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Stereoselective Palladium-Catalyzed Functionalization of Homoallylic Alcohols: A Convenient Synthesis of Di- and Tri-Substituted Isoxazolidines and β-Amino-δ-Hydroxy Esters

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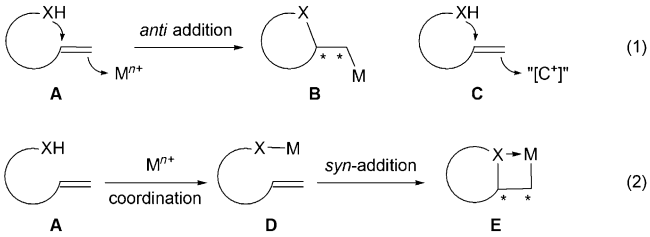
Dedicated to Professor John E. McMurry on the occasion of his 70th birthday.

Abstract: Enantiopure, Boc-protected alkoxyamines **12** and **13**, derived from the readily available homoallylic alcohols **4** via a reaction that involves either inversion or retention of configuration, undergo a diastereoselective Pd-catalyzed ring-closing carbonylative amidation to produce isoxazolidines **16/17** (≤50:1 diastereoisomer ratio (d.r.)) that can be readily converted into the *N*-Boc-protected esters of β-amino-δ-hydroxy acids and their γ-substituted homologues **37**. The key carbonylative cyclization proceeds through an unusual *syn* addition of the palladium and the nitrogen nucleophile across the C=C bond (**19**→**21**), as revealed by the reaction of **15**, which afforded isoxazolidine **18** with high diastereoselectivity.

Keywords: amidopalladation · amino acids · carbonylation · palladium · stereocontrol

Introduction

Carbon–carbon bond formation is traditionally regarded as the ultimate goal of synthetic organic chemistry.[1] However, a stereocontrolled functionalization through the construction of a carbon–heteroatom bond is of no less importance and there are myriads of examples of its application in total synthesis.[1,2] Thus, stereocontrolled electrophilic addition across a C=C bond stands as a cornerstone of organic chemistry,[2] with halolactonization, haloetherification, and related reactions employing S, Se, Pd, Pt, Hg, Tl, Au, and other electrophiles being the prime examples (Scheme 1, (1)).[27] When metals, such as Pd[2,5] or Hg,[2,5,7] are employed



Scheme 1.

as the electrophilic triggers of the reaction, the initially formed organometallic product **B** can be utilized in a subsequent reaction that would allow the construction of a new C–C bond from the C–M bond. The overall result would then be the formation of a C–X and C–C bond, where X is introduced as a nucleophile, and the new carbon substituent formally as an electrophile (**C**).[2,8–10]

In their seminal paper, Semmelhack and Bodurow[10] had shown that olefinic alcohols can be readily cyclized in a stereocontrolled manner by palladium(II) (Scheme 1, (1), $M^{n+}=Pd^{2+}$, X=O) in the presence of carbon monoxide and the resulting organopalladium intermediate **B** would then undergo carbonylation (with retention of configuration) to produce the corresponding ester ($M=CO_2Me$).[10–14] Semmelhack and co-workers had also developed a catalytic cycle, in which the Pd^0 resulting from the reaction is re-oxidized by Cu^{II},[10,11,15,16] in reminiscence of the Wacker process.[17] The cyclization was formulated as an *anti* addition of Pd^{2+} and the alkoxy group across the double bond

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(Scheme 1, (1)),[10,11] which is in line, for example, with the mechanism of the Bäckvall oxidation, where the initially generated η^4-Pd^{II}-complex of a conjugated diene is attacked by a nucleophile from the face opposite to Pd.[16]

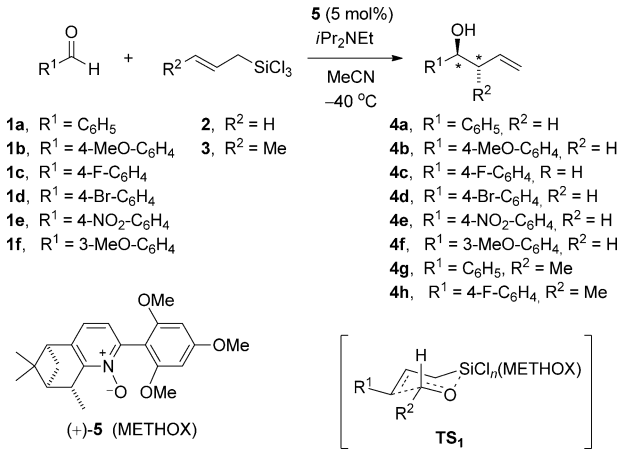
Aside from the *anti* mechanism (Scheme 1, (1)), the *syn* addition (Scheme 1, (2)) can also operate in the Pd-catalyzed reactions, especially in the absence of the strongly coordinating ligand, such as carbon monoxide;[18] here, the hydroxyl can pre-coordinate the metal and steer its approach to the C=C bond[19,20] in a similar way as, for example, in the Sharpless epoxidation.[2c] Thus, Hayashi has demonstrated the *syn* addition for the cyclopalladation of olefinic alcohols and showed that the stereochemical outcome is strongly affected by the chloride ion, either added (LiCl) or originating from the oxidant ($CuCl_2$): in the absence of Cl^-, a clean *syn* addition was observed, whereas addition of an excess of LiCl to the reaction mixture (with *para*-benzoquinone as the oxidant) reversed the mechanism to mainly *anti* addition. The latter outcome was rationalized by the reduced propensity of Pd to associate with the hydroxyl due to the strongly bonded Cl^- in its coordination sphere.[21] Stoltz and co-workers have also documented the *syn* cyclopalladation of olefinic alcohols but noted the *anti* pathway for analogous carboxylic acids.[22] This dichotomy was tentatively attributed to the combination of a number of factors, such as pK_a differences, variation of nucleophilicity (OH vs. CO_2H), and geometrical constraints in the substrate molecules, illustrating the sheer complexity of this problem.[22] Wolfe and co-workers studied a Heck-type Pd-catalyzed cycloarylation of olefinic alcohols with aryl halides,[23] in which a strong base is employed (that presumably deprotonates the hydroxyl, making it prone to coordinate Pd) and found preferential *syn* addition of the hydroxyl and the Ar–[Pd] species.[24,25]

Aminopalladation of ethylene with dimethylamine was shown by Åkermark and co-workers to occur with *anti* stereochemistry (in the presence of Cl^-).[26] On the other hand, Taniguchi found a *syn* mechanism for the intramolecular amidation with an acetamido group [**A**, X=N(R)Ac], catalyzed by $(PhCN)_2PdCl_2$.[27] Wolfe has developed an intramolecular aminoarylation of olefinic amines (**A**, X=HNR) with aryl halides (in the presence of a strong base) and demonstrated the *syn* pathway (Scheme 1, (2)), assuming an amine-palladium pre-coordination,[28] in analogy to the alkoxyarylation.[24,25] Arylation of the related Boc-protected olefinic amines (**A**, X=NHBoc, Boc=*tert*-butoxycarbonyl) was also found to be dominated by the *syn* mechanism.[28b,29] In fact, the groups of Wolfe[30] and Hartwig[31] have been able to prepare the N-Pd complexes (**D**, X=NR) from the corresponding amines through deprotonation with a strong base, followed by treatment with Pd^{II}, and confirm the *syn* mechanism with the aid of deuterium labeling. By contrast, amidocarbonylation of an olefinic tosylurea derivative (**A**, X=NCONHTs) with $(AcO)_2Pd$, $CuCl_2$, and CO, was reported by Tamaru and Yoshida to proceed as a clean *anti* addition[32] in consonance with the Semmelhack findings for cyclative carbonylation of olefinic alcohols (in the presence of CO).[10,11]

Herein, we report on a diastereoselective, palladium-catalyzed ring-closing amidocarbonylation of the Boc-protected homoallylic alkoxyamines **A** (XH=O–NHBoc), derived from enantiopure homoallylic alcohols, conversion of the initially formed isoxazolidines into the corresponding esters of β-amino-δ-hydroxy acids, and the stereochemistry of this sequence.

