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Synthesis of Diverse Azolo[*c*]quinazolines by Palladium(II)-Catalyzed Aerobic Oxidative Insertion of Isocyanides

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Abstract: We report the palladium(II)-catalyzed aerobic oxidative coupling of isocyanides with various (2-aminophenyl)azoles using air as the stoichiometric oxidant. A diverse range of medicinally valuable azolo[*c*]quinazolines was obtained by this new approach.

Keywords: homogenous catalysis; isocyanides; oxidation; palladium; quinazolines

The adenosine A_{2A} receptor is widely recognized for its numerous possibilities for therapeutic applications. More specifically, selective antagonists for this receptor are of high current interest as potential drugs against Parkinson's disease.[1] CGS-15943 was the first highly potent, non-xanthine adenosine receptor antagonist with modest A_{2A} selectivity (Figure 1).[2] As a result, the structural motif of CGS-15943 has received significant attention in the last decades, leading to the discovery of preladenant (Figure 1). Preladenant very recently successfully completed phase II clinical trials for the treatment of Parkinson's disease,[3] but unfortunately failed phase III trials. It is likely that derivatives of these lead compounds will be more successful or other applications for this class of compounds might arise. A convenient and convergent synthetic route allowing straightforward and quick library synthesis is therefore highly desirable.

A recent approach to CGS-15943 (and related compounds) is based on the coupling of readily accessible triazoles (**1**) and cyanogen bromide (Route 1, Scheme 1).[4] Triazolo[*c*]quinazolines containing an unsubstituted 5-amino group (**2**, $R^3 = H$) are easily obtained in this manner, but direct substitution of the exocyclic amino group is not possible *via* this non-convergent approach. In contrast, mono-alkylated amino groups are typically installed by nucleophilic displacement of an appropriate leaving group by an amine, requiring more synthetic steps.[2c] Both approaches are not complementary because they require different precursors and library synthesis is therefore tedious.

Isocyanides have emerged as highly useful C_1 building blocks in palladium catalysis during the last couple of years.[5] Most of the developments have focused on imidoylative cross-coupling of aryl halides

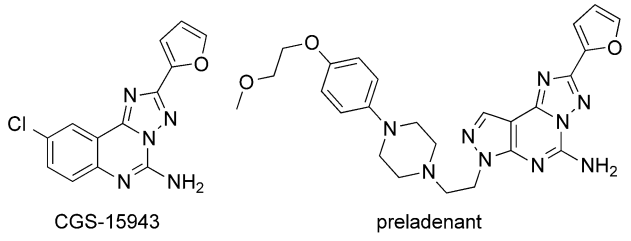
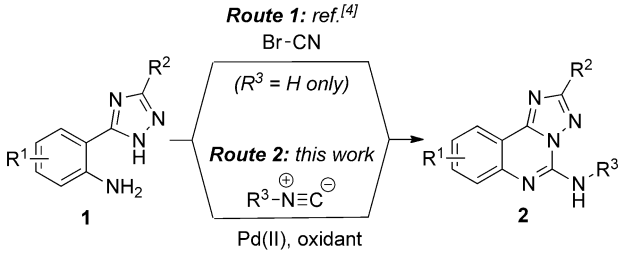


Figure 1. A_{2A} selective adenosine receptor antagonists.



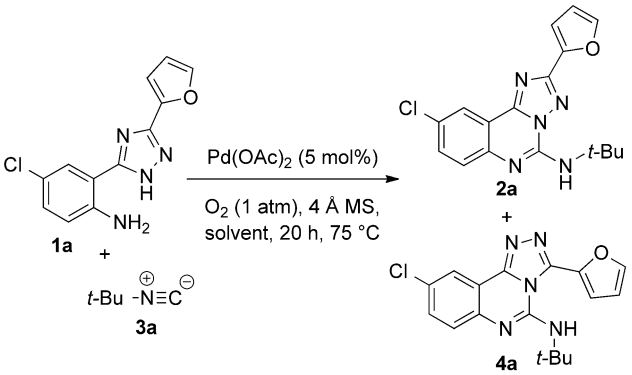
Scheme 1. Synthesis of triazolo[*c*]quinazolines.

