A Coupling of Benzamides and Donor/Acceptor Diazo Compounds To Form γ-Lactams via Rh(III)-Catalyzed C−H Activation

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S *Supporting Information*

ABSTRACT: The coupling of *O*-pivaloyl benzhydroxamic acids with donor/acceptor diazo compounds provides isoindolones in high yield. The reaction tolerates a broad range of benzhydroxamic acids and diazo compounds, including substituted 2,2,2-trifluorodiazoethanes. Mechanistic experiments suggested that C−H activation is turnover-limiting and irreversible and that insertion of the diazo compound favors electron-deficient substrates.

Multicomponent reactions catalyzed by transition metals represent a powerful approach for the synthesis of heterocycles.[1] This concept has been extensively explored in the Rh(III)-catalyzed synthesis of nitrogen-containing heterocycles mediated by C−H activation.[2] A wide swath of unsaturated heterocycles can be accessed though coupling of amides, amines, oximes, and anilines with alkynes to access isoquinolones,[3] pyridones,[3d,4] isoquinolines,[5] pyridines,[5g,6] indoles,[7] and pyrroles.[7b,8]

The ability to access nitrogen-containing heterocycles bearing stereogenic carbons is important because of their prevalence in medicinal targets and natural products.[9,10] Recently, Glorius[11] and Fagnou[3e] demonstrated that alkenes can be used to access partially saturated nitrogen-containing heterocycles (eq 1). In the presence of an enzyme or chiral

· *Previous Unsaturated Heterocycle Synthesis (1)*

Seminal Studies:
Glorius
Fagnou

Asymmetric Studies:
Rovis & Ward
Cramer

· *Previous 1-Carbon Components (2)*

X = O
Rovis

X = NSO₂Ar:
Zhu/Falck

· *Yu and Coworkers (3)*

DG =
Oxime, Amine
Carboxylic Acid

· *Proposed Synthesis of Iso-Indolone (4)*

-High Yield
-Mild Condition
-Quaternary Carbon

cyclopentadiene ligand, this reaction can be rendered asymmetric.[12] Currently absent from this family of reactivity

is the ability to access γ-lactams with the potential to control the stereochemistry of the process. The key to achieving this reactivity is the identification of a suitable one-carbon component.

Examples of one-carbon components in Rh(III)-catalyzed C−H activation reactions are rare. Previously, we found that amides could be coupled with CO to provide a range of phthalimides in good yield (eq 2).[13] Concurrent work by Zhu and Falck found isocyanides to be competent coupling partners in an analogous reaction.[14] CO and isocyanides function as one-carbon components because the carbon has carbenic character. Elegant work by Yu took advantage of the carbenic character of electron-deficient diazo compounds to ortho-functionalize a variety of directing-group-containing arenes (eq 3).[15] In view of the importance of γ-lactams, we were interested in using diazo compounds as one-carbon components in a cyclization reaction that would provide isoindolones (eq 4).

We believed that a significant barrier to this reactivity would be the need to inhibit protonation of the metallacycle. The report by Yu suggested that protonation of the rhodacycle occurs rapidly when monodentate directing groups are used.[15] Fagnou[3e] and Glorius[11] found that use of a bidentate directing group precludes β-hydride elimination in the synthesis of dihydroisoquinolones. We imagined that this type of directing group would also be effective in inhibiting unwanted protonation events. In a set of initial experiments, we chose to explore donor/acceptor diazo compounds because they are less prone to dimerization and can provide interesting products with a stereogenic carbon.

Initial coupling of amide **1a** with diazo ester **2a** using superstoichiometric CsOPiv in MeOH gave the desired product in 24% yield, with the remainder of the mass balance being methanolysis of the pivalate ester in the starting material (Table 1, entry 1). A screen of solvents revealed CH₃CN to be ideal, providing lactam **3a** in 78% yield (entry 4). Replacing CsOPiv with CsOAc gave a comparable yield (entry 5). We were pleased to find that using a substoichiometric amount of base did not have a detrimental effect on the yield (entry 6). Finally, modification of the concentration allowed the desired lactam to be isolated in 81% yield after 150 min. The catalyst loading can be decreased to 0.4 mol % when the reaction is performed on a gram scale (entry 8). The use of *O*-methyl hydroxamic acid in place of **1a** delivered only a 10% yield of the protonated product and none of the desired product.
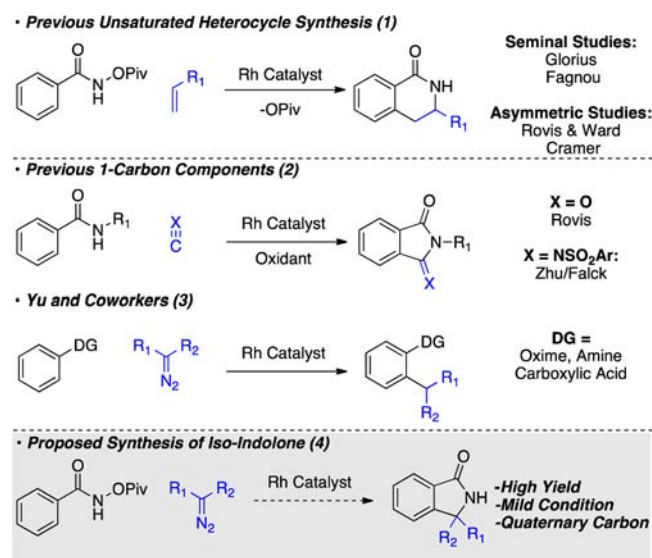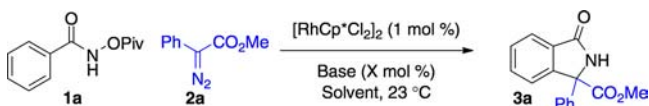
Table 1. Optimization of the Reaction Conditions

