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Synthesis of Diamino Carboxylic Esters by Palladium-Catalyzed Oxidative Intramolecular Diamination of Acrylates

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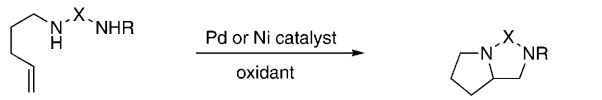
Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: Unligated palladium(II) salts catalyze the oxidative diamination of acrylic esters to yield 2,3-diamino carboxylic esters. The reaction employs copper(II) bromide as oxidant and proceeds with good to excellent stereoselectivities and complete chemoselectivity. Preliminary mechanistic studies provide evidence for the involvement of a direct amination of the C–Pd bond in the α position relative to the ester group. This protocol significantly broadens the overall scope of the palladium-catalyzed diamination of alkenes and represents the first direct diamination of functionalized nonterminal substrates. The reaction yields readily protected 2,3-diamino acid derivatives, which can be considered as highly functionalized building blocks for subsequent synthesis. The use of one of these new diamination products as a suitable starting material in a short synthesis of the alkaloid absouline is demonstrated as an example.

Keywords: acrylates · diamines · natural products · oxidation · palladium

Introduction

We recently developed first catalysis protocols for the intramolecular diamination of unfunctionalized alkenes (Scheme 1). By employing tethered nitrogen sources such as



ureas: X = CO, R = Tos
sulfamides: X = SO_2, R = carbamoyl
guanidines: X = CNR, R = carbamoyl

cyclic ureas, sulfamides, and guanidines

Scheme 1. Transition-metal-catalyzed intramolecular diamination.

ureas, sulfamides, or guanidines, these approaches convert terminal alkenes into the corresponding diamine-based heterocycles.[1–3] Reactions of this type employ iodosobenzene diacetate as oxidant and proceed through high-oxidation catalyst states such as palladium(IV).[1b] Reaction conditions involving such a catalyst state also exercise control over the amidation of benzylic positions in diamination reactions that generate new heterocycles.[2]

The recent observation that copper salts can be employed as reoxidants in diamination reactions that rely on ureas and guanidine substrates, has allowed for the development of complementary protocols.[4–6] These reactions can also be expanded to nonterminal alkene substrates.[4a]

To provide diamination products for further derivatization, the incorporation and toleration of functional groups is clearly warranted. We decided to address this issue in combination with the development of a direct diamination of internal alkenes, and to this end our attention was turned to acrylic derivatives. These compounds constitute an attractive opportunity to provide 2,3-diamino carbonyl products[7] and, in a broader sense, 1,2,3-trisubstituted building blocks. Unsaturated esters represent privileged substrates for diamination with imidoosmium(VIII) reagents[8] and dichlorosulfonamides;[9] however, a selective homogeneous catalysis protocol would be of value.

Results and Discussion

To realize the catalytic diamination of acrylates under intramolecular-reaction control, the previously described alkene

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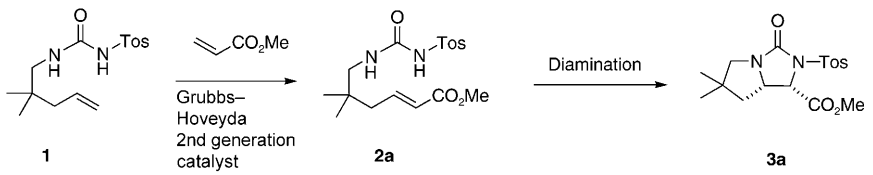


Scheme 2. Synthetic approach to diamino carboxylic ester **3a** by palladium-catalyzed diamination. Tos = 4-toluenesulfonyl.

1 was subjected to cross-metathesis in the presence of an excess of methyl acrylate (Scheme 2).[10,11] This reaction yielded exclusively the *E*-configured acrylate **2a**, which was employed as substrate in an exploratory series of reactions to establish the optimum diamination conditions for its conversion into the corresponding product **3a** (Table 1). Initial studies revealed that a combination of palladium acetate and iodosobenzene diacetate[1,2] is not useful for the present case (Table 1, entries 1 and 2). Instead, introduction of copper bromide as reoxidant realized the desired palladium catalysis (Table 1, entry 3). Upon optimization of solvent, temperature, and base (Table 1, entries 4–12), it was possible to identify a combination that leads to complete conversion and excellent selectivity (Table 1, entry 13). Under such conditions, the palladium source could be extended to palladium chloride or even a palladium(0) source (Table 1, entries 18 and 19).[12] Copper chloride as reoxidant was inefficient (Table 1, entry 14), and

Abstract in German: Ligandenfreie Palladium(II)salze katalysieren die oxidative Diaminierung von Acrylsäureestern zu 2,3-Diaminocarbonsäureestern. Die Reaktion verwendet Kupfer(II)bromid als Oxidationsmittel und verläuft mit guten bis ausgezeichneten Stereoselektivitäten sowie kompletter Chemoselektivität. Vorläufige mechanistische Studien stützen einen Verlauf über eine direkte Aminierung der C–Pd-Bindung eines α-palladierten Esterintermediats. Das vorliegende Verfahren erweitert die synthetische Bandbreite der palladium-katalysierten Diaminierung von Alkenen und stellt die erste direkte Diaminierung von funktionalisierten, nichtterminalen Alkenen dar. Die Reaktion liefert direkt geschützte 2,3-Diaminocarbonsäurederivate als Produkte, die als hochfunktionalisierte Bausteine für nachfolgende Synthesen eingestuft werden können. In diesem Zusammenhang wird der Einsatz eines dieser neuen Diaminierungsprodukte als geeignete Ausgangsverbindung in einer kurzen Synthese des Alkaloids Absoulin gezeigt.

Abstract in Spanish: Sales de paladio (II) sin ligandos catalizan la reacción de diaminación oxidante de ésteres acrílicos para dar los correspondientes 2,3-diamino derivados. La reacción emplea bromuro de cobre (II) como reoxidante y transcurre con excelente estereoselectividad y completa químioselectividad. Estudios preliminarios del mecanismo de reacción muestran una aminación directa del enlace C–Pd en posición alfa al grupo éster. Con este tipo de protocolo se aumenta significativamente el rango de aplicación de la reacción de diaminación de alquenos catalizada por paladio y representa la primera diaminación directa de subtratos funcionalizados no-terminales. Mediante ésta reacción se obtienen derivados de 2,3-diaminoácidos, los cuales pueden ser considerados como moléculas de partida altamente funcionalizadas para una posterior aplicación en síntesis. Bajo este contexto, uno de estos nuevos productos de diaminación se utilizó como sustrato de partida en una síntesis del alcaloide absulina demostrando la viabilidad de este proceso.

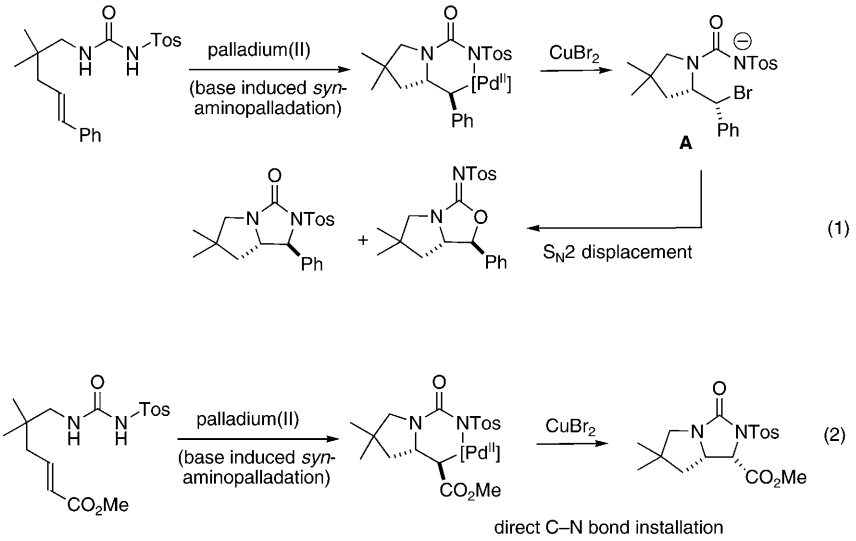
Table 1. Optimization of reaction conditions for catalytic conversion of **2a** into diamine **3a**.

