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Orthogonal Reactivity of Acyl Azides in C−H Activation: Dichotomy between C−C and C−N Amidations Based on Catalyst Systems

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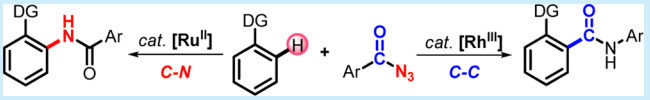
Supporting Information

ABSTRACT: The dual reactivity of acyl azides was utilized successfully in C−H activation by the choice of catalyst systems: while selective C−C amidation was achieved under thermal Rh catalysis, a Ru catalyst was found to mediate direct C−N amidation also highly selectively. Investigations of the mechanistic dichotomy between two catalytic systems are also presented.

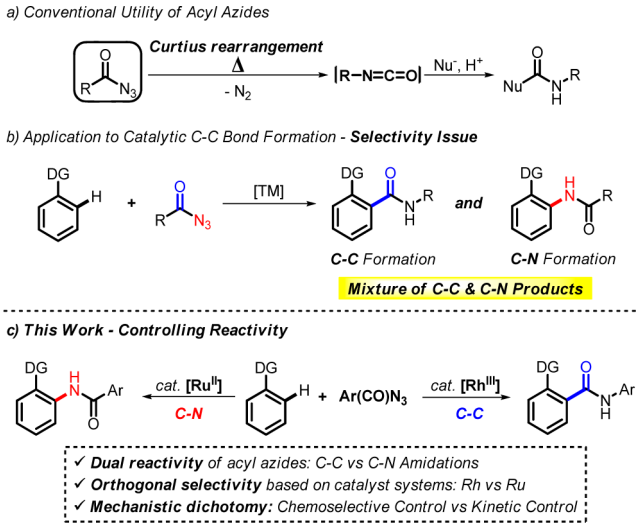


Transition-metal-catalyzed direct C−H bond functionalization has emerged as a straightforward tool for the construction of carbon−carbon or carbon−heteroatom bonds.[1] Along with the notable advances in the C−H bond activation methods, metal-mediated C−H additions to carbon−carbon multiple bonds have been extensively investigated.[2] On the other hand, C−H addition across unsaturated carbon−nitrogen bonds is still in its infancy.[3,4] In particular, procedures allowing for the direct insertion of C−H bonds into isocyanates are highly demanding since it can effectively provide synthetically valuable amide moieties.[4] While Re-catalyzed C−H addition of (hetero)arenes to isocyanates were reported earlier,[4a,b] Rh-[4c,e] and Ru-catalyzed[4d] procedures were disclosed more recently.

Acyl azides have been widely used in organic synthesis, and among those examples, the most notable utility is to employ them as precursors for isocyanates via the 'Curtius rearrangement' which can be induced most often thermally (Scheme 1a).[5] Nucleophiles react with the carbon center of *in situ* generated isocyanates to afford amide products.[6] However, to the best of our knowledge, acyl azides have never been applied to the direct C−H functionalization as precursors of isocyanates mainly due to the difficulty in controlling the dual reactivity of acyl azides, thus leading to a mixture of C−C and C−N amidated products (Scheme 1b).

In the context of our studies to utilize organic azides as efficient amino sources in the C−H functionalizations,[7] we have developed the Rh-[8] and Ru-catalyzed[9] C−H amination protocols using sulfonyl, aryl, and alkyl azides. Acyl azides were also found to work as an amido source in the Ir-catalyzed amidation under mild conditions.[10] In these studies, we were curious about whether acyl azides can be employed in a selective manner, thus serving not only as an amino source but also as a carbon donor. Described herein is the first example of controlling the dual reactivity of acyl azides between C−C and C−N amidations depending on catalyst systems (Scheme 1c). In addition, mechanistic studies on this orthogonal selectivity are also presented.

