Organic LETTERS
Letter
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A Versatile, Traceless C−H Activation-Based Approach for the Synthesis of Heterocycles

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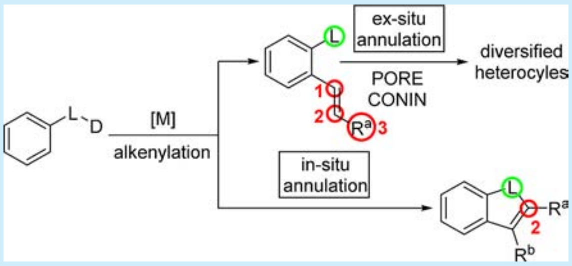
S Supporting Information

ABSTRACT: A versatile, traceless C−H activation-based approach for the synthesis of diversified heterocycles is reported. Rh(III)-catalyzed, *N*-amino-directed C−H alkenylation generates either olefination products or indoles (in situ annulation) in an atom- and step-economic manner at room temperature. The remarkable reactivity endowed by this directing group enables scale-up of the reaction to a 10 g scale at a very low catalyst loading (0.01 mol %/0.1 mol %). Ex situ annulation of olefination product provides entry into an array of heterocycles.

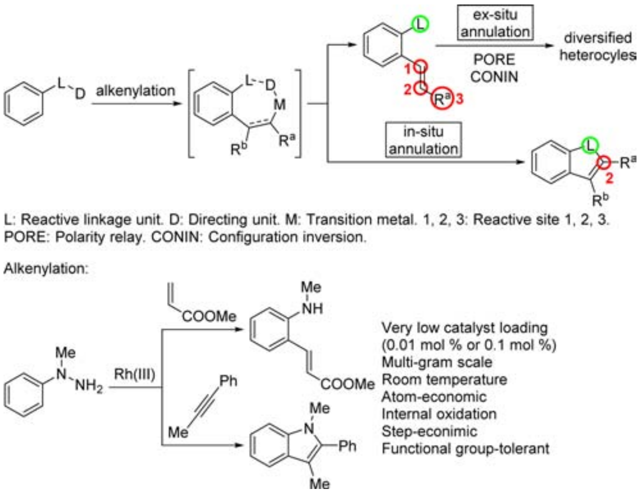


Transition-metal-catalyzed C−H activation (CHA) has emerged as an important synthetic tool for the construction of heterocycles.[1] The key annulation step, which involves the participation of directing group (with reaction at either the linkage unit site[2] or directing unit site[3]) and CHA-installed structure, can proceed only through the matching of reactivity. Depending on the reactivity profiles of annulation partners, two distinct synthetic manifolds can be envisioned, in situ annulation (either on-cycle[4] or off-cycle,[5] one-pot) and ex situ annulation (off-cycle, stepwise[6]). The in situ method provides a facile step-economic way of generating a target product, but its associated efficiency and convenience come at the cost of limited structural diversity under CHA-compatible conditions. Indeed, the original reactive sites are typically all sequestered into a single type of molecular framework. The ex situ method takes advantage of separate steps for annulation, thus allowing the potential of reactive sites to be fully harnessed and generation of diversified frameworks. Despite the appealing features associated with ex situ annulation, virtually all documented heterocycle synthesis protocols[6] thus far require additional synthetic manipulation, generally in an ad hoc fashion, to expose the reactive sites for annulation. Herein, we report on a versatile, traceless CHA-based approach for both ex situ and in situ synthesis of heterocycles.

We have recently launched a CHA synthetic program by using a labile N−N bond-containing functionality as the directing group.[7] A traceless, in situ synthesis of the indole framework has been achieved with the *N*-nitroso group. In the search for a more labile N−N bond (lowered lability in the *N*-nitroso group because of partial double bond character), we have turned our attention to the *N*-amino, or hydrazine, group (a *N*-alkyl group as the reactive linkage and substituent-free amino group as the directing unit, which is different from previous systems that rely on an amide bond for the increase of proton acidity on the amino group[8]) in view of the weak nature of this single bond.

