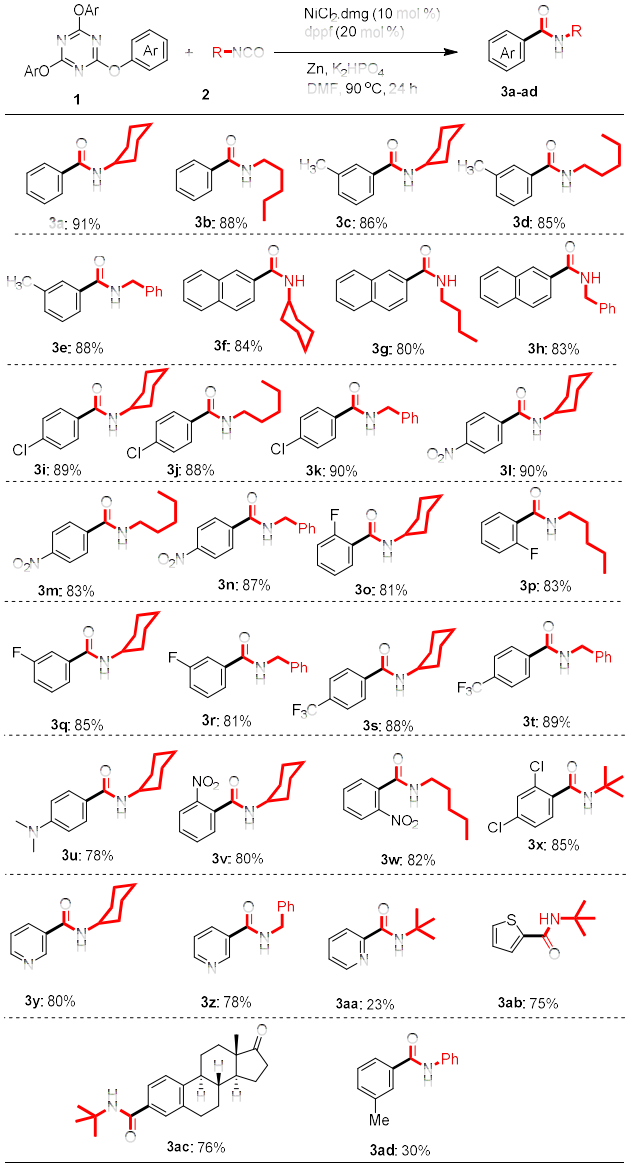
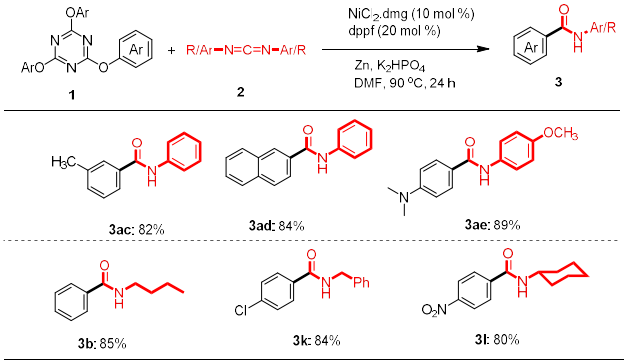
compounds **3i-k** were synthesized successfully. Activated 2-naphthol was subjected to the Ni-catalyzed amidation and corresponding benzamides **3f-h** and **3ac** in high yields. 2,4-Dichlorophenol as a sterically hindered substrate gave the desired product (**3x**) in moderate yield. Heterocyclic substrates including thiophene and pyridine can be employed in this protocol and amide products (**3y-ab**) were obtained in satisfactory yields. In the case of 2-pyridyl substrate low yield of product was observed. Other commercially available isocyanates including *tert*-butyl-, *n*-pentyl- and benzyl isocyanates, were fruitfully converted to the amide derivatives using this procedure. The synthetic usefulness of this methodology in organic synthesis was further highlighted using successful synthesis of a steroid estrone amide derivative using *tert*-butyl isocyanate under our optimized condition (**3ab**).



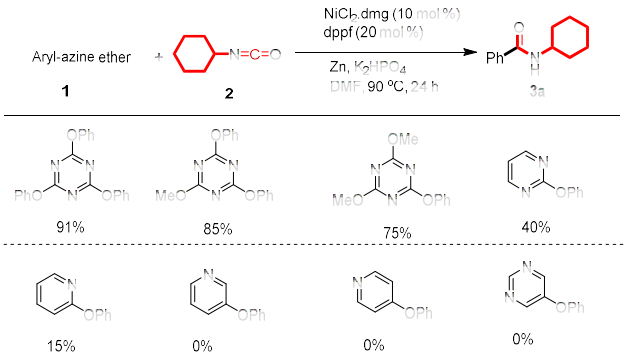
Scheme 2. Products of Ni-catalyzed reductive amidation of activated phenols with cyanuric chloride. Reaction conditions: **1** (0.2 mmol), **2** (1.0 mmol), catalyst (10.0 mol%), ligand (20.0 mol %), Zn (1.2 mmol), K_2HPO_4 (1.2 mmol), dry DMF (2 mL) and under inert gas conditions. [b] Yields correspond to isolated products.