with nucleophiles to furnish amidines, amides or imidates,[6] while applications to other reaction types have been scarce.[7] We recently introduced the oxidative coupling of bisnucleophiles and isocyanides to afford cyclic guanidines as a new reaction type to address this limitation.[8] The use of *ortho*-azoloanilines such as **1** in this reaction type would result in a practical and general approach to triazolo[*c*]quinazolines (**2**, Route 2, Scheme 1), but it also poses several new challenges to this chemistry. Two regioisomers can be formed in this case and the presence of many heteroatoms in the heterocyclic core of **2** provides several unproductive coordination sites for Pd(II), which has proven difficult in other studies.[8a] Furthermore, the low nucleophilicity of azoles is a potential problem that has not yet been addressed. To the best of our knowledge, azoles have never been used in imidoylative cross-coupling chemistry before. Owing to the importance of triazolo[*c*]quinazolines in medicinal chemistry, we here report this challenging expansion of our Pd-catalyzed oxidative guanidine synthesis.

We started our investigations by studying the coupling of **1a** with *tert*-butyl isocyanide in the presence of $Pd(OAc)_2$ (5 mol%) and 4 Å MS under an O_2 atmosphere in toluene. A good yield of the desired product (**2a**) was obtained, along with the regioisomeric product (**4a**, Table 1, entry 1). The formation of a significant amount of **4a** is surprising considering that the less nucleophilic nitrogen is coupled and the sterically more encumbered product is formed. Fortunately, the two regioisomers are readily separated by flash chromatography. Extensive NMR studies did not provide conclusive evidence for the structures assigned to the regioisomers, but an X-ray crystal structure unambiguously confirmed the identity of the major isomer **2a** (Figure 2). A solvent screen revealed that the selectivity and yield are highly dependent on the solvent (entries 2–6). MeTHF and acetonitrile gave **2a** in high yields and good selectivity, while only dioxane had a slightly higher selectivity for **4a**. We chose the renewable MeTHF as solvent for further studies.[9] A control experiment revealed that 4 Å MS are essential for good yield and selectivity (entry 7). The catalyst loading and amount of solvent could be lowered with only a minor loss in selectivity (entry 8). Surprisingly, when the reaction was performed under an air atmosphere a higher yield and selectivity were found compared to an O_2 atmosphere (entry 9). This result is in stark contrast with our previous work,[8] where an O_2 atmosphere was important for good results. The use of an air atmosphere is much more convenient and should make our protocol amenable to large-scale production.

We next evaluated the substrate scope with respect to the triazole (**1**) in the Pd-catalyzed coupling with *tert*-butyl isocyanide using the optimized reaction conditions (Table 2). Pleasingly, a wide range of (hetero)-

Table 1. Reaction optimization.[a]



Entry	Solvent	**1a**[b]	**2a**[b]	**4a**[b]
1	PhMe	<5%	65%	15%
2	MeCN	<5%	80%	–
3	*t*-BuOH	<5%	74%	6%
4	dioxane	<5%	58%	16%
5	DMF	50%	21%	6%
6	MeTHF	<5%	83%	2%
7[c]	MeTHF	23%	43%	7%
8[d]	MeTHF	<5%	72%	7%
9[d,e]	MeTHF	<5%	81%	4%

[a] *Conditions*: $Pd(OAc)_2$ (5 mol%), **1a** (0.50 mmol), **3a** (0.6 mmol), 4 Å MS (150 mg) in solvent (5 mL) for 20 h at 75 °C under O_2 (1 atm).
[b] Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.
[c] No 4 Å MS used.
[d] $Pd(OAc)_2$ (2 mol%) and 2.5 mL MeTHF used.
[e] Air atmosphere.

