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Convergent Synthesis of Stereodefined *exo*-Alkylidene-γ-Lactams from β-Halo Allylic Alcohols

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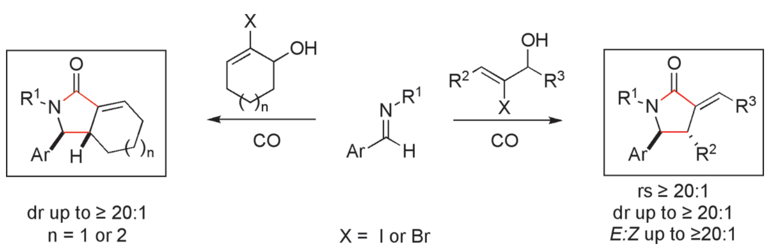
ABSTRACT



A convergent process for the assembly of stereodefined mono- and bicyclic *exo*-alkylidene-γ-lactams is described that proceeds through the union of β-halo allylic alcohols, aromatic imines, and CO. Overall, regio- and stereoselective Ti-mediated reductive cross-coupling, followed by Pd-catalyzed carbonylation, can be performed in a one- or two-pot procedure, defining a highly selective three-component coupling process for heterocycle synthesis.

Nitrogen-containing heterocycles are ubiquitous structural motifs in natural products and small molecules of biomedical relevance.[1] Among this class, stereodefined pyrrolidines and γ-lactams are abundant (Figure 1). A wealth of chemical pathways are indeed available for the synthesis of these functionalized heterocycles.[2] However, strategic considerations for the preparation of highly substituted and stereodefined systems often limit the utility of many available methods. In a program aimed at defining convergent coupling reactions for complex molecule synthesis, we have been investigating the potential of reductive cross-coupling processes between imines and alkynes, alkenes, or allenes to serve as a general foundation for heterocycle synthesis.[3] Recently, we set our sights on the development of a multicomponent coupling reaction suitable for the synthesis of *exo*-alkylidene-γ-lactams (Figure 2A). These architectures, while representing interesting heterocycles in their own right, possess a rich reactivity profile suitable for diverse elabora-

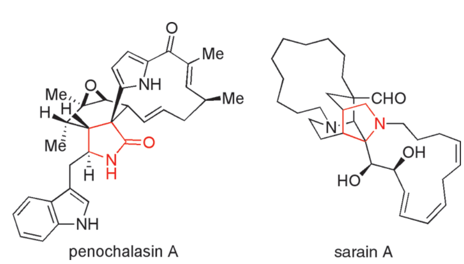


Figure 1. Examples of natural products bearing a substituted γ-lactam or pyrrolidine.

(1) Fischer, J., Ganellin, C. R., Eds. *Analogue-based Drug Discovery*; Wiley-VCH: Weinheim, 2002.

(2) For reviews that cover the synthesis of nitrogen heterocycles, see: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (c) Barluenga, J.; Santamaría, J.; Tomás, M. *Chem. Rev.* **2004**, *104*, 2259–2283. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (e) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352. (f) Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Chem. Rev.* **2004**, *104*, 2353–2399. (g) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401–2432. (h) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553–2581. (i) Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493–35131. (j) Harrison, T. *Contemp. Org. Synth.* **1995**, *2*, 209–224.

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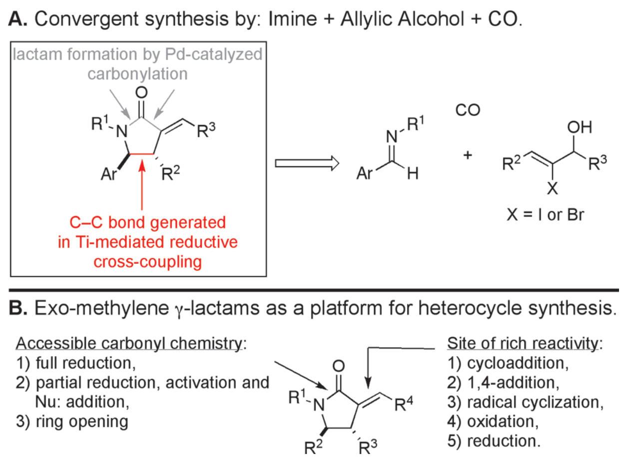