Scheme 1



We initially tried to find optimal conditions for the selective C−C amidation of 2-phenylpyridine (**1a**) with benzoyl azide (**2a**) (Table 1). A combination of $[RhCp^*Cl_2]_2$ with $AgSbF_6$, a catalyst system widely employed in C−H functionalizations,[11] resulted in both C−C (**3a**) and C−N (**4a**) amidations in high yield, but with low selectivity (entry 1). Employing other silver additives possessing weakly coordinating counterions did not improve the selectivity in 1,2-dichloroethane (entries 2−4). Whereas the use of other solvents resulted in only marginal effects (entries 5−7), an additive of acetonitrile gave rise to a significant increase of selectivity. For instance, the C−C amidation product (**3a**) was formed highly favorably (17:1) over the C−N product (**4a**) with the addition of 1.0 equiv of CH_3CN (relative to **1a**, entry 8). However, an excessive amount was detrimental (entry 9). When a cationic Rh species

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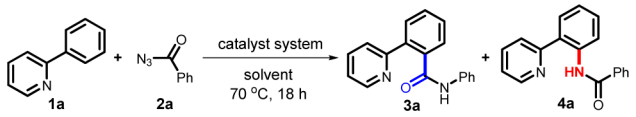
Table 1. Optimization Table of the Rh-Catalyzed C−C Amidation Reaction[a]



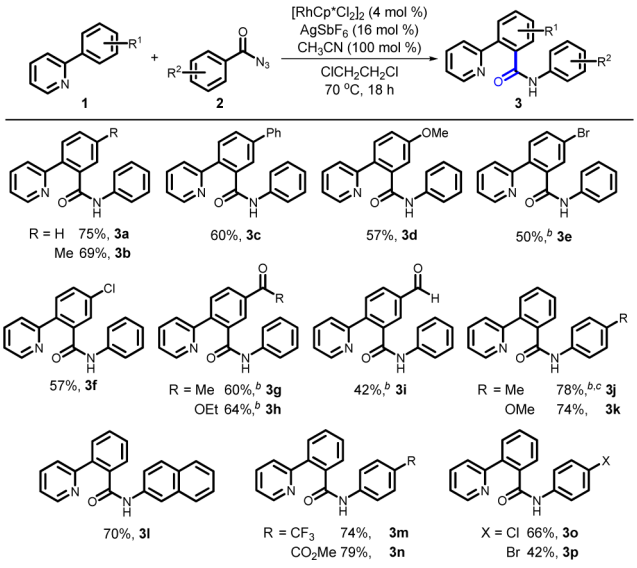
entry	catalyst system (mol %)	solvent	3a/4a	yield (%)[b]
1	$[RhCp^*Cl_2]_2$ (4) + $AgSbF_6$ (16)	1,2-DCE	1.7:1	80
2	$[RhCp^*Cl_2]_2$ (4) + $AgNTf_2$ (16)	1,2-DCE	1.2:1	68
3	$[RhCp^*Cl_2]_2$ (4) + $AgBF_4$ (16)	1,2-DCE	1.5:1	90
4	$[RhCp^*Cl_2]_2$ (4) + $AgPF_6$ (16)	1,2-DCE	1.3:1	90
5	$[RhCp^*Cl_2]_2$ (4) + $AgSbF_6$ (16)	THF	1.3:1	79
6	$[RhCp^*Cl_2]_2$ (4) + $AgSbF_6$ (16)	1,4-dioxane	2.1:1	90
7	$[RhCp^*Cl_2]_2$ (4) + $AgSbF_6$ (16)	toluene	3.8:1	82
8[c]	**$[RhCp^*Cl_2]_2$ (4) + $AgSbF_6$ (16)**	**1,2-DCE**	**17:1**	**73**
9[d]	$[RhCp^*Cl_2]_2$ (4) + $AgSbF_6$ (16)	1,2-DCE	17:1	36
10	**$[RhCp^*(MeCN)_3][SbF_6]_2$ (8)**	**1,2-DCE**	**8.1:1**	**91**

[a] **1a** (0.2 mmol) and **2a** (0.36 mmol) in solvent (0.5 mL). [b] Total yield of **3a** and **4a**, determined by ^1H NMR. [c] CH_3CN (100 mol %) was added. [d] CH_3CN (0.2 mL) was added.

bound to CH_3CN, prepared separately according to the literature,[12] was used as a catalyst, a slightly lower selectivity, but with a still synthetically satisfactory ratio, was observed (entry 10).