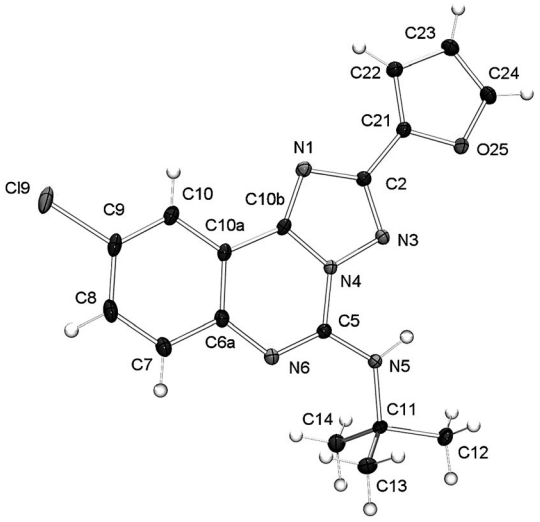
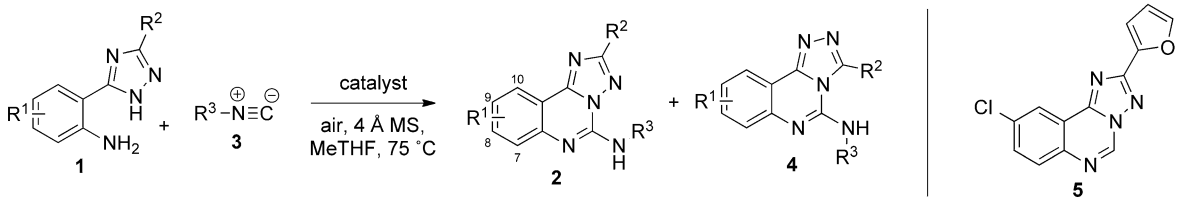
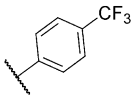
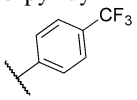
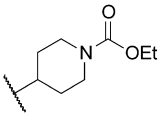
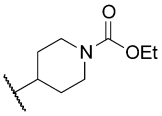


Figure 2. X-ray structure of compound **2a**. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are represented as spheres of arbitrary radius.

aromatic groups are tolerated on the triazole (R^2 position) after minor tuning of the catalyst loading and reaction time (Table 2, entries 1–4). A remarkably

Table 2. Substrate scope.[a]



Entry	Catalyst	Time	R^{1}[b]	R^{2}	R^{3}	Isomer (**4**)	Product (**2**)
1	$Pd(OAc)_2$ (2 mol%)	20 h	9-Cl	2-furyl	*t*-Bu	4% (**4a**)	81% (**2a**)
2	$Pd(OAc)_2$ (4 mol%)	20 h	9-Cl	Ph	*t*-Bu	6% (**4b**)	78% (**2b**)
3	$Pd(OAc)_2$ (5 mol%)	44 h	9-Cl		*t*-Bu	<5% (**4c**)	83% (**2c**)
4	$Pd(OAc)_2$ (10 mol%)	44 h	9-Cl	3-pyridyl	*t*-Bu	–	65% (**2d**)
5	$Pd(OAc)_2$ (2 mol%)	20 h	9-F	2-furyl	*t*-Bu	–	71% (**2e**)
6	$Pd(OAc)_2$ (4 mol%)	20 h	H	Ph	*t*-Bu	9% (**4f**)	75% (**2f**)
7	$Pd(OAc)_2$ (4 mol%)	20 h	H	2-furyl	*t*-Bu	13% (**4g**)	74% (**2g**)
8	$Pd(OAc)_2$ (2 mol%)	20 h	7-Me	3-pyridyl	*t*-Bu	–	80% (**2h**)
9	$Pd(OAc)_2$ (6 mol%)	20 h	7-Me		*t*-Bu	–	72% (**2i**)
10	$Pd(OAc)_2$ (5 mol%)	44 h	8,9-$(OMe)_2$	Ph	*t*-Bu	–	74% (**2j**)
11	$Pd(OAc)_2$ (10 mol%)	44 h	9-Cl	2-furyl	*n*-Pent	–	39% (**2k**)
12	$Pd(OAc)_2$ (15 mol%)	72 h	9-Cl	2-furyl	*n*-Pent	–	54% (**2k**)
13	$Pd(OPiv)_2$ (15 mol%)	72 h	9-Cl	2-furyl	*n*-Pent	–	62% (**2k**)
14	$Pd(OPiv)_2$ (15 mol%)	72 h	9-Cl	2-furyl	Bn	–	11% (**2l**)
15	$Pd(OPiv)_2$ (10 mol%)	72 h	9-Cl	2-furyl	*i*-Pr	–	43% (**2m**)
16	$Pd(OAc)_2$ (7.5 mol%)	20 h	9-Cl	2-furyl	*c*-Hex	–	50% (**2n**)
17	$Pd(OPiv)_2$ (15 mol%)	72 h	9-Cl	2-furyl		–	43% (**2o**)
18	$Pd(OPiv)_2$ (15 mol%)	72 h	9-Cl	Ph	*n*-Pent	–	51% (**2p**)
19	$Pd(OAc)_2$ (10 mol%)	72 h	9-Cl	Ph	*i*-Pr	–	45% (**2q**)
20	$Pd(OAc)_2$ (10 mol%)	72 h	9-Cl	Ph	*c*-Hex	–	57% (**2r**)
21	$Pd(OAc)_2$ (10 mol%)	72 h	9-Cl	Ph		–	38% (**2s**)

[a] *Standard conditions:* **1** (0.5 mmol), **3** (0.6 mmol), catalyst and 4 Å MS (150 mg) in MeTHF (2.5 mL) at 75 °C under air. Yields refer to isolated material.

