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A Modular Approach to Dibenzo-fused ε-Lactams: Palladium Carbene Bridging C-H Activation and Its Synthetic Application

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Dedication ((optional))

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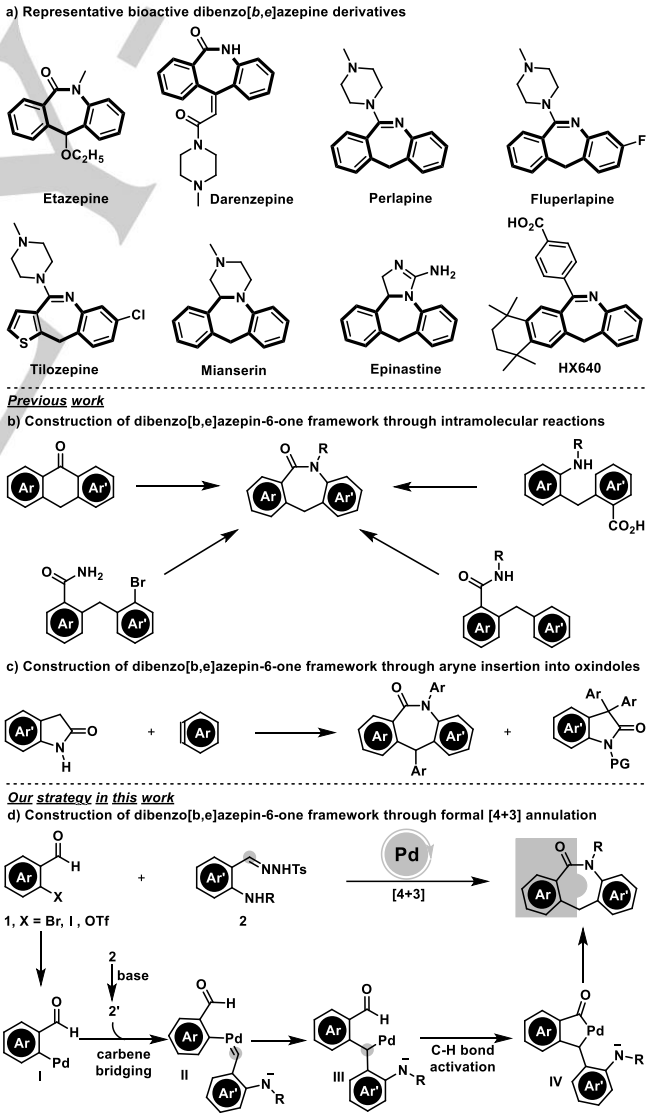
Abstract: Tricyclic ring systems possessing a dibenzo structure joined to a seven-membered heterocyclic ring frequently show important biological activities. However, a modular approach to these molecules based on efficient intermolecular reaction of readily available chemicals is lacking. Herein, an unprecedented palladium-catalyzed formal [4+3] annulation for modular construction of these tricyclic systems is described. This reaction features easily accessible reactants (*o*-haloarylaldehydes and *N*-tosylhydrazones), broad substrate scope, and excellent functional group compatibility. The synthetic potential is demonstrated by the easy scale-up reactions, late-stage modification of complex molecules, and collective synthesis of bioactive molecules and approved drugs.

Due to the potential biological activities and versatile synthetic utility for drug discovery (Scheme 1a),[1] compounds bearing dibenzo-fused seven-membered *N*-heterocyclic system have attracted considerable attention. Classical approaches to construct dibenzo[*b*,*e*]azepin-6-one framework usually relied on intramolecular reaction of molecules with proper preinstalled functionalities (Scheme 1b).[2] However, the requirement of multi-step manipulation to access the carefully engineered reactants may render these protocols less practical for buildup a library of congeners, a strategy which has been proved to helpful for drug discovery.[3] While this goal could be achieved by development of efficient intermolecular reactions of readily accessible reactants, a single example involving aryne insertion into oxindoles only appeared recently,[4] and the target products were obtained in low to moderate yields (Scheme 1c).