Entry	Palladium source[a]	Oxidant	Reaction conditions[b]	Conv. [%]	Yield [%]
1	$Pd(OAc)_2$	$PhI(OAc)_2$[c]	Me_4NOAc, CH_2Cl_2, RT	< 10	–
2	$Pd(OAc)_2$	$PhI(OAc)_2$[c]	Me_4NOAc, DMF, RT	< 10	–
3	$Pd(OAc)_2$	$CuBr_2$[d]	K_2CO_3, DMF, RT	76	52
4	$Pd(OAc)_2$	$CuBr_2$[d]	$NaHCO_3$, DMF, RT	31	< 10
5	$Pd(OAc)_2$	$CuBr_2$[d]	NaOAc, DMF, RT	25	< 10
6	$Pd(OAc)_2$	$CuBr_2$[d]	K_2CO_3, dioxane, RT	< 10	–
7	$Pd(OAc)_2$	$CuBr_2$[d]	K_2CO_3, THF, RT	< 10	–
8	$Pd(OAc)_2$	$CuBr_2$[d]	Na_3PO_4, DMF, RT	82	54
9	$Pd(OAc)_2$	$CuBr_2$[d]	K_2CO_3, DMF, 40 °C	88	58
10	$Pd(OAc)_2$	$CuBr_2$[d]	Na_3PO_4, DMF, 40 °C	90	80
11	$Pd(OAc)_2$	$CuBr_2$[d]	K_2CO_3, DMF, 70 °C	100	14
12	$Pd(OAc)_2$	$CuBr_2$[d]	Na_3PO_4, DMF, 70 °C	100	< 10
13	$Pd(OAc)_2$	$CuBr_2$[d]	Na_3PO_4, DMF, 50 °C	100	72
14	$Pd(OAc)_2$	$CuCl_2$[d]	Na_3PO_4, DMF, 40 °C	< 10	–
15	$Pd(OAc)_2$[e]	–	Na_3PO_4, DMF, 40 °C	0	–
16	–	$CuBr_2$[d]	Na_3PO_4, DMF, 40 °C	0	–
17	$Pd(OAc)_2$	$CuBr_2$[d]	no base, DMF, 40 °C	0	–
18	$[Pd(NCCH_3)_2Cl_2]$	$CuBr_2$[d]	Na_3PO_4, DMF, 40 °C	100	83
19	$[Pd_2(dba)_3]$	$CuBr_2$[d]	Na_3PO_4, DMF, 40 °C	100	84
20[f]	$Pd(OAc)_2$	$CuBr_2$[d]	Na_3PO_4, DMF, 40 °C	100	86

[a] 10 mol %. [b] Base: 2 equivalents, 0.05 M. [c] 2 equivalents oxidant. [d] 3 equivalents oxidant. [e] Stoichiometric amount of palladium acetate. [f] Base: 2 equivalents, 0.1 M. dba = dibenzylideneacetone, DMF = *N*,*N*-dimethylformamide.

no reaction took place upon removal of palladium salt, copper bromide reoxidant, or base (Table 1, entries 15–17).

For compound **3a**, the observed ^{1}H NMR coupling constant of 10.0 Hz between the two hydrogen atoms of the former double bond indicates *syn* positioning (Figure 1). Solid-state crystal structure analysis of **3a** confirmed the assumed constitution.[13] This stereochemical outcome is reminiscent of that from deuterium-labeled terminal alkenes in the diamination of terminal alkenes,[1] but opposite to that from related reactions with terminal phenyl and alkyl substitution at the alkene.[4a]



Scheme 3. Comparison of mechanisms for nonterminal alkenes: phenyl versus ester substitution.

In view of the previously established *syn* aminopalladation as the initial aminopalladation event,[1,14,15] particular interest was derived from the exact conditions for reductive elimination of the C–N bond from the presumed intermediary amidato–palladium complex. Clearly, the observed overall *syn* stereochemistry differs from the *anti* configuration of diamination products from related phenyl-substituted alkenes (Scheme 3). For the latter, involvement of a brominated intermediate **A** was identified to be responsible for the overall stereochemical course (Scheme 3, Eq. (1)).[4a,16] For the present case, such a brominated intermediate can be excluded, as the product configuration is inconsistent with two *anti*-substitution processes at the α-carbon atom of the ester. Instead, the observed product stereochemistry provides evidence that the second C–N bond is indeed the result of a direct amidation upon metal displacement (Scheme 3, Eq. (2)). Such a process had been targeted earlier, albeit without success.[17]

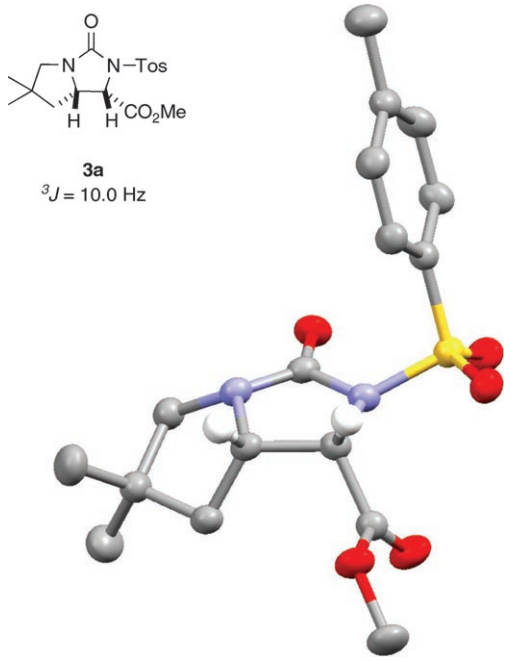


Figure 1. Chemical structure and crystal structure of **3a** displaying the *cis* configuration of the hydrogen atoms at the imidazolidinone.

As a consequence, the observed diamination of acrylates represents the apparently first direct diamination of internal, functionalized alkenes under the conditions of palladium catalysis with copper(II) reoxidants. Furthermore, this direct diamination suppresses the potential competition between the urea oxygen atom and the tosylamide for the final functionalization of the second carbon atom. Whereas phenyl-substituted alkenes give a mixture of two isomers (Scheme 3, Eq. (1)), the present reaction of acrylates benefits from complete chemoselectivity in favor of diamination.

Scheme 4 shows a suggested catalytic cycle that accounts for the correct product configuration. In agreement with our earlier observation on ureas,[1] the diamination of acrylates requires the presence of a base (Table 1, entry 17), which leads to deprotonation of the tosylamide NH group.[1b] Coordination of palladium induces a state **B** for *syn* aminopalladation to intermediate **C**, as disclosed previously for a variety of conditions, including the presence of copper(II) oxidants. This step is truly palladium-catalyzed[18] and not an aza-Michael reaction as no reaction takes place in the absence of palladium (Table 1, entry 16). Palladium-catalyzed aza-Michael additions are known,[19] but they proceed through catalyst-based carbonyl activation, not through aminopalladation.

