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Catalytic Aza-Wacker Annulation: Tuning Mechanism by the Activation Mode of Amide and Enantioselective Syntheses of Melinonine-E and Strychnoxanthine

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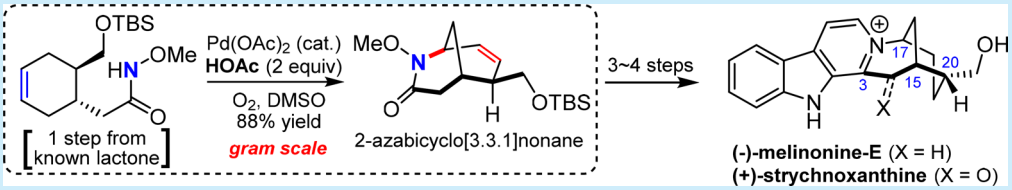
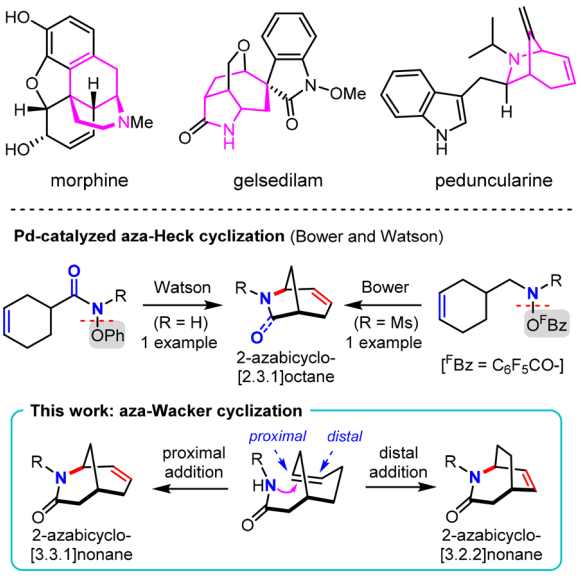
Supporting Information



ABSTRACT: An unprecedented N-substituent of the amide was found to be crucial for the successful annulation to establish 2-azabicyclo[3.3.1]nonane and other ring skeletons in good yield. The novel catalytic aza-Wacker annulation methodology was further illustrated in the concise syntheses and the absolute configuration determinations of melinonine-E and strychnoxanthine.

The construction of various N-containing bridged heterocycles (e.g., morphine, gelsedilam, and peduncularine) through C−N bond formation has been of prominent interest for synthetic chemists to devise novel strategies and tactics (Scheme 1).[1] In the context of our continued interest in developing methods to address synthetic problems,[2] we initially proposed that a palladium-catalyzed cyclization via C−N bond formation would easily construct a bridged lactam because the numerous studies on transition-metal-catalyzed hydroamination or aza-Wacker-type reaction of alkenes.[3] However, it was rather striking to us that very limited examples associated with a bridged lactam ring through aza-Heck cyclization have been reported. The Bower and Watson groups realized the oxidative cleavage of the N−O bond by optimal palladium(0) complexes and subsequent cross addition to the pendant alkene to release a cyclized product (Scheme 1).[4] While the practicality of these aza-Heck conditions remains uncertain, the annular variant of the aza-Wacker reaction is largely underdeveloped despite substantial efforts having been devoted to various N-containing mono and fused heterocycles.[5,6]

Scheme 1. Palladium-catalyzed construction of a bridged lactam via C−N bond formation



The bridged ring implementing unfavorable energetics might retard the actual lactam formation, as the denoted cyclization in Scheme 1 may require dramatic conformational alignment. Moreover, the regioselectivity of the addition to the alkene (proximal or distal) would result in different bridged rings. To establish a proof of concept, cyclohexenyl amide 1 was designed as a model substrate. One of the possible cyclization products, a 2-azabicyclo[3.3.1]nonane (morphan) skeleton derived from the proximal addition, is abundant in natural products and a privileged structure in drug development.[7] The Larock protocol ($Pd(OAc)_2$ and NaOAc in DMSO)[8] for aerobic Wacker oxidation was adopted for the initial attempt due to its success on the construction of the bridged lactone.