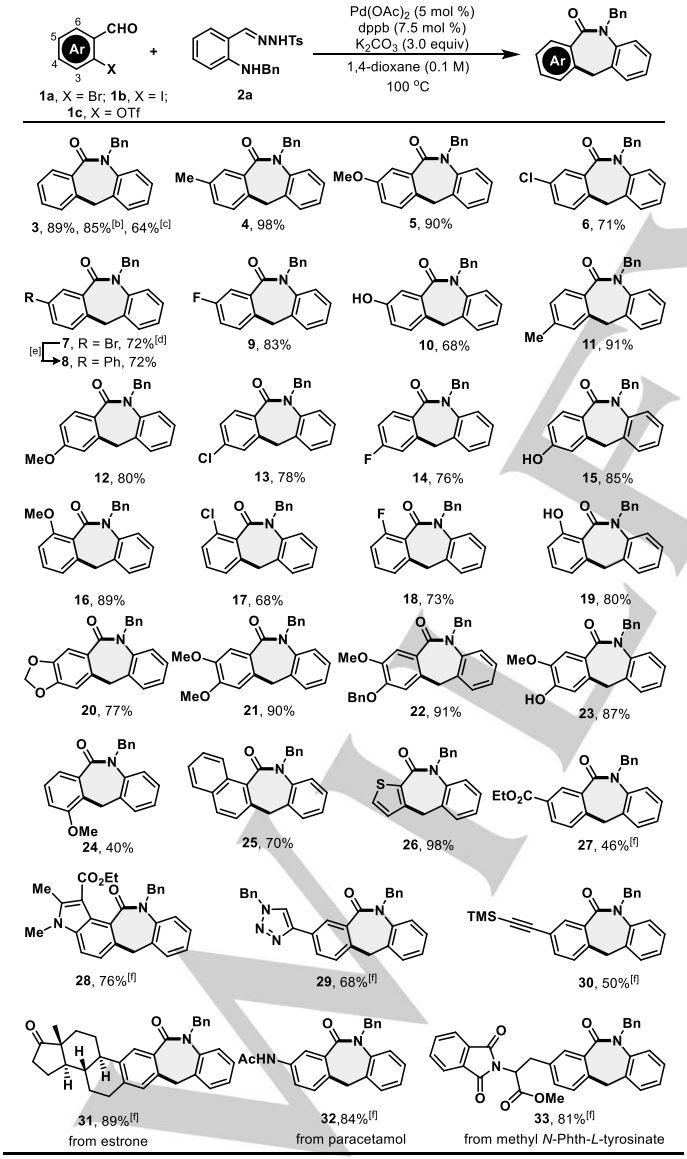
Formal [4+3] cycloaddition is a fundamental strategy to construct seven-membered cyclic compounds.[5] Disconnection of the bonds in the central ring of dibenzo[*b*,*e*]azepin-6-one framework leads to two simple fragments (Scheme 1d). Encouraged by recent advances in palladium carbene participated cross coupling reactions[6] and our achievements in this area,[7] we envision that the fragments arsing from aforementioned retro-synthetic analysis could derive from two easily accessible reactants, *ortho*-halo/trifluoromethylsulfonyl benzaldehydes **1** and *N*-tosylhydrazones **2**.[8] As depicted, the reaction between **1** and Pd(0) catalyst would generate Pd(II) intermediate **I**; at this stage, due to the high strain energy, a



Scheme 1. Strategies for the construction of dibenzo[*b*,*e*]azepin-6-one frameworks.