entry[a]	base	solvent	yield (%)[b]
1	CsOPiv (200 mol %)	MeOH (0.5 M)	24
2	CsOPiv (200 mol %)	EtOH (0.5 M)	33
3	CsOPiv (200 mol %)	TFE (0.5 M)	59
4	CsOPiv (200 mol %)	MeCN (0.5 M)	78
5	CsOAc (200 mol %)	MeCN (0.5 M)	80
6	CsOAc (20 mol %)	MeCN (0.1 M)	81[c]
7	—	MeCN (0.1 M)	0
8[d]	CsOAc (20 mol %)	MeCN (0.1 M)	75[c]

[a]Standard conditions: **1a** (1 equiv), **2a** (1 equiv), [RhCp*Cl$_2$]$_2$ (1 mol %). [b]Determined by HPLC. [c]Isolated yield. [d]Catalyst loading 0.4 mol %

With the ideal conditions in hand, we tested the scope of isoindolone formation with differentially substituted benzhydroxamic acids (Table 2). For a variety of electronically
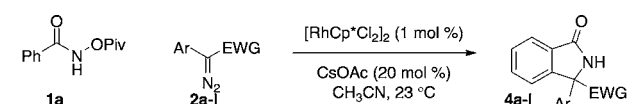
Table 2. Benzhydroxamic Acid Scope[a]

[a]For the standard reaction conditions, see Table 1. [b]Isolated as a 1.1:1 ratio of regioisomers. [c]The reaction was conducted at 60 °C. [d]Isolated as a 2:1 ratio of regioisomers.

different para-substituted amides, the reaction afforded the desired products in high yield (**3b−f**). Substitution at the meta position plays an important role in controlling the regioselectivity of the C−H activation event. When *m*-methyl benzhydroxamic acid was used (**3h**), C−H activation occurred exclusively para to the methyl group, presumably to avoid sterically disfavored interactions. However, when a methoxy group was placed at the meta position (**3g**), a 1.1:1 ratio of regioisomers was observed. This effect was also observed with naphthyl amides (**3i**), where a 2:1 ratio of regioisomers was observed. By comparison, the less electron-deficient tetrahydronaphthyl benzhydroxamic acid gave a single regioisomer

(**3j**). Presumably this decrease in regioselectivity can be attributed to the increase in acidity of the ortho C−H bond. Increasing the kinetic acidity of the C−H bond overwhelms the steric bias of the C−H activation, giving a mixture of products. A gallic acid-derived amide (**3k**) and a heterocyclic substrate (**3l**) also fared well in the reaction, although increased reaction temperatures were required.

We next explored the scope of diazo compounds (Table 3). Acceptor diazo compounds[16] dimerized rapidly under the
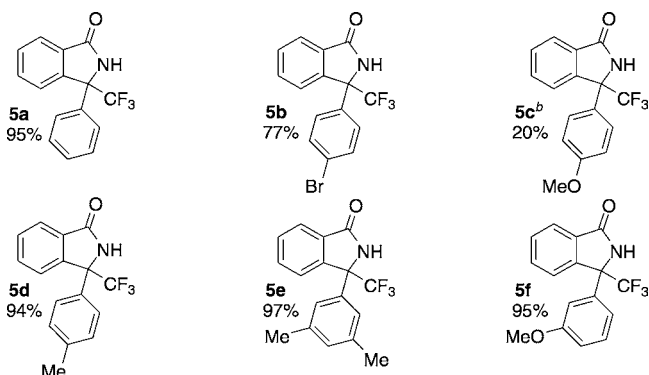
Table 3. Scope of Donor/Acceptor Diazo Compounds[a]

[a]For the standard reaction conditions, see Table 1. [b]The reaction was conducted at 60 °C. [c]The reaction was conducted at 80 °C.

reaction conditions, while acceptor/acceptor diazo compounds were almost completely unreactive, with yields of <5% observed under these reaction conditions. Donor/acceptor diazo compounds were broadly tolerated with reasonable scope. Differential substitution on the ester gave the desired products in high yield (**4a**, **4b**). Cyclic diazo substrates delivered the desired spiro compounds in high yields under the reaction conditions (**4c**, **4d**). A wide range of substituents on the aromatic ring were tolerated.[17] While electron-poor substrates provided the desired product rapidly under the standard reaction conditions (**4e**, **4j**, **4i**), electron-rich substrates were far more sluggish and required elevated temperatures and prolonged reaction times (**4f**, **4h**). We were pleased to find that heteroaryl diazo esters also provided the corresponding products, albeit in lower yields (**4k**, **4l**). Elevated temperatures allowed acceptor diazo esters to be incorporated in good yields (**4m**, **4n**).