Figure 2. *exo*-Alkylidene-γ-lactams.

tion (Figure 2B). Herein, we report the realization of a synthesis of *exo*-alkylidene-γ-lactams from the convergent and stereoselective union of homoallylic alcohols, imines, and carbon monoxide.

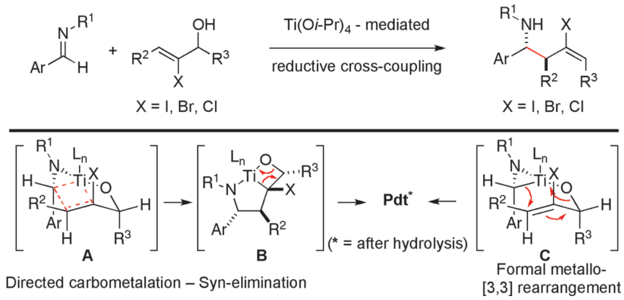
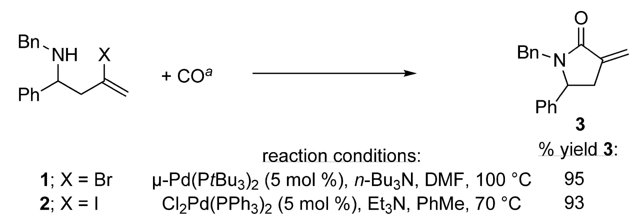


Figure 3. Imine−allylic alcohol coupling reaction.

Recently, we reported a stereoselective synthesis of homoallylic amines that proceeds by regioselective reductive cross-coupling of allylic alcohols with aromatic imines.[3d] Of particular interest to our goals here, coupling of 2-halo allylic alcohols to aromatic imines was found to provide stereoselective access to *anti*-homoallylic amines that contain a stereodefined vinyl halide (dr ≥ 20:1; *E*:*Z* ≥ 20:1; Figure 3). While the mechanistic details that result in these high levels of stereoselection remain undefined, an empirical model has emerged to explain the patterns of reactivity and selectivity observed. The proposed model, based on a sequence of directed carbometalation and *syn*-elimination (**A** → **B**; Figure 3), embraces a boat-like geometry in the transition state for C−C bond formation to reflect the presumed mechanistic requirement of preassociating the allylic alkoxide to the Ti-center of the azametallacyclopropane and the orbital requirements for carbometalation (coplanarity of the σ_{Ti-C} and the $\pi_{C=C}$). A key factor for stereocontrol then derives from the minimization of A-1,2 strain in the boat-like orientation **A** (minimize steric interaction between R^3 and X). As a consequence, high selectivity is observed for the formation of products containing a pendant *E*-alkene. Overall, the general reactivity pattern is consistent with formal metallo-[3,3] rearrangement by way of **C**.[4]

While having a stereoselective coupling reaction in place for the synthesis of highly functionalized homoallylic amines, we were aware of the potential of halogenated homoallylic amines to participate in Pd-catalyzed carbonylation chemistry.[5,6] As depicted in Figure 4, this was indeed the case. Carbonylation of vinylbromide **1** and vinyliodide **2** resulted in the production of the *exo*-methylene-γ-lactam **3** in ≥93% yield.



a CO was introduced by a balloon.

Figure 4. Pd-catalyzed carbonylative cyclization.