With the optimized conditions in hand, we then investigated the generality of the selective C−C amidation reaction by using a range of substrates and acyl azides (Scheme 2). Aryls bearing

Scheme 2. Scope of the Rh-Catalyzed C−C Amidation[a]



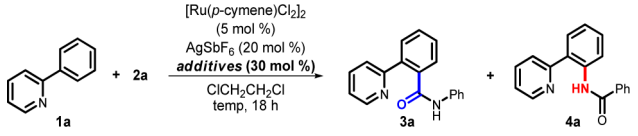
[a] **1** (0.2 mmol) and **2** (0.36 mmol) in 1,2-DCE (0.5 mL). Isolation yields are given. [b] $[RhCp^*(MeCN)_3][SbF_6]_2$ (8 mol %). [c] A side product (C−N amidated **4j**) was also detected (**3j**/**4j**, 8:1).

electron-neutral or -donating substituents were smoothly amidated at the *ortho*-position relative to the 2-pyridyl group with moderate to high yields (**3a**−**3d**). Substrates bearing a bromo or chloro group were selectively reacted to afford the desired products (**3e**−**3f**), thus offering potential for further functionalizations. The reaction conditions were compatible with various sensitive functional groups such as ketone, ester, or aldehyde in addition to a halide (**3g**−**3i**).

The scope of acyl azides was next examined by varying substituents. Benzoyl azides substituted with electron-donating or -neutral groups underwent the C−C amidation smoothly, providing the desired products in good yields with high chemoselectivity (**3j**−**3l**). Similarly, reactants bearing electron-withdrawing groups were viable for the present amidation (**3m**−**3n**), indicating that electronic variation of azides did not much affect the reaction efficiency and selectivity. Azides substituted with bromo and chloro groups also participated in the reaction (**3o**−**3p**). The preference for the C−C amidation over C−N amidation was observed to be over 10:1 (measured by ^1H NMR of crude reaction mixture) in all cases examined (except **3j** where it was 8:1).

Having established the Rh-catalyzed selective C−C amidation procedure, we next tried to develop a new system allowing for selective C−N amidation using acyl azides as amino sources. While we were unable to switch the chemoselectivity favoring C−N amidation by using rhodium catalysts even under various conditions,[13] we were pleased to see that a ruthenium(II) catalyst[14] could accomplish this goal (Table 2). While a cationic

Table 2. Additive Effects in the Ru-Catalyzed Amidation[a]



entry	additives	temp (°C)	yield (**3a**, %)	yield (**4a**, %)
1	none	70	<5	17
2	NaOAc	50	<5	72
3	1-$AdCO_2H$	50	<5	50
4	$MesCO_2H$	50	<5	68
5	***o*-$NO_2C_6H_4CO_2H$**	**50**	**<5**	**85(80[b])**
6	*o*-$NO_2C_6H_4CO_2H$	25	<5	70

[a] **1a** (0.2 mmol) and **2a** (0.36 mmol) in 1,2-DCE (0.5 mL). Yields are determined by ^1H NMR. [b] Isolated yields are given.

species, generated *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and $AgSbF_6$, catalyzed the C−N amidation at 70 °C with high selectivity but in low efficiency (entry 1), the product yield was significantly increased in the presence of additives.

Among various additives screened,[15] a Brønsted acid of high acidity was most effective leading to the desired C−N amidation product (**4a**) in high yield and selectivity (entry 5).[14,16] The C−N amidation proceeded even at 25 °C (entry 6), highlighting the effect of the acid additive on the reactivity.

With the optimized conditions in hand, we investigated the scope of the Ru-catalyzed selective C−N amidation reaction (Scheme 3). In general, product yields of **4** were higher than those of C−C amidated products (**3**) that employed the Rh catalytic system (Scheme 2). Electronic influence on the reaction efficiency was negligible (**4a**−**4d**). Substrates possessing various sensitive functional groups such as bromo, chloro, ketone, ester, or aldehyde all smoothly underwent the C−N amidation to provide the desired products in synthetically acceptable yields (**4e**−**4i**). The scope of benzoyl azides under the present Ru-catalyzed conditions was also broad to include either electron-donating or -withdrawing substituents (**4j**−**4m**). More notably, benzoyl azides substituted with ester or halide groups were also amidated without difficulty (**4n**−**4p**). It needs