Results and Discussion

In the past few years we and others have developed an enantio- and diastereoselective allylation of aromatic and α,β-unsaturated aldehydes **1a–f** with allyl/crotyl trichlorosilanes **2/3** to produce the homoallylic alcohols **4a–h** (Scheme 2).[33–38] The reaction is catalyzed by various chiral

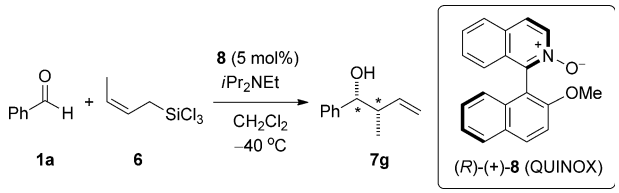


Scheme 2.

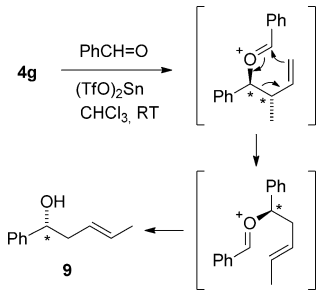
Lewis basic pyridine *N*-oxides,[33–38] in particular METHOX (**5**)[35] and QUINOX (**9**).[36] It is pertinent to note that METHOX offers an interesting advantage in the case of *trans*-crotyl silane **3**: here, the required silane is prepared in one step through the copper(I)-mediated coupling of Cl_3SiH with technical crotyl chloride,[39] which is an 87:13 mixture of *trans* and *cis* isomers, and this ratio is reproduced in the composition of the silane **3**.[35,36] METHOX (**5**) exhibits a strong kinetic preference for the *trans*-configured **3** (presumably resulting from the transition state $\mathbf{TS_1}$), so that when excess of the latter reagent is used, only the *trans* isomer is consumed, and the resulting homoallylic alcohols **4** are obtained as pure *anti*-configured diastereoisomers in high enantiopurity.[35,38e]

In contrast to **3**, the *cis*-crotylsilane **6**, obtained on the palladium(II)-catalyzed 1,4-hydrosilylation of butadiene with Cl_3SiH,[40] reacts best when QUINOX (**8**) is used as catalyst, affording the *syn*-configured homoallylic alcohol **7g** in high enantio- and diastereoselectivity (Scheme 3).[36]

The portfolio of the available products based on this strategy was further extended by us to the homoallylic alcohols, such as **9**, which arises from **4g** (Scheme 4) in an unprece-



Scheme 3.

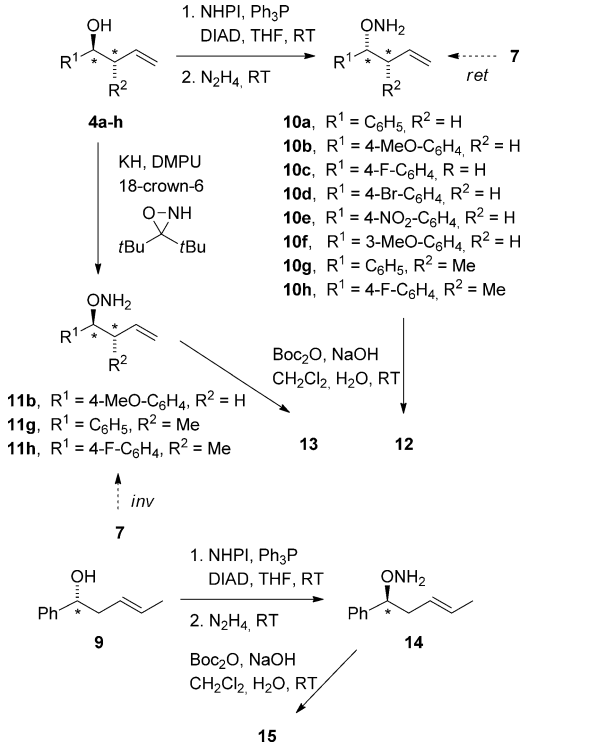


Scheme 4.

dented stereopurity through the oxonia-Cope rearrangement.[41]

Along the lines discussed in the Introduction (Scheme 1), Bates[42,43] and co-workers have shown that the simple Boc-protected homoallylic alkoxyamine (±)-**12a** (i.e., lacking the R^2 substituent) readily undergoes a Pd-catalyzed ring-closing carbonylation, in which the nitrogen of the carbamate group serves as an internal nucleophile. Aiming at the extension of this methodology to the crotyl series, we embarked on a detailed investigation, employing our readily available homoallylic alcohols **4a–h**, and **9** as starting model compounds (Scheme 5); in this series, **4a** was prepared through the allylation catalyzed by DMF as a Lewis base and was therefore racemic. The remaining members of this set were scalemic, since they were obtained through the allylation catalyzed by METHOX (**5**). The main goal was to find out whether the stereochemical and functional group manipulations were compatible with this ring-closing amidocarbonylation, to what extent various combinations would affect the stereoselectivity and yield, and what is the overall stereochemistry of the addition across the C=C bond.

Synthesis of alkoxyamines and their Boc derivatives: There are essentially two methods available for the conversion of an alcohol (R–OH) into the corresponding alkoxyamine ($R–ONH_2$): one involving the Mitsunobu inversion, in which a new C–O bond is formed,[42b,44] and one relying on retention, in which the O–N bond is constructed instead, leaving the chiral center unaffected.[45,46] According to the former approach, alcohols **4a–h** were treated with *N*-hydroxyphthalimide (NHPI) in the presence of diisopropyl diazodicarboxylate (DIAD) and triphenylphosphine under the standard Mitsunobu conditions[42b,44] and the resulting phthalimides were deprotected[42b,44] on reaction with hydrazine hydrate to afford the required alkoxyamines **10a–h** in good



Scheme 5.

yields (Scheme 5 and Table 1). In all cases, except one (Table 1, entry 2), the inversion of configuration was almost perfect (with very little loss of the stereochemical integrity, if any). However, the *p*-methoxy derivative **4b** (96% enantiomeric excess (*ee*)) produced the corresponding alkoxyamine **10b**, which turned out to be almost racemic (ca. 10% *ee*). This result represents a serious blow to the general belief in the Mitsunobu reaction[47] as a reliable means for clean inversion and will deserve further investigation.[48,49]

The retention pathway (Scheme 5) is based on the construction of the O–N bond (i.e., without touching the chiral center) through the reaction of the corresponding alkoxide (generated in situ) with 3,3′-di-*tert*-butyloxaziridine, which involves a nucleophilic substitution at the oxaziridine nitrogen.[44,45] According to this scenario, alcohols **4b**, **4g**, and **4h** were deprotonated with potassium hydride in the presence of the potassium-specific 18-crown-6 ether and the resulting alkoxides were allowed to react with 3,3′-di-*tert*-butyloxaziridine to produce **11b** (88%), **11g** (65%), and **11h** (33%).[50]

The inversion method, applied to the enantiopure homoallylic alcohol **9**,[41] afforded alkoxyamine **14** (Scheme 5), again with no appreciable loss of enantiopurity (Table 1, entry 9).

