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Pd-Catalyzed Asymmetric Synthesis of *N*-Allenyl Amides and Their Au-Catalyzed Cycloisomerizative Hydroalkylation: A New Route Toward Enantioenriched Pyrrolidones

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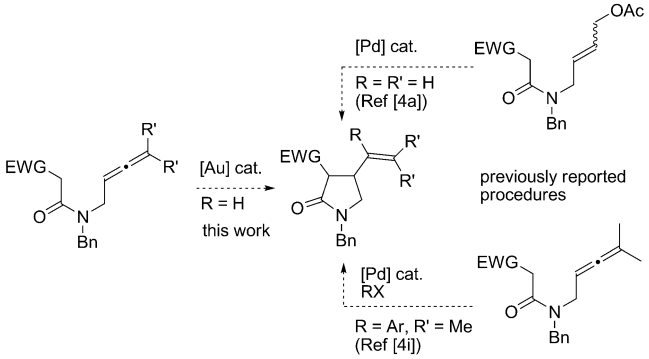
Dedicated to Professor Cesare Gennari on the occasion of his 60th birthday

Over the past decade, much attention has been devoted to gold catalysis for the synthesis of heterocycles through carbon–carbon and carbon–heteroatom bond formation.[1] Indeed, Au^{I} and Au^{III} complexes are carbophilic Lewis acids that are able to activate unsaturated carbon–carbon bonds towards nucleophilic attack. However, gold-catalyzed hydroalkylations involving an activated methylene function have only been rarely studied,[2] and, to the best of our knowledge, only two examples have so far involved intramolecular gold-catalyzed allene hydroalkylations.[3]

Our ongoing research is focused on the development of new atom economical methodologies for the synthesis of heterocyclic structures.[4] We thus envisioned that a gold-catalyzed intramolecular hydroalkylation of *N*-allenyl amides bearing an active methylene might allow to access 4-vinyl-γ-lactams. Such a full atom-economical process (Scheme 1, left) would represent a valuable alternative to the palladium-catalyzed intramolecular alkylation of the corresponding *N*-(4-acetoxy)allylamides (Scheme 1, top right),[4a] or to the palladium-catalyzed allene carbopalladation/allylation of *N*-allenyl amides (Scheme 1, bottom right),[4i] previously reported by some of us.

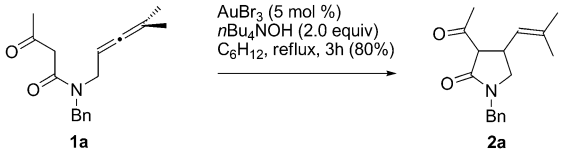
Herein we report our results on the gold-catalyzed cycloisomerisation reaction of *N*-allenyl amides leading to the corresponding 4-vinyl-γ-lactams. We also demonstrate that a clean axial-to-central chirality transfer occurs when starting from a stereogenic allene moiety. Furthermore, the preparation of the requisite enantioenriched allenyl β-ketoamide



Scheme 1. Synthesis of 4-vinyl-γ-lactams: comparison between the old palladium-catalyzed strategies and the new gold-catalyzed one.

was achieved by means of an original palladium-catalyzed allenylic amination reaction.

N-Allenyl β-ketoamide **1a**[5] was chosen as our model substrate to test the cycloisomerization. After a preliminary screening of catalysts[6] ($AuBr_3$, AuCl, $Au(OH)_3$, $[PdCl_2(CH_3CN)_2]$, $[Pd(CH_3CN)_4][BF_4]_2$, $[Pd(OCOCF_3)_2]$), additives (nBu_4NI, AgOTf), solvents (CH_2Cl_2, toluene, hexane, cyclohexane, THF), bases (EtONa, DBU, nBu_4NOH, KOH, no base), and temperature for this reaction, the following optimal conditions were established: $AuBr_3$ (5 mol%), nBu_4NOH (2.0 equiv), cyclohexane, reflux. Under such conditions the desired lactam **2a** was produced regio- and stereoselectively in 80% yield (Scheme 2).



Scheme 2. Cycloisomerization of the model *N*-allenyl β-ketoamide **1a**.

