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Rhodium Catalyzed Annulation of *N*-Benzoylsulfonamide with Isocyanide via C-H Activation

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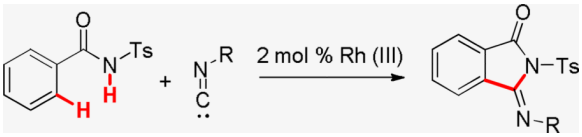
Abstract



Isocyanide insertion: the first rhodium-catalyzed annulation of *N*-benzoylsulfonamide incorporating with isocyanide via C-H activation is described. The transformation is broadly compatible with *N*-benzoylsulfonamides bearing various electron-properties as well as isocyanides. From practical point of view, this methodology provides the most straightforward approach to a series of 3-(imino)isoindolinones.

Keywords

N-benzoylsulfonamide; isocyanide; C-H bond activation; annulation; 3-(imino)isoindolinone

The occurrence of amides as directing group has introduced privileged capability in the chemistry of C-H bond functionalization, since the amides can not only serve for acceptable reactivities and selectivities but also provide the precursor to a C-N bond.[1] Indeed, much effort has been made to such concept to explore the annulation of amides with various partners, albeit mostly focuses on alkenes and alkynes.[2, 3] To extend the versatility and utility in construction of complex heterocycles, in addition to those reactions involving alkenes and alkynes, new reaction types are extremely anticipated. More recently, Chatani et al. and Yu et al. reported successful examples of annulation of amides with carbon monoxide employing ruthenium or palladium catalyst, respectively (Scheme 1).[4] Isocyanide has been considered as a unique C1 source that enabling the transformations which could not be accomplished with carbon monoxide.[5] However, to date the reaction of amide incorporating with isocyanide 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, the straightforward surrogate is desired. Herein, we disclose the first rhodium-catalyzed annulation of N-benzoylsulfonamide with isocyanide via C-H activation.

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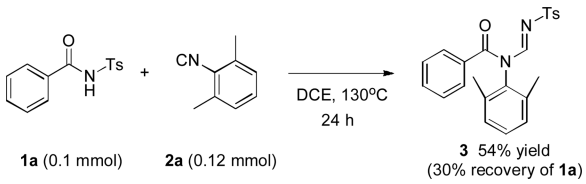
At the outset, we realized the challenges emerging from our studies: 1) a frustrating background reaction, that isocyanide inserted into the acidic N-H bond of N-benzoylsulfonamide and afforded unexpected rearranged product **3** under simply heating the mixture of two components, was detected (eq 1);[9] 2) isocyanides are prone to polymerization in presence of transition metal.[10] Apparently, those competitive reactions significantly raise the barrier of achieving a competent condition that promoting the annulation and simultaneously suppressing the side reaction.



(1)

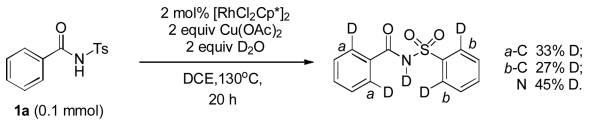
After unsuccessful trials by using other transition metal catalysts,[11] we found rhodium catalyst [{$RhCl_2Cp^*$}$_2$] proceeded the desired transformation.[12] A survey of reaction parameters was shown in Table 1. With the standard conditions, the annulated product **4a** was furnished in satisfactory yield, and, more importantly, the formation of by-product **3** was virtually inhibited (entry 1). Re-oxidizing agent had critical influence on the reaction. For examples, molecular oxygen as oxidant was unable to suppress the competitive reaction that **3** was obtained as major product (entry 2); silver salts as oxidant resulted in none reaction since isocyanide could perform as a good ligand to silver cation (entry 3). Moreover, replacing $Cu(OAc)_2 \cdot H_2O$ with anhydrous surrogate, the output was almost same (entry 4). Other solvents such as toluene or THF notably decelerated the reaction rate (entries 5 and 6). Adding extra base, acid or silver salt to the reaction was not beneficial for improving the chemical yield (entries 7–9). As one of the advantages exhibited 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 had not been detected (entries 10–12).