The preliminary screening revealed that the substituent on the amide N was crucial to proceed the requisite cyclization (Table 1).[9] Only a *N*-sulfonylated amide gave the aza-Wacker product in 79% yield along with trace of double-bond isomer **3** (entry 3). Further decreasing the catalyst loading, as the typical Larock's

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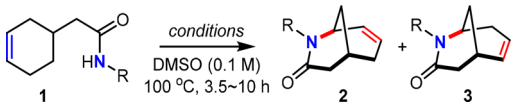
Table 1. Optimization of the aza-Wacker Cyclization[a]



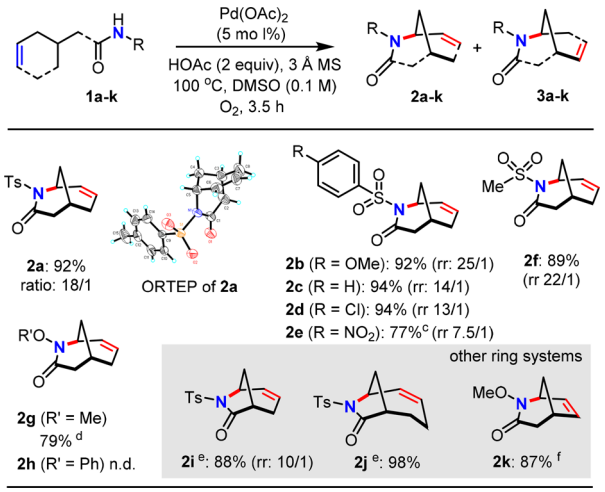
entry	R	conditions cat. (mol %)	additive (equiv)	conv.[b] 1 (%)	yield (2) (%)[c]
1	Bn	$Pd(OAc)_2$ (20), O_2	NaOAc (2)	<5	n.d.[d]
2	OBn	$Pd(OAc)_2$ (20), O_2	NaOAc (2)	49	<5
3	Ts	$Pd(OAc)_2$ (20), O_2	NaOAc (2)	>99	79
4	Ts	$Pd(OAc)_2$ (10), O_2	NaOAc (2)	92	87
5	Ts	$Pd(OAc)_2$ (5), O_2	NaOAc (2)	50	44
6	Ts	$Pd(OAc)_2$ (10), O_2		>99	65
7	Ts	$Pd(OAc)_2$ (10), O_2	LiOAc (2)	90	77
8	Ts	$Pd(OAc)_2$ (10), O_2	CsOAc (2)	66	42
9	Ts	$Pd(OAc)_2$ (10), O_2	$^tBuCO_2Na$ (2)	65	46
10	Ts	$Pd(OAc)_2$ (10), O_2	NaOAc (2), BPY[e]	86	76
11	Ts	$Pd(OAc)_2$ (10), O_2	NaOAc (2), DAF[f]	93	82
12	Ts	$Pd(OAc)_2$ (5), O_2	NaOAc (2), DAF[f]	68	55[g]
13	Ts	$PdCl_2(PPh_3)_2$ (10), O_2	NaOAc (1.5), THF	<5	n.d.
14[h]	Ts	$Pd(TFA)_2$ (10), O_2		56	21
15	Ts	$Pd(OAc)_2$ (10), O_2	NaOAc/HOAc (1/1)	>99	89 (>25/1)[i]
16	Ts	$Pd(OAc)_2$ (5), O_2	HOAc (2)	>99	92 (18/1)[i]
17[j]	Ts	$Pd(OAc)_2$ (5), O_2	HOAc (2)	>99	91 (25/1)[i]