It is pertinent to note that these two routes are stereocomplementary (Scheme 5): thus, the *anti*-configured alcohols **4** afford the *syn*-configured alkoxyamines **10** on the Mitsunobu inversion, whereas the oxaziridine route gives rise to the *anti* products **11**. On the other hand, starting with the *syn*-configured alcohols, such as **7**, the inversion pathway

Table 1. Synthesis of alkoxyamines **10a–h** and **14** from **4a–h** and **9** via Mitsunobu inversion (Scheme 5).[a]

Entry	Alcohol[b]	*ee*[c] [%]	d.r.[d]	alkoxyamine	Yield [%][e]	*ee*[f] [%]	d.r.[g]
1	(±)-**4a**	racemic	n/a	(±)-**10a**	85	racemic	n/a
2	(*S*)-(−)-**4b**	96	n/a	(*R*)-(+)-**10b**	74	≈10	n/a
3	(*S*)-(−)-**4c**	95	n/a	(*R*)-(+)-**10c**	78	90	n/a
4	(*S*)-(−)-**4d**	91	n/a	(*R*)-(+)-**10d**	86	90	n/a
5	(*S*)-(−)-**4e**	92	n/a	(*R*)-(+)-**10e**	84	92	n/a
6	(*S*)-(−)-**4f**	94	n/a	(*R*)-(+)-**10f**	91	88	n/a
7	(1*S*,2*S*)-(−)-**4g**	95	55:1	(1*R*,2*S*)-(+)-**10g**	89	95[h]	35:1[i]
8	(1*S*,2*S*)-(−)-**4h**	98	35:1	(1*R*,2*S*)-(+)-**10h**	54	98[h]	28:1[j]
9	(*R*)-(+)-**9**	92[k]	n/a	(*S*)-(−)-**14**	81	90	n/a

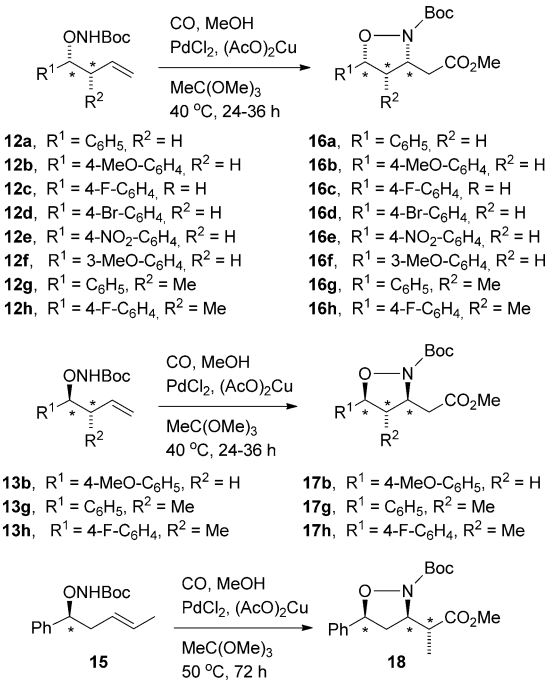
[a] The reactions were carried on a 1 mmol scale. [b] The absolute configuration of the starting alcohols **4** has either been established previously or is inferred by analogy, based on the fact that the allylation of aromatic aldehydes catalyzed by (+)-METHOX (**5**) is known to produce (*S*)-alcohols (see Refs. [33]–[36]); **4a** in entry 1 was prepared by the allylation catalyzed with DMF (instead with METHOX), and was therefore, racemic. [c] The enantiomeric purity of the starting alcohols was established by chiral HPLC, as reported previously (see Refs. [35] and [36]). [d] Established by ^{1}H NMR spectroscopy (or ^{19}F NMR, where applicable). [e] Isolated product yield after purification; note that conversions were practically quantitative. [f] The enantiomeric purity was inferred from the ^{19}F NMR spectra of the corresponding Mosher derivatives. [g] Established by ^{1}H NMR spectroscopy for **10g** (by integrating the signals of the benzylic protons of the crude products) and by ^{19}F NMR spectroscopy for **10h**. [h] The enantiomeric purity is assumed to be identical to that of the starting material, as the second chiral center remained unchanged. [i] Increased to 55:1 purity by chromatography. [j] The conversion was ≈70%. The *syn/anti* ratio could not be accurately established due to the overlap of the relevant signals in the ^{1}H NMR spectrum of the crude product with those of the unreacted starting material; the 28:1 ratio corresponds to the product after purification. [k] Previously obtained with up to 96% *ee* by using the same method (see Ref. [41]).

would produce *anti*-alkoxyamines **11**, whereas retention would furnish the *syn*-configured diastereoisomers **10**. Naturally, the absolute configuration in this exercise can be controlled by the absolute configuration of the organocatalysts **5** and **8**, which offers full stereo-complementarity.[51] It is noteworthy that the stereopure *p*-MeO derivatives (e.g., **10b** or those with another chiral center), not available through the Mitsunobu pathway, could thus be obtained in all stereochemical combinations by construction of the N–O bond.

In the next step, Boc-derivatization of **10**, **11**, and **14** was carried out under the standard Schotten-Bauman-type conditions, using di-*tert*-butyl dicarbonate (Boc anhydride) and NaOH in a two-phase system, and the model alkoxycarbamates **12**, **13**, and **15** were isolated in high yields (Scheme 5 and Scheme 6).

Ring-closing carbonylative amidation of the Boc-derivatized homoallylic alkoxyamines: Treatment of the unsaturated alkoxycarbamates **12a–h** with methanol and carbon monoxide at an atmospheric pressure in the presence of $PdCl_2$ as catalyst (10 mol%) and $(AcO)_2Cu$ (3 equiv) to reoxidize the palladium, was expected to result in the formation of isoxazolidines **16a–h** (Scheme 6 and Table 2). However, the first attempts with just methanol as a solvent and reactant were rather disappointing: thus, at 0°C or at room temperature, there was practically no reaction detected, whereas at 30°C, especially in the presence of a weak base, such as Et_3N, AcONa, $PhCO_2Na$, or tetramethylguanidine, and so on, precipitation of Pd-black was observed within approximately 10 min, apparently as the result of a stoichiometric oxidation of CO and/or MeOH at the expense of Pd^{II}.[52] Finally, after much experimentation, we were able to identify a 1:1 mixture of methanol and methyl orthoacetate as the medium of choice, with no additional base required.[12e,g,m] Here, the apparent role of the orthoacetate is to "mop up" the Brønsted acid generated during the reaction; the latter process also produces MeOH, which is present anyway, and one equivalent of the innocuous AcOMe. Significantly, under these neutral conditions, the reduction of Pd^{II} by CO/MeOH was prevented, so that the desired carboamidation could proceed.