While screening electron-withdrawing groups on the donor/acceptor diazo compound, we found that amides and phosphonates provide very low product yields. In contrast, we were pleased to find the 1-phenyl-2,2,2-trifluoro diazoethane, as described by Davies and co-workers,[18] delivered the desired product in high yield (Chart 1, **5a**). Electron-deficient

**Chart 1. Scope of 1-Aryl-2,2,2-trifluoro Diazoethanes**[a]

[a]For the standard reaction conditions, see Table 1. [b]The reaction was conducted at 60 °C.

aromatic groups on these trifluoroethyl diazo substrates functioned well in the reaction, with high yields and short reaction times (**5b** and **5d–f**). As observed previously, electron-rich aromatic groups provided substantially lower product yields even at high temperatures (**5c**). These products contain quaternary carbons with a trifluoromethyl group, a substitution pattern not easily accessed using other methods.[19]

A series of mechanistic experiments were performed to elucidate the nuances of the reaction (Scheme 1). Competition

Scheme 1. Mechanistic Experiments
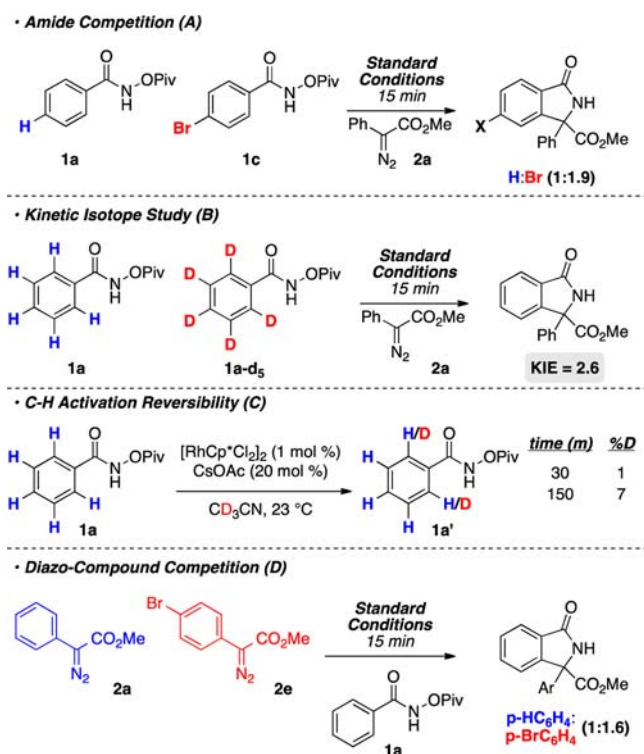
experiments were used to determine the electronic preference of the reaction. When p-bromobenzamide **1c** was run in competition with the unsubstituted amide **1a** the reaction favors the electron deficient amide in a 1.9:1 ratio (Scheme 1a). This experiment suggest that C–H activation favors more acid C–H bonds. Indeed, initial rate kinetic isotope studies revealed a KIE value of 2.6 (Scheme 1b). Together these studies suggest that C–H activation occurs via a concerted-metalation deprotonation (CMD) mechanism, and the C–H activation does not proceed through a Wheland intermediate.[20] These experiments are consistent with the observation that reactions involving substrates bearing more electron donating groups are sluggish.

The reversibility of the C–H activation was determined by removing the diazo compound and running the reaction in the presence of MeCN-d_3 (Scheme 1c). After 15 min, <1% deuterium incorporation at the ortho positions was observed, as determined by ^{1}H NMR analysis. After 150 min, the degree of deuterium incorporation increased to 7%. These results suggest that C–H activation in largely irreversible on the time scale of the reaction, which is consistent with previous reports by Fagnou[3e] and Glorius.[21]

A competition experiment was used to determine the preference of the reaction for electronically different donor/acceptor diazo compounds (Scheme 1d). When methyl p-bromophenyl diazo acetate (**2e**) was used in competition with **2a**, the electron-deficient substrate was favored 1.6:1 after 15 min. These results suggest that migratory insertion or reductive elimination favors the more electron-deficient substrate. Since reductive elimination should favor a more electron-rich substrate, it is reasonable to surmise that migratory insertion favors an electron-deficient diazo substrate because of its increased electrophilicity.

In conclusion, we have developed a new approach to access isoindolones bearing a tetrasubstituted carbon. A wide range of substrates are tolerated, including 1-aryl-2,2,2-trifluoroethyl diazo compounds. Mechanistic studies revealed that the reaction operates under a mechanism similar to that for the synthesis of dihydroisoquinolones.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, characterization data, and mechanistic 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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