The resulting α-palladated ester **C** can undergo stabilization through the mesomeric oxallylic form **C′**.[20,21] A subsequent amide dissociation from palladium followed by C–C bond rotation leads to intermediate **D**, which can again benefit from an oxallylic mesomer **D′**. Transient oxidation by

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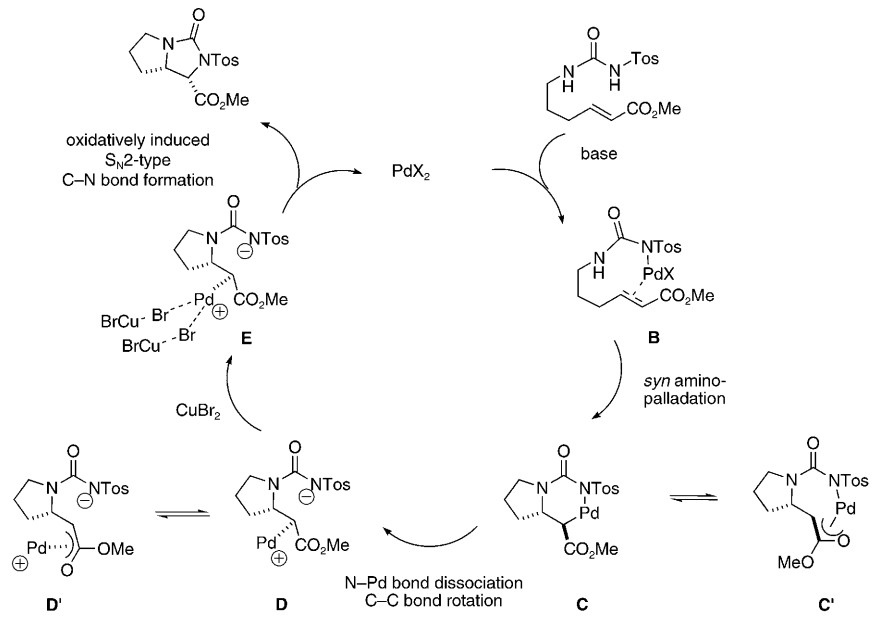


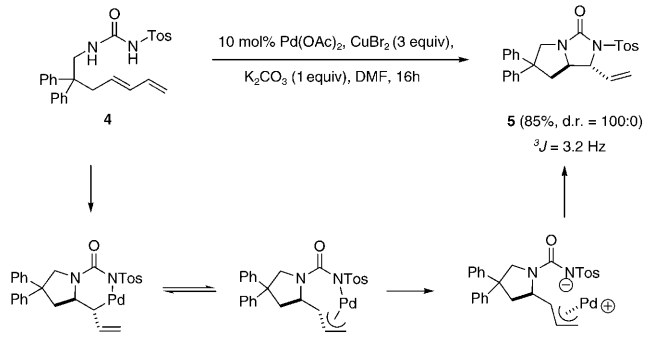
Scheme 4. Mechanistic proposal for palladium-catalyzed intramolecular diamination of acrylates. X = Br, OAc.

copper(II) bromide[22] enhances the electrophilicity of the α-carbon atom in intermediate **E**, and an S_N2-type C–N bond formation accounts for product formation with correct stereochemistry as well as concomitant regeneration of the palladium(II) catalyst.

Importantly, the potential involvement of the postulated η^3-oxallyl intermediates **C′** and **D′** does not allow for direct reductive C–N bond installment through reductive elimination at the palladium oxidation state of +2 as the reaction does not proceed in the presence of stoichiometric amounts of palladium acetate alone (Table 1, entry 15); rather, the presence of oxidant is required. This is in marked contrast to the related diamination of 1,3-butadienes, in which the second C–N bond is installed within an allylic substitution. These reactions were recently elaborated by Lloyd-Jones and Booker-Milburn[23] and, to a remarkable extent, by Shi and co-workers.[24] An intramolecular diamination of this type was investigated for compound **4**, which was converted into diamine **5** in a chemo- and stereoselective fashion (Scheme 5). In notable contrast to the case of **3a**, this compound displayed *anti* positioning of the two hydrogen atoms of the former double bond, as deduced from ^{1}H NMR spectroscopic data and X-ray analysis[13] (Figure 2).

This stereochemical observation of the diamination of **4** is in complete agreement with the results from Shi and coworkers on the comparable intermolecular diamination of butadienes.[24] It characterizes the overall reaction as a sequence of *syn* aminopalladation, formation of an allylic intermediate, and subsequent intramolecular allylic amidation.[25,26] In marked contrast to the diamination of acrylates and an oxallylic intermediate, the allylic palladium complex allows for reductive C–N bond formation at a palladium oxidation state of +2 and hence proceeds readily within the classical Pd^0/Pd^{II} cycle. As expected, the reaction between palladium acetate and **4** gave diastereomerically pure **5** in 87% yield, and replacement of copper bromide by benzoquinone allowed for a catalytic reaction with a similar outcome to the catalysis from Scheme 5.

Under the optimized reaction conditions for the intramolecular diamination of acrylates (Table 1, entry 20), the reaction is of general scope, and various substrates **2** were cleanly converted into the corresponding diamino esters **3**. Table 2 shows several representative examples that address the major characteristics of this new diamination reaction.



Scheme 5. Palladium-catalyzed diamination of butadiene **4**.

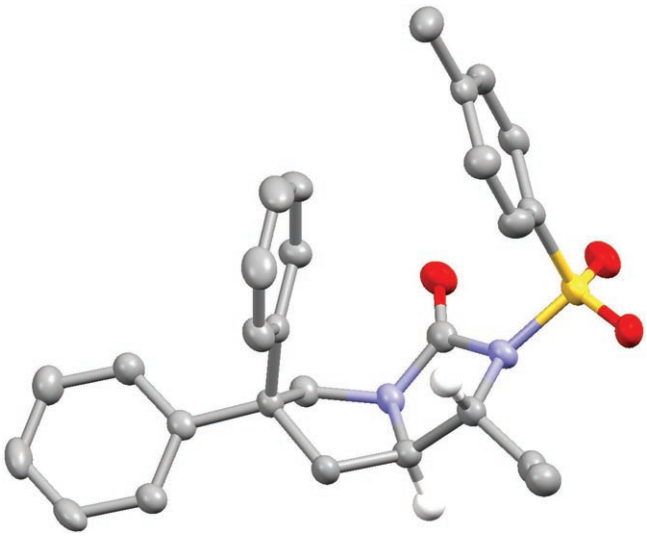
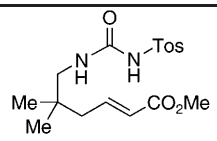
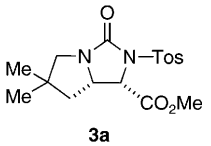
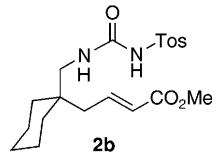
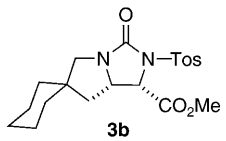
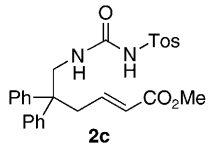
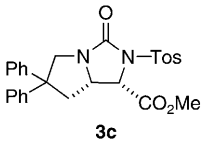
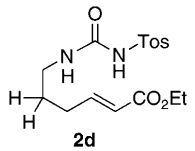
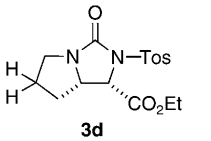
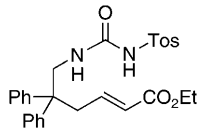
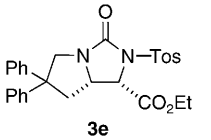
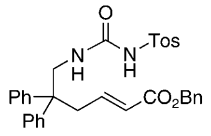
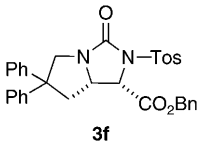
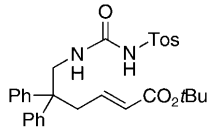
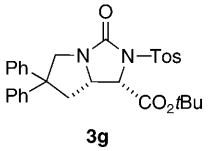
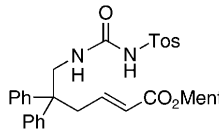
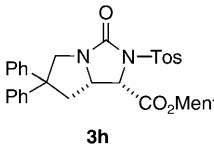


Figure 2. Crystal structure of **5** displaying the *trans* configuration of the hydrogen atoms at the imidazolidinone.