The cyclization of **12a–f** and **13b**, that is, terminal olefins lacking another substituent (R^2=H), proceeded with very high diastereoselectivity (24:1 to >50:1; Table 2, entries 1–6 and 9). The cyclization of their homologues with an additional methyl (R^2=Me) exhibited dependence on the configuration at this additional center. Thus, the *syn*-configured alkoxycarbamates **12g** and **12h** produced the less stereochemically pure *syn,syn*-isozaxolidines **16g** and **16h** (Table 2, entries 7 and 8), whereas the *anti*-configured analogues **13g** and **13h** afforded the



Scheme 6.

anti,anti-isoxazolidines **17g** and **17h** of high diastereoisomeric purity (Table 2, entries 10 and 11). Homologue **15**, with a more sterically hindered disubstituted double bond, required a slightly higher temperature and an extended reac-

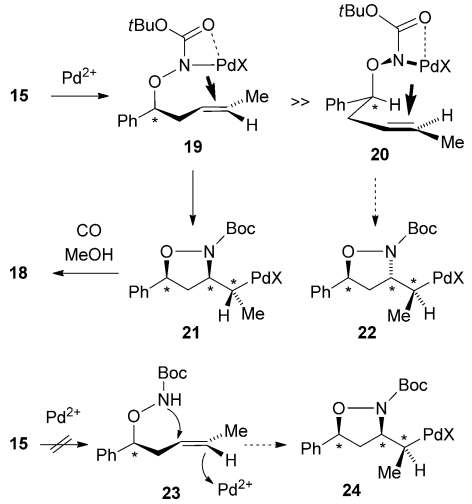
Table 2. Palladium-catalyzed ring-closing carbonylation of *N*-Boc protected alkoxyamines 12, 13 and 15 (Scheme 6).[a]

Entry	Alkene	*ee* [%]	d.r.	Isoxazolidine	Yield [%][b]	d.r.[c]
1	**12a**	racemic	n/a	**16a**	93	>50:1
2	**12b**	racemic	n/a	**16b**	80	>50:1
3	**12c**	90	n/a	**16c**	76	20:1[d,e]
4	**12d**	90	n/a	**16d**	93	>50:1
5	**12e**	92	n/a	**16e**	73	25:1
6	**12f**	88	n/a	**16f**	96	>50:1
7	**12g**	95	55:1	**16g**	69	4.5:1[f,g]
8	**12h**	98	28:1[h]	**16h**	60	5.7:1[g]
9	**13b**	96	n/a	**17b**	78	>35:1[f]
10	**13g**	95	55:1	**17g**	71	>20:1[f,g]
11	**13h**	98	35:1	**17h**	66	17:1[fh]
12	**15**	90	n/a	**18**	55	22:2:1[i]

[a] The reactions were carried on a 1 mmol scale with 10 mol% of the catalyst. [b] Isolated yield after purification; note that conversions were practically quantitative. [c] Established for the crude product by ^{1}H NMR spectroscopy (by integrating the signals of benzylic protons). [d] The ^{19}F NMR spectrum of the crude product showed a 16:1 ratio. [e] Increased to ≥40:1 by chromatography. [f] Increased to >50:1 by chromatography. [g] In principle, three diastereoisomers could be formed here. However, the third isomer could not be detected, presumably because its concentration was below the detection limit of the NMR spectroscopy. [h] Established by ^{19}F NMR spectroscopy. [i] Increased to 40:2.5:1 by chromatography.

tion time to produce **18** as an almost pure diastereoisomer (Table 2, entry 12), whose configuration was established by NMR spectroscopy and confirmed by X-ray crystallographic analysis of the derivative **40**, that is, after the removal of the Boc group (see below).

Mechanistic considerations: The experiment involving carbamate **15** was of key importance for establishing the stereochemistry of the Pd-catalyzed cyclization: here, the formation of diastereoisomer **18** corresponds to a *syn* addition ((2) in Scheme 1) of Pd and the nitrogen across the C=C bond. Apparently, the carbamate group is capable of coordinating the Pd^{II} catalyst[53] (Scheme 7), possibly by nitrogen

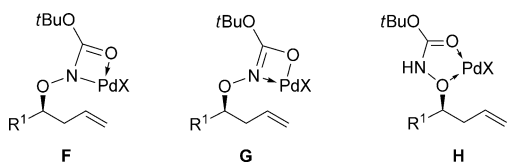


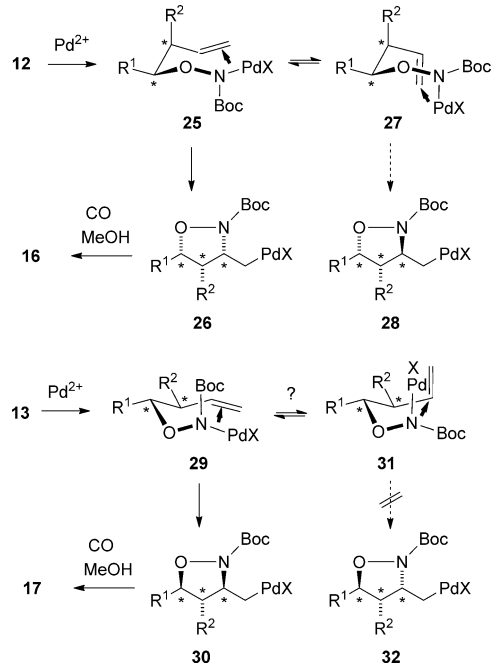
Scheme 7.

upon its deprotonation (**19**; see below), followed by a *syn* addition across the neighboring C=C bond, to generate the palladium species **21**, whose carbonylation (with retention of configuration) gives rise to ester **18**. The *syn* attack on the opposite face of the double bond, as in **20**, would generate a 1,3-strain, so that the corresponding Pd intermediate **22** is apparently not generated in any appreciable amount. Moreover, the *anti* pathway (**23**→**24**) would give rise to yet another diastereoisomer of **18**, whose formation was not observed.

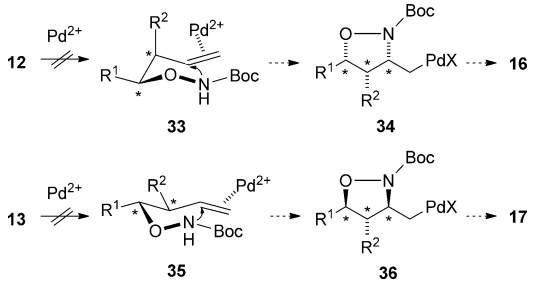
The *syn* mechanism (Scheme 7) mirrors the findings by the groups of Wolfe[28–30] and Hartwig[31] for the Pd-catalyzed arylation of olefinic alcohols and amines with aryl halides under basic conditions.[54] Wolfe[30b] also demonstrated the *syn* addition by isotopic labeling for the Pd-catalyzed arylation of the Boc derivative **12a** and its congeners, involving *N*-deprotonation by *t*BuONa. Furthermore, the *syn* stereochemistry is also compatible with the report by Taniguchi et al.,[27] who studied the cyclopalladation of olefinic acetamides (see above). However, these reactions differ from our system in one crucial point: we have studied carbonylation (i.e., reaction with CO) under neutral conditions. Therefore, comparison with the Semmelhack cyclative carbonylation of olefinic alcohols,[10,11] and with the Tamaru–Yoshida carbonylation of the olefinic tosylurea derivative (**A**, X=NCONHTs),[32] which all prefer the *anti* pathway, would be more appropriate. The *syn* pathway, observed for the carbonylation of **15** under similar conditions, is thus rather surprising. It may be attributed to the different nature of the nitrogen, which in our case is part of an alkoxyamine moiety, whose propensity to coordinate transition metals can differ from that of the hydroxyl and carbamate-type groups.

