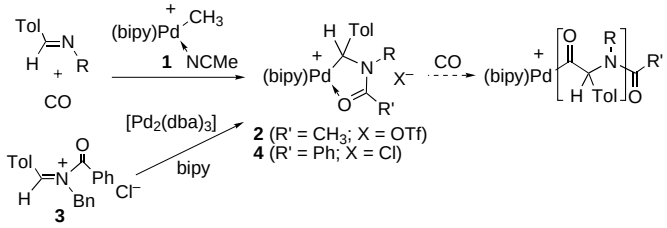
The Use of Carbon Monoxide and Imines as Peptide Derivative Synthons: A Facile Palladium-Catalyzed Synthesis of α-Amino Acid Derived Imidazolines**

Rania D. Dghaym, Rajiv Dhawan, and Bruce A. Arndtsen*

Of the many basic building blocks used in pharmaceutical development, the peptide unit is perhaps the most ubiquitous. In addition to linear polypeptides, this unit is found in a range of biologically relevant heterocyclic compounds.[1] Traditional routes to prepare peptide-containing compounds have focused on the use of presynthesized or isolated α-amino acid derivatives as synthons.[2] However, examination of the peptide structure suggests that it might also be conceived to arise from the coupling of an imine and carbon monoxide, and its synthesis approached by metal-mediated alternating insertion (Scheme 1).[3] Considering the ready availability and

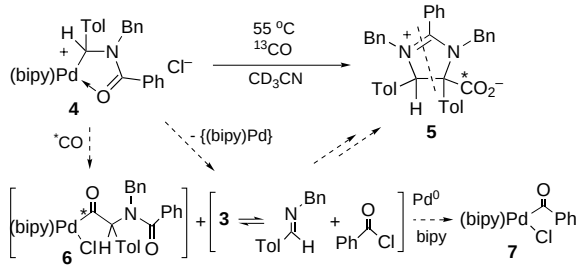


Scheme 1. Palladium-mediated synthesis of peptides. dba = dibenzylidene acetone.

flexibility of imines as substrates, CO and imine coupling would provide an attractive general route to both natural and nonnatural amino acid containing products. We have recently reported that the sequential insertion of CO and an imine can be achieved with $[(bipy)Pd(CH_3)(NCCH_3)]^+OTf^-$ (**1**) (bipy = 2,2′-bipyridine), which demonstrates the feasibility of this process.[3–5] Here we report the development of a novel catalytic method to construct α-amino acid containing heterocycles, by using an imine, CO, and an acid chloride as the sole building blocks.

The addition of Tol(H)C=NR (Tol = p-$C_6H_4CH_3$) and 1 atm CO to complex **1** has been found to lead to the formation of the Pd-chelated amide complex **2**.[3] In order to generate an amino acid derivative from **2**, the further insertion of CO into the Pd–C bond is necessary. However, the attempted reaction of **2** with CO has been unsuccessful, even at elevated temperature and pressure. A plausible rationale for this behavior is that strong chelation of the amide ligand in **2** effectively blocks the coordination site required for CO insertion.[3] To address this issue, we examined the use of the more coordinating halide counteranion, which might weaken amide chelation through coordination, or stabilize the product of CO insertion.[6]

Anion exchange of **2** with NaCl allows the in situ incorporation of the chloride anion into the metallacycle; however, a more facile route to this class of compounds is described in Scheme 1. This involves the oxidative addition of acyliminium salt **3** to $[Pd_2(dba)_3]\cdot CHCl_3$ in the presence of 2,2′-bipyridine to form **4** in 92% yield.[7, 8] In contrast to the behavior of **2**, the reaction of **4** with 1 atm CO in CD_3CN leads to the slow disappearance of starting materials over the course of 5 days at 55 °C. Surprisingly, however, product isolation yields the carboxylate-substituted imidazoline **5** in 35% yield (Scheme 2).



Scheme 2. Formation of the carboxylate-substituted imidazoline **5**.

Carboxylate-substituted imidazolines such as **5** are biologically relevant heterocycles, formally incorporating an α-amino acid residue into the heterocyclic core.[10–12] Thus, the generation of **5** from palladium complex **4** suggests that the imine and CO have been coupled into a peptide unit, followed by subsequent reactions. To determine the origin of **5**, and to optimize its synthesis, the mechanism of the transformation was examined. Performing the reaction of **4** with ^{13}CO leads to the incorporation of ^{13}C label in the carboxylate group (δ = 166.4). This presumably arises from insertion of ^{13}CO into **4** to form the palladium-bound amino acid derivative **6** (Scheme 2). Examination of the structure of **5** suggests that it is formed by the coupling of the amino acid ligand in **6** with the imine. However, no imine was added to the reaction. The source of additional imine was determined by monitoring the reaction by ^1H NMR, which revealed the concurrent formation of [(bipy)Pd(COPh)Cl] (**7**) (40% yield) along with imidazoline **5**. In the light of the synthesis of **4** by the oxidative addition of acyliminium salt **3**, a plausible explanation for the formation of **7** involves the reductive fragmentation of **4** to regenerate **3** and Pd^0.[9] The ^1H NMR of **3** in CD_3CN at 55 °C reveals that it is in rapid equilibrium with PhCOCl and Tol(H)C=NBn. This would both provide a source of free imine, and allow for the formation of **7** by oxidative addition of PhCOCl to Pd^0.