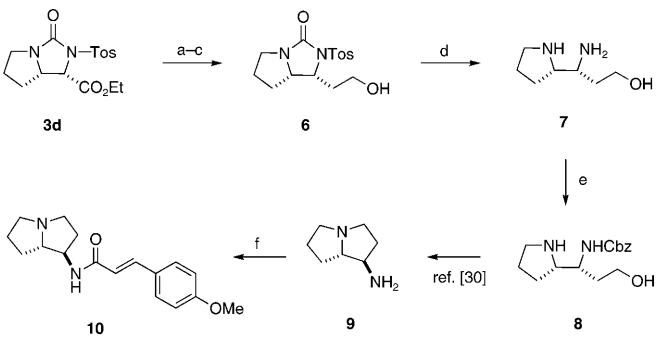
Table 2. Palladium-catalyzed intramolecular diamination of acrylates **2** to diamines **3**.[a]

Entry	Starting material	Product	d.r.[b]	Yield [%][c]
1	 **2a**	 **3a**	>15:1	86
2	 **2b**	 **3b**	>15:1	94
3	 **2c**	 **3c**	>15:1	92
4	 **2d**	 **3d**	1.3:1	56 (92)[d]
5	 **2e**	 **3e**	>15:1	91
6	 **2f**	 **3f**	3:1	81
7	 **2g**	 **3g**	3:1	88
8	 **2h**	 **3h**	12:6:3:2[e]	95

[a] General conditions: **2** (0.25 mmol), DMF (2.5 mL), $Pd(OAc)_2$ (0.025 mmol), Na_3PO_4 (0.5 mmol), $CuBr_2$ (0.75 mmol), 40 °C, 15 h. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture after reductive workup. [c] Yield of isolated product. [d] Yield after 24 h, yield after 60 h in parentheses. [e] Ratio of stereoisomers. Bn = benzyl, Ment* = (−)-menthyl.

First, a series of methyl esters were investigated, which differ in the respective backbone substitution (Table 2, entries 1–3). All reactions proceeded with high diastereoselectivity (d.r. > 15:1) and complete chemoselectivity. The observation that the nonsubstituted derivative **2d** underwent diamination at a significantly lower rate (Table 2, entry 4) was unexpected. Diamination reactions with the corresponding terminal alkenes had revealed no influence of backbone substitution.[1] The present outcome suggests that a Thorpe–Ingold effect may be present in the diamination of acrylates. For example, a competition experiment between **2d** and **2e** showed a factor of 16 in relative rate in favor of the latter diamination reaction. Furthermore, the diastereoselectivity diminished significantly, but, gratifyingly, the depicted *syn* diastereomer **3d** was easily crystallized out of the reaction mixture from ethanol. Second, a change in ester group revealed that the diastereoselectivity of the reaction depends on the size of the ester group. Whereas simple alkyl groups such as methyl and ethyl gave rise to very high diastereoselectivities (Table 2, entries 3 and 5), more-bulky groups such as benzyl and *tert*-butyl led to diminished diastereoselectivity (Table 2, entries 6 and 7). This may be the result of hindered rotation in the final C–N bond formation, thus leading to the involvement of alternative pathways with opposite stereochemistry. Substrate **2h**, which bears a menthyl substituent, gave an inseparable mixture of four possible stereoisomers in a 12:6:3:2 ratio. In agreement with the observation in Table 2, entries 6 and 7, the two major compounds are the *syn*-configured stereoisomers, which were identified by the ^1H NMR coupling constants for the hydrogen atom next to the ester group (10.0 and 9.9 Hz, respectively), whereas the minor compounds are the *anti*-configured isomers, as shown by the respective coupling constants of 4.1 and 3.8 Hz.

This new diamination protocol broadens the scope of alkene diamination to polarized alkenes. The products from this intramolecular diamination represent protected 2,3-diamino acid derivatives.[7,27] This motif should allow for further application in synthesis through appropriate modification of the urea group and the carboxylic ester. To demonstrate the versatility of the new diamination with its concomitant installment of a pyrrolidine group, one of the reaction products was converted into the natural alkaloid absouline[28,29] within a short series of steps (Scheme 6). Product



Scheme 6. Synthesis of absouline (**10**) with diamination product **3d** as starting material. Reagents and conditions: a) NaOMe, MeOH, H_2O, 2 h; b) Arndt–Eistert reaction;[31] c) BH_3–SMe_2, THF, 16 h (71% from **3d**); d) EtOMg, EtOH, 65 °C, 12 h, then TFA, CH_2Cl_2, 2 h (77% from **6**); e) CbzCl, CH_2Cl_2, NEt_3, room temperature, 12 h (88%); f) 4-methoxycinnamic acid, DCC, DMAP, CH_2Cl_2, room temperature (93%). Cbz = benzyloxycarbonyl, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid.

3d was hydrolyzed to the free acid and directly subjected to Arndt–Eistert homologation followed by borane reduction to give alcohol **6**. Treatment with magnesium ethanolate to remove the tosyl substituent followed by cleavage of the urea under acid conditions gave the free diamino alcohol **7**, which was isolated as its bistrifluoroacetic acid salt. Cbz protection of **7** proceeded selectively at the primary amine to yield compound **8**, which is a known precursor of **9**.[30] Finally, conversion of **9** into (±)-absouline (**10**) was accomplished by standard amide formation.[29]

Conclusions

In summary, we have developed a new palladium-catalyzed diamination that converts acrylic esters into the corresponding 2,3-diamino carboxylates. The reaction proceeds under mild conditions with high stereoselectivity and chemoselectivity in favor of the *syn*-configured 2,3-diamino esters and broadens the oxidative diamination reactions to polarized alkenes. The versatility of these compounds as interesting potential building blocks in organic synthesis was demonstrated by using one of them in a short synthesis of the alkaloid absouline.

Experimental Section

General

All organic reagents were purchased from Acros unless otherwise noted. $Pd(OAc)_2$ was purchased from Acros. Dichloromethane was dried over $CaCl_2$ and distilled from CaH_2. THF and Et_2O were distilled from Na/benzophenone. DMF was purchased from Fischer Chemicals and stored over 4-Å molecular sieves. Column chromatography was performed with silica gel (Merck, type 60, 0.063–0.2 mm). Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm E. Merck silica-gel plates (60F-254) with UV light as visualizing agent and 10% ethanolic phosphomolybdic acid or ninhydrin solution and heat as developing agents. NMR spectra were recorded on Bruker Avance 400 MHz, Bruker DPX 300 MHz, and Bruker DRX 500 MHz spectrometers. All NMR chemical shifts are reported in ppm downfield from tetramethylsilane (TMS). The following calibrations were used: $CDCl_3$: $\delta = 7.26$ and 77.00 ppm. LCMS (ESI) experiments were performed by using an Agilent 1100 HPLC chromatograph with a Bruker micro-TOF instrument (ESI). Unless otherwise stated, a Supelco C8 (5 cm × 4.6 mm, 5-μm particles) column was used with an linear elution gradient from 100% H_2O (0.5% HCO_2H) to 100% MeCN in 13 min at a flow rate of 0.5 mL min^{-1}. MS (EI) and HRMS experiments were performed on a Kratos MS 50 spectrometer within the service centers at the Kekulé Department, Bonn University and on a Bruker Daltonik Autoflex II TOF/TOF spectrometer. Infrared spectra were recorded on a Thermo Scientific Nicolet 6700 FTIR spectrometer (smart orbit Diamond).

