Annulations

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Dienamine Activation of Diazoenals: Application to the Direct Synthesis of Functionalized 1,4-Oxazines

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Abstract: *A novel rhodium-catalyzed dienamine activation of diazoenals resulted in a new class of γ-functionalized donor–acceptor dienamines. The synthetic utility of these dienamines has been demonstrated in a cooperative rhodium(II)/Brønsted acid and gold(I)-catalyzed direct [3+3] annulation of enal-diazo ketones with N-propargyl anilines, thus leading to highly substituted enal-functionalized 1,4-oxazines. The reaction is proposed to involve dienamine activation through the diacceptor rhodium enalcarbenoid NH-insertion and a gold-catalyzed intramolecular site-selective 6-exo-dig heterocyclization. The methodology was applied to the efficient synthesis of structurally complex [1,4]oxazino[4,3-a]quinolone, which is present in the antibacterial agent PNU-286607.*

1,4-Oxazines, including morpholines (tetrahydro-1,4-oxazines), are privileged heterocyclic motifs displayed in many natural products and pharmaceuticals.[1,2] The diverse biological properties associated with the complex monocyclic, as well as fused 1,4-oxazines (Figure 1),[2] underscores the importance of efficient synthetic strategies for drug discovery applications. The known approaches to the C-substituted oxazines[3–11] include SnAP reagents based imine radical cyclizations,[4] vinyl sulfone-β-amino alcohol annulations,[5] ring expansion of oxetanone spirocycles,[6] intramolecular heterocyclization of alkyne-derived ruthenium vinylcarbenes,[7] and hydroamination and hydroalkoxylation of olefins and alkynes.[8–10] With the ever increasing demand for biologically relevant chemical space,[12] strategies for the creation of functionalized oxazines, wherein the functional groups with their rich chemistry could be utilized to introduce structural diversity, would be highly useful to chemical biology and drug discovery research.[13]

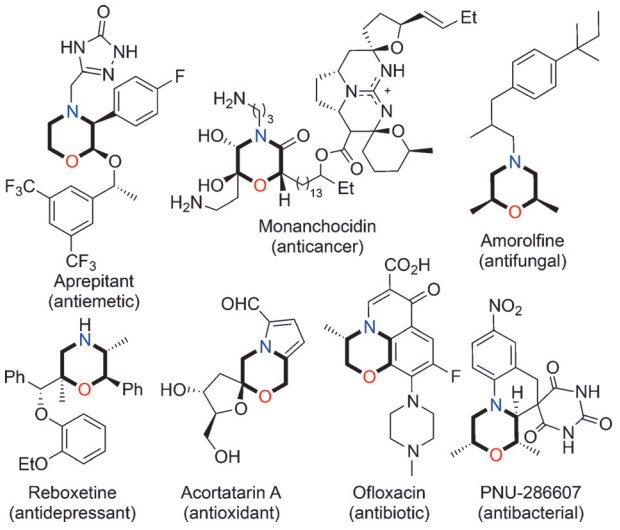
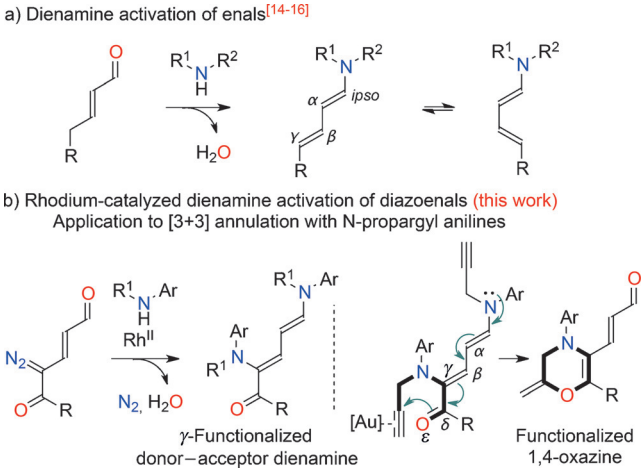


Figure 1. Representative 1,4-oxazine natural products and pharmaceuticals.