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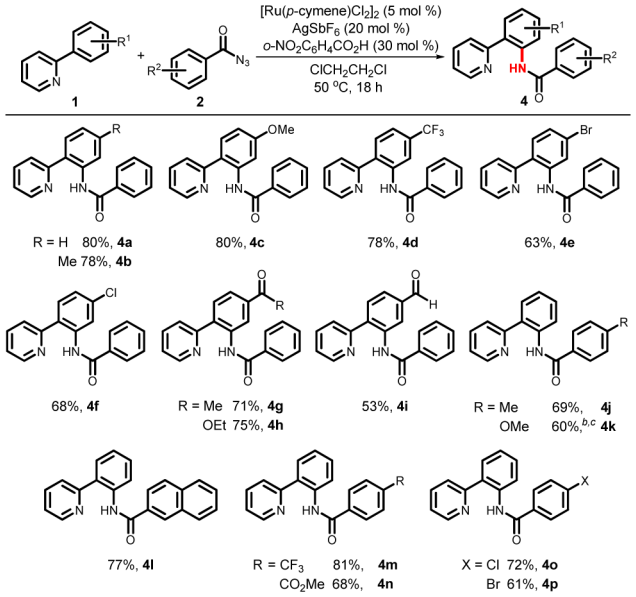
Scheme 3. Scope of the Ru-Catalyzed C−N Amidation[a]

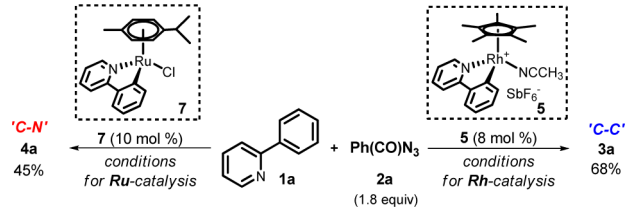


[a] **1** (0.2 mmol) and **2** (0.36 mmol) in 1,2-DCE (0.5 mL). Isolation yields are given. [b] NaOAc (30 mol %) was used instead of (*o*-NO_2)$C_6H_4CO_2H$. [c] A side product (C−C amidated **3k**) was also detected (**3k**/**4k**, 1:6).

to be mentioned that the C−N amiadtion occurred with high selectivity to form C−C amidated products in <5% in all cases examined except **4k**, where **4k**/**3k** ≈ 6:1.

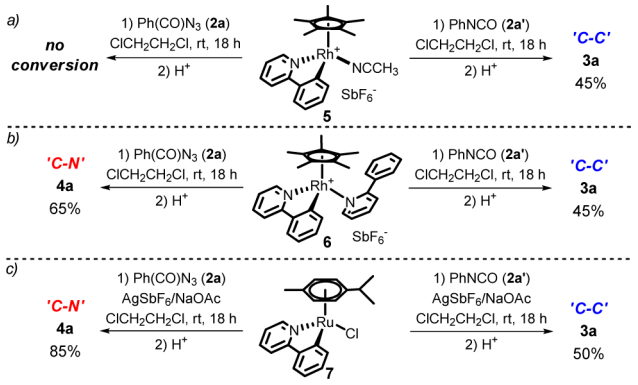
Considering the notable chemoselectivity between Rh- and Ru-systems, a working mode leading to this dichotomy was preliminarily investigated. As anticipated, when separately prepared metallacycles of rhodium (**5**) and ruthenium (**7**)[17] were employed as catalysts in the reaction of 2-phenylpyridine (**1a**) with benzoyl azide (**2a**), each species was found to catalyze the C−C and C−N amidations, respectively (Scheme 4).[15]

Scheme 4. Catalytic Reactivity of Metallacycle Catalysts



To further shed light on orthogonal reactivity depending on catalytic conditions used, stoichiometric reactions of rhodacycles were subsequently examined (Scheme 5). It was found that an acetonitrile-bound cationic rhodacycle (**5**) reacted with isocyanate (**2a**′) to lead to C−C amidation (**3a**), but reaction with benzoyl azide (**2a**) did not occur (Scheme 5a).[15] In contrast, a rhodacycle (**6**)[17] containing a 2-phenylpyridine ligand displayed an interesting dual reactivity: both C−C and C−N amidations took place by changing reactants (Scheme 5b).[15] This notable difference in reactivity between complexes **5** and **6** toward acyl azides and isocyanates clearly indicates the critical role of the acetonitrile ligand on the selectivity. On the other hand, a neutral ruthenacycle (**7**) exhibited dual activity for both C−C and C−N amidations under otherwise identical