We expected that the high lability would allow the exposure of the reactive linkage for both ex situ and in situ annulation. In particular, we disclose herein diversified heterocycle synthesis based on an initial Rh(III)-catalyzed C−H alkenylation process, with alkene (bearing an ester group) and alkyne as the coupling partner (Scheme 1). The *N*-amino group exhibits a remarkable directing reactivity at a very low catalyst loading (0.01 mol %/0.1 mol %). In addition, the alkenylation step features a mild reaction condition (room temperature), atom economy (release of a small fragment), step economy (internal oxidation), and functional group tolerance. The alkenylated scaffold contains plentiful reactive sites[9] on the CHA-installed

Scheme 1. Schematic of CHA-Based, ex Situ, and in Situ Synthesis of Heterocycles



Received: April 2, 2016
Published: May 2, 2016

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DOI: 10.1021/acs.orglett.6b00949
Org. Lett. 2016, 18, 2427−2430

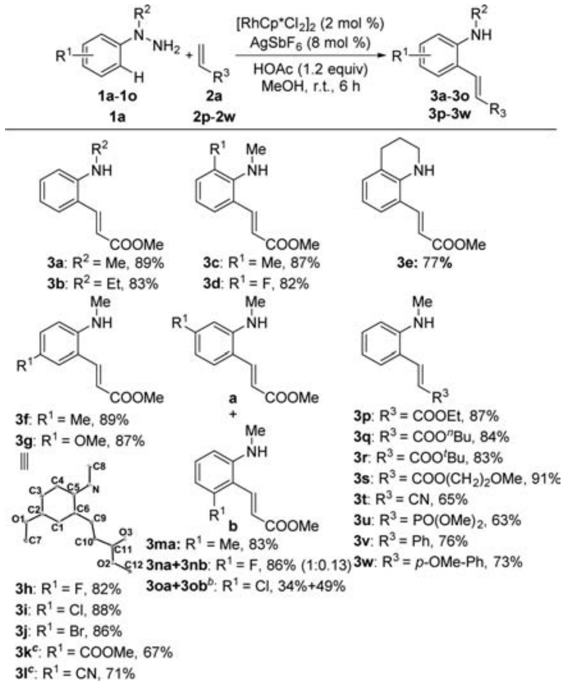
structure (Scheme 1: sites 1, 2, 3) for annulation with the reactive linkage (ex situ for sites 1, 2, 3 with an olefin, in situ for site 2 with an alkyne). The ex situ annulation is enabled by either polarity relay (PORE), through the participation of an additional coupling partner, or configuration inversion (CONIN) at the original C═C bond (from *trans* to *cis*). The in situ annulation occurs through an on-cycle annulation and N−N bond cleavage process.

We commenced our investigation by screening experimental conditions for *N*-amino-directed C−H olefination reactions. Arylhydrazine substrate **1a** and alkene substrate **2a** were used as the model reactants, and $[RhCp^*Cl_2]_2/4AgSbF_6$ was used as the catalyst precursor. A variety of conditions can lead to the traceless synthesis of **3a**. The basic conditions are not as ideal as acidic conditions, and with the replacement of KOAc by HOAc as the proton shuttle, an improvement in yield from <60% to 89% was observed. Importantly, room temperature proves to be suitable for the transformation. The standard reaction system includes 2 mol % $[RhCp^*Cl_2]_2$, 8 mol % $AgSbF_6$, 1.2 equiv of HOAc, and MeOH as the solvent. An external oxidant is not necessary for the reaction. In fact, the addition of AgOAc resulted in the generation of undesired side products and a substantially lowered yield (20%). This example nicely illustrates the advantage of using an internal oxidant system for C−H functionalization.

