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# Rhodium-Catalyzed Annulation of *N*-Benzoylsulfonamide with Isocyanide through C–H Activation

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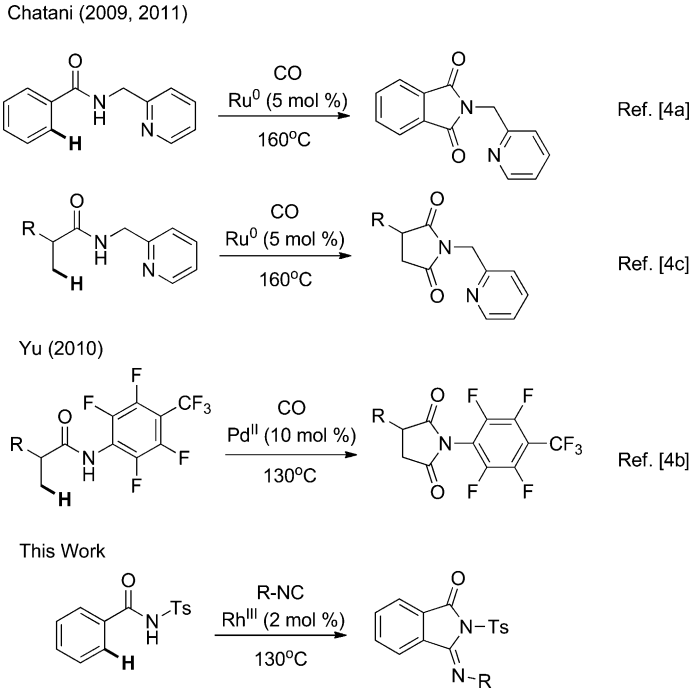
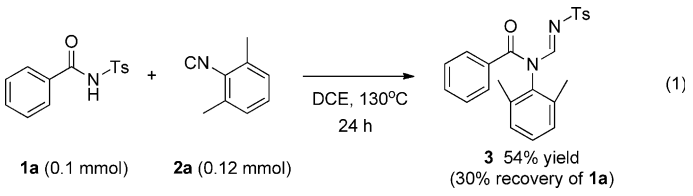
The use of amides as directing group has notably improved the chemistry of C–H bond functionalization, because these compounds do not only lead to good reactivities and selectivities but are also precursors of C–N bonds.[1] Indeed, much effort has been made to explore the annulation of amides with various partners, albeit mostly focusing on the chemistry of alkenes and alkynes.[2,3] To extend the versatility and utility in the construction of complex heterocycles, in addition to the reactions involving alkenes and alkynes, new reaction types are extremely sought after. Recently, Chatani, Yu and their co-workers reported successful examples of annulation of amides with carbon monoxide employing ruthenium or palladium catalyst, respectively (Scheme 1).[4] Isocyanide has been considered a unique source of C1 that enables transformations that could not be accomplished with carbon monoxide.[5] However, to date, the reaction of amides with isocyanides by means of C–H bond activation has not been developed.

We have revealed that the N–H acidity of *N*-benzoylsulfonamide shows superiority in the C–H olefination.[6] These results prompted us to investigate the annulation of *N*-benzoylsulfonamide with isocyanide which would result in 3-(imino)isoindolinone, a class of amidines from isoindoline ubiquitously existing as substructures in bioactive compounds.[7] Despite the documented methods,[8] in view of atom economy, a more straightforward alternative is desired. Herein, we disclose the first rhodium-catalyzed annulation of *N*-benzoylsulfonamide with isocyanide through C–H activation.

At the outset, we realized the key challenges that characterize our studies: 1) an undesired background reaction, obtained upon insertion of isocyanide into the acidic N–H bond of *N*-benzoylsulfonamide and leading to unexpected rearranged product **3** under simply heating the mixture of two components [Eq. (1)];[9] 2) isocyanides are prone to polymerize in presence of transition metals.[10] Apparently, these competitive reactions significantly raise the barrier of achieving a suitable condition that promotes the annulation and simultaneously suppresses the side reaction.