Syntheses

General procedure for diamination of acrylates: A flame-dried Schlenk tube was charged with the starting material urea (0.25 mmol), $Pd(OAc)_2$ (10 mol%, 5.6 mg), base (2 equiv, 0.5 mmol), and $CuBr_2$ (3 equiv, 168 mg). Dry DMF (0.1 M, 2.5 mL) was added under inert gas, and the mixture was stirred for 15 h at 40 °C. The reaction was allowed to cool to room temperature before addition of saturated aqueous $Na_2S_2O_3$ (2 mL) and further stirring for 30 min. Brine was added (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried over $MgSO_4$, concentrated, analyzed by ^{1}H NMR spectroscopy, and purified by flash chromatography. Yields are as given in Table 2.

3a: *syn*-Methyl hexahydro-6,6-dimethyl-3-oxo-2-tosyl-1*H*-pyrrolo[1,2-*e*]-imidazole-1-carboxylate: Synthesized according to the general procedure. Crystallization from methanol gave a diastereomerically pure fraction as a white solid. IR (diamond): $\tilde{\nu} = 3027, 2958, 1739, 1598, 1447, 1358, 1272, 1167, 1092, 906$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.08$ (s, 3H), 1.12 (s, 3H), 1.26 (dd, $J = 10.2, 12.2$ Hz, 1H), 1.69 (dd, $J = 6.1, 12.2$ Hz, 1H), 2.46 (s, 3H), 2.87 (d, $J = 11.0$ Hz, 1H), 3.14 (d, $J = 11.0$ Hz, 1H), 3.81 (s, 3H), 4.44 (ddd, $J = 6.1, 10.0, 10.2$ Hz, 1H), 5.15 (d, $J = 10.0$ Hz, 1H),7.42 (d, $J = 8.3$ Hz, 2H), 7.95 ppm (d, $J = 8.3$ Hz, 2H); ^{1}H NMR (400 MHz, MeOD, 25 °C, TMS): $\delta = 1.08$ (s, 3H), 1.09 (s, 3H), 1.26 (t, $J = 10.5, 11.7$ Hz, 1H), 1.57 (dd, $J = 5.8, 11.7$ Hz, 1H), 2.43 (s, 3H), 2.86 (d, $J = 11.0$ Hz, 1H), 3.20 (d, $J = 11.0$ Hz, 1H), 3.79 (s, 3H), 4.29 (dd, $J = 5.8, 9.9, 10.5$ Hz, 1H), 5.02 (d, $J = 9.9$ Hz, 1H), 7.32 (d, $J = 8.3$ Hz, 2H), 7.99 ppm (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, MeOD, 25 °C): $\delta = 21.6, 27.5, 28.1, 41.8, 43.0, 54.0, 57.9, 59.0, 59.7, 129.7, 130.5, 137.0, 146.6, 156.9, 170.0$ ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 21.7, 27.7, 27.8, 40.7, 42.2, 52.6, 56.5, 57.9, 58.1, 128.9, 129.3, 135.6, 144.9, 155.1, 168.3$ ppm; MS: m/z (%) = 366 (4), 351 (2), 307 (53), 243 (82), 211 (100), 155 (28), 91 (47); HRMS: m/z calcd for $C_{16}H_{19}N_2O_5S$: 351.1015 $[M-CH_3]^+$; found: 351.1013.

3b: *syn*-Methyl spirocyclohexan-1′,6-hexahydro-3-oxo-2-tosyl-1*H*-pyrrolo-[1,2-*e*]imidazole-1-carboxylate: Synthesized according to the general procedure. IR (diamond): $\tilde{\nu} = 3025, 2957, 1739, 1598, 1448, 1359, 1271, 1167, 1091, 907, 815, 752$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.20–1.51 (m, 9H), 1.70 (dd, $J = 5.9, 12.3$ Hz, 1H), 2.42 (s, 3H), 2.94 (d, $J = 11.4$ Hz, 1H), 3.24 (d, $J = 11.4$ Hz, 1H), 3.80 (s, 3H), 4.22 (ddd, $J =$ 5.9, 9.9, 12.3 Hz, 1H), 5.00 (d, $J = 9.9$ Hz, 1H), 7. 32 (d, $J = 8.1$ Hz, 2H), 7.99 ppm (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 21.7, 22.8, 23.6, 25.5, 35.8, 37.6, 44.6, 52.5, 55.8, 57.7, 128.8, 129.3, 135.4, 144.8, 155.0, 168.3$ ppm; MS: m/z (%) = 406 (14), 391 (26), 347 (71), 283 (82), 291 (100), 195 (11), 91 (8); HRMS: m/z calcd for $C_{20}H_{26}N_2O_5S$: 391.1328 $[M-CH_3]^+$; found: 391.1323.

3c: *syn*-Methyl hexahydro-6,6-diphenyl-3-oxo-2-tosyl-1*H*-pyrrolo[1,2-*e*]-imidazole-1-carboxylate: Synthesized according to the general procedure. IR (diamond): $\tilde{\nu} = 3028, 2954, 1733, 1597, 1494, 1446, 1357, 1271, 1163, 1121, 1088, 909, 813, 753, 700, 727, 664$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.07$ (dd, $J = 11.4, 11.4$ Hz, 1H), 2.20 (dd, $J = 4.7, 11.4$ Hz, 1H), 2.35 (s, 3H), 3.53 (d, $J = 11.2$ Hz, 1H), 3.74 (s, 3H), 4.06 (ddd, $J = 4.7, 10.2, 11.4$ Hz, 1H), 4.14 (d, $J = 11.2$ Hz, 1H), 4.94 (d, $J = 10.2$ Hz, 1H), 6.96–7.00 (m, 2H), 7.07–7.26 (m, 8H), 7.17 (d, $J = 8.5$ Hz, 2H), 7.92 ppm (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 21.7, 40.0, 52.7, 55.8, 55.9, 56.3, 57.7, 126.3, 126.7, 126.9, 127.0, 128.6, 128.6, 128.9, 129.2, 135.4, 144.8, 144.9, 145.0, 155.3, 168.3$ ppm; MS: m/z (%) = 492 $[M]^+$ (44%), 328 (40), 308 (40), 283 (50), 243 (60), 196 (20); HRMS (MALDI-TOF): m/z calcd for $C_{27}H_{26}N_2O_5S$: 513.1460 $[M+Na]^+$; found: 513.1467.

3d: *syn*-Ethyl hexahydro-3-oxo-2-tosyl-1*H*-pyrrolo[1,2-*e*]imidazole-1-carboxylate: Synthesized according to the general procedure. IR (diamond): $\tilde{\nu} = 2853, 1923, 1734, 1596, 1353, 1200, 1165, 1090, 1022, 815, 752, 665$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.25–1.30 (m, 1H), 1.34 (t, $J = 7.0$ Hz, 3H), 1.40–1.45 (m, 1H), 1.86–1.89(m, 1H), 2.00–2.06 (m, 1H), 2.46 (s, 3H), 3.05–3.09 (m, 1H), 3.59–3.65 (m, 1H), 4.05–4.10 (m, 1H), 4.32 (q, $J = 7.0$ Hz, 2H), 5.03 (d, $J = 9.7$ Hz, 1H), 7.35 (d, $J = 8.2$ Hz, 2H), 8.03 ppm (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.2, 21.7, 24.3, 30.8, 44.8, 57.7, 60.6, 62.0, 128.9, 129.3, 135.4, 144.8, 169.5$ ppm; MS: m/z (%) = 353 $[M]^+$ (100%), 279 (30), 259 (40), 224 (20), 197 (40), 170 (10); HRMS (MALDI-TOF): m/z calcd for $C_{16}H_{20}N_2O_5S$: 375.0991 $[M+Na]^+$; found: 375.0970.

