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Facile Synthesis of Unsymmetrical Acridines and Phenazines by a Rh(III)-Catalyzed Amination/Cyclization/Aromatization Cascade

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Supporting Information

ABSTRACT: We report formal [3 + 3] annulations of aromatic azides with aromatic imines and azobenzenes to give acridines and phenazines, respectively. These transformations proceed through a cascade process of Rh(III)-catalyzed amination followed by intramolecular electrophilic aromatic substitution and aromatization. Acridines can be directly prepared from aromatic aldehydes by in situ imine formation using catalytic benzylamine.

Rh(III)-catalyzed C−H functionalization has proven to be a versatile and highly functional-group-compatible approach for the synthesis of important classes of heterocycles,[1,2] with additions to alkynes,[3] alkenes,[4] allenes,[5] aldehydes,[6] imines,[6c] CO,[7] isonitriles,[8] isocyanates,[9] and diazo compounds[10] all having been utilized. Capitalizing on recent reports of Rh(III)-catalyzed C−H functionalization with aromatic and sulfonyl azide coupling partners,[11a−c,12,13] Glorius very recently described a novel Rh/Cu-cocatalyzed synthesis of 1*H*-indazoles through C−H amidation of benzimidates with sulfonyl azides followed by oxidative N−N bond formation.[11d] Herein we report new formal [3 + 3] annulations for the preparation of acridines and phenazines by Rh(III)-catalyzed C−H amination with aromatic azides followed by in situ intramolecular electrophilic aromatic substitution and aromatization (Figure 1). Despite the prevalence of acridines and phenazines in natural products, pharmaceuticals, and materials (e.g., photosensitizers and photocatalysts),[14,15] regioselective preparation of derivatives with substitution on both rings can be challenging.[16,17] In contrast, the approach reported here provides very rapid access to unsymmetrical derivatives with precise placement of diverse functionality at almost any position.

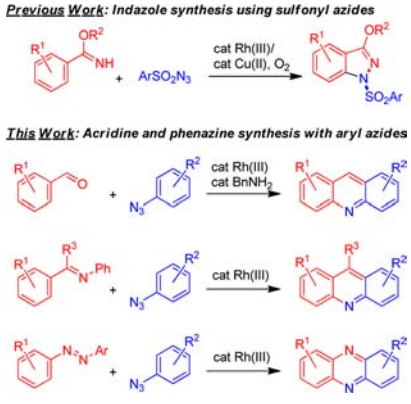

Figure 1. Heterocycles by tandem C−H amination and cyclization.

We initiated our investigation by exploring the Rh(III)-catalyzed addition of *N*-phenyl benzaldehyde imine (**1a**) to phenyl azide (**2a**) (see the Supporting Information for the optimization table). The use of a 10 mol % loading of the convenient preformed cationic rhodium catalyst [Cp*Rh-$(CH_3CN)_3(SbF_6)_2$] in dichloroethane (DCE) was found to be optimal, providing **3a** in 57% yield (eq 1). Because the aniline

released upon cyclization and aromatization might interact with the catalyst, $CF_3CO_2CH_2CF_3$ and acetic anhydride were used as scavengers of this byproduct, resulting in significant increases in the yield to 71% and 77%, respectively.

Having defined an effective catalyst and reaction conditions for the synthesis of acridine **3a** from preformed imine **1a**, we next explored the possibility of conducting the reaction directly from aldehydes in the presence of a catalytic amount of an amine. This approach would enhance the utility of the method because a vast number of aldehydes are commercially available, thus providing rapid access to a wide range of acridines. The proposed cascade sequence would require in situ condensation of an aldehyde and an amine to form the imine necessary to direct the C−H amination, followed by cyclization to generate the acridine with release of the amine for another catalytic cycle. Although we had previously found that released aniline is detrimental to the reaction, we reasoned that if catalytic amounts of the amine were used, it might be sequestered as the imine until the reaction neared completion.

The importance of the imine directing group was first demonstrated by attempting the direct coupling of benzaldehyde (**4a**), which resulted in only a trace amount of product (Table 1, entry 1). Addition of 10 mol % aniline provided **3a** in 15% yield (entry 2), and including $MgSO_4$ as drying agent along with 10 and 20 mol % of aniline further increased the yield to 26% and

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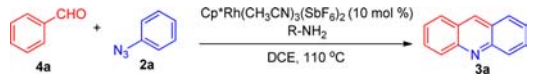
Table 1. In Situ Imine Formation with Catalytic Amine[a]



entry	R	amine loading (mol %)	additive	**4a** Conc. [M]	yield (%)[b]
1	--	--	--	0.10	<3
2	Ph	10	--	0.10	15
3	Ph	10	$MgSO_4$	0.10	26
4	Ph	20	$MgSO_4$	0.10	40
5	*p*-OMePh	20	$MgSO_4$	0.10	33
6	*p*-CF_3Ph	20	$MgSO_4$	0.10	24
7	Benzyl	20	$MgSO_4$	0.10	49
8	Benzyl	40	$MgSO_4$	0.10	65
9	Cyclohexyl	40	$MgSO_4$	0.10	50
10	Benzyl	40	$MgSO_4$	0.05	76 (76)[c]