The HOMO activation of enals (α,β-unsaturated aldehydes) by dienamine catalysis has emerged as a powerful strategy to access divergent reaction modes available through the four-carbon dienamine moiety (Scheme 1a).[14] The pioneering contributions during the past decade have led to the discovery of various highly enantioselective α-, β-, γ-functionalizations and cycloaddition reactions of enals.[14–16] Inspired by the synthetic potential of dienamine activation, we investigated the recently designed enaldiazo compounds (diazoenals)[17,18] as precursors for novel dienamines. Our studies revealed that rhodium-catalyzed reactions of enal-diazo carbonyl compounds with secondary arylamines readily furnishes novel γ-amino-substituted donor–acceptor dienamines (Scheme 1b). To the best of our knowledge, this is the first report on the formation of functionalized dienamines through carbenoids.[19,20] To explore the synthetic utility of these dienamines, we envisioned that an arylamine tethered



Scheme 1. Dienamine activation of enals and diazoenals.

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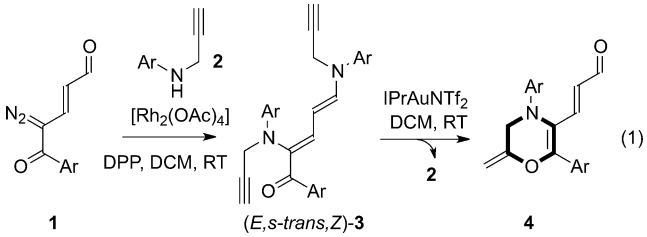
electrophile (R^1 = electrophile) would enable an intramolecular cyclization to give valuable nitrogen heterocycles. Herein we report a novel rhodium(II)/Brønsted acid and gold(I)-catalyzed [3+3] annulation of enaldiazo ketones with N-propargyl anilines, thus leading to highly substituted functionalized 1,4-oxazines (Scheme 1b). These novel oxazines serve as substrates for structural diversification through the appended olefin and enal functionalities.

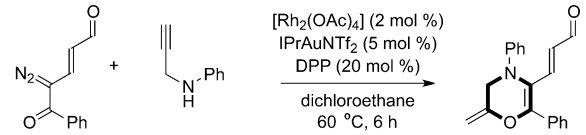
Preliminary investigations revealed that the rhodium(II)carboxylate-catalyzed reaction of the enaldiazo ketone **1** with N-propargyl aniline **2** proceeds efficiently in the presence of a Brønsted acid catalyst, diphenyl phosphate (DPP), thus leading to the conformationally stable, γ-functionalized donor–acceptor dienamine (*E,s-trans,Z*)-**3** [Eq. (1); DCM = dichloromethane, Tf = trifluoromethanesulfonyl].[21] For the subsequent intramolecular cyclization of **3**, gold catalysts were considered for π-activation of the N-tethered alkyne moiety.[22] Gratifyingly, exposure of **3** to the 10 mol % $IPrAuNTf_2$ exclusively produced the oxazine **4** with concomitant release of **2**.



To utilize **2**, which was released in the gold-catalyzed reaction, a tandem [3+3] annulation reaction involving a cooperative merger of the dienamine and gold catalysis was envisaged. Indeed, slow addition of excess enaldiazo ketone **1a** to a solution of N-propargyl aniline (**2a**), DPP, dirhodium acetate, and $IPrAuNTf_2$ at 60 °C resulted in the complete consumption of **2a** and produced the oxazine **5** in 76% yield (Table 1, entry 1). The successful merger of the both catalytic cycles prompted us to study the annulation reaction in detail. As shown in Table 1, several rhodium and gold catalysts were screened for the reaction. Other rhodium(II)carboxylates, such as $[Rh_2(oct)_4]$, $[Rh_2(esp)_2]$, and $[Rh_2(TFA)_4]$, gave moderate yields (entries 2–4). In the case of gold catalysts, AuCl and $AuCl_3$ resulted in complete decomposition of the dienamine and no product was obtained (entries 5 and 6). However, phosphine- and carbene-based organo gold(I) catalysts promoted the dienamine cyclization (entries 7–13). The nature of the counter ion of the gold(I) catalysts has a dramatic effect on the catalytic efficiency, and triflimide showed the highest efficiency over chloride, triflate, hexafluoroantimonate, and hexafluorophosphate (entries 1 and 7–13).