The scope of the reaction was then examined under standard reaction conditions. Substitution patterns on arylhydrazine were systematically altered to test the reaction outcome, with **2a** as the coupling partner (Scheme 2). The reaction proceeds efficiently for a substrate bearing either an *N*-Et (**1b**) or a cyclic *N*-alkyl substituent (**1e**). Both electron-rich (Me, **1c**, **1f**; OMe, **1g**) and electron-poor (halogen, **1d**, **1h**, **1i**, **1j**) groups at a variety of *ortho* and *para* positions of arylhydrazines are tolerated. Especially notable is the compatibility of highly electron-withdrawing CN (**1k**) and COOMe (**1l**) groups. The reaction is high-yielding for *meta* substitution (Me, **1m**; halogen, **1n**, **1o**), but the regioselectivity was observed only for **1m**. This is most likely caused by the steric effect. We next examined the olefin scope using **1a** as the coupling partner. Olefins bearing an electron-withdrawing group can participate in the reaction effectively. The yield is not negatively impacted by the variation of substituent on ester from Me (**2a**) to a bulkier group (Et, **2p**; Bu, **2q**, **2r**; $(CH_2)_2OMe$, **2s**). A change from the ester group to either CN (**2t**) or $PO(OMe)_2$ (**2u**) leads to a slightly diminished yield. In addition, styrene (**2v**) and *p*-methoxystyrene (**2w**) are appropriate substrates. The reaction with unactivated olefins (1-octene) yielded virtually no product under current standard conditions.

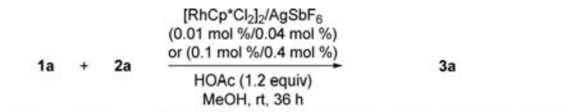
The remarkable reactivity offered by the *N*-amino directing group is demonstrated by the ability to scale-up the reaction to 10 g scale (Scheme 3) at a very low catalyst loading (0.01 mol %/0.1 mol %).

Scheme 2. Synthetic Scope of Olefination Reaction[a,b,c]



[a] Conditions: arylhydrazine (0.5 mmol), alkene (1.5 equiv), MeOH (2 mL). [b] Isolated yields. [c] Reaction time: 12 h.

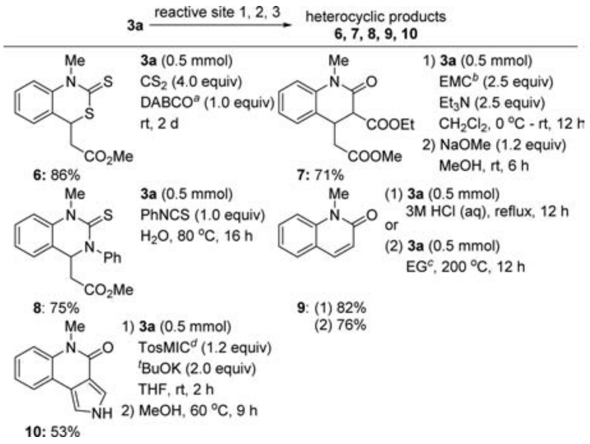
Scheme 3. Gram-Scale Olefination Reaction at a Very Low Catalyst Loading



1a	2a	catalyst	3a
100 mmol	150 mmol	(0.01 mol %/0.04 mol %)	11.9 g, 62% yield (TON = 6200)
67.5 mmol	93.8 mmol	(0.1 mol %/0.4 mol %)	9.5 g, 74% yield (TON = 740)

With olefination products in hand, we next performed heterocycle synthesis using **3a** as the model substrate. Analysis of the functional groups reveals the matching of polarity and therefore reactivity. The amino group is nucleophilic (NP), and C atoms next to the phenyl ring and on the ester group are both electrophilic (EP), but the reactions between polarity-matched centers are energetically disfavored under CHA conditions because of the requirement for either the formation of a four-membered ring or a change from the *trans* to *cis* configuration. With the use of CS_2, EtO_2CCH_2COCl, and PhNCS[10] as the PORE reagents, six-membered rings can be formed through an NP−EP−NP−EP system, thus leading to the synthesis of **6**, **7**, and **8** (Scheme 4). A *trans* to *cis* change of the configuration can be effected by a suitable CONIN