The reaction yields for aryl isocyanates using this methodology were low (**3ad**) and this refer to the formation of isocyanurates via trimerization of the aryl isocyanate in the presence of a zerovalent metal Zn or Ni.[13] In order to obtain these compounds in high yields we used their corresponding carbodiimides based on the previous report.[14] Interestingly, this procedure also worked well with carbodiimides as an amidating agent (Scheme 3, compounds **3ad-af**). Also, this procedure works well with aliphatic carbodiimides to produce corresponding amides in good yields (Scheme 3, compounds **3b**,**k**,**l**).



Scheme 3. Nickel-catalyzed synthesis of benzamides using carbodiimides. Reaction conditions: **1** (0.2 mmol), **2** (1.0 mmol), catalyst (10.0 mol%), ligand (20.0 mol %), Zn (1.2 mmol), K_2HPO_4 (1.2 mmol), dry DMF (2 mL) and under inert gas conditions. [b] Yields correspond to isolated products.

This protocol was also checked with other aryl-azine ethers and results show that the numbers of nitrogen in the azine ring and also position of nitrogen related to C-O bond are two important factors in the reaction outcome (Scheme 4).



Scheme 4. Nickel-catalyzed synthesis of benzamides using different aryl-azine ethers. Reaction conditions: aryl-azine ether (0.6 mmol per aryl ring), isocyanatocyclohexane (1.0 mmol), catalyst (10.0 mol%), ligand (20.0 mol %), Zn (1.2 mmol), K_2HPO_4 (1.2 mmol), dry DMF (2 mL) and under inert gas conditions. [b] Yields correspond to isolated products.

We proposed a reaction pathway for Ni-catalyzed amidation of activated phenolic compounds by isocyanates based on the literature (Scheme 5).[15]

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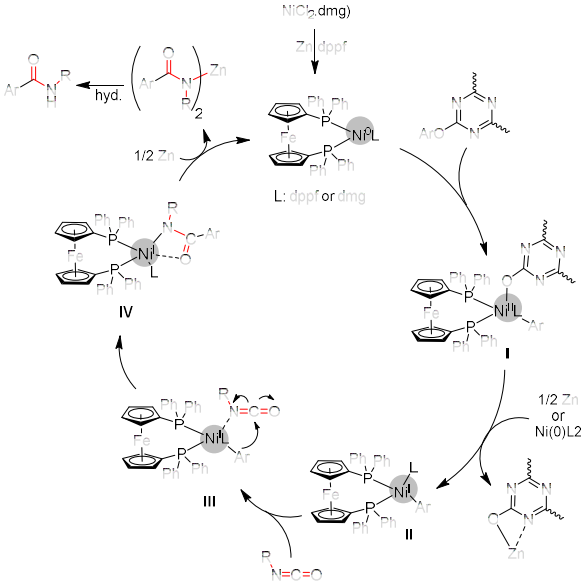
As shown in Scheme 5, oxidative addition of aryl C-O electrophiles to Ni(0) complex led to the formation of intermediate **I**. Intermediate **II** is formed through interaction of isocyanate with Ni complex **I**. This mechanism may be involving a Zn-mediated reduction of the Ni(II) to generate a Ni(I) species to produce intermediate **II**. Isocyanate can coordinate with intermediate **II** to form intermediate **III**. In intermediate **III**, aryl ring added to carbon of isocyanate group and the formed amide can coordinate with metal center (**IV**) which in the presence of Zn the Ni(0) catalyst is regenerated again and next cycle is started.



Scheme 5. Proposed mechanism for nickel-catalyzed synthesis of benzamides using aryl-azine ethers