With the optimized condition in hand, we investigated the scope of the reaction (Table 2). Both parts of *N*-benzoylsulfonamides and isocyanides were evaluated. Naphthyl could replace phenyl substrate to afford the best chemical yield (entry 2). Both electron-rich and electron-poor substrates were tolerated in the reaction. Generally, the former tends to give better results than the latter (entries 3, 4 *vs* entries 5, 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 (entry 7). The prolonged time was required to produce acceptable yield for *o*-fluoro substrate **1h** implied that the substituent at the adjacent position hampered the conversion (entry 8). If further increasing the steric hindrance at *ortho*-position, such as installing a methoxyl group, only trace product was gained. Putting a halogen atom on isocyanide did not compromise the chemical yield (entry 9). However, phenyl and *p*-methoxyphenyl isocyanide did not give the respect products since these simple aryl isocyanides were too reactive and prone to polymerization under the reaction conditions. Significantly, the transformation also proceeded readily with aliphatic isocyanides. All benzylic, primary and secondary aliphatic isocyanides provided useful yields (entries 10–12).

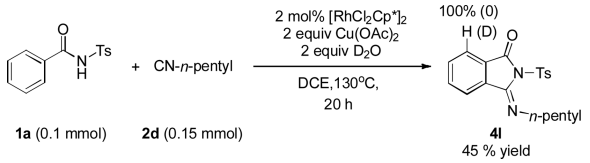
An intriguing trend of *Z*/*E* ratio affiliated to the imino subunit of annulated product was also observed in Table 2.[13] The use of isocyanide **2a** predominantly afforded the *E* isomer (entries 1–7), while the use of isocyanide **2b** switched the configuration to Z (entry 9).

Specifically, the *Z* isomer was exclusively formed as utilizing aliphatic isocyanide **2c–2e** (entries 10–12).

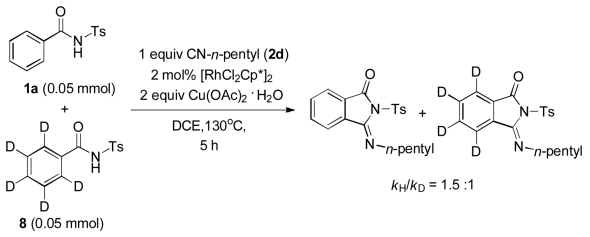
To understand the possible mechanistic pathway in the transformation, some assistant deuterium experiments: 1) replacement of $Cu(OAc)_2 \cdot H_2O$ by an equimolar combination of anhydrous $Cu(OAc)_2$ and D_2O (eqs 2 and 3); 2) intermolecular competitive reaction (eq 4), were conducted. Equation 2 indicated that without coupling partner the proton on *ortho*-position of benzoyl or tosyl side is exchangeable. None deuteration occurred at the *ortho*-position in equation 3 suggested that, under the reaction condition, the C-H insertion step is irreversible. The KIE value (k_H/k_D = 1.5) gained from equation 4 might indicate that the C-H cleavage is fast, thus not involved as the rate-limiting step.



(2)



(3)



(4)

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 centre to form complex (**II**), followed by 1,1-insertion of isocyanide into 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 factor which affects the tendency of *Z*/*E* ratio appeared in Table 2 is ambiguous 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 Rh-C bond (Intermediate **III** in Figure 1). As shown in Figure 2, when isocyanide is relative small (like **2c**–**2e**), *N*-substituent is facing the most repulsion from *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 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 incorporating with isocyanide via C-H activation is described. The transformation successfully suppresses the competitive reaction, and is broadly compatible with *N*-benzoylsulfonamides bearing various electron-properties as well as isocyanides. From practical point of view, this methodology 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. Anhydrous methylene chloride (0.8 mL) solution of isocyanide **2a** (19.6 mg, 0.15 mmol) were syringed into the mixture which 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 (eluent: 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 (eluent: methylene chloride/hexane 10:1).

E-isomer, yellow solid. ^{1}H NMR (500 MHz): δ = 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 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz): δ = 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): 2361, 2342, 1762, 1677, 1380, 1267, 1191, 1178, 1057, 694 cm^{-1}. HRMS calcd for $C_{23}H_{21}N_2O_3S$ $[M+H]^+$ 405.1267, found 405.1264.

