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Rh(III)-Catalyzed Coupling of *N*-Chloroimines with α-Diazo-α-phosphonoacetates for the Synthesis of 2*H*-Isoindoles

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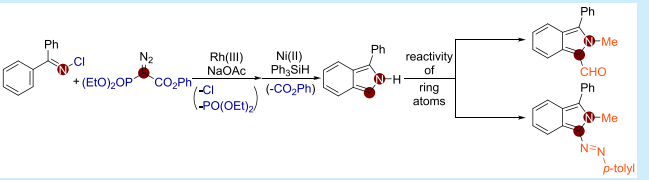
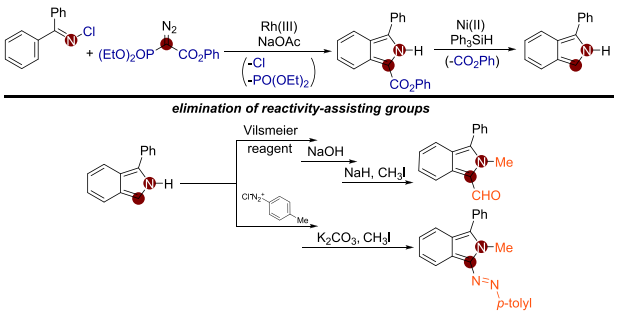
Supporting Information

ABSTRACT: We report herein the first use of *N*-chloroimines as effective synthons for directed C−H functionalization. Rh(III)-catalyzed coupling of *N*-chloroimines with α-diazo-α-phosphonoacetates allows for efficient dechlorinative/dephosphonative access to 2*H*-isoindoles. Further deesterification under Ni(II) catalysis enables the complete elimination of reactivity-assisting groups and full exposure of reactivity of C3 and N2 ring atoms for attaching structurally distinct appendages.



Transition-metal-catalyzed directed C−H functionalization has recently emerged as a promising step-economic strategy for the synthesis of a diverse range of structures.[1] Heterocycles, as privileged molecular skeletons for pharmaceutical applications, have been the center of focus in this nascent field.[2] In this regard, an important driving force for innovations in synthetic protocols is the development of new directing groups. Herein, we report the first use of *N*-chloroimines for directed C−H functionalization (Scheme 1).[3]

Scheme 1. Rh(III)-Catalyzed, *N*-Chloroimine and α-Diazo-α-Phosphonoacetate Coupling for Access to 2*H*-Isoindoles



In particular, in coupling with α-diazo-α-phosphonoacetates under Rh(III) catalysis, regiochemically allowed, polarity-matched reaction between N(δ+)−Cl(δ−) and C(δ−)−P(δ+) bonds allows for dechlorinative/dephosphonative synthesis of 2*H*-isoindoles. Further deesterification under Ni(II) catalysis enables the complete elimination of reactivity-assisting groups and full exposure of reactivity of C3 (electrophilic substitution: e.g., dimethylaminomethylidene derivatization and formylation, azo derivatization) and N2 (nucleophilic reaction: e.g., methylation) ring atoms for attaching structurally distinct appendages.

Isoindoles are important structural moieties in biologically active molecules (e.g., lenalidomide[4] as a drug against multiple myeloma). Although various methods have been developed for the synthesis of isoindoles,[5−8] their drawbacks are apparent, including complicated synthetic procedures, harsh reaction conditions, limited substrate scope, etc. Rh(III)-[9] and Ru(II)-catalyzed[10] C−H activation has been recently explored as an alternative strategy to address these issues. Despite the effectiveness, all these protocols employ acrylates for ring closure, thus inevitably leaving carboxylate ester groups that are recalcitrant for complete removal, due to extra carbon atoms between the isoindole skeleton and ester groups.

