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Palladium-catalyzed intramolecular allylic alkylation of α-sulfinyl carbanions: a new asymmetric route to enantiopure γ-lactams

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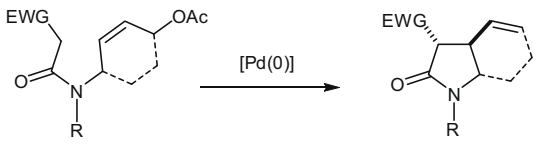
ABSTRACT

Asymmetric intramolecular palladium-catalyzed allylic alkylation allowing access to disubstituted sulfinyl γ-lactams is described. The use of unsaturated amides bearing a sulfinyl group of defined absolute configuration together with enantiopure BINAP as the ligand in a biphasic medium provided good diastereoselectivities with clear solvent effect.

Transition metal-catalyzed allylic substitutions have proven to be a fundamental tool for carbon–carbon bond formation.[1] In 1998, we reported an intramolecular palladium-catalyzed route to 3,4-substituted γ-lactams.[2] The cyclization process was based on the interaction between a resonance-stabilized carbanion and an allylic acetate linked by an amide function (Eq. 1). This reaction revealed to be highly regio- and stereoselective leading exclusively to the trans product via a 5-*exo* process.



EWG= CO_2Me, CN, COMe; SPh; SO_2Ph; R=Bn, PMB

Equation 1. Palladium-catalyzed intramolecular allylic alkylation.

We applied this strategy to the synthesis of various racemic natural or non natural compounds of biological interest.[3]

The development of an asymmetric version of this cyclization process was therefore highly desirable in order to access to enantioenriched γ-lactams. To this purpose, two complementary approaches have been planned. The former one was based on the use of enantiopure atropoisomeric ligands and produced enantiopure 3,4-substituted γ-lactams in er's up to 92:8.[4] The latter one, object of the present communication, allows to obtain enantiopure 3,4-substituted γ-lactams via the use of a covalently linked configurationally defined sulfinyl group as chirophoric moiety.

Whereas palladium-catalyzed allylic alkylation of stabilized α-sulfenyl- and α-sulfonyl carbanions has been thoroughly described,[5] the related reaction involving α-sulfinyl carbanions has been so far nearly ignored.[6] This lack, despite the inherent importance of the stereogenic sulfur atom in α-sulfinyl carbanions, may be connected to the high coordination power of the sulfoxide function toward palladium, which very likely inhibits a facile catalysis.[7] Indeed, such a coordination prevents the direct transposition of classical reaction conditions developed for α-sulfenyl or α-sulfonyl-activated carbanions to the corresponding α-sulfinyl analogs. For example, in the palladium-catalyzed intramolecular allylic alkylation of unsaturated amides, the expected vinylpyrrolidones could be satisfactorily obtained when a sulfenyl or a sulfonyl-based additional carbanion stabilizing group was present, whereas under the same conditions, the corresponding sulfinyl-based derivative refused to cyclize (Table 1).

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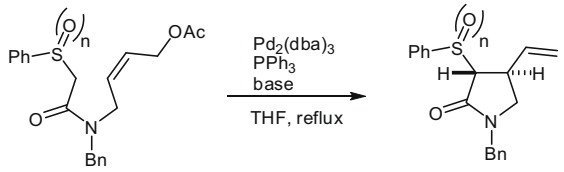
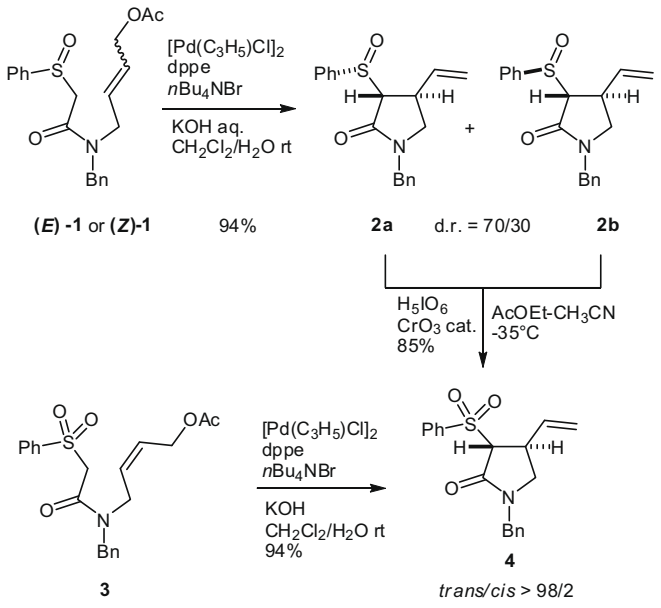
Table 1
Palladium-catalyzed intramolecular allylic alkylation of sulfur substituted amides[a]



Entry	*n*	Base	% Yield[b]
1	2	BSA/AcOK	78
2	0	NaH	58
3	1	NaH	0

[a] Reagents and conditions: substrate, $Pd_2(dba)_3$ (5 mol %), PPh_3 (50 mol %), base (BSA, 1.2 equiv and AcOK, 10 mol % or NaH, 1.1 equiv) in THF, reflux, 12 h.
[b] Yields are given for isolated products.