[a]Reactions conditions: amide (0.1 mmol), catalyst (mol %), O_2 (1 atm), additive (equiv), and 3 Å molecular sieves (30 mg) in DMSO (1 mL) at 100 °C. [b]The conversion was determined by ^1H NMR. [c]Isolated yield of **2** was given when the conversion was >99%; the NMR yield for the rest of the entries was determined by ^1H NMR with internal standard, see the SI for details. [d]n.d. = not determined. [e]BPY (6,6′-dimethyl-2,2′-bipyridine): 10 mol %. [f]DAF (4,5-diazafluoren-9-one): 10 mol %. [g]12 h. [h]DMSO (2 equiv) as ligand, toluene (1 mL). [i]The ratio of **2**/**3** was determined by ^1H NMR. [j]One gram scale. DMSO = dimethyl sulfoxide. Ts = 4-methylphenylsulfonyl.

condition,[8c] resulted in a dramatic detriment on the conversion due to the rapid precipitate of Pd-black after 2 h (entry 5). In the absence of NaOAc, the increase of the isomeric product **3** deteriorated the yield of **2** (ratio: **2**/**3** = 4/1) (entry 6).[9] Other metal acetates and a steric bulky carboxylate ion reduced both the conversion and yield (entries 7−9). Although bipyridine-derived ligands were reported to facilitate the aza-Wacker reaction under several circumstances,[10] in this study, these ligands were found to be less efficient to promote the cyclization (entries 10−12). Other palladium catalysts, which have been proven beneficial for selected substrates,[11,12] were less effective for the current process (entries 13 and 14). The turning point commenced with the addition of HOAc; both the reaction rate and the selectivity (**2**/**3**) were amended (entry 15). The catalyst efficiency was further improved when 2 equiv of HOAc was introduced (entry 16). Given the denoted challenge for catalytic turnover in the aerobic aza-Wacker reaction, the profound effect via the addition of HOAc might sustain the catalytic cycle with an intriguing mechanism.[13,14] The catalyst system was ratified by a gram scale synthesis without detriment on the yield and selectivity (entry 17).

With the optimized conditions in hand, we first investigated the substitution effect on the amide. A series of para-substituted benzenesulfonamides (MeO, Me, H, and Cl) generally gave excellent yields (**2a**−**d**) (Scheme 2). For the strong electron-

Scheme 2. N-Substituents in the aza-Wacker Annulation[a,b]



[a]Isolated yield of **2**. [b]The ratio (rr) of **2**/**3** was determined by ^1H NMR. [c]The conversion was 82% after 6 h. [d]Thirty mol % of $Pd(OAc)_2$ for 6 h. [e]Compounds **2i** and **2j** were confirmed by X-ray analysis; see the SI. [f]Ten mol % of $Pd(OAc)_2$. A fused bicyclo compound **4** was found for the N-Ts substrate; see the SI.

withdrawing group (p-NO_2) in **1e**, both the reaction rate and selectivity decayed. A similar trend was also observed by Stahl in aza-Wacker cyclization and may implicate the reversible nature of C−N bond formation through a possible Pd-amidate complex.[13] A principally more electron-rich sulfonyl group, $MeSO_2$-(N), also gave the desired product **2f** in excellent yield (89%). Interestingly, cyclization of the amide bearing N-OMe also delivered lactam **2g** in good yield (79%), albeit a slow rate under higher catalyst loading. For amide **2h** bearing the same functional group as in Waston's report,[4b] no annulation proceeded. Of note, the catalyst system was also applicable for the construction of the other ring systems (**2i**−**k**) in excellent yields under the optimal conditions.