The actual mode of coordination of Pd^{II} to the *N*-Boc-alkoxyamine moiety is not clear. In principle, three models can be considered, namely **F** (featured in **19** and **20** and in Scheme 8 and Scheme 9), **G**, and **H**. Model **F** was chosen in analogy with the work of Wolfe[28–30] and Hartwig[28–30] on Boc-protected amines, which were first deprotonated by a strong base. However, the N–H of our *N*-Boc-alkoxyamines is likely to be more acidic than that in carbamates, so that a strong base may not be required here. Model **G** represents a reversed role of the nitrogen and carbonyl oxygen in chelation of Pd. The present data cannot shed light on this dichotomy but it is pertinent to note that both models are compatible with the experimentally observed *syn* addition. Finally, the third chelation mode **H**, assuming a five-membered chelation through the two oxygens, is unlikely, as it would move either the nitrogen or the palladium away from the double bond, so that the cyclization could not be





Scheme 8.



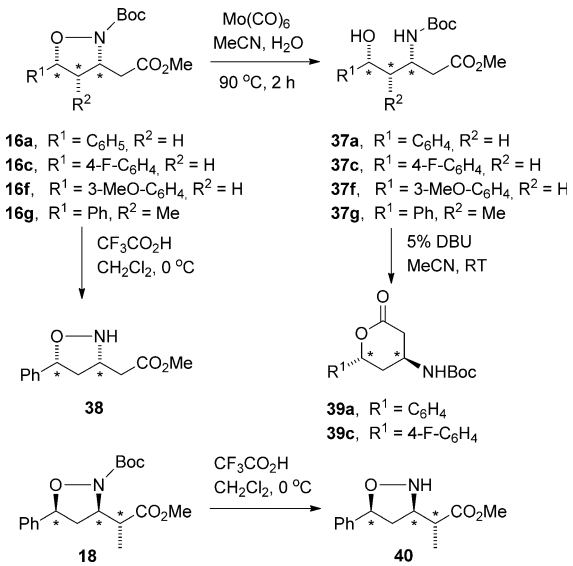
Scheme 9.

achieved. For the sake of simplicity, coordination of Pd to the nitrogen is depicted in Scheme 7, Scheme 8, and Scheme 9 but one should bear in mind that the actual mode of coordination is likely to be more complex.

Similar mechanistic arguments can be applied to the remaining members of the series, that is, **12** and **13** (Scheme 8). Thus, carbamates **12** apparently prefer the pathway involving the palladium complexes **25** and **26** to give **16**; in analogy, carbamates **13** can be assumed to react via **29** and **30**, giving rise to **17**. In the case of the *syn*-configured carbamates **12**, the reactive intermediate **25** is more congested than the analogous species **29** arising from the *anti*-configured carbamate **13**, which can account for the clean formation of one diastereoisomer in the latter instance (**17**) and the less stereochemically homogeneous reaction in the former **16** (compare entries 10 and 11 with 7 and 8 with in Table 2). In the absence of the R^2 substituent (i.e., $R^2 = H$), the diastereoselectivity was high in all instances (Table 2, entries 1–6 and 9).

The alternative *anti*-addition mechanism (Scheme 9) would produce the same cyclic derivatives as does the *syn* pathway in the case of **12** and **13** (but not **15**). Thus, the *syn*-configured carbamate **12** could be predicted to give rise to **16** through **33** and **34** and, in a similar way, **13** would afford **17** via **35** and **36**. However, the key experiment with carbamate **15** ruled out the *anti* mechanism (Scheme 6 and Scheme 7), which can now be extrapolated to the terminal olefins **12** and **13**. Hence, the original mechanism, which Bates formulated as the *anti*-addition,[42a] appears unlikely to operate in light of the present experiments.

Examples of a synthetic utilization of the isoxazolidines: The cleavage of the O–N bond in the *N*-Boc-protected isoxazolidines **16** (Scheme 10) and in the related isoxazolidines



Scheme 10.

17 and **18**, would open an interesting access to β-amino-δ-hydroxy acids, with an optional substituent (R^2) at the γ-position. Of the existing methods for the O–N bond cleavage, we chose one that uses $Mo(CO)_6$,[43c–e,55] as this reagent appears to be tolerant to the *N*-Boc group and a number of other functionalities. Indeed, on treatment with a stoichiometric amount of $Mo(CO)_6$ at 90 °C (Scheme 10), the selected *N*-Boc protected isoxazolidines **16a**,**16c**,**16f**, and **16g** afforded the expected *N*-Boc-protected β-amino-δ-hydroxy esters **37a** (78%), **37c** (65%), **37f** (86%), and **37g** (77%), respectively. The latter products can actually serve as orthogonally protected tri-functional species, currently with free OH, and protected amino and carboxyl groups; utilization of these derivatives can be multifaceted, as they can be envisioned to serve a number of purposes, for example, in peptide chemistry, relying on selective reactivities of the individual groups. As an example, we have observed partial lactonization of **37c** during the workup of the reaction that cleaved the O–N bond in **16c**, when a hot (rather than pre-

cooled) reaction mixture was quenched with aqueous $NaHCO_3$, to afford δ-lactone **39c** (19%) as a by-product, demonstrating the ease of this process. In an optimized preparative experiment, racemic hydroxy ester **37a**, obtained from (±)-**16a**, was treated with DBU (5 mol%) at room temperature for 4 h; under these conditions, lactone (±)-**39a** was isolated in 88% yield.[56,57] Note that, in fact, isoxazolidines **16**–**18** can also be utilized as orthogonally protected surrogates of β-amino-δ-hydroxy acids, offering further versatility and protecting group compatibility of our chemistry.

Standard *N*-Boc deprotection of (±)-**16a** and (−)-**18** resulted in a clean formation of free isoxazolidines (±)-**38** (90%) and (−)-**40** (88%), respectively. X-ray crystallographic analysis of (−)-**40** confirmed the relative configuration at the three chiral centers (Figure 1), which was the key issue for the mechanistic considerations (see above).

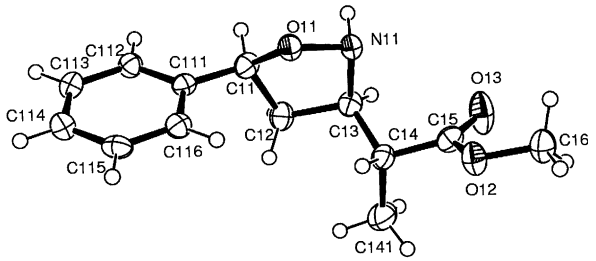


Figure 1. ORTEP diagram for (3*R*,5*S*,1′*R*)-(−)-**40** showing the atom labeling scheme. Displacement are shown at 50% probability level. H atoms are shown as spheres of arbitrary radius.

