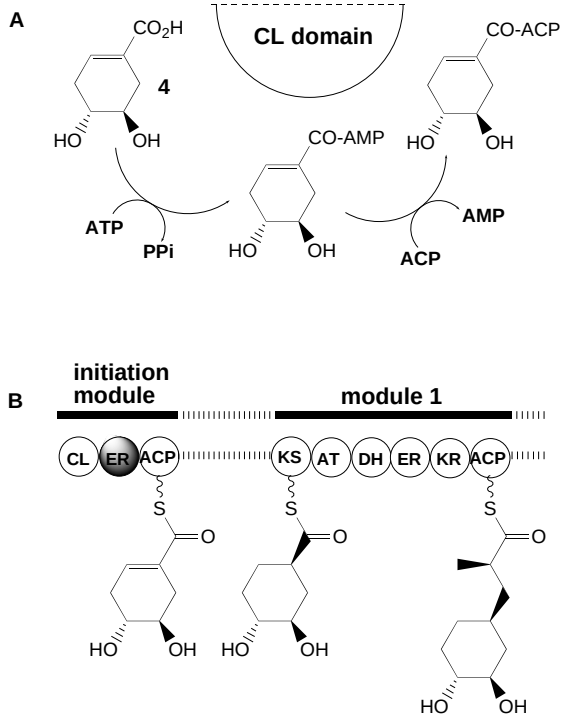
The data in this report, in conjunction with the N-terminal structure of the rapamycin PKS, allow us to identify **4** as the true starter unit for the rapamycin PKS. The differing stereospecificity of the enoyl reductions during the biosynthesis of **1** for FK520, and by extrapolation for rapamycin, is consistent with the use of the initiation module ER domain.[17] The differences in stereochemical detail between the biosynthesis of **1**,[8] and the biosynthesis of CHC[14, 15] suggest that precursors of **4** occur as the free acids.[18] By analogy to non-ribosomal peptide synthesis[19] we suggest (Scheme 3) that the



Scheme 3. A) Proposed pathway for CL-catalyzed activation and subsequent attachment of **4** to the rapamycin PKS; B) translocation of ACP-bound **4** involves reduction of the Δ^1 bond by the initiation module ER domain prior to chain elongation on module one of RAPS1, the N-terminus of which is shown with a linear arrangement of the predicted catalytically active domains. AMP = adenosine monophosphate; Ppi = inorganic phosphate; CL = carboxylic acid ligase; ER = enoyl reductase; ACP = acyl carrier protein; KS = β-ketoacyl synthase; AT = acyl transferase; DH = dehydratase; KR = β-ketoacyl reductase.

CL domain catalyses formation of an AMP-activated form of **4**, which is subsequently transferred to the ACP domain. Reduction by the ER domain is followed by transfer to the KS1 domain of RAPS1 to initiate chain elongation. The observation that **1** can also be directly incorporated points to a broad substrate specificity in the CL domain which may allow for its use for the production of analogues of rapamycin by incorporation of a variety of alicyclic starter acids.

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A Novel Approach for the One-Pot Preparation of α-Amino Amides by Pd-Catalyzed Double Carbohydroamination**

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Developing new synthetic methods for the preparation of amino acids and their derivatives has attracted much attention due to their applications to the fine chemical, agrochemical, and pharmaceutical business sectors.[1] Although a variety of elegant routes has been discovered for the synthesis of amino acids, amidocarbonylation (Wakamatsu reaction) is the only method involving a transition metal complex catalyzed three-component reaction of an aldehyde, an amide, and carbon monoxide.[2] Domino reactions, which include amidocarbony-

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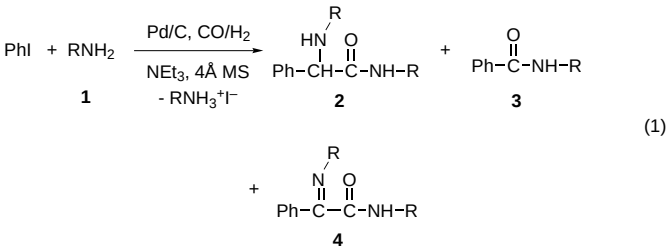
lation, have proven effective for the one-pot synthesis of organic compounds.[3]

The first double carbonylation reaction, for introducing two adjacent CO groups into an organic moiety, was found by using cobalt carbonyl complexes as catalysts in converting benzyl halides to the corresponding arylpyruvic acids.[4] Development of the double carbonylation reaction has been realized, for example, in the conversion of aryl and alkenyl halides to the corresponding α-ketoamides and esters by using palladium complexes as catalysts,[5] and in the synthesis of α-ketolactones from epoxides by phase-transfer Co-catalyzed reactions.[6] It is also known that α-keto acids are precursors of α-amino acids.[7] Research in our laboratory has previously led to useful methods for the hydrogenation of imines, α-ketoesters, and α-ketoamides.[8] We now report a new domino reaction, involving a sequence of double carbonylation, amine condensation, and hydrogenation to produce α-amino amides.