With the knowledge gleaned from these initial studies, we moved on to explore the compatibility of more complex substrates in this two-step reductive cross-coupling/carbonylation process as a means to access a variety of stereodefined γ-lactams (Table 1).[7] As depicted in entries 1−3, the size of the alkyl group at the allylic position plays an important role in stereoselection. While reductive cross-coupling of allylic alcohol **5** with imine **4** proceeds in a fairly unselective manner (*E*:*Z* = 1.5:1), union of imine **4** with allylic alcohol **7** occurs with increased levels of stereoselection and produces the homoallylic amine **8** in 76% yield (*E*:*Z* = 4:1). Subsequent carbonylation then delivers the stereodefined unsaturated γ-lactam **9** in 99% yield. As

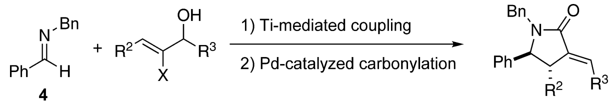
(3) For the coupling of homoallylic alcohols to imines, see: (a) Takahashi, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 7514–7416. For the coupling of homopropargylic alcohols to imines, see: (b) McLaughlin, M.; Takahashi, M.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3912–3914. For the coupling of allenic alcohols to imines, see: (c) McLaughlin, M.; Shimp, H. L.; Navarro, R.; Micalizio, G. C. *Synlett* **2008**, 735–738. For the coupling of allylic alcohols to imines, see: (d) Takahashi, M.; McLaughlin, M.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3702–3706. (e) Lysenko, I. L.; Lee, H. G.; Cha, J. K. *Org. Lett.* **2009**, *11*, 3132–3134.

(4) For related reductive cross-coupling reactions that appear to proceed by formal metallo-[3,3] rearrangement, see: (a) Kolundzic, F.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 15112–15113. (b) Shimp, H. L.; Hare, A.; McLaughlin, M.; Micalizio, G. C. *Tetrahedron* **2008**, *64*, 6831–6837. (c) Belardi, J. K.; Micalizio, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 16870–16872. (d) Lysenko, I. L.; Kim, K.; Lee, H. G.; Cha, J. K. *J. Am. Chem. Soc.* **2008**, *130*, 15997–16002.

(5) For a review of Pd-catalyzed carbonylation for the synthesis of lactams and lactones, see: (d) Farina, V.; Magnus, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2002; pp 2351−2375.

(6) For early examples of Pd-catalyzed carbonylation for lactam synthesis, see: (a) Miwako, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684–1687. (b) Miwako, M.; Washioka, Y.; Urayama, T.; Yoshiura, Y.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1983**, *48*, 4058–4067. (c) Crisp, G. T.; Meyer, A. G. *Tetrahedron* **1995**, *51*, 5585–5596.

Table 1. *exo*-Alkylidene-γ-lactams via Imine−Allylic Alcohol Reductive Cross-Coupling



entry	allylic alcohol	% yield[a]	homoallylic amine	% yield[e]	γ-lactam
1	**5**	81[b]	**6** *E*:*Z* = 1.5:1	–	–
2	**7**	76[b]	**8** *E*:*Z* = 4:1	99[c]	**9**
3	**10**	58[d]	**11** *E*:*Z* ≥ 20:1	94	**12**
4	**13**	53[b]	**14** dr ≥ 20:1	66	**15**
5	**16**	67[d]	**17** dr ≥ 20:1	87	**18**
6	**19**	53[d]	**20** dr ≥ 13:1	92	**21**

[a] General reaction conditions for the Ti-mediated coupling: imine, $ClTi(Oi\text{-}Pr)_3$, $c\text{-}C_5H_9MgCl$, Et_2O, or PhMe (−70 to −40 °C), then the sodium alkoxide of the allylic alcohol was added as a solution in THF.[7] [b] 4 equiv of imine was employed. [c] The major isomer of **8** was employed in the carbonylation reaction. [d] 1.5 equiv of allylic alcohol was used. [e] Reaction conditions: $Cl_2Pd(PPh_3)_2$ (3−5 mol %), Et_3N, PhMe, or MeOH (entry 4), CO (balloon), 70 °C.