With the optimized reaction conditions in hand, the scope of the hydroalkylation was examined on a 0.5 mmol scale, using various allenyl β-ketoamide precursors (Scheme 3). The monosubstituted allene **1b** afforded γ-lactam **2b** in

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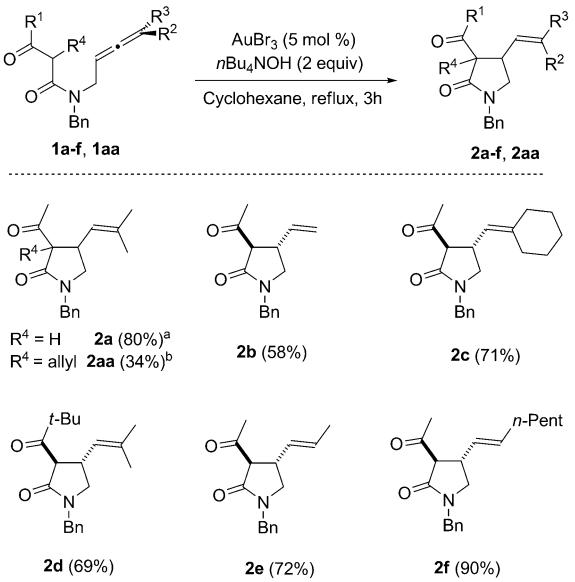


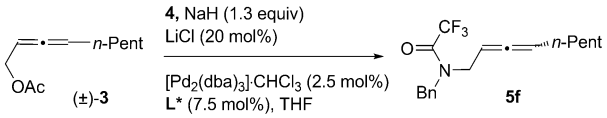
Scheme 3. Scope of the hydroalkylation reaction (all reactions were run on a 0.5 mmol scale. Yields refer to isolated yields). a) Only the *trans* isomer was observed. b) 75:25 diastereoisomeric mixture.

a moderate yield (58%). As the same lactam **2b** had been previously obtained by us by means of a Pd^0-catalyzed allylation process, the stereochemistry was unambiguously assigned as the *trans* configuration between the newly formed stereocenters.[4a,7] The cyclohexyl-substituted precursor **1c** reacted smoothly to afford the desired lactam **2c** in 71% yield. The replacement of the acetyl group by the bulkier pivaloyl group was also well tolerated, leading to pyrrolidone **2d** in 69% yield. Precursors bearing a stereogenic allenyl moiety, such as **1e** and **1f** afforded the (*E*)-alkene cyclization products **2e** and **2f** in good (72%) to excellent (90%) yields, respectively.[8] The allyl-substituted allenyl β-ketoamide **1aa** could also be cyclized to the corresponding pyrrolidone **2aa** bearing a quaternary carbon atom, although in a rather moderate yield (34%). Unfortunately, related substrates bearing electron-withdrawing groups other than a ketone (MeO_2C-, NC-, $PhSO_2$-) failed to cyclize.

The observation that the chiral racemic allenic precursors **1e** and **1f** led to single *trans*-(*E*)-diastereomers suggested that the transformation might be stereospecific. This would imply that starting from an enantioenriched substrate, axial-to-central chirality transfer should be at work. Therefore, we decided to test the cyclization of an enantioenriched sample of **1f**. For this purpose, we planned to synthesize the parent *N*-allenyl amine by an asymmetric palladium-catalyzed amination of the corresponding racemic *N*-allenyl acetate. Such type of asymmetric transformation has already two precedents in the literature.[9] However, the reported methods were mainly developed for the synthesis of tertiary allenyl amines. As our synthetic plan required the use of a secondary *N*-allenyl amine, we selected *N*-benzyl trifluoroacetamide (**4**) as the nucleophile. Indeed, we reasoned that its easy deprotonation together with the smooth hydrolytic cleavage of the CF_3CO moiety might render this amide an ideal nucleophile for our purpose.

The asymmetric conversion of racemic allenyl acetate (±)-**3** into allenyl trifluoroacetamide **5f** was thus investigated (Table 1). Preliminary tests indicated no reactivity in the presence of the Trost standard ligand **L1**,[10] whereas promising results were obtained with (*R*)-BINAP (**L2**; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl). A careful screening with this ligand involving reaction temperature, palladium source, base, solvent, and additives as parameters allowed to retain the following conditions: [NaH, [$Pd_2(dba)_3$]·$CHCl_3$ (dba = dibenzylideneacetone; 2.5 mol%), (*R*)-BINAP (7.5 mol%), LiCl (20 mol%), THF, RT.[11] Subsequent use of these optimized reaction conditions in the presence of (*S,S*)-DIOP (**L3**),[12] (*S,S*)-CHIRAPHOS (**L4**),[13] (*S*)-*t*Bu-PHOX (**L5**),[14] SL-W001-1 (**L6**),[15] SL-J005-1 (**L7**),[16] (*R*)-SYNPHOS (**L8**),[17] (*S*)-MeOBIPHEP (**L9**),[18] (*S*)-3,5-*t*BuMeOBIPHEP (**L10**),[19] and (*R*)-3,5-*t*Bu-4-MeO-MeOBIPHEP (**L11**)[19] indicated the atropoisomeric ligands **L2** (Table 1, entry 1) and **L9** (Table 1, entry 8) as the ligands of choice.