direct C-H bond activation[9] of the aldehyde moiety to form a four-membered palladacycle is unlikely.[10] Thus, **I** would prefer to react with the *in situ* generated bifunctional diazo compound **2'**[11] to produce a palladium carbene intermediate **II**.[12] Migratory insertion of **II** could produce a one-carbon bridging unit, in turn promoting the subsequent C-H bond palladation to form a five-membered palladacycle **IV**. Ring expansion **IV** may eventually afford the final product dibenzo[*b*,*e*]azepin-6-one. Such a carbene bridging C-H activation strategy may address the unmet challenge for modular preparation of pharmacophoric dibenzo[*b*,*e*]azepin-6-ones through an efficient intermolecular reaction by using easily accessible chemicals as reactants. Another prominent feature of this chemistry is that, it offers an unconventional approach to functionalize an inert C-H bond that is within three-bond distance from the palladium atom.[13],[7] Herein, we describe our efforts on execution of this designed principle, applying this protocol as key step for collective synthesis of a range of bioactive molecules.

Table 1. Reaction Scope with Respect to Aldehydes **1**.[a]



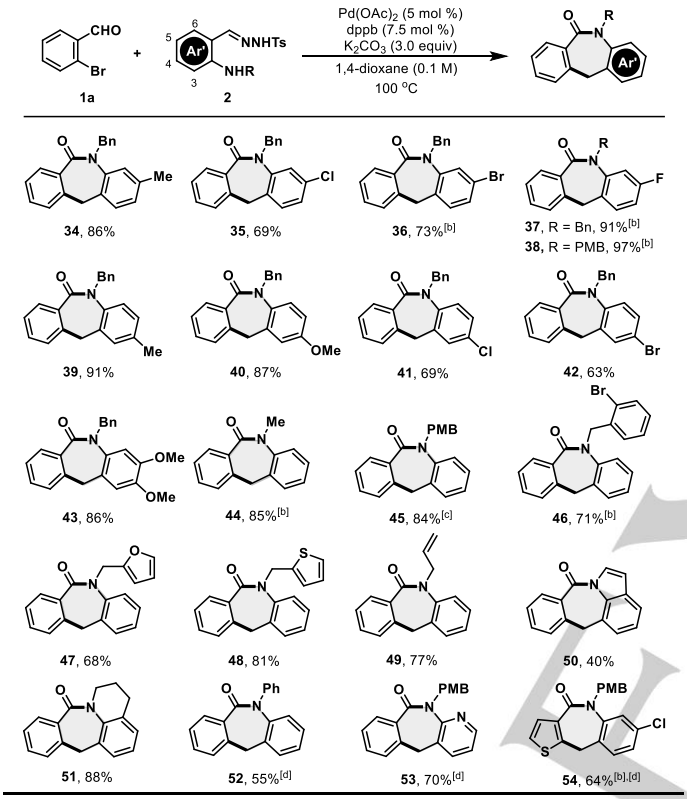
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), ligand (7.5 mol %), K_2CO_3 (3.0 equiv) in anhydrous 1,4-dioxane (2.0 mL), stirred under an atmosphere of argon at 100 °C. Unless otherwise noted, *o*-bromo aryl aldehyde was employed as the electrophile. [b] Aldehyde **1b** was used. [c] Aldehyde **1c** was used. [d] Scale-up to 1 mmol scale. [e] Reaction conditions: $Pd(OAc)_2$, Johnphos, $PhB(OH)_2$, KF, THF, 60 °C. [f] Aryl triflate was used instead of aryl bromide.