Scheme 1. Annulation with C1 source via C–H activation




After unsuccessful trials by using other transition-metal catalysts,[11] we found that rhodium catalyst $[RhCl_2Cp^*]_2$ led to the desired transformation.[12] A survey of reaction parameters is shown in Table 1. With the standard conditions, the annulated product **4a** was formed in satisfactory yield, and, more importantly, the formation of by-product **3** was virtually inhibited (Table 1, entry 1). The use of a reoxidizing agent had critical influence on the reaction. For examples, molecular oxygen as oxidant was unable to suppress the competitive reaction and **3** was obtained as major prod-

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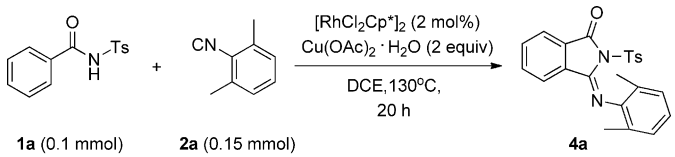
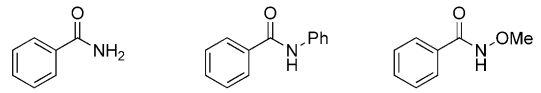
Table 1. Reaction parameters.




| Entry | Conditions | Yield |
|---|---|---|
| 1 | standard conditions[a] | 70% (<5% **3**) |
| 2 | $Cu(OAc)_2{\cdot}H_2O$ (5 mol%)+$O_2$ as oxidant | <5% (48% **3**) |
| 3 | $Ag_2CO_3$ and AgOAc as oxidants | n.d. |
| 4 | $Cu(OAc)_2$ as oxidant | 68% |
| 5 | toluene as solvent | 32% |
| 6 | THF as solvent | 10% |
| 7 | $Na_2CO_3$ (2 equiv) as additive | <5% |
| 8 | HOAc (10 equiv) as additive | n.d. |
| 9 | $AgSbF_6$ (10 mol%) as additive | 50% |
| 10 | **5** instead of **1a** | n.d. |
| 11 | **6** instead of **1a** | n.d. |
| 12 | **7** instead of **1a** | n.d. |

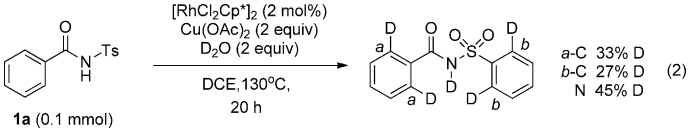
[a] Standard conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $[RhCl_2Cp^*]_2$ (0.002 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (0.2 mmol) in 0.8 mL dichloroethane. N.D = not detected, Ts = 4-toluenesulfonyl.

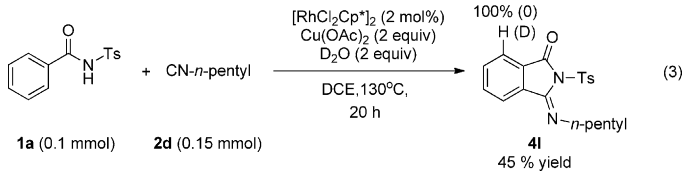
uct (Table 1, entry 2); the use of silver salts as oxidant resulted in no reaction as isocyanide acted as a good ligand to the silver cation (Table 1, entry 3). Moreover, the replacement of $Cu(OAc)_2{\cdot}H_2O$ with an anhydrous surrogate, led almost to the same output (Table 1, entry 4). Other solvents such as toluene or THF notably decelerated the reaction rate (Table 1, entries 5 and 6). Adding extra base, acid, or silver salt to the reaction was not beneficial for improving the chemical yield (Table 1, entries 7–9). As it represented an advantage in our previous work,[6] the N–H acidity was examined herein as well. It was noted that using unprotected benzamide **5** or weaker N–H acidic benzamides (**6** and **7**) instead of **1a**, the corresponding annulated products was not detected (Table 1, entries 10–12).

With the optimized conditions in hand, we investigated the scope of the reaction (Table 2). Both *N*-benzoylsulfonamides and isocyanides were evaluated. Naphthyl could replace phenyl substrate to afford the best yield (Table 2, entry 2). Both electron-rich and electron-poor substrates were tolerated in the reaction. Generally, the former tend to give better results than the latter (Table 2, entries 3 and 4 vs. entries 5 and 6). Impressively, in the case of *meta*-substituted substrate **1g**, the reaction led to high regioselectivity (*para*/*ortho* = 7:1) as well as good yield (Table 2, entry 7). The prolonged time required to produce an acceptable yield for *o*-fluoro substrate **1h** implied that the substituent at the adjacent position hampered the conversion (Table 2, entry 8). When the steric hindrance at the *ortho*-position was further increased through the introduction of a methoxyl group, only traces of the product were gained. The insertion of a halogen atom on the isocyanide did not compromise the chemical yield (Table 2, entry 9). However, phenyl and *p*-methoxyphenyl isocyanide did not give the respective products since these simple aryl isocyanides were too reactive and prone to polymerization under the given reaction conditions. Significantly, the transformation also proceeded readily with aliphatic isocyanides. All benzylic, primary, and secondary aliphatic isocyanides provided useful yields (Table 2, entries 10–12).