The substrate scope of the [3+3] annulation reaction was investigated with a variety of enaldiazo ketones (**1**) and N-propargyl anilines (**2;** Table 2). High yields of the oxazines (e.g., **9**–**13**) were obtained with the Me-, Cl-, Br-, and MeO-substituted aryl enaldiazo ketones, thus indicating that the reaction was not sensitive to the electronic nature of the aryl

Table 1: Optimization of the [3+3] annulation reaction.[a]



Entry	Deviation from standard reaction conditions	Yield [%][b]
1	No deviation	76
2	$[Rh_2(oct)_4]$ instead of $[Rh_2(OAc)_4]$	61
3	$[Rh_2(TFA)_4]$ instead of $[Rh_2(OAc)_4]$	52
4	$[Rh_2(esp)_2]$ instead of $[Rh_2(OAc)_4]$	65
5	AuCl instead of $IPrAuNTf_2$	0[c]
6	$AuCl_3$ instead of $IPrAuNTf_2$	0[c]
7	$(PPh_3)AuCl$ instead of $IPrAuNTf_2$	15
8	$(PPh_3)AuOTf$ instead of $IPrAuNTf_2$	21
9	$(PPh_3)AuNTf_2$ instead of $IPrAuNTf_2$	47
10	IPrAuCl instead of $IPrAuNTf_2$	18
11	IPrAuOTf instead of $IPrAuNTf_2$	35
12	$IPrAuSbF_6$ instead of $IPrAuNTf_2$	51
13	$IPrAuPF_6$ instead of $IPrAuNTf_2$	43

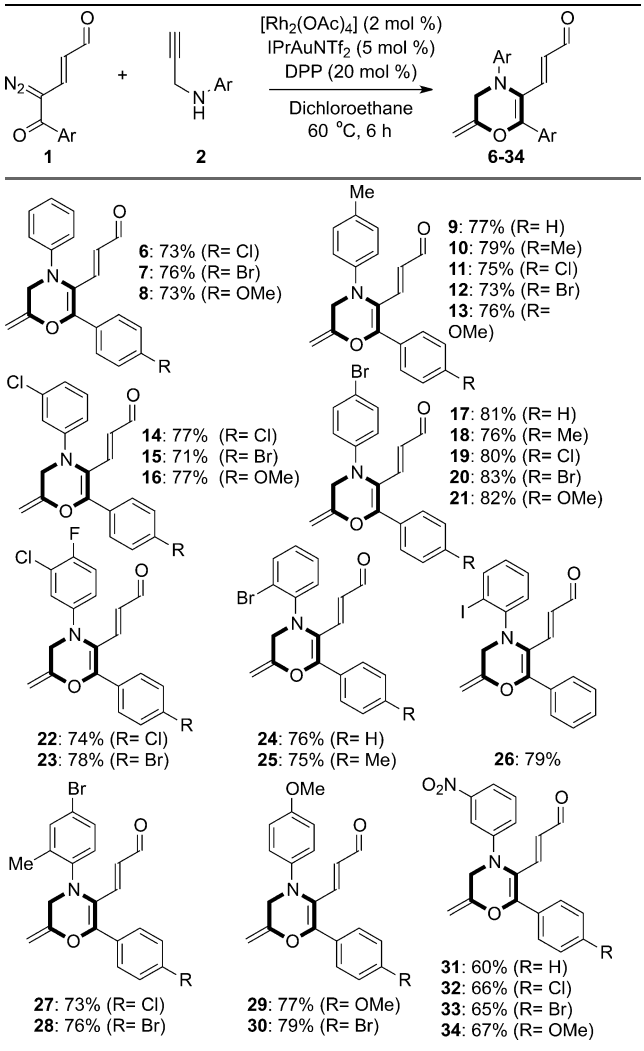
[a] See the Supporting Information for complete optimization studies. Reaction conditions: A solution of **1a** (1.5 mL) was added over 4 h to a solution of **2a**, rhodium, gold, and DPP (2 mL), and the reaction was stirred for an additional 2 h. [b] Yield of isolated product. [c] Dienamine was decomposed. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, IPr = 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene), TFA = trifluoroacetate.