Scheme 4. Ex Situ Formation of Heterocycles



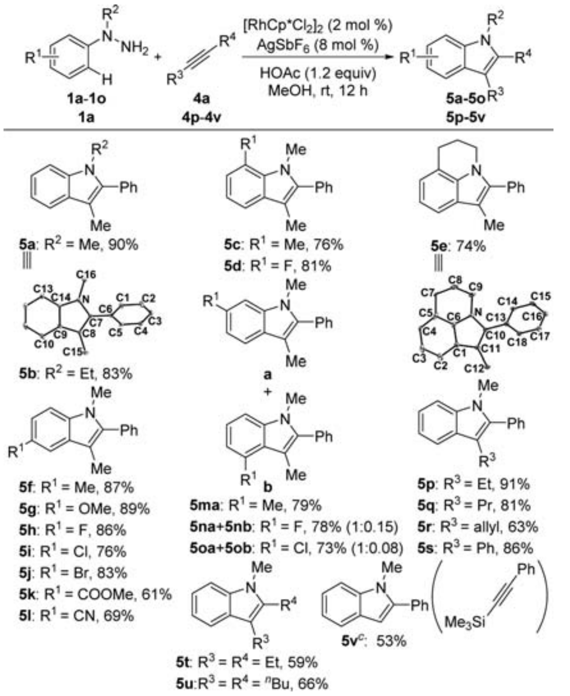
[a] 1,4-Diazabicyclo[2.2.2]octane. [b] Ethyl malonyl chloride. [c] Ethylene glycol. [d] Tosylmethyl isocyanide.

DOI: 10.1021/acs.orglett.6b00949
Org. Lett. 2016, 18, 2427−2430

condition or reagent. An elevated temperature can directly facilitate such a change. Also, Michael addition at the C=C double bond can lead to the temporary formation of a single bond, its subsequent free rotation, and further fixing of configuration with the formation of a ring structure. Indeed, under these two CONIN conditions,[11] ester−amide exchange allows the formation of six-membered rings, furnishing **9** and **10** as the products.

We then examined if the standard reaction conditions for alkenes could be applied to the alkyne settings. Satisfactorily, the reaction proceeds equally well and provides indole derivatives in a traceless fashion (Scheme 5). Tolerance of a broad range of functional groups on arylhydrazine is observed. The substituents on the alkyne can be Ph/alkyl, alkyl/alkyl, or, in the case of synthesis with a terminal alkyne equivalent, Ph/silyl.

Scheme 5. In Situ Formation of Indoles[a,b,c]

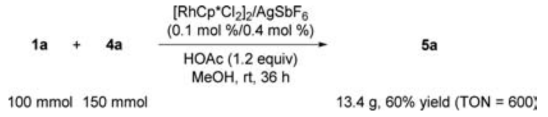


[a]Conditions: arylhydrazine (0.5 mmol), alkyne (1.5 equiv), MeOH (2 mL). [b]Isolated yields. [c]The structure of the alkyne substrate is placed in the parentheses.

Notably, the room temperature reaction conditions reported herein are unprecedented for a CHA-based, traceless indole synthetic protocol.[8,12] In addition, the remarkable directing reactivity of the *N*-amino group is likewise evidenced by the scale-up reaction (Scheme 6).

Although acetyl-modified hydrazines and in situ generated hydrazones have been previously used in the synthesis of indoles,[8,12] the exact coordination site, the N atom, is in a substantially different environment (amide-like and imine-like, respectively) as compared to our *N*-amino group system. The substituent-free structural environment for our coordination N atom translates to a superior reactivity for the C−H functionalization reactions reported herein (Scheme 1). Taken together, the combination of so many desired features in a single transition-metal-catalyzed directed C−H functionalization system (Scheme 1) should be able to instill confidence in the organic community that CHA is not only an academic curiosity but also a synthetically useful tool.

