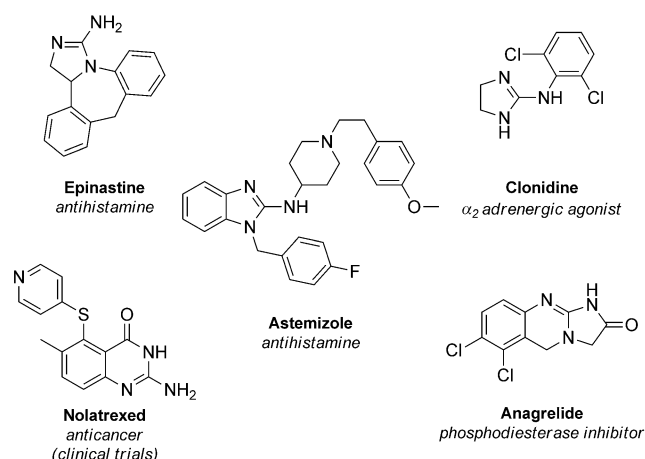


Sustainable Synthesis of Diverse Privileged Heterocycles by Palladium-Catalyzed Aerobic Oxidative Isocyanide Insertion**

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Heterocycles containing a guanidine moiety are of great importance in medicinal chemistry (Scheme 1).^[1] As a result, several methods for the synthesis of these “privileged scaffolds” have been reported.^[2,3] Classical approaches, such



Scheme 1. Clinically used guanidine-containing heterocycles.

as the addition of diamines to isothiocyanates followed by condensation and the coupling of diamines with cyanogen bromide,^[2,4] have some clear limitations, such as the availability and toxicity of reagents. Moreover, these procedures

suffer from poor atom and/or step efficiency, thus making them unattractive from a sustainability point of view.

We envisioned the aerobic oxidative coupling of diamines and isocyanides using palladium catalysis could provide access to a wide range of guanidine-containing heterocycles in a single step with water as the sole byproduct. The oxidation sensitivity of, for example *o*-phenylenediamines—which form the basis for most permanent hair dyes—makes this approach particularly challenging. Oxidative palladium catalysis has drawn considerable attention because of its mild and environmentally benign character, especially when molecular oxygen is used as the terminal oxidant.^[5] Isocyanides have emerged as valuable C₁ building blocks in palladium catalysis that readily undergo similar transformations as carbon monoxide. Isocyanides are more easily handled than carbon monoxide and contain a diversity point. It is therefore not surprising that there has been a recent surge of interest in palladium-catalyzed processes that involve isocyanide insertion.^[6] However, only two oxidative processes utilizing molecular oxygen have been reported.^[7] In light of our interest in Pd-catalyzed cascade reactions^[8] involving isocyanide insertion, we report herein the atom-efficient synthesis of diverse cyclic guanidines from diamines and isocyanides by using aerobic oxidative palladium catalysis.^[9]

We started our investigations with the benchmark reaction between *o*-phenylenediamine (**1a**) and *tert*-butyl isocyanide (**2a**) to give 2-aminobenzimidazole (**3a**). After optimization of the conditions (see the Supporting Information for details) we found that the reaction proceeds quantitatively in the presence of Pd(OAc)₂ (1 mol %) in the absence of an external ligand or base in an atmosphere of molecular oxygen (1 atm) in the renewable solvent 2-methyltetrahydrofuran (MeTHF)^[10] at 75 °C.

To evaluate the reaction scope, we first tested a range of electronically diverse *o*-phenylenediamines (Table 1, entries 1–11). Pleasingly, all examined substrates underwent clean conversion to the desired 2-aminobenzimidazoles **3a–k** in excellent yields (83–99 %), and the only noticeable difference was observed in the reaction rate. Electron-donating groups (OMe, Me) and weak or moderately electron-withdrawing groups (F, Cl, COOMe) gave full conversion under the standard conditions, whereas strong electron-withdrawing groups (CN, CF₃, NO₂) required more catalyst and longer reaction times. 4-Bromo-*o*-phenylenediamine curiously also reacts slower, although the product **3g** was obtained in good yield (83 %, Table 1, entry 7). Aza analogue **11** also underwent clean, albeit slower, conversion to product **3l** in 65 % yield (Table 1, entry 12). Finally, an interesting theophylline

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[**] This work was financially supported by The Netherlands Organization for Scientific Research (NWO) by means of a TOP grant to R.V.A.O. and by the Hercules Foundation. We thank Elwin Janssen for technical assistance, Sanne Bouwman for HRMS measurements, and Dr. Andreas W. Ehlers for NMR spectroscopic measurements.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201207410>.