ring. Interestingly, the annulation reaction with enaldiazo esters was unsuccessful as the dienamine remained unreactive. N-propargyl anilines having alkyl, halo, and methoxy substitutions on the aromatic ring were well tolerated and led to the oxazines **9**–**30** in excellent yileds,[23] whereas a nitro substituent resulted in slightly diminished yields of the oxazines **31**–**34**. With respect to the steric influence, substitution on the propargyl moiety (e.g., Me and phenyl groups) disfavored the reaction. However, the *ortho*-substituted anilines such as 2-bromo, 2-iodo, and 2-methyl anilines smoothly participated in the annulation (**24**–**28**).

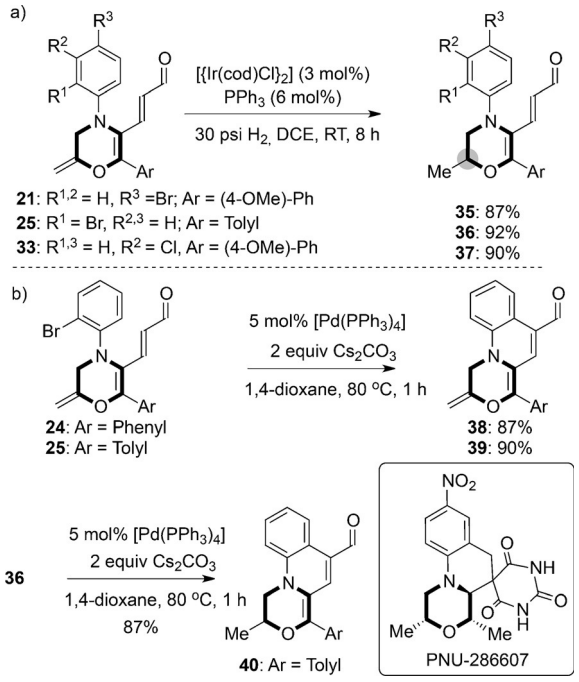
The tetrasubstituted oxazines obtained from [3+3] annulation are amenable to structural diversification through the appended enal and exomethylene functionalities. Controlled hydrogenation experiments using a sterically hindered iridium(I) catalyst[24] have shown that the *exo*-methylene moiety of the oxazines (**21**, **25,** and **33**) could be selectively reduced without affecting the enal moiety and endocyclic unsaturation (Scheme 2a). Delightfully, the N-propargyl-2-bromoaniline-derived oxazines **24** and **25** readily participated in an efficient α-arylation of the unmodified enal[25] through an *6-endo*-trig intramolecular Heck reaction,[26] thus leading to the structurally divergent [1,4]oxazino[4,3-a]quinolines **38** and **39**, respectively (Scheme 2b). The versatility of the α-arylation was further demonstrated with the partially hydrogenated oxazine **36**, thus resulting in an excellent yield of **40**. It is noteworthy that [1,4]oxazino[4,3-a]quinoline is a privileged tricyclic core present in the antibacterial agent PNU-286607.[2c]

A plausible mechanism for the [3+3] annulation reaction, involving cooperative rhodium(II)/Brønsted acid and gold(I)