On the basis of our mechanistic assumption, we have identified a set of optimal conditions for this novel palladium-catalyzed dibenzofusedazapinone synthesis.[14] As depicted, readily available 2-bromo benzaldehyde **1a** (0.2 mmol) and diazo precursor *N*-tosylhydrazone **2a** (0.4 mmol) were exposed to K_2CO_3 (0.6 mmol) in the presence of the catalyst assembled from $Pd(OAc)_2$ (5 mol %) and dppb (L_4, 7.5 mol %) in 1,4-dioxane (0.1 M) at 100 °C. The anticipated product **3** was formed in 89% yield after isolation by flash column chromatography. As depicted in Table 1, besides *o*-bromo benzaldehyde **1a**, *o*-iodo benzaldehyde **1b** and triflate **1c** were viable electrophiles to react with **2a** to give lactam **3** in 85% and 64% yields, respectively. Subsequently, we found that a wide range of *o*-bromo arylaldehydes with electronically varied substituents, such as Me, MeO, Cl, Br and F, at the 5 position of the phenyl ring could readily participate in the current palladium-catalyzed formal annulation reactions, affording the corresponding tricyclic products in good yields (Table 1, **4**-**7**, **9**). The toleration of an additional halogen group has offered an opportunity for downstream manipulations. For example, a palladium-catalyzed Suzuki cross-coupling of **7** with $PhB(OH)_2$ could afford **8** in high yield. Furthermore, substrates with substituents at different positions were compatible with this reaction, regardless of the electronic nature of the substituents (Table 1, **11**-**14** and **20**-**22**). Pleasingly, sterically hindered substrates bearing substituents at 3 or 6 positions could react with **2a**, and converted to corresponding products with high efficiency (Table 2, **16**-**18** and **24**-**25**). Notably, free hydroxyl groups settled on different positions affect the reactions slightly, giving the corresponding lactams in moderate to high yields (Table 1, **10**, **15**, **19** and **23**). Aldehydes bearing naphthyl, and heteroaryl moieties were also suitable for this transformation; the corresponding lactams **25**, **26** and **28** were obtained in 75%, 98%, and 76% yields, respectively. Functional groups, such as triazole moiety and alkyne bearing labile trimethylsilyl group, were tolerated as well (Table 1, **29** and **30**). Aryltriflates derived from biologically active molecules, such as estrone, paracetamol and methyl *N*-phth-*L*-tyrosinate, could also formally coupled with **2a**; the corresponding products embedded with additional pharmacophoric fragments were obtained in very good yields (Table 1, **31**-**33**).

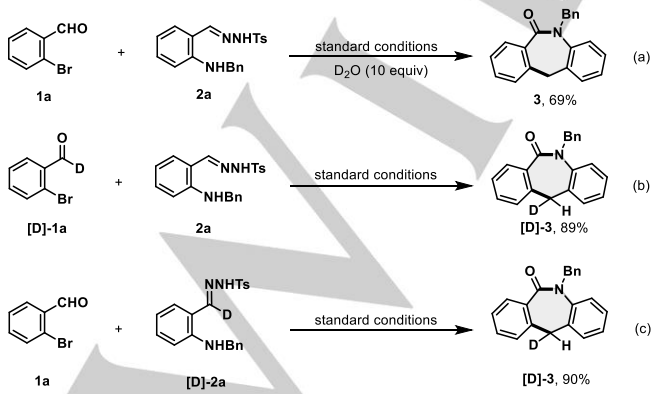
Subsequently, the substrate scope with respect to *N*-tosylhydrazones **2** was investigated. As summarized in Table 2, the introduction of various substituents, including Me, Cl, Br and F, at the 4 position of the phenyl ring (Ar') in **2** was well tolerated in this reaction, and the corresponding products **34**-**38** were obtained in good yields (69-86% yields). Similarly, variation of the substituents at other positions, the reactions could also proceed well. Hydrazones possessing electron donating groups reacting with **1a** generally gave the corresponding lactams in higher yields (**39**, **40** and **43** vs **41** and **42**). Aliphatic groups other than benzyl group on the nitrogen atom, including methyl, *para*-methoxybenzyl (PMB), furan-2-ylmethyl and thiophen-2-ylmethyl, were all compatible; the lactams **43**-**48** were isolated in high yields. A potentially reactive allyl group which may cause other side reactions kept intact in product **49**. The activities of

hydrazones derived from 1*H*-indole-7-carbaldehyde and 1,2,3,4-tetrahydroquinoline-8-carbaldehyde were also evaluated. As depicted, both reactions could proceed smoothly; products **50** and **51** were isolated in 40% and 88% yields, respectively. Hydrazones bearing pyridinyl scaffold could also engage in current formal [4+3] annulations, and the corresponding lactams **53** was obtained in 70% isolated yield. The reactions could be scaled-up to 1 or 2 mmol scale while maintaining the efficiencies (**37**, **38**, **45** and **46**).