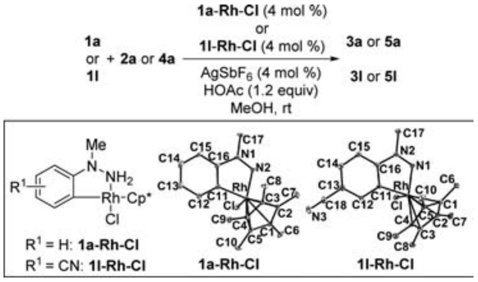
Scheme 6. Gram-Scale Indole Synthesis at a Very Low Catalyst Loading



The high efficiency of the alkenylation reaction prompted us to investigate the reaction mechanism. A competition experiment revealed preferred conversion for a substrate bearing an electron-donating group. A kinetic isotope effect of 2.85 was observed using a parallel reaction method. These data suggest an electrophilic, rate-limiting CHA step.

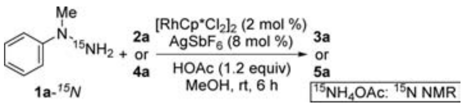
Thus, far, no five-membered rhodacycle has been isolated relevant to a substituent-free amino group-directed CHA process. We were able to obtain two such complexes (**1a-Rh-Cl** and **1l-Rh-Cl**) and characterize their structures with ^{1}H NMR, ^{13}C NMR, HRMS, elemental analysis, and X-ray single crystal diffraction (Scheme 7). Important structural features are the substantial shortening of the original N−N bond (bond length: 126 and 128 pm, respectively; the elasticity of the N−N bond is due to, most likely, its weak bond strength) and coplanarity of five atoms comprising the rhodacycle. These complexes, when activated with AgSbF$_6$, could not only react stoichiometrically with **2a** and **4a** but also catalyze the reactions between **1a**, **1l** and **2a**, **4a**, to generate the desired products **3a**, **3l**, **5a**, and **5l**. These observations are consistent with the intermediacy of a five-membered rhodacycle in the catalytic cycle.

Scheme 7. Olefination and Indole Synthesis Catalyzed by a Rhodacycle



The reaction system was further probed by the identification of a side product. A ^{15}N-labeled substrate (**1a-^{15}N**) was allowed to react with either **2a** or **4a**, respectively, and in both cases, a single, clean ^{15}N NMR signal consistent with the formation of a ^{15}NH$_4$OAc (with commercially available ^{15}NH$_4$OAc as the reference) was observed (Scheme 8). This provides evidence for an internal oxidation mechanism through the cleavage of the N−N bond (formation and subsequent sequestration of NH$_3$ by HOAc).

Scheme 8. Characterization of a Side Product



In summary, we have developed a versatile, traceless CHA-based approach for the synthesis of heterocycles. Arylhydrazine can undergo Rh(III)-catalyzed alkenylation with both alkenes and alkynes at room temperature at a very low catalyst loading (0.01 mol %/0.1 mol %). Mechanistic investigation revealed the intermediacy of a five-membered rhodacycle and NH_3 as the N−N bond cleavage side product. Further ex situ and in situ annulation has allowed the synthesis of a diversity of heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00949.

Experimental procedure, characterization of the products (PDF)

Copies of the ^{1}H and ^{13}C NMR spectra of selected products (PDF)

Crystallographic data for complex **3g** (CIF)

Crystallographic data for complex **5a** (CIF)

Crystallographic data for complex **5e** (CIF)

Crystallographic data for complex **1a-Rh-Cl** (CIF)

Crystallographic data for complex **1l-Rh-Cl** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge support from the National Natural Science Foundation of China (21425415, 21274058) and the National Basic Research Program of China (2015CB856303).

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