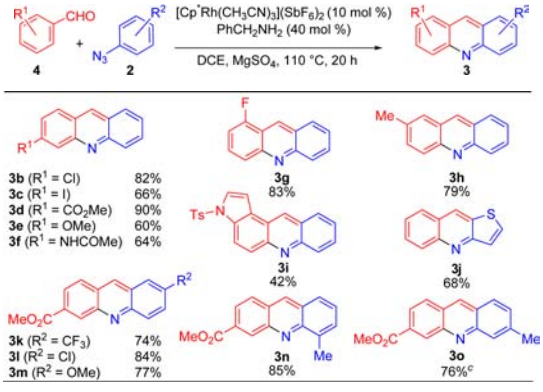
[a]Conditions: **4a** (0.10 mmol) and **2a** (0.15 mmol) in solvent (1.0 or 2.0 mL) for 20 h. [b]^{1}H NMR yields using 2,6-dimethoxytoluene as an external standard. [c]Isolated yield at 0.20 mmol scale of **4a**.

40%, respectively (entries 3 and 4). While the use of anilines with either electron-rich or -deficient substituents failed to improve the yield (entries 5 and 6), benzylamine gave a slightly higher yield (entry 7). Moreover, doubling the benzylamine loading resulted in a further improvement of the yield to 65% (entry 8). The branched and more sterically hindered cyclohexylamine was not as effective (entry 9). However, diluting the reaction mixture 2-fold significantly enhanced the yield to 76% (entry 10), which was comparable to the yield observed in the reaction with preformed imine (eq 1). Although catalytic in situ imine formation has been used in Rh(I) catalysis,[18] to the best of our knowledge this is the first example of its use in Rh(III)-catalyzed C−H functionalization.

The substrate scope was explored with a diverse set of aromatic aldehydes and aromatic azides (Table 2). The reaction showed excellent functional group compatibility, providing acridines **3** in good yields for aldehydes substituted with chloro (**3b**), iodo (**3c**), fluoro (**3g**), ester (**3d**, **3k**−**o**), methoxy (**3e**), indole (**3i**), and acetamide (**3f**) groups and aromatic azides substituted with trifluoromethyl (**3k**), chloro (**3l**), methoxy (**3m**), and alkyl (**3n**, **3o**) groups. Moreover, thiophene could also be incorporated (**3j**). While both electron-neutral and -rich aromatic aldehydes were found to be suitable for this transformation, electron-poor aldehydes afforded the products in higher yields (**3d** vs **3e**, **3f**, and **3i**). Aromatic aldehydes with ortho (**3g**), meta (**3h**) and para (**3b**−**f**,**k**-**o**) substitution were compatible, with *m*-methyl-substituted benzaldehyde exclusively providing product **3h** resulting from C−H activation at the less hindered site. Interestingly, the yields obtained in this transformation were not sensitive to the electronic or steric effects introduced by substitution on the aromatic azide. Substitution with electron-donating (**3j**, **3m**−**o**), -neutral (**3b**−**i**), or -withdrawing (**3k**, **3l**) groups at the ortho (**3n**), meta (**3o**), or para (**3k**−**m**) position all provided good to excellent yields. However, in contrast to the complete regioselectivity observed for cyclization of a meta-substituted aromatic aldehyde (see **3h**), *m*-methyl substitution on the phenyl azide proceeded with good but not absolute regioselectivity favoring cyclization at the least hindered site (**3o**). Heterocycles on both aldehyde (**3i**) and azide (**3j**) were well-tolerated and provided the corresponding products in moderate to good yields.

