Letter

Rhodium-Catalyzed Synthesis of Amides from Functionalized Blocked Isocyanates

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Rhodium-Catalyzed Synthesis of Amides from Functionalized Blocked Isocyanates

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ABSTRACT: Isocyanates are useful building blocks for the synthesis of amides, though their widespread use has been limited by their high reactivity, which often results in poor functional group tolerance and a propensity to oligomerize. Herein, a rhodium-catalyzed synthesis of amides is described coupling boroxines with blocked (masked) isocyanates. The success of the reaction hinges on the ability to form both the isocyanate and the organorhodium intermediates *in situ*. Relying on masked isocyanate precursors and on the high reactivity of the organorhodium intermediate results in broad functional group tolerance, including protic nucleophilic groups such as amines, anilines and alcohols.

The ubiquitous presence of amides in biological systems and in an array of useful products has led chemists to develop new syntheses of this functional group.[1] Innovations on this front also have high relevance in drug discovery where amide formation is amongst the most common processes in medicinal chemistry.[2] The low cost and broad commercial availability of isocyanates make them attractive amide precursors.[3-4] The synthesis of amides from isocyanates has been known for over a century, with the reaction of isocyanates with carboxylic acids (Figure 1A).[5] More recently, addition of nucleophiles such as Grignard and organolithium reagents have been reported, providing useful alternatives to traditional amide bond formation.[6] Milder catalytic alternatives have attracted much interest with strategies including the directed metalation of C-H bonds,[7] reductive couplings,[8] and redox neutral variants employing organoboron or tin reagents.[9] Despite these advances, the use of isocyanates bearing critical functional groups such as N-heterocycles, alcohols, amines, remain exceedingly limited.[10] Moreover, their propensity to oligomerize, which can be exacerbated by metal catalysts or common ligands,[11] can result in major limitations or prevent reaction development.[6d,8d] Lastly, their acute toxicity can have serious consequences (pulmonary edema, sensitization, death).[12] Thus, we became interested in achieving transition metal catalysis with safe, easily-handled isocyanate equivalents. Herein we report a rhodium-catalyzed synthesis of amides from functionalized masked isocyanate precursors and boroxines that addresses these issues (Figure 1B), and operates via the chemoselective reaction of a transiently formed isocyanate with a catalytic rhodium aryl nucleophile (Figure 1C).

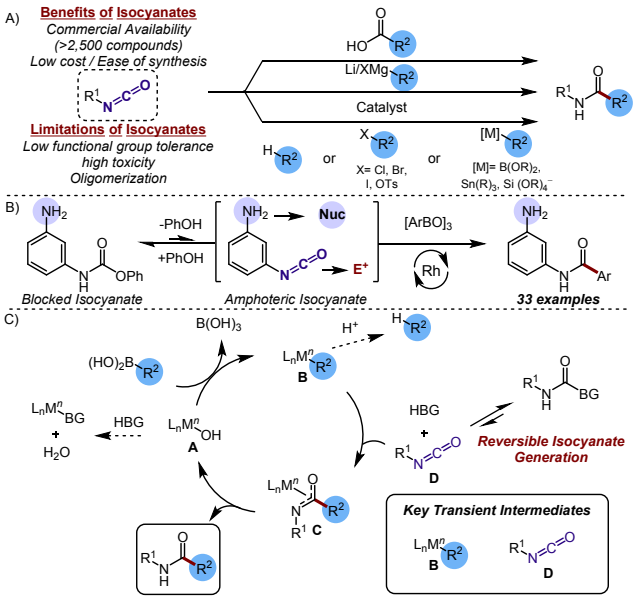
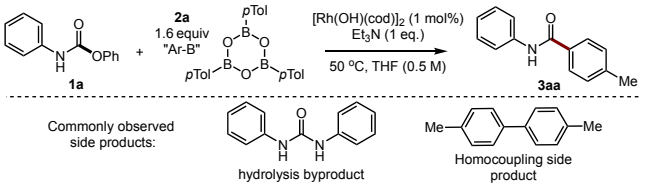


Figure 1. (A) Prior reports of isocyanates as amide building blocks. (B) Current work using blocked isocyanates as amide building block. (C) Prototypical catalytic cycle.