Table 1: Substrate scope of the aerobic oxidative coupling of *o*-phenylenediamines and isocyanides.^[a]

Entry	Diamine	Product	<i>t</i> [h]	Yield [%] ^[b]
1	1 a (R = H)	3 a (R = H)	20	99 (97 ^[c])
2	1 b (R = 4-Me)	3 b (R = 5-Me)	20	95
3	1 c (R = 3-Me)	3 c (R = 4-Me)	20	90
4	1 d (R = 4-OMe)	3 d (R = 5-OMe)	20	93
5	1 e (R = 4-F)	3 e (R = 5-F)	20	99
6	1 f (R = 4-Cl)	3 f (R = 5-Cl)	20	92
7 ^[d]	1 g (R = 4-Br)	3 g (R = 5-Br)	72	83
8	1 h (R = 4-CO ₂ Me)	3 h (R = 5-CO ₂ Me)	20	99
9 ^[d]	1 i (R = 4-CN)	3 i (R = 5-CN)	72	95
10 ^[d]	1 j (R = 4-CF ₃)	3 j (R = 5-CF ₃)	66	95
11 ^[d]	1 k (R = 4-NO ₂)	3 k (R = 5-NO ₂)	72	98
12 ^[d]	1 l	3 l	72	65
13 ^[d]	1 m	3 m	20	43
14 ^[e,f]	1 a	3 n	5	54
15	1 n	3 o	22	88
16	1 n	3 p	2	97
17 ^[d]	1 n	3 q	20	87
18	1 o	3 r	4	92
19 ^[d]	1 o	3 s	18	94
20 ^[g,h]	1 a	3 t	26	93

[a] Standard conditions: diamine (1.0 mmol), isocyanide (1.2 mmol), Pd(OAc)₂ (1 mol %), and 4 Å molecular sieves (MS) in MeTHF (5 mL) at 75 °C in O₂ atmosphere (1 atm, balloon). PMB = *p*-methoxybenzyl.

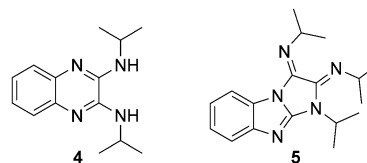
[b] Yields of isolated products. [c] 10 mmol scale. [d] 5 mol % Pd(OAc)₂.

[e] Slow addition of isocyanide (1.5 equiv) over 5 h, *t*BuOH as solvent.

[f] 10 mol % Pd(OAc)₂. [g] Toluene as solvent. [h] *t*BuNC used; concentrated HCl added after 20 h, then 6 h reflux.

analogue (**3m**) could be prepared in 43% yield from diaminouracil **1m**, thereby further illustrating the broad substrate scope. Importantly, the reaction is amenable to scale-up with negligible loss of yield (Table 1, entry 1).

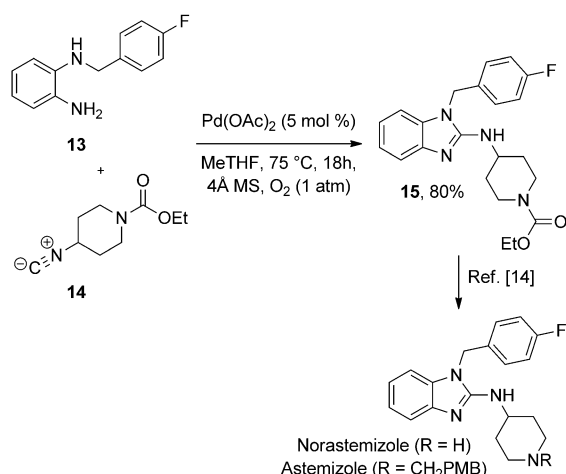
The substrate scope of isocyanides in palladium-catalyzed processes is often limited and occasionally only *t*BuNC is viable.^[6] Indeed, selective double insertion of primary and secondary aliphatic isocyanides has been reported.^[11] We were therefore not surprised that *i*PrNC (**2b**) was a poor reactant in the reaction with **1a** to give **3n** under the standard conditions. Surprisingly, we found selective formation of a compound incorporating three isocyanide molecules, to which we assigned structure **5** (Scheme 2). Compound **5** is