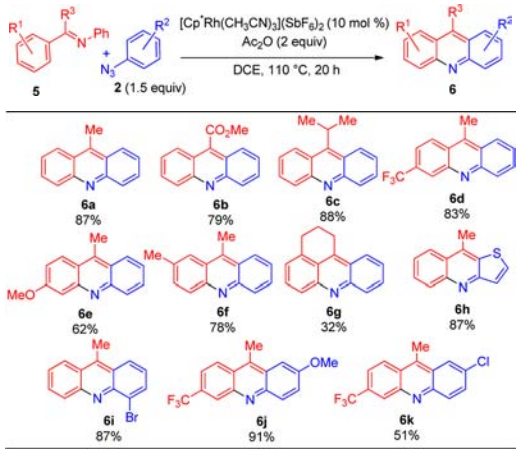
We next investigated the possibility of extending the substrate scope to ketones, which would lead to acridines with substitution at the 9-position. Ketones are much less efficiently converted to imines than are aldehydes, so the protocol for in situ imine formation using a catalytic amount of amine gave a yield of <10%, not only with $MgSO_4$ and molecular sieves but also with more powerful water scavengers and Lewis acid additives such as Ti(*i*-OPr)$_4$. We therefore turned our attention to the use of preformed imines under the conditions optimized for coupling preformed aldimines with azides (eq 1). Under these conditions, the ketimine-derived 9-substituted acridines were obtained in good to excellent yields (Table 3). Both electron-deficient (**6b**) and sterically hindered (**6c**) substituents could be installed at the central position of the acridine ring. In analogy to the steric and electronic effects observed for the reactions with aldehydes, electron-donating groups (**6e**) resulted in lower yields than electron-withdrawing (**6d**, **6j**) and -neutral (**6f**) groups. Moreover, meta substitution selectively generated the product as a single isomer with amination at the least hindered site (**6f**). In contrast to the high yields observed for the reaction with an

Table 2. Scope of Acridine Synthesis with Aldehydes[a,b]



[a]Conditions: aldehyde (0.20 mmol), azide (0.30 mmol), and $MgSO_4$ (100 mg) in DCE (4.0 mL) for 20 h. [b]Isolated yields are shown. [c]Formed in a 7:1 ratio with the 8-methyl-substituted isomer; the combined yield is shown.

Table 3. Scope of Acridine Synthesis with Ketone-Derived Imines[a,b]



[a]Conditions: imine (0.20 mmol), azide (0.30 mmol), and Ac_2O (0.40 mmol) in DCE (2.0 mL) for 20 h. [b]Isolated yields are shown.

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ortho-substituted benzaldehyde (see **3g** in Table 2), ortho substitution on the ketimine resulted in a modest yield (**6g**), although ortho substitution on the aromatic azide provided **6i** in high yield. An electron-deficient phenyl azide (**6k**) provided the product in a moderate yield compared with the very good yields observed for electron-rich (**6j**) and -neutral (**6a–f**) azides. A heterocyclic azide (azidothiophene) afforded **6h** in high yield.

Having established the broad scope of the synthesis of acridines with or without substitution at the central 9-position, we next considered the possibility of extending this formal [3 + 3] annulation approach to the synthesis of phenazines **8** from azobenzenes **7** (Table 4). The conditions previously optimized

Table 4. Optimization of Phenazine Synthesis[a]

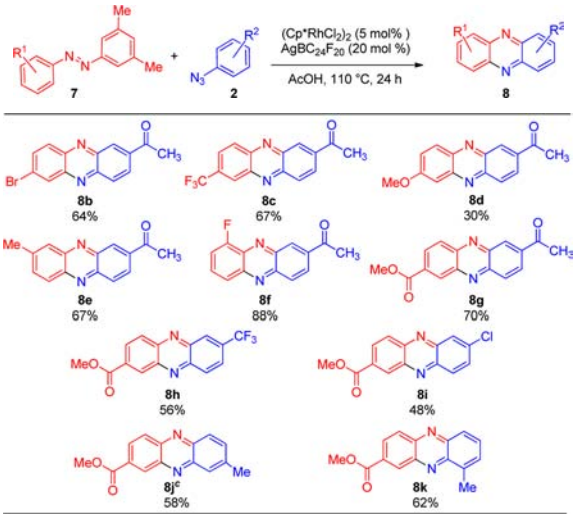
entry	R	Rh(III) source	additive	solvent	yield (%)[b]
1	H	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	--	DCE	17
2	H	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	Ac_2O	DCE	3
3	H	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	--	AcOH	48
4	H	$(Cp^*RhCl_2)_2$	$AgSbF_6$	AcOH	43
5	H	$(Cp^*RhCl_2)_2$	$AgB(C_6F_5)_4$	AcOH	67 (61)[c]
6	Me	$(Cp^*RhCl_2)_2$	$AgB(C_6F_5)_4$	AcOH	63

[a]Conditions: **7** (0.10 mmol) and **2a** (0.15 mmol) in solvent (2.0 mL) for 24 h. [b]^{1}H NMR yields using 2,6-dimethoxytoluene as an external standard. [c]Isolated yield at 0.20 mol scale of **7a**.

