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Regio- and stereoselective microwave-assisted synthesis of 5-alkyl-4-alkenyl-4-phenyl-1,3-oxazolidin-2-ones

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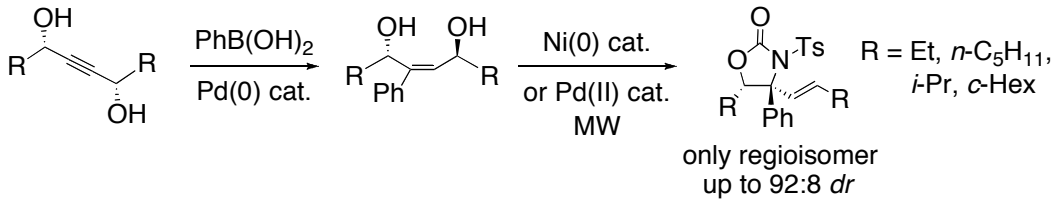

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TETRAHEDRON LETTERS

Regio- and stereoselective microwave-assisted synthesis of 5-alkyl-4-alkenyl-4-phenyl-1,3-oxazolidin-2-ones

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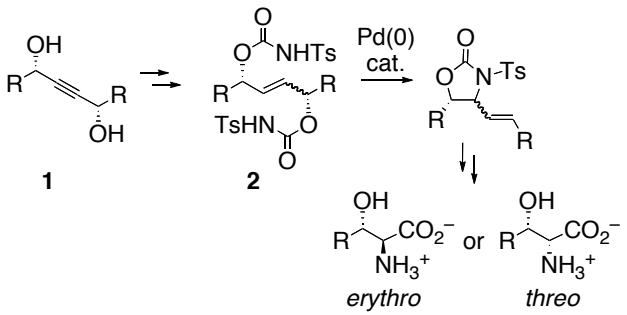
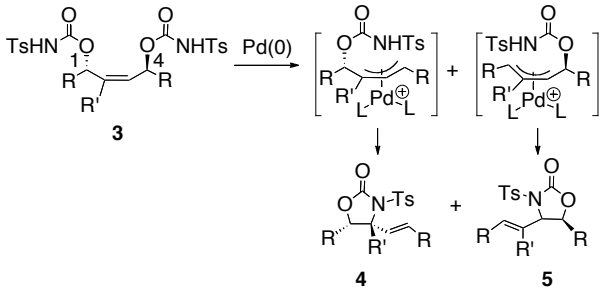
Abstract—Chiral symmetrical alk-2-yne-1,4-diols have been stereoselectively transformed into 5-alkyl-4-alkenyl-4-phenyl-1,3-oxazolidin-2-ones, which are precursors of quaternary α-amino β-hydroxy acids. The key step was the cyclization of the bis(tosylcarbamates) of 2-phenylalk-2-yne-1,4-diols, easily obtained from the starting chiral diols. These cyclizations were accomplished with complete regioselectivity and up to 92:8 *dr* in the presence of catalytic amounts of Ni(0) or Pd (II) derivatives under microwave heating.

Enantioenriched 1,4-diols have been shown to be versatile synthons for asymmetric synthesis.[1] In the course of a project aimed to develop synthetic applications of unsaturated 1,4-diols,[2] we have recently reported the preparation of both *erythro* and *threo* β-hydroxy α-amino acids from a common precursor, namely a C_2-symmetrical alk-2-yne-1,4-diol (**1**) (Scheme 1).[3] The key step of our approach was a stereoselective Pd(0)-catalyzed intramolecular *N*-alkylation of the allylic (*Z*)- or (*E*)-1,4-dicarbamates (**2**) derived from **1**.[4] It should be noted that, due to the C_2-symmetrical properties of the starting materials, only one regioisomer was possible in such processes.



Scheme 1. Reported synthesis of *erythro* and *threo* β-hydroxy α-amino acids.