3e: *syn*-Ethyl hexahydro-3-oxo-6,6-diphenyl-2-tosyl-1*H*-pyrrolo[1,2-e]imidazole-1-carboxylate: Synthesized according to the general procedure. IR (diamond): $\tilde{\nu} = 3028, 2958, 1740, 1598, 1447, 1358, 1272, 1167, 1090, 907, 815, 753$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.32$ (t, $J =$ 7.2 Hz, 3H), 2.19 (dd, $J = 9.0, 11.3$ Hz, 1H), 2.27 (dd, $J = 5.2, 11.3$ Hz, 1H), 2.42 (s, 3H), 3.58 (d, $J = 11.2$ Hz, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 4.21 (d, $J = 11.2$ Hz, 1H), 4.31 (td, $J = 7.2, 12.7$ Hz, 1H), 4.98 (d, $J = 10.1$ Hz, 1H), 7.04 (d, $J = 6.9$ Hz, 4H), 7.16 (d, $J = 8.4$ Hz, 2H), 7.19–7.32 (m, 6H),

7.99 ppm (d, $J=8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=14.3$, 21.7, 40.0, 55.8, 55.9, 56.4, 57.9, 62.2, 126.4, 126.8, 128.6, 128.7, 129.0, 129.3, 135.6, 167.8, 154.8, 144.9 ppm; MS: m/z (%) = 507 $[M]^+$ (91%), 506 (40), 283 (60), 243 (30), 198 (100), 182 (30); HRMS (MALDI-TOF): m/z calcd for $C_{28}H_{28}N_2O_5S$: 527.1617 $[M+Na]^+$; found: 527.1620.

3f: *syn*-Benzyl hexahydro-3-oxo-6,6-diphenyl-2-tosyl-1*H*-pyrrolo[1,2-e]-imidazole-1-carboxylate: Synthesized according to the general procedure. IR (diamond): $\tilde{\nu}=3027$, 2922, 1740, 1638, 1597, 1494, 1445, 1358, 1259, 1165, 1089, 912, 813, 753, 732, 697, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.87$–1.92 (m, 2H), 2.42 (s, 3H), 3.46 (d, $J=11.1$ Hz, 1H), 4.05 (ddd, $J=1.75$, 5.26, 10.5 Hz, 1H), 4.15 (d, $J=11.1$ Hz, 1H), 5.03 (d, $J=10.2$ Hz, 1H), 5.18 (d, $J=11.7$ Hz, 1H), 5.34 (d, $J=11.7$ Hz, 1H), 6.67–6.72 (m, 2H), 7.06 (d, $J=8.5$ Hz, 2H), 7.20–7.41 (m, 13H), 8.02 ppm (d, $J=8.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=22.6$, 31.9, 39.8, 55.5, 55.8, 56.2, 57.8, 126.3, 126.6, 126.8, 128.4, 128.5, 128.7, 128.9, 129.0, 129.2, 129.5, 134.8, 135.5, 144.7, 144.9, 155.2, 167.7 ppm; MS: m/z (%) = 570 $[M]^+$ (52%), 457 (20), 371 (20), 283 (30), 238 (70), 196 (70), 167 (100); HRMS (MALDI-TOF): m/z calcd for $C_{33}H_{30}N_2O_5S$: 589.1773 $[M+Na]^+$; found: 589.1792.

3g: *syn-tert*-Butyl hexahydro-3-oxo-6,6-diphenyl-2-tosyl-1*H*-pyrrolo[1,2-e]-imidazole-1-carboxylate: Synthesized according to the general procedure. IR (diamond): $\tilde{\nu}=3029$, 2922, 1740, 1597, 1495, 1447, 1367, 1253, 1165, 1123, 1090, 908, 815, 753, 730, 702, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=1.53$ (s,3H), 2.27 (dd, $J=5.2$, 11.9 Hz, 1H), 2.41 (s, 3H), 3.55 (dd, $J=5.1$, 11.4 Hz, 1H), 4.08–4.13 (m, 1H), 4.12 (d, $J=7.08$ Hz, 1H), 4.20 (d, $J=11.12$ Hz, 1H), 4.86 (d, $J=10.02$ Hz, 1H), 7.03 (d, $J=6.8$ Hz, 4H), 7.18 (d, $J=8.5$ Hz, 2H) 7.15–7.32 (m, 6H), 7.99 ppm (d, $J=8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=28.0$, 39.9, 55.7, 55.8, 56.4, 58.6, 59.2, 83.7, 126.5, 126.3, 126.7, 126.9, 127.0, 128.6, 128.6, 129.0, 129.2, 135.7, 144.8, 145.0, 145.0, 155.2, 166.9 ppm; MS: m/z (%) = 535 $[M]^+$ (70%), 321 (40), 283 (30), 238 (50), 198 (60), 167 (100); HRMS (MALDI-TOF): m/z calcd for $C_{30}H_{32}N_2O_5S$: 555.1930 $[M+Na]^+$; found: 555.1918.

3h: (−)-Menthyl hexahydro-3-oxo-6,6-diphenyl-2-tosyl-1*H*-pyrrolo[1,2-e]-imidazole-1-carboxylate: Synthesized according to the general procedure and obtained as a 12:6:3:2 mixture of four stereoisomers. Major isomer (unknown configuration): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=$ 0.80–1.20 (m, 5H), 0.84 (d, $J=7.0$ Hz, 3H), 0.92 (d, $J=7.0$ Hz, 3H), 1.00 (d, $J=6.7$ Hz, 3H), 1.37–1.62 (m, 2H), 1.63–1.80 (m, 3H), 1.94–2.03 (m, 1H), 2.16–2.38 (m, 1H), 2.44 (s, 3H), 3.58–3.66 (m, 1H), 4.12–4.16 (m, 1H), 4.90 (dt, $J=2.7$, 9.1 Hz, 1H), 5.02 (d, $J=10.0$ Hz, 1H), 7.08 (d, $J=7.8$ Hz, 2H), 7.01–7.44 (m, 10H), 8.02 ppm (d, $J=7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=16.4$, 20.7, 22.0, 22.0, 23.6, 26.3, 31.4, 34.2, 40.9, 47.0, 47.1, 50.2, 55.4, 56.0, 74.1, 125.1, 126.9, 127.9, 128.4, 128.6, 129.8, 143.5, 143.9, 144.0, 144.5, 165.5 ppm; HRMS (MALDI-TOF): m/z calcd for $C_{36}H_{42}N_2NaO_5S$: 614.2814 $[M+Na]^+$; found: 614.2820.

4: (*E*)-*N*-(2,2-Diphenylhepta-4,6-dienylcarbamoyl)-4-methylbenzenesulfonamide: Absolute dichloromethane (6 mL) and (*E*)-7-amino-6,6-diphenylpentyl-1,3-diene[11] (2 mmol, 1.0 equiv) were introduced into a flame-dried Schlenk flask. The reaction mixture was cooled to 0 °C, and 4-toluenesulfonyl isocyanate (2.15 mmol, 1.1 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. Evaporation of the solvent provided the crude material, which was purified by crystallization from $CHCl_3$ to remove minor amounts of 4-toluenesulfonyl amide. IR (KBr): $\tilde{\nu}=3373$, 3008, 2822, 1683, 1598, 1551, 1497, 1447, 1420, 1341, 1157, 1091, 998, 911, 812, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=2.33$ (s, 3H), 2.76 (d, $J=7.3$ Hz, 2H), 3.81 (d, $J=5.3$ Hz, 2H), 4.83 (dd, $J=1.2$, 10.2 Hz, 1H), 4.92 (dd, $J=1.2$, 17.0 Hz, 1H), 5.15 (dt, $J=7.3$, 15.2 Hz, 1H), 5.80 (dd, $J=10.2$, 15.2 Hz, 1H), 6.03 (dt, $J=10.2$, 17.0 Hz, 1H), 6.22 (t, $J=5.3$ Hz, 1H), 7.06–7.35 (m, 14H), 8.81 ppm (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=21.6$, 40.7, 47.2, 49.9, 116.0, 126.6, 126.8, 127.8, 128.4, 129.0, 129.4, 134.6, 136.5, 136.7, 144.5, 144.7, 151.8 ppm; LCMS (ESI): m/z (%) = 483 $[M+Na]^+$ (10), 265 (13), 204 (28), 196 (100), 167 (48), 131 (26), 91 (19); HRMS (MALDI-TOF): m/z calcd for $C_{27}H_{29}N_2O_3S^+$: 461.1893; found: 461.1917.