Conclusion

Homoallylic alkoxyamines **10a–h** and **14** were synthesized from the corresponding homoallylic alcohols **4a–h** and **9**, respectively, by using the Mitsunobu reaction with *N*-hydroxyphthalimide as the key reagent (Scheme 5). This transformation at the benzylic position proceeded with an almost pure inversion of configuration, except for the *p*-methoxy derivative (**4b**), in which a practically complete racemization was observed (Table 1). Additional alkoxyamines, namely **11b**, **11g**, and **11h**, were obtained from alcohols **4b**, **4g**, and **4h** on reaction with 3,3-di-*tert*-butyl-oxaziridine, which proceeds through O–N bond formation, that is, with retention of the original configuration of the alcohol (away from the chiral center). The *N*-Boc-derivatives of the latter alkoxyamines, namely **12**, **13**, and **15**, have been shown to undergo a diastereoselective Pd-catalyzed ring-closing carbonylative amidation to produce isoxazolidines **16a–h**, **17b**, **17g**, and **17h** and **18**, respectively (Scheme 6 and Table 2).[58] The *N*-Boc alkoxyamines **12a–f** lacking an additional substituent (R^2 = H) and their *anti*-configured congeners **13b**, **13g**, and **13h** (R^2 = Me) exhibited high diastereoselectivity in favor of the formation of the corresponding isoxazolidines **16a–f** and **17b**, **17g**, and **17h** (17:1 to ≥50:1 diastereoisomer ratio (d.r.)). The *syn*-configured derivatives **12g** and **12h** followed a similar pattern but the diastereoselectivity was lower (4.5:1 to 5.7:1). In most cases, the crude products were purified by flash chromatography to give a ratio of ≥50:1. These findings can be regarded as a considerable extension of the mosaic originally assembled by Bates and co-workers.[42–44]

The experiments carried out with carbamate **15** showed that the initial addition of the nitrogen and the palladium across the homoallylic double bond proceeds as a *syn* attack, presumably via a species in which Pd is coordinated to the carbamate group (**15**→**19**→**21**→**18**; Scheme 7), in other words through insertion of the C=C bond into the N–Pd bond. This mechanism stands in stark contrast to that of the related carbonylative cyclization of olefinic alcohols and the urea-type analogue of **12/13**, which are known to proceed with *anti* stereochemistry.[10,11,32] In this respect, our findings represent the first example of the *syn* cyclization in the Pd^{II}-catalyzed carbonylation of heterosubstituted olefins of type **A** (Scheme 1). On the other hand, the behavior of our carbamates mirrors the mechanism of the cyclization of olefinic alcohols, amines, and Boc-derivatized amines in the Pd-catalyzed addition of aryl halides and related species, which has been demonstrated to proceed with *syn* stereochemistry.[28–31] Note, however, that free alkoxyamines **10**, **11**, and **14** do not undergo the Pd-catalyzed carbonylative cyclization and have to be first converted into the corresponding carbamates **12**, **13**, and **15**, as shown here and by Bates,[42–44] or into related derivatives, such as *N*-tosyl carbamates, ureas, and so on.[12m,59,60] Apparently, the catalytic reaction requires rather more acidic N–H, which is available in carbamates, and related groups, but not in free amines.

The present method can be regarded as a complementary, stereocontrolled approach to di- and tri-substituted isoxazolidines, some of which can also be synthesized, for example, by cycloaddition of nitrones[61] and other approaches[62,63] but not always with the selectivity as high as reported here. Furthermore, the Boc-protected isoxazolidines **16** can be readily converted into the protected β-amino-δ-hydroxy esters and their γ-substituted homologues, for example, **37**, by cleavage of the N–O bond (Scheme 10). In fact, isoxazolidines **16** can be regarded as fully and orthogonally protected surrogates of β-amino-δ-hydroxy acids: thus, the carboxyl function of **16** can be envisaged to be deprotected by hydrolysis (whereas O and N remain protected). Conversely, the Boc group can be removed and the resulting product **38/40** could be functionalized at the nitrogen with an option of a selective deprotection either at oxygen (by a subsequent cleavage of the O–N bond) or at the carboxyl (by hydrolysis). Finally, cleavage of the N–O bond in **16** gives the O-deprotected product **37** with the two other functional groups remaining to be orthogonally protected. Lactonization of **37a** to produce **39a**, as an example of yet another selective transformation under very mild conditions, has also been demonstrated (Scheme 10).

Experimental Section

General Methods: Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated with an error of $< \pm 0.1$. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra were recorded for $CDCl_3$ solutions, ^{1}H at 400 MHz, ^{13}C at 100.6 MHz and ^{19}F at 376 MHz with chloroform-d_1 ($\delta = 77.0$, ^{13}C), tetramethylsilane ($\delta = 0.00$, ^{1}H) and trichlorofluoromethane ($\delta = 0.00$, ^{1}H) as internal standards unless otherwise indicated. The IR spectra were recorded for $CHCl_3$ solutions. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free argon in oven-dried glassware twice evacuated and filled with the argon. Solvents and solutions were transferred by syringe-septum and cannula techniques. Solvents for the reactions were of reagent grade and were dried; acetonitrile was distilled immediately before use from calcium hydride, THF was obtained from Pure-Solv™ Solvent Purification System (Innovative Technology) and DMPU was dried with molecular sieves (4 Å), which were activated at 300 °C. The enantiomeric purity was determined by using chiral HPLC and GC techniques (for alcohols) and by ^{19}F or ^{1}H NMR measurements of Mosher derivatives (for *O*-alkoxyamines).[64] The starting homoallylic alcohols were prepared previously: (±)-**4a**;[42b] (*S*)-(−)-**4b** (96 % *ee*);[35] and (*S*)-(−)-**4c** (95 % *ee*). This sample has now been obtained on the allylation reaction using (+)-**5** as catalyst; previously, its enantiomer was prepared via the reaction catalyzed by (*R*)-(+)-**8**;[36]] (*S*)-(−)-**4e** (92 % *ee*; this sample has now been obtained on the allylation reaction using (+)**5** as catalyst; (1*S*,2*S*)-(−)-**4g** (95 % *ee* by GC; 55:1 *anti/syn* by ^{1}H NMR spectroscopy;[41] its enantiomer was also prepared by us;[36] (*R*)-(+)-**9** (92 % *ee*)).[41,65] The alkoxyamine **10a** and its Boc derivative **12a** were also prepared previously.[42b] Single crystal X-ray diffraction data were collected at 100 K on Bruker APEX-II (lactone **39a**) and Nonius KappaCCD (isoxazolidine **40**) diffractometers using $Mo_{K\alpha}$ radiation (0.71073 Å). Data were merged and averaged using SORTAV[66] and structures were solved using the programs SIR92[67] for lactone **39a** and SUPERFLIP[68] for isoxazolidine **40**. Structures were refined by full-matrix least-squares methods using the program SHELXL-97.[69] General experimental syntheses are given below; full compound characterization can be found in the Supporting Information.

