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Direct Access to Functionalized Azepanes by Cross-Coupling with α-Halo Eneformamides

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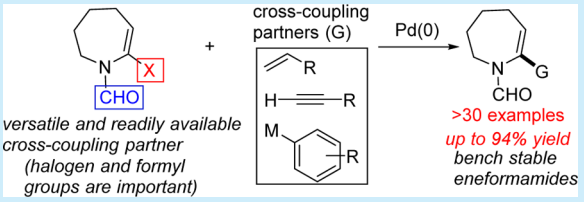
Supporting Information

ABSTRACT: The synthesis of functionalized azepanes was accomplished through the palladium-mediated cross-coupling of α-halo eneformamides with mostly unactivated nucleophiles under mild conditions. Alkenylations proceeded with excellent stereoselectivitiy. In most cases, high yields of the coupling products were obtained.



Functionalized azepanes constitute the core of many medicinally important heterocyclic compounds and bioactive alkaloids (see highlighted rings in Figure 1). These include stemona (e.g., stenine), ergot (e.g., aurantioclavine and clavicipitic acid), kopsia (e.g., arboflorine), and securinega (e.g., securinine) alkaloids.

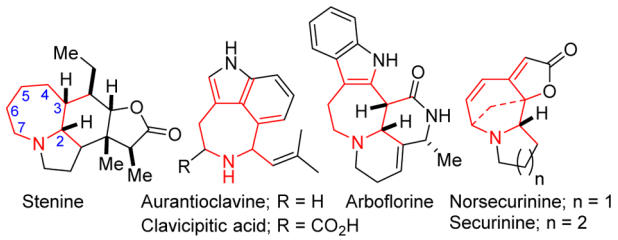


Figure 1. Representative azepane-containing alkaloids.

An effective strategy that would provide efficient access to the differentially substituted azepanes found in these molecules would be to functionalize an enamide or enecarbamate derivative of the saturated azacycle. In general, enamides and enecarbamates offer several advantages as a starting point for access to differentially functionalized azacycles.[1−5] As has been demonstrated for piperidine and pyrrolidine-based heterocycles, the double bond of the corresponding enamide or enecarbamate can be reduced or oxidized[4,6] or may participate in carbon−carbon bond-forming events. Notably C-2 functionalization in these cases has been achieved by utilizing cross-coupling strategies either from a vinyl triflate,[7,8] vinyl phosphate,[9] or stannane.[10] C-3 functionalization has also been achieved using Lewis acids[11] or cross-couplings facilitated by palladium,[2,3] iron,[5] or iridium catalysis.[12] However, it is well recognized that reactivity trends from 5- to 6- to 7-membered azacycles are *not* easily predictable.

In order to achieve C-2 and/or C-3 functionalization of azepanes, which would provide access to the majority of the substitution patterns resident in the alkaloids shown in Figure 1, we reasoned that cross-coupling offered the best approach. Previously, Occhiato, Coudert, and Sulikowski have reported isolated examples of cross-couplings of vinyl triflate (**I**, Figure 2, top),[7] vinyl phosphate (**II**),[9] and α-iodo enecarbamate (**III**),[13] respectively, with metalated coupling partners.[7] The *instability* of **I**, **II**, and **III**, as noted by the authors,[7,13] likely necessitated the use of highly reactive metalated cross-coupling partners. The *lability* of the substrates under the coupling conditions, and especially of the enecarbamate-derived products (due to their proneness to ring-opening[7]), diminishes the practicality of these previously reported methodologies.

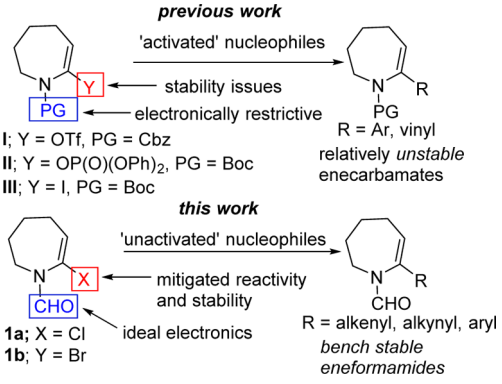


Figure 2. C-2 functionalization strategies.