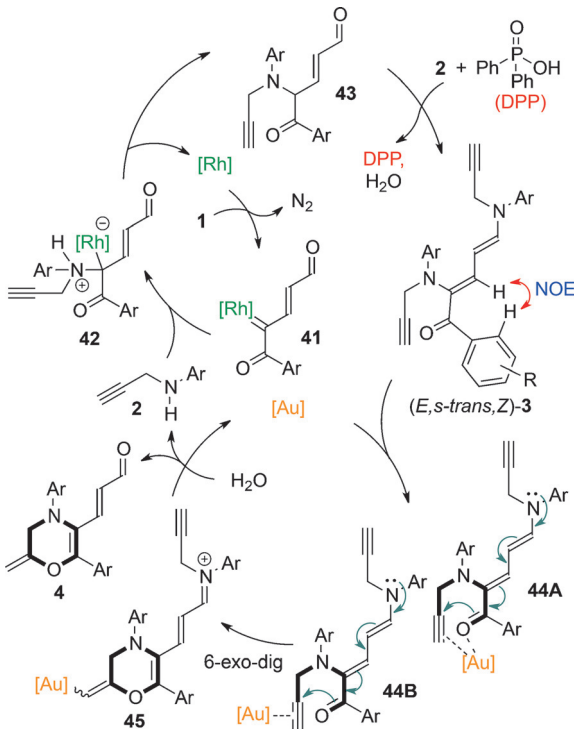
Table 2: Substrate scope of the [3+3] annulation reaction.[a]



[a] Reaction was performed using the standard reaction conditions from the optimization studies (Table 1). Yields are those of the isolated products.



Scheme 2. Synthetic transformations of functionalized 1,4-oxazines. cod = 1,5-cyclooctadiene.



Scheme 3. Plausible mechanism of the [3+3] annulation.

catalytic cycles is depicted in Scheme 3. Rhodium-catalyzed γ-amination of **1** by insertion of the rhodium enalcarbenoid **41** into the N–H bond of **2** via the protic ammonium ylide **42** leads to the γ-amino enal **43**.[27] Subsequent, DPP-catalyzed dienamine formation with **2** furnishes the γ-functionalized donor–acceptor dienamine (*E,s-trans,Z*)-**3**.[21] The cooperative gold catalytic cycle initiates the site-selective π-activation of the pendant γ-substituted alkyne moiety of **3,** presumably through gold coordination to the carbonyl group (**44A** and **44B**). The intramolecular *6-exo-dig* heterocyclization of **44**, by the synergistic alkyne and dienamine activation, leads to the alkenyl gold tethered oxazine **45**. Finally, proto-demetallation and iminium hydrolysis in **45** furnishes the enal-functionalized 1,4-oxazine **4**. The compound **2** is released and will be consumed in the rhodium catalytic cycle. Thus, the overall [3+3] annulation reaction involves only N_2 as the by-product.

In summary, we have disclosed that enaldiazo carbonyl compounds readily undergo rhodium-catalyzed dienamine activation in the presence of secondary arylamines leading to conformationally stable γ-functionalized donor–acceptor dienamines. The synthetic utility of the novel dienamine activation has been demonstrated in the direct synthesis of functionalized 1,4-oxazines by a cooperative rhodium(II)/Brønsted acid and gold(I)-catalyzed [3+3] annulation of

enaldiazo ketones with N-propargyl anilines. Structural diversification of the substituted 1,4-oxazines through an intramolecular α-arylation of the tethered enal functionality gave the [1,4]oxazino[4,3-a]quinolone core present in the antibacterial agent PNU-286607. We hope that the rich chemistry of the enal functionality will allow access to biologically important chemical space associated with the 1,4-oxazine motifs. Further studies toward the synthetic applications of the novel dienamine activation of diazoenals, functionalized donor–acceptor dienamines, and the [3+3] annulations are currently underway.

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