We initiated the reaction development by screening experimental conditions for the coupling of *N*-chloro-1-phenylethan-1-imine (**1a**) with ethyl 2-diazo-2-(diethoxyphosphoryl)acetate (**2a**) (Supporting Information). Initial examination of the reaction in dichloroethane (DCE) at 80 °C under the catalysis of $[RhCp^*Cl_2]_2$ (2 mol %)/$AgSbF_6$ (8 mol %) shows that NaOAc (1 equiv) is the best additive for transformation into an expected dechlorinative/dephosphonative product, ethyl 3-methyl-2*H*-isoindole-1-carboxylate (**3aa**, 64% yield after 12 h). Virtually no conversion can be observed in the absence of either $AgSbF_6$ or NaOAc. A decrease or increase of the NaOAc quantity to 0.5 or 2 equiv substantially retards the reaction. A switching of the solvent to MeOH, trifluoroethanol (TFE), MeCN, 1,4-dioxane, or THF is not beneficial. The generation of a cationic Rh(III) catalyst is essential for the transformation; the reaction does not occur under $[RhCp^*(OAc)_2]_2$ (2 mol %) but proceeds to afford a 79% yield of **3aa** utilizing $[RhCp^*(MeCN)_3](SbF_6)_2$ (4 mol %). The replacement of $AgSbF_6$ with either AgO_2CCF_3 or $AgBF_4$ identifies $AgBF_4$ as an even better halide abstraction

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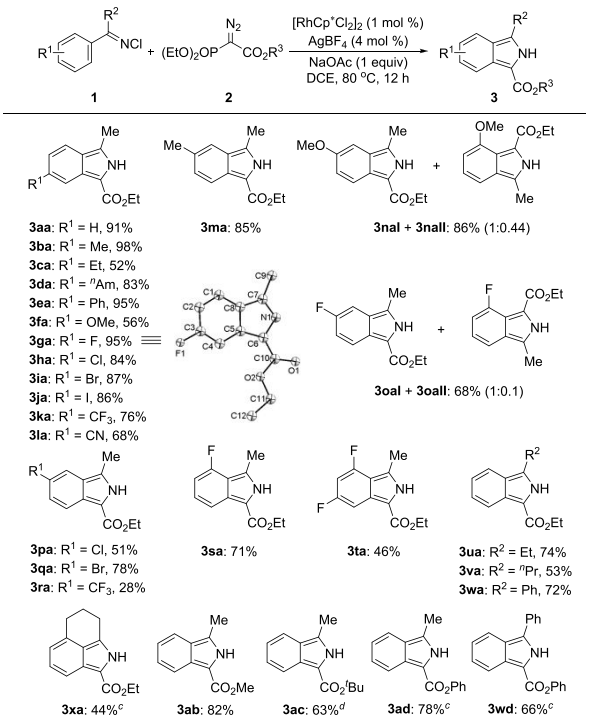
reagent (84% **3aa** yield). A negative control experiment under $AgBF_4$/NaOAc evidences the critical role played by $[RhCp^*Cl_2]_2$. Further optimization of the $[RhCp^*Cl_2]_2$/$AgBF_4$ quantity indicates that 1 mol %/4 mol % gives the best **3aa** yield (91%).

Under the previous optimized reaction conditions, we then undertook an extensive survey of the substrate scope (Scheme 2). By fixing **2a** as the coupling partner, the substrate scope of

Scheme 2. Substrate Scope for the Synthesis of 2*H*-Isoindoles[a,b]



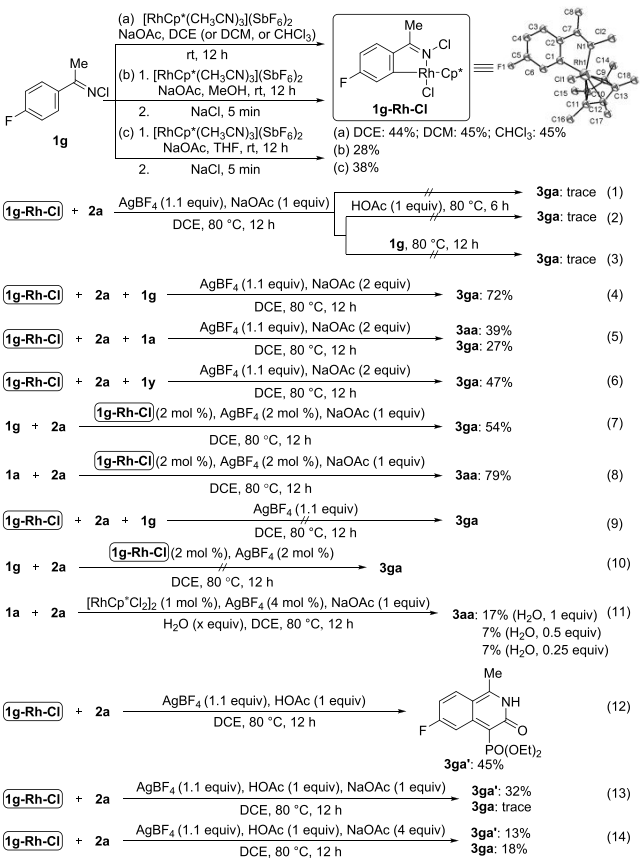
[a]Conditions: *N*-chloroimine (0.2 mmol), *α*-diazo-*α*-phosphonoacetate (0.3 mmol), DCE (2 mL). [b]Yield of isolated product. [c]$[RhCp^*Cl_2]_2$ (2 mol %), $AgBF_4$ (8 mol %). [d]$AgSbF_6$ instead of $AgBF_4$.