We hereby report the α- and α,β-functionalization of caprolactam-derived α-halo eneformamides (**1a**/**b**, Figure 2, bottom) to afford functionalized azepanes. The current work stands as an advance over existing coupling methodology given that the coupling of **1a** with nonmetalated alkenes can now be achieved, obviating the need for vinyl stannanes (toxic) or vinyl boronic acids/esters (unstable, prohibitive cost) as coupling partners. Importantly, the *bench stable* α-halo eneformamides employed in this study are prepared in a *single* step and display

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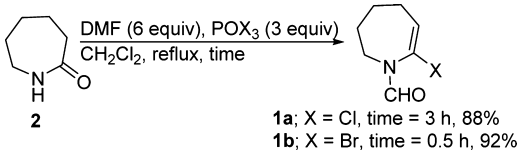
a *unique* balance of *reactivity* and *stability*, in contrast to the previously employed electrophiles (**I**, **II**, and **III**), which are relatively unstable and require multiple steps for their syntheses.[7,9]

The α-halo eneformamides (**1a**/**b**) were prepared from caprolactam (**2**) (Scheme 1, see the Supporting Information, for details) in a single step using a Vilsmeier–Haack reaction.

Scheme 1. Synthesis of α-Halo Eneformamides 1a and 1b

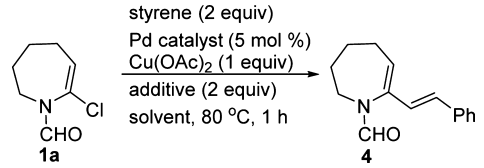


α-Alkenylation of 1a/b

Our studies on the α-alkenylation of **1** began with chloro eneformamide **1a** (Table 1). Vinylated adducts of azepenes are highly sought after since they serve as valuable synthons. For example, they may be used as dienes in hexannelations en route to the synthesis of polycylic alkaloids such as stenine (see Figure 1).[13] Historically, palladium-catalyzed alkenylation of enamides related to **1a**/**b** is possible at C-2 under Heck-type conditions and at C-3 under the Fujiwara–Moritani[14] conditions.[3] As such, a mixture containing **1a**, styrene (**3a**), 5 mol % of $Pd(OAc)_2$, and 1 equiv of $Cu(OAc)_2$,[3,15] in DMF was warmed to 80 °C. After 1 h at this temperature, no conversion of **1a** was observed. When K_2CO_3 was added, adduct **4** was obtained in 79% yield (Table 1, entry 1). The regioselective formation of **4** indicates a preference for the Heck coupling at C-2 over the Fujiwara–Moritani coupling at C-3. Lowering the catalyst loading to 2 mol % of $Pd(OAc)_2$ diminishes the yield, which is improved to satisfactory levels when longer reaction times are employed (entry 2). Sodium trifluoroacetate[15] (NaTFA) performs as efficiently as K_2CO_3 (entry 3) as the added base. Performing the coupling in the absence of the oxidant (i.e., $Cu(OAc)_2$) has no adverse effect on the efficiency of the reaction (entries 4 and 5). The use of Pd(0) precatalysts such as $Pd_2(dba)_3$ (entry 6) and $Pd(PPh_3)_4$ (entry 7) results in a decrease in the rate of reaction. Finally, the efficacy of the coupling marginally diminishes when 1,4-dioxane is employed as the solvent and longer reaction times are required (entry 8).

With the optimized conditions (entry 5) in hand, the scope of the alkene coupling partner was explored (Scheme 2). Electronically diverse, monosubstituted, 1,1-disubstituted, and 1,2-disubstituted (acyclic and cyclic) alkenes were surveyed. Electron-rich styrenes react faster than their electron-poor counterparts (see **4**–**6**). With NaTFA as the base additive, moderate yields are generally obtained when electron-poor alkenes such as acrylates are employed. In these cases, vicinally vinylated byproducts arising from competing Fujiwara–Moritani coupling at C-3, were detected. However, high yields are obtained when K_2CO_3 is used in place of NaTFA (see **8**–**11**). Using vinyl acetate as the alkene coupling partner, a vinyl group can be introduced at C-2 of the eneformamide (see **13**) where coupling proceeds with loss of the acetate group. However, coupling of **1a** with allyl acetate affords conjugated diene **14**, where the acetate group remains intact. Reaction of **1a** with cycloheptene affords an inseparable mixture of unconjugated dienes **17a**–**c**,[16] which are converged to protected 2-cycloheptylazepane (**18**) after catalytic hydrogenation. In the absence of a coupling partner at 100 °C, **1a** affords homocoupling products **19** and **20**.[17]