Table 2. Reaction Scope with Respect to Hydrazones **2**.[a]

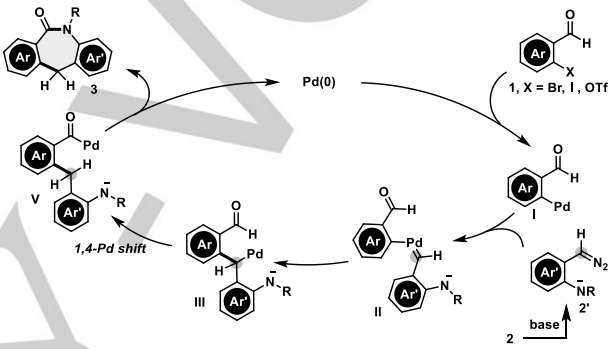


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), ligand (7.5 mol %), K_2CO_3 (3.0 equiv) in anhydrous 1,4-dioxane (2.0 mL), stirred under an atmosphere of argon at 100 °C. [b] Scale-up to 1 mmol scale. [c] Scale-up to 2 mmol scale. [d] 10 mol % $Pd(OAc)_2$ was employed. PMB = *p*-methoxybenzyl.



Scheme 2. Mechanistic studies.

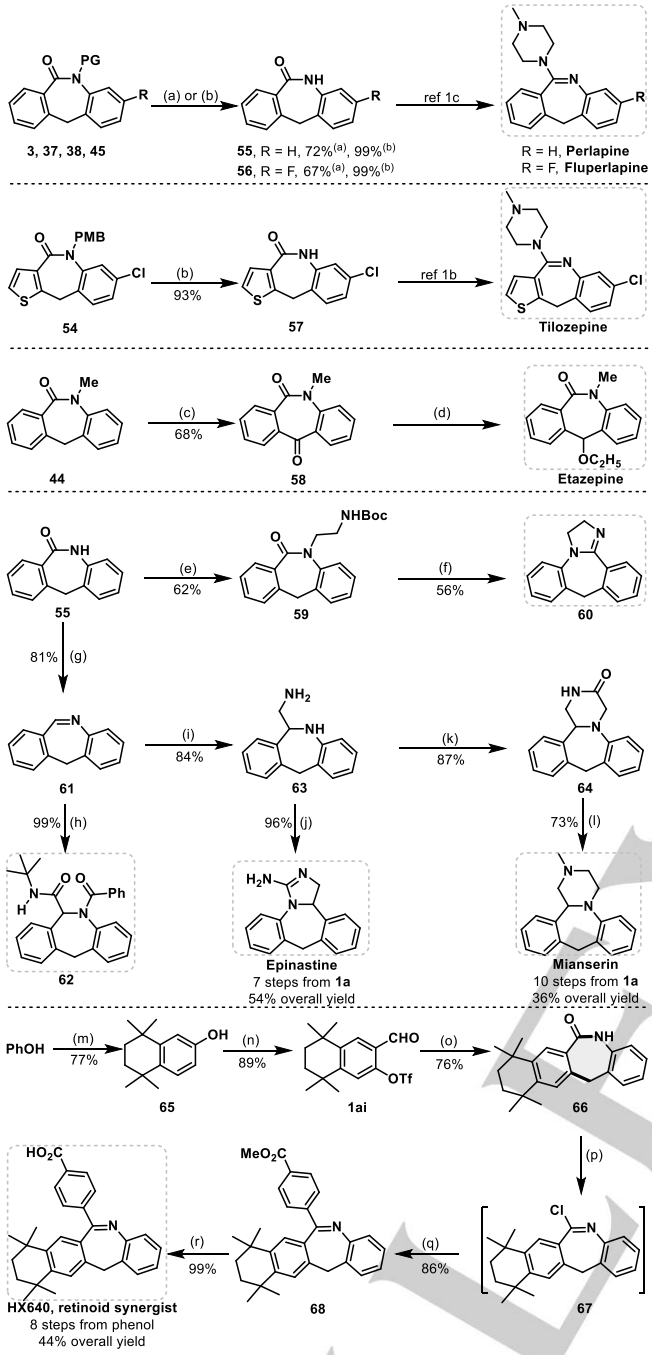
To probe the mechanism of this transformation, we have performed several deuterium labeling experiments. As depicted, under otherwise identical conditions, aldehyde **1a** reacted with 2-amino *N*-tosylhydrazone **2a** in presence of 10 equiv. of D_2O, **3** without any incorporation of deuterium atom was isolated in 69% yield (Scheme 2a). By contrast, the reaction **[D]-1a** with **2a** under standard conditions, giving **[D]-3** in 89% yield, with complete deuterium atom migrated to the dibenzylic position (Scheme 2b). As expected, the reaction of **1a** with **[D]-2a**[15] also gave **[D]-3a** with deuterium retaining at the dibenzylic position (Scheme 2c). These experiments explained the origin of hydrogen atoms on the central ring. Collectively, the data obtained here are in agreement with our intial mechanistic hypothesis, which involves metal carbene migratory insertion enabled 1,4-palladium shift (Scheme 3).[16]