Table 1. Search for the best chiral ligand.[a,b]

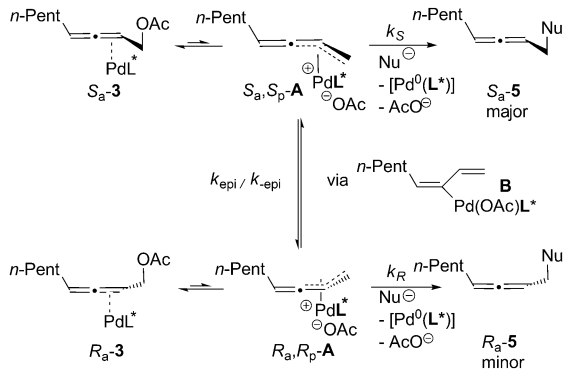


Entry	Ligand	*t* [h]	*T* [°C]	Yield [%]	e.r.[c]
1	**L2**	6	25	87	21:79
2	**L3**	4	25	79	47:53
3	**L4**	24	55	8	50:50
4	**L5**	16	55	43	32:68
5	**L6**	4	25	96	51:49
6	**L7**	3	25	92	50:50
7	**L8**	24	25	64	14:86
8	**L9**	24	25	68	86:14
9	**L10**	24	25	49	87:13
10	**L11**	24	25	75	17:83

[a] For the structures of the chiral ligands see the Supporting Information. [b] No reaction was observed when using ligand **L1**. [c] e.r.'s determined by chiral HPLC SFC (AD-H, CO_2/*i*PrOH 90:10, 2.5 mL min^{-1}, 85 bar).

Further experiments[20] showed that the product isolated after partial conversion possessed the same enantiomeric ratio (e.r.)[21] (22:78) as that isolated after total substrate conversion. Furthermore, the unreacted substrate recovered from the above experiment was found to be enantioenriched (e.r. 71:29) and its resubmission to the same reaction conditions until full conversion, gave the final amide (−)-**5f**, again in 21:79 e.r.[21] (61% yield). This result clearly rules out a static kinetic resolution phenomenon and points to a dynamic kinetic asymmetric resolution (DYKAT)[22] without the involvement of a memory effect.[23] Finally, resubmission of a racemic sample of the allenyl trifluoroacetamide **5** to the asymmetric amination conditions, gave back, as expected, the unchanged racemic material, thereby confirming the irreversibility of the N–C bond-formation step.

Each enantiomer of **3** is expected to undergo pre-complexation to the catalytic system [Pd^0(**L***)] *anti* to the alkyl substituent, to reversibly[24] form a diastereomeric couple of vinylidene-allyl η^3-complexes S_a,S_p-**A**[25] and R_a,R_p-**A**, which can rapidly equilibrate via the η^1-dienyl intermediate **B** (Scheme 4). Eventually, the irreversible rate- and enantio-



Scheme 4. Mechanistic proposal for the palladium-catalyzed DYKAT process (±)-**3**→**5** using **L9** (or *ent*-**L2**) as ligand. Indexes a and p specify the axial and the planar chirality descriptors, respectively.

discriminating addition of the amide enantioselectively generates the allenyl amides **5**. It is worth noting that although consumption of the enantiomeric substrates takes place at unequal rates (see the above experiment at partial substrate conversion), no correlation can exist between this initial kinetic resolution and the sense of the final asymmetric induction, which solely depends on the energy difference (ca. 3.8 kJ)[26] between the diastereomeric transition states of the final N–C bond-forming step. The ensemble of the above information allows proposing a mechanism as well as some qualitative considerations.

It is also worth noting that the relative energy differences between the barriers to interconversion in the equilibrating steps, (internal barriers as depicted in Figure 1) do not govern the enantioselectivity of the process (Curtin–Hammett conditions), as long as $k_{epi} > k_S > k_R$.