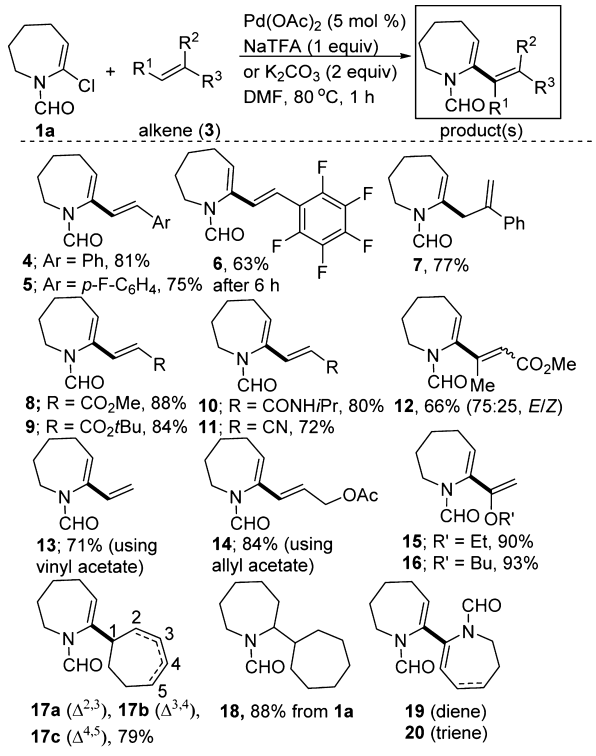
Table 1. Optimization of the Heck Coupling of 1a with Styrene



entry	Pd catalyst	additive	solvent	yield (%)
1	$Pd(OAc)_2$	K_2CO_3	DMF	79
2[a]	$Pd(OAc)_2$	K_2CO_3	DMF	63
3	$Pd(OAc)_2$	NaTFA	DMF	81
4[b]	$Pd(OAc)_2$	K_2CO_3	DMF	80
5[b]	$Pd(OAc)_2$	NaTFA	DMF	82
6[c]	$Pd_2(dba)_3$	K_2CO_3	DMF	67
7[c]	$Pd(PPh_3)_4$	K_2CO_3	DMF	65
8[d]	$Pd(OAc)_2$	K_2CO_3	dioxane	76

[a]With 2 mol % of $Pd(OAc)_2$ for 6 h. [b]Without $Cu(OAc)_2$. [c]Time = 8 h. [d]Time = 2 h.

Scheme 2. Alkene Scope in the Pd-Catalyzed Alkenylation of 1a



Importantly, under the conditions described in Scheme 2, other leaving groups at C-2 of the eneformamide (e.g., triflates and phosphates) *fail* to undergo the Heck coupling, thus highlighting the *uniqueness* of the α-halo eneformamides as coupling partners. Furthermore, it is illuminating that the more stable α-chloro eneformamide (**1a**) is more reactive than the bromo variant (**1b**), suggesting that electronegativity far outweighs leaving group ability in these coupling reactions.

α-Alkynylation of 1a

The utility of **1a** in alkynylation protocols was also investigated. Using the conditions described in Scheme 3, Sonogashira

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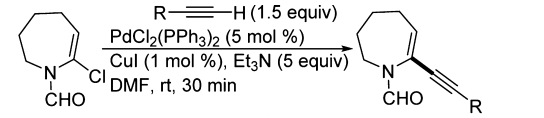
Scheme 3. Sonogashira Coupling of 1a with Terminal Alkynes

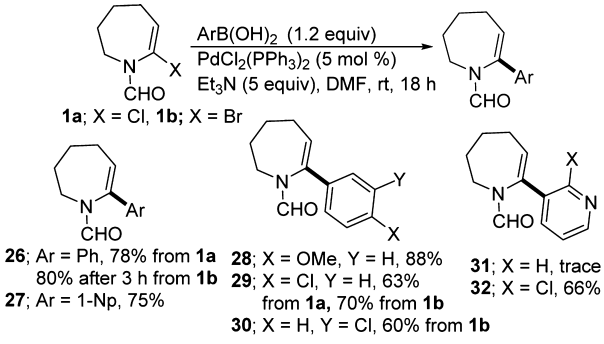


coupling[18] of **1a** with phenyl acetylene affords cyclic conjugated enyne **22** in 88% yield. Couplings of **1a** with trimethylsilyl acetylene (**21b**), 1-ethynylcyclohexene (**21c**), and 5-chloro-1-pentyne (**21d**) proceed efficiently, affording **23**, **24**, and **25**, respectively. In one case, coupling proceeds in the absence of the CuI additive. The importance of conjugated enynes such as those illustrated in Scheme 3 is supported by their use in nickel- and cobalt-catalyzed thermal [2 + 2] cycloadditions with alkenes.[19,20]

α-Arylation of 1a/b

Palladium-catalyzed coupling of **1a** or **1b** with either electron-rich or electron-deficient nonmetalated arenes under a variety of reaction conditions was unsuccessful. As such, we investigated the possibility of synthesizing the α-arylated azepenes via Suzuki coupling under *mild* reaction conditions (Scheme 4). Thus, coupling of **1a** with phenyl boronic acid for 12 h affords **26** in 78% yield using the conditions outlined. With α-bromo eneformamide **1b** as the substrate, a similar yield of **26** is obtained after just 3 h. As shown in Scheme 4, an electron-neutral but sterically demanding naphthyl group can be introduced (see **27**). An electron-rich aryl substituent undergoes faster and more efficient coupling with **1a** compared to the electron-neutral case (**28** vs **26**). Conversely, electron-poor and π-deficient heteroaryl nucleophiles react slowly and less efficiently (see **29**–**32**).