depicted in entry 3, branched alkyl substitution on the allylic alcohol leads to the highest levels of *E*-selectivity in this coupling reaction. Here, the homoallylic amine **11** is forged in 58% yield with greater than 20:1 selectivity for the formation of the stereodefined *E*-alkene. Palladium-catalyzed carbonylation then furnishes γ-lactam **12** in 94% yield. Moving on to a more highly substituted allylic alcohol, the conversion of **13** to homoallylic amine **14** proceeds in 53% yield and delivers the stereodefined *anti*-product as essentially a single isomer. Similarly, carbonylation then provides the highly substituted *exo*-alkylidene-γ-lactam **15** in 66% yield.

Finally, this two-step, three-component heterocycle synthesis is useful for the synthesis of stereodefined bicyclic lactams. As illustrated in entries 5 and 6, reductive cross-coupling of cyclic allylic alcohols **16** and **17** with imine **4** can be accomplished in a highly stereoselective manner to deliver vinyliodides **17** and **20** (dr up to ≥20:1) These substrates are equally effective in the Pd-catalyzed carbonylative cyclization and deliver the bicyclo[4.3.0] and [5.3.0] systems **18** and **21** in 87% and 92% yield.

While this two-step procedure is effective for the stereoselective convergent synthesis of mono- and bicyclic γ-lactams, this multicomponent coupling sequence can be streamlined. Specifically, we have defined a one-pot, three-component coupling reaction that converts 2-halo allylic alcohols, imines, and carbon monoxide directly to stereodefined *exo*-alkylidene-γ-lactams. Aware of the compatibility of Pd-catalyzed coupling processes with water and base, we speculated that aqueous quenching of the titanium-mediated reductive cross-coupling reaction may directly furnish a suitable environment for Pd-catalyzed carbonylation. This expectation was indeed the case.

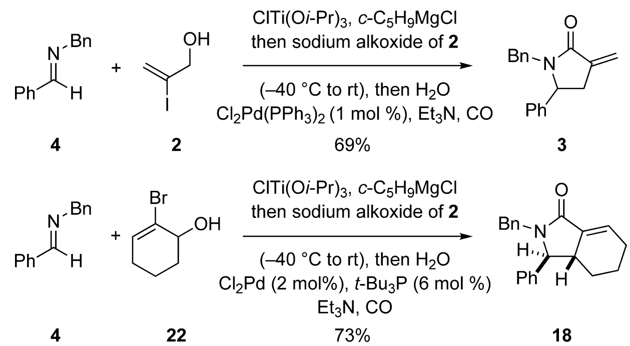


Figure 5. One-pot, three-component coupling for heterocycle synthesis.

As depicted in Figure 5, this sequential multicomponent coupling process for the synthesis of substituted γ-lactams

(7) General experimental procedure for the two-step γ-lactam synthesis described in Table 1. **Synthesis of (*S**)-*N*-benzyl-1-((*R**)-2-iodocyclohex-2-enyl)-1-phenylmethanamine 17:** To a solution of imine **4** (563 μL, 586 mg, 3.00 mmol) and $ClTi(Oi\text{-}Pr)_3$ (1.0 M in diethyl ether, 3.75 mmol) in diethyl ether (12 mL) at −70 °C was added $c\text{-}C_5H_9MgCl$ (2.00 M in diethyl ether, 7.50 mmol) in a dropwise manner with a syringe. The brown solution was slowly warmed to −40 °C over 30 min and stirred at −40 °C for a further 1.5 h. A solution of the sodium alkoxide, generated from the deprotonation of alcohol **16** (1.01 g, 4.50 mmol) with NaH (60% suspension, 225 mg, 5.63 mmol), in THF (15 mL) at 0 °C, was added in a dropwise manner via Teflon cannula to the brown solution of the imine−Ti complex at −40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (5 mL) was added, and the resulting biphasic mixture was stirred rapidly. The resulting solution was further diluted with saturated aqueous $NaHCO_3$ (150 mL) and extracted with ether (3 × 150 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (1/40→1/30 EtOAc/Hexanes) to yield haloallylic amine **17** as a colorless oil (811 mg, 67%, dr ≥ 20:1). **Synthesis of (3*S**,3*S**)-2-benzyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one 18:** To a round-bottom flask equipped with a reflux condenser was sequentially added amine **17** (169 mg, 0.420 mmol), toluene (4.2 mL), $Cl_2Pd(PPh_3)_2$ (14 mg, 0.021 mmol), and Et_3N (114 μL, 83 mg, 0.820 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C) and stirred for 12 h. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (1/10→1/5 EtOAc/Hexanes) to yield γ-lactam **18** as a white solid (111 mg, 87%).