5: *anti*-6,6-Diphenyl-2-tosyl-1-vinyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one: Synthesized according to the general diamination procedure by employing the conditions given in Scheme 5. IR (KBr): $\tilde{\nu}=3010$, 2926, 1734, 1596, 1495, 1449, 1395, 1359, 1328, 1172, 1089, 943, 897, 809, 752, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=2.03$ (dd, $J=10.8$, 12.0 Hz, 1H), 2.34 (s, 3H), 2.47 (dd, $J=5.0$, 12.0 Hz, 1H), 3.43 (ddd, $J=3.2$, 5.0, 10.5 Hz, 1H), 3.87 (d, $J=12$ Hz, 1H), 3.96 (d, $J=12$ Hz, 1H), 4.47 (dd, $J=3.2$, 8.2 Hz, 1H), 5.20 (d, $J=10.2$ Hz, 1H), 5.31 (d, $J=17.0$ Hz, 1H), 5.78 (ddd, $J=8.2$, 10.2, 17.0 Hz, 1H), 6.95 (d, $J=8.2$ Hz, 2H), 7.00–7.26 (m, 10H), 7.81 ppm (d, $J=8.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=$ 21.6, 42.9, 56.2, 57.2, 62.0, 62.4, 118.8, 126.5, 126.7, 126.8, 127.4, 128.3, 128.5, 129.4, 130.2, 135.7, 137.4, 144.6, 145.6, 145.8, 157.2 ppm; MS: m/z (%) = 458 $[M]^+$ (100), 431 (1), 394 (2), 366 (1), 303 (55), 291 (2), 278 (6), 260 (1), 235 (1), 220 (2), 205 (2), 193 (16), 165 (10), 144 (3), 123 (8), 96 (2), 91 (14), 81 (12), 65 (2); HRMS (MALDI-TOF): m/z calcd for $C_{27}H_{26}N_2O_3S$: 458.1664 $[M]^+$; found: 458.1666.

6: Hexahydro-1-(2-hydroxyethyl)-2-tosylpyrrolo[1,2-*e*]imidazol-3-one: Diamination product **2b** (1 mmol) was dissolved in aqueous sodium methanolate (10 ml, 2 M), and the mixture was stirred for 2 h. The solution was acidified by addition of concentrated hydrochloric acid and extracted with dichloromethane. The resulting colorless oil was directly subjected to homologation by following the Seebach protocol for the Arndt–Eistert reaction.[31] The crude acid was dissolved in THF, and the mixture was treated with borane–dimethylsulfide adduct (260 μL) at room temperature. The reaction mixture was stirred overnight and evaporated to dryness. Column chromatography (silica gel, hexanes/ethyl acetate = 4:1 *v*/*v*) gave **6** (230 mg, 71%) as a grey solid. IR (KBr): $\tilde{\nu}=3008$, 2956, 1744, 1328, 1152, 1109, 955, 873, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=$ 1.40–1.76 (m, 6H), 2.30 (s, 3H), 3.61–3.73 (m, 4H), 4.02 (dt, $J=7.2$, 10.0 Hz, 1H), 4.18–4.22 (m, 1H), 7.41 (d, $J=7.9$ Hz, 2H), 7.90 ppm (d, $J=7.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=21.4$, 22.1, 32.6, 36.8, 40.0, 49.2, 50.0, 58.7, 128.6, 129.2, 135.3, 145.1, 156.4 ppm; MS: m/z (%) = 324 $[M]^+$ (24%), 306 (43), 280 (100), 155 (92), 125 (59), 65 (23); HRMS (MALDI-TOF): m/z calcd for $C_{15}H_{20}N_2O_4S^+$: 324.1144; found: 324.1149.

7: 3-Amino-(3-pyrrolidin-2-yl)propan-1-ol: Urea **6** (1.5 mmol) was dissolved in a solution of magnesium ethanolate (2 M) in ethanol, and the mixture was heated at reflux for 12 h. It was then cooled to room temperature, washed with water, and extracted with dichloromethane. The dichloromethane phase was washed several times with brine and finally with water, dried over magnesium sulfate, filtered, and reduced to a volume of approximately 2 mL. The same volume of TFA was added, and the mixture was stirred at room temperature. The solvents were removed under reduced pressure, and the remaining oily residue was triturated with chloroform to give **7** as a hygroscopic bis-TFA salt (430 mg, 1.12 mmol, 77%). IR (KBr): $\tilde{\nu}=3008$, 2956, 1744, 1328, 1152, 1109, 955, 873, 772 cm^{-1}; ^{1}H NMR (MeOD, 400 MHz): $\delta=1.89$–2.31 (m, 8H), 3.41–3.46 (m, 2H), 3.91–4.12 (m, 2H), 4.30–4.49 (m, 2H), 8.68 (br s, 1H), 9.16 ppm (br s, 2H); ^{13}C NMR (MeOD, 100 MHz): $\delta=23.1$, 23.2, 26.5, 45.6, 50.6, 62.4, 64.4, 115.7 (q, $J=288$ Hz), 159.6, 160.0 ppm; HRMS (MALDI-TOF): m/z calcd for $C_9H_{18}F_3N_2O_3^+$: 259.1270 $[M-TFA]^+$; found: 259.1281.

8: Benzyl 3-hydroxy-(1-pyrrolidin-2-yl)propylcarbamate: Diamino alcohol **7** (260 mg, 0.7 mmol) was dissolved in freshly distilled dichloromethane (5 mL), and triethylamine (1.5 mL) was added by syringe. The resulting solution was cooled to −10 °C, treated with CbzCl (115 mg, 0.74 mmol), and stirred overnight. All volatile materials were removed under reduced pressure, and the crude material was purified by column chromatography (silica gel, EtOAc→EtOAc/MeOH = 2:1 *v*/*v*) to give **8** as a colorless oil (171 mg, 0.62 mmol, 88%). The ^{1}H and ^{13}C NMR spectroscopic data match those previously reported.[30]