Scheme 3. Proposed catalytic cycle.

With sufficient amount of products in hand, the synthetic potential for current modular protocol to dibenzoazepinones was demonstrated by the facile access to a variety of synthetic intermediates of biologically active molecules (Scheme 4). After the removal of protecting groups (PG = benzyl or PMB), antipsychotic drugs perlapine[1c], fluperlapine[1c] and tilozepine[1b] could be obtained according to reported procedures. Copper-catalyzed oxidation of **44** could give dibenzofusedazepin-di-one **58** in 68% yield upon isolation.[17] **58** could further serve as key intermediate for the synthesis of etazepine, a compound that was shown to be a potent and long-acting anticonvulsant.[1d] Interestingly, compound **60** bearing an additional imidazoline ring could be prepared through a two-step procedure from **55**.[18] Treatment of **55** with LAH, followed by MnO_2 oxidation could furnish 11*H*-dibenzo[*b*,*e*]azepine **61**, which could further applied for a Ugi-type reaction to provide **62**.[19] Vicinal amine **63** was prepared through a one-pot two-step manipulation on **61**. The NO_2 group in the adduct obtained from *t*-BuOK promoted aza-Henry reaction could be reduced with $NaBH_4/NiCl_2$,[20] and **63** was produced in 84% overall yield from **61**. With **63** in hand, antihistamine epinastine could be facilely prepared by the reaction with cyanogen bromide.[21] Reaction of **63** with 2-chloroacetyl chloride gave **64** in 87% yield. LAH reduction of **64** followed by Eschweiler-Clarke methylation could give antidepressant drug mianserin in high efficiency.

The synthetic potential of current formal [4+3] annulation was further demonstrated by the streamline synthesis of retinoid synergist HX640[1e] from simple phenol. The total synthesis of HX640 commenced with a $AlCl_3$ catalyzed Friedel-Crafts