N-chloroimines was first investigated. The reaction proceeds well for *N*-chloroimines bearing both electron-donating (Me, **1b**; Et, **1c**; ^{n}Am, **1d**; Ph, **1e**; OMe, **1f**) and electron-withdrawing (F, **1g**; Cl, **1h**; Br, **1i**; I, **1j**; CF_3, **1k**; CN, **1l**) groups at the *para* position of the phenyl ring. The yields of **3ba**, **3ea**, and **3ga** reach the impressive 98%, 95%, and 95%, respectively. A single-crystal X-ray diffraction of **3ga** unambiguously confirms the 2*H*-isoindole structure. *Meta* substitution, irrespective of its electronic character (Me, **1m**; OMe, **1n**; F, **1o**; Cl, **1p**; Br, **1q**; CF_3, **1r**), can be tolerated in general. Regiospecific coupling is exclusively observed for sterically more demanding substituents (**1m**, **1p**, **1q**, **1r**) whereas regioisomers are identified for sterically less bulky ones (**1n**, **1o**). *Ortho* substitution is also synthetically compatible (F, **1s**), albeit with a slightly lower yield compared to the *para* and *meta* counterparts. Disubstitution (**1t**) further hinders the reactivity. The alteration of the imino *C*-Me group to either *C*-Et (**1u**), *C*-^{n}Pr (**1v**), or *C*-Ph (**1w**) group results in a diminished yield, suggestive of a steric effect. The steric effect is more pronounced for a fused ring system (**1x**). Preliminary examination of the substrate scope for *α*-diazo-*α*-phosphonoacetates shows largely preserved reactivity for different acetate substituents (Me, **2b**; ^{t}Bu, **2c**; Ph, **2d**). With Ph as both the imino *C*-substituent (**1w**) and acetate substituent (**2d**), the reaction proceeds to a comparable extent to that with either **1w** and **2a** or **1a** and **2d** as the reactants.

With the substrate scope inspected, we then proceeded to the mechanistic studies. A H/D scrambling experiment on **1a** shows 14% *N*-chloroimine-*ortho* D labeling (Supporting Information). An intermolecular competition experiment (between either **1b**/**1g** or **1f**/**1g** and **2a**) reveals no significant electronic preference (**3ba**/**3ga** = 1.4, **3fa**/**3ga** = 1.4). A kinetic isotope effect (KIE) experiment (between **1a**/**1a**-d_5 and **2a**) furnishes a k_H/k_D value of 3.0. These observations support a concerted metalation−deprotonation (CMD), turnover-limiting C−H activation pathway.

We further sought to delineate the reaction pathway by examining the reactivity of five-membered rhodacycles. A reaction between $[RhCp^*(MeCN)_3](SbF_6)_2$ and **1g** under NaOAc in DCE, dichloromethane (DCM), or $CHCl_3$ at room temperature (rt) affords the rhodacycle **1g-Rh-Cl** (Scheme 3).

Scheme 3. Mechanistic Studies Involving 1g-Rh-Cl



In this case, rhodacycle-stabilizing ligand Cl^- comes from DCE, DCM, or $CHCl_3$. A switching of the solvent to either MeOH or THF mandates the addition of Cl^- (e.g., from NaCl) for acquiring **1g-Rh-Cl**. Further comprehensive experiments offer the following observations: (1) initial attempt at the stoichiometric reaction between **1g-Rh-Cl** and **2a** fails to deliver **3ga** (eq 1); (2) neither HOAc nor **1g** is capable of changing the reaction outcome for **1g-Rh-Cl** and **2a** when added at the postreaction stage (eqs 2 and 3); (3) the reaction between **1g-Rh-Cl** and **2a** can proceed to the **3ga** stage with the additional participation of **1g** (eq 4); (4) a reaction for **1g-**