can be conducted in a single reaction vessel. Here, union of imine **4** with allylic alcohol **2** furnishes lactam **3** in 69% yield. Similarly, union of imine **4** with allylic alcohol **22** provides the stereodefined bicyclic lactam **18** in 73% yield.[8] Notably, avoiding the requirement for purification of the intermediate homoallylic amines substantially improves the overall yield for this γ-lactam forming annulation process.

(8) General experimental procedure for the one-pot γ-lactam synthesis described in Figure 5: **Synthesis of (3*S**,3a*S**)-2-benzyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one 18:** To a solution of imine **4** (74 μL, 78 mg, 0.400 mmol) and $ClTi(Oi\text{-}Pr)_3$ (1.0 M in diethyl ether, 0.500 mmol) in toluene (1.6 mL) at −70 °C was added $c\text{-}C_5H_9MgCl$ (2.00 M in diethyl ether, 1.00 mmol) in a dropwise manner with a syringe. The orange-brown solution was slowly warmed to −40 °C over 30 min and stirred at −40 °C for a further 1.5 h. A solution of the sodium alkoxide, generated from the deprotonation of allylic alcohol **22** (106 mg, 0.600 mmol) with NaH (60% suspension, 30 mg, 0.750 mmol), in THF (1.6 mL) at 0 °C, was added in a dropwise manner via Teflon cannula to the brown solution of the imine−Ti complex at −40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. The following morning H_2O (36 μL, 36 mg, 2.00 mmol) was added and the solution was then rapidly stirred for 2 h at ambient temperature. To the yellow solution of the reaction mixture was added $PdCl_2$ (1 mg, 0.008 mmol), $t\text{-}Bu_3P$ (1.0 M toluene, 0.024 mmol), and Et_3N (223 μL, 161 mg, 1.60 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C) and stirred for 12 h. The reaction vessel was then allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc (10 mL), and the solids were removed by filtration through celite. The filtrate was further diluted with EtOAc (75 mL) and washed with 1 M HCl aq. (75 mL), saturated aqueous $NaHCO_3$ (75 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (1/10→1/5 EtOAc/Hexanes) to yield γ-lactam **18** as a white solid (89 mg, 73%, dr ≥ 20:1).

Overall, we describe a multicomponent coupling process for the synthesis of stereodefined *exo*-alkylidene-γ-lactams. In short, titanium-mediated regio- and stereoselective coupling of aromatic imines with 2-halo allylic alcohols furnishes intermediate homoallylic amines that are well-suited for palladium-catalyzed carbonylation. This two-step process has been demonstrated with a variety of allylic alcohols and has defined a convergent and stereoselective pathway to mono- and bicyclic γ-lactams. Finally, a one-pot procedure has been developed that enables direct preparation of stereodefined lactams from allylic alcohols and imines. Given the flexibility of the titanium-mediated coupling with respect to imine structure[3d] and the ability to translate stereochemical information from the allylic alcohol to the homoallylic amine intermediates,[3d] we anticipate that this heterocycle-forming annulation will be of utility in medicinal chemistry and natural product synthesis.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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