The mechanism described in Scheme 2 shows that palladium complex **4** is in rapid equilibrium with imine and acid chloride under the reaction conditions. This suggests that the synthesis of the imidazoline core might be more easily achieved by starting directly from imine, CO, and acid chloride. Indeed, the one-pot reaction of Tol(H)C=NBn,

[*] Prof. B. A. Arndtsen, R. D. Dghaym, R. Dhawan
Department of Chemistry, McGill University
801 Sherbrooke St. W., Montreal, Quebec H3A 2K6 (Canada)
Fax: (+1) 514-398-3797
E-mail: bruce.arndtsen@mcgill.ca

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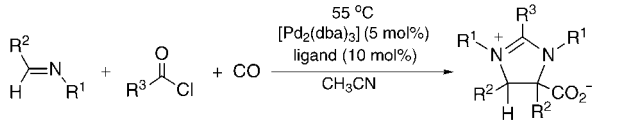
PhCOCl, and 1 atm CO with $[Pd_2(dba)_3]\cdot CHCl_3$ and 2,2′-bipyridine results in the direct coupling of these fragments into imidazoline **5** in 70% yield of isolated product.[7] This reaction occurs with remarkable selectivity, and the four separate units are cleanly combined to form **5** as the only observable reaction product.

One limitation of this imine/acid chloride/CO coupling is that it is stoichiometric in palladium. However, monitoring this reaction by ^{1}H NMR reveals the formation of HCl as well as the imidazoline product. Thus, all fragments of the reagents added to Pd^0 (imine, acid chloride, CO) are liberated after the coupling, which suggests that Pd^0 is regenerated and may be able to mediate further coupling cycles. This does turn out to be the case. The reaction of Tol(H)C=NBn, PhCOCl, and 1 atm CO with 5 mol% $[Pd_2(dba)_3]\cdot CHCl_3$ and 2,2′-bipyridine leads to the clean coupling of these fragments into a single imidazoline product (Table 1). This imidazoline formation proceeds in high yield with a number of imines of

Table 1. Palladium-catalyzed synthesis of imidazolines.[a]

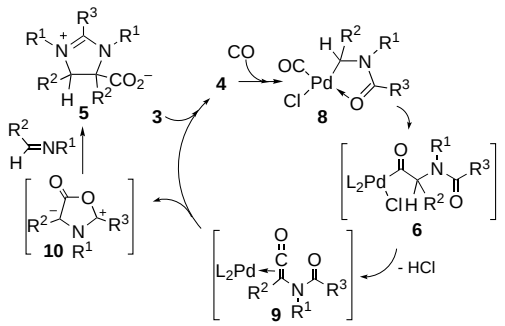


Entry	Ligand	R^1	R^2	R^3	Yield [%][b]
1	bipy	$PhCH_2$	p-$CH_3C_6H_4$	Ph	82
2	bipy	CH_3	p-$CH_3C_6H_4$	Ph	92
3	bipy	$PhCH_2$	p-$CH_3SC_6H_4$	Ph	73
4[c]	bipy	$PhCH_2$	p-ClC_6H_4	Ph	62
5	bipy	$CH_2CH_2OCH_3$	p-$CH_3C_6H_4$	Ph	78
6	bipy	$PhCH_2$	p-$CH_3C_6H_4$	CH_3	70
7	bipy	Ph	p-$CH_3C_6H_4$	Ph	–
8	bipy	$PhCH_2$	p-$NO_2C_6H_4$	CH_3	–
9	pyridine	$PhCH_2$	p-$CH_3C_6H_4$	Ph	87
10	diphos	$PhCH_2$	p-$CH_3C_6H_4$	Ph	–
11[d]	–	$PhCH_2$	p-$CH_3C_6H_4$	Ph	83

[a] 0.57 mmol imine, 0.57 mmol acid chloride, 1 atm CO with 5 mol% $[Pd_2(dba)_3]\cdot CHCl_3$ and 10 mol% ligand for 4 days at 55 °C. [b] Yields of

aromatic aldehydes. Notably, the incorporation of functionality into the imine substrate (entries 3–5) does not retard the reaction. In addition, both aryl and alkyl acid chlorides can be employed (entry 6), as well as bidentate and monodentate nitrogen ligands (entry 9). However, phosphane ligands completely block the formation of imidazolines under these conditions (entry 10), as does the use of less nucleophilic imines (entries 7 and 8). The present methodology represents what is to our knowledge the first catalytic generation of a peptide-containing heterocycle (**5**) from an imine and CO. Considering that these heterocycles are typically prepared by the cyclization of presynthesized 1,2-diamino acids,[13, 14] this four-component coupling provides an exceedingly simple and general method to both construct the α-amino acid unit, and incorporate it directly into the imidazoline core.