Herein, we extend the scope of our work to allylic 1,4-dicarbamates **3**, in which symmetry is broken by an additional substituent R' on the double bond. Cyclization on **3** is a challenging issue since two regioisomers, **4** or **5** are possible (Scheme 2). We were interested in the preferential formation of carbamates **4**, potential precursors of quaternary amino acids after the oxidative cleavage of the double bond. In particular, we envisaged that when R' = Ph in **3**, the ionization of the carbamate group on C(4), leading to **4**, will be favored for steric and electronic reasons. Thus, the Ph group could better extend the conjugation of the transient π-allylic cations in a Pd(0)-catalyzed process.



Scheme 2. Cyclization of dicarbamates **3**

Thus, we embarked on a study aimed to obtain compounds **3** (with R' = Ph) and their further transformation into the

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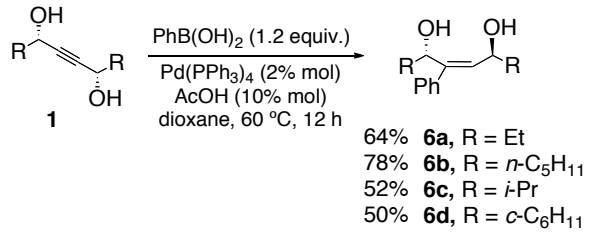
quaternary carbamates **4**. We wish to report herein our findings in this connection.

As expected, starting chiral diols **1** were readily desymmetrized by reaction with phenylboronic acid in the presence of $[Pd(PPh_3)_4]$.[5] As observed in Scheme 3, diols **6a–d** were isolated in 50–78% yield with complete *Z* selectivity using 2% mol of Pd catalyst and 10% mol of AcOH in dioxane.[6] Diols **6** were quantitatively transformed into dicarbamates **3** by treatment with tosyl isocyanate (2 equiv.) in CH_2Cl_2.



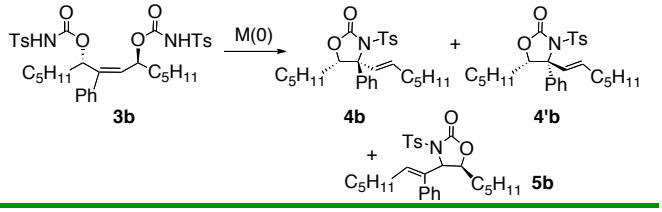
Scheme 3. Preparation of 2-phenylalk-2-ene-1,4-diols, **6.**

We chose **3b** as a representative model to test the cyclization step. We first applied to **3b** the experimental conditions used for the Pd(0)-catalyzed intramolecular *N*-alkylation of **2**.[3a] Unfortunately, the expected quaternary compound **4b** was not observed (Table 1, entries 1 and 2) or appeared just as a minor component in a mixture (entry 3). A series of experiments were then undertaken in which we changed the solvent (DMF, DMSO, mixtures with THF and CH_3CN), the source of palladium ($[Pd(Ph_3P)_4]$, $[(C_3H_5)ClPd]_2$), additives [$(PhO)_3P$, dppe, dppp] and temperatures (rt to 80 ºC) without success.[7] Although in some cases the overall yields of cyclic carbamates were acceptable, mixtures of regio- and stereoisomers were always obtained.

We then moved to other low valent metal complexes that were able to give allylic alkylation via π-allyl complexes looking for a better control of regioselectivity. Among others, Mo,[8] Ir[9] or Ni[10] derivatives, are less efficient catalyst for allylic substitution than Pd(0)-complexes. As a result, high temperatures and longer reactions times are usually required. However, these complexes often showed regio– and stereoselectivities quite different from those recorded in palladium complex–catalysed allylic aminations.[11] In practice, the treatment of **3b** with 20% mol of $[Mo(CO)_6]$ or $[Mo(CO)_4(bpy)]$[12] in refluxing toluene afforded preferently isomer **5b** in low yields (Table 1, entries 4 and 5). The use of an Ir(0)-catalyst generated as described in the literature in some examples of intermolecular allylic amination[9b,c] gave only the undesired isomer **5b** (entry 6).[13]