Z-isomer, colorless solid. ^{1}H NMR (500 MHz): δ = 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 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz): δ = 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): 2361, 2342, 1762, 1609, 1380, 1316, 1150, 1078, 899, 827, 710, 660 cm^{-1}. HRMS calcd for $C_{23}H_{21}N_2O_3S$ $[M+H]^+$ 405.1267, found 405.1258.

Acknowledgments

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11. For details, see Supporting Information.

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

13. Because of the electronic shielding effect, the signal of H-4 on *E*-isomer appears at high field (δ = 5.9–6.5 ppm). In contrast, the signal of H-4 on *Z*-isomer appears at low field (δ = 8.7–9.0 ppm). For the related study, also see ref. 8b.

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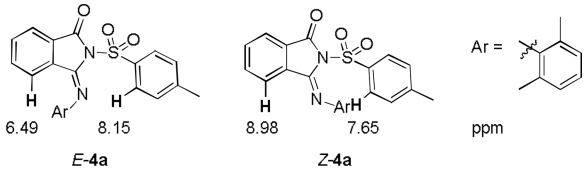
15. These presumed interactions are demonstrated in the ^{1}H NMR spectra of both product isomers. The chemical shift of the proton which the, *N*-aryl group towards significantly moves to upfield.



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

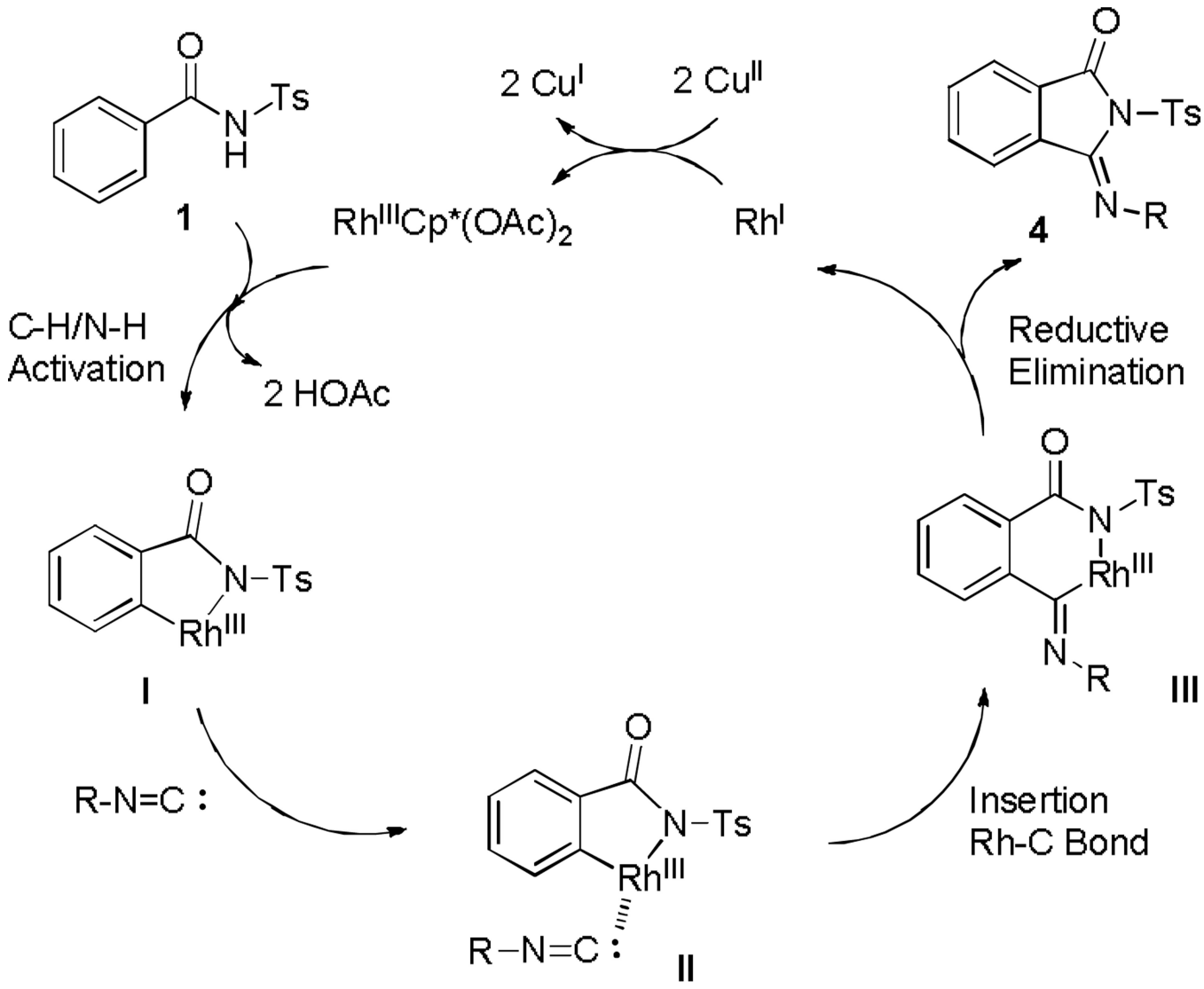


Figure 1.
Plausible Mechanism

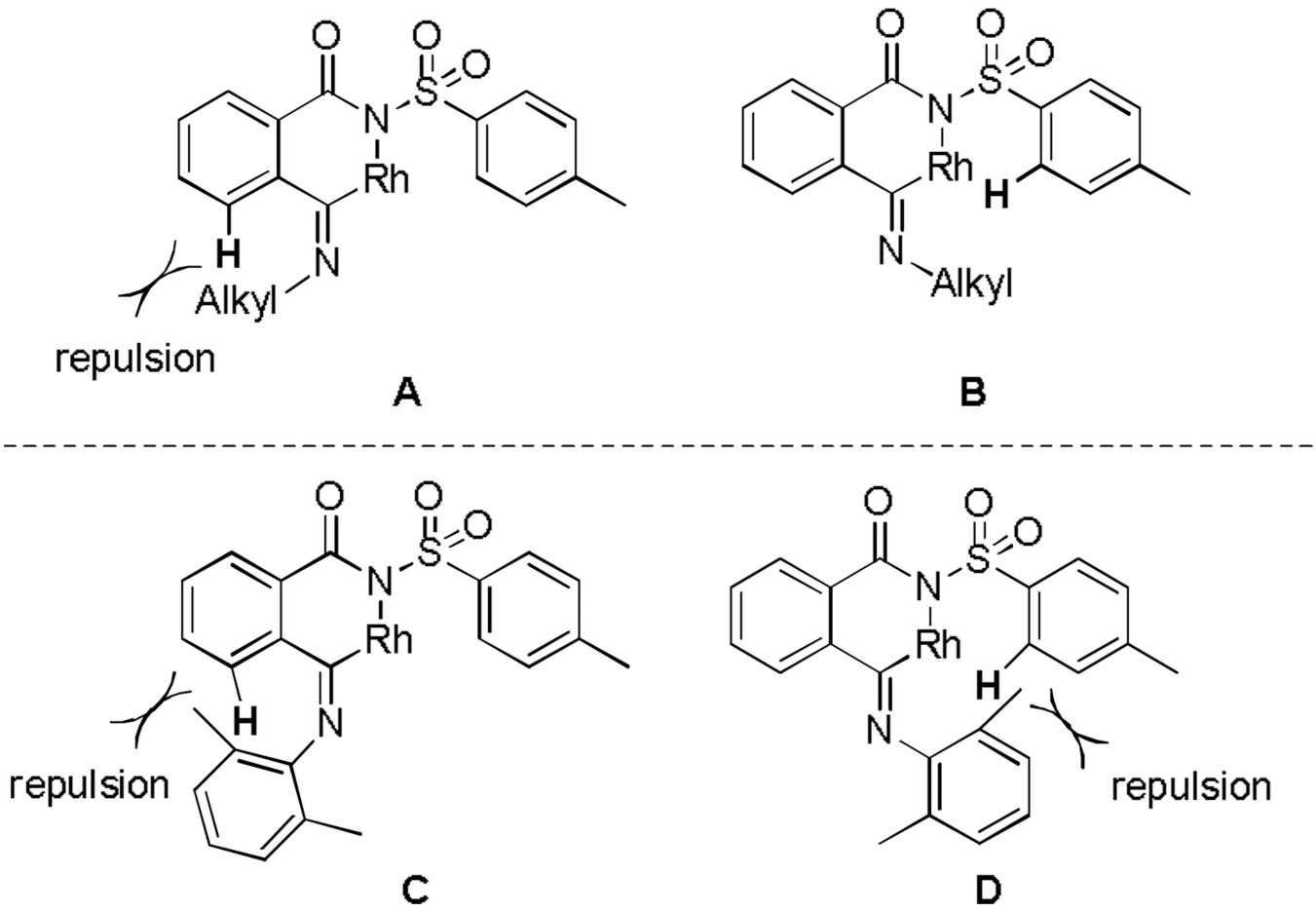
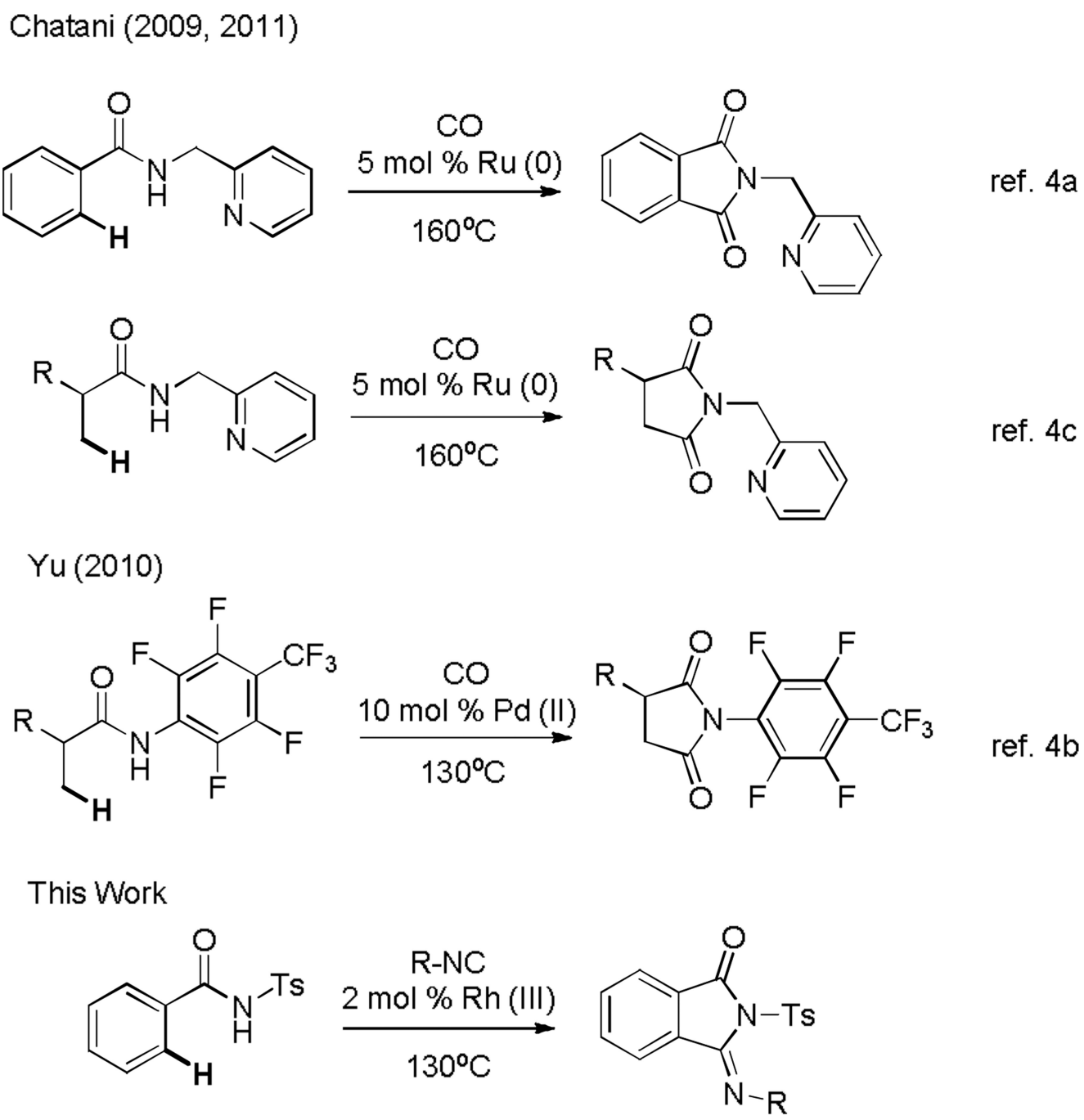