In summary, we have developed a novel and efficient methodology for the conversion of phenolic compounds to their corresponding benzamides. The reaction proceeds with a catalytic amount of Ni under mild conditions. This procedure is characterized by its operational simplicity and the ready availability of the substrates employed. This approach also established a new choice for the synthesis of amides using isocyanates as amidating agent without the need for the preparation of sensitive organometallic reagents. Carbodiimides could be used instead of aryl isocyanates to resolve the trimerization problem associated with them in the presence of zerovalent metal Zn or Ni.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) L. Crespo, G. Sanclimens, M. Pons, E. Giralt, M. Royo, and F. Albericio, *Chem. Rev.* 2005, **105**, 1663-1682;(b) E. Valeur and M. Bradley, *Chem. Soc. Rev.* 2009, **38**, 606–631.
2 D. G. Brown and J. Boström, *J. Med. Chem.* 2016, **59**, 4443−4458.
3 A. Gomtsyan. *Chem. Heterocycl. Comp*. 2012, **48**, 7-10.
4 A. Greenberg. The amide linkage: Structural significance in chemistry, biochemistry, and materials science. John Wiley & Sons; 2000.
5 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaksh and T. Y. Zhang. *Green Chem.* 2007, **9**, 411-20.
6 R. M. de Figueiredo, J.-S. Suppo and J.-M. Campagne, *Chem. Rev.* 2016, **116**, 12029–12122.
7 (a) E. Kianmehr, A. Rajabi and M. Ghanbari, *Tetrahedron Lett.* 2009, **50**, 1687. (b) T. Miura, Y. Takahashi and M. Murakami, *Chem. Commun.* 2007, 3577. (c) T. Koike, M. Takahashi, N. Arai and A. Mori, *Chem. Lett.* 2004, 1364. (d) S. Roy, S. Roy and G. W. Gribble, *Tetrahedron* 2012, **68**, 9867-9923. (e) T. T. S. Lew, D. S. W. Lima and Y. Zhang, *Green Chem.* 2015, **17**, 5140-5143. (f) E. Serrano and R. Martin, *Eur. J. Org. Chem.* 2018, 3051–3064.
8 (a) K.Shin, J. Ryu and S. Chang, *Org. Lett.* 2014, **16**, 2022. (b) B.Zhou, W. Hou, Y. Yang, Y. Li, *Chem. Eur. J.*2013, **19**, 4701. (c) K. Muralirajan, K. Parthasarathy and C.-H. Cheng, *Org. Lett.* 2012, **14**, 4262. (d) K. D. Hesp, R. G. Bergman and J.A. Ellman, *J. Am. Chem. Soc.* 2011, **133**, 11430.
9 A. Correa and R. Martin, *J. Am. Chem. Soc.* 2014, **136**, 7253–7256.
10 a) J. Cornella, C. Zarate and R. Martin, *Chem. Soc. Rev.*, 2014, **43**, 8081-8097. b) C. Zarate, M. van Gemmeren, R.J. Somervillea, R. Martin, *Adv. Organomet. Chem.* 2016, **66**, 143-222. c) M. Tobisu and N. Chatani, *Top Curr. Chem. (Z)* 2016, 374:41. d) M. Tobisu and N. Chatani, *Acc. Chem. Res.* 2015, **48**, 1717–1726.
11 a) N. Iranpoor and F. Panahi, *Org. Lett.* 2015, **17**, 214–217. b) Y. Zhao, G.King, M.H.T. Kwan, and A. J. Blacker, *Org. Process Res. Dev.* 2016, **20**, 2012–2018. c) M. M. Heravi, F. Panahi, and N. Iranpoor, *Org. Lett.*, 2018, **20**, 2753–2756. d) L. Wang, Y. Wang, J. Shen, Q. Chen and M.-Y. He, *Org. Biomol. Chem.*, 2018, **16**, 4816-4820. f) E. Etemadi-Davan and N. Iranpoor, *Chem. Commun.*, 2017, **53**, 12794-12797. g) N. Iranpoor, F. Panahi and F. Jamedi, *J. Organomet. Chem.* 2015, **781**, 6-10. h) Y. Wang, J. Shen, Q. Chen, L. Wang and M. He, Chinese *Chem. Lett.*, 2018, DOI: 10.1016/j.cclet.2018.09.009.
12 Some example of nickel catalyzed reductive functionalization reactions: a) A. Dey, S. Sasmal, K. Seth, G. K. Lahiri and D. Maiti, *ACS Catal.* 2017, **7**, 433-437. b) A. Maji, S. Rana, Akanksha, D. Maiti, *Angew. Chem. Int. Ed.* 2014, **53**, 2428-2432. c) T. Patra, S. Agasti, A. Modak and D. Maiti *Chem. Commun.*, 2013, **49**, 8362-8364. d) A. García-Domínguez, Z. Li, C. Nevado, *J. Am. Chem. Soc.* 2017, **139**, 6835-6838. e) Y. Jin and C. Wang *Angew. Chem. Int. Ed.* 2019, **58**, 6722-6726.
13 F. Paul, S. Moulin, O. Piechaczyk, P. Le Floch, J. A.Osborn, *J. Am. Chem. Soc.* 2007, **129**, 7294.
14 F. Panahi, F. Jamedi and N. Iranpoor, *Eur. J. Org.* 2016, 780-788
15 E. Serrano and R. Martin, *Angew. Chem. Int. Ed.* 2016, **55**, 11207−11211; *Angew. Chem.* 2016, **128**, 11373−11377.