[b] Position is indicated for the product **2**, see Scheme for numbering.

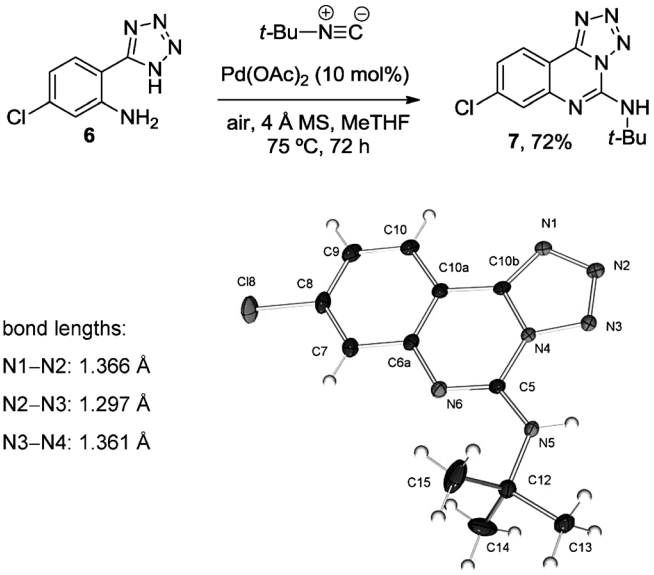
strong effect on the reaction rate of this group was found, considering the group is far away from the reaction site. In the case of the 3-pyridyl group (entry 4) a catalyst loading as high as 10 mol% was required to obtain an acceptable conversion to the desired product. It is possible that the pyridine nitrogen competes as a ligand for Pd(II) and thereby retards the reaction. In contrast, product **2h** containing the same 3-pyridyl group could be obtained in high yield with a much lower catalyst loading (2 mol%). We have no explanation for this surprising result. Various electron-withdrawing and electron-donating groups are tolerated at the R^{1} position and afford the corresponding products in good yields (Table 2, entries 5–10). The use of sterically more congested substrates is tolerated and does not deteriorate the yield or rate of the reaction (entries 8 and 9). Notably, taking into account the oxidative conditions, a highly electron-rich substrate possessing two methoxy groups is readily converted to the tricyclic guanidine product (**2j**, 74%).

We then turned our attention to the compatibility of the reaction with other isocyanides. *n*-Pentyl isocyanide was readily coupled with **1a** under the standard

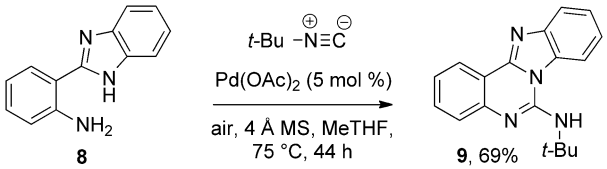
reaction conditions with a slightly higher catalyst loading, albeit in moderate yield (39%, entry 11, Table 2). Compound **5**, lacking the 5-amino group, was isolated as a side product (18%). There is literature precedence for such a transformation,[10] but it is unclear why it only occurs when *n*-pentyl isocyanide is used. Possibly, non-oxidative nucleophilic addition of the amine to pentyl isocyanide is more pronounced because the latter is more electrophilic compared to secondary and tertiary isocyanides. The efficiency of the oxidative coupling of **1a** and *n*-pentyl isocyanide could be improved by employing more catalyst, which surprisingly also reduced the formation of **5** to just 5% (entry 12). This could suggest the formation of **5** is not catalyzed by palladium. $Pd(OPiv)_2$ is a slightly better catalyst than $Pd(OAc)_2$ and affords the product in 62% yield (entry 13).