An intriguing trend of *Z*/*E* ratio affiliated to the imino subunit of annulated product was also observed in Table 2.[13] The use of isocyanide **2a** predominantly afforded the *E* isomer (Table 2, entries 1–7), while the use of isocyanide **2b** switched the configuration to Z (Table 2, entry 9). Specifically, the *Z* isomer was exclusively formed by using aliphatic isocyanides **2c–e** (Table 2, entries 10–12).

To understand the possible mechanistic pathway in the transformation, some isotopic labeling experiment have been carried out: 1) $Cu(OAc)_2{\cdot}H_2O$ has been replaced by an equimolar combination of anhydrous $Cu(OAc)_2$ and $D_2O$ [eqs. (2) and (3)]; 2) intermolecular competitive reactions [Eq. (4)], were conducted. Equation (2) indicated that without coupling partner the proton on the *ortho*-position of benzoyl or tosyl side is exchangeable. The absence of deuteration at the *ortho*-position [Eq. (3)] suggested that, under




the reaction conditions, the C–H insertion step is irreversible. The kinetic isotope effect value ($k_H/k_D = 1.5$) gained from Equation (4) might indicate that the C–H cleavage is fast, and thus does not take part into the rate-determining step of the reaction.

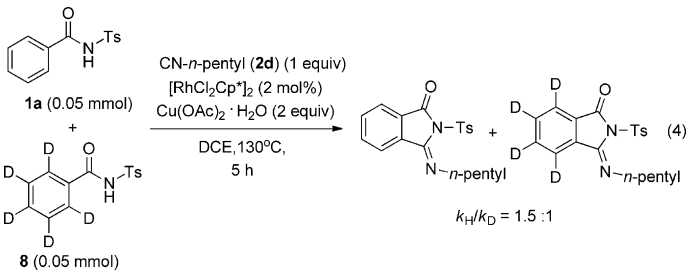
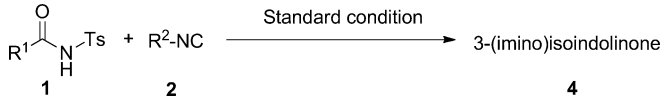
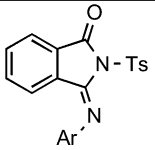
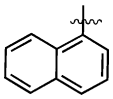
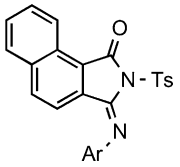
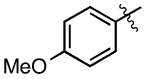
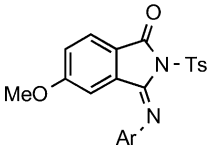
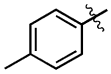
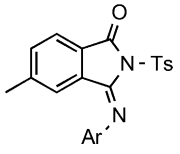
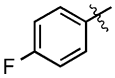
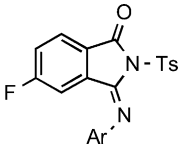
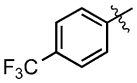
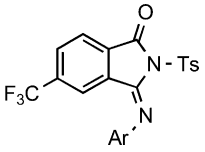
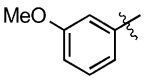
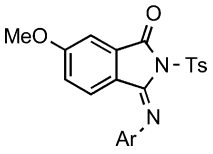
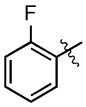
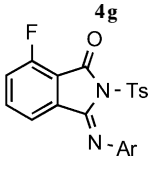


Table 2. Substrate scope[a]




1 2 4

| Entry | $R^1$ | $R^2$ | Product | Yield [%][b] | *Z*/*E* Ratio[c] |
|---|---|---|---|---|---|
| 1 |  **1a** | **2a** |  **4a** | 70 | 1:3 |
| 2 |  **1b** | **2a** |  **4b** | 81 | 1:7 |
| 3 |  **1c** | **2a** |  **4c** | 70 | 1:6 |
| 4 |  **1d** | **2a** |  **4d** | 65 | 1:5 |
| 5 |  **1e** | **2a** |  **4e** | 52 | 1:3 |
| 6 |  **1f** | **2a** |  **4f** | 40 | 1:5 |
| 7 |  **1g** | **2a** |  **4g** | 72[d] | 1:3 |
| 8[e] |  **1h** | **2a** |  **4h** | 46 | 2:1 |