The most favorable results were obtained with Ni(0) catalysts. To our knowledge only a few Ni(0)-catalyzed allylic aminations have been reported[14] and none of them related with the creation of quaternary centers. After a few preliminary experiments with $[Ni(COD)_2]$,[15] we achieved more reliable results with the Ni(0) catalyst generated in situ from $[NiCl_2(PPh_3)_2]$ or $[NiCl_2(dppe)]$ and *i*-PrMgCl, following a protocol described by Cuvigny *et* Julia.[10b]

Table 1. M(0)–Catalyzed cyclization of **3b**.



Entry	Catalyst, additive	Solvent, T	Time	Yield (%)	Ratio **4b**:**4'b**:**5b**
1[a]	$Pd_2(dba)_3{\cdot}CHCl_3$ $(i\text{-PrO})_3P$	THF, rt	20 h	10<	-
2[a,b,c]	$Pd_2(dba)_3{\cdot}CHCl_3$ $(i\text{-PrO})_3P$	THF, MW	2 h	80	0:0:100
3[a]	$Pd_2(dba)_3{\cdot}CHCl_3$ $(i\text{-PrO})_3P$	CH_3CN, rt	4 h	89	41:0:59
4[d]	$[Mo(CO)_6]$	Toluene, reflux	12 h	20	15:8:77
5[d]	$[Mo(CO)_4(bpy)]$	Toluene, reflux	12 h	11	11:6:83
6[a,c]	$[Ir(COD)Cl]_2$ $(PhO)_3P$	EtOH, reflux	20 h	35	0:0:100
7[d]	$[NiCl_2(PPh_3)_2]$ *i*-PrMgCl	THF reflux	20 h	15	83:17: 0
8[d]	$[NiCl_2(dppe)]$ *i*-PrMgCl	THF reflux	20 h	10	83:17: 0
9[b,d]	$[NiCl_2(PPh_3)_2]$ *i*-PrMgCl	THF, MW	2 h	58	92:8: 0
10[b,d]	$[NiCl_2(PPh_3)_2]$	THF, MW	2 h	–	–:–: –

[a]5% mol catalyst was used.

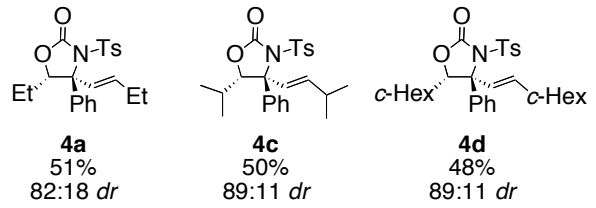
[b]MW heating at 120 ºC.

[c] ^1H NMR of **5b** indicated a mixture of 2:1 *cis*/*trans* oxazolidinones.

[d]20% mol catalyst was used.

In sharp contrast with our previous attempts, the quaternary carbamates **4** were readily obtained with complete regioselectivity, and high stereoselectivity,[16] albeit in low yield (entries 7 and 8). With Ni(0) catalyst showing promise, we performed the reaction heating in a microwave oven to accomplish the consumption of the starting material.[17] To our satisfaction, **4b** was isolated in 58% yield and a remarkably 92:8 diastereomeric ratio (entry 9).[18] In

an additional experiment in which the addition of *i*-PrMgCl was omitted, neither **4** nor **5** was observed. Thus, the possibility that a Ni(II) specie acts as the true catalyst was ruled out.

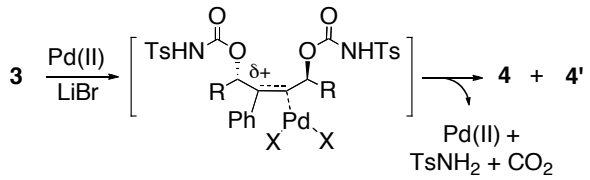


4a 51% 82:18 *dr* **4c** 50% 89:11 *dr* **4d** 48% 89:11 *dr*

Scheme 4. Ni(0)-Catalyzed cyclization of dicarbamates **3**.