Benzyl isocyanide is sterically and electronically similar to pentyl isocyanide, but only a trace amount of the *N*-benzyl product **2l** was formed (entry 14). The only side-product we could identify was again compound **5**. The most plausible explanation for the poor reactivity of benzyl isocyanide is an undesired reaction on the more activated α-position compared to pentyl isocyanide. The use of isopropyl isocyanide affords **2m** in 43% yield (entry 15). We anticipated a higher yield considering that secondary aliphatic isocyanides generally perform better than primary isocyanides. A possible explanation is the volatility of isopropyl isocyanide, and cyclohexyl isocyanide indeed performs slightly better under less forcing conditions (entry 16). Unfortunately, commercially available 2,6-dimethylphenyl isocyanide did not provide an appreciable amount of product (not shown). Pleasingly, an isocyanide containing a protected amine was readily coupled and provides **2o** in 43% isolated yield (entry 17). This is quite remarkable considering that the isocyanide scope is often limited in imidoylative palladium catalysis and in many reactions only *tert*-butyl isocyanide works well.[5] A less reactive triazole possessing a phenyl group at the R^1 position also reacted with various isocyanides under the standard conditions (entries 18–21). We chose to use 10 mol% $Pd(OAc)_2$ as catalyst with a long reaction time (72 h) as standard conditions for the reactions with secondary isocyanides for convenience and to illustrate generality. It is likely that lower catalyst loadings and/or reaction times are possible after additional optimization.

Tetrazole **6** also reacted with *tert*-butyl isocyanide under the standard reaction conditions to afford **7** in 72% yield (Scheme 2). The X-ray crystal structure unambiguously confirms the identity of this highly nitrogen-rich compound. To the best of our knowledge, this is the first example of a 5-aminotetrazolo[1,5-*c*]quinazoline containing a monosubstituted 5-amino group.



Scheme 2. Synthesis and X-ray structure of **7**. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are represented as spheres of arbitrary radius.



Scheme 3. Synthesis of benzimidazoquinazoline **9**.

A benzimidazole can also be employed as the nucleophile as illustrated by the conversion of commercially available **8** to benzimidazoquinazoline **9** in 69% yield (Scheme 3).

In summary, we have shown that azoles are suitable nucleophiles in the Pd(II)-catalyzed aerobic oxidative coupling of bisnucleophiles and isocyanides. Various medicinally important azolo[*c*]quinazolines were readily obtained by oxidative coupling of α-(2-aminophenyl)azoles with isocyanides using air as the stoichiometric oxidant. In most of these reactions two regioisomeric products could potentially be formed, but high selectivity is achieved if renewable 2-MeTHF is used as the solvent. The high number of heteroatoms present in the products is challenging for this chemistry because it offers several unproductive coordination sites for Pd(II), which possibly explains the higher catalyst loading required for some substrates. The relative ease with which the aerobic oxidative guanidine synthesis could be applied to these difficult substrates is indicative of the broad utility of this chemistry. Moreover, the use of an air atmosphere makes the procedure exceedingly simple and practical, promoting its general use by chemists.

Experimental Section

General Procedure for the Aerobic Oxidative Coupling of α-(2-Aminophenyl)azoles and Isocyanides

A 10-mL round-bottom flask equipped with a reflux condenser was charged with the corresponding α-(2-aminophenyl)azole (0.5 mmol), Pd catalyst and 4 Å MS (150 mg). Next, 2-methyltetrahydrofuran (2.5 mL) and the isocyanide (0.6 mmol) were added and the reaction mixture was stirred at 75 °C for the indicated time under an air atmosphere. The mixture was cooled, filtered through Celite (DCM) and purified by flash chromatography (SiO_2). ***Note:*** some of the solvent evaporated during the course of most reactions, especially with longer reaction times. It is possible this affected the reaction outcome.

Acknowledgements

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References

[1] M. de Lera Ruiz, Y.-H. Lim, J. Zheng, *J. Med. Chem.* **2013**, DOI: 10.1021/jm4011669.

[2] a) M. Williams, J. Francis, G. Ghai, A. Braunwalder, S. Psychoyos, G. A. Stone, W. D. Cash, *J. Pharmacol. Exp. Ther.* **1987**, *241*, 415–420; b) G. Ghai, J. E. Francis, M. Williams, R. A. Dotson, M. F. Hopkins, D. T. Cote, F. R. Goodman, M. B. Zimmerman, *J. Pharmacol. Exp. Ther.* **1987**, *242*, 784–790; c) J. E. Francis, W. D. Cash, S. Psychoyos, G. Ghai, P. Wenk, R. C. Friedmann, C. Atkins, V. Warren, P. Furness, *J. Med. Chem.* **1988**, *31*, 1014–1020; d) K. A. Jacobson, P. J. M. Van Galen, M. Williams, *J. Med. Chem.* **1992**, *35*, 407–422.