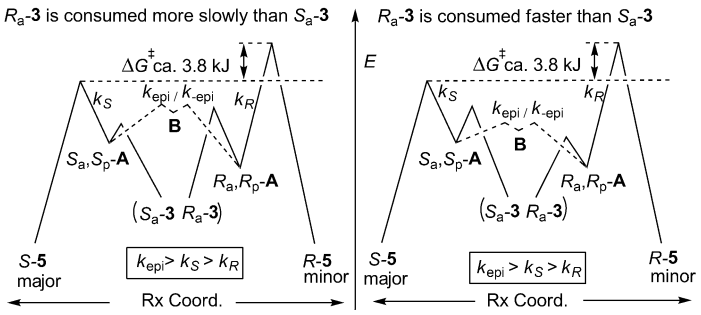
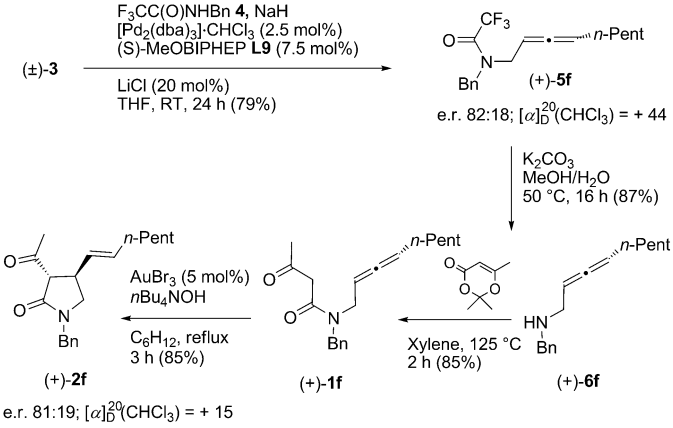


Figure 1. Qualitative energetic profile of the Pd-catalyzed DYKAT process (±)-**3**→**5** using **L9** (or *ent*-**L2**). Comparison between two arbitrarily selected manifolds indicates the absence of correlation between the sense of the asymmetric induction observed in the products and the initial kinetic resolution of the starting racemic substrate.

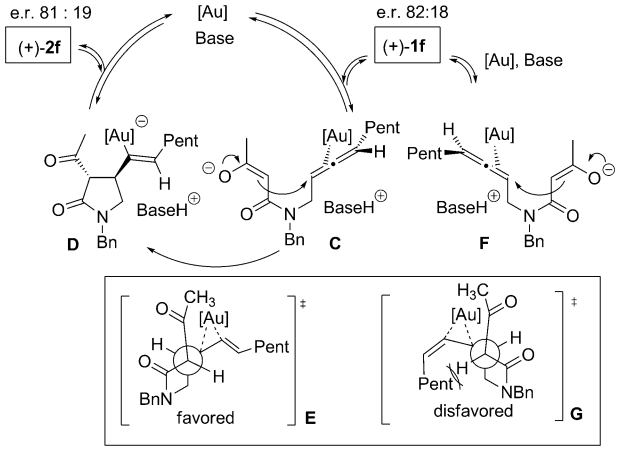
The allylic amination in the presence of the best performing ligand **L9**, was then repeated on a 2.0 mmol scale, obtaining allenamide (+)-**5f** in 79% yield and 82:18 e.r. (Scheme 5).



Scheme 5. Asymmetric amination of ***rac*-3** and chirality transfer experiment.

Treatment of the latter with K_2CO_3 in MeOH/H_2O 10/1 at 50 °C led to *N*-benzyl-(non-2,3-dien-1-yl)-1-amine ((+)-**6f**) in 87% yield. Acylation of this amine with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one afforded the enantioenriched *N*-allenyl β-ketoamide (+)-**1f** in 85% yield. Finally, treatment of (+)-**1f** under the previously optimized gold-catalyzed cycloisomerization conditions produced the expected pyrrolidone (+)-**2f** in 85% yield and 81:19 e.r..[21] As the enantiomeric ratios of (+)-**1f** and of (+)-**2f** are virtually identical, the stereospecificity of the axial-to-central chirality transfer of the hydroalkylation process is proved.