Scheme 1. Palladium-catalyzed intramolecular allylic alkylation of α-sulfinyl carbanions under phase transfer conditions and determination of the relative *trans*-configuration.

However, we recently reported that the palladium-catalyzed intramolecular allylic alkylation of unsaturated amides could be efficiently achieved under phase transfer conditions,[8] and that these conditions allowed the intermolecular palladium-catalyzed allylic alkylation of sulfinyl-based carbanions.[9] In this context, it was attractive to test the sulfoxide moiety, a potential covalently linked chiral auxiliary, in the corresponding intramolecular process, and study its influence on the diastereoselectivity of the cyclization.

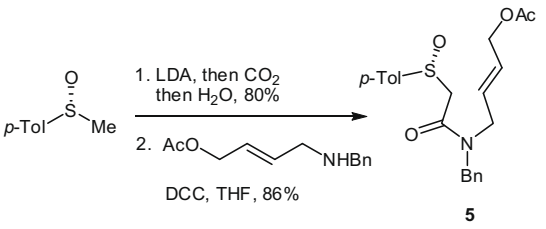
The intramolecular palladium-catalyzed allylic alkylation of the racemic (*E*)-phenylsulfinyl-substituted precursor **1** was first studied (Scheme 1). To our satisfaction, the use of $[Pd(C_3H_5)Cl]_2$ (5 mol %) as the palladium source, dppe (12.5 mol %) as the ligand, KOH (2.0 equiv) as the base and *n*-Bu_4NBr (10 mol %) as the phase-transfer agent in a biphasic CH_2Cl_2/H_2O (1/1; v/v) solvent system led after 2 h at room temperature to the desired cyclization product **2** in 94% yield. Remarkably, the cyclization product was isolated as a mixture of only two, over the four possible, diastereomers **2a–b** in a 70:30 ratio. The configuration of the starting allylic system has no influence on the ring closure process. Indeed, switching from (*E*)-**1** to (*Z*)-**1** led to a comparable yield and diastereomeric ratio.

Removal from **2a–b** of the stereogenic center located on the sulfur atom was accomplished via sulfoxide-to-sulfone oxidation. This reaction turned out to be rather tricky as the starting sulfoxides easily suffered sulfenic acid elimination to the corresponding 1,3-diene.[10] After some experimentation we finally found that treatment with catalytic CrO_3/H_5IO_6 at −35 °C in AcOEt–CH_3CN[11] gave cleanly the *trans* sulfone **4** in 85% yield as a single diastereoisomer.[12] This product was identical in each respect to that obtained via the analogous cyclization of the sulfonyl-substituted precursor **3**[8] (Scheme 1). In view of the above results and considering that the elimination of sulfenic acid is known to take place via a *syn* process, it follows that **2a**/**2b** are epimeric at the sulfoxide center and 3,4-trans disubstituted.

The use of enantiopure sulfoxide precursors was next envisaged, so as to obtain a sulfinyl-pyrrolidin-2-one in enantiopure form. This study was combined with the employ of enantiopure ligands,[4] in the hope of obtaining a matching combination maximizing the diastereoselectivity.

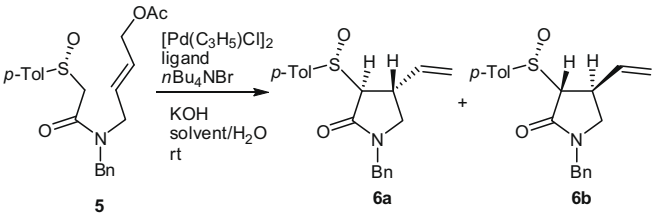
The enantiopure cyclization precursor **5** was obtained in two steps starting from commercially available (+)-(*R*)-methyl-tolylsulfoxide (Scheme 2). Deprotonation of this sulfoxide with LDA, followed by condensation of the resulting anion onto carbon dioxide afforded the corresponding α-sulfinyl carboxylic acid. A subsequent coupling reaction with (*E*)-4-benzylamino-but-2-enyl acetate in the presence of DCC led to the desired amide **5** in 86% yield.