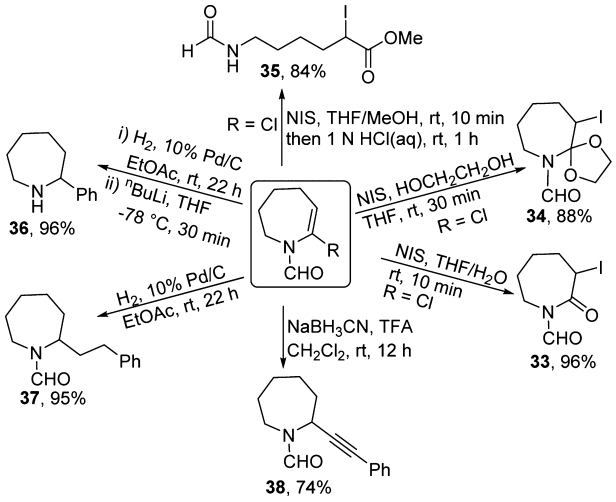
Scheme 4. Suzuki Coupling of α-Halo Enamides with Aryl Boronic Acids



Functionalization of 2-Substituted Azepenes

With a small library of α-substituted (halo, alkenyl, alkynyl, and aryl) enamides in hand, we began our studies toward the synthesis of vicinally functionalized azepanes by starting with halo enamide **1a** (Scheme 5). We first explored the use of **1a** in carbon–heteroatom (C–X) bond forming processes. This would provide highly functionalized intermediates that would in turn act as substrates for further coupling reactions. Treatment of **1a** with *N*-iodosuccinimide (NIS) in a mixture of THF and H_2O at room temperature, affords α-iodo lactam

Scheme 5. Functionalization of 2-Substituted Eneformamides



33. The use of ethylene glycol ($HOCH_2CH_2OH$) as the nucleophile affords spiro ketal **34**. With MeOH as the nucleophile, partial ring-opening of the initially formed dimethyl ketal to ester **35** is observed. *N*-Acyl 2-substituted azepanes are *not* readily accessible largely because unlike the corresponding piperidines and pyrrolidines, the direct α-lithiation/substitution of *N*-Boc azepane is a low-yielding process.[21] Thus, catalytic hydrogenation of **26** affords formyl protected 2-phenylazepane, which is deformylated to give the free amine (**36**). Similarly, hydrogenation of diene **4** furnishes 2-alkyl azepane **37**. This high yielding, three-step sequence to saturated 2-alkyl azepanes such as **18** and **37**, from readily available lactams, provides an effective route to this class of compounds. This is noteworthy since the most straightforward approach to 2-alkyl azacycles, i.e., $C(sp^3)$–$C(sp^3)$ coupling[22] of the 2-lithiated heterocycle with alkyl halides is plagued by competing single electron transfer (SET), as well as elimination (E2) processes.[23] Furthermore, the availability of saturated *N*-acyl-2-alkynyl heterocycles is somewhat limited partly because α-lithiation followed by copper-mediated "alkynylation" often affords the allene.[24] However, using our strategy, an *N*-acyl iminium reduction of **22** affords alkyne **38**.

In summary, azepane and azepene derivatives are readily obtained by exploiting the Pd-mediated cross-coupling of halo enamide derivatives. The α-alkenylation, alkynylation, and arylation of caprolactam-derived α-halo eneformamides using Heck, Sonogashira, and Suzuki coupling conditions, respectively, can now be accomplished. The alkenylation reaction proceeds with excellent stereoselectivity, and with a broad scope of nonmetalated alkene coupling partners. Finally, the 2-substituted eneformamides have been applied to the synthesis of various functionalized azepanes.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and spectroscopic data. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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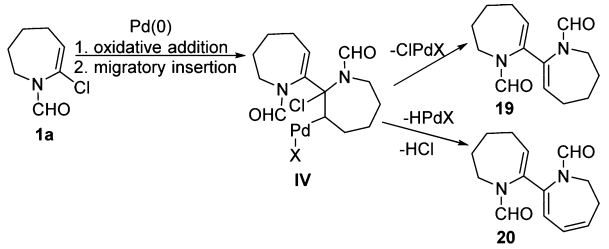

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