Blocked (masked) isocyanates are often bench stable solids alleviating the hazards intrinsic to isocyanates. Moreover, blocking groups regulate isocyanate concentration and reactivity with *in situ* generation of the reactive isocyanate in a controlled manner, proving a powerful strategy during polymerization reactions.[13] This strategy was successfully implemented by our group in new reactions of nitrogen- and oxygen-substituted blocked isocyanates to mitigate the oligomerization of these reactive species.[14] Surprisingly, the use of blocked isocyanates as amide precursors is rare.[15] Moreover, their use in metal-catalyzed reactions is virtually absent from the literature.[11c,16,17] Intimations of the value of such a strategy in transition metal catalysis are garnered from Buchwald's syntheses of complex ureas,[16a,d] in which the desired reactivity relied on the masking of an isocyanate to achieve the desired catalytic transformation. In contrast, a catalytic amide synthesis from masked isocyanates demands that two transient species present in low concentrations react chemoselectively while avoiding common side reactions (protodemetallation, homocoupling, etc.) (Figure 1C). Moreover, potential blocking group interference with the catalytic generation of the organometallic intermediate must be avoided.

Experiments began with masked isocyanate **1a** possessing a phenol blocking group. Though phenol blocked isocyanates undergo thermal deblocking generating the isocyanate around 120 °C, base-promoted deblocking can occur at room temperature.[13] Boroxine **2a** was chosen as the nucleophilic partner due to the broad availability and low toxicity of ogranoboron species. Unfortunately, reported conditions using organoboron reagents and isocyanates failed to provide product **3aa** from blocked isocyanate **1a**.[9d-e,15h] Gratifyingly, after extensive catalyst surveying and optimization, mild conditions using 1 mol% of commercially available $[Rh(OH)(cod)]_2$, 1 equiv of Et_3N, at 50 °C provided the desired amide product **3aa** in high yield (Table 1, entry 1).[18] These conditions allowed both the lowering of catalyst and boroxine loadings relative to work on 'free' isocyanates.[9d] This is in stark contrast to Mori's work where stoichiometric phenol inhibited a related reaction of 'free' isocyanates.[9c] Increasing the base loading led to a lower yield, with more urea side product (entry 2). In contrast, a reaction without Et_3N yielded mostly starting material (entry 3). These results suggest precise control over base-promoted isocyanate generation is necessary to form amide **3aa** efficiently. The formation of **3aa** also occurred in the absence of base at 120 °C (thermal deblocking conditions, entry 4).[13] In contrast, sluggish reactivity was observed at room temperature even with increased catalyst loading and longer reaction time (entry 5). A cationic rhodium catalyst displayed similar reactivity (entry 7) though $[Rh(OH)(cod)]_2$ proved optimal due to its shorter reaction time and bench stability. Both copper and palladium catalysts yielded no detectable product (e.g. entry 8). Finally, control reactions lacking the rhodium catalyst yielded no detectable product (entries 9-10).