[3] R. A. Hauser, M. Cantillon, E. Pourcher, F. Micheli, V. Mok, M. Onofrj, S. Huyck, K. Wolski, *Lancet Neurol.* **2011**, *10*, 221–229.

[4] C. Balo, C. López, J. M. Brea, F. Fernández, O. Caamaño, *Chem. Pharm. Bull.* **2007**, *55*, 372–375.

[5] a) T. Vlaar, E. Ruijter, B. U. W. Maes, R. V. A. Orru, *Angew. Chem.* **2013**, *125*, 7222–7236; *Angew. Chem. Int. Ed.* **2013**, *52*, 7084–7097; b) S. Lang, *Chem. Soc. Rev.* **2013**, *42*, 4867–4880; c) G. Qiu, Q. Ding, J. Wu, *Chem. Soc. Rev.* **2013**, *42*, 5257–5269.

[6] a) T. Vlaar, E. Ruijter, A. Znabet, E. Janssen, F. J. J. de Kanter, B. U. W. Maes, R. V. A. Orru, *Org. Lett.* **2011**, *13*, 6496–6499; b) G. Van Baelen, S. Kuijer, L. Rýček, S. Sergeyev, E. Janssen, F. J. J. de Kanter, B. U. W. Maes, E. Ruijter, R. V. A. Orru, *Chem. Eur. J.* **2011**, *17*, 15039–15044; c) Y. Wang, H. Wang, J. Peng, Q. Zhu, *Org. Lett.* **2011**, *13*, 4604–4607; d) Y. Wang, Q. Zhu, *Adv. Synth. Catal.* **2012**, *354*, 1902–1908; e) G. Qiu, G. Liu, S. Pu, J. Wu, *Chem. Commun.* **2012**, *48*, 2903–2905; f) T. Vlaar, P. Mampuys, M. Helliwell, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *J. Org. Chem.* **2013**, *78*, 6735–6745; g) G. Qiu, C. Chen, L. Yao, J. Wu, *Adv. Synth. Catal.* **2013**, *355*, 1579–1584; h) J. V. Geden, A. K. Pancholi, M. Shipman, *J. Org. Chem.* **2013**, *78*, 4158–4164; i) Z. Hu, J. Wang, D. Liang, Q. Zhu, *Adv. Synth. Catal.* **2013**, *355*, 3290–3294; j) V. N. Bochatay, P. J. Boissarie, J. A. Murphy, C. J. Suckling, S. Lang, *J. Org. Chem.* **2013**, *78*, 1471–1477; k) F. Ji, M.-f. Lv, W.-b. Yi, C. Cai, *Adv. Synth. Catal.* **2013**, *355*, 3401–3406; l) B. Liu, H. Gao, Y. Yu, W. Wu, H. Jiang, *J. Org. Chem.* **2013**, *78*, 10319–10328.

[7] a) T. Nanjo, C. Tsukano, Y. Takemoto, *Org. Lett.* **2012**, *14*, 4270–4273; b) B. Liu, Y. Li, M. Yin, W. Wu, H. Jiang, *Chem. Commun.* **2012**, *48*, 11446–11448; c) T. Vlaar, B. U. W. Maes, E. Ruijter, R. V. A. Orru, *Chem. Heterocycl. Compd.* **2013**, *49*, 902–908; d) T. Nanjo, S. Yamamoto, C. Tsukano, Y. Takemoto, *Org. Lett.* **2013**, *15*, 3754–3757.

[8] a) T. Vlaar, R. C. Cioc, P. Mampuys, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *Angew. Chem.* **2012**, *124*, 13235–13238; *Angew. Chem. Int. Ed.* **2012**, *51*, 13058–13061; b) T. Vlaar, R. V. A. Orru, B. U. W. Maes, E. Ruijter, *J. Org. Chem.* **2013**, *78*, 10469–10475.

[9] a) D. F. Aycock, *Org. Process Res. Dev.* **2007**, *11*, 156; b) R. K. Henderson, C. Jimenez-Gonzalez, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13*, 854–862.

[10] Y. Ito, I. Ito, T. Hirao, T. Saegusa, *Synth. Commun.* **1974**, *4*, 97–103.

[11] CCDC 974815 (**2a**) and CCDC 974816 (**7**) contain 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.