Initial experiments were conducted by using iodobenzene, cyclohexylamine (**1a**), carbon monoxide (800 psi; 1 psi = 6894.76 Pa), hydrogen (100 psi), and Pd on charcoal as the



(1)

catalyst in the presence of triethylamine and 4Å molecular sieves [Eq. (1); **a**: R = cyclohexyl, **b**: R = *n*-butyl, **c**: R = benzyl]. This reaction proceeded well to form α-cyclohexylamino amide (**2a**, R = cyclohexyl) as the major product (87% yield, Table 1, entry 1). To our knowledge, this novel domino reaction, *double carbohydroamination*, is unprecedented and the first example of a one-pot preparation of α-amino amides from the corresponding aryl halides. In addition, it is a rare example of the transition metal catalyzed formation of α-amino acid derivatives, a previous case being Co- and Pd-catalyzed amidocarbonylation.[2] α-Amino amides, like α-amino acids and their derivatives, are of medicinal value.[9]

The structure of the cyclohexylamino amide **2a** was established by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, as well as by elemental analysis.[10] In addition to the formation of **2a**, cyclohexylamide (**3a**) was obtained as a by-product, and traces to small amounts of α-*N*-cyclohexylimino amide (**4a**) and *N*-benzylidenecyclohexylamine were also detected in the reaction mixture. Various reaction conditions were examined and the results are listed in Table 1. Addition of triethylamine is essential for obtaining a higher proportion of **2a** over **3a** (Table 1, entry 2). In the absence of 4Å molecular sieves, some **4a** was formed thus reducing the yield of the amino amide (Table 1, entry 3). Reducing the reaction temperature from 120 °C to 105 °C lowered the conversion of iodobenzene to **2a** (Table 1, entry 4). Increasing the hydrogen pressure from 100 to 400 psi afforded 5% of $PhCH_2NHCy$ (by hydrogenation of the other by-product PhCH=NCy, Table 1, entry 6). In all of the reactions, an ammonium iodide $RNH_3^+I^-$ was formed as a salt.[11]

Primary amines other than cyclohexylamine can also be used for the reaction. *n*-Butylamine (**1b**) gave the corresponding α-amino amide (**2b**) in 67% yield together with 29% of amide **3b** (Table 1, entry 7).[10] Using benzylamine (**1c**) gave **2c** in only 24% yield, **3c** in 34% yield, and several other by-products (Table 1, entry 8).

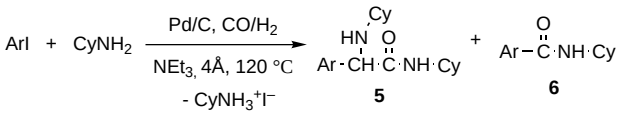
The double carbohydroamination reaction is applicable to various iodoarenes, giving the corresponding α-amino amides **5** usually as the dominant products, together with amide **6** (Table 2).[10] Iodoarenes with electron-donating or electron-withdrawing substituents afforded α-amino amides in 60 to 88% yields (Table 2, entries 1–5). Except for *p*-iodotrifluoromethylbenzene, the amides were formed in low yields.

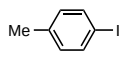
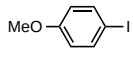
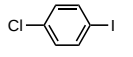
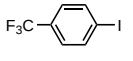
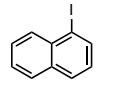
Table 1. Palladium-catalyzed double carbohydroamination of iodobenzene.[a]

Entry	Amine	CO [psi]	H_2 [psi]	*T* [°C]	Products [%][b] 2	3	4
1[c]	**1a**	800	100	120	87	5	0
2[d]	**1a**	800	100	120	59	41	trace
3[c,e]	**1a**	800	100	120	66	18	10
4	**1a**	800	200	105	46	18	18
5[c]	**1a**	700	300	120	77	9	trace
6[f]	**1a**	800	400	120	73	8	0
7	**1b**	700	300	120	67	29	trace
8[g]	**1c**	800	100	120	24	34	5

[a] Reaction conditions: PhI (1 mmol), amine (10 mmol), Et_3N (3 mL), 4 Å MS (1 g), 10% of Pd/C (0.02 mmol), and CO/H_2 were employed in the reactions for 24 h. [b] The yields were determined by ^{1}H NMR spectroscopy. [c] A small amount of PhCH=NCy (less than 5%) was obtained. [d] The reaction was carried out by using **1a** (4 mL) as solvent instead of Et_3N. [e] The reaction was carried out in the absence of 4 Å molecular sieves. [f] PhCH=NCy (5%) and $PhCH_2NHCy$ (5%) were also formed as by-products. [g] $PhCH{=}NHCH_2Ph$ (31%) and a small amount of $(PhCH_2)_2NH$ were produced.