Scheme 2. Observed side products with isopropyl isocyanide.

most likely formed from the desired product (**3n**), and a control experiment starting from **3n** confirmed this. After considerable optimization (see the Supporting Information), we were able to isolate the target compound **3n** in 54% yield by using modified conditions (10 mol % Pd(OAc)₂, 1.5 equiv *i*PrNC, slow addition, *t*BuOH; Table 1, entry 14). We reasoned that N1-substituted substrates lack the possibility to form products like **5**, since no second NH group would be present for an additional oxidative isocyanide insertion. Moreover, double insertion would not lead to a favorable aromatic system like **4**. Indeed, when reacting *N*-methyl-*o*-phenylenediamine (**1n**) with *i*PrNC under the standard reaction conditions (1 mol % Pd(OAc)₂, 22 h) we isolated the desired 2-aminobenzimidazole **3o** in 88% yield (Table 1, entry 15). Also primary isocyanides can be used, as exemplified by *n*-pentyl isocyanide, which coupled selectively with **1n** in very good yield (Table 1, entry 17). When comparing tertiary, secondary, and primary isocyanides, the reaction rate decreased in this order (Table 1, entries 15–17). N1-Benzylated 2-aminobenzimidazoles often display unique biological activity (e.g. astemizole, Scheme 1). Therefore, *N*-*p*-methoxybenzyl-*o*-phenylenediamine (**1o**) was tested and gratifyingly found to be a suitable substrate for aerobic oxidative coupling (Table 1, entries 18 and 19). Furthermore, we were able to access unsubstituted 2-aminobenzimidazoles by a one-pot acid-promoted dealkylation sequence. Addition of concentrated HCl to the reaction mixture (after the formation of **3a** was complete) and subsequent heating under reflux furnished 2-aminobenzimidazole (**3t**) in an excellent 93% yield (Table 1, entry 20). This procedure provides a valuable alternative to the use of highly toxic cyanogen bromide, especially since *t*BuNC is an easily accessible and stable isocyanide.

Most importantly, the aerobic oxidative coupling proves to be a general, reliable, and broadly applicable reaction for the synthesis of various other aminoheterocycles with only



Scheme 4. Formal synthesis of astemizole and norastemizole.

variety of pharmaceutically relevant heterocyclic systems, as illustrated by a formal synthesis of astemizole and norastemizole. Easily handled and relatively low-cost $\text{Pd}(\text{OAc})_2$ is used as the catalyst without an additional ligand or base, and molecular oxygen, which is the most sustainable oxidant available, is used as the oxidant. The procedure is operationally simple, since bench solvents (i.e. no distillation or drying of synthesis grade solvents is required) and atmospheric pressure are used, and environmentally benign owing to the low catalyst loading, renewable solvent, and high atom efficiency.

Experimental Section

Representative procedure: A 25 mL round-bottom flask equipped with a reflux condenser was charged with *o*-phenylenediamine (**1a**, 108 mg, 1.0 mmol, 1 equiv) and 4 Å molecular sieves (300 mg). Vacuum was applied and the flask was back-filled with O_2 (3×). Subsequently, a MeTHF stock solution (5 mL) containing $\text{Pd}(\text{OAc})_2$ (2.2 mg, 0.01 mmol, 1 mol%) was added, followed by *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv). The reaction mixture was stirred at 75 °C in O_2 atmosphere (balloon) for 20 h. The mixture was filtered through Celite, concentrated, and purified by flash chromatography (SiO_2) to yield **3a** as a colorless solid (188 mg, 0.99 mmol, 99%).

Received: September 13, 2012

Published online: November 14, 2012

Keywords: guanidines · heterocycles · homogeneous catalysis · isocyanides · oxidation

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