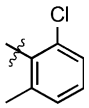
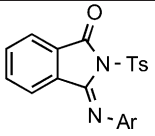
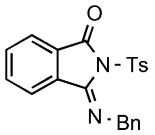
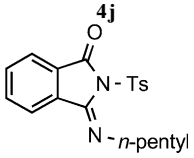
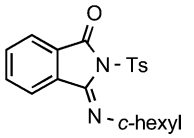
The postulated mechanism is depicted in Figure 1. We speculate that the cycle originates from the generation of five-membered rhodacycle **I** via rapid C–H activation. Subsequently, the isocyanide is bonded to rhodium center to form complex **II**, followed by 1,1-insertion of isocyanide into the Rh–C bond (**III**).[14] Finally, the annulated product **4** is released through reductive elimination, and meanwhile, the rhodium catalyst is regenerated by copper oxidation.

The factors that affect the tendency of the *Z*/*E* ratio shown in Table 2 are not clear at this earlier stage. However, with the insight gained from the mechanistic analysis, we assume that the isomer ratio is determined at the step of isocyanide insertion into the Rh–C bond (intermediate **III** in Figure 1). As shown in Figure 2, when the isocyanide is relatively small (like **2c–e**), the *N*-substituent is facing the highest repulsion from the *ortho*-hydrogen (**A**) rather than tosyl (**B**), thus the formation of *Z*-imine is favorable. However, in the case of **2a**, the bulky *N*-aryl substituent suffers the competitive repulsion from both sides. Based on the experimental results reported in Table 2, more likely, turning to tosyl (**D**) side may encounter stronger repulsion than from *ortho*-hydrogen (**C**), so the generation of *E*-imine becomes favorable.[15]

In summary, the unprecedented rhodium-catalyzed annulation of *N*-benzoylsulfonamide with isocyanide through C–H activation has been described. The transformation successfully suppresses the competitive reaction, and is broadly compatible with *N*-benzoylsulfonamides as well as isocyanides with different electronic properties. From a prac-

Table 2. (Continued)

| Entry | $R^1$ | $R^2$ | Product | Yield [%][b] | *Z*/*E* Ratio[c] |
|---|---|---|---|---|---|
| 9 | |  |  | 60 | 6:1 |
| | | **2b** | **4i** | | |
| 10 | | Bn |  | 41 | only *Z* |
| | **1a** | **2c** | **4j** | | |
| 11 | | *n*-pentyl |  | 54 | only *Z* |
| | | **2d** | **4k** | | |
| 12 | | *c*-hexyl |  | 50 | only *Z* |
| | | **2e** | **4l** | | |

[a] Standard conditions: **1** (0.1 mmol), **2** (0.15 mmol), $[RhCl_2Cp^*]_2$ (0.002 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (0.2 mmol) in 0.8 mL dichloroethane at 130 °C for 20 h. [b] Yield of isolated product. [c] *Z*/*E* configuration of the imino bond. Except **4h**, all other pairs of isomers are separable on preparative TLC. [d] Product ratio *para*/*ortho* = 7:1. [e] 48 h. Bn = benzyl.

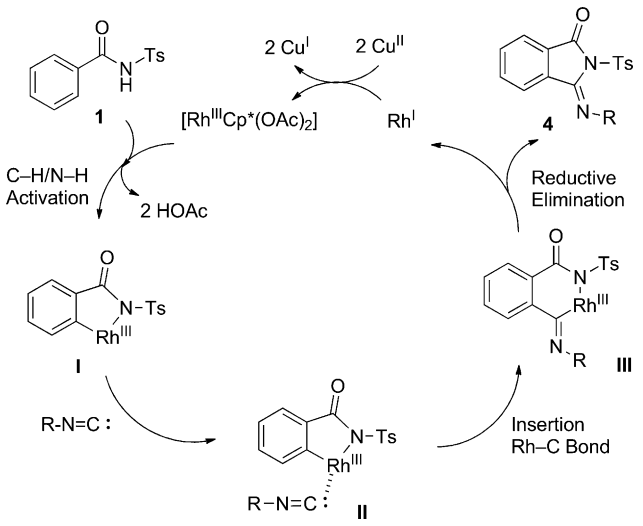



Figure 1. Plausible reaction mechanism.

tical point of view, this method provides the most straightforward approach to a series of 3-(imino)isoindolinones.

