

# Direct synthesis of bicyclic guanidines through unprecedented palladium(II) catalysed diamination with copper chloride as oxidant†‡

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Received (in Cambridge, UK) 19th December 2007, Accepted 11th February 2008

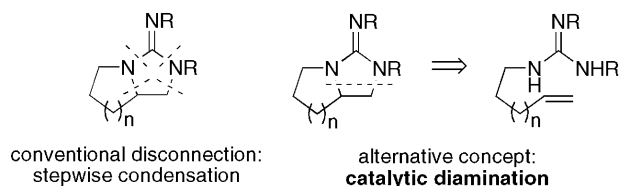
First published as an Advance Article on the web 14th March 2008

DOI: 10.1039/b719479j

**Palladium catalysed intramolecular guanidine transfer to alkenes can be accomplished with copper chloride as the oxidant to give bicyclic guanidines with complete selectivity and in high yields.**

Cyclic guanidines constitute important functional molecules. For example, they are widely present in the fascinating structural world of marine natural products,<sup>1</sup> and employed as organocatalysts,<sup>2</sup> for metal ligation<sup>3</sup> or in anion recognition.<sup>4</sup> As a consequence, the general demand for the facile accessibility of cyclic guanidines is of synthetic interest. However, their respective synthesis can be challenging and usually requires multi-step condensation events from prefabricated amine and diamine precursors.<sup>1–3</sup> On the other hand, their introduction through oxidation processes is a rarely observed approach. The development of tethered guanidines for intramolecular C–H amination represents a noteworthy exception to this end.<sup>5</sup>

We recently reported the first catalysis protocols for intramolecular diamination of unfunctionalised alkenes, which employed ureas and sulfamides as the respective nitrogen sources.<sup>6–8</sup> This previous work employed high oxidation palladium and nickel catalyst states derived from iodosobenzene diacetate as stoichiometric oxidant. Recently, an alternative protocol for cyclisation of urea molecules was elaborated<sup>9</sup> that relies on copper bromide as the terminal oxidant and hence provides a more sustainable method than Ph(OAc)<sub>2</sub>.<sup>10,11</sup> Motivated by these results, we considered the construction of cyclic guanidines by direct catalytic alkene oxidation as an attractive synthetic alternative to successive multiple-step synthesis:



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† Electronic supplementary information (ESI) available: Experimental procedures and characterisation, spectral reproduction for new compounds and crystallographic data in CIF or other electronic format for CCDC 671505 & 677355. See DOI: 10.1039/b719479j

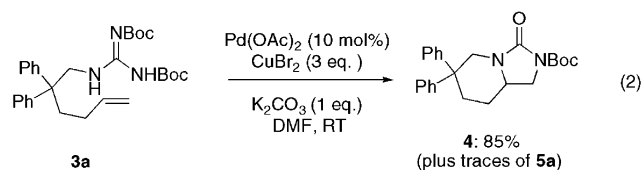
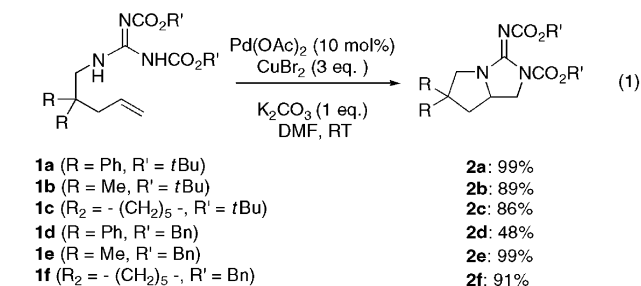
‡ Dedicated to Prof. Dr Irina Beletskaya on the occasion of her 75th birthday.

To this end, either Boc or Cbz substituents<sup>12</sup> in precursors such as **1** were preferred for the major reason that these would provide only a single regioisomer and after oxidation should be easily removed to give free guanidines. An initial attempt to implement the copper bromide oxidation mode<sup>9</sup> into the desired guanidine transfer already met with success. Several substrates underwent formation of the desired cyclic guanidines in moderate to very good yields in the presence of 3 equivalents of CuBr<sub>2</sub> (Scheme 1).