Allylation and crotylation of aldehydes catalyzed by METHOX (Method A): The respective allylic trichlorosilane (3 mmol) was added to a solution of the respective aldehyde (1.5 mmol), Hünig base (1.57 mL, 9 mmol), and METHOX (28 mg, 0.075 mmol) in freshly distilled CH_3CN (10 mL) under argon at −40 °C. The reaction mixture was stirred at the corresponding temperature for 24 h and monitored by TLC. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and the mixture was diluted with ethyl acetate (150 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed in vacuum. The product was purified on a column of silica gel (2.5 × 25 cm) using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 85:15). The enantiomeric and diastereoisomeric purity was established for both the crude product and the purified material.

Synthesis of alkoxyamines with inversion of configuration using the Mitsunobu reaction (Method B): Triphenylphosphine (1.2 mmol) and *N*-hydroxy-phthalimide (1.2 mmol) were added to a solution of the respective alcohol (1 mmol) in freshly distilled THF (10 mL) under argon at 0 °C and the mixture was stirred for 2 min. Diisopropyl azodicarboxylate (1.2 mmol) was then added dropwise over a period of 30 min and the resulting solution was stirred at room temperature under argon for 2 h. Hydrazine hydrate (100 % $N_2H_4 \cdot H_2O$, 0.1 mL) was then added and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with deionized water (5 mL) and the mixture was diluted with a mixture of ethyl acetate and petroleum ether (1:1; 10 mL). The organic layer was separated and the aqueous layer was extracted with a mixture of ethyl acetate and petroleum ether (1:1; 3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and the solvents were removed in vacuum. The product was purified on a column of silica gel (1.5 × 20 cm) using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10). The enantiomeric and diastereoisomeric purity was established for both the crude product and the purified material.[70]

Synthesis of alkoxyamines with retention of configuration (Method C).[45] The respective alcohol (1.0 mmol), 18-crown-6 ether (0.2 mmol), and KH (1.2 mmol), obtained by rinsing its oil suspension with hexane, were added consecutively to 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU; 1.5 mmol) and the mixture was stirred at room temperature for 1 h under Ar. The resulting mixture was then added dropwise to a solution of 3,3-di-tert-butyl-oxaziridine (1.2 mmol) in DMPU (1.5 mL) at −40 °C and the resulting mixture was stirred first at −40 °C, then slowly allowed to warm to room temperature over a period 2 h (the reaction starts at ca. −20 °C; if heated too fast, the mixture tends to overflow from the flask). The reaction was quenched with brine (5 mL) and the mixture was diluted with a mixture of ethyl acetate and petroleum ether (1:1; 10 mL). The organic layer was separated and the aqueous layer was extracted with an ethyl acetate-petroleum ether mixture (1:1; 3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed in vacuum. The product was purified on a column of silica gel (1.5 × 20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10). The enantiomeric and diastereoisomeric purity was established for both the crude product and the purified material.

Synthesis of N-Boc derivatives of alkoxyamines (Method D):[42a] A solution of the respective alkoxyamine (1.0 mmol) and $(Boc)_2O$ (2.0 mmol) in CH_2Cl_2 (15 mL) was added to a solution of NaOH (2.0 mmol) in deionized water (5 mL) and the resulting two-phase mixture was stirred at room temperature for 24 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed in vacuum. The product was purified on a column of silica gel (1.5 × 20 cm) using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 85:15).

Palladium-catalyzed cyclization/carbonylation (Method E): A round-bottom flask was charged with $PdCl_2$ (0.1 mmol) and $(AcO)_2Cu \cdot 2H_2O$ (3.0 mmol) and flushed with CO. The flask was then connected to a CO balloon (atmospheric pressure). Methyl orthoacetate (10 mL) was added and the resulting solution was stirred at room temperature for 30 min. A solution of the respective Boc-protected alkoxyamine (1.0 mmol) in MeOH (10 mL)[71] was added in one portion and the mixture was stirred at 40 °C until completion of the reaction (monitored by TLC), typically 48 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (5 mL), the mixture was diluted with deionized water (5 mL) and extracted with ethyl acetate (4 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuum. The product was purified by chromatography on a column of silica gel (1.5 × 10 cm) using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10). The diastereoisomeric purity was established for both the crude product and the purified material.

Reduction of the cyclization products with $Mo(CO)_6$ (Method F): A solution of the respective isoxazolidine (0.1 mmol) in a 9:1 mixture of CH_3CN and H_2O (2.5 mL) was added to $Mo(CO)_6$ (0.5 mmol) and the resulting solution was heated to reflux (≈90 °C) under argon for 2 h, during which time the color had changed from white to black. The mixture was then cooled to room temperature, filtered through Celite, which was then washed with ether (3 × 5 mL), and the combined filtrate was evaporated. The residue was purified by chromatography on a column of silica gel (1 × 7 cm), using a gradient of petroleum ether and ethyl acetate from 9:1 to 2:1.

Preparation of Mosher amides from N-Alkoxyamines (Method G).[64] (*R*)-(+)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionyl chloride (150 mg, 0.6 mmol), prepared in situ from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (99 % *ee* from Sigma–Aldrich),[33f] was added to a solution of the alkoxyamine (0.5 mmol) and triethylamine (0.6 mmol) in CH_3CN (1 mL) and the reaction mixture was stirred at room temperature for 1 h. The solvent was then removed in vacuo and the resulting oil was dissolved in ether (20 mL). The ethereal solution was washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4) and concentrated in vacuo to give an oil, which was analyzed by ^{19}F and ^{1}H NMR techniques.

Acknowledgements

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[49] We reasoned that the effect of the strongly donating *p*-MeO substituent effect could be mitigated by replacing the MeO with a less-donating oxygen group, such as AcO. Indeed, the *anti*-configured *p*-acetoxy derivative (**4**, R^1 = 4-$AcOC_6H_4$, R^2 = Me, 96% *ee*, 28:1 d.r.) underwent the Mitsunobu reaction with a practically clean inversion of configuration to produce the corresponding *syn*-alkoxyamine (25:1 d.r.). Details of this and other examples will be revealed in due course.

[50] The reaction proved to be rather capricious and low conversions were observed in some batches; it turned out that the system must be rigorously dry.

[51] METHOX (+)-**5** was synthesized in four steps from (+)-α-pinene (see Ref. [35a]). Its enantiomer could be prepared in the same way from (−)-α-pinene, which is also commercially available. QUINOX (*R*)-(+)-**8** was obtained from the racemate on a very efficient resolution by (*S*)-(−)-BINOL (see Ref. [36]). The opposite enantiomer was recovered from the mother liquor (Ref. [36]), and may also be obtained by using (*R*)-(+)-BINOL for the resolution.

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[56] Lactonization of hydroxy esters is typically carried out by treatment with Brønsted or Lewis acids, or is catalyzed by enzymes (see Ref. [57]). In our case (compound **37**), the presence of the acid-sensitive Boc group limited the choice of acidic conditions. Nevertheless, 10% of *p*-TsOH in toluene was sufficient to complete the reaction and mild enough to avoid deprotection. However, partial epimerization at the benzylic center was observed, so that this method was abandoned. The use of a strong mineral base, such as KOH, in polar solvents or water resulted in the saponification of the ester group. A stoichiometric amount of DBU (a strong, non-nucleophilic base) in acetonitrile triggered a quantitative conversion to the desired lactone **39a** within minutes but this process was acompanied by the formation of several byproducts. On the other hand, employing just 5 mol% of DBU in diluted reaction mixture (in MeCN) was found to be an optimal protocol, as it resulted in a clean conversion of **37a** into lactone **39a** in a few hours at room temperature. The X-ray analysis of the final product confirmed the relative configuration for the whole series of transformations.