Scheme 4. Collective synthesis of bioactive molecules. Conditions and reagents: (a) **3** or **37**, 10% Pd/C, $HCOONH_4$, MeOH, reflux, 15 h; (b) **45** or **38**, TFA, reflux, 12 h; (c) $Cu(OAc)_2$, *t*-BuOOH/H_2O, 80 °C, 36 h, 68%; (d) ref 1d; (e) *tert*-butyl (2-chloroethyl)carbamate, NaH, DMF, 100 °C, 12 h, 62%; (f) 4 M HCl in dioxane, RT, overnight; toluene, reflux, 24 h; 56% over two steps; (g) $LiAlH_4$, THF, reflux, 3 h, 90%; MnO_2, toluene, reflux, 24 h, 90%; (h) *t*-BuNC, $PhCO_2H$, MeOH, 60 °C, 22 h, 99%; (i) *t*-BuOK, CH_3NO_2, RT, 48 h; $NiCl_2$, $NaBH_4$, 0 °C, 1 h; 84% yield over two steps; (j) ref 21: BrCN, EtOH/THF, 25 °C, 96%; (k) 2-chloroacetyl chloride, DCM, 0 °C, 1 h; NaI, $NaHCO_3$, acetone, reflux, 72 h; 87% yield over two steps; (l) $LiAlH_4$, THF, reflux, 3 h; HCHO, HCO_2H, EtOH, reflux, 3 h; 73% yield over two steps; (m) 2,5-dichloro-2,5-dimethylhexane, $AlCl_3$, DCM, RT to 40 °C, 77%; (n) $(HCHO)_n$, $MgCl_2$, Et_3N, THF, 75 °C, overnight; Tf_2O, pyridine, DCM, RT, 3 h; 89% yield over two steps; (o) standard conditions: table 1, entry 1; TFA, reflux, overnight; 76% yield over two steps; (p) $POCl_3$, *N*,*N*-dimethylaniline, reflux, overnight; (q) 4-(methoxycarbonyl)phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O, 90 °C 3 h; 86% yield over two steps; (r) 2 N NaOH, EtOH, RT, 6 h, 99%.

dialkylation of phenol to prepare tetramethyl-tetrahydronaphthlanol **65**. Then, a two-step one-pot manipulation on **65** with *ortho*-formylation and *O*-trifluoromethylsulfornylation could give the requisite reactant **1ai**, which was engaged in the key step for palladium-catalyzed formal [4+3] annulation with *N*-tosylhydrazone **2m** under standard condition. After removal of PMB group, dibenzo[*b,e*]azepin-6-one **66** was obtained in 76% isolated yield over two steps from **1ai**. Crude 6-chloro-11*H*-dibenzo[*b,e*]azepine **67** could be used for next step without purification by column chromatography. A Suzuki type cross coupling of **67** with 4-(methoxycarbonyl)phenylboronic acid gave **68**. Saponification of **68** could afford retinoid synergist HX640 in quantitative yield.

In summary, a novel modular approach to pharmacophoric dibenzo-[*b*,*e*]azepin-6-ones through palladium-catalyzed formal [4+3] annulation is developed. The reaction exhibits broad substrate scope and good functional group compatibility. The practicality and synthetic potential were demonstrated by the scale-up experiments and application on preparation of several bioactive molecules. By using this annulation as key step, approved drug antihistamine epinastine was obtained in seven linear steps with 54% overall yield, and antidepressant drug mianserin was obtained in ten linear steps with 36% overall yield. Moreover, retinoid synergist HX640 was prepared in 44% yield over eight linear steps from phenol. Based on these findings, we believe that a range of potentially bioactive molecules containing similar frameworks could be prepared in a modular manner. Further studies on carbene bridging C-H activation are ongoing in our laboratory.

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Keywords: Palladium carbene • bridging C-H activation • dibenzo[*b*,*e*]azepin-6-one • collective synthesis • bioactive molecules

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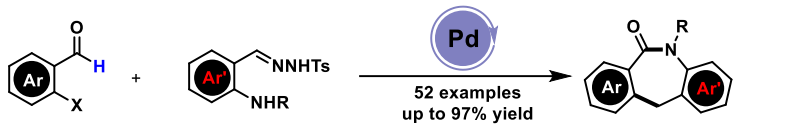

- palladium carbene bridging C-H activation
- broad scope, good funtional group compatibility
- modular access to pharmacophoric dibenzo-[*b,e*]azepin-6-ones
- bioactive molecule synthesis

A modular approach to access dibenzo-fused ε-lactams through catalytic palladium carbene bridging C-H activation is described. The reaction employs easily accessible chemicals as reactants, and displays broad substrate scope with good functional group compatibility. The synthetic utility of this protocol is demonstrated by serving as key step for collective synthesis of 9 biologically active molecules.

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