Not unexpectedly, cyclization of **5** under biphasic conditions afforded the pyrrolidones **6a** and **6b** (90% yield) in a 70:30 mixture of isomers (Table 2, entry 1), whereas replacement of dppe for racemic BINAP as the ligand did not lead to significant changes (entry 2). Solvent effect was next tested in the presence of dppe or racemic BINAP. Surprisingly, the use of a biphasic toluene/H_2O



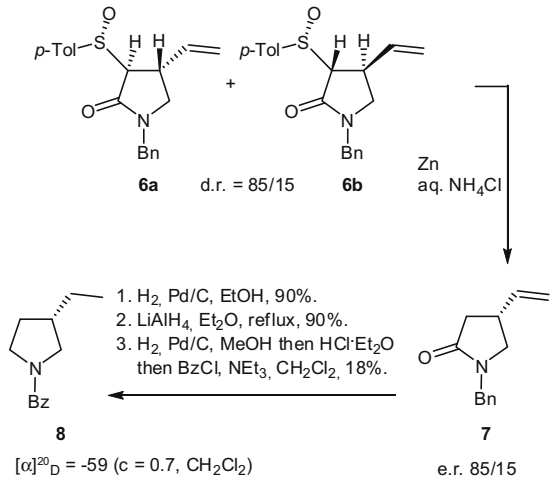
Scheme 2. Preparation of the cyclization precursor **5** in enantiopure form.

Table 2
Palladium-catalyzed intramolecular allylic alkylation of tolylsulfinylamide **5**: study of the diastereoselectivity[a]



Entry	Solvent	Ligand	Yield[b] (%)	**6a**/**6b**[c]
1	CH_2Cl_2	dppe	90	70/30
2	CH_2Cl_2	(±)-BINAP	75	70/30
3	Toluene	dppe	68	30/70
4	Toluene	(±)-BINAP	70	40/60
5	CH_2Cl_2	(*S*)-BINAP	61	85/15
6	CH_2Cl_2	(*R*)-BINAP	95	50/50
7	Toluene	(*S*)-BINAP	45	70/30
8	Toluene	(*R*)-BINAP	69	20/80

[a] Reagents and conditions: substrate, $[Pd(C_3H_5)Cl]_2$ (5 mol %), ligand (12.5 mol %), KOH (50% aq soln, 2.0 equiv), solvent/H_2O (1:1).
[b] Yields are given for isolated product.
[c] Diastereomeric ratio determined by ^1H NMR.



Scheme 3. Determination of the absolute configuration for the major diastereoisomer.

system led to an inversion of the diastereoselectivity, affording the sulfinyl-pyrrolidin-2-ones **6a** and **6b** in, respectively, 30:70 and 40:60 diastereomeric ratios (entries 3 and 4).

Coming back to the CH_2Cl_2/H_2O system, use of enantiopure (*S*)-Binap and (*R*)-Binap ligands afforded the sulfinyl-pyrrolidinones **6a–b** in 61% and 95% yield, and 85:15 and 50/50 diastereomeric ratios, respectively (entries 5 and 6). On the other hand, switching again to toluene/H_2O, the same (*S*)-Binap and (*R*)-Binap ligands gave **6a–b** in 70:30 and 20:80 diastereomeric ratios (entries 7 and 8).[13]

Assignment of the relative configuration the diastereomeric sulfoxides **6a** and **6b** was established through conversion of the 85:15 mixture as from entry 5 of Table 2 into (*S*)-*N*-benzoyl-3-ethylpyrrolidine and comparison of its optical rotation with that reported for the enantiopure *R*-configurated sample.[14] Accordingly, zinc-mediated desulfinylation of **6a–b**[15] yielded the corresponding vinyl-pyrrolidone **7** without any trace of the 1,3-diene arising from sulfenic acid elimination. Pd/C-catalyzed hydrogenation of the latter afforded the corresponding saturated lactam, which was submitted to $LiAlH_4$ reduction to give *N*-benzyl-3-ethylpyrrolidine. Finally, hydrogenolysis followed by immediate N-benzoylation gave *N*-benzoyl-3-ethylpyrrolidine **8**, which showed an $[\alpha]_D^{20}$ −59 (*c* 0.7, CH_2Cl_2). Since the sample of enantiopure *R* **8** reported by Pedrosa and co-workers[14] had an $[\alpha]_D^{20}$ +104 (*c* 0.7, CH_2Cl_2), the relative configurations of **6a** and **6b** were attributed as indicated in Scheme 3. Therefore, we can conclude that, when the reaction is conducted in CH_2Cl_2, the (*R*)-configurated sulfoxide stereocenter favors an (*R*)-configurated C-4 stereocenter on the pyrrolinone ring, whereas the corresponding (*S*)-configurated C-4 stereocenter is privileged when the reaction is carried out in toluene. Such solvent effect is exalted upon using the appropriate matching BINAP enantiomeric form. Specifically, (*S*)-Binap/CH_2Cl_2 (entry 5) and (*R*)-Binap/toluene (entry 8) represent the matching ligand/solvent combination.