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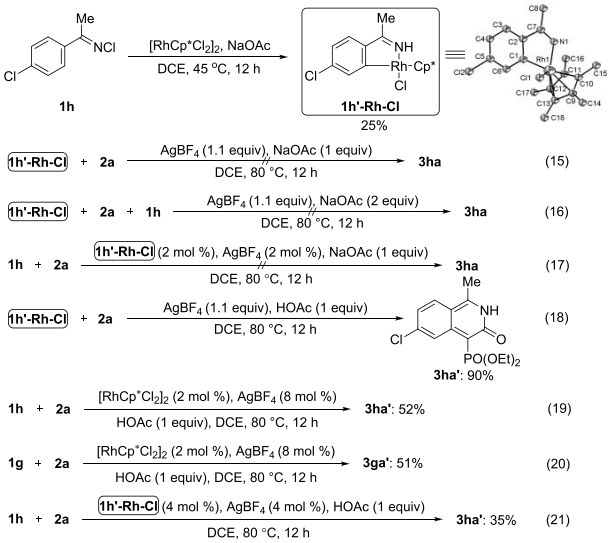
Rh-Cl, **1a**, and **2a** gives a mixture of **3ga** and **3aa** (eq 5); (5) although 1-phenylethan-1-one oxime (**1y**) does not react with **2a**, it can effect the reaction between **1g-Rh-Cl** and **2a** (eq 6); (6) **1g-Rh-Cl** can efficiently catalyze the reaction between **1g** and **2a** as well as between **1a** and **2a** (eqs 7 and 8); (7) neither the stoichiometric reaction nor the catalytic reaction involving **1g-Rh-Cl** (as well as **2a** and **1g**) can proceed without NaOAc (eqs 9 and 10); (8) the rhodacycle **1h′-Rh-Cl** (synthesized from $[RhCp^*Cl_2]_2$ and **1h** under NaOAc in DCE at 45 °C) (Scheme 4), with the Cl portion of the *N*-chloroimine group

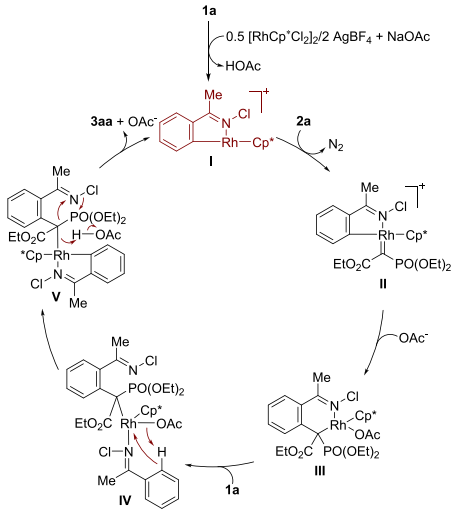
Scheme 4. Mechanistic Studies Involving 1h′-Rh-Cl



removed, neither exhibits reactivity toward **2a** (without or with the additional participation of **1h**) (eqs 15 and 16) nor catalyzes the reaction between **1h** and **2a** (eq 17), which advocates the importance of the Cl moiety of the *N*-chloroimine group at the early stage of the reaction pathway and is consistent with the proposal of P−Cl bond formation as a late-stage event; and (9) adventitious H_2O is excluded as a necessary component for cleaving the C−P bond based on its negative effect on the transformation (eq 11). Taken together, these observations are consistent with the following associative covalent relay mechanism[1a] (with **1a** and **2a** as the illustrative reactants) (Scheme 5): the reaction between **1a**, $[RhCp^*Cl_2]_2$, $AgBF_4$, and NaOAc produces C−H-activated intermediate **I**;[11] coordination of **I** with **2a** furnishes Rh(III) carbene species **II**; OAc^- coordination and 1,1-migratory insertion provide **III**; further coordination of **III** with **1a** results in the formation of coordination site-exchanged species **IV**; C−H activation of coordinated **1a** under the assistance of OAc^- delivers **V** and HOAc; proto-demetalation of **V** with HOAc releases **I** and OAc^- and simultaneously initiates C−P/N−Cl bond cleavage and C−N/P−Cl bond formation/ring closure for the generation of **3aa** (via tautomerization). In perspective, associative relay[1a] might be a prevalent operating mechanism in transition metal catalysis, especially for directed C−H functionalization reactions. It is speculated that many directing groups, along with the coupling partners, can trap transition metals in the nonreacting chelating states (e.g., **III** in Scheme 5); only via competitive binding from the directing group of the next catalytic cycle, the final turnover steps can occur.