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[1] a) J. Streuff, C. H. Hövelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.* **2005**, *127*, 14586; b) K. Muñiz, C. H. Hövelmann, J. Streuff, *J. Am. Chem. Soc.* **2008**, *130*, 763.
[2] K. Muñiz, *J. Am. Chem. Soc.* **2007**, *129*, 14542.
[3] K. Muñiz, J. Streuff, C. H. Hövelmann, A. Núñez, *Angew. Chem.* **2007**, *119*, 7255; *Angew. Chem. Int. Ed.* **2007**, *46*, 7125.
[4] a) K. Muñiz, C. H. Hövelmann, E. Campos-Gómez, J. Barluenga, J. M. González, J. Streuff, M. Nieger, *Chem. Asian J.* **2008**, *3*, 776; b) C. H. Hövelmann, J. Streuff, L. Brelot, K. Muñiz, *Chem. Commun.* **2008**, 2334.
[5] For a recent copper-catalyzed diamination of alkenes, see: a) B. Zhao, W. Yuan, H. Du, Y. Shi, *Org. Lett.* **2007**, *9*, 4943; b) B. Zhao, H. Du, Y. Shi, *Org. Lett.* **2008**, *10*, 1087.
[6] For diamination of alkenes with copper promoters, see: a) T. P. Zabawa, D. Kasi, S. R. Chemler, *J. Am. Chem. Soc.* **2005**, *127*, 11250; b) T. P. Zabawa, S. R. Chemler, *Org. Lett.* **2007**, *9*, 2035.
[7] A. Viso, R. Fernandez de La Pradilla, A. Garcia, A. Flores, *Chem. Rev.* **2005**, *105*, 3167.
[8] a) K. Muñiz, M. Nieger, *Synlett* **2003**, 211; b) K. Muñiz, A. Iesato, M. Nieger, *Chem. Eur. J.* **2003**, *9*, 5581; c) K. Muñiz, M. Nieger, H. Mansikkamäki, *Angew. Chem.* **2003**, *115*, 6140; *Angew. Chem. Int. Ed.* **2003**, *42*, 5958; d) K. Muñiz, M. Nieger, *Chem. Commun.* **2005**, 2729; e) K. Muñiz, *New J. Chem.* **2005**, *29*, 1371.
[9] a) J. Han, T. Li, Y. Pan, A. Kattuboina, G. Li, *Chem. Biol. Drug Des.* **2008**, *71*, 71; b) G. Li, H.-X. Wei, S. H. Kim, M. D. Carducci, *Angew. Chem.* **2001**, *113*, 4407; *Angew. Chem. Int. Ed.* **2001**, *40*, 4277; c) W. Pei, C. Timmons, X. Xu, H.-X. Wie, G. Li, *Org. Biomol. Chem.* **2003**, *1*, 2919.
[10] a) *Handbook of Metathesis*, *Vol. 1–3* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**; b) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117; c) S. J. Connon, S. Blechert, *Angew. Chem.* **2003**, *115*, 1944; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.
[11] Please see Supporting Information for further details.
[12] Unligated palladium salts readily catalyze the reaction without the need for ligands. In agreement with earlier observations,[1–3] attempts to employ bidentate ligands led to dissociation prior to initiation of the catalysis.
[13] CCDC-682533 (compound **3a**) and -682534 (compound **5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.
[14] A. Minatti, K. Muñiz, *Chem. Soc. Rev.* **2007**, *36*, 1142.
[15] For a more detailed discussion on amide–palladium interactions and *syn* aminopalladation, see: a) V. Kotov, C. C. Scarborough, S. S. Stahl, *Inorg. Chem.* **2007**, *46*, 1910; b) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2007**, *129*, 6328, and references therein.
[16] Reference [14] discusses the combination of palladium catalyst and copper reoxidant for aminohalogenation reactions: a) A. Lei, X. Lu, G. Liu, *Tetrahedron Lett.* **2004**, *45*, 1785; b) M. R. Manzoni, T. P. Zabawa, D. Kasi, S. R. Chemler, *Organometallics* **2004**, *23*, 5618; c) P. Szolcsányi, T. Gracza, *Tetrahedron* **2006**, *62*, 8498; for related carboamination reactions, see: d) W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948; e) P. H. Fuller, S. R. Chemler, *Org. Lett.* **2007**, *9*, 5477.
[17] J. E. Ney, J. P. Wolfe, *J. Am. Chem. Soc.* **2006**, *128*, 15415.
[18] For leading references to palladium-catalyzed oxidative amidation of acrylates, see: a) J. M. Lee, D.-S. Ahn, D. Y. Jung, J. Lee, Y. Do, S. K. Kim, S. Chang, *J. Am. Chem. Soc.* **2006**, *128*, 12954; b) B. Zou, H.-F. Jiang, Z.-Y. Wang, *Eur. J. Org. Chem.* **2007**, 4600; c) A. M. M. Antunes, S. J. L. Marto, P. S. Branco, S. Prabhakar, A. M. Lobo, *Chem. Commun.* **2001**, 405; d) A. M. M. Antunes, V. D. B. Bonifácio, S. C. C. Nascimento, A. M. Lobo, P. S. Branco, S. Prabhakar, *Tetrahedron* **2007**, *63*, 7009.
[19] For leading references to palladium-catalyzed amination of Michael acceptors, see: a) K. K. Hii, *Pure Appl. Chem.* **2006**, *78*, 341; b) M. Sodeoka, Y. Hamashima, *Pure Appl. Chem.* **2006**, *78*, 477; c) Y. Hamashima, M. Sodeoka, *Chem. Rec.* **2004**, *4*, 231.
[20] For recent involvement of α-palladated carbonyls and oxallyl–palladium intermediates in homogeneous catalysis, see: a) A. Minatti, X. Zheng, S. L. Buchwald, *J. Org. Chem.* **2007**, *72*, 9253; b) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234.
[21] a) For an excellent structural investigation on oxallylic palladium complexes, see: A. C. Albéniz, N. M. Catalina, P. Espinet, R. Redón, *Organometallics* **1999**, *18*, 5571; for the structural characterization of a C-bound phenacyl palladium(IV) complex, see: b) P. K. Byers, A. J. Canty, B. W. Skelton, P. R. Traill, A. A. Watson, A. H. White, *Organometallics* **1992**, *11*, 3085.
[22] For the conceptual introduction of transient palladium oxidation with $CuCl_2$, see: a) H. Stangl, R. Jira, *Tetrahedron Lett.* **1970**, *11*, 3589; O. Hamed, P. M. Henry, *Organometallics* **1998**, *17*, 5184; b) *Palladium-Catalyzed Oxidation of Hydrocarbons* (Ed.: P. M. Henry), Reidel, Dordrecht, **1980**.
[23] G. L. J. Bar, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2005**, *127*, 7308.
[24] a) H. Du, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 762; b) H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 7496; c) H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 11688; d) W. Yuan, H. Du, B. Zhao, Y. Shi, *Org. Lett.* **2007**, *9*, 2589; e) L. Xu, H. Du, Y. Shi, *J. Org. Chem.* **2007**, *72*, 7038; f) L. Xu, Y. Shi, *J. Org. Chem.* **2008**, *73*, 749.
[25] a) For leading references on palladium-catalyzed intramolecular allylic amidation, see: B. M. Trost, D. L. VanVranken, *Chem. Rev.* **1996**, *96*, 395; for recent discussions on stereochemical issues, see: b) G. Broustal, X. Ariza, J.-M. Campagne, J. Garcia, Y. Georges, A. Marinetti, R. Robiette, *Eur. J. Org. Chem.* **2007**, 4293; c) T. Oshitari, R. Akagi, T. Mandai, *Synthesis* **2004**, 1325.
[26] For a palladium-catalyzed direct oxidative allylic amidation, see: K. J. Fraunhoffer, M. C. White, *J. Am. Chem. Soc.* **2007**, *129*, 7274.
[27] For an alternative synthesis of these compounds by Pd catalysis, see: J.-O. Baeg, C. Bensimon, H. Alper, *J. Am. Chem. Soc.* **1995**, *117*, 4700.
[28] K. Ikhiri, A. Ahond, C. Poupat, P. Potier, J. Pusset, T. Sévenet, *J. Nat. Prod.* **1987**, *50*, 626.
[29] Syntheses: a) C. Christine, K. Ikhiri, A. Ahond, A. A. Mourabit, C. Poupat, P. Potier, *Tetrahedron* **2000**, *56*, 1837; b) T. Tang, Y.-P. Ruan, J.-L. Ye, P.-Q. Huang, *Synlett* **2005**, 231; c) M. Vargas-Sanchez, F. Couty, G. Evano, D. Prim, J. Marrot, *Org. Lett.* **2005**, *7*, 5861.
[30] N. Giri, M. Petrini, R. Profeta, *J. Org. Chem.* **2004**, *69*, 7303.
[31] S. Abele, G. Guichard, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 2141.

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