Table 2. Pd-catalyzed double carbohydroamination of aromatic iodides.[a]



Entry	ArI	5	Yield [%][b]	6	Yield [%][b]
1[c]		**5a**	88	**6a**	6
2[c,d]		**5b**	68	**6b**	13
3[c,d]		**5c**	65	**6c**	17
4		**5d**	60	**6d**	40
5[c,d]		**5e**	64	**6e**	18

[a] Reaction conditions: Iodide (1 mmol), cyclohexylamine (10 mmol), NEt_3 (3 mL), 4Å molecular sieves (1 g), 10% of Pd/C (0.02 mmol), CO (800 psi), and H_2 (100 psi) were employed at 120 °C for 24 h. [b] Yields were determined based on ^{1}H NMR spctroscopy. [c] Trace amounts of ArCH=NCy were detected. [d] A small amount of α-imino amide (less than 3%) was detected in the mixture.

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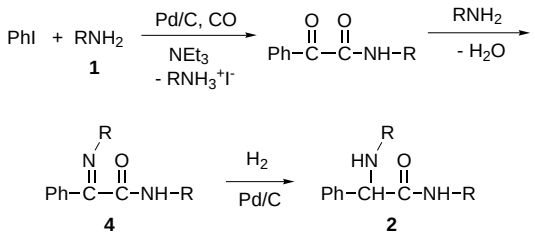
A possible pathway for the formation of α-amino amides (Scheme 1) may involve the following sequence: double carbonylation of the iodoarene to give the α-keto amide,



Scheme 1. Reaction pathway for the double carbohyroamination of iodobenzene. **a**: R = cyclohexyl, **b**: R = *n*-butyl, **c**: R = benzyl.

amine condensation with the α-keto group of the latter to form an α-imino amide **4** as an intermediate, and hydrogenation of the imino double bond of **4** to give the α-amino amide **2**. α-Keto amide formation in the double carbonylation process can be considered to be related to that described by Yamamoto and co-workers, via formation of an acylcarbamoylpalladium intermediate followed by reductive elimination.[12] Palladium-catalyzed double carbonylation of aryl halides in the presence of a secondary amine to give α-keto amides has been extensively studied.[13] Using a primary instead of a secondary amine in the double carbonylation reaction has only been described in several papers.[5b, 12] However, the double carbohydroamination reaction sequence, described herein can, for the first time, produce α-amino amides in a one-pot manner. The formation of the amide by-product results by monocarbonylation of iodobenzene. The formation of the by-product imine can be attributed to competitive reactions of hydroformylation of iodobenzene with subsequent amine condensation.

In conclusion, palladium-catalyzed double carbohydroamination, consisting of double carbonylation, amine condensation, and hydrogenation, is a novel domino reaction for the one-pot production of α-amino amides. The reaction is simple in execution and workup, and is of considerable potential for the synthesis of α-amino amides and other α-amino acid derivatives.

Experimental Section

General procedure for the double carbohydroamination: A mixture of iodobenzene (0.112 mL, 1 mmol), cyclohexylamine (1.14 mL, 10 mmol), triethylamine (3 mL), Pd/C (10%, 0.0213 g, 0.02 mmol), and 4Å molecular sieves (1 g) was placed in a 45-mL stainless steel autoclave equipped with a glass liner and magnetic stirrer. The autoclave was purged three times with carbon monoxide and then pressurized with CO and H_2, respectively, to the desired level (see Tables 1 and 2). The reaction was carried out in an oil bath for 24 h and the autoclave was cooled to room temperature and the gas was released. The reaction mixture was filtered through Celite, washed several times with CH_2Cl_2, and filtrate was evaporated to give a pale yellow oily residue. Addition of ether gave a white precipitate, identified as $CyNH_3^+I^-$. After filtration, the diethyl ether solution was evaporated and the resulting oil was subjected to ^1H NMR spectroscopy, and then to preparative TLC, using hexane/ethyl acetate as eluant, affording the pure α-amino amide.[10]

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[10] For details on ^1H and ^{13}C NMR spectroscopy, mass spectrometry, IR spectroscopy, and elemental analysis of α-amino amides **2** and **5**, see Supporting Information.

[11] It is noteworthy that using a catalyst other than Pd/C, such as the palladium(0) complex $[Pd(PPh_3)_4]$ or palladium(II) complex $[PdCl_2(MeCN)_2]$, together with Ph_2MeP, gave rise to the formation of **4a** and oxamide CyNHCOCONHCy as major products, respectively.

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A Neutral Three-Coordinate Alkylrhodium(I) Complex: Stabilization of a 14-Electron Species by γ-C–H Agostic Interactions with a Saturated Hydrocarbon Group**

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Selective activation and functionalization of alkanes by transition metals is a highly attractive goal[1] which has led to considerable efforts to understand hydrocarbon interactions

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