To gain further mechanistic insights into the amidopalladation process, two stereochemically defined deuterated amides were prepared and subjected to the aza-Wacker cyclization (Scheme 3).[15] Under the optimal conditions, the N-Ts amide performed a nucleophilic anti addition to the activated alkene by Pd species and subsequent *β*-D *cis*-elimination to result in a cyclized product **2a** as a major product (92%), while the deuterated **2a**-*d* was only 8%. This scenario is consistent with previous mechanistic studies on the aza-Wacker cyclization with the similar functionalized amide.[11,16] Interestingly, the cyclization of the N-OMe amide would largely go through syn-amidopalladation to afford **2g**-*d* in a 83% D-incorporation (only 17% of the Hb signal was integrated in the NMR spectra).[15] Notwithstanding, further mechanistic investigation is warranted to understand the profound effect of the N substituent, this scenario would be advantageous for the

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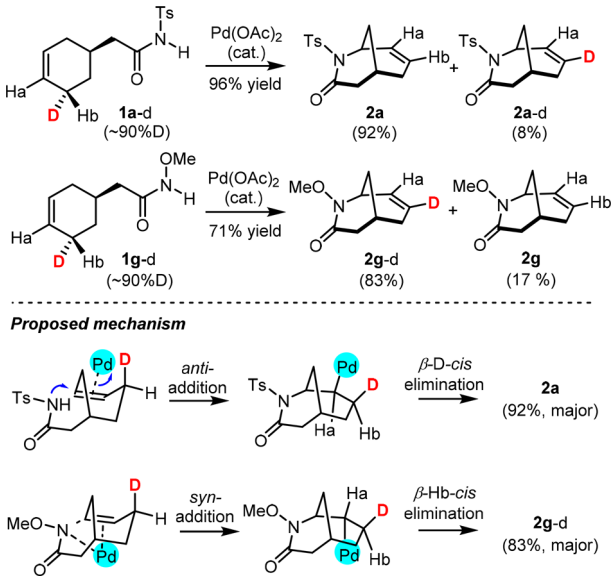
Scheme 3. Cyclization of Deuterated Amides and Proposed Mechanism[a]



[a]The ratio in parentheses was determined by ^{1}H NMR; the coordinating ligands of palladium were omitted for clarity.

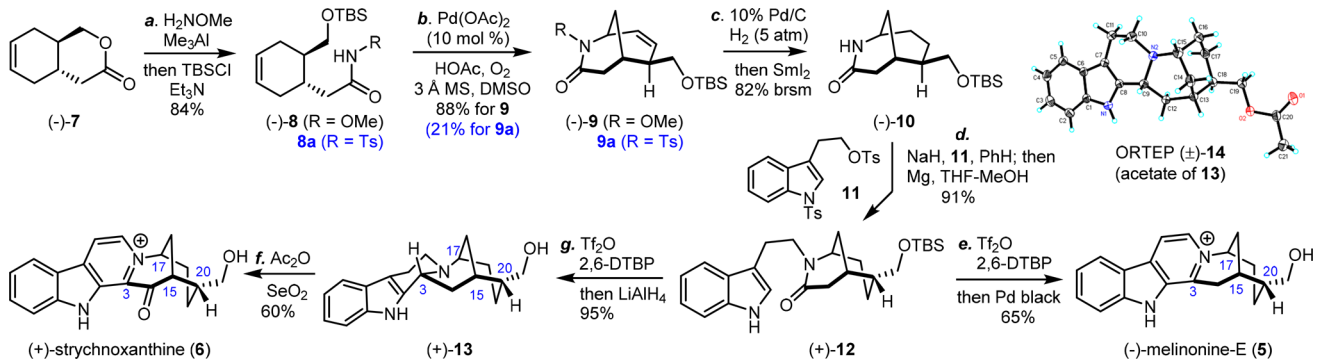
diverted synthesis of cyclized products by tuning the activation mode of the amide.