for ketimines provided product **8a** in low yield whether or not acetic anhydride was used as an additive (entries 1 and 2). Glacial acetic acid was evaluated as a solvent because we envisioned that it might facilitate cyclization as well as sequester the released aniline by hydrogen bonding or salt formation (entry 3). Encouraged by the considerably improved yield, we next explored alternative counterions. While the use of $(Cp^*RhCl_2)_2$ and $AgSbF_6$ resulted in a yield comparable to that observed with the corresponding preformed catalyst (entry 4), use of the completely noncoordinating counterion $B(C_6F_5)_4$ resulted in a significant improvement, providing **8a** in 67% yield (entry 5). A comparable yield was also obtained when unsymmetrical azobenzene **7b** was used (entry 6). With this substrate, the reaction exclusively occurred on the unsubstituted ring, consistent with the strong steric bias against Rh(III)-selective C–H functionalization adjacent to a meta substituent.[6a]

We evaluated the reaction scope by preparing unsymmetrical bis-substituted derivatives for which the regioselective placement of functionality can be challenging using alternative methods (Table 5).[17] Unsymmetrical azobenzenes with 3,5-dimethylaniline acting as a directing group were employed because this type of azobenzene can readily be prepared by simple condensation between commercially available anilines and 3,5-dimethylnitrosobenzene. Consistent with the results for the acridine synthesis, good functional group compatibility was observed, as products with bromo (**8b**), chloro (**8i**), fluoro (**8f**), trifluoromethyl (**8c**), methoxy (**8d**), keto (**8b–g**), and ester (**8a**, **8h–k**) substitution were obtained. Azobenzenes with diverse electronic properties proved to be effective substrates, although electron-donating groups (**8d**) provided significantly lower yields than

Table 5. Scope of Phenazine Synthesis[a,b]

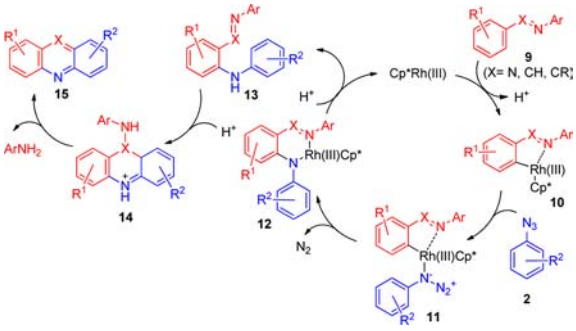


[a]Conditions: azobenzene (0.20 mmol) and azide (0.30 mmol) in AcOH (4.0 mL) for 24 h. [b]Isolated yields are shown. [c]8:1 ratio with the separable 6-methyl-substitued minor isomer.

electron-withdrawing (**8c**, **8f**, **8g–k**) and -neutral (**8a**, **8b**, **8e**) groups. Substitution at the ortho (**8f**), meta (**8e**), and para (**8b–d**, **8g–k**) positions was tolerated, and *m*-methyl substitution produced a single isomer with amination at the least hindered site (**8e**). Both electron-deficient (**8a–h**) and -neutral (**8j**, **8k**) azides were effective coupling partners, and ortho substitution was not detrimental to the reaction yield (**8k**).

The proposed mechanistic pathway for this cascade reaction is shown in Scheme 1. Imine or azobenzene **9** undergoes ortho-

Scheme 1. Proposed Cascade Mechanism



directed C–H bond activation to give metallacycle **10**[19] followed by coordination and migratory insertion of the azide to afford metallacycle **12**. This sequence of reactions corresponds to mechanisms previously proposed for other Rh(III)-catalyzed reactions with organic azides[11a–c] and is also consistent with the lack of reactivity of the aromatic azide with the Rh(III) catalyst unless the azobenzene or imine substrate is present. Protonation of metallacycle **12** then releases diarylamine **13** and the Rh(III) catalyst. Under the reaction conditions, **13** undergoes intramolecular electrophilic aromatic substitution to give **14**, and subsequent aromatization gives the desired acridine or phenazine **15**. Under the standard conditions, **13** did not accumulate even for the coupling of electron-deficient aryl azide **2b** with azobenzene **7b**. However, when these coupling partners were allowed to react at 90 °C for 7 h, a trace amount of **13** and ~10% phenazine **8a** were detected by ^{1}H NMR and LC-MS analyses.

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When the reaction was repeated on a larger scale, chromatography resulted in the isolation of 86% of the azobenzene starting material **7** along with a 9% yield of product **8a** and ∼1% uncyclized diarylamine **13**.

In summary, formal [3 + 3] annulations of aromatic azides with imines to give acridines and with azobenzenes to give phenazines have been developed. These transformations proceed by Rh(III)-catalyzed ortho C−H amination followed by intramolecular electrophilic aromatic substitution and aromatization. A broad range of acridines and phenazines can be generated with precise placement of diverse functionality, including unsymmetrical disubstituted derivatives. Moreover, through the use of catalytic benzylamine to generate the requisite imine in situ, aromatic aldehydes can be used to rapidly and directly access acridines lacking substitution at the 9-position.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and spectral data. This material 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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