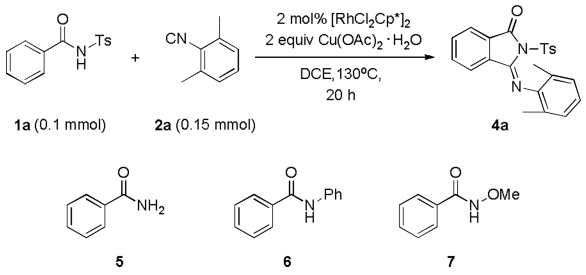
Figure 2.
Steric Influence of Isocyanide on Isomer Ratio



Scheme 1.
Annulation with C1 Source via C-H Activation

Table 1

Reaction Parameters Survey



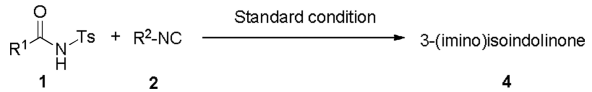
Entry	Conditions	Yield
1	Standard condition[a]	70% (< 5% 3)
2	5 mol % $Cu(OAc)_2 \cdot H_2O$ + O_2 as oxidant	< 5% (48% 3)
3	Silver salts, eg. Ag_2CO_3, AgOAc, as oxidant	N.D.
4	$Cu(OAc)_2$ as oxidant	68%
5	Toluene as solvent	32%
6	THF as solvent	10%
7	2 equiv Na_2CO_3 as additive	< 5%
8	10 equiv HOAc as additive	N.D
9	10 mol % $AgSbF_6$ as additive	50%
10	5 instead of 1a	N.D.[b]
11	6 instead of 1a	N.D.
12	7 instead of 1a	N.D.

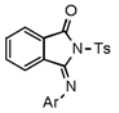
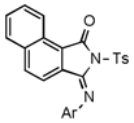
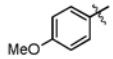
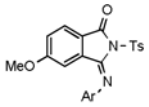
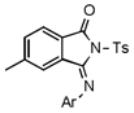
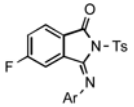
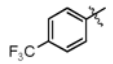
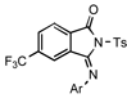
[a] Standard condition: **1a** (0.1 mmol), **2a** (0.15 mmol), $[RhCl_2Cp^*]_2$ (0.002 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol) in 0.8 mL dichloroethane.

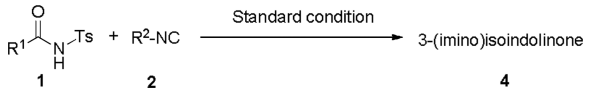
[b] Not detected for corresponding product. N.D. = not detected.

Table 2

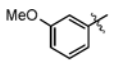
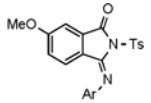
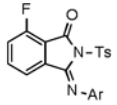
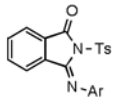
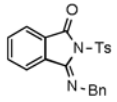
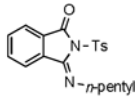
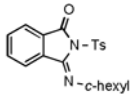
Substrate cope[a]



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



1 2 4

Entry	R^1	R^2	Product	Yield (%)[b]	Z/E Ratio[c]
7	 **1g**	**2a**	 **4g**	72[d]	1:3
8[e]	 **1h**	**2a**	 **4h**	46	2:1
9	**1a**	 **2b**	 **4i**	60	6:1
10	**1a**	Bn **2c**	 **4j**	41	only *Z*
11	**1a**	*n*-pentyl **2d**	 **4k**	54	only *Z*
12	**1a**	*c*-hexyl **2e**	 **4l**	50	only *Z*

[a] Standard condition: **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] Isolated yield.

[c] *Z*/*E* configuration of imino bond. Except **4h**, other pairs of isomers are separable on preparative TLC.

[d] The positional product ratio: *para*/*ortho* = 7:1.

[e] 48 h.