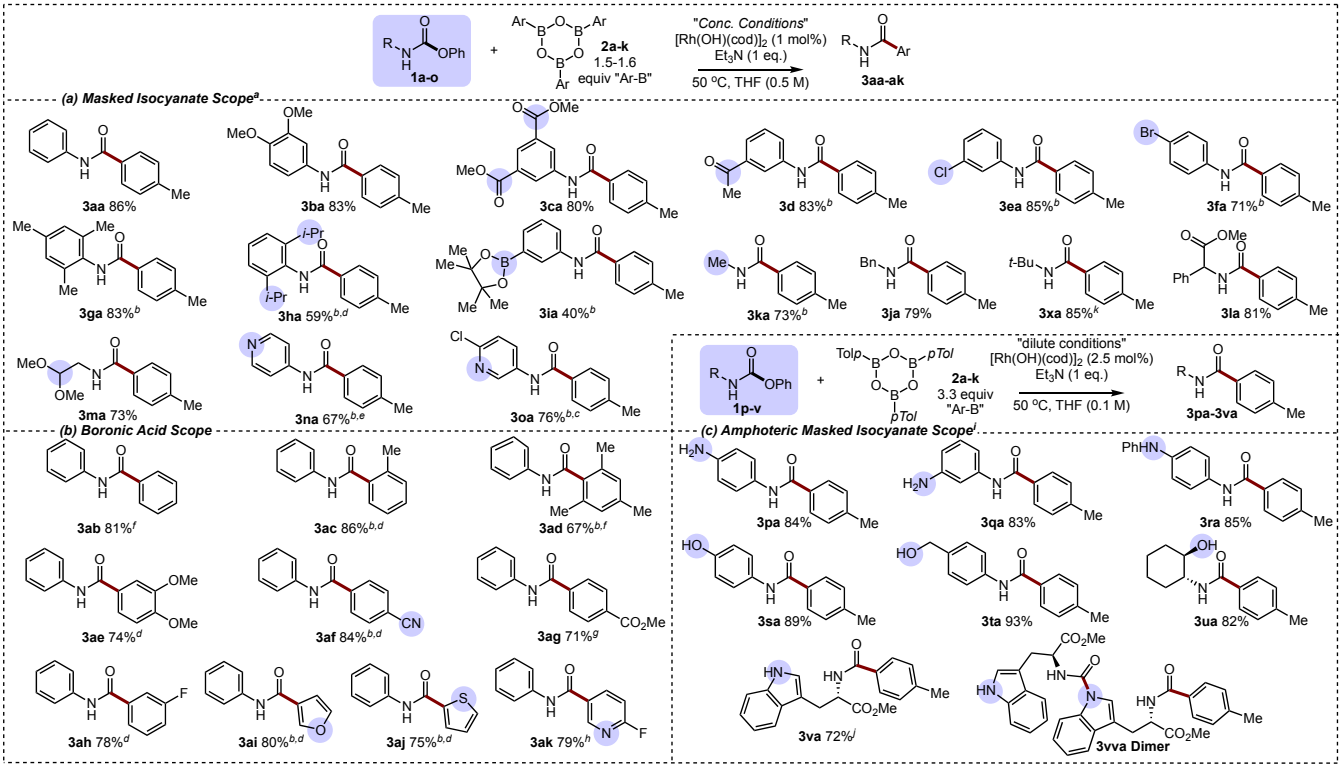
Table 1. Variation from Optimized Conditions[a,b]



Entry	Deviation from optimized conditions	Yield
1	none	**89%**
2	3 equiv of Et_3N	79%
3	No Et_3N	0%
4	No Et_3N at 120 °C	70%
5	Room temperature[c]	44%
6	$[Rh(Cl)(cod)]_2$	0%
7	$[Rh(MeCN)_2(cod)]BF_4$[d]	89%
8	$Cu(OAc)_2$[e] or $Pd(OAc)_2/PPh_3$[f]	0%
9	No catalyst, no Et_3N at 120 °C	0%
10	No catalyst	0%

[a]Conditions: **1a** (0.2 mmol), **2a** (1.6 equiv "Ar-B"), catalyst (1 mol%), Et_3N (0.2 mmol), THF (0.5 M), 50 °C. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]$[RBO]_3$:$RB(OH)_2$ = 1:2.1 see SI. [c]2.5 mol% catalyst. [d]2 mol% catalyst. [e]2 equiv. [f]$Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%).