While the complete mechanistic details of this process are still under investigation, the above findings are consistent with the process shown in Scheme 3. The insertion of CO into the Pd–C bond of **4** would generate **6**. The role of chloride in



Scheme 3. Proposed mechanism for the formation of **5** involving Münchnone **10**.

allowing CO insertion with **4**, while the triflate salt (**2**) is inert, is postulated to arise from labilization of L_2 rather than dechelation of the amide ligand. Evidence for this is found by monitoring the catalytic reaction by ^{1}H NMR, which reveals the presence of the intermediate **8** in a 1:3 ratio to complex **4**.[15] The generation of **8** implies that the added ligand L_2 may be slowing the catalytic process by hindering the complete formation of this intermediate. Consistent with this hypothesis, the strongly coordinating diphos ligand blocks imidazoline formation. More importantly, the reaction in the absence of any ligand results in greatly accelerated catalysis, with the reaction complete within 24 h (entry 11). Thus, the optimized catalysis conditions by using imine, acid chloride, and CO with $[Pd_2(dba)_3]\cdot CHCl_3$ and no ligand provides a rapid and high yield route to synthesize imidazolines. Following CO insertion, the elimination of HCl would generate metallo–ketene complex **9**. Amido-substituted ketenes have been demonstrated to be in dynamic equilibrium with the mesoionic Münchnone structure **10**.[16a] The latter can undergo a 1,3-dipolar cycloaddition with free imine, followed by C–O bond scission to generate imidazoline **5**.[16, 17] This mechanism suggests, therefore, that the role of palladium in this process is to mediate the catalytic formation of an amino acid based Münchnone intermediate,[18, 19] which is subsequently converted to the observed product with additional imine.[20]

In conclusion, these studies have demonstrated that the palladium-catalyzed coupling of an imine and CO can be utilized for the construction of a peptide unit and its direct incorporation into heterocyclic substrates (i.e. imidazoline **5**). Considering the ready availability of these building blocks and the mild conditions employed (1 atm CO, 55 °C, palladium catalysis), this represents one of the most facile routes to prepare this class of compounds. The diverse reactivity of the putative Münchnone intermediates[16, 19] generated in this process suggests this coupling may prove useful for the synthesis of range of amino acid derived and/or heterocyclic products. The further development of this chemistry towards these synthetic targets and the full elucidation of the reaction mechanism are currently the subject of research in our laboratories.

Experimental Section

All reactions were carried out under an N_2 atmosphere with a Vacuum Atmospheres 553-2 drybox or by standard Schlenk techniques.

Catalytic synthesis of **5**: Imine (0.57 mmol) and acid chloride (0.57 mmol) were combined in 10 mL of CH_3CN and stirred for 15 min. To this solution was added $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol%) in 10 mL of CH_3CN. The reaction mixture was transferred to a 100 mL reaction bomb and left to stir at room temperature for 30 min. 790 Torr of CO was then added to the reaction mixture, and it was allowed to stir at 55 °C for 24 h. The resulting solution was filtered through celite, redissolved in $CHCl_3$, then washed with dilute HCl, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, followed by drying over Na_2SO_4. After filtration, the solvent was removed in vacuo, and the resultant material dissolved in diethyl ether and cooled to −40 °C. The imidazoline **5** was then collected as a white precipitate.

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[20] This process is mechanistically similar to the palladium-catalyzed coupling of aldehydes, amides, and CO into α-amino acids,[4] although the formation of **5** proceeds under mild conditions, and involves the in situ trapping of the amino acid-based intermediate with imine to form imidazoline.

Synthesis of a Trisaccharide Library by Using a Phenylsulfonate Traceless Linker on Synphase Crowns**

Takashi Takahashi,* Hitoshi Inoue, Yuichi Yamamura, and Takayuki Doi

The development of novel linkers and linkage strategies has become essential in solid-phase synthesis for the discovery of new drugs and materials. In recent years, many efficient linkers were developed.[1] Traceless linkers are advantageous in that the original functional group of the linker does not remain in the product.[2] We have reported a phenylsulfonate traceless linker,[3] which acts as a leaving group under nucleophilic-displacement reaction conditions.[4, 5] With this linker a diversity of products can be obtained, because various functional groups can be introduced at the final stage in a solid-phase synthesis. Herein, we report a high-speed synthesis of a functionalized trisaccharide library utilizing the phenylsulfonate linker on Synphase Crowns.[6, 7]

The synthetic strategy is illustrated in Scheme 1. The trisaccharide derivatives **I**, **II**, and **III** which have various functional groups **Z** at the 6 position of their glucose unit could be synthesized from solid support **4**, which consists of a

[*] Prof. Dr. T. Takahashi, H. Inoue, Y. Yamamura, Prof. Dr. T. Doi
Department of Applied Chemistry
Graduate School of Science and Engineering
Tokyo Institute of Technology
2-12-1 Ookayama, Meguro, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-2884
E-mail: ttakashi@o.cc.titech.ac.jp

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