[57] For an effective and mild lactonization of hydroxy esters, see, for example: a) H. Kuno, M. Shibagaki, K. Takahashi, I. Honda, H. Matsushita, *Chem. Lett.* **1992**, 571; b) J. Fujita, S. Watanabe, K. Suga, Y. Higuchi, T. Sotoguchi, *J. Org. Chem.* **1984**, *49*, 1975; c) C. Bonini, P. Pucci, R. Racioppi, L. Viggiani, *Tetrahedron: Asymmetry* **1992**, *3*, 29; d) D. Berkeš, A. Kolarovič, R. Manduch, P. Baran, F. Považanec, *Tetrahedron: Asymmetry* **2005**, *16*, 1927; e) J. D. White, N. J. Green, F. F. Fleming, *Tetrahedron Lett.* **1993**, *34*, 3515; f) A. Makita, T. Nihira, Y. Yamada, *Tetrahedron Lett.* **1987**, *28*, 805. For lactonization with DBU, see: g) J. J. Gaudino, C. S. Wilcox, *Carbohydr. Res.* **1990**, *206*, 233; h) Y. Yoshida, Y. Ukaji, S. Fujinami, K. Inomata, *Chem. Lett.* **1998**, 1023; i) Z. Yang, W. Zhou, *Tetrahedron* **1995**, *51*, 1429.

[58] Extension of this methodology to the realm of non-aromatic starting materials was also briefly explored. Thus, the Mitsunobu reaction of *N*-hydroxyphthalimide with $PhCH{=}CHCH(OH)CH_2CH{=}CH_2$ (88% *ee*), which in turn was obtained from the METHOX-catalyzed allylation of cinnamaldehyde with allytrichlorosilane (Ref. [35b]), followed by deprotection with hydrazine, produced an inseparable 2:1 mixture of the alkoxyamines corresponding to a direct substitution (S_N2) and that arising by allylic rearrangement (S_N2'), as revealed by ^1H NMR spectroscopy. The ^{19}F NMR spectrum of the Mosher derivatives, obtained from this mixture, showed ≈40% *ee* for the former product, while the latter rearranged derivative was practically racemic. Boc-derivatization of the latter mixture afforded a 2:1 mixture, in which the desired "normal" product, that is, $PhCH{=}CHCH(ONBoc)CH_2CH{=}CH_2$ prevailed. Palladium-catalyzed carbonylation of this mixture proceeded as expected, giving rise to the corresponding isoxazolidine, as a result of the reaction of the homoallylic double bond, whereas its allylic C=C bond remained intact. The isomeric Boc derivative remained unreacted, which allowed the isolation of the desired isoxazolidine. This promising chemoselectivity demonstrated the wider applicability of this methodology. The current bottle neck, that is, obtaining the desired alkoxyamine, will be addressed in due course.

[59] Protected hydrazines, obtained from **4** via the Mitsunobu reaction with dialkyl diazodicarboxylate (for the method, see: M. J. Di Grandi, J. W. Tilley, *Tetrahedron Lett.* **1996**, *37*, 4327), undergo analogous, ring-closing amidocarbonylation to produce the pyrrazolidine analogues of isoxazolidines **16**; details of this new procedure will be disclosed in due course.

[60] a) For the Pd-catalyzed cyclization of *N*-tosyl carbamates in the absence of CO, see: F. Nahra, F. Liron, G. Prestat, C. Mealli, A. Messaoudi, G. Poli, *Chem. Eur. J.* **2009**, *15*, 11078 and references cited therein. For correction, see: b) F. Nahra, F. Liron, G. Prestat, C. Mealli, A. Messaoudi, G. Poli, *Chem. Eur. J.* **2010**, *16*, 1414. In a similar way, our carbamate **15** undergoes an analogous cyclization in the

absence of CO, giving rise to the corresponding oxazolidine with a pendant vinyl group; details will be communicated in due course.
[61] For selected examples of the synthesis of isoxazolidines by nitrone cycloaddition, see, for example: a) X. Ding, K. Taniguchi, Y. Hamamoto, K. Sada, S. Fujinami, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1059; b) Y. Ukaji, K. Taniguchi, I. Sada, *Chem. Lett.* **1997**, 547. For the synthesis of negamycin via nitrone addition, see: c) H. Iida, K. Kasahara, C. Kibayashi, *J. Am. Chem. Soc.* **1986**, *108*, 4647; d) D. Socha, M. Jurczak, M. Chmielewski, *Tetrahedron Lett.* **1995**, *36*, 135. For the nitrone approach to monomorine, see: e) M. Ito, C. Kibayashi, *Tetrahedron Lett.* **1990**, *31*, 5065; f) M. Ito, C. Kibayashi, *Tettrahedron* **1991**, *47*, 9329; g) N. Morita, K. Fukui, J. Irikuchi, H. Sato, Y. Takano, I. Okamoto, H. Ishibashi, O. Tamura, *J. Org. Chem.* **2008**, *73*, 7146.
[62] For the construction of isoxazolidines via the organocatalyzed intramolecular addition of an *N*-Boc-protected hydroxylamine moiety across a conjugated double bond, see: Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328.
[63] For the IBX-mediated cyclization of *N*-acyl analogues of **12**, see Ref. [44].
[64] Mosher acid: (R/S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid. For the synthesis and utilization, see: a) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543; b) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512; c) H. Iwagami M. Yatagai, M. Nakazawa, H, Orita, Y. Honda, T. Ohnuki, T. Yukawa, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 175; d) For checking the enantiopurity of the Mosher acid purchased from Aldrich, see Ref. [33f].
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[70] For comparison, see Ref. [44] and the following: T. Ishikawa, M. Kawakami, M. Fukui, A. Yamashita, J. Urano, S. Saito, *J. Am. Chem. Soc.* **2001**, *123*, 7734.
[71] The minimum amount of the solvent for 1 mmol of the substrate is 5 mL of $MeC(OMe)_3$ and 5 mL of MeOH, in which the reaction is faster but less diastereoselective. Using 10 mL of each solvent gives better yields and the *anti* product could not be detected in the ^1H NMR spectrum of the crude product.

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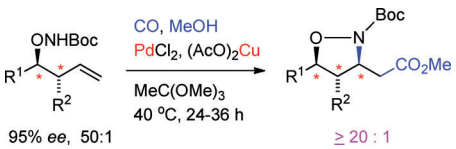

***Syn*-full cyclization!** Enantiopure, Boc-protected alkoxyamines undergo a diastereoselective Pd-catalyzed ring-closing carbonylative amidation to produce isoxazolidines ($\leq$50:1 d.r.) that can be readily converted into the *N*-Boc-protected esters of β-amino-δ-hydroxy acids and their γ-substituted homologues (see scheme). The key carbonylative cyclization proceeds through an unusual *syn* addition of the palladium and the nitrogen nucleophile across the C=C bond.

Stereocontrol

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Stereoselective Palladium-Catalyzed Functionalization of Homoallylic Alcohols: A Convenient Synthesis of Di- and Tri-Substituted Isoxazolidines and β-Amino-δ-Hydroxy Esters