## Experimental Section

**General procedure for rhodium-catalyzed annulation of *N*-benzoylsulfonamide with isocyanide**: *N*-Benzoylsulfonamide **1a** (27.5 mg, 0.1 mmol), $[RhCl_2Cp^*]_2$ (1.2 mg, 0.002 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (40.0 mg, 0.2 mmol) were loaded in a dry vial which was subjected to evacuation/flushing with dry argon three times. A solution of isocyanide **2a** (19.6 mg, 0.15 mmol) in anhydrous methylene chloride (0.8 mL) was syringed into the mixture that was then stirred at 130 °C for 20 h or until the starting material had been consumed as determined by TLC. Upon cooling to room temperature, all volatiles were evaporated and the residue was purified by preparative TLC (ethyl acetate/hexane = 1:2) to give 3-(imino)-isoindolinone **4a** in 70 % yield (*E*/*Z* = 3:1). *Z* and *E* isomers were further separated by preparative TLC (methylene chloride/hexane = 10:1).

***E* Isomer, yellow solid**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.84 (s, 6H), 2.44 (s, 3H), 6.49 (d, $J$ = 7.5 Hz, 1H), 7.02 (dd, $J$ = 6.5, 8.0 Hz, 1H), 7.07 (d, $J$ = 7.5 Hz, 2H), 7.34 (d, $J$ = 8.0 Hz, 2H), 7.38 (dd, $J$ = 7.5, 8.0 Hz, 1H), 7.60 (dd, $J$ = 7.5, 7.5 Hz, 1H), 7.94 (d, $J$ = 7.5 Hz, 1H), 8.15 ppm (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 17.9, 22.0, 124.3, 124.9, 125.0, 126.1, 128.6, 129.2, 129.3, 129.7, 130.6, 133.3, 135.3, 136.5, 145.5, 145.6, 147.3, 163.6 ppm; FT-IR ($CH_2Cl_2$): $\tilde{\nu}$ = 2361, 2342, 1762, 1677, 1380, 1267, 1191, 1178, 1057, 694 cm$^{-1}$; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{21}N_2O_3S$: 405.1267 $[M+H]^+$; found: 405.1264.

***Z* Isomer, colorless solid**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 2.14 (s, 6H), 2.38 (s, 3H), 7.14 (d, $J$ = 7.5 Hz, 2H), 7.20 (d, $J$ = 8.0 Hz, 2H), 7.25 (dd, $J$ = 7.5, 7.5 Hz, 1H), 7.65 (d, $J$ = 8.0 Hz, 2H), 7.84 (dd, $J$ = 7.5, 7.5 Hz, 1H), 7.89 (dd, $J$ = 7.5, 7.5 Hz, 1H), 8.01 (d, $J$ = 7.5 Hz, 1H), 8.98 ppm (d, $J$ = 7.5 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 18.3, 21.8, 124.5, 126.6, 128.5, 129.5, 129.6, 129.7, 130.1, 130.6, 131.2, 134.7, 134.8, 136.9, 139.1, 143.5, 160.1, 166.6 ppm; FT-IR ($CH_2Cl_2$): $\tilde{\nu}$ = 2361, 2342, 1762, 1609, 1380, 1316, 1150, 1078, 899, 827, 710, 660 cm$^{-1}$; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{21}N_2O_3S$: 405.1267 $[M+H]^+$; found: 405.1258.

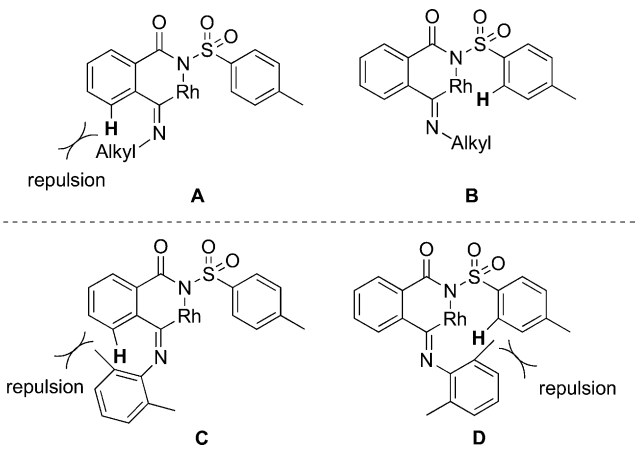



Figure 2. Steric influence of the isocyanide on the isomer ratio.

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**Keywords:** annulations · C–H activation · heterocycles · isocyanide · rhodium

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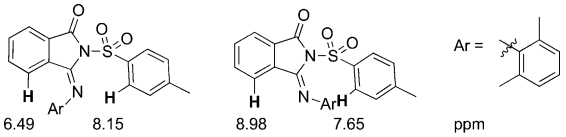


*E*-**4a** *Z*-**4a**

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