Absolute configuration[11] was established by comparison of the experimental circular dichroism spectra of (+)-**1f** and (+)-**2f** with those simulated from DFT calculations and accordingly, a proposed mechanism for the process is shown in Scheme 6.[27,28] Reversible gold complexation on (+)-**1f** may



Scheme 6. Mechanistic proposal for the gold-catalyzed hydroalkylation reaction.

occur on both unsaturated sites and on both faces of the allenyl moiety. However, only coordination of the internal double bond from the same side as the pentyl group leads to the reactive intermediate **C**. The *anti*-to-Au enolate addition[29] appears unconstrained and generates the vinylgold complex **D** via transition state **E**. This event has to be compared with the alternative *anti*-to-Au enolate addition on the intermediate complex **F** that would entail a disfavored sp-to-sp^2 carbon rehybridization via the strained transition state **G**. Finally, a likely rate-determining,[30,31] protodeauration of **D** generates γ-lactam (+)-**2f** as the major enantiomer, the absolute configuration of which is in accord with that deduced from circular-dichroism-based experiments.

In conclusion, we have developed a new gold-catalyzed cycloisomerizative hydroalkylation affording regioselectively 4-vinyl-γ-lactams. This transformation is stereospecific and takes place with a total axis-to-center chirality transfer. The required enantioenriched *N*-allenyl amide was successfully obtained by means of an original Pd-catalyzed DYKAT process.

Experimental Section

General procedure for gold-catalyzed hydroalkylation reaction: In a Schlenk tube, tetrabutylammonium hydroxide (1.25 mL, 1 mmol, 2.0 equiv, 0.8 M solution in MeOH) was added to a solution of appropriate *N*-allenyl β-ketoamide (0.5 mmol, 1.0 equiv) in dry cyclohexane (5 mL), under argon atmosphere. The initially colorless solution turned bright yellow and the gold complex $AuBr_3$ (11 mg, 25 μmol, 5 mol%) was introduced. The resulting mixture was stirred at 80 °C. After completion of the reaction, monitored by TLC, the mixture was filtered on a pad of silica gel eluting with pure AcOEt and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

General procedure for palladium-catalyzed amination reaction: The chiral ligand **L*** (7.5 mol%) was added to a solution of $[Pd_2(dba)_3]\cdot CHCl_3$ (13 mg, 12.5 μmol, 2.5 mol%) in dry THF (0.5 mL). The reaction mixture was stirred at room temperature for 10 min. Allenyl acetate (0.5 mmol, 1.0 equiv) diluted in dry THF (1 mL) was added by means of a cannula. In another flask sodium hydride (26 mg, 0.65 mmol, 1.3 equiv, 60% dispersion in mineral oil) was slowly added to a solution of *N*-benzyltrifluoroacetamide (122 mg, 0.6 mmol, 1.2 equiv) in dry THF (1 mL). The resulting mixture was stirred at room temperature for 10 min and added via cannula in the first flask. The resulting orange mixture was stirred at room temperature and the completion of the reaction was monitored by TLC. The reaction was quenched with a saturated solution of NH_4Cl and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried on $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography.

Acknowledgements

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Keywords: allene · dynamic kinetic asymmetric transformation · gold · lactams · palladium

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[5] *N*-Allenyl β-ketoamides **1a–d** and **1f** were obtained from the appropriate propargyl alcohols according to the following sequence: *O*-THP protection, hydroxymethylation, S_N2' $LiAlH_4$-mediated reduction, O-acylation, Pd-catalyzed allylic amination with *N*-benzyltrifluoroacetamide, *N*-trifluoroacetamide hydrolysis, N-acylation. Compound **1e** was obtained by a variant of the above route entailing mesylation of penta-2,3-dien-1-ol, substitution with benzylamine, and final acylation. **1aa** was obtained by allylation of **1a**. See Supporting Information for details.

[6] $PtCl_2$, $Ag(OTf)$, $Cu(OTf)_2$, $FeCl_3$, or $[RhCl(PPh_3)_3]$ proved totally ineffective.

[7] The *trans* configuration between the newly formed stereocenters of **2b** was, by analogy, extended to the other disubstituted lactams **2a–f**

obtained in this study. Close similarities among the NMR spectra of **2a**–**f** further strengthened our confidence in the configuration assignments.

[8] The *E* configuration of the double bond in **2e** and **2f** was unambiguously determined [^{1}H NMR (J_{vic} = 15.0 Hz)] for both compounds.

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[20] These experiments were performed using the allenyl *p*-methoxybenzoate substrate, instead of the acetate (±)-**3**, and (*R*)-BINAP as the ligand.

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[26] Value obtained from the experimentally observed enantiomeric ratio (86:14), according to the Boltzmann distribution at 300 K.

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