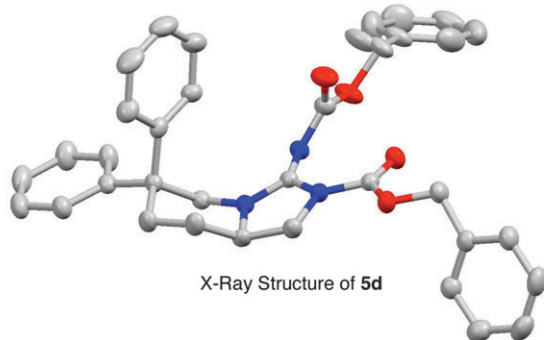
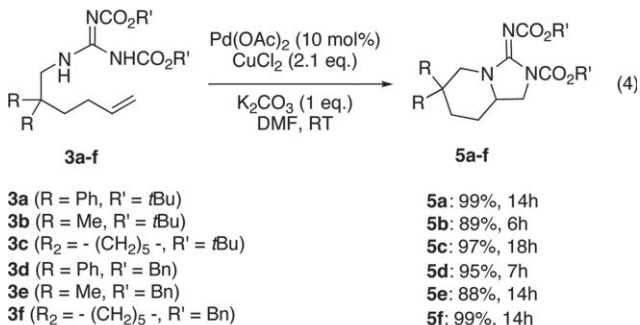
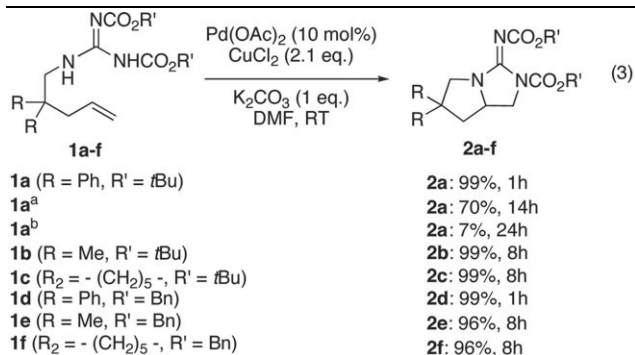
However, it was noted that the reaction time had to be optimized carefully, as prolonged exposure of the cyclic guanidine products **2** to copper bromide salts led to gradual conversion to the respective urea compounds. This undesired reaction was observed as dominant pathway in the cyclisation under concomitant six-membered ring annelation, where the urea **4** was obtained as the major product.

To our delight, a simple change in oxidant to copper chloride generated reaction conditions that led to mild construction of the bicyclic guanidines **2a–f** within a completely chemo- and regioselective 1,2-diamination reaction (Scheme 2). Work-up of the reaction can be carried out by the addition of aqueous thiosulfate solution followed by extraction with dichloromethane. This gives the bicyclic guanidine as sole product in an analytically pure form.

A range of cyclic guanidines bearing either Boc or Cbz protecting groups could be constructed under these conditions, in some cases within reaction times of just one hour. In all cases, DMF as solvent provided the best conditions concerning reaction time and conversion. Both the amount of



**Scheme 1** Diamination of alkenes with copper bromide as reoxidant.



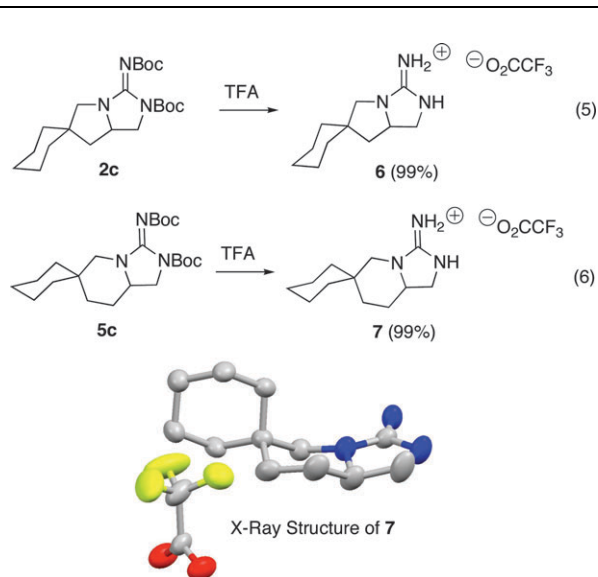
**Scheme 2** Palladium-catalysed guanidine transfer to alkenes: pyrrolidine- and piperidine annelation. <sup>a</sup>5 mol% palladium diacetate. <sup>b</sup>Oxygen (1 atm), 20 mol% CuCl<sub>2</sub>.

palladium acetate (10 mol%) and the copper chloride concentration are important. As determined for substrate **1a**, lowering the palladium catalyst to 5 mol% led to a reaction with still complete chemoselectivity, albeit under incomplete conversion (Scheme 2, footnote a).