Table 2. Rhodium-Catalyzed Amide Synthesis Using Masked Isocyanates: Reaction Scope



[a]Conditions: **1** (0.6 mmol), **2a** (1.6 equiv "Ar-B", see footnote b, Table 1), $[Rh]_2$ (1 mol%), Et_3N (0.6 mmol), THF (0.5 M), 50 °C; isolated yields. [b]$[Rh]_2$ 2.5 mol%. [c]3.3 equiv "Ar-B". [d]0.3 mmol $[RBO]_3$. [e]5.4 equiv "Ar-B", 120 °C. [f]0.9 mmol $RB(OH)_2$. [g]$[Rh]_2$ 0.5 mol%. [h]0.6 mmol $[RBO]_3$, $[Rh]_2$ 2.5 mol%, 80 °C. [i]Conditions: **1** (0.6 mmol), **2a** (3.3 equiv "Ar-B"), $[Rh]_2$ (2.5 mol%), Et_3N (0.6 mmol), THF (0.1 M), 50 °C; isolated yields. [j]At 80 °C. [k]At 100 °C.

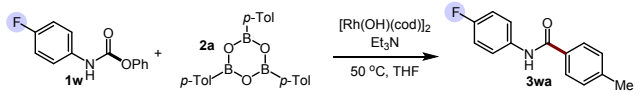
With optimized conditions, the scope of blocked isocyanate reagents was investigated (Table 2a). The model reaction on 0.6 mmol scale provided the desired product **3aa** in 86% isolated yield. Both electron-donating (**3ba**) and electron-withdrawing (**3ca**) groups were tolerated on the isocyanate precursor. To our delight, ketones (**3da**) and aryl halides (**3ea-3fa**) were compatible with the reaction. Sterically hindered substrates also provided the desired products in excellent to moderate yields (**3ga-3ha**). Conceptually this provides a catalytic alternative to Bode's synthesis of sterically hindered/electronically deactivated amides from isocyanates using Grignard nucleophiles.[6b] Despite the tendency for boron species to equilibrate *in situ*,[19] a boronic acid pinacol ester bearing starting material provided the desired product **3ia**, albeit in modest yield. Pleasingly, a benzylamine-derived blocked isocyanate was a competent reaction partner despite the decreased deblocking rate of aliphatic masked isocyanates compared to their aromatic counterparts (**3ja**).[13] Methyl amide **3ka** was also formed in good yield, thus providing a safe alternative to the use of methyl isocyanate.[12] An amino acid derivative and a precursor containing an acetal also formed the desired products efficiently (**3la-3ma**). The readily epimerizable stereocenter in the former was not conserved under the reaction conditions. Gratifyingly, given the typically problematic Lewis basic motif,[10a-b] product **3na** could be formed using higher temperatures and loadings of the organoboron reagent and rhodium.[18,20] In contrast, a heterocyclic substrate with attenuated Lewis basicity provided product **3oa** under milder conditions.

The effect of different organoboron reagents on the transformation was then surveyed (Table 2b). A variety of boroxines were competent reaction partners including sterically hindered (**3ac-3ad**), electron-rich (**3ae**), electron-deficient (**3af-3ag**), halide-containing (**3ah**), and heterocyclic reagents (**3ai-3aj**). Remarkably, a pyridyl boroxine was compatible with the reaction, though modified conditions were necessary (**3ak**).[20] It is noteworthy that catalyst loadings as low as 0.5 mol% were possible in some cases (**3ag**).

It was hypothesized that this catalytic system could be used with blocked isocyanates containing nucleophilic motifs. The blocking group would allow access to amphoteric (ambident) reagents which are typically beyond the reach of standard isocyanate chemistry. Moreover, stringent control over the isocyanate concentration imparted by the blocking group would allow high chemoselectivity for the transient organometallic catalyst to outcompete stoichiometric nucleophiles. Gratifyingly, lowering the concentration and increasing the boroxine/catalyst loading[18] resulted in efficient amide formation with a variety of amphoteric masked isocyanates (Table 2c). Aniline derivatives produced the desired products in high yields (**3pa-3ra**). A phenolic motif was also tolerated. Alcohols (**3ta**) were compatible, even in cases where a rapid intramolecular cyclization may be expected (**3ua**). Finally, the reaction could also be achieved with an unprotected (N-H) tryptophan derivative with minimal loss of the stereochemical information.[21] Interestingly, when the reaction was performed at 50 °C, competitive dimer formation occurred (**3vva**). This was alleviated by increasing the reaction temperature to 80 °C (**3va**).[21] In addition, variation on the structure of the blocking group allowed the reaction to be compatible with primary and secondary amines (see Supporting Information). Overall, the blocking group strategy enabled the high degree of chemoselectivity required to achieve product formation from amphoteric isocyanates.