Having accessed the aza-Wacker cyclization to construct bridged lactams, our attention was drawn toward two morphan-core-embedded alkaloids. Melinonine-E (**5**) was first isolated in 1957 by Bächli et al. from the bark of *Strychnos melinoniana* Baillon (Loganiaceae), a plant used as an African folk medicine for the treatment of malaria.[17] The plain structure was later revised by Hesse et al. as a pentacyclic skeleton of a 2-azabicyclo[3.3.1]nonane-fused β-carbolinium cation, which is unprecedented in this category of alkaloids.[18] Angenot et al. also identified a biogenetically related structure (C14-oxo), strychnoxanthine (**6**), from *Strychnos gossweileri* Exell (Loganiaceae).[19] The uncertainty of the absolute configuration poses the question whether these two structurally related alkaloids are indeed biogenically correlated with other concomitant compounds.[18]

To streamline the synthesis, *trans*-lactone (−)-7[20] was reacted with methoxylamine in the presence of trimethylaluminum[21] and immediate silylation to afford amide **8** (Scheme 4). A two gram scale aza-Wacker reaction proceeded smoothly to deliver the bridged compound **9** in 88% yield without affecting the acid-labile silyl protecting group. Notably, in our initial attempt, sulfonamide **8a** was examined without notable success (**9a** in 21% yield),[15] implicating that the antiamidopalladation of the N-Ts amide is more sterically demanding toward the silylated alkyl chain. After hydrogenation and facile cleavage of the N−O bond by Kagan's reagent (SmI_2),[22] the corresponding secondary amide **10** reacted with tryptophol tosylate **11** to give compound **12** in 91% yield. In contrast to previous reports,[23] the classic conditions ($POCl_3$) applied to **12** only resulted in severe decomposition. We reasoned that the labile silyl group was intolerable under harsh conditions. A mild activation of the tertiary amide with Tf_2O/2,6-DTBP (2,6-di*tert*-butylpyridine)[20,24] proved effective in the cyclization to give product **13** in 95% yield. The X-ray determination of the acetate derivative **14** also confirmed the stereochemistry of the ring-formation step. The combination of acetylation and subsequent exhaustive SeO_2-mediated oxidation[23b] yielded strychnoxanthine (chloride salt) ($[\alpha]^D$ + 66.6 (c 1.18 in MeOH)). However, the cyclization of **12** and dehydrogenation[25] in "one-pot" delivered melinonine-E as a yellow solid in 65% yield. The spectra of the synthetic melinonine-E (chloride salt) was identical to the literature data (chloride salt)[17] and confirmed the absolute configuration of this β-carbolinium alkaloid (synthetic: $[\alpha]^D$ −11.1 (c 0.86 in MeOH); natural: $[\alpha]^D$ −13.9 (c 1.02 in MeOH)). The stereochemical confirmation validated the biogenetic relevance of melinonine-E and matadine.[17,26] Moreover, the circular dichroism (CD) spectrum of the synthetic strychnoxanthine (chloride salt) showed a positive Cotton effect ($\Delta\varepsilon$ + 3.0) at 360 nm,[15] which reconciles the reported data[18] and thus can assign the absolute configuration as (15*R*,17*R*,20*R*).

In summary, a unified approach to access 2-azabicyclo-[3.3.1]nonane and other ring systems was realized by palladium-catalyzed aza-Wacker cyclization for the first time. The method described here is complementary to other synthetic approaches to access various bridged lactams bearing tunable alkene and carbonyl functionalities. The application was further illustrated in the concise and enantioselective syntheses of melinonine-E and strychnoxanthine in 5−6 steps from the readily available chiral lactone **7**. Through adjusting the substituents on the amide N, the amidopalladation pathway can be altered to realize the cyclization of synthetically valuable substrates, which may inaugurate the incorporation of aza-

Scheme 4. Divergent Syntheses of Melinonine-E and Strychnoxanthine (Chloride Salts)[a]



[a]THF = tetrahydrofuran; TBSCl = *tert*-butyldimethylsilyl chloride; Tf_2O = trifluoromethanesulfonic anhydride; brsm = based on the recovered starting material.

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bridged rings into drug development and natural product syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00725.

Experimental procedures, spectroscopic data, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1500763 and 1814867−1814869 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(9) For the extensive optimization of aza-Wacker cyclization, including N-substituents, solvent, catalyst, additives, and temperature, see the Supporting Information for details.

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