In particular, the efficient oxidation to six-membered bicyclic products **5a–f** is without precedence in all currently available alkene diamination protocols.<sup>6,8</sup> The reactions proceed at room temperature, under comparably low catalyst loading and with complete selectivity. The structure of compounds **5a–f** was unambiguously secured from an X-ray analysis of compound **5d**.<sup>†</sup>

Subsequent manipulation of the biscarbamate theme under standard deprotection conditions gives rise to the free guanidines for five- and six-membered annelated compounds **6** and **7** (Scheme 3, eqn (5) and (6)). The latter structure was also established *via* an X-ray analysis of compound **7**.<sup>†</sup>

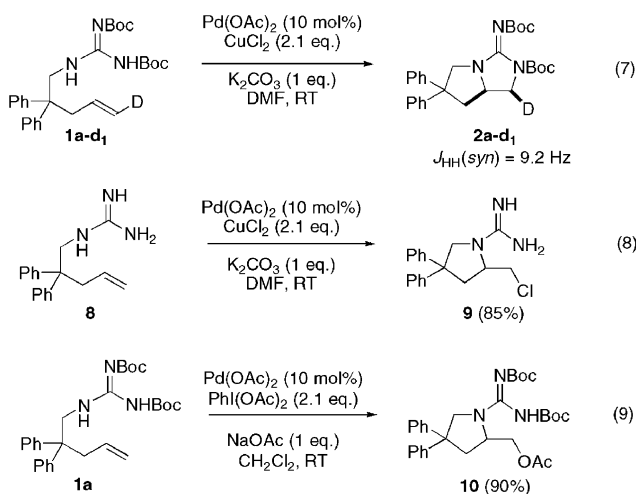
The unprecedented role of copper chloride represents the most important feature from the present work. First, the



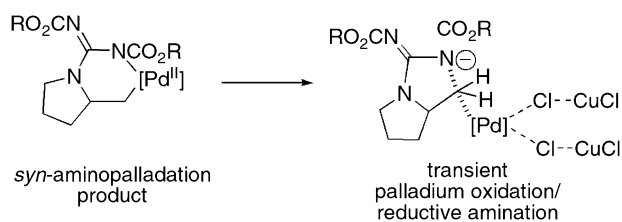
**Scheme 3** Examples for generation of free guanidines **6** and **7** from Boc-disubstituted oxidation products **2c** and **5c**, respectively.

observed beneficial effect of the copper chloride over the copper bromide is noteworthy, especially where reaction time and prevention of guanidine degradation are concerned.<sup>13</sup> Secondly, the complete selectivity in pyrrolidine and piperidine annelation compares favorably to related aminopalladation reactions.<sup>14</sup> While the exact nature of the successful pairing of a palladium(II) catalyst with copper chloride is unknown to date, several additional observations help to gain a broader understanding.

Apparently, copper chloride concentration is of key importance as attempts to run the reaction under aerobic conditions with only 0.2 equivalents of CuCl<sub>2</sub> resulted in significantly reduced rate (Scheme 2, footnote b), and Wacker oxidation under aqueous conditions did not work at all for the present transformation. In agreement with the stereochemical pathways from previous diamination reactions,<sup>6</sup> guanidine formation proceeds with *syn*-diastereoselectivity for oxidation of (*E*)-configured alkenes such as **1a–d**<sub>1</sub> (eqn (7)).



These facts suggest the absence of traditional Pd(0)/Pd(II) catalysis and the direct involvement of copper chloride already



**Fig. 1** Mechanistic key step of Pd oxidation and carbon amination.

in the final amination. We have previously disclosed a *syn*-aminopalladation<sup>15,16</sup> for related urea groups<sup>6</sup> that should be even more pronounced for the present guanidines with their high metal-coordination ability.<sup>3</sup> Such a resulting alkyl palladium(II) intermediate has been suggested to undergo reductive C–N bond formation upon transient palladium oxidation<sup>17</sup> (Fig. 1).

Since the reductive amination proceeds *via* nucleophilic displacement, this step requires an inversion of configuration as noted from eqn (7). This mechanistic proposal is strongly supported by the observation that the carbamate groups are essential for this second amination to proceed, as free guanidine with its less nucleophilic nitrogen atoms leads exclusively to aminochlorination product **9** (eqn (8)). Finally, a stronger oxidant such as  $\text{PhI}(\text{OAc})_2$  induces aminoacetoxylation product **10** (eqn (9))<sup>18</sup> from a discrete Pd(IV) intermediate<sup>19</sup> as previously observed for related sulfamide groups.<sup>8</sup> Hence, only the palladium(II)/copper chloride pairing provides the required balanced conditions that allow palladium oxidation and nucleophilic amination to proceed with complete chemoselectivity for catalytic room-temperature guanidination of alkenes.

In summary, we have accomplished an oxidative guanidine transfer to alkenes with significant operational simplicity that closes a methodological gap in the synthesis of cyclic guanidines. This reaction also represents the first practical synthesis of piperidine-annulation in catalytic diamination reactions. It further enlarges the available oxidative diamination protocols to environmentally benign copper chloride reoxidation conditions with unprecedented selectivity.

This work was supported by the Fonds der Chemischen Industrie and by the Agence Nationale de la Recherche.

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