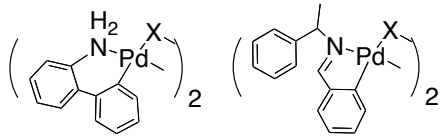
As shown in Scheme 4, this new Ni(0)-catalyzed process was extended to dicarbamates **4a**, **4c** and **4d** with complete regioselectivity but in moderate yields. As far as the diastereoselectivity is concerned, a similar trend of ~9:1 ratio was observed when R was α-branched, and slightly lower for a smaller R (**4a**).

We then considered using a Lewis acid to promote the cyclization.[19] Lu *et al* recently described the cyclization of allylic dicarbamates using $Pd(AcO)_2$ and LiBr in THF.[20] We presumed that in compounds **3**, the Ph group could act as directing group by stabilizing the positive charge in the benzylic position (Scheme 5).



Scheme 5. Pd(II)-catalyzed transformation of **3** into **4**.

As expected, treatment of **3c** with $Pd(AcO)_2$ and LiBr in refluxing THF yielded the expected product **4** with total regioselectivity but low stereoselectivity (entry 1, Table 2). Once again, the use of microwave heating was beneficial since the ratio **4b**/**4'b** was improved to 80:20 (entry 2).



7, X = OAc
8, X = Cl
9, X = OAc

Figure 1. Palladacycles **7**–**9**.

We also attempted the use of palladacycles **7**–**9** as a source of Pd(II).[21] Palladacycles are organometallic compounds of growing interest in catalysis.[22] Remarkably, the performance of **7** was comparable to or even slightly better than that obtained with the above mentioned Ni(0) catalyst (Table 2, entries 9 and 10). These positive preliminary results and the structural variety of palladacycles, indicated that there is room for future improvements in this field.

Table 2. Pd(II)–Catalyzed cyclization of **3**.

Entry	**3** R	Catalyst, additive	Solvent T	Time	Yield (%) ratio **4**:**4'**
1[a]	**3b** C_5H_{11}	$Pd(AcO)_2$ LiBr	THF, reflux	15 h	52 56:49
2[a,b]	**3b** C_5H_{11}	$Pd(AcO)_2$ LiBr	THF, MW	2 h	50 80:20
3[a]	**3b** C_5H_{11}	$[PdCl_2(PPh_3)_2]$ LiCl	THF, reflux	15 h	<10
4[a]	**3b** C_5H_{11}	$[PdCl_2(PhCN)_2]$ LiCl	THF, reflux	15 h	<10
5[c]	**3b** C_5H_{11}	**7** LiBr	THF, reflux	15 h	55 80:20
6[c]	**3b** C_5H_{11}	**8** LiBr	THF, reflux	15 h	48 80:20
7[c]	**3b** C_5H_{11}	**9** LiBr	THF, reflux	15 h	36 78:22
8[b,c]	**3b** C_5H_{11}	**7** LiBr	THF, MW	2 h	61 80:20
9[b,c]	**3c** *i*-Pr	**7** LiBr	THF, MW	2 h	40 92:8
10[b,c]	**3d** *c*-Hex	**7** LiBr	THF, MW	2 h	52 91:9

[a]10% mol Pd(II) catalyst was used.

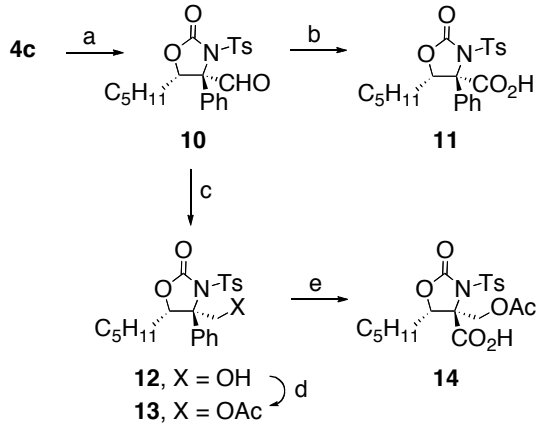
[b]MW heating at 120 ºC.