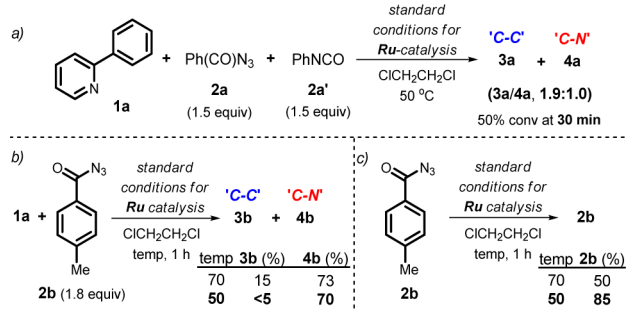
Scheme 5. Stoichiometric Reactions with Metallacycles



conditions (Scheme 5c).[15] This last result suggests that the observed high selectivity in the case of the ruthenium catalyst system is not intrinsic, but it is originated rather from the relative concentrations of acyl azides and isocyanates present under the reaction conditions (*vide infra*).

The postulated nonintrinsic chemoselectivity of the ruthenium catalytic system was further verified by a series of control experiments (Scheme 6). When equimolar amounts of

Scheme 6. Control Studies Using Ru-Catalytic System



benzoyl azide (**2a**) and phenyl isocyanate (**2a**′) were allowed to react with 2-phenylpyridine under the Ru-catalyzed conditions, **2a**′ showed higher reactivity than **2a** at an early stage of conversion (Scheme 6a).[15] In addition, while the C−N amidation gave a mixture of product **3b** and **4b** at 70 °C, the same reaction at 50 °C gave **4b** exclusively (Scheme 6b).[15] The higher selectivity seen at 50 °C is probably due to the slower decomposition rate of azide **2b** at that temperature (Scheme 6c).[15] These results suggest that the observed high chemoselectivity for the C−N amidation under the ruthenium catalytic conditions is mainly due to the fast amidation with the concomitant slow rearrangement of acyl azides.

On the basis of above studies, a plausible rationale for the mechanistic dichotomy between C−C and C−N amidation is depicted in Scheme 7. In the Rh-catalyzed system, the selective C−C bond formation may be attributed to the difference in binding affinity of a metal center between acyl azides and *in situ* generated isocyanates. It is assumed that while acyl azides display low binding affinity to an acetonitrile-bound cationic Rh species (**5**), those azides rather undergo a thermal Curtius rearrangement to isocyanates that readily replaces an acetonitrile ligand, eventually leading to a C−C amidated product. On the other hand, the Ru-catalyzed amidation is proposed to be governed by kinetic parameters. At temperatures 50 °C or below, since the formation of isocyanates is

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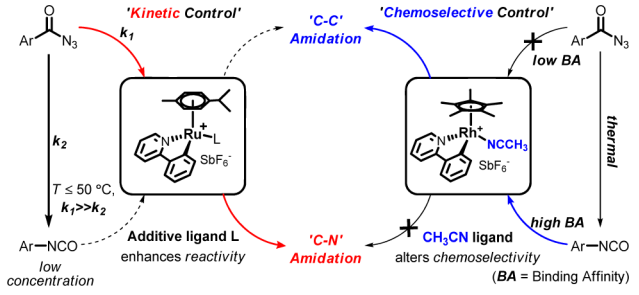
Scheme 7. Catalytic Dichotomy between C−C (Rh) and C−N (Ru) Amidations



negligible residing in low concentration, a direct reaction of acyl azides with a ruthenacyclic intermediate (**7**) will be predominant ($k_1 \gg k_2$).

In summary, the dual reactivity of acyl azides was controlled in the C−H functionalization by altering catalyst systems. Rhodium catalysis enabled the selective C−C amidation with isocyanates *in situ* generated from acyl azides. In contrast, a ruthenium catalyst system facilitated the selective C−N amidation with acyl azides.[18] Mechanistic studies revealed that the dichotomy between two catalytic systems might originate from chemoselective and kinetic control. This work opens the way to utilizing acyl azides in C−H functionalization by controlling their dual reactivity as a nitrogen or carbon source.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{1}H and ^{13}C NMR spectra). 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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(15) See the Supporting Information for details.

(16) For selected examples of the additive effects of carboxylates in Ru-catalyzed C−H functionalizations, see: (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (b) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032. (c) Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161.

(17) Rhodacylic intermediates **5**, **6** and ruthenacyclic complex **7** are well characterized in the previous reports (see the Supporting Information).

(18) When cyclohexanecarbonyl azide was applied to either Rh- or Ru-catalyzed amidation conditions, the reactions were sluggish only leading to low conversions (<30%).

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