An interesting finding for **1h′-Rh-Cl** is its conversion, when reacting with **2a**, to an isoquinolin-3(2*H*)-one derivative

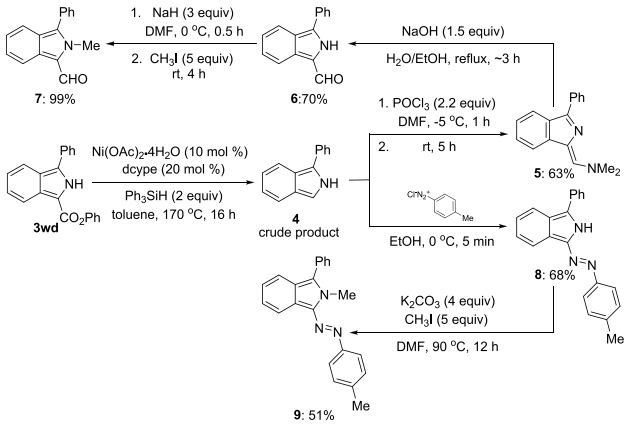
Scheme 5. Proposed Reaction Mechanism



(**3ha′**), under HOAc (eq 18). The same type of isoquinolin-3(2*H*)-one derivative (**3ga′**) can be acquired starting from **1g-Rh-Cl** (with **2a**) (eq 12). Reexamination of the reaction either between **1h** and **2a** or between **1g** and **2a** shows the Rh(III)-catalyzed transformation to the respective target product (**3ha′** or **3ga′**) utilizing HOAc (eqs 19 and 20). In addition, **1h′-Rh-Cl** also allows catalytic access to **3ha′** from **1h** and **2a** only using HOAc (eq 21). Essentially, the NaOAc and HOAc processes are in direct competition with each other (eqs 13 and 14): basic conditions favor a late-stage N−Cl cleavage pathway, whereas acidic conditions bias the reaction for an early stage N−Cl cleavage pathway.

Structural diversification can be envisaged through the complete elimination of reactivity-assisting groups and exploitation of the exposed reactivity of ring atoms (Scheme 6). To this end, the ester groups on the C3 site of 2*H*-

Scheme 6. Structural Diversification for 2*H*-Isoindoles



isoindoles should be removed first. For proof-of-concept demonstration, **3wd** was selected and subjected to deesterification reaction. The ester group can be removed to afford target product **4** under $Ni(OAc)_2$/dcype/Ph_3SiH catalysis.[12] Unlike **3wd**, **4** exhibits high reactivity at the C3 site, which also renders itself an unstable molecule against chromatography.[13] However, electrophilic substitution can be performed on **4** without purification. For example, reaction between the crude product of **4** and Vilsmeier reagent affords a C3-dimethylami-

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nomethylidene derivative **5**.[14] Hydrolysis of **5** in NaOH generates C3-formyl derivative **6**.[14] **6** can be deprotonated at the N2 site with NaH and undergo further nucleophilic methylation with CH_3I to produce **7**. Collectively, these transformations have allowed the complete erasure of any trace of original reactivity-assisting groups and installation of structually completely unrelated appendages, thus offering an enabling tool for accessing distinct chemical space. As a second illustrative example, **4** can also undergo initial azo derivatization at the C3 site[15] and subsequent methylation at the N2 site, affording **8** and **9**, respectively.

In summary, we have developed herein an efficient strategy for the synthesis of 2*H*-isoindoles based on Rh(III)-catalyzed coupling of *N*-chloroimines with *α*-diazo-*α*-phosphonoacetates. The initial dechlorination/dephosphonation and subsequent deesterification allow the full elimination of reactivity-assisting groups from the 2*H*-isoindole skeleton. The structural diversification potential with the exposure of C3 and N2 ring atoms is exemplified by the ability to achieve electrophilic substitution and nucleophilic reaction, respectively.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02501.

Experimental procedures, structural characterization, mechanistic studies, and copies of the ^1H and ^{13}C NMR spectra of selected products (PDF)

Accession Codes

CCDC 1858032, 1858042, and 1858398 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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