[c]8% mol Pd(II) catalyst was used.

Finally, in order to demonstrate the value of compounds **4** in synthesis, we successfully transformed **4c** into quaternary amino acids **11** and **14** (Scheme 6). Thus, ozonolysis of **4c** followed by oxidation of the crude aldehyde **10** with $NaClO_2$[23] gave protected α-amino α-phenyl β-hydroxy acid **11**. On the other hand, aldehyde **10** was reduced and then the resulting primary alcohol **12** was protected as acetate **13**. Ruthenium-mediated oxidation[24] of the phenyl group afforded the α-amino β,β'-dihydroxy acid **14**. It should be noted that the substructure of the α-amino α-hydroxymethyl β'-hydroxy acid is present in a number of bioactive natural products such as myriocin, mycesterycins, and sphingofungins.[25]

In summary, we have developed a new, stereoselective, approach to 5-alkyl-4-alkenyl-4-phenyl-1,3-oxazolidin-2-ones. The key step was either a Ni(0)- or Pd(II)-catalyzed cyclization in which the use of palladacycles and the

microwave heating are pivotal. The cyclic carbamates obtained are precursors of quaternary α-amino β-hydroxy acids, as demonstrated with the compound in which R = *n*-C_5H_{11}. Further applications, specially on palladacycle catalysts, will be reported in due course.



Scheme 6. Reagents and conditions: (a) O_3, CH_2Cl_2, –78 ºC, then Me_2S, rt, 98%; (b) $NaClO_2$, H_2O_2, NaH_2PO_4, H_2O/CH_3CN, 95%; (c) $NaBH_4$, THF, 0 ºC, 100%; (d) Ac_2O, Et_3N, 4-DMAP cat., CH_2Cl_2, 0 ºC, 97%; (e) $RuCl_3$ cat., $NaIO_4$, $CH_3CN/CCl_4/ H_2O$ 1:1:1.5, 45%.

Acknowledgments

This work has been supported by the Ministerio de Educación y Ciencia (BQU2003-01269 and CTQ2006-13249); We thank the Secretaría de Estado de Universidades e Investigación (MEC, Spain) for a postdoctoral fellowship to J.B. and to the Universidad de Barcelona for doctoral studentships to M.A. and L.D.