In summary, we have reported a new and operationally very simple protocol for the intramolecular palladium-catalyzed allylic alkylation of α-sulfinyl carbanions, a transformation not satisfactorily achievable under classical conditions. The new reaction conditions allow the preparation of enantiopure sulfinyl-pyrrolidin-2-ones in good yields. The concomitant use of an enantiopure sulfinyl-derived substrate and an enantiopure atropo-isomeric ligand under biphasic (CH_2Cl_2/H_2O or toluene/H_2O) conditions allowed to obtain opposite diastereoselectivites with clearly solvent effects. Applications of this cyclization process for the synthesis of chiral compounds of biological interest are currently under investigation.

Acknowledgments

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12. The use of Oxone® and wet alumina in refluxing chloroform (Greenhalgh, R. P. *Synlett* **1992**, 235–236) afforded sulfone 4 in poor yield (28% y) together with the corresponding 1,3-diene (72% y).
13. *General procedure for palladium-catalyzed intramolecular allylic alkylation under biphasic conditions:* To a solution of tetrabutylammonium bromide (46.3 mg, 0.14 mmol, 10 mol %) in dichloromethane (2.5 mL) under neutral atmosphere were added allylpalladium chloride dimer (26.3 mg, 0.07 mmol, 5 mol %) and dppe (68.7 mg, 0.17 mmol, 12.5 mol %). The solution was stirred at room temperature for 5 min. Then, a solution of acyclic substrate **5** (574 mg, 1.43 mmol in 12.5 mL of dichloromethane), 13 mL of water and 50% KOH aqueous solution (0.213 mL, 2.87 mmol, 2 equiv) were successively added. The resulting biphasic system was stirred vigorously at room temperature for 2 h. A saturated aq NH_4Cl solution (15 mL) was added and the aqueous phase was extracted with Et_2O (3 × 15 mL). The collected organic phases were washed with brine (15 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (1:1 AcOEt/cyclohexane). Major diastereomer **6a**: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53–7.55 (m, 2H), 7.25–7.33 (m, 5H), 7.01–7.04 (m, 2H), 5.78 (m, 1H), 5.12 (d, 1H, *J* = 11.1 Hz), 5.09 (d, 1H, *J* = 4.0 Hz), 4.59 (d, 1H, *J* = 14.6 Hz), 4.03 (d, 1H, *J* = 14.6 Hz), 3.31 (m, 1H), 3.99 (d, 1H, *J* = 3.8 Hz), 2.83 (dd, 1H, *J* = 10.1, 3.5 Hz), 2.60 (dd, 1H, *J* = 8.3, 10.1 Hz), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 142.2, 138.0, 136.0, 135.1, 129.7, 128.7, 128.2, 127.8, 125.1, 116.5, 70.3, 50.4, 46.7, 33.1, 21.6. IR (neat): ν (tilde) = 2922, 1686, 1493, 1493, 1443, 1257, 1048, 1016 cm^{-1}. MS (CI–NH_3) *m*/*z*: 340 (MH^+). HRMS *m*/*z* calcd for $C_{20}H_{21}NNaO_2S$ (MNa^+) 362.11907, found 362.11852. $[\alpha]_D^{20}$ +94.0 (*c* 1.06 in $CHCl_3$). Minor diastereomer **6b**: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24–7.51 (m, 9H), 5.23–5.31 (m, 1H), 4.65 (d, 1H, *J* = 10.4 Hz), 4.54 (s, 2H), 4.48 (d, 1H, *J* = 16.9 Hz), 3.49 (m, 1H), 3.43 (m, 2H), 3.01 (dd, 1H, *J* = 4.6, 9.2 Hz), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.9, 141.6, 137.9, 137.0, 135.4, 129.9, 128.9, 128.2, 128.1, 124.3, 116.3, 72.0, 50.9, 47.3, 31.1, 21.5. $[\alpha]_D^{20}$ +297.0 (*c* 0.96 in $CHCl_3$).
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