Finally, efforts were directed at gaining insight on the reaction mechanism using the variable time normalization analysis (VTNA) developed by Burés (Table 3).[22] Under 'concentrated conditions' employed for substrates in Table 2a-b, a 0th order dependence in **1w** and a 0.75 order dependence in catalyst was observed. Taken together, these results support a rate limiting transmetallation, in line with facile base-mediated isocyanate unmasking (formation of **B**, Figure 1).[23] Moreover, the 0.75 order in catalyst suggest the presence of an equilibrium with an inactive dimeric species, analogous to related rhodium catalyzed additions onto enone electrophiles.[24] Given the need for alternative reaction conditions to achieve efficient product formation with ambiphilic isocyanates (Table 2c), we speculated a potential change in rate determining step. In fact, VTNA revealed a 0th order dependence in catalyst and a 0.6 order in **1w**. Taken together, these results support a rate determining isocyanate unmasking under the 'dilute conditions' (formation of D, Figure 1). Moreover, the 0.6 order in **1w** suggests the presence of an H-bonded dimer in solution.[25] Despite the increased loading of catalyst and organoboron reagent in the latter conditions, their concentration were halved overall as a result of the dilution of the reaction media. Consequently, the rate of transmetallation would be expected to decrease slightly under these conditions. However, the 5-fold dilution of the base and masked isocyanate **1w** under 'dilute conditions' has a much more pronounced effect on the rate of base mediated isocyanate unmasking, resulting in the change in rate limiting step. Thus, the successful amidation of ambiphilic isocyanate hinged on the ability to control the rate of isocyanate release. These results are expected to have broad implications for further developments towards functional group tolerant isocyanate based transformations.

Table 3: Results of kinetic studies



Conditions	1w order	Catalyst order	Proposed rate-determining step
Table 2a-b	0	0.75	transmetallation
Table 2c	0.6	0	deblocking

In conclusion, a robust catalytic synthesis of functionalized amides has been developed relying on blocked isocyanate precursors. Mechanistic studies suggested that reaction optimization led to conditions with different rate determining steps which proved vital to achieve the desired transformation with amphoteric isocyanates. This work provides a rare example of the use of blocked isocyanates in transition metal catalysis, highlighting the broad functional group tolerance possible and the use of otherwise 'impossible' isocyanates, and enabling their application in complex settings typically beyond the reach of normal isocyanates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Optimization data, experimental procedures, characterization data, kinetic data and discussion, NMR spectra.

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Notes

The authors declare no competing financial interests.

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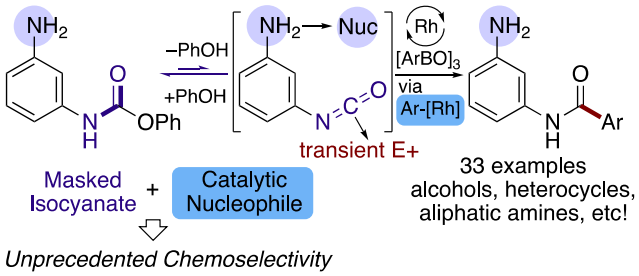
NH2
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alcohols, heterocycles,
aliphatic amines, etc!
Masked
Isocyanate
+
Catalytic
Nucleophile
Unprecedented Chemoselectivity