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6. *Typical experimental procedure*: Acetic acid (43 μL, 0.75 mmol) was added to a solution of (*S*,*S*)-**1c** (1.707 g, 7.54 mmol), phenylboronic acid (1.103 g, 9.05 mmol) and $Pd(PPh_3)_4$ (174 mg, 0.15 mmol) in dioxane (20 mL) at 0 ºC under Ar. The mixture was heated to 60-65 ºC until the TLC (hexane/AcOEt 7:3) revealed the disappearance of the starting diol (12 h) and then quenched by addition of water (15 mL). The mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with water (15 mL), dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography (hexane/AcOEt 7:3) to afford **6c** (1.790 g, 78%). Colorless oil; R_f (CH_2Cl_2): 0.48; $[\alpha]_D^{20}$= +32.0 (*c*=1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, *J* = 6.8 Hz, 3H, CH_3), 0.90 (t, *J* = 7.0 Hz, 3H, CH_3), 1.22-1.37(m, 10H, CH_2), 1.38-1.45 (m, 2H, CH_2), 1.51-1.59 (m, 2H, CH_2), 1.62-1.69 (m, 2H, CH_2), 2.36 (bs, 2H, OH), 4.70 (dt, *J* = 8.8, 6.8 Hz, 1H, =CH-C<u>H</u>-OH), 4.74 (dd, *J* = 8.0, 5.2 Hz, 1H, =CPh-C<u>H</u>-OH), 5.58 (d, *J* = 8.8 Hz, 1H, CH=), 7.28-7.35 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 13.9 and 14.0 (CH_3), 22.5, 22.6, 25.3, 25.8, 31.6, 31.8, 36.6, and 37.8 (CH_2), 67.6 (=CH<u>C</u>H-OH), 72.8 (CPh<u>C</u>H-OH), 127.3, 127.8, 127.8, 128.1 and 128.1 (Ar), 134.2 (CH=), 141.4 (Ar), 146.0 (CPh=); IR (film): ν_{max} 3388, 2956, 2931, 2860, 1493, 1459, 1028.
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15. A series of experiments were performed in which we changed the amount of catalyst (0.1–0.4 % mol of $[Ni(COD)_2]$), in presence or absence of base (LiHMDS), ligands (PPh_3, BINAP) and temperatures (rt to MW heating to 120 ºC) gave poor and/or erratic results.
16. Relative configuration of cyclic carbamates **4** were readily determined by ^{1}H NMR nOe experiments.
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18. *Typical procedure*: To a solution of $[NiCl_2(PPh_3)_2]$ (19 mg, 28.6 μmol) in dry THF (0.6 mL) was added *i*-PrMgCl (29 μL, 57.2 μmol, 2.0M solution in Et_2O) at 0 ºC under Ar. After 10 min the solution changed from green to brownish. Then the mixture was transfered via cannula to a flask containing a solution of dicarbamate (*S*,*S*)-**3c** (100 mg, 0.143 mmol) in THF (0.6 mL) under Ar and the mixture was heated in a microwave oven for 2 h to 120 ºC (inside pressure was 5–6 bars). Then, the solvent was removed and the crude was filtered through a short pad of Celite (AcOEt). The solvent was removed and the residue was purified by flash chromatography (hexane/AcOEt 8:2) to afford a 92:8 mixture of **4c**/**4'c** (40 mg, 0.083 mmol, 58%). (b) Compound **4c**: white solid, mp 84–85 ºC ;R_f (hexane/AcOEt 7:3): 0.47; $[\alpha]_D^{20}$= –47.0 (*c*=0.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (t, *J* = 6.8 Hz, 3H, CH_3), 0.92 (t, *J* = 7.2 Hz, 3H, CH_3), 1.15-1.20 (m, 6H, CH_2), 1.33-1.40 (m, 6H, CH_2), 1.49-1.54 (m, 2H, CH_2), 2.25-2.31 (m, 2H, CH_2), 2.42 (s, 3H, CH_3-Ar), 4.44 (dd, *J* = 10.0, 2.8 Hz, 1H, C<u>H</u>-O), 5.92 (dt, *J* = 15.6, 1.4 Hz, 1H, C<u>H</u>=CHCH$_2$), 6.18 (dt, *J* = 15.6, 6.8 Hz, 1H, CH=C<u>H</u>-CH$_2$), 7.23 (d, *J* = 8.4 Hz, 2H, Ar), 7.39-7.49 (m, 5H, Ar), 7.63 (d, *J* = 8.4 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 13.8 (CH_3), 14.0 (CH_3), 21.6 (CH_3-Ar), 22.2, 22.4, 25.5, 28.5, 28.9, 31.3, 31.4 and 32.7 (CH_2), 74.1 (CPh-NTs), 87.9 (CH-O), 123.5 (TsNCPh -<u>C</u>H=), 127.6, 128.5, 129.0, 129.1, 129.2 and 135.8 (Ar), 137.1 (CH_2<u>C</u>H=), 138.9 (C(Ar)), 145.0 (C(Ar)-SO_2)), 152.5 (C=O).; IR (KBr): ν_{max} 2929-2860, 1781, 1175, 1090.
19. Experiments performed with **3c** and DBU in the presence of 20% mol of $Sc(OTf)_2$ (THF, rt or 60 ºC) caused the degradation of starting material. The use of $PtCl_2$ led to the recovery of starting dicarbamate. In THF no reaction was observed.
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